Derivatives of (+)-Limonene. III. A Stereospecific Synthesis of *cis*- and *trans*-$\Delta^{8(9)}$-*p*-Menthene 1,2-Epoxides[1]

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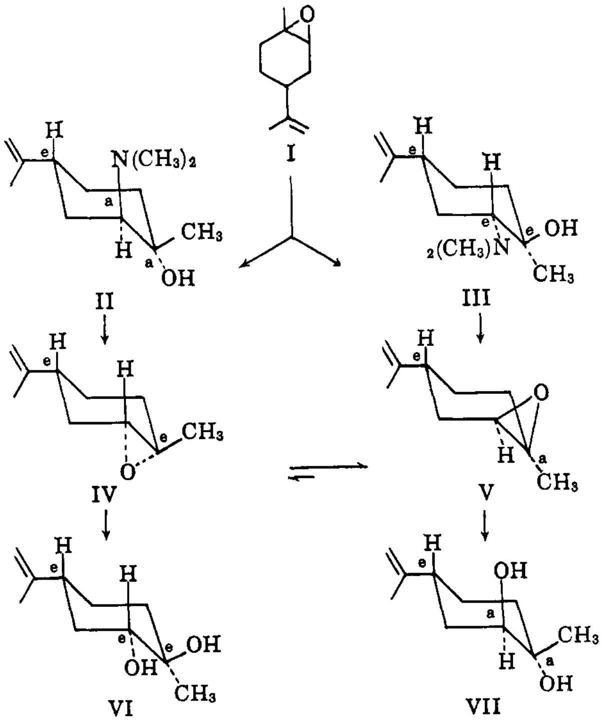
The *cis* and *trans* isomers of $\Delta^{8(9)}$-*p*-menthene 1,2-epoxide have been prepared by Hofmann degradation of the two isomeric *trans*-2-dimethylamino-$\Delta^{8(9)}$-*p*-menthen-1-ols. Both degradations proceed by displacement of the C-2 nitrogen by C-1 oxygen with consequent reformation of the epoxide ring. The conformations of the amino alcohol precursors, the epoxides, and the glycols formed from the epoxides are discussed.

Epoxidation of the endocyclic double bond in (+)-limonene with organic peracids affords an equal mixture of *cis*- and *trans*-1,2-epoxides[2–4] (I). This has been verified by gas chromatographic analysis which shows two partially resolved peaks of equal intensity. This epoxide mixture is difficult to separate even by gas chromatographic methods and rearrangement to carbonyl compounds occurs to some extent.[5] These epoxides were found to be inseparable by even the most efficient methods of fractional distillation. The reason for this became evident during the course of this work when the pure *cis* (IV) and *trans* (V) epoxides were prepared by chemical means and found to have boiling points of 82.3° and 81.1°, respectively, at 15.0 mm.

For these reasons and also to simplify synthetic work based on $\Delta^{8(9)}$-*p*-menthene 1,2-epoxide (I) as a starting material, a convenient synthesis of IV and V has been developed. The *cis* epoxide (IV) has been prepared from *trans*-$\Delta^{8(9)}$-*p*-menthene-1,2-diol (VII) by Kuczynski and Piatkowski,[6] but the *trans* isomer (V) has not been reported previously. These authors refer to IV as a "*trans*" oxide because it is the *trans*-1,4-isomer with respect to the methyl and isopropenyl groups.



The reaction of the mixed *cis–trans* epoxides[7] (I) with aqueous dimethylamine gave the two *trans* isomers of 2-dimethylamino-$\Delta^{8(9)}$-*p*-menthen-1-ol[8] (II, III) which were separated by fractional crystallization of their picrate salts. The solubility differences between these two picrates were so great that the more insoluble one was removed completely from the mixture after two successive crystallizations from benzene–methanol solution. The two picrates were found to occur in equal quantities in the mixture. The regenerated amino alcohols (II, III) were converted separately to their quaternary ammonium iodide derivatives which were then degraded by brief warming with aqueous potassium hydroxide solution (30%). Each amino alcohol gave a single 1,2-epoxide (IV or V) in high yield. The purity of both epoxides was verified by gas chromatographic analysis. The formation of IV and V as the sole products of these degradations indicates that a displacement of the C-2 nitrogen, from the rear, by C-1 oxygen has occurred in each case.

The conformations of IV and V were established from a consideration of the 1,2-diols obtained on cleaving them with dilute aqueous acid. In each case, acid cleavage should proceed by way of the more stable tertiary carbonium ion at C-1.[9] *trans* diols would be expected, since the over-all result of oxide formation and cleavage is equivalent to *trans* addition.[10] One oxide gave the known $\Delta^{8(9)}$-*p*-menthene-1,2-diol[11–13] (VII, m.p. 70–71.6°) which was first prepared by Prileschaev[14] and is the main product of the peracetic acid oxidation of (+)-limonene.[15] By analogy with the work of Jefferies and Milligan[16] and Cole and Jefferies[17] on the *racemic* *p*-menthane-1,2-diols, VII must be the *trans*-1,2-*trans*-1,4 isomer in which both hydroxyls are axial. Thus the parent epoxide must have the *trans* conformation (V) in which the oxide ring and isopropenyl group are on opposite sides of the plane of the cyclohexane ring.

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The other oxide gave the same 1,2-diol (VII) on acid cleavage plus a second diol (m.p. 65–66°) which must have the *trans*-1,2-*cis*-1,4-conformation (VI) in which both hydroxyls are equatorial. The latter has not been reported previously as an oxidation product of (+)-limonene. Although the melting point is somewhat lower, this is undoubtedly the *trans* diol synthesized by Schmidt[12] from *d*-terpineol. The parent epoxide of VI must then have the *cis* conformation (IV) in which the oxide ring and the isopropenyl group are on the same side of the plane of the ring. Further evidence that IV is the *cis* epoxide is furnished by a comparison of its physical constants with those reported by Kuczynski[2] for this isomer. With the exception of the specific rotation (+92.7) which is slightly higher than the value reported (+83.7), agreement is good. The higher rotation is indicative of higher purity. It is interesting to note that the specific rotation of the *trans* epoxide V (+55.0) is much lower than that of the *cis* isomer (IV). As would be expected, the arithmetic average of these two rotation values (+73.8) is in close agreement with the specific rotation (+70.9) of the original $\Delta^{8(9)}$-*p*-menthene-1,2-epoxide (I).

The formation of two diols from IV may proceed by an acid-catalyzed rearrangement of IV to the *trans* epoxide[16] (V). This would explain why VII is the major product of the peracid hydroxylation of (+)-limonene. This is in contrast to the alkaline cleavage of the mixed epoxides (I) with amines which has been shown to give equal amounts of the two *trans* amino alcohols (II, III).

The infrared absorption curves of the two *trans* amino alcohols (II, III) and the two *trans* diols (VI, VII), were almost identical from 1 to 7 μ, as would be expected. The only differences were in the molecular vibration region from 7 to 15 μ. The same was true for the *trans* (V) and *cis* (IV) epoxides, the greatest difference being one sharp peak of medium intensity at 10.53 μ in V which is totally absent in IV. The absorption maxima for these compounds are tabulated in Experimental.

During the course of this work, the mixed *trans* isomers of 2-amino- and 2-methylamino-$\Delta^{8(9)}$-*p*-menthen-1-ol also were prepared by reaction of I with the appropriate amines. In general these compounds were prepared in a similar manner to their saturated analogs reported previously.[3]

Experimental

All melting points reported are uncorrected.

2-Dimethylamino-$\Delta^{8(9)}$*p*-menthen-1-ols (II and III).—Sixty-four milliliters (59.5 g.) of $\Delta^{8(9)}$-*p*-menthene-1,2-epoxide (I) and 100 ml. of aqueous dimethylamine (25%) were stirred and heated in a 300 ml. bench-scale autoclave at 135–140° for 7 hr. This procedure was repeated and the two crude products were combined, concentrated to dryness, and then vacuum distilled through an 18-in. Vigreux column. At 98–103° (1.5 mm.), 119.4 g. (77.4%) of the mixed *trans* isomers (II and III) distilled as a colorless, slightly viscous liquid. A redistilled sample boiled at 86–93° (1.1 mm.), d^{23} 0.9538, $n^{23}\text{D}$ 1.4890, $[\alpha]^{23}\text{D}$ +24.6.

Anal. Calcd. for $C_{12}H_{23}ON$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.94; H, 11.62; N, 7.01.

The 119.4 g. of the mixed *trans* isomers was dissolved in 1.5 l. of 10% methanol in benzene, and sufficient solid picric acid added to make the solution just acidic. On cooling, yellow needles of the picrate of II (88.5 g., m.p. 152–157°) separated from solution. The filtrate was concentrated to 500 ml. and a second crop obtained (9.3 g., m.p. 150–156°). The combined batches (97.8 g.) after recrystallization once from benzene–methanol solution afforded 92.5 g. of the picrate of II, m.p. 156–158°. This corresponds to 42.8 g. of II and represents a separation yield of 71.7% since the theoretical yield of II is half of the 119.4 g. or 59.7 g.

A small sample of this picrate recrystallized from benzene–methanol solution melted at 156.4–157.4°.

Anal. Calcd. for $C_{18}H_{26}O_8N_4$: C, 50.70; H, 6.15; N, 13.14. Found: C, 51.37; H, 6.25; N, 12.43.

The free base (II) was isolated by treating the picrate (92.5 g.) with excess dilute aqueous sodium hydroxide solution followed by ether extraction. The combined ether extracts were washed several times with dilute aqueous sodium hydroxide solution and dried over anhydrous sodium sulfate. After removal of the ether at reduced pressure, the residual oil was distilled under vacuum. At 86° (0.7 mm.), 37.8 g. (63%, based on half the original 119.4 g.) of II distilled as a colorless slightly viscous liquid, d^{25} 0.9528, $n^{25}\text{D}$ 1.4872, $[\alpha]^{25}\text{D}$ +35.5 (pure liquid); $\lambda_{\text{film}}^{\text{capillary}}$ 2.87, 3.38, 6.07, 6.83, 7.27, 8.45, 8.81, 9.66, 11.27 μ.

Anal. Calcd. for $C_{12}H_{23}ON$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.84; H, 11.66; N, 7.05.

The filtrates from the 97.8 g. of the picrate of II were combined and concentrated to dryness at reduced pressure. An orange gum (98.0 g.) was obtained which could not be induced to crystallize. Amino alcohol (III) was regenerated from this amorphous picrate exactly as described previously. The residual oil from the ether extracts was distilled under vacuum. At 92° (0.7 mm.), 40.0 g. (67%, based on half the original 119.4 g.) of III distilled as a colorless viscous liquid which crystallized on standing to colorless oily needles (indeterminate melting point at about 50°), $n^{25}\text{D}$ (supercooled liquid) 1.4949, $[\alpha]^{25}\text{D}$ +34.4 (10% acetone solution); $\lambda_{\text{max}}^{\text{KBr}}$ 2.92, 3.38, 6.06, 6.82, 7.28, 8.00, 8.40, 9.55, 9.70, 9.82, 11.20, 11.33 μ.

Anal. Calcd. for $C_{12}H_{23}ON$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.85; H, 11.78; N, 6.96.

***cis*-$\Delta^{8(9)}$-*p*-Menthene 1,2-Epoxide (IV).**—Twenty-five grams of II was refluxed for 4 hr. in 100 ml. of acetone containing excess (18 ml.) methyl iodide. The solution was concentrated to dryness at reduced pressure. The residue rapidly crystallized (colorless needles) to give a quantitative yield (43.0 g.) of the methiodide of II (*p*-menth-8-en-1-ol,2-dimethylamino-methiodide). A small sample recrystallized twice from acetone melted at 167.4–168°, $[\alpha]^{25}\text{D}$ −9.5 (10% aqueous solution).

Anal. Calcd. for $C_{13}H_{26}ONI$: C, 46.02; H, 7.72; N, 4.13. Found: C, 46.29; H, 7.81; N, 4.23.

Forty-two grams of the methiodide of II was warmed at 75–80° for 1.5 hr. in 200 ml. of 30% aqueous potassium hydroxide solution. During this time there was a copious evolution of trimethylamine and the epoxide generated in the degradation formed an upper liquid level. The cooled mixture was diluted with 100 ml. of water and extracted three times with ether. The combined extracts were washed several times with water, dried over anhydrous sodium sulfate, and the ether removed at reduced pressure. The residue was 17.7 g. (94%) of the colorless fluid *cis* epoxide (IV). The purity of this product was indicated when vacuum distillation of the 17.7 g. through an 18 in., 0.5-in. i.d. column packed with stainless steel rings and having a "hold-up" of 3–4 g. gave 14.1 g. (75%) of pure IV, b.p. 82.3° (15.0 mm.), d^{25} 0.9305, $n^{25}\text{D}$ 1.4661, $[\alpha]^{25}\text{D}$ +92.7 (pure liquid); $\lambda_{\text{max}}^{\text{path 0.0114 mm.}}$ 3.37, 6.06, 6.90, 7.23, 8.27, 8.93, 9.12, 9.78, 9.88, 10.31, 10.91, 11.25, 11.88, 13.17 μ.

***trans*-$\Delta^{8(9)}$-*p*-Menthene 1,2-Epoxide (V).**—Twenty-five grams of the amino alcohol (III) was refluxed for 4 hr. in 100 ml. of acetone containing excess (18 ml.) methyl iodide. The quaternary methiodide of III was isolated exactly as described for the preparation of the methiodide of II. This procedure gave a quantitative yield (43.0 g.) of III methiodide as a colorless amorphous glass which could not be crystallized.

Therefore, the entire product was degraded to the *trans* epoxide (V) using the same procedure described previously. This afforded 16.2 g. (86%) of the colorless fluid *trans* epoxide (V) which was vacuum distilled through the same 18-in. packed column used to distil IV. This gave 13.0 g. (69%) of pure V, b.p. 81.1° (15.0 mm.), d^{25} 0.9259, $n^{25}\text{D}$ 1.4643, $[\alpha]^{25}\text{D}$ +55.0 (pure liquid); $\lambda_{\text{max}}^{\text{path 0.0114 mm.}}$ 3.37, 6.06, 6.90, 7.23, 8.27, 8.48, 8.93, 9.62, 10.53, 11.25, 11.88, 13.15 μ.

***trans*-$\Delta^{8(9)}$-*p*-Menthene-1,2-diols (VI and VII).**—Three milliliters (2.79 g.) of the *cis* epoxide (IV) was shaken with 30 ml. of

4% aqueous sulfuric acid at room temperature for 20 min. The mixture was cooled to 0° and the crystalline glycol hydrates were collected on a filter, dissolved in ethyl ether, and the solution dried over anhydrous sodium sulfate. The ether was removed at reduced pressure, and the residue dissolved in benzene–petroleum ether and seeded with a crystal of the known diol (VII). Crystallization was allowed to proceed for 24 hr. at room temperature. This gave 0.870 g. (28%) of large colorless prisms, m.p. 69–71.4°. A recrystallized sample melted at 70–71.6° and had an infrared absorption curve identical in all respects with that of an authentic sample of diol VII. The filtrate from the 0.870 g. gave a mixture of diols (VII in prisms and VI in needles), 0.60 g., m.p. 48–68°.

The aqueous filtrate from the glycol hydrates was made weakly basic with aqueous sodium bicarbonate solution and extracted three times with ethyl ether. The combined extracts were dried over anhydrous sodium sulfate and the ether removed under vacuum. The residue was dissolved in petroleum ether (b.p. 30–60°) and crystallized at 40°. Long colorless needles, m.p. 55–61°, separated from the solution. Several crystallizations afforded 0.230 g. (7.4%) of diol VI melting at 65–66° which was further purified by vacuum sublimation. A mixture melting point of this diol with VII was 40–48°. The yield of VI obtained using this procedure is not representative of the amount actually present. These losses were necessary in order to obtain a sample free of the more insoluble diol (VII). The specific rotation of VI was $[\alpha]^{25}\text{D}$ +28 (10% acetone solution).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.52; H, 10.64.

The infrared absorption maxima of VI and VII are compared: $\lambda^{\text{KBr}}_{\text{max}}$ (VI) 2.97, 3.38, 6.05, 6.85, 7.23, 8.74, 9.26, 11.30 μ; (VII) 2.93, 3.38, 6.04, 6.83, 7.23, 8.40, 9.48, 9.68, 11.29 μ.

One milliliter (0.926 g.) of the *trans* epoxide (V) was shaken for 15 min. at room temperature with 15 ml. of 4% sulfuric acid. The glycol hydrate which formed was collected on a filter, dissolved in ether, and the ether layer dried over anhydrous sodium sulfate. Removal of the ether at reduced pressure afforded 0.677 g. (66%) of colorless prisms, m.p. 66–69°. One recrystallization from benzene–petroleum ether solution gave 0.537 g. melting at 70–71.4° which proved to be identical in all respects to the known *trans* diol (VII). The yield and high degree of purity of VII obtained directly from the ether residue indicate that it is the main product. None of the more soluble diol (VI) could be recovered from the filtrates.

2-Amino-$\Delta^{8(9)}$-*p*-menthen-1-ol.—A 300-ml. capacity autoclave (Autoclave Engineers, Inc., Model No. ABA-300) was charged with 64 ml. (59.4 g.) of $\Delta^{8(9)}$-*p*-menthene 1,2-epoxide (I) and 100 ml. of aqueous ammonium hydroxide (28%). The mixture was stirred and heated at 135–140° for 4 hr. The crude product was then concentrated to dryness under vacuum using a film evaporator (water bath temp. 40°) and the residual dark viscous oil was vacuum distilled. At 95–99° (1.2 mm.), 49.0 g. (75%) of the mixed *trans* isomers of 2-amino-$\Delta^{8(9)}$-*p*-menthen-1-ol distilled as a colorless viscous oil. Redistillation afforded material boiling at 96–99° (1.2 mm.), d^{23} 0.9868, $n^{23}\text{D}$ 1.5032, $[\alpha]^{23}\text{D}$ +28.5.

Anal. Calcd. for $C_{10}H_{19}ON$: C, 70.96; H, 11.31; N, 8.28. Found: C, 71.25; H, 11.21; N, 8.26.

2-Methylamino-$\Delta^{8(9)}$-*p*-menthen-1-ol.—Sixty-four milliliters (59.4 g.) of $\Delta^{8(9)}$-*p*-menthene 1,2-epoxide (I) and 100 ml. of aqueous methylamine (30%) were stirred and heated at 135–140° in an autoclave for 5 hr. Concentration of the crude product to dryness gave a viscous oil which was vacuum distilled. At 89–94° (1.2 mm.), 46.7 g. (65%) of the mixed *trans* isomers of 2-methylamino-$\Delta^{8(9)}$-*p*-menthen-1-ol distilled as a colorless viscous oil. Redistillation afforded material boiling at 93–96° (1.3 mm.), d^{23} 0.9703, $n^{23}\text{D}$ 1.4964, $[\alpha]^{23}\text{D}$ +30.3.

Anal. Calcd. for $C_{11}H_{21}ON$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.84; H, 11.43; N, 7.68.

Synthesis of β-Carotene and Certain Polyenes *via* Thiapyran Intermediates

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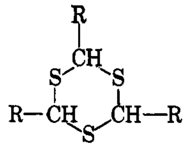
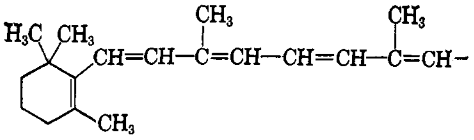
β-Carotene has been synthesized by treating retinal with hydrogen sulfide and desulfurizing the new thio derivative thus formed, with metals in a basic solvent. The intermediate sulfur derivative of retinal has been assigned a 2,4-disubstituted 2*H* thiapyran structure (IIIa, R = B). Desulfurization of this thiapyran with amalgamated zinc in pyridine gave a good yield of β-carotene (70% over-all from retinal). Other β-methyl substituted conjugated aldehydes, such as β-ionylidene acetaldehyde, likewise gave 2,4-disubstituted thiapyrans and were desulfurized to polyenes.

The reaction of aromatic aldehydes with hydrogen sulfide to form trimeric thioaldehydes which can be desulfurized to ethylenic hydrocarbons is known. The reactions are illustrated by the conversion of trithiobenzaldehyde I to stilbene.[1]



I, R = C_6H_5

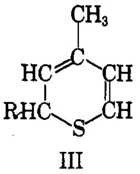
Ia, R = A



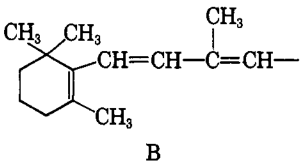
A

An attempt to prepare β-carotene in good yield from trithioretinal was, however, unsuccessful. Reaction of all *trans*-retinal with hydrogen sulfide, in ethanol, under conditions similar to those previously employed to prepare trimers[2] gave a compound Ia having properties consistent with I. This gave less than a 4% yield of β-carotene by the usual desulfurization procedures[1].

However, when hydrogen sulfide reacted with either all *trans*-retinal or 13-*cis*-retinal at low temperatures in amine solvents (*e.g.*, aniline, pyridine, etc.) a different type of sulfur containing intermediate was formed. Studies provided evidence that this intermediate had the thiapyran structure IIIa (R = B). We consider a 1,6-addition of hydrogen sulfide to retinal followed by ring closure to be a plausible mechanism for the forma-

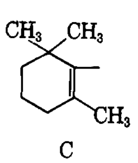


III



B

IIIa, R=B



C

IIIb, R=C

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[1] E. Campaigne, *Chem. Rev.*, **39**, 52 (1946).

[2] E. Campaigne, *ibid.*, **39**, 4, 11 (1946).