

fine needles from methanol-methylene chloride brought the melting point to 256–256.5°.

Anal. Calcd. for C₂₂H₂₂O₇: C, 66.32; H, 5.57. Found: C, 66.29; H, 5.56.

Comparison of the infrared spectrum of this racemic material with that of optically active desoxyisopodophyllotoxin,¹⁰ when both materials were taken as mulls with mineral oil, showed some differences. For example, the lactone absorption of the racemic material appeared at 5.67 μ , while that of the optically active form appeared at 5.61 μ . However, when the spectra were determined with the materials dissolved in methylene chloride, the two curves showed the same lactone absorption at 5.61 μ and were also superimposable at all other points.

The mixture melting point of the synthetic and the optically active material (m.p. 252°) was 246–248°, with softening at 240°.

Ethyl DL-Isopodophyllate Acetate (XI) by Reaction of DL-Isopodophyllotoxin Acetate (IV) with Alcoholic Sodium Acetate.—Absolute alcohol (10 ml.) containing 30 mg. of acetate IV and 200 mg. of anhydrous sodium acetate was boiled for 2.5 hr. The solid gradually dissolved. Most of the alcohol was removed by distillation under reduced pressures on the steam bath, 10 ml. of water was added, and the resulting precipitate collected by filtration. The solids, washed with water and air-dried, weighed 21 mg. and showed m.p. 159–163°. Three crystallizations from acetone-petroleum ether (30–60°) afforded the analytically pure acetyl derivative of ethyl DL-isopodophyllate (XI) in the form of fine needles, m.p. 166–167°. Infrared absorption peaks were noted at 2.99 and 5.80 μ .

Anal. Calcd. for C₂₆H₃₀O₁₀: C, 62.14; H, 6.02. Found: C, 62.2; H, 6.2.

Desoxypicropodophyllin (X) by Hydrogenolysis of Picropodophyllin (IX).—Picropodophyllin (0.5 g.) dissolved in 50 ml. of glacial acetic acid containing 0.5 g. of 10% palladium-on-charcoal catalyst was stirred under hydrogen for 1.5 hr. at 60°. No hydrogen absorption was noted after this time. The glassy material obtained after removal of catalyst and solvent was dissolved in 25 ml. of 9:1 benzene-ether, and the solution was allowed to percolate through a 7 × 1 cm. column of Merck acid-washed alumina (10 g.). The material was eluted with 210 ml. of 9:1 benzene-ether. Removal of solvent left a glass, which when triturated with methanol gave 0.3 g. (60%) of crystalline desoxypicropodophyllin (X), m.p. 167–168.5°. Sublimation at 156° (5 × 10⁻⁵ mm.) gave product with m.p. 169°. A sample for analysis, prepared by several recrystallizations from methanol, showed m.p. 170–171.5°. This product had a rotation of [α]_D²⁵

+34.4° (*c* 1.65 in chloroform), and gave an absorption peak at 5.68 μ but none in the hydroxyl region. The crystals tended to become electrically charged. These characteristics correspond well to those previously reported¹⁰ for desoxypicropodophyllin prepared in a different way.

Anal. Calcd. for C₂₂H₂₂O₇: C, 66.32; H, 5.57. Found: C, 66.52; H, 5.52.

To show that picropodophyllin (IX) is not dehydrated under the hydrogenolysis conditions employed, a mixture of picropodophyllin (0.1 g.), glacial acetic acid (10 ml.), and 0.1 g. of 10% palladium-on-charcoal was stirred for 2 hr. at 60° under an atmosphere of nitrogen. Unchanged picropodophyllin could be recovered to an extent of 75%.

DL-Epiisopodophyllotoxin (XIV) by Zinc Borohydride Reduction of DL-Isopodophyllotoxone (XIII).—A solution of 0.10 g. (1.05 mmoles) of zinc borohydride in 4 ml. of ether was added to a solution of 28 mg. (0.68 mmole) of DL-isopodophyllotoxone (XIII) in benzene (2 ml.) plus ether (4 ml.). After 20 hr. at 5°, the mixture was hydrolyzed by cautious addition of 1 ml. of water. When no further effervescence was evident, 1 ml. of acetic acid was added. The ether layer was removed, and the aqueous layer was filtered. The collected solids, after thorough washing with water, were dissolved in 50 ml. of methylene chloride-methanol solvent. The ether layer was diluted with more ether, was washed twice with water, once with saturated sodium bicarbonate solution (20 ml.), and again with water. The combined ether and methylene chloride-methanol solutions were concentrated and cooled to give 21 mg. (79%) of needle-like crystals, m.p. 248–251°. Two further crystallizations from methanol furnished 12 mg. of DL-epiisopodophyllotoxin (XIV), m.p. 255°. The compound absorbed at 5.61 and 2.90 μ , but not in the tetralone-carbonyl position. The infrared absorption curve did not resemble that of either of the two forms of DL-isopodophyllotoxin (VII). When mixed with DL-isopodophyllotoxin (VII), compound XIV softened at 236°, melted at 238–244°, and was entirely liquid at 250°.

Anal. Calcd. for C₂₂H₂₂O₈: C, 63.76; H, 5.35. Found: C, 63.75; H, 5.28.

Acknowledgment.—We wish to thank Dr. Jonathan L. Hartwell, who provided a sample of desoxypicropodophyllotoxin, and Dr. E. Schreier, who very kindly made his collection of pertinent n.m.r. curves¹³ available to us for study.

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The Total Synthesis of (\pm)-Thujopsene¹

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Thujopsene, a tricyclic sesquiterpene, has been synthesized and has been shown to possess the *cis* structure I.

Thujopsene, a tricyclic sesquiterpene, has been shown to be a constituent of the wood oil and of the heartwood of many genera belonging to the natural order Cupressales.³ It has been suggested by Erdtman and Norin⁴ that all conifers possessing the sweet odor of "pencil wood" apparently contain this odoriferous principle. In the past few years the chemistry of this widely occurring hydrocarbon has been extensively investigated and of the three structures for the material tentatively suggested,^{5–7} it recently has been shown that the compound possesses the gross structure I.^{3,4,8–11}

(1) This work was supported in part by the National Science Foundation, Grant No. G-14526.

(2) Procter and Gamble Predoctoral Fellow, 1962–1963.

(3) For a summary of the numerous isolations of thujopsene, see T. Norin, *Acta Chem. Scand.*, **15**, 1676 (1961).

(4) H. Erdtman and T. Norin, *Chem. Ind.* (London), 622 (1960).

(5) H. Erdtman and B. R. Thomas, *Acta Chem. Scand.*, **12**, 267 (1958).

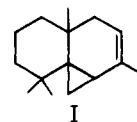
(6) H. Kobayashi, S. Nagahama, and S. Akiyoshi, *Bull. Chem. Soc. Japan*, **32**, 203 (1959).

(7) K. S. Sisido and H. Nozaki, *J. Org. Chem.*, **25**, 875 (1960).

(8) T. Nozoe, H. Takeshita, S. Ito, T. Ozeki, and S. Seto, *Chem. Pharm. Bull.*, **8**, 936 (1960).

(9) S. Forsen and T. Norin, *Acta Chem. Scand.*, **15**, 592 (1961).

(10) K. S. Sisido, H. Nozaki, and I. Imagawa, *J. Org. Chem.*, **26**, 1964 (1961).



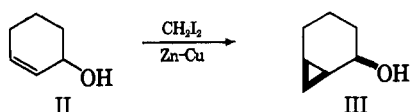
The steric relationship between the angular methyl group and the cyclopropane ring, however, has been assigned both *cis*³ and *trans*^{8,10} orientations, but the evidence presented for each postulate does not permit an unequivocal conclusion to be reached. This problem has now been settled by a stereospecific synthesis of thujopsene.¹²

The synthetic approach was based on the recent finding¹³ that when an alicyclic allyl alcohol, such as cyclohexenol (II), was allowed to react with methylene iodide in the presence of zinc-copper couple (the Simmons reagent), the exclusive product formed was the bicyclo[4.1.0]heptane-2-ol (III) with the cyclo-

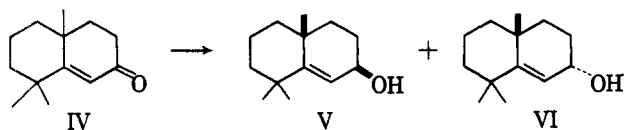
(11) H. Kobayashi, S. Nagahama, and S. Akiyoshi, *Bull. Chem. Soc. Japan*, **34**, 1123 (1961).

(12) Since this work was completed, Dr. T. Norin has informed us of some of his recent results which clearly establish the *cis* stereochemistry (*Acta Chem. Scand.*, **17**, 738 (1963)).

(13) W. G. Dauben and G. H. Berezin, *J. Am. Chem. Soc.*, **85**, 468 (1963).

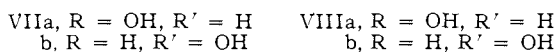
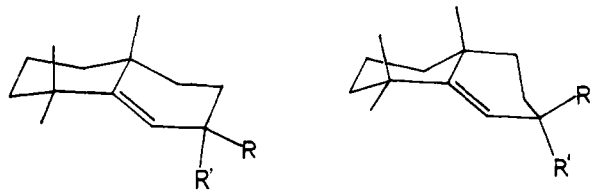


propane ring and the hydroxyl group in a *cis* arrangement. In addition to the specificity introduced into this reaction by the presence of the hydroxy function, this grouping also greatly catalyzed the reaction. To apply this reaction sequence to the preparation of thujopsene, the *cis*-7-hydroxy-4,4,10-trimethyl- Δ^5 -octalin (V) was required.¹⁴



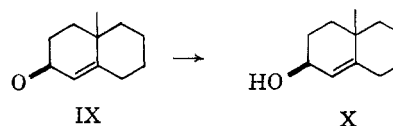
The starting material for the synthesis was the related ketone IV which previously had been prepared by Enzell¹⁵ and used in his total synthesis of (\pm)-widdrol. The preparation of IV used in this present work differed slightly from the published procedure and is described in the Experimental section. Reduction of the trimethyloctalone IV with lithium aluminum hydride yielded a mixture of alcohols V and VI in a ratio of 95:5. When the ketone was reduced *via* the Meerwein-Ponndorf reaction under irreversible conditions or when the hydride reduction mixture was equilibrated with acetone and aluminum isopropoxide in 2-propanol, the ratio of V to VI was 58:42. By chromatography on alumina of the latter mixture it was possible to obtain a fraction containing approximately 90% of the isomer VI.

Although these reductions showed that the major alcohol was the more stable thermodynamically,¹⁶⁻¹⁹ a configurational assignment could not be made since in this octalin series, owing to the presence of the Δ^5 -double bond, the ring containing the hydroxy group can adopt two conformations. This flexibility permits both the 7β - and the 7α -isomers to assume an equatorial conformation, VIIa and VIIIb, respectively. The n.m.r. spectra of the two isomeric materials V and VI, however, clearly showed that the ring system in each isomer must possess the same conformation. The spectrum of the major alcohol V showed the C-6 vinyl proton absorption ($\tau = 4.63$ p.p.m.) to be a doublet with

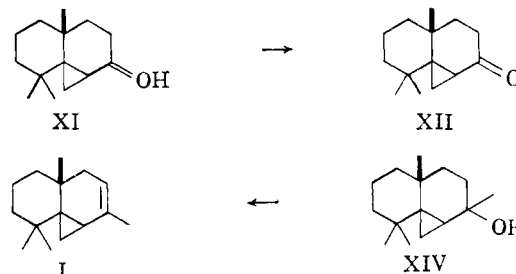


a $J = 1.3$ c.p.s. while with the minor alcohol VI the absorption for this proton ($\tau = 4.48$ p.p.m.) was a doublet with a $J = 4.5$ c.p.s. Using the dihedral relationship for spin-spin coupling,²⁰ these J -values indicate that in the major alcohol V the C-7 proton is quasi-axial while in the minor alcohol VI it is quasi-equatorial, *i.e.*, V is a quasi-equatorial alcohol (VIIa or VIIIb) while VI is a quasi-axial alcohol (VIIb or

VIIIa). Evaluation of nonbonded atom interactions indicated that the alcohol with the hydroxyl group *cis* to the angular methyl group would clearly prefer the equatorial conformation VIIa rather than the axial conformation VIIIa. Thus the major alcohol must be the *cis*-alcohol V and the minor alcohol must have the *trans* orientation VI. In line with these qualitative arguments, Henbest and McEntee²¹ proved that the major isomer formed by the lithium aluminum hydride reduction of the related 3-keto-10-methyl- Δ^4 -octalin (IX) possessed the *cis* configuration X.



The lithium aluminum hydride reduction product containing V and VI in a ratio of 19:1 was allowed to react with an excess of iodomethylzinc iodide. After 1 hr., the usual time required for complete reaction of an allylic alcohol in the Simmons reaction, very little reaction had occurred. After a 70-hr. period, the reaction product had reached a maximum yield and after distillation and chromatography of the reaction mixture a single crystalline alcohol (XI) was obtained in 23% yield. The cyclopropylcarbinol XI was oxidized with chromic acid to yield the crystalline ketone XII. When the *trans*-alcohol VI was allowed to react with iodozinc methyl iodide again the reaction was



slow and a low melting cyclopropylcarbinol was obtained. Oxidation of the material gave a low melting ketone which was isomeric with XII but did contain a few per cent XII (formed from the 7% of V in the original allyl alcohol). The over-all yield was 17%. Thus, although the Simmons reaction was very slow compared to rate of reaction of the simple cyclohexenols studied previously, the formation of a single reaction product from each isomeric alcohol V and VI showed that the reaction had retained its stereospecificity.²² As mentioned earlier, a hydroxyl group stereospecifically introduces the cyclopropane ring so that the two groupings bear a *cis* relationship to one another. Since the hydroxyl group was *cis* to the angular methyl group in V, it follows that the cyclopropylcarbinol XI and the related ketone XII possess an all-*cis* structure and the ketone derived from *trans*-alcohol VI, a *trans* stereochemistry.

A ketone possessing the same gross structure as the synthetic ketone XII had been obtained by Nozoe and his co-workers³ in their degradational studies of thujopsene. The infrared spectrum and the retention time on v.p.c. of their ketone²³ were identical with those of the synthetic *cis*-ketone XII and different from those of the *trans*-ketone, thus establishing the *cis* stereo-

(14) Throughout this paper, steroid numbering will be employed.

(15) C. Enzell, *Tetrahedron Letters*, 185 (1962).

(16) D. H. R. Barton, *J. Chem. Soc.*, 1627 (1953).

(17) W. G. Dauben, G. F. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(18) W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *ibid.*, **78**, 3752 (1956).

(19) D. S. Noyce and D. B. Denney, *ibid.*, **72**, 5743 (1950).

(20) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

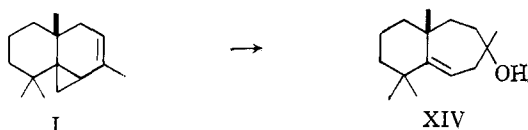
(21) H. B. Henbest and J. McEntee, *J. Chem. Soc.*, 4478 (1961).

(22) It was shown that the hydroxyl group in V and VI still had a catalytic effect on the Simmons reaction since the related hydrocarbon 4,4,10-trimethyl- Δ^5 -octalin failed to react with this reagent in a 70-hr. period. The extra steric hindrance introduced by the presence of the 4,4-dimethyl group must be responsible for the slow rate of reaction.

(23) The authentic sample was kindly supplied by Professor T. Nozoe.

chemistry of the angular methyl group and the cyclopropane ring in thujopsene. The synthetic ketone XII was allowed to react with methylmagnesium bromide and the resulting tertiary alcohol XIII dehydrated spontaneously upon processing the Grignard product with ammonium chloride. The hydrocarbon obtained was essentially one compound (less than 1% of an isomeric olefin was shown to be present by v.p.c.) and was shown to be (\pm)-thujopsene (I) by comparison of its infrared and n.m.r. spectra with those of the natural product.

A characteristic reaction of thujopsene is its rearrangement under acid conditions to the sesquiterpene alcohol widdrol (XIV). As a final check on the identity of our synthetic material, it was subjected to such a rearrangement and it was found to yield (\pm)-widdrol, identical with the (\pm)-widdrol recently syn-



thesized by Enzell.^{15,24}

Experimental²⁵

3-Keto-4,4,10-trimethyl- Δ^5 -octalin.—Following the procedure of Woodward, *et al.*, for the 4,4-dimethylation of a steroid,²⁶ 107 g. (0.65 mole) of 3-keto-10-methyl- Δ^4 -octalin was allowed to react with 222 g. (1.98 moles) of potassium *tert*-butoxide and 542 g. (3.82 moles) of methyl iodide to yield 97.2 g. (77.4%) of 95% pure 3-keto-4,4,10-trimethyl- Δ^5 -octalin, b.p. 115–118° (10 mm.) [lit.²⁷ b.p. 105–107° (2 mm.)]. The yellow 2,4-dinitrophenylhydrazone melts at 160.8–161.5° (lit.²⁷ m.p. 163°) and the semicarbazone melts from 231.4–232.0° dec.

Anal. Calcd. for $C_{14}H_{22}ON_2$ (249.35): C, 67.43; H, 9.30; N, 16.87. Found: C, 67.27; H, 9.51; N, 16.80.

4,4,10-Trimethyl- Δ^5 -octalin.—Using the method for reduction of hindered ketones developed by Barton, Ives, and Thomas,²⁸ 198 g. (1.04 moles) of 3-keto-4,4,10-trimethyl- Δ^5 -octalin was treated with anhydrous hydrazine and sodium diethylene glycolate in diethylene glycol. There was obtained 160 g. (87.4%) of pure 4,4,10-trimethyl- Δ^5 -octalin, b.p. 97–99° (10 mm.); ν_{max}^{neat} 797, 1642 cm^{-1} (lit.¹⁵ $\nu_{max}^{CCl_4}$ 795, 1640 cm^{-1}).

Anal. Calcd. for $C_{13}H_{22}$ (178.31): C, 87.56; H, 12.44. Found: C, 87.42; H, 12.40.

7-Keto-4,4,10-trimethyl- Δ^5 -octalin (IV).—A solution of 150 g. (0.816 mole) of 4,4,10-trimethyl- Δ^5 -octalin in 1 l. of glacial acetic acid and 550 ml. of acetic anhydride was allowed to react at 30–40° for 40 hr. with 395 g. (2.48 moles) of anhydrous sodium chromate.²⁸ The reaction mixture was diluted with 3 l. of water, neutralized with sodium carbonate, and extracted three times with petroleum ether. The combined ethereal extracts were washed with water, dried over sodium sulfate, and the solvent evaporated under reduced pressure. The residue was distilled under reduced pressure using a spinning-band column to give 98 g. (62.5% yield) of 98% pure product, b.p. 129–130° (10 mm.). A forerun (b.p. 123–129° (10 mm.)) of 38 g. and a tail fraction (b.p. 130–131° (10 mm.)) of 3 g. were combined (v.p.c. analysis showed the combined material to contain over 80% of desired ketone) and allowed to react with semicarbazide hydrochloride and sodium acetate in the usual manner to yield 21 g. of a semicarbazone, m.p. 242–243°. *Anal.* Calcd. for $C_{14}H_{23}ON_3$ (249.35): C, 67.43; H, 9.30; N, 16.85. Found: C, 67.47; H, 9.19; N, 16.84. The ketone was regenerated from this derivative by steam distillation from phthalic anhydride and there was obtained 14.7 g. of pure ketone. The total yield obtained was 112.7 g. (72%),

(24) Enzell (*Acta Chem. Scand.*, **18**, 1553 (1962)) has shown that widdrol (and, hence, thujopsene) most likely possesses the absolute configuration which is the mirror image of the form written in this paper.

(25) Analyses were performed by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley. The v.p.c. analyses were performed using a 5 ft. \times 1/8 in. column containing a packing composed of 10% Carbowax 6000, 10% sodium hydroxide, and 80% Chromosorb W, operating at a temperature of 150° and a flow rate of 25 ml./min. of helium, and an hydrogen flame ionization detector.

(26) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelley, *J. Am. Chem. Soc.*, **76**, 2852 (1954).

(27) S. L. Mukherjee and P. C. Dutta, *J. Chem. Soc.*, 67 (1960).

(28) D. H. R. Barton, D. A. Ives, and B. R. Thomas, *ibid.*, 2056 (1955).

(29) C. W. Marshall, R. E. Ray, L. Laos, and B. Riegel, *J. Am. Chem. Soc.*, **79**, 6308 (1957).

λ_{max}^{EtOH} 242 μ (ϵ 13,700). *Anal.* Calcd. for $C_{13}H_{20}O$ (192.29): C, 81.20; H, 10.48. Found: C, 81.18; H, 10.64. The 2,4-dinitrophenylhydrazone melts from 201–202° (lit.¹⁵ m.p. 203°).

7 β - and 7 α -Hydroxy-4,4,10-trimethyl- Δ^5 -octalin (V and VI).
(a) **Lithium Aluminum Hydride Reduction.**—To a stirred suspension of 2.36 g. (0.062 mole) of lithium aluminum hydride in 400 ml. of anhydrous ether there was added, dropwise, a solution of 39.8 g. (0.21 mole) of 7-keto-4,4,10-trimethyl- Δ^5 -octalin in 40 ml. of anhydrous ether. After the initial heat of reaction had subsided, the reaction mixture was stirred at room temperature for 3 hr. A saturated aqueous ammonium chloride solution was cautiously added until all inorganic salts had precipitated, the ether layer was decanted from the slurry of inorganic salts, and the salts were washed with two 50-ml. portions of ether. The ether extracts were washed, successively, with 50-ml. portions of saturated aqueous ammonium chloride, saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The ether was removed by flash distillation and the residue distilled through a spinning-band column to give 38.4 g. (95.4%) of isomeric alcohols, b.p. 125.4–126.0° (5 mm.). *Anal.* Calcd. for $C_{13}H_{22}O$ (194.31): C, 80.35; H, 11.41. Found: C, 80.61; H, 11.48. Analysis of the product by v.p.c. showed the presence of 95% of the 7 β -isomer (V) and 5% of the 7 α -isomer (VI).

A phenylurethan was prepared, m.p. 88.0–89.0°.

Anal. Calcd. for $C_{26}H_{27}O_2N$ (313.42): C, 76.64; H, 8.68; N, 4.47. Found: C, 76.52; H, 8.47; N, 4.31.

(b) **Meerwein-Ponndorf Reduction.**—In a 250-ml. flask fitted with a partial reflux head³⁰ was placed 6.0 g. (0.03 mole) of distilled aluminum isopropoxide, 100 ml. of isopropyl alcohol, and 3.94 g. (0.021 mole) of 7-keto-4,4,10-trimethyl- Δ^5 -octalin. The reaction mixture was heated in an oil bath at a temperature of 95–100° and the solvent distilled at a rate of 0.5 ml. per hour; the amount of acetone in the distillate was determined by v.p.c. After 44 hr., the theoretical amount of acetone had distilled (0.021 mole) in a total volume of 25.3 ml. of distillate. At the end of this reaction period, the reaction mixture was poured into 100 ml. of saturated aqueous ammonium chloride and the solution extracted with two 50-ml. portions of ether. The ethereal extracts were washed, in turn, with 100 ml. of saturated aqueous ammonium chloride solution and 100 ml. of saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The ether was evaporated to yield 3.82 g. of a clear viscous oil which on v.p.c. was found to contain the 7 β - and the 7 α -isomer in a ratio of 57:43.

A cyclohexane solution of 2.8 g. of the reaction mixture was chromatographed on 400 g. of Woelm Activity II neutral alumina (height–diameter ratio 32:1) and the material was eluted with 100-ml. portions of benzene. The first 13 fractions were combined and yielded 125 mg. of hydrocarbons. The next 6 fractions gave 405 mg. of material with composition of 90% of the 7 α - and 7% of the 7 β -alcohols and 3% of hydrocarbons. Further elution with 500 ml. of solvent yielded 580 mg. of alcohols with a composition of 67% 7 α - and 33% 7 β -isomers. Continued elution gave only material containing more 7 β -isomer, so the solvent was changed to ether and the remainder of the material composed of 77% of the 7 β - and 23% of the 7 α -isomers was obtained. The 90% enriched material was used in the n.m.r. studies.

7 β -Hydroxy-4,4,10-methyl-5,6 β -methylene-decalin (XI).—A suspension of iodomethylzinc iodide in 900 ml. of anhydrous ether and 104 ml. of dimethoxyethane was prepared from 320 g. (97 ml., 1.2 moles) of methylene iodide and 81 g. (1.2 moles) of zinc-copper couple prepared following the exact procedure described by Dauben and Berezin.¹⁸ To this suspension there was added a solution of 34.6 g. (0.2 mole) of 7 β -hydroxy-4,4,10-trimethyl- Δ^5 -octalin (prepared in the lithium aluminum hydride reduction described above and containing 5% of the 7 α -isomer) in 30 ml. of anhydrous ether and the reaction mixture was heated under reflux (oil bath temperature 38°) for 70 hr. Saturated aqueous ammonium chloride solution was added and the ether decanted from the precipitated inorganic salts. The slurry of salts was washed with two 400-ml. portions of ether, the three ether layers washed successively with saturated aqueous ammonium chloride solution, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution. The ether layers were combined, dried over sodium sulfate, and the solvent removed by flash distillation at atmospheric pressure.

The residue was distilled through a spinning-band column and the fractions were analyzed by v.p.c. A 30-g. forerun, b.p. 60–130° (10 mm.), consisted only of hydrocarbons and methylene iodide. Next, three fractions boiling over a range of 130–165° (10 mm.) were collected. The 11.4-g. middle fraction, b.p. 141–149° (10 mm.), solidified on standing. The solid was removed by filtration and recrystallized from acetone–water to yield 4.67 g. of the cyclopropane derivative, m.p. 72–77°. The oil from the fraction was combined with the distillate fraction,

(30) The design of this head is described by A. L. Wilds in "Organic Reactions," Vol. II, J. Wiley and Sons, Inc., New York, N. Y., 1942, p. 197.

b.p. 130–141° (10 mm.), and the material carefully chromatographed on 200 g. of Woelm neutral alumina (Act. II). Elution with petroleum ether gave only oily material which consisted mostly of methylene iodide and several unidentified hydrocarbons. Elution with benzene gave 2.5 g. of starting material, 0.9 g. of an intermediate fraction, and 2.4 g. of cyclopropane derivative. The 2.97 g. highest boiling fraction, b.p. 149–165° (10 ml.), also was chromatographed in the same manner on 100 g. of alumina, and 1.7 g. of cyclopropane derivative was obtained. The total yield of 7 β -hydroxy-4,4,10-trimethyl-5,6 β -methylene-decalin was 8.77 g. (23% based on recovered starting material). The combined material was recrystallized twice from petroleum ether; m.p. 76.5–78.5°; $\nu_{\text{max}}^{\text{CCl}_4}$ 3060, 1480 cm^{-1} ; n.m.r., multiplet equivalent to 2 protons centered at $\tau = 9.7$.

Anal. Calcd. for $\text{C}_{14}\text{H}_{24}\text{O}$ (208.33): C, 80.71; H, 11.61. Found: C, 80.57; H, 11.43.

7-Keto-4,4,10-trimethyl-5,6 β -methylene-decalin (XII).—To a solution of 4.0 g. (0.019 mole) of 7 β -alcohol XI in 100 ml. of acetone (distilled from potassium permanganate) there was added 7.84 ml. of a solution of chromic acid in sulfuric acid (prepared by dissolving 26.72 g. of chromium trioxide in 23 ml. of concentrated sulfuric acid and diluting the solution to 100 ml. with water). The reaction mixture was stirred in a water bath at 25° for 5 min., poured into 10 ml. of 2-propanol, and the precipitate removed by filtration. The precipitate was dissolved in water and the solution extracted with 10 ml. of ether which was added to the acetone filtrate. The combined solvents were removed under reduced pressure and the residue dissolved in 100 ml. of ether. The ethereal solution was washed, successively, with two 100-ml. portions of saturated aqueous potassium bicarbonate solution, two 100-ml. portions of saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The ether was evaporated and the residual oil crystallized; yield 3.87 g. (97.6%). The solid was first recrystallized from acetone to give white needles, m.p. 98.0–100.5°, and then sublimed at 95° (2 mm.), m.p. 100.5–101.5°; $\nu_{\text{max}}^{\text{CCl}_4}$ 3040, 1690, 1485 cm^{-1} ; $\lambda_{\text{max}}^{\text{hexane}}$ 187 $\text{m}\mu$, ϵ 14,600. The infrared spectrum of the product was superimposable on a spectrum of a cyclopropane ketone with this assigned structure, obtained from natural thujopsene.^{18,23} The synthetic material showed a single peak in v.p.c. using a carbowax column at 176° and co-injection with the degradation product from thujopsene only increased the intensity of the band.

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$ (206.32): C, 81.50; H, 10.75. Found: C, 81.72; H, 10.55.

7-Keto-4,4,10-trimethyl-5,6 α -methylene-decalin.—Following the Simmons reaction conditions used for the preparation of the 5,6 β -isomer, 0.365 g. (1.88 mmoles) of a mixture of 90% VI and 7% V (from enriched Meerwein–Ponndorf reduction mixture) was allowed to react with 0.934 g. (0.014 mole) of zinc–copper couple and 3.70 g. (0.014 mole) of methylene iodide. The reaction was allowed to proceed for 63 hr. and then processed in the usual way to give 344 mg. of a yellow oil. The oil was chromatographed on 10 g. of Woelm neutral alumina (Act. II) and elution with 100 ml. of pentane gave unreacted methylene iodide and hydrocarbon impurities and elution with 100 ml. of ether gave 204 mg. of a yellow oil which was shown by v.p.c. to be composed of 22% of unreacted starting material, 5% of 7-keto-4,4,10-trimethyl- Δ^5 -octalin (IV), <5% of 7 β -hydroxy-4,4,10-trimethyl-5,6 β -methylene-decalin (XI), and 67% of the related 7 α -hydroxy isomer.

The crude mixture was oxidized in 0.39 ml. of chromic acid solution as described for the preparation of XII and the crude reaction product (168 mg.) was analyzed by v.p.c. and found to contain 23% of IV, 5% of XII, and 70% of 7-keto-4,4,10-trimethyl-5,6 α -methylene-decalin. An attempt was made to separate the products by alumina chromatography but only a partial separation was achieved. Therefore, the mixture was

separated by preparative v.p.c. to give 65.5 mg. (17% over-all yield) of a colorless oil which slowly solidified to a white, waxy solid, m.p. 45.0–46.5°; $\lambda_{\text{max}}^{\text{hexane}}$ 192 $\text{m}\mu$ (ϵ 18,000); $\nu_{\text{max}}^{\text{CCl}_4}$ 1687 cm^{-1} , fingerprint region completely different from that of XII.

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}$ (206.32): C, 81.50; H, 10.75. Found: C, 81.72; H, 10.55.

(\pm)-**Thujopsene, 4,4,7,10-Tetramethyl-5,6 β -methylene- Δ^7 -octalin (I).**—A solution of 2.06 g. (0.01 mole) of 7-keto-4,4,10-trimethyl-5,6 β -methylene-decalin (XII) in 25 ml. of anhydrous ether was added to the Grignard reagent prepared from 0.973 g. (0.04 g.-atom) of magnesium turnings, 4.4 ml. (0.08 mole) of methyl bromide, and 50 ml. of anhydrous ether. After the initial exothermic reaction ceased, the mixture was heated under reflux for 30 min., 25 ml. of saturated aqueous ammonium chloride solution was added, and the mixture was poured into 250 ml. of water. The ethereal layer was separated and the aqueous layer extracted twice with 50 ml. portions of ether. The ether solutions were washed, in turn, with 50 ml. of saturated aqueous ammonium chloride, one 50-ml. portion of saturated aqueous sodium bicarbonate solution, one 50-ml. portion of saturated aqueous sodium chloride solution, and the combined ether solutions dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and v.p.c. analysis of the residue showed the presence of only three components, one being present only in trace amounts. The major component had a retention time identical with natural thujopsene³¹ and the other component with that of starting ketone XII. The reaction product was chromatographed on Woelm neutral alumina (Act. II) and 1.45 g. of hydrocarbons were eluted with petroleum ether and 280 mg. of the starting ketone was eluted with ether. The hydrocarbon eluate was purified by preparative v.p.c. and there was obtained 1.36 g. (77% based on recovered starting material) of a colorless mobile oil which upon analytical v.p.c. was shown to be 100% pure. The infrared spectrum of the product was superimposable upon the spectrum of natural thujopsene.

Anal. Calcd. for $\text{C}_{15}\text{H}_{24}$ (204.34): C, 88.16; H, 11.84. Found: C, 87.87; H, 11.51.

(\pm)-**Widdrol (XIV).**—A solution of 0.20 g. (0.98 mmole) of (\pm)-thujopsene in 2 ml. of 95% ethanol was heated under reflux for 10 hr. with a solution of 0.10 g. of oxalic acid in 10 ml. of water. The reaction solution was diluted with 10 ml. of water, extracted with 10 ml. of ether, the ether extract washed with a saturated aqueous solution of sodium chloride, and dried. The ether was removed under reduced pressure and the 194 mg. of remaining pale yellow oil was chromatographed on 4 g. of Woelm neutral alumina (Act. II). Elution with petroleum ether gave 126 mg. of a colorless oil which was found to be a mixture of hydrocarbons. Elution with benzene gave 4 mg. of an intermediate fraction and 36 mg. of a solid compound. The solid material was recrystallized from acetone and sublimed at 95° (2 mm.), m.p. 83–85° (lit.¹⁵ m.p. 86–89°).

Attempted Simmons Reaction on 4,4,10-Trimethyl- Δ^5 -octalin.—To a stirred suspension of 1.22 g. (0.018 mole) of zinc–copper couple in 50 ml. of anhydrous ether under a nitrogen atmosphere, there was added 1.345 g. of ethylene glycol dimethyl ether (distilled from lithium aluminum hydride) and 4.83 g. (0.018 mole) of methylene iodide. The mixture was heated under reflux for 3 hr., a solution of 0.48 g. (0.003 mole) of 4,4,10-trimethyl- Δ^5 -octalin in 0.5 ml. of anhydrous ether added, the heating under reflux continued for 67 hr., and processed in the usual manner. The product from the reaction was examined by v.p.c. and shown to be pure starting material; a sample of the compound was collected; it possessed an infrared spectrum identical with starting material. No trace of a cyclopropane derivative could be found.

(31) Our sample of natural thujopsene was obtained by vacuum distillation of the wood oil of *Juniperus virginiana* (kindly supplied by Dr. N. T. Mirov) followed by preparative v.p.c.