generous supplies of the resin acids. Grateful appreciation is also due to Professor M. T. Rogers of Michigan State University as well as Dr. Edwards for the n.m.r. spectra. We are grateful to Professor L. H. Briggs of the University of Auckland (New Zealand) for providing a sample of rimuene.

Experiments Directed toward the Total Synthesis of Terpenes. VI. The Stereochemistry of Isopimaric Acid[1,2]

ROBERT E. IRELAND AND JOHN NEWBOULD

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan

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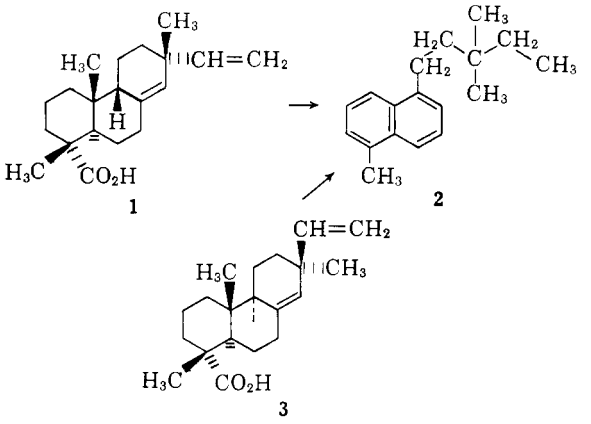
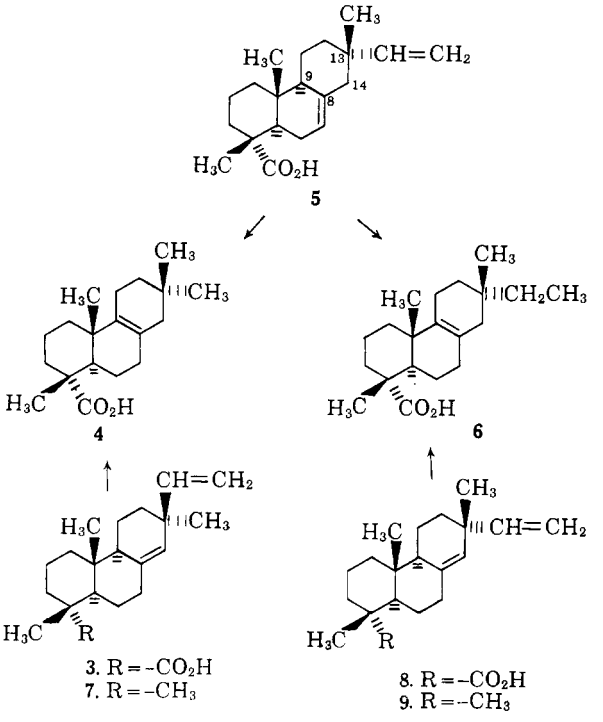
The stereochemistry of isopimaric acid (**5**) is elucidated by conversion to 13,13-dimethylpodocarpane (**16**), and comparison of this hydrocarbon with its racemate (**22**).

The synthesis of the epimeric (±)-9-isopimaradienes[3] conclusively showed that the long accepted structure 1 for isopimaric acid was incorrect, when neither diene was found identical with isopimaradiene. Needless to say, this result occasioned careful scrutiny of the properties of this acid and its corresponding diene to determine where the discrepancy lay.

In the initial investigation of the structure of isopimaric acid in 1948, Harris and Sanderson[4a] suggested that the resin acid had the pimaric acid carbon skeleton, and it was as a result of their degradation of both isopimaric (**1**) and pimaric (**3**) acid to the same naphthalenoid hydrocarbon (**2**) that they placed the nuclear double bond of both acids in the 8(14)-position. This proof of the position of this double bond has been accepted by all subsequent workers, in spite of some of the contortions to which they had to resort in order to rationalize their results. While such an interrelation would appear substantial enough, the reaction sequence used involved several reactions, such as ozonization and palladium-catalyzed dehydrogenation, during which skeletal rearrangements and redistributions might have occurred. Application of the more modern methods together with spectral interpretations seems advisable.



The well executed and extensive studies of Edwards and his collaborators[4b,c] have served to establish more rigorously that isopimaric (**5**) and pimaric (**3**) acids have the same carbon skeleton. Thus, both acids were converted to the same $\Delta^{8(9)}$-19-norpimaric acid (**4**).[4c] While this transformation establishes the identity of the carbon skeletons of the two acids, it implies nothing concerning their relative stereochemistry at C-9 and C-13 nor the location of the nuclear double bond.



Correlation[5] of isopimaric (**5**) and sandaracopimaric (**8**) acids through the identity of the $\Delta^{8(9)}$-dihydrosandaracopimaric acid (**6**) obtained from both acids meant that isopimaric acid (**5**) must differ from sandaracopimaric acid (**8**) only in the stereochemistry at C-9 and/or the location of the nuclear double bond. The latter possibility was not considered at the time.

Several investigations[4b-m,5] have been made of the stereochemistry at C–13 of the pimaric acids. While all

(1) For a preliminary report of this work, see R. E. Ireland and J. Newbould, *J. Org. Chem.*, **27**, 1930 (1962).

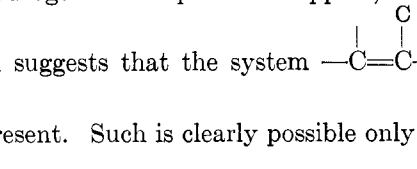
(2) This work was made possible through a grant from the National Science Foundation (G-19481).

(3) R. F. Church and R. E. Ireland, *J. Org. Chem.*, **28**, 17 (1963).

(4) (a) G. C. Harris and T. F. Sanderson, *J. Am. Chem. Soc.*, **70**, 2081 (1948); (b) O. E. Edwards and R. Howe, *Can. J. Chem.*, **37**, 760 (1959); (c) O. E. Edwards and R. Howe, *Chem. Ind.* (London), 537 (1959); (d) E. Wenkert and J. W. Chamberlin, *J. Am. Chem. Soc.*, **81**, 688 (1959); (e) B. Green, A. Harris, and W. B. Whalley, *J. Chem. Soc.*, 4715 (1958); (f) A. K. Bose, *Chem. Ind.* (London), 1105 (1960); (g) H. H. Bruun, *Acta Acad. Aboensis, Math. Phys.*, **19** (3), 7 (1954); (h) H. H. Bruun, *Finska Kemistsam-Fredets Medd.*, **63**, 22 (1945); (i) H. H. Bruun, *Acta. Chem. Scand.*, **6**, 798 (1952); (j) H.H. Bruun, I. Fishmeister, and E. Stenhagen, *ibid.* **13**, 379 (1959); (k) H. H. Bruun, R. Ryage, and E. Stenhagen, *ibid.*, **12**, 789 (1958); (l) Le-van-Thoi and J. Ourgand, *Bull. soc. chim. France*, 202 (1956); (m) G. W. A. Milne and H. Smith, *Chem. Ind.* (London), 1307 (1961).

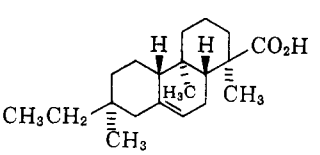
(5) O. E. Edwards, A. Nicolson, and M. N. Rodger, *Can. J. Chem.*, **38**, 663 (1960).

of these are subject to the criticism that the differences in chemical and spectral properties used to draw stereochemical conclusions are very small and tenuous, all give the same result—*i.e.*, the vinyl group of pimaric acid (**3**) is beta(quasi-axial) oriented and that of isopimaric (**5**) and sandaracopimaric (**8**) acids is alpha(quasi-equatorial) oriented. Recently, the stereorational syntheses of both pimaradiene (**7**) and sandaracopimaradiene (**9**) in these laboratories[6] have verified not only these stereochemical assignments at C-13, but also the correctness of the positioning of the nuclear double bond in the two acids between carbons 8 and 14 in a fashion that is not subject to the above criticism.[7]

While these results are definitive with regard to the stereochemistry and structure of pimaric (**3**)[4b,d,e] and sandaracopimaric (**8**)[5] acids, they are only deductive proof that the structure of isopimaric acid is represented by the formulation **1**. This reasoning becomes strong if one accepts (as did previous workers) the original degradative work of Harris and Sanderson.[4a] However, that there must have been a rearrangement during this degradation sequence is indicated by even the small portion of the n.m.r. spectrum of methyl isopimarate reported by Wenkert and Beak.[8] It is clear in this spectrum that the signal due to the nuclear vinyl hydrogen of methyl isopimarate is a doublet, while that of methyl sandaracopimarate is only a singlet. The latter situation is what is to be expected for a hydrogen on a carbon with no adjacent hydrogens with which it is spin coupled, and is consistent with the structure **8** for sandaracopimaric acid.[5] The doublet in the spectrum of methyl isopimarate is therefore not consistent with the 8(14)-position for the double bond, since the nuclear vinyl hydrogen must be spin-coupled with at least one adjacent allylic hydrogen. This situation is more nearly satisfied if the nuclear double bond of isopimaric acid is in either the 7(8)- or the 9(11)-position, where the C-7 or C-11 vinyl hydrogen would be split by coupling with the C-6 or C-12 methylene. Both positions satisfy the requirement that double bond is readily isomerized by anhydrous mineral acid to the more highly substituted 8(9)-position.[5b] A tentative conclusion as to which of the two possible trisubstituted locations is more likely can be made by inspection of the full n.m.r. spectrum of methyl isopimarate, where a strong signal due to a pair of uncoupled hydrogens appears centered at 8.04 τ. This is the region of the spectrum where signals due to the allylic hydrogens are expected to appear, and this strong signal suggests that the system  is present. Such is clearly possible only if isopimaric acid has the double bond in the 7(8)-position. This location is also more consistent than the 9(11)-position with the biogenetic hypothesis for these resin acids. Definitive proof of this suggestion has recently been provided by the work of Edwards and coworkers.[9]

Acceptance of the 7(8)-position for the nuclear double bond necessitates a re-evaluation of the stereochemical assignment at C-9, for there is now no compelling reason to retain the *trans-syn* backbone. Thus the fact that sandaracopimaric acid (**8**) differs from isopimaric acid (**5**) can be attributed solely to the difference in the location of the nuclear double bond without requiring the C-9 hydrogen to be beta-oriented in the latter acid. Of course, there is no reason, *a priori*, that the C-9 hydrogen in isopimaric acid (**5**) could not be beta-oriented as well as the double bond be in the 7(8)-position. This point had to be proved.

At the outset there was some evidence suggesting that the C-9 hydrogen in isopimaric acid (**5**) was indeed alpha-oriented. Thus the rotatory dispersion curve[4f] of dihydroisopimaric acid **10** is a plain negative curve. On reinterpretation in light of the 7(8)-double bond assignment, the closest analogy to this system is Δ^5-cholestene (**11**) which also exhibits a plain negative rotatory dispersion curve.[10] If this analogy is valid, and it would indeed appear to be, then the C-9 hydrogen of the resin



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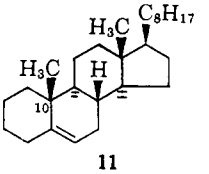

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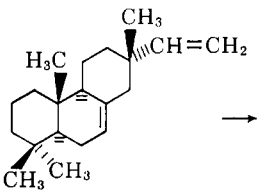
acid must be oriented in the same fashion as the C-10 methyl group of the steroid—*i.e.*, betaoriented.

In order to gain more definitive proof of this assignment for the C–9-hydrogen, we have degraded isopimaradiene (**12**),[3] itself a simple degradation product of isopimaric acid (**5**) in which the critical C-9 position has not been disturbed, to the pentamethyl hydrocarbon **16**. This was effected by first conversion of the diene **12** to the olefin **13** by the same sequence used by Edwards[4c]



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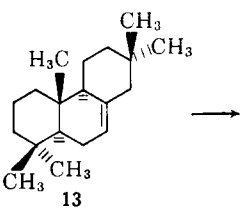

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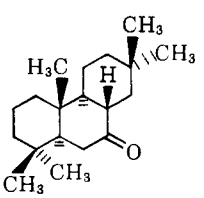

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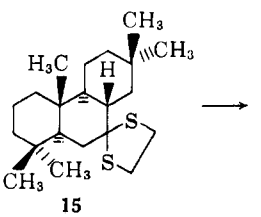

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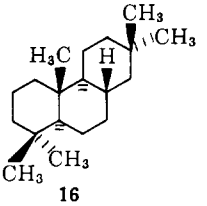


16

(6) R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28**, 6 (1963).

(7) The anticlimatic report of Milne and H. Smith[4m] of the partial synthesis of dihydropimaradiene is claimed as a proof of the stereochemistry of pimaric and isopimaric acids. Not only is this work subjectively evaluated evidence (even after a long introduction by the authors criticizing the previous work of others), but again the authors overlook the possibility of the 7(8)-position for the nuclear double bond in isopimaric acid.

(8) E. Wenkert and P. Beak, *J. Am. Chem. Soc.*, **83**, 998 (1961).

(9) W. Antkowiak, J. W. ApSimon, and O. E. Edwards, *J. Org. Chem.*, **27**, 1930 (1962).

(10) C. Djerassi, W. Clossen, and A. E. Lipman, *J. Am. Chem. Soc.*, **78**, 3163 (1956).

to prepare 19-norpimaric acid. Thus hydroxylation of isopimaradiene (**12**) with one equivalent of osmium tetroxide in dioxane afforded the corresponding diol.

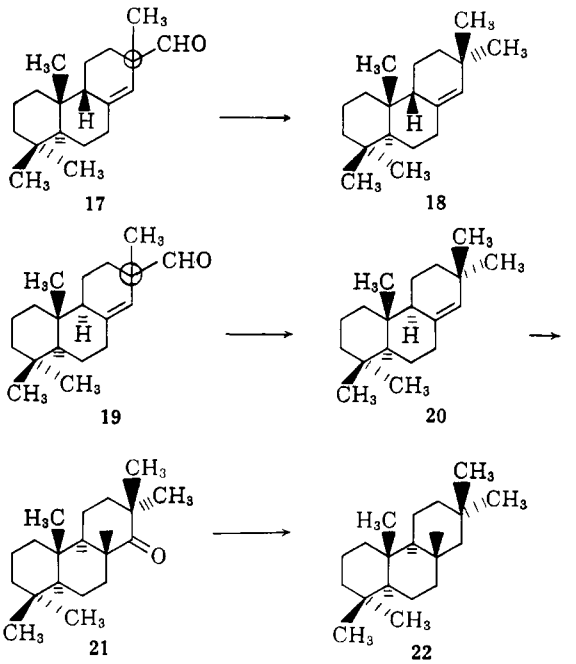
This diol was an oil but on cleavage with periodic acid in ether, there resulted an olefinic aldehyde from which a 51% overall yield of semicarbazone could be isolated. The formation of a mono-aldehyde showing no ketone carbonyl absorption in its infrared spectrum attests to the attack by the osmium tetroxide principally at the vinyl grouping. On modified[6] Wolff–Kishner reduction this semicarbazone produced an 82% yield of the desired olefin (**13**).

Further degradation was carried out by hydroboration[11] and oxidation[12] of the olefin (**13**) to introduce the ketone function at C-7. The crude ketonic product was chromatographed on basic alumina in order to insure isomerization of any of the less stable ketone—the *trans-anti-cis* product, if the C-9 hydrogen were alpha oriented or the *trans-syn-trans* material if it were beta oriented. By this procedure we were able to isolate a 60% yield of the ketone (**14**).

In order to ensure that the B/C ring fusion remained in its more stable configuration and was not isomerized during the reduction, we chose to use the desulfurization of the dithioketal to remove the C-7 ketone. This desulfurization sequence has been shown[13] to proceed independent of the stereochemistry at the α-carbon atoms, while it is conceivable that the ketone with the less stable B/C ring fusion (in equilibrium with the more stable ketone (**14**) in the presence of acid or base) might undergo reduction more rapidly than its epimer and lead to an inhomogeneous hydrocarbon of no stereochemical value. Thus conversion[14] of the ketone (**14**) to its ethylenedithioketal (**15**) and desulfurization of this crude material produced the desired hydrocarbon (**16**), m.p. 53.5–54°, in 78% yield. This hydrocarbon was either the 13,13-dimethylpodocarpane (**16**) shown or its C-9 epimer, 13,13-dimethyl-9-isopodocarpane, depending on the orientation of the C-9 hydrogen in the original isopimaric acid (**5**). The sequence used here to obtain this hydrocarbon can in no way have affected the stereochemistry at this center, and thus definition of the structure of this hydrocarbon will settle the point in question.

To gain information concerning the stereochemistry of the hydrocarbon (**16**) we turned to intermediates available from our syntheses of the pimaradienes.[3,6] We had previously[3] prepared both of the aldehydes (**17**) and (**19**) and converted them by Wolff–Kishner reduction to the corresponding olefins (**18**) and (**20**). Neither of these olefins was identical with the olefin (**16**) obtained above from isopimaradiene (**12**), further confirmation that isopimaric acid (**5**) did not possess an 8(14)-double bond.

Inasmuch as the olefin (**20**) was not only more readily available than its epimer (**18**), but also possessed the C-9 hydrogen in the expected alpha orientation, we chose to remove the double bond in this isomer first. In order to assure that the olefin (**20**) was converted to the (±)*trans-anti-trans* hydrocarbon (**22**), we again employed the same hydroboration[11] and oxidation[12] sequence as above, so as to introduce the C-14 ketone function. This ketone (**21**), after chromatography on basic alumina to effect equilibration at C-8, was available in 70% yield from the olefin (**20**). Conversion[14] of the ketone (**21**) to its ethylenedithiolketal and then desulfurization with W-2 Raney nickel led to a 74% overall yield of the racemic modification of the hydrocarbon (**22**), as an oil. Comparison of the infrared spectrum of this racemic hydrocarbon and that of the



optically active analog (**16**) obtained from isopimaradiene (**12**) revealed their identity and thus conclusively established that the C-9 hydrogen was alpha-oriented in the isopimaric acid (**5**) series. This evidence, taken together with that of Edwards and coworkers[9] which conclusively defines the 7(8)-position for the nuclear double bond, firmly proves the structure of this resin acid to be as shown in formula **5**.

Experimental[15]

13β-Methylpodocarp-7-ene-13α-carboxaldehyde Semicarbazone.—A solution of 1.08 g. (4.0 mmoles) of isopimaradiene[3] in 20 ml. of dry dioxane was treated with 1.00 g. (4.0 mmoles) of osmium tetroxide and the black solution allowed to stand at room temperature for 17 hr. The solution was then saturated with hydrogen sulfide, filtered, the filter cake washed with methylene chloride and the combined filtrates evaporated to dryness at reduced pressure. The resulting crude, oily diol (930 mg.) was not purified, but dissolved in 50 ml. of dry ether and treated with a solution of 570 mg. (3.0 mmoles) of periodic acid in 30 ml. of dry ether. After stirring for 1 hr. at room temperature, the ethereal solution was decanted from the precipitated iodic acid, washed with water, 10% aqueous potassium bicarbonate, water,

(11) H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *ibid.*, **82**, 4233 (1960).

(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); see also, C. Djerassi, R. R. Engle, and A. Powers, *J. Org. Chem.*, **21**, 1547 (1956).

(13) R. E. Ireland and J. A. Marshall, *ibid.*, **27**, 1620 (1962).

(14) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

(15) Unless specified otherwise, the term "petroleum ether" refers to reagent grade material boiling in the range 30–60°. All gas–liquid chromatograms were obtained on a F & M Scientific Company Model 500 gas-liquid chromatography unit using a 6-foot column packed with 10% diethylene glycol succinate on Chromosorb P, and were temperature programmed. Melting points were determined on a Kofler Hot Stage and are corrected for stem exposure. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan. Infrared spectra were measured on a Perkin–Elmer Model 237 spectrometer and are recorded in cm.$^{-1}$ ($\bar{\nu}$); strong bands are marked (s); all others reported are of moderate intensity unless otherwise specified. Florisil refers to the product of the Floridin Company, Tallahassee, Florida, 60/100 mesh.

saturated salt solution, dried (Na_2SO_4) and evaporated. The infrared spectrum (recorded on a Perkin–Elmer Infrarcord 137) of this crude aldehyde showed λ_{max}^{film} 3.2 μ (w) (vinyl H); 3.67μ (w) (C*H*O); and 5.82 μ (s) (>C=O).

Formation of the semicarbazone was accomplished by treatment of a methanol solution of this crude aldehyde with 3.0 ml. of a standard[16] aqueous solution of semicarbazide hydrochloride and 10 drops of pyridine. In this manner there was obtained 770 mg. (51%) of the derivative, m.p. 218–222°. After several crystallizations from methanol there remained 485 mg. of analytically pure material, m.p. 222–223°.

Anal. Calcd. for $C_{20}H_{33}N_3O$: C, 72.46; H, 12.68; N, 10.03. Found: C, 72.37; H, 12.75; N, 10.29.

13,13-Dimethylpodocarp-7-ene (13).—Employing the same procedure described earlier,[3] 450 mg. (1.36 mmoles) of the above semicarbazone in 36 ml. of diethylene glycol was reduced by heating at 210° under a nitrogen atmosphere with 12.0 g. of potassium hydroxide. After the usual work-up and passage through an alumina (30 g.) column in petroleum ether, there was obtained 290 mg. (82%) of the olefin **13**, evaporatively distilled at 110° (bath temperature; 0.1 mm.), m.p. 29–31°.

Anal. Calcd. for $C_{19}H_{32}$: C, 87.62; H, 12.38. Found: C, 87.51; H, 12.23.

Infrared: $\tilde{\nu}_{max}^{film}$ 3040 cm.$^{-1}$ (w) (vinyl H); 1664 cm.$^{-1}$ (w) (>C=C<); 860 cm.$^{-1}$, 828 cm.$^{-1}$ and 810 cm.$^{-1}$ (skeletal vibrations).

13,13-Dimethylpodocarpanone-7 (14).—To a solution of 170 mg. (0.654 mmole) of the olefin **13** in 5 ml. of dry tetrahydrofuran was added 10 ml. (2.7 mmoles) of a 0.27 *M* solution of diborane in dry tetrahydrofuran, and the reaction mixture stirred in a nitrogen atmosphere at room temperature for 1 hr. The excess diborane was decomposed by the addition of 4 ml. of 10% aqueous sodium hydroxide and the alkylborane oxidized with 4 ml. of 30% aqueous hydrogen peroxide. After heating this mixture for 1.5 hr. under reflux, the product was isolated by ether extraction in the usual manner. The crude alcohol so formed was oxidized with 0.2 ml. of Jones reagent,[12] and the resulting, crude solid ketone chromatographed on 15 g. of alumina. Elution with 400 ml. of 25% benzene:petroleum ether afforded 121 mg. (67%) of the ketone **14**. Crystallization of this material from petroleum ether gave 108 mg. (60%) of this ketone, m.p. 151–151.5°, in an analytically pure condition.

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.43; H, 11.77.

Infrared: $\tilde{\nu}_{max}^{HCCl_3}$ 1698 cm.$^{-1}$ (s) (>C=O).

13,13-Dimethylpodocarpane (16).—To a solution of 105 mg. (0.38 mmole) of the ketone **14** in 0.4 ml. of ethanedithiol was added 0.4 ml. of boron trifluoride etherate, and after standing 1 hr. at room temperature, the precipitated dithioketal **15** (184 mg. crude weight) was collected by filtration. The infrared spectrum of this material show no carbonyl band.

A solution of this crude dithioketal in 40 ml. of ethanol was stirred and heated under reflux overnight with 10 g. of W-2 Raney nickel.[17] After removal of the catalyst by filtration, the filtrate was evaporated to dryness and the residue passed through 5 g. of alumina in petroleum ether. There resulted 92 mg. (93%) of solid hydrocarbon, m.p. 50–53°. Crystallization of this material from ethanol afforded 78 mg. (78%) of the hydrocarbon **16**, m.p. 53.5–54.0°, in an analytically pure condition. This material was eluted at 203° on gas-liquid chromatography[15] when the rate of heating was 7.9°/min.; this analysis showed the substance to be entirely homogeneous.

Anal. Calcd. for $C_{19}H_{34}$: C, 86.96; H, 13.04. Found: C, 86.77; H, 12.82.

Infrared: $\tilde{\nu}_{max}^{supercooled\ liquid\ film}$ 970 cm.$^{-1}$ (w) 940 cm.$^{-1}$ (w) and 850 cm.$^{-1}$ (w) together with the normal bands associated with the C—H and C—C vibrations.

(±)-13,13-Dimethylpodocarpanone-14 (21).—To a solution of 107 mg. (0.413 mmole) of the olefin **20**[3] in 10 ml. of dry tetrahydrofuran was added 1.5 ml. (1.10 mmoles) of a 0.73 *M* solution of diborane in dry tetrahydrofuran and the reaction mixture was stirred at room temperature in a nitrogen atmosphere for 1 hr. Then 3 ml. of 10% aqueous sodium hydroxide and 3 ml. of 30% hydrogen peroxide were added, and the mixture heated under reflux for 1 hr., after which the product was isolated by ether extraction in the usual manner. The crude alcohol was not purified but dissolved in 6 ml. of acetone and oxidized with 0.15 ml. of Jones reagent.[12] Chromatography of the crude, solid ketone on 10 g. of alumina afforded 80 mg. (70%) of the ketone **21**, m.p. 58–60°, eluted with 200 ml. of 25% benzene:petroleum ether. The analytical sample was obtained by evaporative distillation of this material at 80° (bath temperature; 0.025 mm.).

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 82.45; H, 11.70.

Infrared: $\tilde{\nu}_{max}^{HCCl_3}$ 1700 cm.$^{-1}$ (s) (>C=O).

(±)-13,13-Dimethylpodocarpane (22).—A solution of 80 mg. (0.29 mmole) of the ketone **21** in 0.2 ml. of ethanedithiol was treated with 0.2 ml. of boron trifluoride etherate, and the reaction mixture allowed to stand at room temperature for 0.5 hr. Then dilution with 2 ml. of methanol, filtration and chromatography of the solid on 5 g. of alumina afforded 92 mg. (90%) of white, crystalline thioketal eluted with 100 ml. of petroleum ether. Sublimation of a small sample of this material at 160° (bath temperature; 0.025 mm.) gave the thioketal, m.p. 181–183°, in an analytically pure condition.

Anal. Calcd. for $C_{21}H_{36}S_2$: C, 71.52; H, 10.29; S, 18.19. Found: C, 71.43; H, 10.11; S, 18.15.

The remainder of the above thioketal was heated overnight with 6 g. of W-2 Raney nickel[17] in 15 ml. of ethanol. After the usual work-up and passage of the hydrocarbon in petroleum ether through 5 g. of alumina, there was obtained 56 mg. (74% overall yield) of the hydrocarbon **22** as an oil. The analytical sample was obtained by evaporative distillation at 80° (bath temperature; 0.025 mm.). The infrared spectrum of a liquid film and mobility on gas-liquid chromatography[15] of this material was identical to that of the hydrocarbon **16** obtained above.

Anal. Calcd. for $C_{19}H_{34}$: C, 86.96; H, 13.04. Found: C, 87.15; H, 12.74.

Acknowledgment.—The authors wish to thank Dr. O. E. Edwards of the National Research Council (Canada) for making his results available to us prior to publication and for many helpful discussions of this problem. The invaluable assistance of Professor Glenn T. Berchtold of Massachusetts Institute of Technology in obtaining numerous n.m.r. spectra is gratefully acknowledged.

(16) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, Mass., 1955, p. 85.

(17) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.