The Structure and Synthesis of β-Vetivone

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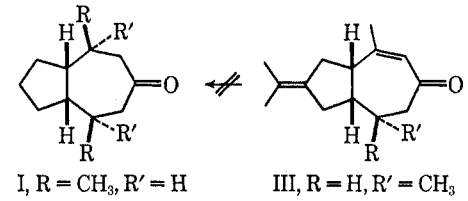
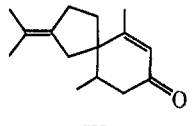
β-Vetivone has been reformulated as a spiro[4.5]decane derivative in lieu of the previously proposed hydroazulene structure. This revision was initially made on the basis of a degradation scheme whereby β-vetivone was converted to *cis*-6,10-dimethylspiro[4.5]decane, a hydrocarbon of known structure synthesized independently by an unambiguous route. Subsequent confirmation of the revised structure was secured upon completion of a total synthesis of racemic β-vetivone by a stereoselective pathway.

In the previous paper[1] we described synthetic work leading to the isomeric *meso*-hydroazulenones I and II. Since both of these differed from the supposedly analogous *meso* ketone, obtained as outlined below from β-vetivone with alleged structure III, we were forced to discard structure III and consider alternative possibilities. In view of the spectral properties of β-vetivone and its degradation products, and the wealth of reported chemical data on these substances,[2] a structure based on the spiro[4.5]decane skeleton (*e.g.*, IV) seemed a likely candidate. In this report we present evidence which supports this proposal and describe a stereoselective synthesis of racemic β-vetivone.



I, R = CH_3, R′ = H
II, R = H, R′ = CH_3

III, R = H, R′ = CH_3
or R = CH_3, R′ = H



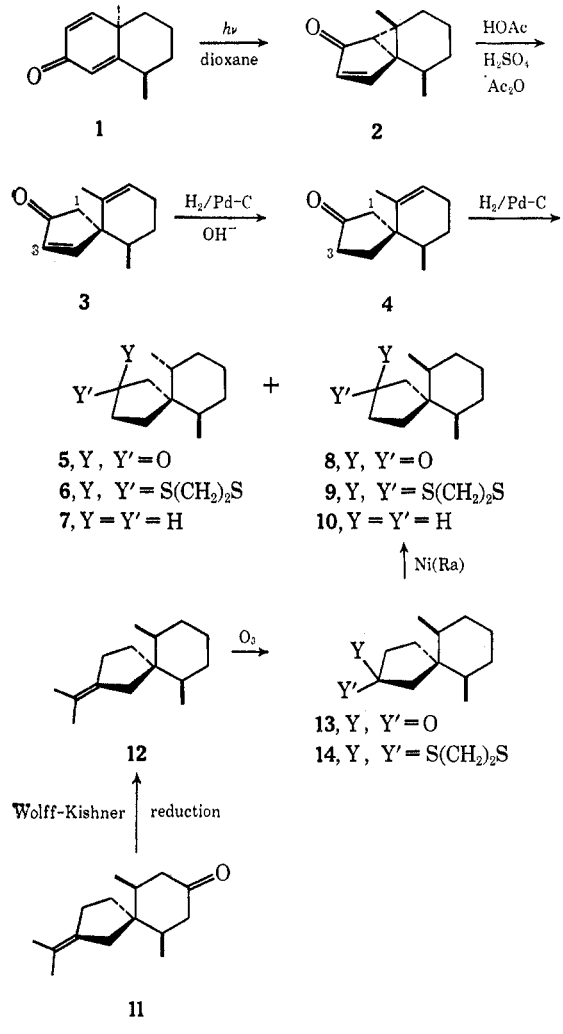
IV

The spiro[4.5]decadienone **3**[3] (Scheme I) offered a facile entry to suitably functionalized derivatives for direct comparison with degradation products of β-vetivone. Moreover, it also represented a potential starting material for a total synthesis of the natural product, if our hypothesis proved correct. Kropp[3] obtained dienone **3** in low yield as one of the solvolysis products of the tricyclic enone **2**, a photochemical rearrangement product of the cyclohexadienone **1**. We found that the efficiency of this route improved markedly when the solvolysis was carried out in strongly acidic solution so as to favor E1 processes. The stereochemistry of the spiro ketone **3** can be assigned on the basis of the established stereochemistry of the starting dienone **1**[4] and the established relationships in the related santonin–lumisantonin rearrangement.[5]

Selective hydrogenation of the dienone **3** in alkaline solution[6] afforded the enone **4**. Further hydrogenation in neutral solution led to a 3:1 mixture of ketones **8** and **5**, which could be separated by preparative gas chromatography. We based our initial assignment of stereochemistry on the nmr spectra of these ketones. The minor (*dl*) isomer **5** exhibited two distinct methyl doublets, whereas the major (*meso*) isomer **8** gave rise to a single methyl doublet, in accord with its symmetrical structure. This distinction was even more apparent in the nmr spectra of the thioketal derivatives **6** and **9**. Subsequent chemical transformations, outlined below, confirmed these assignments.

Hoping to obtain a *meso* ketone related to **8**, we carried out the degradation of *meso*-dihydro-β-vetivone (**11**)[2] as outlined in Scheme I. The modified Wolff–

SCHEME I



1 2 3 4

5, Y, Y′ = O
6, Y, Y′ = $S(CH_2)_2S$
7, Y = Y′ = H

8, Y, Y′ = O
9, Y, Y′ = $S(CH_2)_2S$
10, Y = Y′ = H

12

13, Y, Y′ = O
14, Y, Y′ = $S(CH_2)_2S$

11

(1) J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Org. Chem.*, **34**, 186 (1969).

(2) *Cf.* A. St. Pfau and P. A. Plattner, *Helv. Chim. Acta*, **23**, 768 (1940), and previous papers; Y. R. Naves and E. Perrottet, *ibid.*, **24**, 3 (1941).

(3) P. J. Kropp, *J. Amer. Chem. Soc.*, **87**, 3914 (1965).

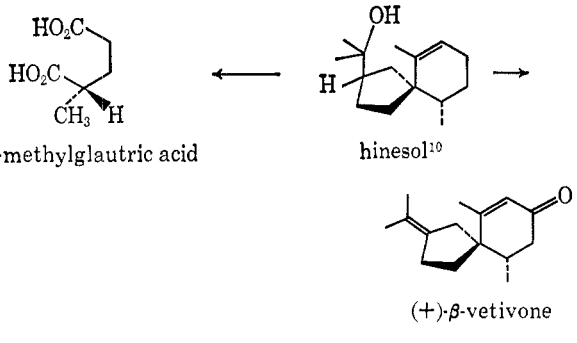
(4) S. M. Bloom, *J. Org. Chem.*, **24**, 279 (1959).

(5) D. H. R. Barton, P. de Mayo, and M. Shafig, *J. Chem. Soc.*, 140 (1958).

(6) *Cf.* R. Howe and F. J. McQillin, *ibid.*, 1194 (1958).

Kishner reduction[7] of this ketone yielded the olefin **12**. Ozonolysis then gave the desired ketone **13**. This ketone exhibited spectral properties which closely resembled those of ketones **5** and **8**, especially the latter, but exact correspondence was lacking. Reduction of ketone **13**, *via* desulfurization of the thioketal derivative **14**, afforded the hydrocarbon **10**. The identical hydrocarbon was secured upon application of this reduction scheme to ketone **8**. The hydrocarbon **7** derived from the *dl*-ketone **5**, on the other hand, showed distinctly different spectral and chromatographic properties.

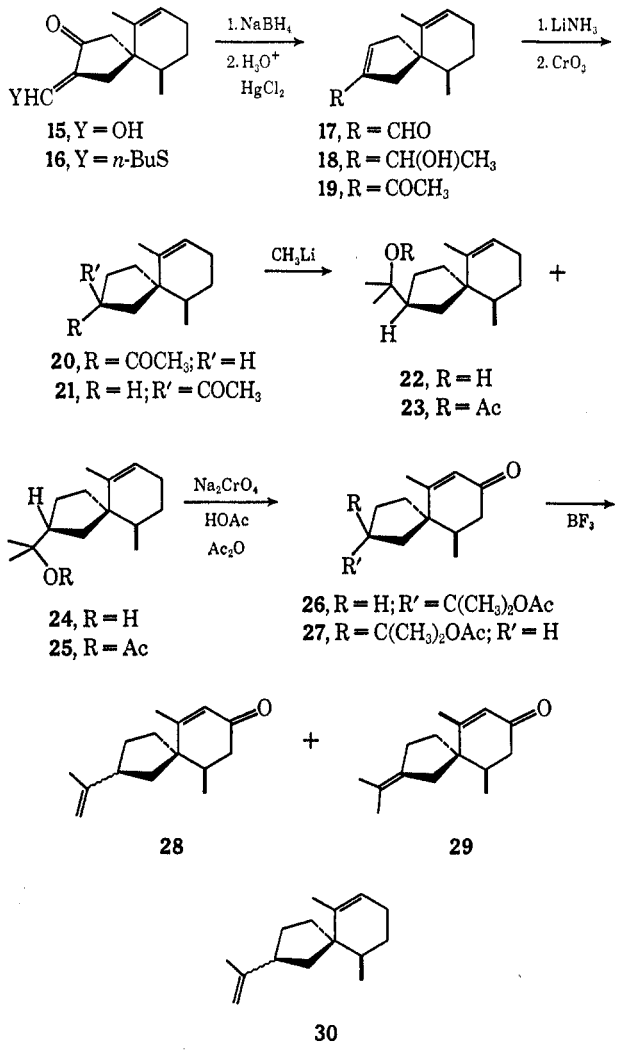
The conversion of ketones **8** and **13** to the same hydrocarbon confirms our proposed spiro[4.5]decane carbon skeleton for β-vetivone. Furthermore, the spectral properties of ketone **13** suggest an epimeric relationship with ketone **8**. Since the stereochemistry of the latter follows from its method of synthesis, the former can be assigned the indicated relative stereochemistry, and this assignment must likewise hold for *meso*-dihydro-β-vetivone (**11**) and β-vetivone itself. The absolute stereochemistry of β-vetivone can be deduced on the basis of Yosioka and Kimura's[8] conversion of hinesol to (+)-β-vetivone, the antipode of the natural isomer, and Šorm and coworkers'[9] degradation of hinesol to (+)-α-methylglutaric acid of known absolute configuration.



(+)-α-methylglautric acid — hinesol[10] — (+)-β-vetivone

As noted earlier, the spiro dienone **3** appeared well suited as a potential starting material for the synthesis of β-vetivone. In view of the relationship between ketones **8** and **13**, the requisite isopropylidene substituent would have to be selectively introduced at C-3 of this or the related dihydro derivative **4**. We assumed that the latter ketone would preferentially undergo condensation reactions at C-3 (*vs.* C-1) on steric grounds. In fact, condensation of ketone **4** with ethyl formate and conversion of the resulting hydroxymethylene derivative **15** to the thio enol ether **16**[11] (Scheme II) afforded a substance whose spectral properties fully supported this assumption. Reduction of ketone **16** with sodium borohydride followed by acidic hydrolysis of the resulting alcohol derivative in the presence of mercuric chloride to trap the liberated

SCHEME II



thiol, thereby preventing subsequent condensation reactions, afforded the unsaturated aldehyde **17**.[12]

Addition of methyllithium to aldehyde **17** afforded the alcohol **18**, presumably a mixture of diastereoisomers. Conversion to the ketone **19** was conveniently effected with manganese dioxide in hexane. Selective reduction of the conjugated double bond of diene **19** could be achieved using lithium in ammonia with ethanol as a cosolvent, whereupon a mixture of alcohols was obtained. Oxidation of this mixture with Jones reagent[13] then gave an epimeric mixture of ketones **20** and **21** (*ca.* 40:60 according to the nmr spectrum). Reduction of the enone **19** without the ethanol cosolvent stopped short of completion, presumably owing to enolate formation in the resulting strongly basic medium.

The ketone mixture could not be separated and was therefore carried further in the sequence as such. Addition of methyllithium yielded the alcohols **22** and **24**, again an inseparable mixture of epimers. Acetylation of this alcohol mixture afforded the acetates **23** and **25**, a 5:3 mixture which could be separated by gas chromatography. The major epimer **23** was identified as hinesol acetate by comparison with an authentic

(7) *Cf.* W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, **89**, 1483 (1967); see p 1496, experiment C.

(8) I. Yosioka and T. Kimura, *Chem. Pharm. Bull.* (Tokyo), **13**, 1430 (1965).

(9) W. Z. Chow, O. Motl, and G. Šorm, *Collect. Czech. Chem. Commun.*, **27**, 1914 (1962).

(10) The relative stereochemistry of the isopropylol side chain has recently been established through total synthesis: J. A. Marshall and S. F. Brady, *Tetrahedron Lett.*, 1387, (1969).

(11) *Cf.* R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962).

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

(13) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

sample.[14] A small amount of hydrocarbon whose spectral properties were in agreement with those reported for the diene **30** derived from agarospirol[15] was also formed in the acetylation reaction. Additional quantities of this diene were produced in the injection port of the gas chromatogram upon analysis and purification of the acetates. Oxidation of the unsaturated acetates **23** and **25** with sodium chromate in acetic acid afforded the keto acetates **26** and **27**. Dehydroacetylation of this mixture with boron trifluoride, according to the method of Yosioka and Kimura,[8] yielded racemic β-vetivone (**29**) contaminated with a small amount of the isopropenyl isomers **28**.

Experimental Section[16]

6,10*t*-Dimethyl-(5*r*C^1)-spiro[4.5]deca-3,6-dien-2-one (3).[16d]—A solution of 11.57 g (65.6 mmol) of the lumi ketone **2**[3] in 4.6 ml of acetic anhydride and 230 ml of acetic acid was stirred for 5 min at room temperature, 4.6 ml of sulfuric acid was carefully added, and stirring was continued for 23 hr.[16a] The solution was poured into a cold, well-stirred solution of 10% NaOH and the basic mixture was extracted with ether.[16b] The product was chromatographed on alumina and the material eluted with benzene was distilled, affording 7.66 g (66%) of dienone **3**,[3] bp 60–63° (0.1 mm), judged 98% pure by gas chromatography.

6,10*t*-Dimethyl-(5*r*C^1)-spiro[4.5]dec-6-en-2-one (4).[16d]—A solution of 4.26 g (24.2 mmol) of dienone **3** in 48 ml of ethanol and 4.8 ml of 10% NaOH solution was stirred with 471 mg of 5% Pd–C under 1 atm of hydrogen. When 620 ml (*ca.* 25 mmol) of hydrogen had been absorbed, the mixture was filtered and the product was isolated with ether[16b] and distilled, affording 3.94 g (92%) of ketone **4**, bp 64–66° (0.05 mm), judged 85% pure by gas chromatography. The ketone was purified for analysis by preparative gas chromatography: ir λ_{max}^{film} 5.74 (CO), 7.11, 7.24, 8.55, 8.61, 9.19, 11.07, 11.80, and 12.42 μ; $\delta_{TMS}^{CCl_4}$ 5.40 ($W_{1/2}$ = 8 Hz, H-7), 2.32, 2.02 (AB q, J = 18 Hz, C-1 CH_2), 1.67 (d, J = 1.7 Hz, C-6 CH_3), and 0.92 ppm (d, J = 6 Hz, C-10 CH_3).

Anal.[16c] Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.9; H, 10.1.

The 2,4-DNP derivative crystallized from ethanol as fine yellow needles, mp 107–109°.

Hydrogenation of Unsaturated Ketone 4.—A solution of 946 mg of ketone **4** in 10 ml of ethanol was stirred with 215 mg of 5% Pd–C under 1 atm of hydrogen for 6 hr. The mixture was filtered and concentrated, affording a mixture of ketones and alcohols. This mixture was oxidized with 0.73 ml of Jones reagent[18] to give a 75:25 mixture of ketones **8** and **5**, which was separated by preparative gas chromatography.

The first component eluted, 6*t*,10*t*-dimethyl-(5*r*C^1)-spiro-[4.5]decan-2-one (**8**),[16d] was distilled, affording 660 mg of material (99% pure): mp 21–23°; ir λ_{max}^{film} 5.75 (CO), 7.10, 7.24, 7.89, 8.53, 9.66, 10.48, and 11.29 μ; nmr $\delta_{max}^{CCl_4}$ 2.13 (C-1 CH_2) and 0.87 ppm (d, J = 5 Hz, CH_3's); $n^{26}D$ 1.4884.

Anal.[16c] Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.9; H, 11.1.

The 2,4-DNP derivative crystallized from ethanol as orange needles, mp 144.5–145°.

The second component eluted, 6*c*,10*t*-dimethyl-(5*r*C^1)-spiro-[4.5]decan-2-one (**5**),[16d] was initially obtained in 86% purity and was therefore rechromatographed, whereupon material of 97% purity was collected: ir λ_{max}^{film} 5.75 (CO), 7.10, 7.23, 7.98, 8.52, 8.62, 9.00, 9.36, 10.22, 10.32, 10.54, 10.65, and 11.25 μ; nmr $\delta_{max}^{CCl_4}$ 2.08 (C-1 CH_2), 1.99 (t, J = 3 Hz, C-3 CH_2), and 0.87 and 0.85 ppm (both d, J = 6 Hz, CH_3's); $n^{26}D$ 1.4908.

Anal.[16c] Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.1; H, 10.9.

The 2,4-DNP derivative crystallized from ethanol as an orange-yellow powder, mp 103–106°.

Ethylene Thioketal Derivative of Ketone 8 (9).—A solution of 571 mg (3.17 mmol) of ketone **8**, 0.80 ml (9.5 mmol) of ethanedithiol, and 0.80 ml (6.3 mmol) of boron trifluoride etherate in 11.1 ml of acetic acid[17] was stirred at room temperature for 3 hr.[16a] The solution was poured into brine, extracted with ether, washed with 10% NaOH, and distilled, affording 588 mg (70%) of crystalline thioketal: mp 54–56.5° after recrystallization from pentane; ir λ_{max}^{film} 7.24, 7.83, 8.40, 10.21, 10.44, 11.85, and 11.97 μ; nmr $\delta_{max}^{CCl_4}$ 3.18 (CH_2S), 2.26 (C-1 CH_2), 2.12 (t, J = 6.5 Hz, C-3 CH_2), 1.51 (t, J = 6.5 Hz, C-4 CH_2), and 0.93 ppm (d, J = 4 Hz, CH_3's).

Material of mp 56–57° was obtained after sublimation.

Anal.[16c] Calcd for $C_{14}H_{24}S_2$: C, 65.57; H, 9.43; S, 25.01. Found: C, 65.7; H, 9.4; S, 25.2.

Ethylene Thioketal Derivative of Ketone 5 (6).—The above procedure was employed on 155 mg of ketone **5**, affording 216 mg (98%) of an oil: ir λ_{max}^{film} 7.23, 7.82, 8.27, 8.51, 10.27, 10.68, and 11.29 μ; nmr $\delta_{max}^{CCl_4}$ 3.18 (CH_2S), 2.12, 2.08 (C-1 CH_2), 0.90, and 0.83 ppm (d, J = 6.6 Hz, CH_3's).

Anal.[16c] Calcd for $C_{14}H_{24}S_2$: C, 65.57; H, 9.43; S, 25.01. Found: C, 65.7; H, 9.3; S, 25.2.

***cis*-6,10-Dimethylspiro[4.5]decane (10).**—A solution of 509 mg of thioketal **9** in 43 ml of ethanol was heated at reflux with 8.7 g of W-2 Raney nickel[18] for 2 hr. The cooled mixture was filtered and the product was isolated with ether,[16b] chromatographed on alumina, and distilled, affording 317 mg (96%) of hydrocarbon: ir λ_{max}^{film} 7.25, 7.38, 9.42, 10.29, 10.38, and 10.74 μ; nmr $\delta_{TMS}^{CCl_4}$ 0.86 ppm (d, J = 5 Hz, CH_3's); $n^{27}D$ 1.4786.

Anal.[16c] Calcd for $C_{12}H_{22}$: C, 86.67; H, 13.33. Found: C, 86.8; H, 13.1.

***trans*-6,10-Dimethylspiro[4.5]decane (7).**—The above procedure was employed on 174 mg of thioketal **6**, affording 121 mg (95%) of hydrocarbon: ir λ_{max}^{film} 7.24, 9.43, 10.26, and 10.76 μ; nmr $\delta_{TMS}^{CCl_4}$ 0.86 ppm (d, J = 6.5 Hz, CH_3's); $n^{28}D$ 1.4811.

Anal.[16c] Calcd for $C_{12}H_{22}$: C, 86.67; H, 13.33. Found: C, 86.5; H, 13.5.

Degradation of β-Vetivone to Hydrocarbon 10.—An enriched sample of vetivones (*ca.* 30% α- and β-vetivone) was secured by repeated partitioning of vetivert acetate[19] between hexane and 1:1:5 pyridine–water–methanol and extraction of the methanol phase with methylene chloride.[20] Repeated chromatography on alumina afforded a mixture of α- and β-vetivone which was separated by preparative gas chromatography. Recrystallization of the β-vetivone fraction from pentane afforded material, mp 42–44°, whose spectral properties matched those reported for β-vetivone.[8]

A 188-mg sample of this material was hydrogenated over 300 mg of W-2 Raney nickel[18] in ethanol at 65° to give 194 mg of dihydro-β-vetivols, a crystalline mixture of epimeric alcohols.[2] Oxidation with 0.19 ml of Jones reagent[18] afforded 177 mg (95%) of *meso*-dihydro-β-vetivone (**11**): nmr $\delta_{TMS}^{CCl_4}$ 1.63 (vinyl CH_3's) and 0.93 ppm (d, J = 6 Hz, CH_3's).

A 278-mg sample of ketone **11**, comparable in quality to the above material, was heated at 130° with 221 mg of hydrazine dihydrochloride and 4.2 ml of 85% hydrazine hydrate in 15 ml of triethylene glycol for 4 hr.[16a] Then 230 mg of KOH was added and the temperature was raised to 225° where it was maintained for 2.5 hr.[21] The cooled mixture was poured into water and the product was isolated with ether[16b] and chromatographed on alumina, affording 177 mg (68%) of hydrocarbon **12**: ir λ_{max}^{film} 7.25, 8.70, 9.03, 9.46, 10.24, and 10.61 μ; nmr $\delta_{TMS}^{CCl_4}$ 1.60 (vinyl CH_3's) and 0.80 ppm (d, J = 4.5 Hz, CH_3's).

Anal.[16c] Calcd for $C_{16}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.2; H, 12.5.

(14) We are indebted to Professor Šorm and Professor Yosioka for samples of natural hinesol.

(15) K. R. Varma, M. L. Maheshwari, and S. C. Bhattacharyya, *Tetrahedron*, **21**, 115 (1965).

(16) (a) The apparatus described by W. S. Johnson and W. P. Schneider ["Organic Syntheses," Coll. Vol. 4, John Wiley & Sons, Inc., New York, N. Y., 1963, p 132] was used to maintain a nitrogen atmosphere. (b) The isolation procedure consisted of thorough extractions with the specific solvent, washing the combined extracts with saturated brine solution, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. (c) Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. (d) Relative stereochemistry is designated by "*c*" and "*t*" to denote a *cis* or *trans* relationship to some reference ("*r*") substituent according to Beilstein ("Handbuch Der Organischen Chemie," E III, Vol. VI, Part 7, p x). Thus, for example, the term "5*r*C^1" indicates that the C^1 carbon attached to C-5 of the parent ring system serves as the reference substituent.

(17) The procedure of L. F. Fieser, *J. Amer. Chem. Soc.*, **76**, 1945 (1954).

(18) R. Mozingo, "Organic Syntheses," Coll. Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1955, p 181.

(19) The Givaudan Corp., Clifton, N. J.

(20) Unpublished procedure of N. H. Andersen.

(21) The procedure of Nagata, *et al.*[7]

The above olefin in 9.4 ml of acetic acid, 3 ml of ethyl acetate, and 0.3 ml of water was stirred at 0° for 4 min while ozone was passed through the solution.[22] Then 2 ml of water and 1 g of powdered zinc were added, and the mixture was efficiently stirred overnight.[16a] The product was isolated with ether,[16b] affording 129 mg (84%) of ketone **13**: ir λ_{max}^{film} 5.76 (CO), 7.10, 7.24, 7.98, 8.41, 8.62, 9.45, 10.27, 10.62, and 11.29 μ; nmr $\delta_{TMS}^{CCl_4}$ 1.92 (C-1 CH_2) and 0.86 ppm (d, J = 5.5 Hz, CH_3's).

The 2,4-DNP derivative exhibited mp 209.5–210.5° (lit.[23] mp 212–214°).

Anal.[16c] Calcd for $C_{18}H_{24}N_4O_4$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.9; H, 6.9; N, 15.6.

Ketone **13** was converted to the thioketal derivative **14** in 90% yield following the procedure described above: ir λ_{max}^{film} 7.25, 7.84, 9.47, 10.14, and 10.26 μ. Desulfurization with W-2 Raney nickel[18] as outlined above afforded the hydrocarbon **10**, identified through spectral and chromatographic comparison with the hydrocarbon secured from thioketal **9**.

3-(Butanethiomethylene)-6,10-dimethyl-(5*r*C^1)-spiro[4.5]dec-6-en-2-one (16).[16d]—A 2.76-g (57.5 mmol) portion of 50% sodium hydride dispersion was washed free of mineral oil with heptane, and 3.37 g of ketone **4** in 337 ml of benzene was added with stirring.[16a] After 30 min, 28 ml of ethyl formate and 3 drops of methanol were added and the mixture was stirred for 9 hr. Ether (200 ml) was added and the solution was washed with five portions of cold 5% NaOH. The aqueous extracts were acidified with cold HCl and saturated with NaCl, and the product was isolated with ether,[16b] affording 3.95 g of hydroxymethylene ketone **15**: ir λ_{max}^{film} 2.9–3.9 (OH), 5.90 (CO), 6.22, and 8.35 μ.

To a well-stirred solution of 4.92 g of hydroxymethylene ketone **15**, comparable with that described above, and 3.1 ml of butanethiol in 124 ml of ether was added 2.5 ml of sulfuric acid.[16a] After 25 min, the solution was poured into cold 10% NaOH, and the product was isolated with ether[16b] and distilled, affording 5.36 g (81%) of ketone **16**, bp 128–133° (0.03 mm): ir λ_{max}^{film} 5.88, 6.32, 7.10, 7.24, 7.72, 8.07, 8.32, 8.56, 11.82, and 11.25 μ; nmr $\delta_{TMS}^{CCl_4}$ 7.34 (vinyl H, triplet, J = 2.5 Hz), 5.40 ($W_{1/2}$ = 8 Hz, H-7), 2.87 (t, J = 7 Hz, SCH_2), 2.42 (4 lines, C-1 CH_2), 2.40 (d, J = 2.5 Hz, C-4 CH_2), 1.59 (d, J = 2 Hz, C-6 CH_3), and 0.92 ppm (d, J = 6 Hz, C-10 CH_3).

Anal.[16c] Calcd for $C_{17}H_{26}OS$: C, 73.35; H, 9.41; S, 11.52. Found: C, 73.4; H, 9.5; S, 11.35.

2-Formyl-6,10*c*-dimethyl-(5*r*C^1)-spiro[4.5]deca-2,6-diene (17).[16d]—To a solution of 731 mg (19.3 mmol) of sodium borohydride in 73 ml of methanol and 1.9 ml of 0.1 *N* NaOH at 0° was added 5.36 g of ketone **16**.[16a] The solution was stirred for 18 hr at room temperature and concentrated under vacuum, and the product was isolated with ether,[16b] affording 5.58 g of alcohol: ir λ_{max}^{film} 2.98 (OH), 6.10 (C=C), 7.24, 9.30, and 12.34 μ.

A solution of this alcohol in 193 ml of acetone was treated with 39 ml of 0.1 *N* HCl and 7.85 g of mercuric chloride.[16a] The mixture was stirred for 20 min and concentrated under vacuum, and the product was isolated with ether[16b] and distilled, affording 3.01 g (83%) of aldehyde **17**: bp 66° (0.04 mm); ir λ_{max}^{film} 3.30 (vinyl CH), 3.69 (aldehyde CH), 5.96 (CO), 6.15 (C=C), 7.24, 7.89, 8.43, 10.22, 11.30, 11.92, 12.45, and 13.70 μ; nmr $\delta_{TMS}^{CCl_4}$ 9.70 (aldehyde H), 6.76 (H-3 multiplet), 5.30 ($W_{1/2}$ = 8 Hz, H-7), 1.56 (d, J = 1.7 Hz, C-6 CH_3), and 0.84 ppm (d, J = 6 Hz, C-10 CH_3); uv λ_{max}^{EtOH} 237 mμ (ε 11,100).

The semicarbazone derivative had mp 189.5–190.5° after recrystallization from methanol.

Anal.[16c] Calcd for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56; N, 16.99. Found: C, 68.0; H, 8.8; N, 17.1.

2-Acetyl-6,10*c*-dimethyl-(5*r*C^1)-spiro[4.5]deca-2,6-diene (19).[16d]—To a solution of 3.01 g (15.8 mmol) of aldehyde **17** in 63 ml of ether at −35° was added, with stirring, 16 ml (29.1 mmol) of 1.82 *M* MeLi in ether.[16a] The solution was stirred for 40 min at ambient temperature, saturated ammonium chloride was added, and the product was isolated with ether[16b] and distilled, affording 3.07 g (94%) of alcohol **18**: bp 77–79° (0.04 mm); judged to be 83% pure by gas chromatography; ir λ_{max}^{film} 2.99 (OH), 3.29 (vinyl CH), 6.01 (C=O), 7.25, 7.80, 8.50, 9.20, 9.36, 10.06, 10.27, 11.15, 11.97, and 12.49 μ; nmr $\delta_{TMS}^{CCl_4}$ 5.43 ($W_{1/2}$ = 6 Hz, H-3), 5.25 ($W_{1/2}$ = 9 Hz, H-7), 4.27 (q, J = 7 Hz, carbinyl H), 3.53 (OH), 1.58 (C-6 CH_3), 1.22 (d, J = 7 Hz, carbinyl CH_3), and 0.85 ppm (d, J = 6.5 Hz, C-10 CH_3).

(22) The procedure of Pfau and Plattner.[2]

(23) I. Yosioka, Y. Saski, and H. Hikina, *Chem. Pharm. Bull.* (Tokyo), **9**, 84 (1961).

A solution of 923 mg of the above alcohol in 46 ml of hexane was stirred vigorously with 8.3 g of manganese dioxide[24] for 19 hr.[16a] The mixture was filtered and distilled, affording 822 mg (90%) of ketone **19** (96% pure by gas chromatography): ir λ_{max}^{film} 6.00 (CO), 6.16 (C=C), 7.28, 8.07, 10.10, 10.59, 11.94, and 12.49 μ; nmr $\delta_{TMS}^{CCl_4}$ 6.49 (7 lines, H-3), 5.20 ($W_{1/2}$ = 7.5 Hz, H-7), 2.17 (CH_3CO), 1.53 (d, J = 1.8 Hz, C-6 CH_3), and 0.84 ppm (d, J = 6 Hz, C-10 CH_3).

The semicarbazone derivative had mp 199–201° after recrystallization from methanol.

Anal.[16c] Calcd for $C_{15}H_{23}N_3O$: C, 68.93; H, 8.87; N, 16.08. Found: C, 68.9; H, 8.8; N, 16.1.

Birch Reduction of Enone 19.—To a solution of 322 mg (48 mg-atoms) of Li wire in 80 ml of liquid ammonia was added a solution of 1.152 g (5.65 mmol) of ketone **19** in 20 ml of ether dropwise over a 10-min period. The solution was stirred for 45 min, 3 ml of EtOH was added dropwise over 1 hr, and, after an additional 2 hr, 4.5 g of ammonium chloride was added. The ammonia was allowed to evaporate and the product was isolated with ether,[16b] affording 1.21 g of alcohol: ir λ_{max}^{film} 3.00 (OH), 7.25, 8.75, 9.32, 10.35, 11.18, and 12.52 μ.

This alcohol was oxidized with Jones reagent[13] and distilled, affording 1.07 g (92%) of ketones **20** and **21** (80% pure by gas chromatography). A sample (90% pure) of the mixture was secured *via* preparative gas chromatography: ir λ_{max}^{film} 5.85 (CO), 7.25, 7.32, 8.27, 8.51, 9.22, 10.45, 11.42, and 12.52 μ; nmr $\delta_{TMS}^{CCl_4}$ 5.17 ($W_{1/2}$ = 8 Hz, H-7), 2.02 (CH_3CO), and 0.90 and 0.85 ppm (d, J = 6 Hz, C-10 CH_3's).

Anal.[16c] Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.2; H, 10.6.

(±)-Hinesol (22) and (±)-Epihinesol 24.—A solution of 1.28 g (6.23 mmol) of the ketone mixture **20** and **21** in 10 ml of ether was added to 38.5 ml of 0.35 *M* MeLi in ether at −30°.[16a] The mixture was stirred at ambient temperature for 3 hr, saturated ammonium chloride was added, and the product was isolated with ether,[16b] affording 1.35 g (98%) of material (86% **22** and **24** by gas chromatography) which was purified by preparative layer chromatography and distillation: ir λ_{max}^{film} 2.94 (OH), 7.26, 8.19, 8.55, 8.80, 10.20, and 12.52 μ; nmr $\delta_{TMS}^{CCl_4}$ 5.11 ($W_{1/2}$ = 8 Hz, H-7), 2.32 (OH), 1.64 (vinyl CH_3), 1.13 (isopropylol CH_3's), and 0.91 ppm (d, J = 6 Hz, C-10 CH_3). Even though this material contains at least 40% of epihinesol **24**, the infrared and nmr spectra were indistinguishable from those of pure hinesol.[8]

Anal.[16c] Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 79.9; H, 11.8.

(±)-Hinesol Acetate (23) and (±)-Epihinesol Acetate 25.—A mixture of 1.35 g of the above alcohol mixture (86% pure) and 0.80 g of sodium acetate in 20 ml of acetic anhydride was heated at reflux for 2 hr.[16a] The cooled mixture was stirred with saturated aqueous sodium bicarbonate, and the product was isolated with ether,[16b] chromatographed on alumina, and distilled (90° at 0.04 mm) to give 1.04 g (65%) of material analyzed as 32% (±)-epihinesol acetate **25**, 50% (±)-hinesol acetate (**23**), and 14% of the diene **30** (formed *via* pyrolysis of the acetates **23** and **25** in the injection port) by gas chromatography.

The acetate mixture was purified by distillation: ir λ_{max}^{film} 5.78 (CO), 7.25, 7.31, 7.95, 8.14, 8.24, 8.50, 8.57, 8.80, 9.03, 9.23, 9.81, 10.62, 12.52, and 13.05 μ; $\delta_{TMS}^{CCl_4}$ 5.15 ($W_{1/2}$ = 8 Hz, H-7), 1.83 (CH_3CO), 1.62 (d, J = 1.5 Hz, C-6 CH_3), 1.40 (isopropyl CH_3's), and 0.90 ppm (d, J = 6 Hz, C-10 CH_3).

Anal.[16c] Calcd for $C_{17}H_{28}O_2$: C, 71.22; H, 10.67. Found: C, 77.4; H, 10.8.

(±)-β-Vetivone (29).—A solution of 1.04 g (3.94 mmol) of the above acetate mixture and 1.61 g (9.90 mmol) of sodium chromate in 10.4 ml of acetic acid and 5.2 ml of acetic anhydride was stirred for 4 hr at 40° and 2 hr at ambient temperature. The solution was added to cold 10% NaOH solution and the product was isolated with ether[16b] and chromatographed on 44 g of silica gel to give 148 mg (14%) of starting material in the benzene fractions, and 573 mg (52%) of keto acetates **26** and **27** in the 10% ether–benzene fractions: ir λ_{max}^{film} 5.79 (CO), 5.99 (CO), 6.19 (C=C), 7.24, 7.31, 7.95, 8.12, 8.23, 8.78, 9.79, 10.60, 10.92, 11.33, 11.40, 12.04, and 13.02 μ; nmr $\delta_{TMS}^{CCl_4}$ 5.60 ($W_{1/2}$ = 3.3 Hz, H-7), 1.93 (C-6 CH_3), 1.90 (CH_3CO), 1.44 (isopropyl CH_3's), and 0.99 ppm (d, J = 6 Hz, C-10 CH_3).

A 358-mg sample of the above keto acetates in 1.8 ml of ether was stirred for 1 hr with 1.8 ml of boron trifluoride etherate at room temperature.[16a] The solution was poured into cold 5%

(24) Beacon Chemical Co., Cambridge, Mass.

NaOH solution and the product was isolated with ether[16b] and distilled, affording 235 mg (90%) of material, bp 80° (0.04 mm), containing 89% β-vetivone (**29**) and 11% of the isopropenyl isomer **28** according to the gas chromatogram and nmr spectrum. Material with mp 43.5–46° was secured after several recrystallizations from pentane at low temperature. The infrared and nmr spectra and the gas chromatographic retention times coincided exactly with those of natural β-vetivone.

Anal.[16c] Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.36; H, 10.17.

The 2,4-DNP derivative crystallized from ethanol as red needles, mp 157–159° [lit.[8] for the 2,4-DNP derivative of (+)-β-vetivone, mp 188–191°].

The semicarbazone derivative crystallized from isopropyl alcohol as white prisms, mp 209–211° [lit. for the semicarbazone derivative of (−)-β-vetivone, mp 228–229[2] and 227°[25]].

Registry No.—**3**, 22196-17-4; **4**, 22196-18-5; **4** (2,4-dinitrophenylhydrazone), 22196-19-6; **5**, 22196-20-9; **5** (2,4-dinitrophenylhydrazone), 22196-21-0; **6**, 22196-22-1; **7**, 22196-23-2; **8**, 22196-24-3; **8** (2,4-dinitrophenylhydrazone), 22196-25-4; **9**, 22196-26-5; **10**, 22196-27-6; **11**, 22196-28-7; **12**, 22196-29-8; **13**, 22196-30-1; **14**, 22196-31-2; **16**, 22196-32-3; **17**, 22196-33-4; **17** (semicarbazone), 22196-34-5; **18**, 22196-35-6; **19**, 22196-36-7; **19** (semicarbazone), 22196-37-8; **20**, 22196-38-9; **21**, 22196-39-0; **22**, 22196-40-3; **23**, 22196-41-4; **24**, 22196-42-5; **25**, 22196-43-6; **26**, 22196-44-7; **27**, 22196-45-8; **29**, 22196-46-9.

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(25) M. Romanuk and V. Herout, *Collect. Czech. Chem. Commun.*, **25**, 2540 (1960).

Hydroboration of Terpenes. VI. Hydroboration of α- and β-Cedrenes. Configurational Assignments for the Related Cedrane Derivatives

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The convenient synthesis of (+)-β-cedrene was achieved by hydrochlorination of (−)-α-cedrene followed by elimination of the tertiary chloride by bases of large steric requirements. Study of a number of representative reactions reveals that the stereochemical course of reaction for both olefins and their derivatives is apparently dominated by the *gem*-dimethyl groups, with the reaction occurring preferentially at the side away from this group (*exo*). Thus, hydroboration and epoxidation of both α- and β-cedrenes (**2**, **11**) take place predominantly from this direction. Similarly, hydrogenation of β-cedrene, although less selective, also takes place from this direction to give 88% (−)-isocedrane (**21**) and 12% (−)-cedrane (**22**). The hydroboration of β-cedrene gives the *endo* intermediate predominantly, corresponding to the preferred *exo* attack of the hybroborating agent. Isomerization of the intermediate converts it predominantly into the more stable *exo* isomer (76% *exo* and 24% *endo*). Similarly, epimerization of 9-isocedranal (**18**) with base yielded the two isomeric aldehydes, **19** and **18**, in a ratio of 80:20. Borohydration–oxidation of α-cedrene yields essentially pure (−)-2-isocedranone (**4**) with the methyl and *gem*-dimethyl groups in a *cis* relationship. The presence of base induces a rapid epimerization, producing 92% (−)-2-cedranone (**5**), having the 3-methyl in the quasiaxial position, and 8% of (−)-2-isocedranone (**4**), having the 3-methyl in the equatorial position. Reduction of the borohydration–oxidation ketone, (−)-2-isocedranone (**4**), with lithium trimethoxyaluminohydride takes place almost exclusively from the *exo* direction, providing (−)-2-neoisocedranol (**8**) with only traces of (+)-2-isocedranol (**3**). Likewise, the epimer, (+)-2-cedranone (**4**), undergoes preferential reduction by this reagent from the *exo* direction to give predominantly (−)-2-cedranol (**7**) with minor amounts of (−)-2-neocedranol (**6**). The tosylate of (−)-2-cedranol (**24**) is readily reduced by lithium aluminum hydride to (−)-cedrane (**22**), but the corresponding reaction with the tosylate of (−)-2-isocedranol (**3**) failed. (The latter reaction would have required attack of the reagent from the *endo* direction.) However, (−)-isocedrane (**21**) was obtained from the reduction of the tosylate of 9-isocedranol (**23**), the reaction path involving far less steric interference from the *gem*-dimethyl substituents. (−)-*exo*-(2,3)Epoxycedrane (**9**) undergoes a facile opening of the epoxide ring by boron trifluoride etherate to give exclusively (−)-2-cedranone (**5**), involving a stereospecific hydride shift from the *endo* direction. On the other hand, the corresponding rearrangement of (−)-*exo*-(3,9)epoxycedrane (**12**), which can involve either *exo* or *endo* hydride shifts, gives preferentially (80%) 9-isocedranal (**18**), indicating a preference for the hydride shift from the *exo* direction. The various compounds were subjected to nmr study and configurations and preferred conformations were assigned.

α-Cedrene (**1**, **2**), a tricyclic sesquiterpenoid hydrocarbon, was first isolated by Walter,[1] in 1841, but its structural features,[2] including its total synthesis[3] and absolute configurational assignments[4] were achieved only recently.

At the time this study had been initiated only a few of the possible derivatives were known; one 2-cedranol,[5,6a] one 2-cedranone,[6] one 9-cedranol,[7–9] one

(1) P. Walter, *Ann. Chem.*, **39**, 247 (1841); **48**, 35 (1843).

(2) G. Stork and R. Breslow, *J. Amer. Chem. Soc.*, **75**, 3291 (1953); P. A. Plattner, A. Fürst, A. Eschenmoser, W. Keller, H. Kläui, S. Meyer, and M. Rosner, *Helv. Chim. Acta*, **36**, 1845 (1953).

(3) G. Stork and F. H. Clarke Jr., *J. Amer. Chem. Soc.*, **77**, 1072 (1955), **83**, 3114 (1961).

(4) G. Büchi, R. E. Erickson, and N. Wakabayashi, *ibid.*, **83**, 927 (1961).

(5) G. Lucius and C. Schäfer, *Z. Chem.*, **2**, 29 (1962).

(6) (a) M. I. Goryaev and G. A. Tolstikov, *J. Gen. Chem. USSR* (Engl. Transl.), **31**, 594 (1961); (b) *ibid.*, **32**, 982 (1962); (c) *Chem. Abstr.*, **59**, 1496 (1963).

(7) Y. R. Naves, G. Papazian, and E. Perrottet, *Helv. Chim. Acta*, **26**, 302 (1943).

(8) M. I. Goryaev and G. A. Tolstikov, *Proc. Acad. Sci. USSR, Chem. Sect.* (Engl. Transl.), **139**, 673 (1961).

(9) M. I. Goryaev and G. A. Tolstikov, *Chem. Abstr.*, **59**, 6443 (1963).