The Structure of Hibaene[1]

By Yoshio KITAHARA and Akira YOSHIKOSHI

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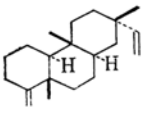
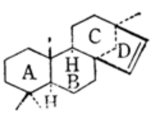
Dolabradiene, a diterpene isolated from the essential oil of the leaves of Hiba (*Thujopsis dolabrata* Sieb. et Zucc.) has been shown[2] by the present authors to have structure I.

A purification by gas liquid chromatography of the fraction of the above oil with a b. p. of 162—167° C/7 mmHg gave a new crystalline diterpene named hibaene. On the basis of the experimental data which will be described below, we could determine the absolute configuration of hibaene to be II.



I



II

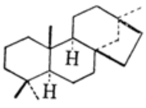
Hibaene is a crystalline compound with a melting point of 30°C; $[\alpha]_D^{23}$ $-49.9°$; the mass spectrum[3] of hibaene showed a molecular weight of 272. The relative abundance of the parent peak (P) and the (P+1) peak indicated the molecular formula $C_{20}H_{32}$, which was also supported by its elemental analysis.

The infrared absorption spectrum of hibaene indicated the presence of a geminal dimethyl group (1385, 1363 cm^{-1}) and *cis*-1, 2-disubstituted ethylene (750 cm^{-1}). When hibaene was hydrogenated catalytically, it absorbed one molar equivalent of hydrogen, thus yielding a saturated hydrocarbon, dihydrohibaene (III). Oxidation of hibaene by peracid afforded monoepoxide (IV). From these facts, it was assumed that hibaene possesses one double bond; therefore, it must be a tetracyclic diterpene. The nuclear magnetic resonance spectrum of hibaene displays the signals (9.27, 9.19, 9.15, 9.03 τ, all singlet)[4] of four methyl groups bonded on quarternary carbon atoms and the typical AB type signals of olefinic protons (4.39, 4.64 τ, $J=6$ c.p.s., two protons). Accordingly, the double bond was attached to carbon which bears no proton, and the partial sturcture V was deduced.

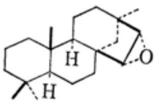
Since these physical constants were different from those of the diterpenes reported hitherto, hibaene was supposed to be a new diterpene.

The dehydrogenation of hibaene by selenium gave pimanthrene (VI), and the oxidation of hibaene using permanganate yielded a dicarboxylic acid (VII) without loss of the carbons. VI was also obtained by the dehydrogenation of VII using selenium. The above facts indicate that three rings out of the four rings of hibaene form a perhydrophenanthrene ring system and that the double bond is contained in the remaining ring (ring D).

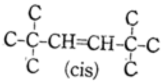
When VII was heated above 220°C or was treated with acetic anhydride, an anhydride (IX) was easily obtained. From the infrared absorption spectrum of IX, this was assumed to be a strainless cyclic anhydride (of the glutaric anhydride type). IX was stable when heated at 300°C and was recovered. The dimethyl ester (VIII) of VII did not undergo hydrolysis with diluted potassium hydroxide; therefore, both of the ester groups are considered to be linked with quarternary carbon. This fact also supports the partial structure V deduced from the nuclear magnetic resonance spectrum of hibaene mentioned before.



III

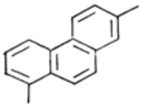


IV

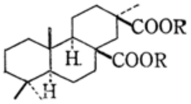


$$\text{C-}\underset{\text{C}}{\overset{\text{C}}{\text{C}}}\text{-CH=CH-}\underset{\text{C}}{\overset{\text{C}}{\text{C}}}\text{-C} \quad \text{(cis)}$$

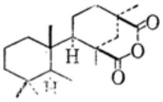
V



VI



VII R=H
VIII R=Me



IX

In view of the experimental facts described so far and from a consideration of the biogenesis[5] of hibaene (Scheme 1), the structure of hibaene is presumed to be II (or its enantiomer).

As was reported earlier, the shifts of methyl group signals observed between II and III in the nuclear magnetic resonance spectra, and those observed between isophyllocladene (X)

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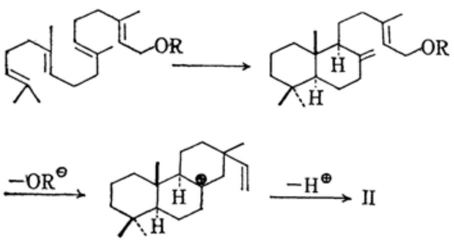
[1] This paper was read at the 5th Symposium on the Chemistry of Natural Products, Japan, July, 1962; Y. Kitahara and A. Yoshikoshi, *Tetrahedron Letters*, 1771 (1964).

[2] Y. Kitahara and A. Yoshikoshi, ibid., 1755 (1964); A. Yoshikoshi, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), 85, 383, 386, 390 (1964).

[3] The mass spectrum was measured using Hitachi RMU-6A. The authors wish to express their gratitude to Hitachi, Ltd.

[4] The assignments of the signals of the methyl groups were made by Y. Kitahara and A. Yoshikoshi, This Bulletin, 37, 890 (1964).

[5] Cf. L. Ruzicka, *Experientia*, 9, 357 (1953).



Scheme 1

and phyllocladane (XI), are parallel.[4] This also supports the theory that hibaene has structure II or its enantiomer.

Further proof for the stereochemistry was obtained as follows.

The hydroboration of II, followed by oxidation with dichromate and chromatographical separation on alumina, gave two isomeric ketones. The infrared adsorption spectrum of the polar ketone showed a band ($1736\ \mathrm{cm}^{-}$) which can be assigned to a five-membered-ring ketone. The ketone reacted with carbonyl reagents to give the corresponding derivatives and underwent oxidation by perbenzoic acid to afford a lactone (XII). On the other hand, the carbonyl band of the less polar ketone shifts to a longer wavelength region ($1727\ \mathrm{cm}^{-1}$) compared with that of the former ketone. The less polar ketone did not react with carbonyl reagents or perbenzoic acid, and the starting material was recovered.

The abnormality of the carbonyl group of the less polar ketone is considered to be due to the steric interference. Consideration using the molecular model of hibaene gave us the following information. Supposing that hibaene is a *trans-anit-trans* perhydrophenanthrene derivative, the methyl group at C-10 is cis to the D ring. Besides, when the carbonyl group is present at C-15, the carbonyl group is considerably hindered by the methyl group at C-10. Accordingly, it is assumed that the less polar ketone and the polar one are XIII and XIV respectively, or their enantiomers.

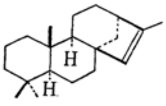
Because the optical rotatory dispersion curve of XIV shows a positive Cotton effect and is antiopodal with that of isosteviol[6] (XV), the absolute configuration of the D ring of XIV is β (Fig. 1).

From the afore-mentioned results, out of the five asymmetric centers of hibaene the absolute configurations of C-13 and C-8 became clear; the others were proved as follows.

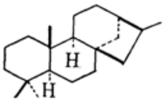
If the absolute configuration of hibaene is shown by II, dihydrohibaene (III) must be an enantiomer of isostevane[7] (XVI). The infrared absorption spectra of the two compounds, III and XVI, are superimposable, but a mixed melting point determination showed an apparent depression. The optical rotatory dispersion curves of both compounds show plane curves with a value of almost 0°.[8]

On the basis of the various results described hitherto, the absolute configuration of hibaene was definitely proved to be II.

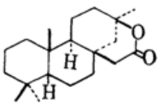
Recently, the fact that hibaene is identical with cupressene[9] and enantiomeric with stachene[10] has been established.[11]



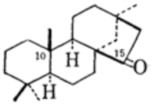
X



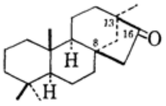
XI



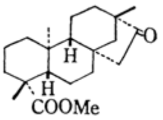
XII



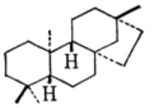
XIII



XIV



XV



XVI

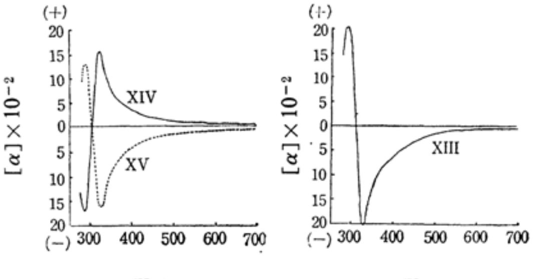


Fig. 1. RD curves of the ketones (XIII, XIV and XV) in methanol.

Experimental[12]

The Isolation of Hibaene (II).—The essential oil obtained from the leaves of Hiba (*Thujopsis*

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[6] C. Djerassi, R. Riniker and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956); C. Djerassi, P. Quitt, E. Mosettig, R. C. Cambie, P. S. Rutledge and L. H. Briggs, ibid., **83**, 3720 (1961).

[7] E. Mosettig and W. Nes, *J. Org. Chem.*, **20**, 884 (1955); E. Mosettig, U. Beglinger, F. Dolder, H. Lichti, P. Quitt and J. A. Waters, *J. Am. Chem. Soc.*, **85**, 2305 (1963).

[8] The reported specific optical rotation of isostevane (XVI) is $[\alpha]_D+4°$,[6] but $[\alpha]_{300\text{-}700\,\mathrm{m}\mu}$ by our measurement was 0° within the range of experimental error.

[9] L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, *Tetrahedron Letters*, No. **8**, 8, 13 (1959).

[10] R. D. H. Murray and R. McCrindle, *Chem. & Ind.* **1964**, 500.

[11] The direct comparison was made by Professor Briggs (Department of Chemistry, University of Auckland, New Zealand), who kindly informed us (letter dated June 26, 1964).

dolabrata) by steam distillation was washed with a diluted sodium hydroxide aqueous solution, dried over anhydrous magnesium sulfate, and fractionally distilled using a spinning band column, the theoretical plate of which was around sixty. The fraction with a b. p. of 162—167°C/7mmHg was obtained in a yield of approximately 5% of the original oil. The gas liquid chromatography (20% DC Silicon oil-Hitachi Carrier. 3 m.; column temperature 235 °C; flowing rate of helium gas 50 ml./min.) of the above fraction indicated that the oil contained a small amount of dolabradiene besides hibaene (retention time 12 min.). By the purification using preparative gas liquid chromatography under the same conditions as the above preliminary chromatography, hibaene was crystallized.

The hibaene fraction obtained from the fractional distillation was cooled to around —50°C; then the crystalline hibaene was added. Most of the liquid hibaene became a crystalline mass, which was then filtered under cooling, recrystallized from ethyl acetate at around −60°C, and further recrystallized from ethanol, thus affording hibaene (II), m. p. 29.5—30.5°C, $[\alpha]_D^{23}$ −49.9° (*c* 0.1, chloroform), molecular weight 272 (mass spectrum).

Found: C, 88.45; H, 11.89. Calcd. for $C_{20}H_{32}$: C, 88.16; H, 11.84%.

IR (KBr disk): 1385, 1363 (*gem.* dimethyl), 750 cm^{-1} (*cis* 1,2-disubstituted ethylene). NMR (10% carbon tetrachloride solution): 9.27, 9.19, 9.15, 9.03 (singlets, 3 protons each), 4.39, 4.64 τ (quartet, J=6 c.p.s., 2 protons).

Dihydrohibaene (III).—When a solution of 0.54 g. of II in 10 ml. of ethyl acetate was submitted to catalytic hydrogenation in the presence of 50 mg. of 10% palladium-charcoal under atomospheric pressure and at room temperature, 0.98 molar equivalent of hydrogen was rapidly absorbed. After the catalyst and the solvent had been removed, the residue was recrystallized from ethanol, yielding colorless plates, m. p. 41.5—42.5°C.

Found: C, 87.83; H, 12.53. Calcd. for $C_{20}H_{34}$: C, 87.51; H, 12.49%.

$[\alpha]_{300-700\mathrm{m}\mu}=0°$ (*c* 0.6, dioxane).[13] IR (carbon disulfide solution) was entirely superimposable on that of isostevane, but the melting point of III was depressed below room temperature on admixture with isostevane.

Monoepoxide (IV) of Hibaene.—A solution of 0.5 g. of hibaene in 3.6 ml. of chloroform containing 0.28 g. of perbenzoic acid was allowed to stand at 0°C for one day. After ether had been added to the solution, it was washed with a 2% sodium hydroxide aqueous solution and then with water, and dried over anhydrous magnesium sulfate. The removal of the solvent gave a semisolid substance, which was purified by submitting it to alumina column chromatography using 20 g. of alumina and benzene - petroleum ether (1 : 1) as eluting solvent; thus 0.53 g. of crystals, m. p. 63—70°C, were afforded. Recrystallization from acetone gave colorless prisms, m. p. 70—71°C.

Found: C, 83.46; H, 10.85. Calcd. for $C_{20}H_{32}$: C, 83.27; H, 11.18%.

The Dehydrogenation of Hibaene by Selenium.—A mixture of 1.5 g. of hibaene and 3.0 g. of selenium was heated at 320—340°C for 43 hr. The reaction mixture was extracted with ether, and the extract was washed with a 10% potassium hydroxide aqueous solution and then with water, and dried over magnesium sulfate. The removal of the ether yielded 1.38 g. of oil, which was chromatographed on alumina (40 g. of alumina was used). From a petroluem ether - benzene (1 : 1) effluent, 0.45 g. of crystals were obtained; they were recrystallized from ethanol to give colorless leaflets, m. p. 83—84°C. This compound was proved to be pimanthrene[14] by mixed melting point determination and from a comparison of their infrared absorption spectra.

Dicarboxylic Acid (VII).—To a solution of 4.9 g. of hibaene in 100 ml. of acetone, 7.5 g. of powdered potassium permanganate was added in portions over a period of 70 min. while the solution was maintained at 30—35°C. After the mixture had been stirred for an additional 90 min. at the same temperature, 30 ml. of water was added. The manganese dioxide formed was reduced by sulfur dioxide gas. The acetone was removed under reduced pressure, and the residue was acidified with diluted hydrochloric acid and extracted with ether. The ether solution was then extracted with a sodium carbonate aqueous solution. The acidification of the sodium carbonate extract yielded 4.17 g. of crystalline dicarboxylic acid, m. p. 240—250°C. Recrystallization from aqueous ethanol gave colorless needles, m. p. 251—253°C (dehydrated around 220°C and thus converted to anhydride).

Found: C, 71.57; H, 9.60. Calcd. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59%.

IR (KBr disk): ~2600, 1710 cm^{-1} (broad)(carboxyl).

The Dehydrogenation of Dicarboxylic Acid (VII) by Selenium.—A mixture of 2.0 g. of dicarboxylic acid and 4.0 g. of selenium was heated at 320—340 °C for 40 hr. The reaction mixture was extracted with ether, and the extract was washed with a 10% potassium hydroxide aqueous solution and water, dried over anhydrous magnesium sulfate, and distilled to yield 1.29 g. of a semisolid sudstance. This was purified by alumina column chromatography using 50 g. of alumina and petroleum ether - benzene (1 : 1) as the solvent, to give 0.41 g. of crystals. Recrystallization from ethanol gave colorless leaflets, m. p. 83—84°C, which were proved to be pimanthrene[14] by a mixed melting point determination and a comparison of their infrared absorption spectra.

Anhydride (IX).—After a mixture of 0.56 g. of dicarboxylic acid (VII) and 4 ml. of acetic anhydride had been refluxed for 1 hr., the excess acetic anhydride and acetic acid was distilled off under reduced pressure to yield 0.55 g. of a crystalline compound, m. p. 250—252°C. This was recrystallized from acetone to afford colorless needles, m. p. 253—254°C.

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12) All melting points are uncorrected. The authors wish to express their thanks to Misses Yoko Endo and Yukiko Endo of this Institute for their microanalyses.

13) Isostevane, m. p. 41.5—43.5°C; $[\alpha]_{300-700\mathrm{m}\mu}=0°$ (*c* 0.6, dioxane).

14) R. D. Haworth, B. M. Letsky and C. R. Mavin, *J. Chem. Soc.*, **1932**, 1789.

Found: C, 75.66; H, 9.71. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50%.

IR (KBr disk): 1790, 1758 cm^{-1} (anhydride).

This anhydride was recovered after the mixture had been heated at 300°C for 10 min. without any product being formed.

Dicarboxylic Dimethyl Ester (VIII).—A solution of 1.50 g. of dicarboxylic acid (VII) in 40 ml. of ether was methylated with a slight excess of a diazomethane etherial solution. When the reaction mixture was treated by the usual method, 1.58 g. of crude dimethyl ester, m. p. 141.5—143.5°C, was obtained. Recrystallization from aqueous ethanol gave colorless plates, m. p. 144—145°C.

Found: C, 72.42; H, 10.09. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96%.

IR (KBr disk): 1736, 1716 cm^{-1} (ester group).

After a solution of 0.73 g. of the dimethyl ester had been refluxed in 30 ml. of a 0.1 N potassium hydroxide methanolic solution for 2 hr., the reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with ether. The acidification of the water layer with diluted hydrochloric acid did not give any substance. From the ether extract, 0.73 g. of a crystalline compound, m. p. 143—144.5°C, was obtained. Recrystallization from diluted ethanol raised the melting point of the compound to 144—145°C; no depression of melting point was observed on admixture with VIII.

Ketones (XIII and XIV).—An excess of diborane was passed to a solution of 7.15 g. of hibaene in 70 ml. of anhydrous tetrahydrofuran under cooling with ice water and under a dry nitrogen atomosphere. After the solution had been allowed to stand at room temperature for 1 hr., the solvent was removed under reduced pressure and the residue was dissolved in 40 ml. of ether. To this solution was added a solution of 11.6 g. of sodium bichromate dissolved in a mixture of 30 ml. of water and 6.0 ml. of sulfuric acid; then the solution was refluxed gently while being stirred at around 40°C for 7 hr. After cooling, the water layer which separated from the ether layer was extracted with ether. The combined ether solution was washed with water and dried over anhydrous magnesium sulfate. The removal of the ether afforded 8.0 g. of a semisolid substance, which was purified by alumina chromatography (200 g. of alumina was used). From the petroleum ether effluent and the successive benzene effluent, 1.98 g. of an oil and 4.75 g. of a crystalline compound respectively were obtained. The crystalline compound was sublimed under reduced pressure (2 mmHg, bath temperature below 120°C) to yield 3.87 g. of crystalline sublimate. This sublimate was further purified using an alumina column containing 200 g. alumina. The results obtained were as follows: i) 0.34 g. of crystals (m. p. 73—84°C) from the petroleum ether - benzene (7 : 3) effluent; ii) 1.66 g. of crystals (m. p. 80—84°C) from the petroleum ether - benzene (5 : 5) effluent; iii) 1.01 g. of crystals (m. p. 66—88°C) from the same solvent as ii; iv) 0.95 g. of crystals (m. p. 95—102°C) from the same solvent as ii, followed by benzene.

Fractions i and ii were combined and recrystallized from methanol to give colorless prisms (XIII), m. p. 88—89°C.

Found: C, 83.19; H, 10.89. Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18%.

IR (KBr disk): 1725 cm^{-1}; (carbon tetrachloride solution): 1727 cm^{-1} (carbonyl group). RD (methanol solution c 0.1): $[\alpha]_{700}$ $-56°$, $[\alpha]_{589}$ $-81°$, $[\alpha]_{323}$ $-2040°$, $[\alpha]_{295}$ $+2010°$.

XIII did not react with 2, 4-dinitrophenylhydrazine or perbenzoic acid under conditions similar to those in the formation of lactone (X), and only the starting material was recovered.

The recrystallization of the crystals from fraction iv from methanol gave colorless prisms (XIV), m. p. 102—103°C.

Found: C, 83.22; H, 10.86. Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18%.

IR (KBr disk): 1733 cm^{-1}; (carbon tetrachloride solution): 1736 cm^{-1} (carbonyl group). RD (methanol solution c 0.1): $[\alpha]_{700}$ $+30°$, $[\alpha]_{589}$ $+48°$, $[\alpha]_{318}$ $+1528°$, $[\alpha]_{278}$ $-1720°$.

2, 4 - Dinitrophenylhydrazone; Recrystallization from ethanol-ethyl acetate gave orange needles, m. p. 231—231.5°C.

Found: N. 12.05. Calcd. for $C_{26}H_{34}O_4N_4$: N, 12.01%.

Lactone (XII).—A solution of 3.86 g. of XIV, 39 ml. of chloroform containing 2.42 g. of perbenzoic acid, 40 ml. of acetic acid and 0.45 ml. of sulfuric acid was allowed to stand at 10—20°C for 5 days. The reaction mixture was then poured into water, and the water layer was extracted with ether. The chloroform solution, combined with the ether extract, was washed with a 2% sodium hydroxide aqueous solution and water, and dried over anhydrous magnesium sulfate. The removal of the solvent gave a crystalline residue, which was purified by a neutral alumina column (100 g. of alumina was used). The crystals from the benzene and benzene-ether (1 : 1) effluents, 3.10 g., m. p. 100—110°C, were recrystallized from *n*-hexane, affording colorless needles, m. p. 111—112°C.

Found: C, 78.82; H, 10.49. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59%.

IR (KBr disk): 1713 cm^{-1} (lactone).

Summary

The structure and absolute configuration of hibaene, a new diterpene isolated from the essential oil of the leaves of hiba (*Thujopsis dolabrata* Sieb. et Zucc.), have been presented.

The authors are indebted to Dr. Yoshio Sato, National Institute of Health, for donating a sample of isostevane and also to the Ogawa Perfumery Co., Ltd., for supplying the original essential oil for this research.

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