UDC 547.913 : 582.998

148. Itiro Yosioka, Hiroshi Hikino, and Yasuko Sasaki : Studies on the Constituents of Atractylodes. IV.[1] The Structure of Hinesol. (1). The Skeleton.

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The crystalline sesquiterpenoid alcohol occurring in the essential oil present in the rhizomes of *Atractylodes lancea* De Candolle (Compositae) has long been considered to be a single substance and named atractylol. It has recently been recognized[1] to be a mixed crystal of eudesmol and hinesol. The purpose of the present investigation was to elucidate the structure of the latter sesquiterpenoid alcohol.

The presence of one ethylenic linkage in hinesol, $C_{15}H_{26}O$, apparent by color test (tetranitromethane), was confirmed by catalytic hydrogenation. Hinesol cannot be readily reduced, as already reported,[1] by using platinum black as a catalyst in neutral medium. Catalytic hydrogenation of hinesol over palladized charcoal furnished a saturated dihydrohinesol, $C_{15}H_{28}O$, m.p. 42~43°, $[\alpha]_D$ +21.6°. Hinesol must therefore be bicyclic. The difficulty of its hydrogenation suggests that the ethylenic linkage is most probably either a tri- or a tetra-substituted type.

The oxygen atom in hinesol was recognized to be present as a tertiary alcoholic group by (i) the difficulty of acetylation, (ii) the comparatively low reactivity with phthalic anhydride even at 130°, (iii) the ease of dehydration to a hydrocarbon or a mixture of hydrocarbons called hinesene, and (iv) the infrared absorption peaks at 923, 1133, and 3300 cm^{-1}.

As indicated above it was observed that hinesol readily lost water by treatment with various dehydrating agents such as formic acid, potassium hydrogen sulfate, and hydrochloric acid with the formation of a doubly unsaturated hydrocarbon, hinesene. This was shown to be a mixture of hydrocarbons in varying proportions from their physical constants, especially from the specific rotation, which exhibited a marked variation depending upon the dehydrating agents and conditions employed. As might have been expected from the variation of physical constants, the infrared spectra of dehydration products, obtained by treatment with various dehydrating agents, were not in agreement with each other. On the other hand, the same spectral charts were obtained with products from repeated experiments, as long as the same dehydrating agent was adopted, even when the physical constants showed considerable variation caused by differences in the dehydrating conditions. Presence of different classes of double bonds, viz. $RHC{=}CR'R''$ and $RR'C{=}CH_2$, was recorded in the infrared spectra, with maxima at 823~824 and 885~888 cm^{-1} assigned respectively to these olefinic double bonds. On detailed examination of the absorption, relative intensities of the bands due to ethylenic linkages indicated marked differences, as shown in Table I. Further, infrared absorption bands

Table I.

Dehydrating agent	Frequencies (in cm^{-1})			
Formic acid	1642w	1618w	888w	823w
HCl	1637m	1617w	885s	823s
$KHSO_4$	1640w	1611w	—	824s

Relative intensity : s, strong; m, medium; w, weak.

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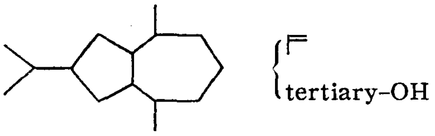
[1] Part III. I. Yosioka, S. Takahashi, H. Hikino, Y. Sasaki : This Bulletin, 7, 319(1959).

at ca. 1615 and 1640 cm^{-1}, and ultraviolet maximum at approximately 240 mμ could be taken as indicative also of the existence of conjugated double bonds in the hydrocarbons prepared by different ways. Moreover, the intensities of ultraviolet absorption at the peak were always almost constant (log ε 4) for the hydrocarbons obtained by any process. If conjugated double bonds exsisted in the molecule of hinesene, it would undergo normal reduction to the corresponding monoëne, dihydrohinesene, on treatment with sodium and alcohol. Attempt to obtain the reduction product was unsuccessful, recovering the starting material, hinesene. This failure can only be explained on the basis of the considerable resistance of the double bonds to reduction. This ultraviolet maximum at 240 mμ was eliminated by saturation of hinesene in acid solution using platinum black catalyst, yielding tetrahydrohinesene, $C_{15}H_{28}$. The fact detailed above suggests the site of the hydroxyl group that, when it is dehydrated, the newly created carbon-carbon double bond can conjugate with the original ethylenic linkage.

In a similar manner, dihydrohinesol was smoothly dehydrated by heating with formic acid to give a mixture of unsaturated hydrocarbons, best designated as isodihydrohinesene, $C_{15}H_{26}$. Its catalytic hydrogenation in the presence of palladized charcoal in methanol resulted in partial reduction to form a hydrocarbon mixture which was found to be still unsaturated by means of tetranitromethane and seemed to consist of the starting material, isodihydrohinesene, and a saturated product, isotetrahydrohinesene. The infrared spectrum of the mixture showed a marked absorption band at 824 cm^{-1}, confirming the retention of the structural feature, RHC=CR'R'', which was also present in the spectrum of the original isodihydrohinesene. This experiment suggests that the isodihydrohinesene is composed of a mixture of isomerides each of which showed a varying degree of resistance against catalytic hydrogenation. Complete hydrogenation of this mixture of partially reduced hydrocarbons could be carried out over platinum oxide in acetic acid. Direct saturation of isodihydrohinesene was effected in acetic acid solution using a platinum black catalyst to form isotetrahydrohinesene, $C_{15}H_{28}$.

The evidence for the carbon skeleton was obtained from dehydrogenation experiments on compounds derived from hinesol, affording a violet azulene. It was converted into a crystalline molecular compound, forming the derivative of vetivazulene, $C_{15}H_{18}$, identified by means of mixed fusion test and spectroscopic comparison with the authentic complex. This determined the relative positions of all 15 carbon atoms present in the alcohol.

On the basis of these experiments it was concluded that the functional groups of hinesol could be formulated as (I).



(I)

Hinesol is probably a sesquiterpenoid alcohol of a novel type having the skeleton derived from vetivazulene which has never been discovered in nature except in the components of the essential oil from vetiver. Moreover, it has been said[2)] that sesquiterpenoid compounds of both naphthalene types, eudesmol from eudalene and globulol from cadalene, should occur in the same oil of ***Eucalyptus globulus***. It is suprising that sesquiterpenoid derivatives of different skeleton types, indeed eudesmol from eudalene and hinesol from vetivazulene, should form mixed crystals, the so-called atractylol, which has long been regarded as a single substance.

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2) J. Simonsen, D. H. R. Barton : "The Terpenes," **III**, 153(1952). The Cambridge University Press, Cambridge.

The authors acknowledge their indebtedness to Assistant Prof. S. Takahashi for the provision of facilities and thank Dr. W. Herz, Department of Chemistry of the Florida State University, for a gift of the synthetic specimen of vetivazulene adduct. Thanks are also expressed to the Research Laboratory of Shionogi & Co., Ltd. and the members of Microanalytical Laboratory and of Photometric Laboratory of this Faculty for carrying out the microanalyses and the infrared spectral measurements.

Experimental*[2]

Hinesol—$C_{15}H_{26}O$, m.p. 59∼60°, $[\alpha]_D$ −40.2°(c=10.0); positive to tetranitromethane test, decolorized Br_2 solution, and rapidly reacted on heating with Denigé's reagent to form an orange precipitate.

Acetylation of Hinesol —Hinesol (4.3∼8.6 mg.) was esterified with approximately equimolar amount of phenylacetic acid at 155° for 1 hr. The product was dissolved in 50% EtOH (2 cc.) and titrated with $0.01N$ NaOH, several determinations giving the value of 7.4∼14.3 for the initial velocity index (reported[3]) index for tertiary alcohols, 1.1∼6.0; for secondary and primary alcohols, 24.5∼30.6 and 57.8∼62.3, respectively).

Reactivity of Hinesol with Phthalic Anhydride—Hinesol (4.6∼4.9 mg.) was reacted with about the equivalent weight of phthalic anhydride at 130° for 2 hr. The product was dissolved in EtOH (1 cc.), $0.01N$ NaOH (10.0 cc.) added, and titrated with $0.01N$ H_2SO_4. Duplicate analyses indicated that 30∼42% of the original alcohol was esterified.

Attempted Catalytic Reduction of Hinesol with Adams Catalyst in Methanol—Hinesol (0.5 g.) in MeOH (20 cc.) was shaken with PtO_2 (30 mg.) in H_2 atmosphere for 70 hr. H_2 uptake did not occur. After filtration, evaporation of the solvent gave a product which was crystallized from aqueous MeOH to unchanged hinesol, m.p. 58∼59°.

Catalytic Reduction of Hinesol with Palladized Charcoal in Methanol—Hinesol (4.0 g.) was hydrogenated over Pd-C (5%; 3.0 g.) in MeOH (40 cc.) for 5 hr. H_2 uptake ceased after absorption of 459 cc. (calcd. for 1 double bond : 403 cc.). The solution was filtered and evaporated. The residual oil crystallized from Me_2CO giving dihydrohinesol (II) as white needles, m.p. 42∼43°, $[\alpha]_D$ +21.6°(c=10.2). *Anal.* Calcd. for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found : C, 80.21; H, 12.52.

Dehydration of Hinesol with Formic Acid—(a) Hinesol (2.5 g.) was boiled with conc. formic acid (5 cc.) for 1 hr. The mixture was basified with Na_2CO_3 and extracted with Et_2O. After removal of the solvent from the dried ethereal extract, the residual oil was heated with a small piece of metallic Na for 1 hr. and fractionally distilled under reduced pressure, furnishing the hydrocarbon, hinesene (IIIa), as colorless, mobile liquid, $b.p_2$ 83∼86°, d_4^{25} 0.910, n_D^{25} 1.511, $[\alpha]_D$ +67.2°. *Anal.* Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found. C, 88.20; H, 12.09. UV : λ_{max} 240 mμ (log ε 4.06).

(b) Hinesol (1.5 g.) was mixed with conc. formic acid (3 cc.), shaken at room temperature for 30 min. When the material became completely fluidized, the mixture was heated on a steam bath for 2.5 hr. The product was extracted and purified in the same way as mentioned above to give hinesene (IIIb), $b.p_6$ 108∼109°, d_4^{25} 0.955, n_D^{25} 1.513, $[\alpha]_D$ +72.6°. *Anal.* Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found : C, 87.95; H, 11.68. UV : λ_{max} 240 mμ (log ε 4.07).

Dehydration of Hinesol with Potassium Hydrogen Sulfate—Hinesol (1.0 g.) and fused $KHSO_4$ (2.0 g.) were heated together at 180∼200° for 2 hr. Ether-extraction of the product gave a brown fluid which was purified by heating with metallic Na and fractionally distilled under a reduced pressure to yield hinesene (IIIc), $b.p_4$ 101∼104°, d_4^{25} 0.920, n_D^{25} 1.501, $[\alpha]_D$ +22.3°. *Anal.* Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11,84. Found : C, 87.79; H, 11.52. UV : λ_{max} 239 mμ (log ε 3.98).

Dehydration of Hinesol with Hydrochloric Acid—Hinesol (0.7 g.) was heated in AcOH (3 cc.), saturated with dry HCl gas, on a steam bath for 1 hr. The product was worked up in the usual way as described above, giving hinesene (IIId), $b.p_3$ 99∼101°, d_4^{25} 0.937, n_D^{25} 1.508, $[\alpha]_D$ +56.0°. *Anal.* Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found : C, 88.04; H, 11.56. UV : λ_{max} 240 mμ (log ε 3.96).

Attempted Reduction of Hinesene with Sodium and Ethanol—Hinesene (IIIa) (0.6 g.) in dehyd. EtOH (40 cc.) was treated with small pieces of metallic Na (3.0 g.) gradually added during 40 min. in the oil bath at 80∼90°. The solution was left at 90∼100°(bath-temp.) for 4 hr., after which water was added (40 cc.). EtOH was removed by distillation and the product was extracted from the aqueous layer with Et_2O. The Et_2O solution was washed with water, dried, and evaporated, leaving a colorless oil, $b.p_3$ 89∼91°, d_4^{25} 0.915, n_D^{25} 1.511, which was identical with the starting material by comparison of the infrared absorption spectra.

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*[2] All m.p.s and b.p.s are uncorrected. Ultraviolet spectra and specific rotations were measured in a solution of EtOH and $CHCl_3$, respectively, unless otherwise stated.

[3] S. Murahashi : Sci. Papers Inst. Phys. Chem. Research (Tokyo), **15**, 1197 (1936).

Catalytic Reduction of Hinesene with Adams Catalyst in Acetic Acid—Hinesene (IIIa) (0.5 g.) in AcOH (10 cc.) was hydrogenated in the presence of PtO_2 (40 mg.), taking up 116 cc. of H_2 (calcd. for 2 double bonds : 109 cc.). The product was isolated in the usual way and distilled to give the hydrocabon, tetrahydrohinesene (IVa), as a colorless, mobile liquid, b.p$_4$ 100°, d_4^{25} 0.889, n_D^{25} 1.479, α_D +2.1°. *Anal.* Calcd. for $C_{15}H_{28}$: C, 86.46; H, 13.54. Found : C, 86.41; H, 13.20.

Tests for unsaturated bonds with tetranitromethane and Br_2 were negative. The intensity of ultraviolet absorption over the range of 220~400 mμ was less than log ε 1.89 and no absorption maximum was found.

Dehydration of Dihydrohinesol with Formic Acid—Dihydrohinesol (2.0 g.) in conc. formic acid (6 cc.) was refluxed for 30 min. The mixture was basified with Na_2CO_3 and isolated by extraction with Et_2O. The washed and dried solution was evaporated and the residual oil was heated with metallic Na for 30 min. Fractional distillation gave a colorless hydrocarbon, isodihydrohinesene (Va), b.p$_5$ 97~98°, d_4^{25} 0.888, n_D^{25} 1.484, α_D +2.1°. *Anal.* Calcd. for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found. C, 87.61; H, 12.82.

Catalytic Reduction of Isodihydrohinesene with Palladized Charcoal in Methanol—Isodihydrohinesene (Va) (0.5 g.) in MeOH (30 cc.) with Pd-C (5%, 0.4 g.) absorbed 43 cc. of H_2 during 1 hr. (calcd. for 1 double bond : 54 cc.). The catalyst was filtered off. After evaporation of the solvent, distillation under a reduced pressure gave a product, d_4^{25} 0.876, n_D^{25} 1.475, α_D +0.8°. It exhibited a strong yellow color with tetranitromethane and immediately decolorized Br_2 solution.

This mixture of hydrocarbons (0.3 g.) was hydrogenated in AcOH (10 cc.) over PtO_2 (30 mg.) and the reduction ceased after 21 cc. of H_2 had been absorbed. The solution was basified and extracted with Et_2O, which was dried, and evaporated. The residue was distilled to give a colorless oil, b.p$_4$ 89°, d_4^{25} 0.872, n_D^{25} 1.474, α_D +0.8°. This substance gave no coloration with tetranitromethane and was identical in the infrared spectra with isotetrahydrohinesene, to be described below.

Catalytic Reduction of Isodihydrohinesene with Adams Catalyst in Acetic Acid—Isodihydrohinesene (Va) (0.5 g.), PtO_2 (40 mg.), and AcOH (10 cc.) were shaken in H_2 for 1.5 hr. Uptake of H_2 was 60 cc. (calcd. for 1 double bond : 48 cc.). The product was worked up in the usual way and purified by fractional distillation to the saturated hydrocarbon, isotetrahydrohinesene (VIa), as colorless liquid, b.p$_{6.5}$ 95~96°, d_4^{25} 0.874, n_D^{25} 1.474, α_D +1.0°. *Anal.* Calcd. for $C_{15}H_{28}$: C, 86.46; H, 13.54. Found : C, 86.90; H, 13.66. It gave a negative tetranitromethane test.

Dehydrogenation of Hinesol with Selenium—Hinesol (0.5 g.) and powdered Se (1.5 g.) were heated together at 280~290° for 2 hr. and at 290~310° for 1 hr. The product was extracted with Et_2O which was washed with 10% NaOH, dried, and evaporated to leave a liquid (0.4 g.). The benzene-soluble portion of this liquid was chromatographed on alumina and an azulene fraction (violet) was first obtained. It was converted to a 1,3,5-trinitrobenzene adduct (0.2 g.), m.p. 140~145°, which was crystallized from EtOH to the vetivazulene adduct as brownish violet needles, m.p. 151~152°. *Anal.* Calcd. for $C_{21}H_{21}O_6N_3$: C, 61.31; H, 5.15; N, 10.21. Found : C, 61.37;, H, 5.20, N, 10.25. This product showed no depression of m.p. on admixture with an authentic vetivazulene-trinitrobenzene complex, identified further by comparison of ultraviolet and infrared absorption spectra with the authentic compound. UV λ_{max} mμ : 246, 290, 332, 347 (authentic specimen : 246, 290, 332, 347 mμ).

This material was decomposed by passing its solution in light petroleum (b.p. 35~45°) through alumina to give free vetivazulene, identified by UV absorption over the range of 230~750 mμ. UV λ_{max}^{hexane} mμ : 291, 334, 349, 546, 575. The azulene gave crystalline products with picric acid and styphnic acid. Picrate, m.p. 122° (reported m.p. 121.5~122°). *Anal.* Calcd. for $C_{21}H_{21}O_7N_3$: N, 9.83. Found : N, 10.08. Styphnate, m.p. 97° (reported m.p. 95~96°). *Anal.* Calcd. for $C_{21}H_{21}O_8N_3$: N, 9.48. Found : N, 9.54.

Summary

Hinesol (I) contains an olefinic linkage since it furnished the saturated dihydrohinesol (II) on catalytic hydrogenation. The oxygen atom is present in a tertiary alcoholic group which was readily dehydrated by various agents to form a double bond which, in the case of (I), could conjugate with the original ethylenic linkage. Catalytic reduction of the anhydro derivatives of (I) and (II) gave the saturated bicyclic hydrocarbons. Dehydrogenation of (I) with selenium afforded vetivazulene.

(Received April 16, 1959)