thank Dr. K. Kotera for measurement of NMR spectra and very helpful cooperation in interpreting the spectra, and Mrs. F. Hisamichi and Mr. T. Kono for microanalyses.

Summary

Hydroboration of Δ^8-desoxycodeine (I) gave a B/C *trans*-fused morphine derivative, (−)-3-methoxy-8α-hydroxy-4,5α-oxy-N-methylisomorphinan (Ⅲ) along with two minor products, dihydropseudocodeine (Ⅳ) and Ⅶ. Ⅲ, by reaction with *p*-toluenesulfonylchloride gave the 8-*p*-toluenesulfonate (Ⅴc), which was treated with lithiun aluminum hydride to give (−)-3-methoxy-4,5α-oxy-N-methylisomorphinan (Ⅶ). Elimination reaction of Ⅴc with 2,4,6-collidine afforded two double-bond isomers, I and 3-methoxy-4,5α-oxy-Δ^7-N-methylisomorphinan (Ⅻ). I gave on hydrogenation the known dihydrodesoxycodeine (XⅢ). Hydrogenation of Ⅻ gave the B/C *trans* isomer, Ⅶ. Some additional studies were made on the hydroboration product (Ⅲ) and its derivatives to support the B/C *trans* pentacyclic structure.

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183. **Itiro Yosioka and Takeatsu Kimura** : Studies on the Constituents of Atractylodes. X.[*1] Correlation of Hinesol and β-Vetivone.

(*Faculty of Pharmaceutical Sciences, Osaka University*[*2])

In the preceding communication,[1] the formula (Ia) was proposed as the structure of hinesol (I), a sesquiterpene alcohol isolated from *Atractylodes lancea* De Candoll.[2] Subsequently, Šorm, *et al.* revised the formula to Ib, and ascertained the absolute configuration of a methyl group on $C_{(6)}$ with an oxidative degradation.[3] On the other hand, the structure of β-vetivone (Ⅱ) was established by St. Pfau and Plattner,[4] and the relative configurations of Ⅱ and α-vetivone (Ⅲ) were proposed by Naves and Perottet,[5] as expressed by the formula (Ⅱa) and (Ⅲa). The experiments described below made the interrelation between I and Ⅱ clear, and confirmed the structure of I. Furthermore, their absolute configurations were partially determined.

On oxidation of hinesol (I) with selenium dioxide in dioxane, a slightly yellow oil was obtained, which gave positive 2,4-dinitrophenylhydrazine-sulfuric acid test, and exhibited absorption maxima at 233.5 mμ (log ε 3.99) in ultraviolet, and 3500 (OH), 2730, 1685, 1626 (C=C-CHO), and 1418 cm^{-1} ($-CH_2-C=$) in infrared spectra. These data suggest that the oily substance contains mainly an α,β-unsaturated aldehyde as expressed by the formula (Ⅳ). So the formula (Ib) having a methyl group on the ethylenic linkage is preferred for I rather than Ia.

[*1] Part Ⅸ. This Bulletin, 12, 755 (1964).

[*2] Toneyama, Toyonaka, Osaka-fu (吉岡一郎, 木村孟淳).

1) I. Yosioka, Y. Sasaki, H. Hikino : This Bulletin, 9, 84 (1961).

2) S. Takahashi, H. Hikino, Y. Sasaki : Yakugaku Zasshi, 79, 544 (1959); I. Yosioka, S. Takahashi, H. Hikino, Y. Sasaki : This Bulletin, 7, 319 (1959).

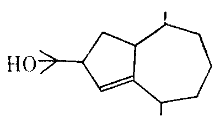
3) W.Z. Chow, O. Motl, F. Šorm : Collection Czechoslov. Chem. Communs., 27, 1914 (1962).

4) A. St. Pfau, Pl. A. Plattner : Helv. Chim. Acta, 23, 768 (1940).

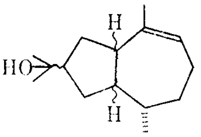
5) Y.R. Naves, E. Perottet : *Ibid.*, 24, 3 (1941).

Hinesol (I), on treatment with chromium trioxide-pyridine complex for one month, furnished a crystalline ketone (V), $C_{15}H_{24}O_2$, m.p. 73.5°. The structure of V was confirmed by the absorption maxima at 242 mμ (log ε 4.28) in ultraviolet, and 3530 (OH), 1656, 1607 (C=C-CO-), and 1414 cm^{-1} ($-CH_2-C=$) in infrared spectra, and the signal peaks at 8.98 (3H, doublet, J=6 c.p.s., $C_{(6)}-CH_3$), 8.76 (6H, singlet, $-C(OH)(CH_3)_2$), 8.02 and 4.23 τ (H, and 1H, doublets, J=1 c.p.s., $-CH=C(CH_3)-$) in nuclear magnetic resonane spectrum.

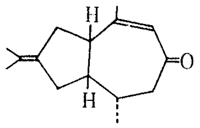
As a matter of course, it was expected that V would be derived to a compound of vetivone type with dehydration reaction. Then, in the first place, V was heated with fused potassium bisulfate and a yellowish brown oil, b.p$_5$ 160~180° (bath temp.), was obtained. In the gas chromatogram of this oily substance (Fig. 1a), a peak corresponding to II in oil of vetiver, together with seven other peaks of by-products was found. The chromatogram of a ketone fraction obtained from oil of vetiver (Fig. 1d) shows essentially same pattern with that of Nigam and Levi,[6] determined on a column of Reoplex 400 as the stationary phase. The peak of II was identified by separation with gas chromatography over the same stationary phase, and isolation in the form of 2,4-dinitrophenylhydrazone.



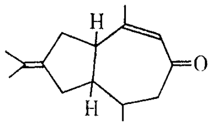
Ia



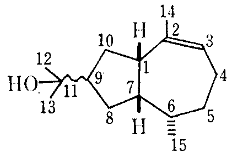
Ib



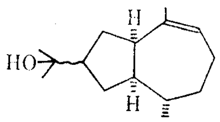
IIa



IIIa



Ic



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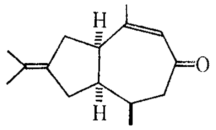
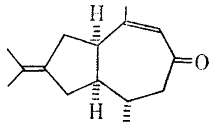
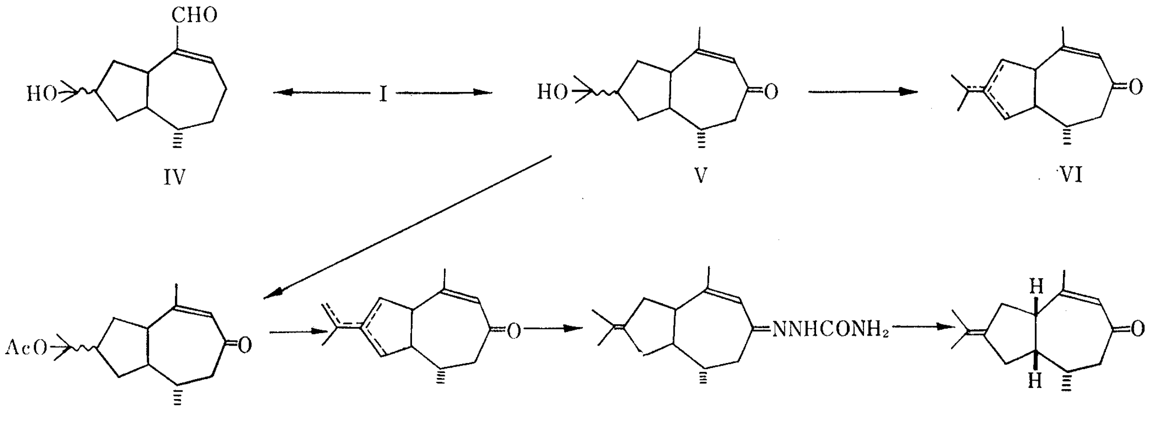


IIb



IIIb



IV V VI

VII VIII IX X

On heating with 90% formic acid, V also furnished a fragrant oil, b.p$_2$ 110~120° (bath temp.). The nuclear magnetic resonance spectrum shows that it is a mixture as expressed by the formula (VI), with these signal peaks; 4.75 τ (broad, olefinic proton) other than 4.19 τ ($C_{(3)}-H$), and 8.31 τ (singlet, $=C(CH_3)_2$) together with 8.91 τ (doublet, J=8 c.p.s., $-CH(CH_3)_2$). The gas chromatogram (Fig. 1b) shows also it is a mixture of three

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[6] I.C. Nigam, L. Levi: Can. J. Chem., **40**, 2083 (1962).

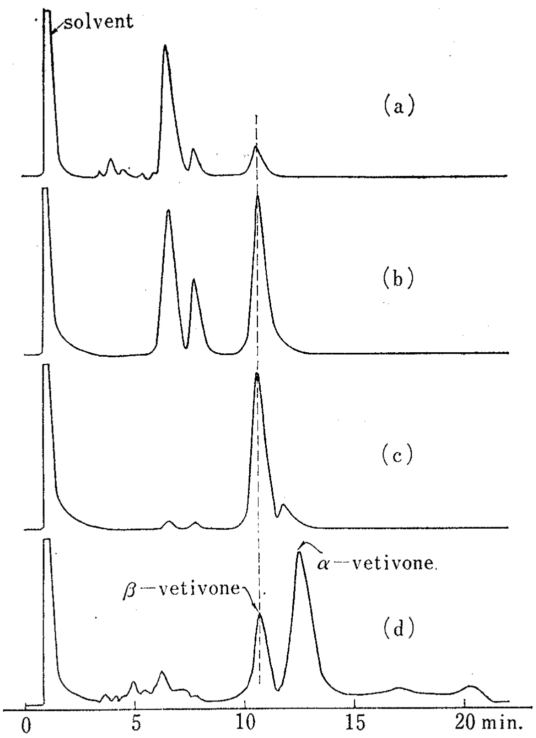

Fig. 1. Gas Chromatography of Dehydrated Products with (a) $KHSO_4$, (b) formic acid, and (c) Ac_2O-BF_3, and (d) a Ketone Fraction from Oil of Vetiver

compounds. But all efforts for further purification of above two reaction products were in vain.

With acetic anhydride, V was refluxed for four hours to give an acetate (VII), whose semicarbazone, m.p. 178°, $C_{18}H_{29}O_3N_3$, was obtained in colorless plates. The structure of VII was confirmed by the absorption maxima of acetoxyl bands at 1732, 1255, and 1136 cm^{-1}, besides disappearance of the hydroxyl band, in infrared spectrum.

This acetate (VII), on treating with boron trifluoride in ether, produced a slightly yellow fragrant oil, b.p$_2$ 135~140° (bath temp.), whose gas chromatogram (Fig. 1c) shows that the greater part of this product is the compound of the third peak (retention time at 10.7 min.), corresponding to II. In the nuclear magnetic resonance spectrum, a small signal peak at 5.21 τ to be assigned to the olefinic proton on the isopropenyl group in addition to 4.19 τ ($C_{(3)}$-H), was found. Therefore, this oily product is presumed to be a mixture as expressed by the formula VIII, containing mainly the desired 4-oxo-$\Delta^{9(11)}$-hinesene (X) of vetivone type compound.

This mixture (VIII) was converted into a semicarbazone, and the product was successively repeated recrystallization to give a colorless crystalline semicarbazone (IX), m.p. 222°, $C_{16}H_{25}ON_3$.

On hydrolysis with phthalic anhydride in boiling water, according to the preparative method of pure vetivone,[4] this semicarbazone (IX) regenarated pure 4-oxo-$\Delta^{9(11)}$-hinesene (X), b.p$_3$ 140~143° (bath temp.), which emits sweet smell like vetiver oil. The nuclear magnetic resonance spectrum shows the existence of three allylic methyl groups, and a methyl group on saturated carbon, with the signal peaks at 8.10 (3H, doublet, J=2 c.p.s., $C_{(2)}$-CH_3), 8.32, 8.34 (2×3H, singlets, isopropylidene), and 9.01 τ (3H, doublet, J=6.5 c.p.s., $C_{(6)}$-CH_3). The infrared spectra of X (Fig. 2), and its 2,4-dinitrophenylhydrazone (XI) are also exactly superimposable to those of β-vetivone (II) determined by Nigam and Levi,[6] and β-vetivone 2,4-dinitrophenlhydrazone (XII) respectively. In gas chromatography, X shows also the same retention time as II.

Although these data indicate the identity of their structure the melting point of a mixture of XI and XII depressed remarkably. Then the optical rotatory dispersion curve of X was compared with that of II, determined by Djerassi, *et al.*[7] As shown in Fig. 2 they have essentially symmetrical pattern each other, consequently it is

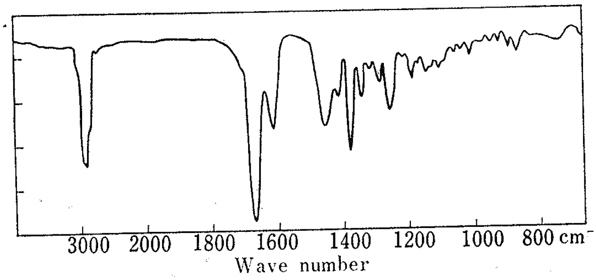

Fig. 2. Infrared Absorption Spectrum of 4-Oxo-$\Delta^{9(11)}$-hinesene (X)

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7) C. Djerassi, R. Riniker, B. Riniker : J. Am. Chem. Soc., 78, 6377 (1956).

evident that 4-oxo-$\Delta^{9(11)}$-hinesene (X) is the enantiomer of β-vetivone (II). This conclusion is supported by the fact that IX shows a specific rotation, $[\alpha]_D$, of $+62.2°$, while that of β-vetivone semicarbazone is $-71.1°$.[5]

Since the relative configurations of the hydrogen atoms at $C_{(1)}$ and $C_{(7)}$ of II and III had been established by Naves and Perottet[5] as *cis*, and the absolute configuration of the methyl group at $C_{(6)}$ of hinesol (I), by Šorm,[3] *et al.*, as [*S*] configuration, it is concluded that hinesol (I) has the structure as expressed by the formula (Ic) of 1[*S*], 6[*S*], 7[*S*], or Id of 1[*R*], 6[*S*], 7[*R*]-configuration. And it is also concluded that the absolute configuration of $C_{(6)}$-methyl groups of β-vetivone (II) is [*R*]-configuration.

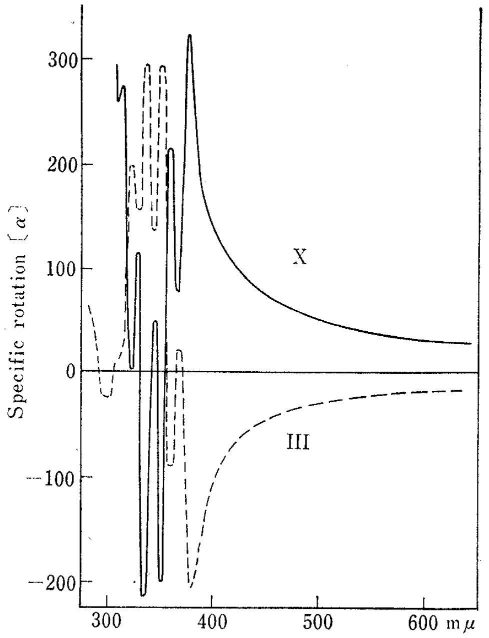

Fig. 3. Optical Rotatory Dispersion Curves of 4-Oxo-$\Delta^{9(11)}$-hinesene (X), and β-Vetivone (II)[7]

On the basis of presumption, proposed by Naves and Perottet,[5] that the relative configurations of $C_{(6)}$-methyl group and $C_{(7)}$-hydrogen atom of II and III are *trans* and *cis* as expressed by the formula IIa and IIIa respectively, I, II and III must have the structure as expressed by the formulas Ic, IIb and IIIb respectively. But because the experiments of Naves and Perottet suggest only the relative configuration of $C_{(6)}$-methyl group and $C_{(7)}$-hydrogen atom, it can not be defined whether the absolute configurations of $C_{(6)}$-methyl group of II and III are different each other or not. Therefore, possibility that III has the structure as expressed by the mirror image of the formula IIIb is still remained.

Studies on the absolute configuration of the hydroxyisopropyl group at $C_{(9)}$ of hinesol (I) are in proceeding.

Experimental[*3]

Oxidation of Hinesol (I) with Selenium Dioxide——Hinesol (I) was disolved in a solution of SeO_2 (0.5 g.) in dioxane (5 ml.), and refluxed for 4 hr. After cooling, the precipitated selenium was filtered off, and the solvent was removed from the filtrate *in vacuo*. The brown residue was taken up in petroleum ether, and chromatographed on alumina. From the $CHCl_3$-eluate, a slightly yellow oil was obtained, which gave positive 2,4-dinitrophenylhydrazine-sulfuric acid test. UV λ_{max} mμ (log ε): 233.5 (3.99), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500, 2950, 2730, 1685, 1626, 1462, 1418, 1380, 1366, 1170, 935, 858.

4-Oxo-hinesol (V)——To a slurry of CrO_3 (1.0 g.) in pyridine (10 ml.), a solution of hinesol (I) (0.7 g.) in pyridine (10 ml.) was added, and allowed to stand at room temperature for 1 month. The reaction mixture was diluted with H_2O, and extracted with ether. The ether layer was washed with H_2O, dried, and evaporated *in vacuo*, leaving a slightly yellow oil. The oily mixture was dissolved in benzene, and chromatographed on alumina. Initially unreacted I was eluted (ca. 0.2 g.), and the second eluate was recrystallized from hexane, and gave 4-oxohinesol (V) (0.38 g.) as colorless needles, m.p. 73.5°, $[\alpha]_D$ $-91.3°$ ($c=3.56$, $CHCl_3$), UV λ_{max} mμ (log ε): 242 (4.28). IR ν_{max}^{Nujol} cm^{-1}: 3530, 1656, 1607, 1414. NMR: 4.23 (doublet, $J=1$ c.p.s., $C_{(3)}$-H), 8.02 (doublet, $J=1$ c.p.s., $C_{(2)}$-CH_3), 7.5~7.8 (multiplet, $C_{(5)}$-H_2 and $C_{(10)}$-H),

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[*3] All melting points were uncorrected. IR spectra were recorded with a NaCl prism on a Hitachi Infrared Spectrophotometer EPI-S2. UV spectra were taken in 95% EtOH solutions with a Hitachi Recording Spectrophotometer EPS-2. NMR spectra were determined at 60 Mc. in $CDCl_3$ solutions containing tetramethylsilane as an internal standard using a Varian A-60 Analytical NMR Spectrometer. Gas-liquid chromatography (GLC), unless otherwise stated, was carried out on a Yanagimoto Gas Chromatograph GCG-3DH with a hydrogen flame ionization detector GCF-103; 5% ethylene glycol adipate polyester (m.p. 40°) on Cerite 545 (60~80 mesh), 0.5×200 cm., at 210°, N_2 60 ml./min.

8.76 (singlet, $-C(OH)(CH_3)_2$), 8.98 τ (doublet, J=6 c.p.s., $C_{(6)}-CH_3$). *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found : C, 76.08; H, 10.19.

Dehydration of V with Potassiun Bisulfate——A mixture of 4-oxohinesol (V) (216 mg.) and fused $KHSO_4$ (440 mg.) was heated at 190～210° for 2 hr. After cooling, H_2O was added and the solution was extracted with ether. The ether layer was dried, evaporated, heated with metalic sodium, and distilled in reduced pressure. The obtained yellowish brown oil, b.p$_5$ 160～180° (bath temp.) was submitted to gas chromatography. GLC : (retention time) 3.45, 4.05, 4.6, 6.0, 6.6, 7.8, 10.7 min. (Fig. 1a).

Dehydration of V with Formic Acid——A solution of 4-oxohinesol (V) (103 mg.) in 90% formic acid (0.3 ml.) was refluxed for 1 hr. at 120～130°. After neutralizing with Na_2CO_3, the reaction mixture was extracted with ether. The ether layer was dried and evaporated. On distillation in reduced pressure, a slightly yellow oil (VI), b.p$_2$ 110～120° (bath temp.), was obtained. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1} : 2960, 1670, 1617, 1450, 1417, 1378, 1289, 1249, 1190. UV $\lambda_{\max}$ mμ : 241. NMR : 4.20 (singlet), 4.75 (broad), 7.50～8.04, 8.09 (doublet, J=2 c.p.s.), 8.13 (singlet), 8.31 (singlet), 8.91 (doublet, J=8 c.p.s.), 9.02 τ (doublet, J=7 c.p.s.). GLC : (retention time) 6.6, 7.8, 10.7 min. (Fig. 1b).

4-Oxohinesol Acetate (VII)——A solution of 4-oxohinesol (V) (117 mg.) in acetic anhydride (2.5 ml.) was refluxed for 4 hr. After removing the excess of reagent, the residue was distilled in reduced pressure to give 4-oxohinesol acetate (VII) (100 mg.), b.p$_3$ 150～165°, as a slightly yellow oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1} : 2950, 1732, 1670, 1618, 1450～1470, 1412, 1379, 1363, 1255, 1136, 1016.

Semicarbazone, colorless plates, m.p. 178°. *Anal.* Calcd. for $C_{18}H_{29}O_3N_3$: C, 64.45; H, 8.72; N, 12.53. Found : C, 64.32; H, 8.60; N, 12.56.

4-Oxo-$\Delta^{9(11)}$-hinesene (X)——To a solution of 4-oxohinesol acetate (VII) (101 mg.) in dried ether (2 ml.), boron trifluoride etherate (0.5 ml.) was added, and allowed to stand at room temperature for 1 hr. After degradation of the excess of reagent with 5% K_2CO_3, the reaction mixture was extracted with ether. The ether layer was dried, evaporated, and distilled in reduced pressure leaving a slightly yellow oil (VIII), b.p$_2$ 135～140° (bath temp.). GLC : (retention time) 6.6, 7.8, 10.7, 11.8 min. (Fig. 1c).

The oil (VIII) was converted into a semicarbazone in usual manner, and repeated recrystallization from EtOH. And 4-oxo-$\Delta^{9(11)}$-hinesene semicarbazone (IX), m.p. 222°, was obtained as colorless needles, $[\alpha]_D$ +62.2° (c=4.28, HOAc). *Anal.* Calcd. for $C_{16}H_{25}ON_3$: C, 69.78; H, 9.15; N, 15.26. Found : C, 69.75; H, 9.12; N, 15.02.

A mixture of this semicarbazone (IX) (260 mg.) and phthalic anhydride (260 mg.) in H_2O (30 ml.) was refluxed for 9 hr., neutralized with Na_2CO_3, and extracted with petroleum ether. After removing the solvent, the residue was distilled in reduced pressure, and 4-oxo-$\Delta^{9(11)}$-hinesene (X) (66.5 mg.), b.p$_3$ 140～143° (bath temp.), $[\alpha]_D$ +38.03° (c=0.66, EtOH), was obtained. UV $\lambda_{\max}$ mμ (log ε) : 240 (4.11). IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1} : 2950, 2910, 1670, 1614, 1449, 1415, 1375, 1245. NMR : 4.19 (1H, doublet, J=2 c.p.s.), 8.10 (3H, doublet, J=2 c.p.s.), 8.32 (3H, singlet), 8.34 (3H, singlet), 9.01 τ (3H, doublet, J=6.5 c.p.s.). ORD*4 : (c=0.50, dioxane) $[\alpha]_{650}$ +30°, $[\alpha]_{589}$ +30°, $[\alpha]_{400}$ +140°, $[\alpha]_{378}^{\mathrm{peak}}$ +322°, $[\alpha]_{367}^{\mathrm{trough}}$ +78°, $[\alpha]_{360}^{\mathrm{peak}}$ +212°, $[\alpha]_{350}^{\mathrm{trough}}$ −204°, $[\alpha]_{346}^{\mathrm{peak}}$ +50°, $[\alpha]_{335}^{\mathrm{trough}}$ −216°, $[\alpha]_{328}^{\mathrm{peak}}$ +114°, $[\alpha]_{322}^{\mathrm{trough}}$ 0°, $[\alpha]_{815}^{\mathrm{peak}}$ +274°, $[\alpha]_{312}^{\mathrm{trough}}$ +258°.

2,4-Dinitrophenylhydrazone (XI), m.p. 188～191°. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1} : 3320, 1629, 1592, 1497, 1413, 1337, 1310, 1251, 1222, 1127. *Anal.* Calcd. for $C_{21}H_{26}O_4N_4$: C, 63.30; H, 6.58; N, 14.06. Fonud : C, 63.33; H, 6.74; N, 14.20.

β-Vetivone 2,4-Dinitrophenylhydrazone (XII)——The Ketone fraction (b.p$_4$ 140～160°), separated from vetiver oil in the manner of St. Pfau and Plattner,[8] was submitted to analytical, GLC : (retention time) 3.6, 4.1, 4.9, 5.5, 6.3, 7.3, 10.7, 12.5, 17.0, 20.3 min. (Fig. 1d), and preparative gas chromatography,*5 and thus crude β-vetivone (II) was isolated. The crude β-vetivone was converted into a 2,4-dinitrophenylhydrazone in usual manner, and repeated recrystallization from EtOH to give pure β-vetivone 2,4-dinitrophenylhydrazone (XII) as red plates, m.p. 188～191°. *Anal.* Calcd. for $C_{21}H_{26}O_4N_4$: C, 63.30; H, 6.58. Found : C, 63.32; H, 6.75. The infrared spectrum was exactly superimposable with that of XI. A mixture of XI and XII melted at 158～162°.

The authors are indebted to Reserch Laboratory, Takeda Chemical Industries, Ltd. and Reserch Laboratory, Dainippon Pharmaceutical Co. Ltd. for determination of NMR spectrum, and to Analytical Laboratory, Faculty of Pharmaceutical Sciences, Osaka University for elemental analyses.

Summary

The enantiomer of β-vetivone (II) was synthesized from hinesol (I), *via* an α,β-unsaturated ketone (V), and its acetate (VII), and thus the absolute configurations of I and II were proposed as expressed by the formula (Ic) and (IIb) respectively.

(Received June 7, 1965)

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*4 Recorded with a Rudolf Automatic Recording Spectropolarimeter 260/655/850.

*5 With thermal conductivity detector; 25% ethylene glycol adipate polyester, 0.5×200 cm., at 220° N_2 70 ml./min.

[8] A. St. Pfau, Pl. Plattner : Helv. Chim. Acta, 22, 640 (1939).