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40. Hiroshi Hikino, Yasuko Hikino, Yasuyoshi Takeshita, Kazuko Shirata, and Tsunematsu Takemoto : Structure and Absolute Configuration of Kessane.[*1]

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Kessane, the sesquiterpenoid oxide isolated from Japanese valerians, has been elucidated to have the stereostructure I on the basis of its spectroscopic and chemical studies and derivation from 2-*epi*-α-kessyl alcohol (Ⅵ; R=H). On Huang-Minlon reduction both α-kessyl ketone semicarbazone (V; R=$NNHCONH_2$) and isokessyl ketone (Ⅶ) have been found to give the same product which is considered to be a mixture of kessane (I) and isokessane (Ⅱ).

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In continuation of our work on the analysis of the constituents of Japanese valerians, we have isolated the new sesquiterpenoid oxide, kessane,[1~3] whose structure and absolute configuration, as shown in formula I, are described in the present paper.[*3]

Kessane analyzed in accordance with the empirical formula $C_{15}H_{26}O$. The ethereal nature of the oxygen atom in the molecule is suggested by the infrared spectrum which reveals the absence of any bands attributable to either hydroxyl or carbonyl grouping, but the presence of a band in the oxidic region at 1095 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum of kessane shows the presence of a secondary methyl and also three unsplit methyl groups attached to the same carbons as the oxygen atom. Further, there are no signals attributed to hydrogen on the carbons bearing the oxidic function which is, therefore, required to be di-tertiary. Of the three double-bond equivalents shown by the molecular formula, one has been accounted for as an oxide bridge. Since no sign of unsaturation can be found, it must be concluded that kessane contains two carbocyclic rings. Thus, on dehydrogenation with sulfur, kessane gave S-guaiazulene (Ⅲ); a result which indicates it to have the guaiane carbon skeleton. The mass spectrum of kessane exhibits the expected molecular ion peak at *m/e* 222. Although peaks at *m/e* 126 (base peak) and below are less indicative of the structure, the fragmentation pattern is identical with that of α-kessyl alcohol (Ⅳ) in this region but there are minor differences in the relative intensities of certain peaks. These results, together with the common occurrence of α-kessyl alcohol and kessane, show the latter to be the deoxy-derivative of the former as being the most probable structure.

Consequently, in order to confirm this conclusion, our next endeavor was directed toward a synthesis of kessane from a substance of known structure. This was achieved in the following way. In the first attempt, α-kessyl ketone semicarbazone (V; R=$NNHCONH_2$) was reduced by the Wolff-Kishner procedure whereupon the deoxo-derivative was obtained. Although this product analyzed correctly for the molecular formula required and gave a single peak on vapor phase chromatography, it was considered to be a mixture of kessane (I) and its isomer (Ⅱ) in the approximate ratio

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[*1] This paper forms Part Ⅷ in the series on Sesquiterpenoids. Preceding paper, Part Ⅶ, S. Itô, M. Kodama, T. Nozoe, H. Hikino, Y. Hikino, Y. Takeshita, T. Takemoto : Tetrahedron, **23**, 553 (1967).

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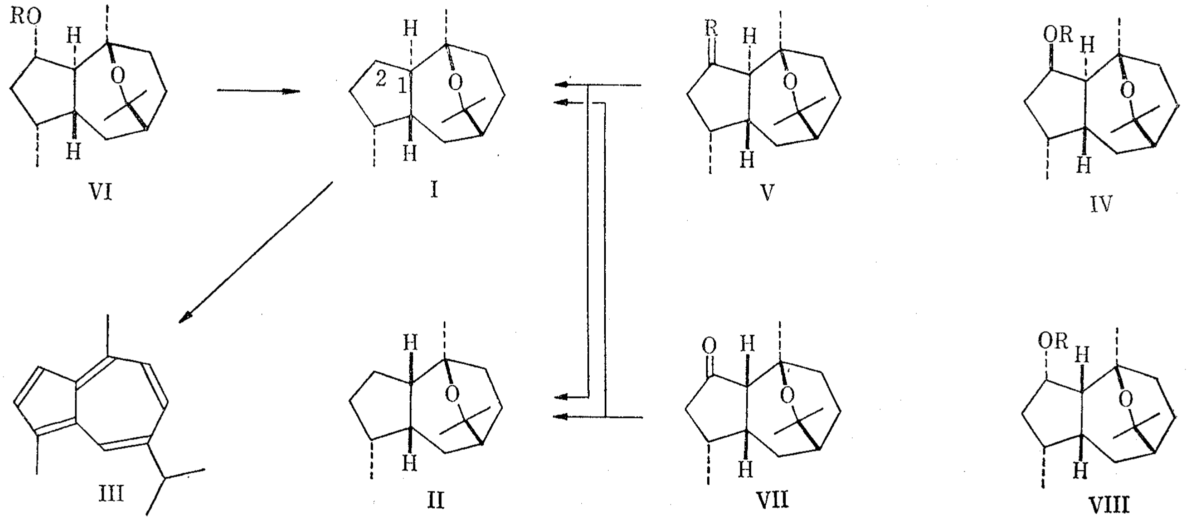
[*3] A part of this work has been outlined in a preliminary communication : This Bulletin, **11**, 547 (1963).

1) H. Hikino, Y. Hikino, H. Kato, Y. Takeshita, T. Takemoto : Yakugaku Zasshi, **83**, 219 (1963).
2) H. Hikino, Y. Hikino, Y. Takeshita, Y. Isurugi, T. Takemoto : *Ibid.*, **83**, 555 (1963).
3) H. Hikino, Y. Hikino, Y. Takeshita, H. Kato, T. Takemoto : *Ibid.*, **85**, 179 (1965).

of 2:3 by the data which follow. The infrared spectrum exhibits no hydroxyl nor carbonyl absorption, but, in addition to the band at 1095 cm^{-1} due to kessane, a band at 1078 cm^{-1} indicating the presence of another oxide. In the NMR spectrum all signals associated with kessane are present whilst another set of signals, namely a methyl doublet and also three methyl singlets on carbons bearing an oxygen, can be seen. Isomerization of α-kessyl ketone (V; R=O), protected as the semicarbazone during Wolff-Kishner reduction, is other than expected since the mechanism of Wolff-Kishner reduction is not known to involve isomerization, *e.g.*, epimerization, at the point α to the carbonyl group. An alternative approach was therefore sought. Attempts to obtain the *p*-toluenesulfonate of α-kessyl alcohol (Ⅳ; R=H) with tosyl chloride in pyridine were abortive, however, because the alcohol (Ⅳ; R=H) was recovered exclusively. In the next trial, tosylation of 2-*epi*-α-kessyl alcohol (Ⅵ; R=H) was employed to give the corresponding *p*-toluenesulfonate (Ⅵ; R=Ts). Reduction with lithium aluminum hydride of the sulfonate (Ⅵ; R=Ts) furnished, together with a small amount of the original alcohol (Ⅵ; R=H), a synthetic kessane which was identical in all respects with the natural kessane. This interconversion from 2-*epi*-α-kessyl alcohol (Ⅵ; R=H) to kessane has established that kessane possesses the same absolute configuration as that of α-kessyl alcohol, since α-kessyl alcohol (Ⅳ; R=H) and 2-*epi*-α-kessyl alcohol (Ⅵ; R=H) have been established as epimers at C-2.4) As the structure and absolute configuration of α-kessyl alcohol (Ⅳ; R=H) has rigorously been elucidated,4) kessane is, therefore, represented by stereoformula I.

For the structural investigation of α-kessyl alcohol and its derivatives, and in particular for the stereochemical study on their NMR spectra, it was required that the deoxy-derivative of isokessyl alcohol, isokessane (Ⅱ), be prepared for use as a reference compound. Thus Huang-Minlon reduction of isokessyl ketone (Ⅶ) was performed; the product so obtained, however, was found to be the same mixture of the two oxides, I and Ⅱ, that had been derived from α-kessyl ketone semicarbazone (V; $R=NNHCONH_2$) on Wolff-Kishner reduction. In confirmation, a modified Huang-Minlon procedure, in which the ketone (Ⅶ) was first reacted with hydrazine hydrate and then treated with alkali, was also carried out to give the same result. Originally, isokessyl ketone (Ⅶ) was prepared by the isomerization of α-kessyl ketone (V; R=O) with alkali; the equilibrium between these ketones lying exclusively in favor of the former. Therefore, the conversion of α-kessyl ketone semicarbazone (V; $R=NNHCONH_2$)



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4) S. Itô, M. Kodama, T. Nozoe, H. Hikino, Y. Hikino, Y. Takeshita, T. Takemoto: Tetrahedron Letters, **1963**, 1787; Tetrahedron, **23**, 553 (1967).

into the mixture of the two oxides as well as the reconversion of isokessyl ketone (VII) to the same mixture seem to indicate that an equilibrium between the hydrazones of both the epimeric ketones may be present and this may be considerably inclined toward the α-isomer under the conditions employed. Attempts at lithium aluminum hydride reduction of 2-*epi*-isokessyl tosylate (VIII; R=Ts) led to an unexpected mixture, the components of which could not be elucidated. Although we have failed to obtain a pure sample of isokessane, the oxide which was formed together with kessane on Wolff-Kishner reduction of both α-kessyl ketone semicarbazone (V; R=NNHCONH$_2$) and isokessyl ketone (VII), is reasonably considered as being the C-1 epimer of kessane, *i.e.*, a *cis* ring-fused isomer (isokessane (II)), from the infrared and NMR properties.

Experimental[*4]

Kessane——$C_{15}H_{26}O$, mol. wt. 222 (mass spec.), b.p$_6$ 110~112°, d_4^{25} 0.970, n_D^{25} 1.491, $[\alpha]_D$ −7.2°(c=10.0), IR (liquid) cm^{-1}: 1095 (oxide), NMR: doublet (3H) at 9.23 τ (J=6.0, $C\underline{H}_3$-CH<), two singlets (3H and 6H, respectively) at 8.98 and 8.82 τ ($C\underline{H}_3$-C<O-).

Dehydrogenation of Kessane with Sulfur——Kessane (270 mg.) and S (270 mg.) were heated together at 230~250° for 6 hr. The mixture was dissolved in light petroleum, washed with *N* NaOH solution and then with H_2O, dried (Na_2SO_4), and evaporated to give the product (108 mg.) which was chromatographed on alumina (5 g.). Elution with light petroleum afforded S-guaiazulene (III) as a blue oil which was converted into the 1,3,5-trinitrobenzene adduct (50 mg.) crystallized from EtOH as dark violet needles, m.p. 147~149°. Identification was carried out in the usual criteria.

Wolff-Kishner Reduction of α-Kessyl Ketone Semicarbazone——A mixture of α-kessyl ketone semicarbazone (V; R=NNHCONH$_2$) (0.52 g.) and KOH (0.41 g.) in triethylene glycol (3 ml.) was kept at 190~200° for 4 hr. The cooled solution was diluted with H_2O and extracted with ether. The product (0.35 g.) in light petroleum was adsorbed on alumina (10 g.). Fractions eluted with the same solvent gave the mixture (0.15 g.) of kessane (I) and isokessane (II) as a colorless mobile oil, b.p$_6$ 110~111°, d_4^{25} 0.970, n_D^{25} 1.490, $[\alpha]_D$ +10.2°, (c=10.1), *Anal.* Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.94; H, 11.76. IR (liquid) cm^{-1}: 1092, 1078 (oxide). NMR: doublet at 9.23 τ (J=6.0), singlets at 8.98, 8.80 τ (kessane) and doublet at 9.11 τ (J=6.3), singlets at 8.95, 8.80 τ (isokessane).

Attempted Tosylation of α-Kessyl Alcohol——α-Kessyl alcohol (IV) (100 mg.) in pyridine (2 ml.) was treated overnight with TsCl (100 mg.) at room temperature. Upon isolation in the usual manner, the product (90 mg.) was crystallized from light petroleum to give the recovered alcohol (IV) as colorless prisms, m.p. and mixed m.p. 85~86°.

Tosylation of 2-*epi*-α-Kessyl Alcohol——2-*epi*-α-Kessyl alcohol (VI; R=H) (1.07 g.) in pyridine (5 ml.) was treated overnight at room temperature with TsCl (2.14 g.). The reaction mixture was poured into crushed ice and extracted with ether. The product (1.20 g.) was crystallized from light petroleum to give 2-*epi*-α-kessyl *p*-toluenesulfonate (VI; R=$SO_2C_6H_4CH_3$) as colorless needles, m.p. 96~97°, *Anal.* Calcd. for $C_{22}H_{32}O_4S$: C, 67.31; H, 8.22. Found: C, 67.34; H, 8.25. IR (KBr) cm^{-1}: 1602, 1355, 1172 (tosylate).

Reduction of 2-*epi*-α-Kessyl Tosylate with Lithium Aluminum Hydride——A mixture of the *p*-toluenesulfonate (VI; R=$SO_2C_6H_4CH_3$) (0.20 g.) and excess $LiAlH_4$ in ether (10 ml.) was stirred overnight at room temperature. The product (0.17 g.) from ether extraction was percolated through alumina (10 g.).

Light petroleum eluted an oily fraction distilled under reduced pressure to yield kessane (I) as a colorless mobile oil, b.p$_5$ 105°, d_4^{25} 0.969, n_D^{25} 1.492, $[\alpha]_D$ −4.9° (c=9.8), *Anal.* Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.94; H, 11.76. IR (liquid) cm^{-1}: 1095 (oxide). NMR: doublet (3H) at 9.23 τ (J=6.0; $C\underline{H}_3$-CH<), two singlets (3H and 6H, respectively) at 8.98 and 8.82 τ ($C\underline{H}_3$-C<O-). The identity with the natural kessane was established by the identical retention time on VPC (Carbowax 6000 and silicone SE 30) and the identical IR and NMR spectra.

Elution with ether gave a crystalline fraction crystallized from light petroleum to afford 2-*epi*-α-kessyl alcohol (VI; R=H) as colorless needles, m.p. 107~108°. The identity was established in the usual criteria.

Wolff-Kishner Reduction of Isokessyl Ketone——a) A mixture of isokessyl ketone (VII) (0.41 g.), KOH (0.42 g.), and $NH_2NH_2 \cdot H_2O$ (80%; 2.7 ml.) in triethylene glycol (7 ml.) was heated gradually to remove NH_2NH_2 and H_2O and kept at 190~200° for 4 hr. After isolation the product in light petroleum was filtered through alumina to afford the mixture of kessane (I) and isokessane (II) as a colorless mobile oil, b.p$_5$ 106°, d_4^{25} 0.975, n_D^{25} 1.491, $[\alpha]_D$ +11.8° (c=11.9), *Anal.* Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.73; H,

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[*4] Melting points and boiling points are uncorrected. Specific rotations were measured in $CHCl_3$ solution. NMR spectra were determined at 60 Mc.p.s. in CCl_4 solution against Me_4Si as internal standard. Chemical shifts are expressed in τ-values and coupling constants (J) in c.p.s.

11.73. IR (liquid) cm^{-1}: 1087, 1078 (oxide), NMR: doublet at 9.22 τ (J=5.9), singlets at 8.98, 8.80 τ (kessane) and doublet at 9.11 τ (J=6.2), singlets at 8.95, 8.80 τ (isokessane).

b) A mixture of isokessyl ketone (VII) (0.10 g.), and $NH_2NH_2 \cdot H_2O$ (80%, 1.5 ml.) in EtOH (2 ml.) was refluxed for 2 hr. and triethylene glycol (2.5 ml.) was added. The mixture was then heated gradually to remove NH_2NH_2 and H_2O, and after addition of KOH (0.4 g.) maintained at 190~200° for 3 hr. Upon isolation, the product (87 mg.) was purified as previously giving the mixture of kessane (I) and isokessane (II) as a colorless mobile oil, which was identified as that obtained above by means of thin-layer chromatography (TLC), VPC, IR and NMR spectra.

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41. Hiroshi Hikino, Yasuko Hikino, Yasuyoshi Takeshita, Kazuko Shirata, Masayasu Ono, and Tsunematsu Takemoto: Structure and Absolute Configuration of Kessanol and 8-*epi*-Kessanol.[*1]

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The sesquiterpenoid alcohols, kessanol and 8-*epi*-kessanol, isolated from certain kinds of Japanese valerian, have been shown to be 2-deoxykessyl glycol (I; R=H) and 2-deoxy-8-*epi*-kessyl glycol (III; R=H), respectively, by physicochemical studies of the alcohols and their oxidation products, kessan-8-one (II). The mixture of the two alcohols (I and III; R=H) has been synthesized from kessyl glycol (IV; R=H, R'=H). The configuration of the hydroxyl at C-8 as being α in kessanol and β in 8-*epi*-kessanol has been confirmed by application of the dissymmetry rule.

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During chemical studies on the valerian roots, we have recently isolated the new sesquiterpenoid oxido-alcohols, kessanol and 8-*epi*-kessanol, as the constituents of certain kinds of Japanese valerian.[1~2] The present communication describes the evidence which leads to the establishment of the structure and absolute configuration of kessanol and 8-*epi*-kessanol as depicted in formulae I (R=H) and III (R=H), respectively.

Kessanol naturally occurs as the oily acetate (I; $R=COCH_3$) whose infrared spectrum shows acetoxyl absorption at 1736 and 1234 cm^{-1} as well as oxide absorption at 1081 cm^{-1}. On alkaline hydrolysis, kessanyl acetate (I; $R=COCH_3$) gave the crystalline alcohol (I; R=H), kessanol, which exhibits bands in the infrared for hydroxyl at 3378 cm^{-1} and for an oxide function at 1096 cm^{-1}. The alcohol and its acetate analyzed for $C_{15}H_{26}O_2$ and $C_{17}H_{28}O_3$, respectively, and the molecular weight of the former was confirmed by mass spectrometry. The nuclear magnetic resonance (NMR) spectra of both the compounds reveal the presence of a doublet methyl (9.18 or 9.19τ), three unsplit methyls (8.97,

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[*1] This paper constitutes Part IX in the series on Sesquiterpenoids. Preceding paper, Part VIII, H. Hikino, Y. Hikino, Y. Takeshita, K. Shirata, T. Takemoto: This Bulletin, **15**, 321 (1967).

[*2] Kita-4-bancho, Sendai (ヒキノヒロシ, 曳野靖子, 竹下保義, 白田和子, 小野雅康, 竹本常松).

[*3] A preliminary report of this work has been published; H. Hikino, Y. Hikino, Y. Takeshita, T. Takemoto: This Bulletin, **11**, 952 (1963).

1) H. Hikino, Y. Hikino, Y. Takeshita, Y. Isurugi, T. Takemoto: Yakugaku Zasshi, **83**, 555 (1963).

2) H. Hikino, M. Ono, Y. Takeshita, T. Takemoto: Unpublished data.