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61. Hiroshi Hikino, Yasuyoshi Takeshita, Yasuko Hikino, Tsunematsu Takemoto,*1 and Shô Itô*2: Structure and Absolute Configuration of β-Kessyl Ketone and β-Kessyl Alcohol.*3

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β-Kessyl ketone obtained by acid-catalyzed isomerization of α-kessyl ketone (II) has been converted into the known β-kessyl alcohol which has been dehydrogenated to give *S*-guaiazulene (V). From chemical and physical evidence on a number of their derivatives, structures III and IV (R=H) are proposed for β-kessyl ketone and β-kessyl alcohol, respectively.

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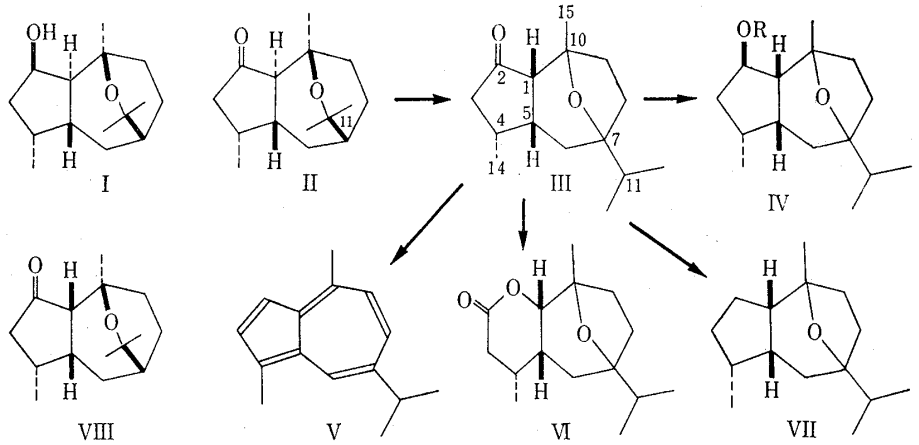
During the structural investigation of the sesquiterpenoid α-kessyl alcohol, one of the main constituents of the Japanese valerian "Kesso", Asahina, *et al.* found that the alcohol and its derivatives were readily isomerized.[1] *Inter alia*, α-kessyl ketone, when treated with hydrochloric acid in ethanol, underwent some rearrangement yielding an isomeric ketone which was designated as β-kessyl ketone.[2] Preliminary work on its chemistry was continued by the same authors[3~5] who recorded the following facts. The ketone was also prepared by treatment with hydrochloric acid in ethanol on isokessyl ketone or deoxy-α-kessyl ketone dichloride. Further, β-kessyl ketone on reduction with sodium and ethanol afforded β-kessyl alcohol, an isomer of α-kessyl alcohol, which was oxidized with chromic acid to regenerate the origlnal ketone. The ketone on treatment with sodium and amyl formate gave the oxymethylene compound.



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*3 Announced previously; This Bulletin, **13**, 520 (1965). This paper is Part X in the Medical School series on Sesquiterpenoids. Preceding paper, Part IX, H. Hikino, Y. Hikino, Y. Takeshita, K. Shirata, M. Ono, T. Takemoto: This Bulletin, **15**, 324 (1967).

1) For the general aspects, see J. Simonsen, P. de Mayo: "Terpenes," **V**, 564 (1957), Cambridge University Press, London.
2) Y. Asahina, G. Hongo: Yakugaku Zasshi, No. 506, 227 (1924).
3) Y. Asahina, S. Nakanishi: *Ibid.*, No. 536, 823 (1926).
4) *Idem*: *Ibid.*, No. 544, 485 (1927).
5) *Idem*: *Ibid.*, No. 599, 21 (1932).

Contrasting with the other isomers, the most striking feature was that on dehydrogenation with active carbon neither β-kessyl alcohol nor β-kessyl ketone yielded guaiazulene. However, no structural assignments have hitherto been made. After our recent studies on the structure and absolute configuration of α-kessyl alcohol (I) were complete[6] our endeavor was then directed toward structural elucidation of β-kessyl ketone and β-kessyl alcohol. New evidence which we now present shows the structure and the partial absolute configuration of β-kessyl ketone to be represented by formula Ⅲ and of β-kessyl alcohol to be formula Ⅳ (R=H).

β-Kessyl ketone, prepared by a modification of Asahina's method, was confirmed as having molecular weight 236, and by elemental analysis as having the empirical formula $C_{15}H_{24}O_2$. Reduction of the ketone with sodium and ethanol or lithium aluminum hydride gave the known alcohol, β-kessyl alcohol.

Our first effort was to establish the carbon skeleton. As mentioned above, it has previously been found that α-kessyl alcohol and its derivatives, except the compounds in the β-series, tend to be easily dehydrogenated even with charcoal alone to give guaiazulene, while β-kessyl alcohol and β-kessyl ketone are resistant to dehydrogenation with charcoal failing to afford the azulene.[5] On the basis of these results, the carbon skeleton has been considered to have changed remarkably during the rearrangement from α-kessyl ketone to β-kessyl ketone. Dehydrogenation of β-kessyl alcohol with palladized charcoal was now carried out and yielded *S*-guaiazulene (Ⅴ) indicating retention of the guaiane skeleton of the molecule, provided that no rearrangement had taken place during the dehydrogenation. This is supported by the nuclear magnetic resonance (NMR) spectra of several derivatives which show the presence of three doublet methyls and also an unsplit methyl group attached to the same carbon atom as an oxygen function (*vide infra*).

The infrared spectrum of β-kessyl ketone exhibits a band at 1727 cm^{-1} attributable to a cyclopentanone moiety. In addition there is absorption at 1406 cm^{-1} due to a methylene α to the carbonyl; this is consistent with the previous observation that the ketone gave the oxymethylene compound.[3] Further, base-catalyzed deuteration of β-kessyl ketone was carried out; the product was shown, by molecular weight measurement, to be the trideuterio-derivative. These facts show that the carbonyl group lies between a methylene and a methine group. On Baeyer-Villiger oxidation β-kessyl ketone gave a δ-lactone (Ⅵ) whose NMR spectrum shows a doublet equivalent to one hydrogen on the carbon bearing the lactonic oxygen. This observation dismisses the possibility of the carbonyl group occurring at C-3, since the signal, which is due to the C-4 hydrogen in this case, must be coupled with the C-14 methyl protons and cannot be a doublet. Therefore, the carbonyl group must be at the C-2 position of the guaiane skeleton.

Of the four double-bond equivalents indicated by the empirical formula of β-kessyl ketone, three have been accounted for as a carbonyl group and two carbocyclic rings. Since there is neither another carbonyl nor double bond in the molecule, it must, therefore, be concluded that β-kessyl ketone contains the second oxygen atom as an oxide function, a fact which is also suggested by an infrared band at 1038 cm^{-1}. For confirmation of this assignment, removal of the oxygen function from the C-2 position was required. It has previously been observed in α-kessyl ketone (Ⅱ) and isokessyl ketone (Ⅷ) that Wolff-Kishner reduction causes inversion at the bridge head position adjacent to the carbonyl group, furnishing the equilibrium mixture with respect to the ring junction even from the more stable isomer, siokessyl ketone (Ⅷ), which has a *cis* ring fusion. In order to prevent such a complexity, therefore, an alternative approach was

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

sought. Attempts to obtain the deoxy-derivative of β-kessyl alcohol by reduction of its crystalline tosylate (Ⅳ; R=Ts) with lithium aluminum hydride were abortive, however, since the parent alcohol (Ⅳ; R=H) was exclusively regenerated. Huang-Minlon reduction of β-kessyl ketone was, therefore, performed to give the deoxo-derivative (Ⅶ), β-kessane, which possessed an infrared band at 1043 cm^{-1} showing the continued presence of the oxide function. The coexistence of the epimer at the ring junction was however precluded in this case since the vapor phase chromatograms and the NMR spectrum show this substance to be homogeneous. As has been described before, the NMR spectra of β-kessyl ketone and its derivatives display the presence of an unsplit methyl and three secondary methyls, two of which must be due to an isopropyl group. This evidence indicates that the ether linkage has migrated from the C-11 position of α-kessyl ketone (Ⅱ) with simultaneous formation of an isopropyl grouping. Since no signal is present between 6 and 7τ (except the C-2 hydrogen signal in β-kessyl alcohol), the nuclear skeleton contains neither primary nor secondary oxidic group. This observation, coupled with the chemical shifts and splitting patterns of the remaining two methyl signals required that the ethereal oxygen must be bound to C-4 or C-10 and C-1 or C-5 or C-7. Furthermore, the presence of an epoxide ring in β-kessyl ketone can be excluded by considering its mode of formation under strongly acidic conditions and its stability to alkali. Although a number of points of attachment of the oxide bridge are possible, these observations, together with the presence of the C-1 hydrogen signal as a doublet in the NMR spectrum of the lactone (Ⅵ), lead to 7,10-oxidoguaiane for the skelton.

On the basis of the above evidence, the constitutional problem on β-kessyl ketone and β-kessyl alcohol can be considered to be settled completely in terms of the structures Ⅲ and Ⅳ (R=H) but without stereochemistry, respectively; the question remaining being their stereochemistry which will be discussed below.

In an attempt to obtain 2-*epi*-β-kessyl alcohol the reduction products of β-kessyl ketone were examined, but no indication could be found for the presence of the epimer. Although the comparable data of the C-2 epimers, therefore, are not available, on application of the "benzoate rule"[7] to β-kessyl alcohol (Ⅳ; R=H) and its benzoate (Ⅳ; R=Bz), the molecular rotation difference ($\Delta[M]_D$ −73°) shows the configuration at C-2 to be *R*; *i.e.*, the C-2 hydroxyl group is β-oriented.

Considering the course of the rearrangement from α-kessyl ketone (Ⅱ) to β-kessyl ketone (Ⅲ) (*vide infra*), it is unlikely that the configuration at C-4 has been inverted. Consequently, the C-4 methyl group is anticipated to retain the original configuration, *i.e.*, an α-orientation. The assignment is supported by the following NMR evidence; comparison of the C-14 methyl proton signals of β-kessyl alcohol (9.13τ), its acetate (Ⅳ; R=Ac) (9.11τ) and β-kessane (Ⅶ) (9.12τ) reveals no influence from the 2β-hydroxyl group in β-kessyl alcohol, as is observed in the case of a pseudo-1,3-diaxial relationship in a cyclopentane ring;[6,8] thus both functions must be situated in the *trans* relation in the alcohol (Ⅳ).

The configuration of the C-1 hydrogen and the C-5 hydrogen is established in the following manner. In the NMR spectrum of the lactone (Ⅵ), the coupling constant of the doublet shown by the C-1 hydrogen is 3.5 c.p.s. which can occur only when the hydrogens at C-1 and C-5 are in a *cis* configuration ($\theta=\sim60°$[9]). As Baeyer-Villiger oxidation is known to proceed with retention of configuration,[10] the *cis* geometry of the lactone (Ⅵ) must also apply to the original ketone (Ⅲ). The *cis* ring fusion was

7) J. H. Brewster : Tetrahedron, **13**, 106 (1961).
8) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, K. Tsuda : This Bulletin, **10**, 338 (1962).
9) M. Karplus : J. Chem. Phys., **30**, 11 (1959).
10) C. H. Hassall : "Organic Reactions", **9**, 73 (1957), John Wiley & Sons. Inc., New York.

further indicated by the absence of epimerization of the ketone (Ⅲ) on alkali treatment. The optical rotatory dispersion of the ketone (Ⅲ) shows a negative Cotton effect ($a=-132$) which is very similar to that of isokessyl ketone (Ⅷ) in shape thus establishing the absolute configuration at C-1 as *S*, *i.e.*, the C-1 hydrogen as β; whereupon that of the C-5 hydrogen is also β.

The configuration at C-7 and C-10 has now to be taken into consideration, because the oxide bridge may not retain the original configuration during the conversion from α-kessyl ketone (Ⅱ) to β-kessyl ketone (Ⅲ) (*vide infra*). In the nuclear magnetic resonance spectra, a downfield shift (−0.15 p.p.m.) is disclosed by the C-15 methyl proton signal of β-kessyl alcohol (Ⅳ; R=H) from that of β-kessane (Ⅶ). Acetylation resulted in an upward shift(+0.15 p.p.m.) for the methyl resonance reverting to the original position. These observations show the spatially close location of the C-10 methyl and the C-2 β-hydroxyl group. This is supported by the fact that the amplitude of the optical rotatory dispersion curve of β-kessyl ketone (Ⅲ) was not reduced by the addition of acid demonstrating that the (hemi)ketal formation was obstructed by a new steric interaction between the oxygenated substituent at C-2 and the methyl group at C-10. A remarkable downfield shift (−0.40 p.p.m.) for the C-15 methyl proton signal of β-kessyl ketone (Ⅲ) due to the anisotropy of the C-2 carbonyl group leads to the assumption that the methyl group lies almost in the plane of the carbonyl group. However, judging by inspection of Dreiding models, those spatially close relations between the C-10 methyl group and the C-2 oxygen functions do not permit any definite conclusion about the configuration of the C-10 methyl group (*i.e.*, of the oxide bridge) to be given due to the flexible nature of the molecules. No other evidence is presently available on this point and, therefore, further studies are required.

Experimental*4

Preparation of β-Kessyl Ketone——A solution of α-kessyl ketone (Ⅱ) (537 mg.) in EtOH (2 ml.) and conc. HCl (5 ml.) was allowed to attain 25° and kept for 5 days. The mixture was diluted with H_2O, made alkaline with Na_2CO_3, and extracted with ether. The product (520 mg.) in benzene was percolated through a column of alumina (20 g.). Removal of the solvent from the filtrate (200 ml.) gave a solid (456 mg.) which was crystallized from light petroleum to afford β-kessyl ketone (Ⅲ) as colorless needles, m.p. 109~110°, $[\alpha]_D$ −182.7° (c=5.0), ORD (c=0.184, MeOH): $[M]_{324}^{trough}$ −7400°, $[M]_{321}^{peak}$ −6600°, $[M]_{316}^{trough}$ −7200°, $[M]_{287}^{peak}$ +5800° (the curve being not changed upon addition of acid), mol. wt. 236 (mass spec.), *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.06; H, 10.35. IR (KBr) cm^{-1}: 1727 (cyclopentanone), 1406 (methylene α to carbonyl), 1038 (ether). NMR: doublet (6H) at 9.12 τ (J=7.2, $(C\underline{H}_3)_2CH$-), doublet (3H) at 8.96 τ (J=5.4, $C\underline{H}_3$-CH<), singlet (3H) at 8.48 τ ($C\underline{H}_3$-C≤O-).

Reduction of β-Kessyl Ketone with Sodium and Ethanol——A solution of β-kessyl ketone (Ⅲ) (500 mg.) in EtOH (10 ml.) was heated under reflux and treated with metallic Na (0.5 g.) added portionwise. The mixture was kept at 100° for 4 hr. The product was precipitated by the addition of H_2O and collected by filtration. Crystallization from light petroleum afforded β-kessyl alcohol (Ⅳ; R=H) as colorless needles, m.p. 150.5~151°, $[\alpha]_D$ −15.1°(c=5.3), *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.58; H, 11.23. IR (KBr) cm^{-1}: 3290 (hydroxyl), 1030 (ether). NMR: doublet (9H) at 9.13 τ (J=6.5, $C\underline{H}_3$-CH<), singlet (3H) at 8.73 τ ($C\underline{H}_3$-C≤O-), multiplet (1H) at 5.70 τ ($\underline{H}$-C≤OH).

Reduction of β-Kessyl Ketone with Lithium Aluminum Hydride——A mixture of β-kessyl ketone (Ⅲ) (500 mg.) and excess $LiAlH_4$ in ether (10 ml.) was stirred at room temperature for 1 hr. The product was isolated in the customary manner and crystallized from light petroleum to yield β-kessyl alcohol (Ⅳ; R=H) as colorless needles, m.p. 149~150°, $[\alpha]_D$ −15.1°(c=5.6). IR (KBr) cm^{-1}: 3300 (hydroxyl), 1030 (ether), which was undepressed on admixture with that obtained above.

Dehydrogenation of β-Kessyl Alcohol with Palladized Charcoal——β-Kessyl alcohol (Ⅳ; R=H) (100 mg.) and Pd-C (10%; 150 mg.) were heated together at 260~300° in an atmosphere of N_2 for 10 min. The product was dissolved in light petroleum and placed on a column of alumina (1.0 g.). Elution with light

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

petroleum yielded *S*-guaiazulene (V) as a blue oil. UV λ_{max}^{EtOH} mμ : 237 (i*5), 243, 280 (i), 285, 289 (i), 304, 349, 366, 603 (the curve being overlapped with that of an authentic sample). The trinitrobenzene adduct crystallized from EtOH as dark violet needles, m.p. 147~149°, *Anal.* Calcd. for $C_{21}H_{21}O_6N_3$: N, 10.21. Found: N, 10.16, showing no melting point depression on admixture with an authentic specimen.

Base-catalyzed Deuteration of β-Kessyl Ketone——A solution of β-kessyl ketone (Ⅲ) (50 mg.) in *N* NaOD (1 ml.) and dioxane (1 ml.) was heated under reflux for 10 min. and the solvent was removed under reduced pressure. The same procedure of experiments was repeated further three times. The product from ether extraction was crystallized from light petroleum to give trideuterio-β-kessyl ketone as colorless needles, m.p. 108~109°, mol. wt. 239 (mass spec.). IR (KBr) cm^{-1} : 2208 (C-D), 1727 (cyclopentanone), 1035 (ether).

Baeyer-Villiger Oxidation of β-Kessyl Ketone——A mixture of β-kessyl ketone (Ⅲ) (300 mg.) and perbenzoic acid (368 mg.) in $CHCl_3$ (13 ml.) was set aside at 25° for 14 days. The mixture was washed with 3% NaOH solution and then with H_2O, dried (Na_2SO_4), and evaporated to afford a solid which on crystallization from light petroleum yield β-kessyl lactone (Ⅵ) as colorless needles, m.p. 156.5~157.5°, $[\alpha]_D$ −2.5°(c=9.7), *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found : C, 71.27; H, 9.48. IR (KBr) cm^{-1} : 1727, 1242 (δ-lactone), 1035 (ether). NMR : doublet (9H) at 9.08 (J=7.2, $C\underline{H}_3$-CH<), singlet (3H) at 8.60 τ ($C\underline{H}_3$-C≤O-), doublet (1H) at 6.10 τ (J=3.5, $\underline{H}$-C≤O-CO-).

Tosylation of β-Kessyl Alcohol——β-Kessyl alcohol (Ⅳ; R=H) (250 mg.) in pyridine (7 ml.) was treated overnight at room temperature with TsCl (500 mg.). After isolation, the product (311 mg.) was crystallized from light petroleum to give β-kessyl *p*-toluenesulfonate (Ⅳ; R=Ts) as colorless needles, m.p. 77~78°, *Anal.* Calcd. for $C_{22}H_{32}O_4S$: C, 67.31; H, 8.22. Found : C, 67.35; H, 8.14. IR (KBr) cm^{-1} : 1600, 1328, 1168 (tosylate), 1040 (ether).

Attempted Reduction of β-Kessyl Tosylate with Lithium Aluminum Hydride——A mixture of the *p*-toluenesulfonate (Ⅳ; R=Ts) (100 mg.) and excess $LiAlH_4$ in ether (5 ml.) was stirred at room temperature for 8 hr. The product was isolated in the usual manner and crystallized from light petroleum gave β-kessyl alcohol (Ⅳ; R=H), m.p. and mixed m.p. 150~151°.

Huang-Minlon Reduction of β-Kessyl Ketone——A solution of β-kessyl ketone (100 mg.) and 80% $NH_2NH_2 \cdot H_2O$ (0.6 ml.) in EtOH (1 ml.) was refluxed for 1 hr. After the addition of KOH (0.1 g.) and triethyl ene glycol (2 ml.), $NH_2NH_2 \cdot H_2O$ and EtOH was then removed by distillation and the mixture was kept at 190~195° for 4 hr. The product was isolated with ether and distilled under diminished pressure to give β-kessane (Ⅶ) as a colorless mobile oil, n_D^{25} 1.476, $[\alpha]_D$ +5.6°(c=10.0), *Anal.* Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found : C, 80.84; H, 11.81. IR (liquid) cm^{-1} : 1043 (ether). NMR : doublet (3H) at 9.12 τ (J=7.1, $C\underline{H}_3$-CH<), doublet (6H) at 9.09 τ (J=6.2, $(C\underline{H}_3)_2$CH-), singlet (3H) at 8.88 τ ($C\underline{H}_3$-C≤O-).

Benzoylation of β-Kessyl Alcohol——β-Kessyl alcohol (100 mg.) in pyridine (1 ml.) was treated overnight at room temperature with BzCl (0.1 ml.). Isolation of the product and crystallization from light petroleum gave β-kessyl benzoate (Ⅳ; R=Bz) as colorless needles, m.p. 56.5~57°, $[\alpha]_D$ −70.4°(c=5.5), *Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found : C, 76.81; H, 8.56. IR (KBr) cm^{-1} : 1715, 1279 (ester), 3106, 1605, 1116, 707 (phenyl), 1026 (ether).

Acetylation of β-Kessyl Alcohol——β-Kessyl alcohol (200 mg.) was acetylated (Ac_2O-AcONa) by refluxing 3 hr. Isolation of the product and distillation under reduced pressure gave β-kessyl acetate (Ⅳ; R=Ac) as a colorless oil, d_D^{25} 1.020, n_D^{25} 1.475, $[\alpha]_D$ −67.3°(c=10.0), *Anal.* Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found : C, 72.75; H, 10.01. IR (liquid) cm^{-1} : 1736, 1250 (acetoxyl), 1032 (ether). NMR : doublet (6H) at 9.14 τ (J=6.9, $(C\underline{H}_3)_2$CH-), doublet (3H) at 9.11 τ (J=7.1, $C\underline{H}_3$-CH<), singlet (3H) at 8.88 τ ($C\underline{H}_3$-C≤O-), singlet (3H) at 8.08 τ ($C\underline{H}_3$-CO-O), multiplet (1H) at 4.94 τ ($\underline{H}$-C≤OAc).

Attempted Isomerization of β-Kessyl Ketone with Alkali——β-Kessyl ketone (50 mg.) in 1% ethanolic KOH solution (1.0 ml.) was heated under reflux for 1 hr. Removal of the solvent and addition of H_2O deposited the product which was collected by filtration and crystallized from light petroleum to give the recovered β-kessyl ketone (Ⅲ) as colorless needles, m.p. 107~108°, which was undepressed when mixed with the starting ketone (Ⅲ); IR spectra of both samples ware identical.

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*5 i : inflection.