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Structure of β-Kessyl Ketone and β-Kessyl Alcochol

During the structural investigation of α-kessyl alcohol, Asahina, *et al.*[1,2] found that α-kessyl ketone gave, with hydrochloric acid and ethanol, an isomer, β-kessyl ketone, which on reduction with sodium and ethanol afforded β-kessyl alcohol. Although work on the chemistry of these two compounds was continued by the same authors,[2~4] no structure has been proposed. Recently, the structures (I) and (II) were attributed to α-kessyl alcohol and α-kessly ketone, respectively, by the present authors.[5] This communication provides evidence from which the structures (III) and (IV) are assigned for β-kessyl ketone and β-kessyl alcohol, respectively.

β-Kessyl ketone (III), mol. wt. 236 (mass spec.), $C_{15}H_{24}O_2$, m.p. 109~110°, $[\alpha]_D$ −182.7°,[*1] was reduced with sodium and ethanol to give β-kessyl alcohol (IV), $C_{15}H_{26}O_2$, m.p. 150.5~151°, $[\alpha]_D$ −15.1°, which on chromic acid oxidation reverted to III.

Dehydrogenation of IV with palladized charcoal afforded S-guaiazulene (V) which indicates the retention of the guaiane skeleton of the molecule.

In the infrared spectrum, III shows bands at 1727 (cyclopentanone) and 1406 cm^{-1} (methylene adjacent to carbonyl). Base-catalyzed replacement of the active hydrogen in III for deuterium afforded the trideuterio-β-kessyl ketone, mol. wt. 239 (mass spec.), m.p. 108~109°, infrared bands at 2208 (C–D) and 1727 cm^{-1} (cyclopentanone). Baeyer-Villiger oxidation of III gave the lactone (VI), $C_{15}H_{24}O_3$, m.p. 156.5~157.5°, $[\alpha]_D$ −2.5°, infrared bands at 1727, 1242 cm^{-1} (δ-lactone), whose nuclear magnetic resonance spectrum ($CDCl_3$) shows the signal of the hydrogen on the carbon bearing the lactonic oxygen as a doublet at 6.10 τ. These findings indicate that the carbonyl group remains at C-2.

In addition to the carbonyl group, III contains an inert oxygen atom assumed to be an ether from the infrared band at 1038 cm^{-1}. This was confirmed by the fact that Huang-Minlon reduction gave the oxide (VII), β-kessane, $C_{15}H_{26}O$, n_D^{25} 1.476, $[\alpha]_D$ +5.6°, infrared band (liquid) at 1043 cm^{-1} (oxide). The nuclear magnetic resonance spectra of III, IV ($CDCl_3$), and VII display, besides a singlet due to a tertiary methyl and a doublet due to a secondary methyl group, a doublet associated with two secondary methyl groups. This evidence indicates that the ether linkage has migrated from the C-11 position of II with simultaneous formation of an isopropyl group. As no signal appears in the 6~7 τ region (except the C-2 hydrogen signal in IV), the skeleton contains no primary nor secondary oxidic group. Furthermore, the presence of a three-membered oxide ring in III can be excluded by considering its mode of formation and stability to alkali. These observations, coupled with the presence of the C-1 hydrogen signal as a doublet in the nuclear magnetic resonance spectrum of VI, lead to 7,10-oxido-guaiane for the skeleton of III, IV, and VII.

On application of the "benzoate rule"[6] to β-kessyl alcohol (IV) and its benzoate, $C_{22}H_{30}O_3$, m.p. 56.5~57°, $[\alpha]_D$ −70.4°, 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.

[*1] Analytical values are in good agreement with the molecular formulae shown. $[\alpha]_D$s refer to $CHCl_3$ solutions and IR spectra to KBr disks unless otherwise indicated. NMR spectra were measured at 60 Mc. in CCl_4 *vs.* $(CH_3)_4Si$ as internal reference unless specified to the contrary.

1) Y. Asahina, G. Hongo: Yakugaku Zasshi, No. 506, 227 (1924).
2) Y. Asahina, S. Nakanishi: *Ibid.*, No. 536, 823 (1926).
3) *Idem*: *Ibid.*, No. 544, 485 (1927).
4) *Idem*: *Ibid.*, No. 599, 21 (1932).
5) S. Itô, M. Kodama, T. Nozoe, H. Hikino, Y. Hikino, Y. Takeshita, T. Takemoto: Tetrahedron Letters, 1787 (1963).
6) J. H. Brewster: Tetrahedron, 13, 106 (1961).

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 have an α-orientation. This assignment was supported by the following nuclear magnetic resonance evidence: comparison of the C-4 methyl signals of Ⅳ (9.13 τ), its acetate [$C_{17}H_{28}O_3$, n_D^{25} 1.475, $[\alpha]_D$ −67.5°] (9.11 τ), and Ⅶ (9.12 τ) reveals no influence from the 2β-hydroxyl group in Ⅳ, as is observed in the case of a pseudo-1,3-diaxial relationship in a cyclopentane ring;[5,7] thus both the functions must be situated in the *trans* relation in Ⅳ.

The configuration of the C-1 hydrogen and the C-5 hydrogen was established in the following manner. In the nuclear magnetic resonance 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 ($\theta = \sim 60°$[8]). As Baeyer-Villiger oxidation is known to proceed with retention of configuration,[9] the *cis* geometry of Ⅵ must also apply to Ⅲ. The *cis* ring fusion was further indicated by the absence of epimerisation of Ⅲ on alkali treatment. The optical rotatory dispersion of Ⅲ shows a negative Cotton effect ($[\alpha]_{324}^{\text{trough}}$ −3130°, $[\alpha]_{321}^{\text{peak}}$ −2750°, $[\alpha]_{316}^{\text{trough}}$ −3050°, $\alpha_{287}^{\text{peak}}$ +2450°, in MeOH) thus establishing the configuration of the C-1 hydrogen as β; whereupon that of the C-5 hydrogen is also β.

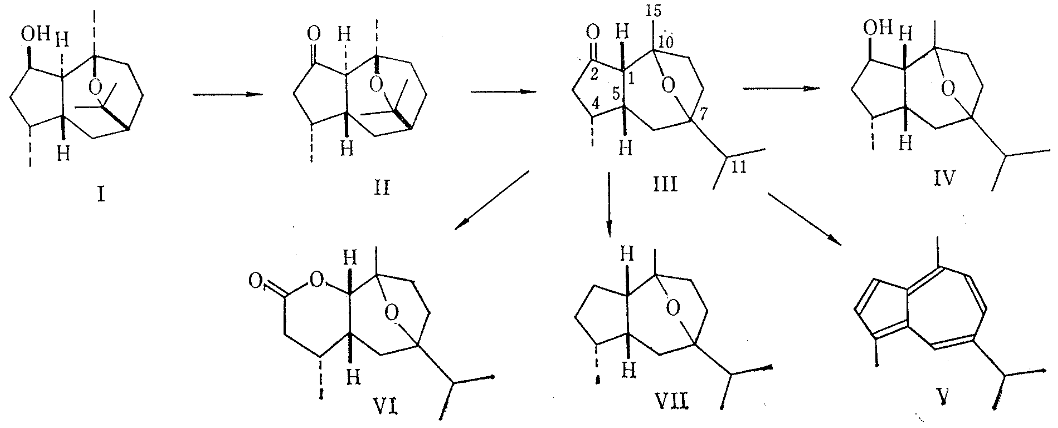

Chart 1.

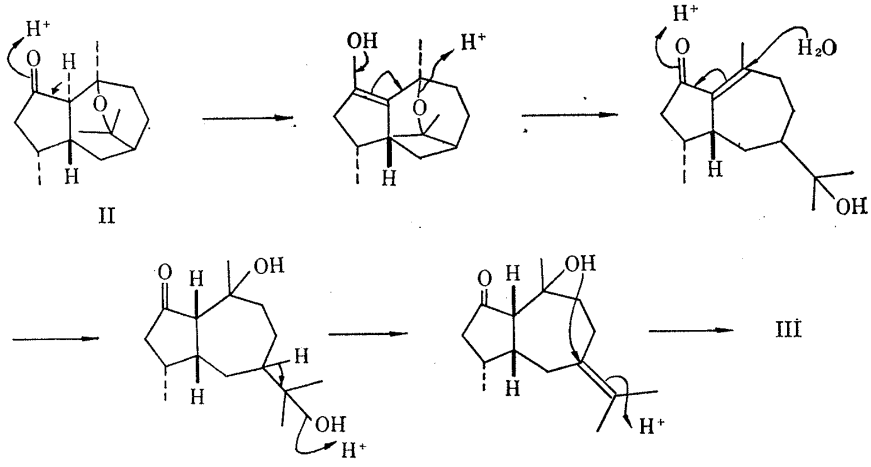

Chart 2.

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

The configuration at C-7 and C-10 has also to be considered, because the oxide bridge may not retain the original configuration during the conversion from α-kessyl ketone (Ⅱ) to β-kessyl ketone (Ⅲ). Although the nuclear magnetic resonance signals of the C-10 methyl groups in Ⅲ, Ⅳ, Ⅷ, and Ⅶ suggest a close steric proximity to the C-2 oxygen functions, inspection of Dreiding models reveals that no difinite conclusion can be drawn concerning the configuration of the C-10 methyl group (*i.e.*, the oxide bridge) due to the flexible nature of the molecules. Further studies on this point are now being pursued.

A possible mechanism for the transformation of α-kessyl ketone (Ⅱ) into β-kessyl ketone (Ⅲ) is outlined in Chart 2.

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Pharmaceutical Institute,
School of Medicine,
Tohoku University,
Kita-4-bancho, Sendai

Hiroshi Hikino (ヒキノヒロシ)
Yasuyoshi Takeshita (竹下保義)
Yasuko Hikino (曳野靖子)
Tsunematsu Takemoto (竹本常松)

Department of Chemistry,
Faculty of Science,
Tohoku University,
Katahira-cho, Sendai

Shô Itô (伊東椒)

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On the Structure of So-called Rotundine

Rotundine was originally isolated in 1944 by Kondo and Matsuno[1] from the rhizome of *Stephania rotunda* LOUREIO indigenous to Indo-China, and the structure (A) was assigned to this alkaloid and (B) to dihydrorotundine, which was claimed to have been obtained by them through catalytic hydrogenation of the former.

Later, for the purpose of providing synthetical support for these structures, Sugasawa and Mizukami[2] synthesized *rac*-dihydroisorotundine (I) and *rac*-dihydrorotundine (Ⅱ), and then, one of the present authors (M.K.)[3] studied behaviour of Ⅱ. By treating Ⅱ with $Hg(OAc)_2$ he obtained (Ⅲ, X=Cl), which, on being reduced catalytically, furnished two partially reduced isomeric compounds of *rac*-dihydrorotundine type. Both of them, however, were found not to be identical with and behaved differently from Matsuno's dihydrorotundine (B); *i.e.*, they smoothly gave the ketone (Ⅳ) when treated with dil. hydrochloric acid, whereas (B) was quite stable to hydrochloric acid. Moreover, the compound (Ⅲ, X=Cl) did not coincide with dehydrorotundinium chloride prepared from (B).

The structure of rotundine as proposed by Matsuno thus appears to be improbable and its reappraisal became necessary. Though our efforts to obtain *S. rotunda* ended

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1) H. Kondo, T. Matsuno: Yakugaku Zasshi, **64B**, 113 (1944).
2) S. Sugasawa, K. Mizukami: This Bulletin, **6**, 313, 359 (1958).
3) M. Kawanishi: *Ibid.*, **10**, 191 (1962).