Tetrahedron Letters No. 26, pp. 1787-1792, 1963. Pergamon Press Ltd.
Printed in Great Britain.

STRUCTURES OF α-KESSYL ALCOHOL AND KESSYL GLYCOL

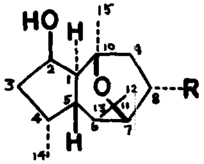
Shô Itô, M. Kodama and T. Nozoe
Department of Chemistry, Faculty of Science,
and
H. Hikino, Y. Hikino, Y. Takeshita and T. Takemoto
Pharmaceutical Department, Faculty of Medicine,
Tohoku University, Sendai, Japan
(Received 12 August 1963)

THE sesquiterpenic oxido-alcohols, α-kessyl alcohol and kessyl glycol (kessoglycol), which were found in Japanese valerian roots (1), have long been the subject of extensive degradative studies by Asahina and his school and by Treibs. Several structures have been proposed by Kaneoka, Ukita, and Treibs, as well as by de Mayo (2). We wish to provide evidence which permits the assignment of the absolute configurations Ia and Ib for α-kessyl alcohol and kessyl glycol, respectively.

It was first necessary to establish the constitution of α-kessyl alcohol. The n.m.r. spectrum[*1] of the alcohol revealed the presence of a methyl group attached to a tertiary carbon (doublets, δ=0.80, J=6.0) and three methyls on quaternary carbons bearing oxygens (δ=1.23, 1.26, and 1.33). These features, in conjunction with the reactions already carried out by the preceding investigators, are only explicable by the de Mayo's formula (Ia without stereochemical significance)(3), which was consequently accepted as the correct constitution. Since kessyl glycol has been cor-

---

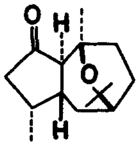
[*1] All n.m.r. measurements were carried out at 60 Mc/sec. for CCl_4 solution unless otherwise indicated. Chemical shifts (δ) are expressed in p.p.m. scale relative to internal Me_4Si, while coupling constants (J) are in c/s.



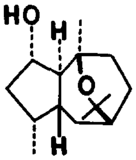
Ia R=H

b R=OH

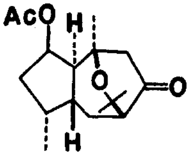
c R=OCOPh



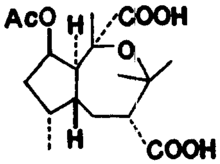
II



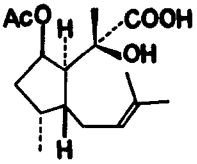
III



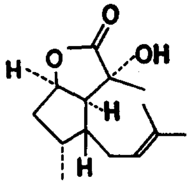
IV



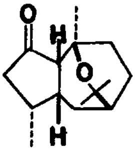
V



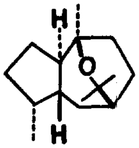
VI



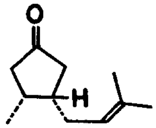
VII



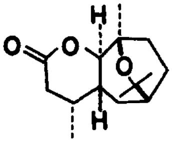
VIII



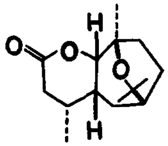
IX



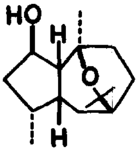
X



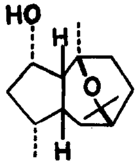
XI



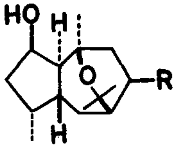
XII



XIII



XIV



XVa R = OH

b R = OCOPh

related with α-kessyl alcohol (4), free use was made of one or the other compound, whichever was convenient, in the elucidation of stereochemistry.

α-Kessyl alcohol Ia, $[\alpha]_D$ -38.4°[*2]; benzoate, m.p. 100-101°, $[\alpha]_D$ -82.7°, had been oxidized to α-kessyl ketone II (5), $[\alpha]_D$ +239°, $\nu_{C=O}$ 1727 cm^{-1}. On lithium aluminum hydride reduction, the ketone afforded 2-epi-α-kessyl alcohol III, m.p. 107-108°, $[\alpha]_D$ +37.8°; benzoate, m.p. 91.5-93°, $[\alpha]_D$ +113.4°, which reverted to the original ketone II on chromic acid oxidation. Application of the "benzoate rule" (6) to these alcohols and their benzoates ($\Delta[M]_D$ -192° for α-series, and +298° for 2-epi-series) resulted in the assignment of the R-configuration to C-2 of α-kessyl alcohol and S-configuration to that of 2-epi-alcohol.

The acetoxy-ketone IV (7), m.p. 138-139°, $\nu_{C=O}$ 1727 cm^{-1}, yielded, on permanganate oxidation, the acetoxy-dicarboxylic acid V, m.p. 175-177°, which was decarboxylated in refluxing acetic acid. The resulting unsaturated carboxylic acid VI (8), after alkaline hydrolysis and subsequent acidification, yielded directly the unsaturated γ-lactone VII (8), $\nu_{C=O}$ 1770 cm^{-1} [*3]. Since a γ-lactone trans-fused to a cyclopentane ring is not known (9), it follows that the C-2 hydroxyl and the C-1 hydrogen must be in a trans-relationship in α-kessyl alcohol. The absolute configuration at C-1 was determined also from the RD curves of α-kessyl ketone II, $[M]^{peak}_{317}$ +9060°, $[M]^{trough}_{278}$ -5780°, and of isokessyl ketone VIII (10), $\nu_{C=O}$ 1727 cm^{-1}, $[M]^{trough}_{315}$ -9840°, $[M]^{peak}_{280}$ +9300°, the isomerization product of the former with dilute alkali or alumina. The more negative nature of the first extremum in the RD curve of the iso-ketone compared with that of the α-ketone, coupled with the ease of the isomerization,

---

[*2] Satisfactory analyses were obtained for all compounds described in this paper. Optical rotations and IR spectra are refered to $CHCl_3$ solution unless otherwise stated.

[*3] Compounds VI and VII are known but have been derived in a different way. N.m.r. spectra of the compounds satisfy the structures assigned.

indicated that the α-disposed C-1 hydrogen, the only active center in α-kessyl ketone, had undergone inversion during the isomerization.

Configuration of the 14-methyl group was deduced from the n.m.r. spectra of the epimeric alcohols, Ia and III. The methyl signals (doublets) of α-kessyl alcohol (vide supra) and its acetate, δ=0.81, J=6.4, were not effected by the presence of the β-oriented oxygen functions at C-2. (Cf. Kessane IX (11), δ=0.77, J=6.0). On the other hand, the signals of the same methyl group in 2-epi-alcohol, δ=0.91, J= J=6.7, and its acetate, δ=0.90, J=6.8, suffered from appreciable down-field shift which can only be explained if the 14-methyl is α-oriented, i.e, bears a 1,3-cis-relationship to the 2α-hydroxyl group (12)*4.

That the C-5 hydrogen has a β-configuration, implied by the fact that Ukita's cyclopentanone X (13) exhibits a positive Cotton effect with smaller amplitude ($[M]_{317}^{peak}$ +2190°, $[M]_{273}^{trough}$ -2130°) than that of 3-methylcyclopentanone (14), was verified by the study of the n.m.r. spectra (in $CHCl_3$) of the lactones prepared by Baeyer-Villiger oxidation of α- and iso-kessyl ketones. α-Kessyl lactone XI, m.p. 140.5-141.5°, $\nu_{C=O}^{KBr}$ 1727 cm^{-1}, exhibited a doublet (δ=4.12, J=10.2) attributed to the C-1 hydrogen, whereas the same hydrogen appears as a doublet with considerably smaller coupling constant (δ=4.31, J=4.0) in isokessyl lactone XII, m.p. 115-116°, $\nu_{C=O}^{KBr}$ 1724 cm^{-1}. Consideration of the dihedral relationship for spin-spin coupling (15) led to the conclusion that C-5 and C-1 hydrogens are trans in α-lactone and cis in the iso-lactone. Since it is known (16) that Baeyer-Villiger oxidation does not cause any change in configuration, the C-5 hydrogen in the original α-ketone II and therefore in α-kessyl alcohol should be β-disposed.

---

*4 A similar down-field shift was observed in the n.m.r. spectrum of 2-epiisokessyl alcohol and not in that of isokessyl alcohol. Both of these compounds will be described later.

While isokessyl ketone VIII gave isokessyl alcohol XIII on reduction with sodium in ethanol (10), the same ketone afforded, on lithium aluminum hydride reduction, 2-epiisokessyl alcohol XIV, m.p. 77-79°; both alcohols were converted to the original ketone VIII on chromic acid oxidation. Accurate measurement of the IR spectra (in CCl_4) of the epimeric alcohols, Ia, III, XIII, and XIV, disclosed an intramolecularly-hydrogenbonded hydroxyl band at 3570 cm^{-1} (concentration-independent in 0.2-0.001 M) in α-kessyl alcohol only. The other three, on the other hand, exhibited bands at 3625 cm^{-1} (free OH) and at around 3430 cm^{-1} (bonded OH), relative intensities of which changed on dilution. The oxide bridge is therefore β-oriented. This conclusion was further supported by the chemical shifts of the 15-methyl in the n.m.r. spectra of these four alcohols. A down-field shift due to the parallel orientation of the 15-methyl and the 2β-hydroxyl group was observed in the case of α-kessyl alcohol[*5].

The above evidence establishes the absolute configuration Ia for α-kessyl alcohol; the orientation of the C-8 hydroxyl group in kessyl glycol remains to be elucidated. This problem was solved by comparison of the molecular rotation difference of kessyl glycol Ib, $[\alpha]_D$-19.3°, and its dibenzoate, $[\alpha]_D$ -50.5°, with that of 8-epikessyl glycol XVa, m.p. 171-173°, $[\alpha]_D$ -35.0° and its dibenzoate XVb, $[\alpha]_D$ -92.2°. Although $\Delta[M]_D$ in both series is laevorotatory (-184° for the kessyl glycol series, and -337° for 8-epi-series), subtraction of the effect of benzoylation at the C-2 hydroxyl group (vide supra) clearly showed that the benzoylation shift at the C-8 hydroxyl is dextrorotatory (+8°) in the kessyl glycol series and laevorotatory (-145°) in the 8-epi-series. Applying "benzoate rule" (6), it is concluded that the configuration at C-8 is R in kessyl glycol as shown in Ib and S in 8-epikessyl glycol XVa.

[*5] This will be discussed in our forthcoming paper.

We are deeply indebted to Professors T. Ukita and S. Shibata, University of Tokyo, for their generous donation of many authentic samples and to Professor W.A. Ayer, University of Alberta, for n.m.r. spectra. Thanks are also due to the Research Laboratory, Shionogi Co., Ltd., for RD curves.

REFERENCES

1. Cf. H. Hikino, Y. Hikino, H. Kato, Y. Takeshita and T. Takemoto, *J. Pharm. Soc. Japan*, **83**, 219 (1963). H. Hikino, Y. Hikino, Y. Takeshita, Y. Isurugi and T. Takemoto, *ibid.*, **83**, 555 (1963).
2. For the historical and general aspects of the research, see J. Simonsen and P. de Mayo, "The Terpenes" Cambridge Univ. Press, London, Vol. 5, 1957, p564 and p568.
3. P. de Mayo, *Perfumery and Essent. Oil Record*, **48**, 18 (1957).
4. T. Ukita, *J. Pharm. Soc. Japan*, **65**, 458 (1945).
5. Y. Asahina and G. Hongo, *ibid.*, **44**, 227 (1924).
6. J.H. Brewster, *Tetrahedron*, **13**, 106 (1961).
7. Y. Kaneoka and U. Tutida, *J. Pharm. Soc. Japan*, **61**, 6 (1941).
8. Y. Kaneoka and S. Kurosaki, *ibid.*, **61**, 9 (1941).
9. P. Crabbé, L.M. Guerrero, J. Romo and F. Sánchez-Viesca, *Tetrahedron*, **19**, 25 (1963) and the references there cited.
10. Y. Asahina and S. Nakanishi, *J. Pharm. Soc. Japan*, **46**, 828 (1926).
11. H. Hikino, Y. Hikino, Y. Takeshita, K. Shirata and T. Takemoto, *Chem. Pharm. Bull.*, **11**, 547 (1963).
12. Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto and K. Tsuda, *ibid.*, **10**, 338 (1962). F.A.C. Anet, *Can. J. Chem.*, **39**, 789 (1960).
13. T. Ukita, *J. Pharm. Soc. Japan*, **64**, 285 (1944).
14. C. Djerassi, L.A. Mitcher and B.J. Mitcher, *J. Amer. Chem. Soc.*, **81**, 947 (1959).
15. M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
16. C.H. Hassall in "*Organic Reactions*" Edited by R. Adams, John Wiley & Sons, Inc., New York, Vol. 9, 1957, p73.