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.

We would like to express our deep gratitude to Prof. W. A. Ayer, University of Alberta, and Research Laboratories, Takeda Chemical Industries, Ltd., for the NMR spectra, to Hitachi, Ltd., for the mass spectra, and to Analytical Laboratories, this Institute, for microanalyses and the infrared spectra.

[Chem. Pharm. Bull. 15(3) 324~328 (1967)]

UDC 547.597.02 : 581.19

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.

(Received June 20, 1966)

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).

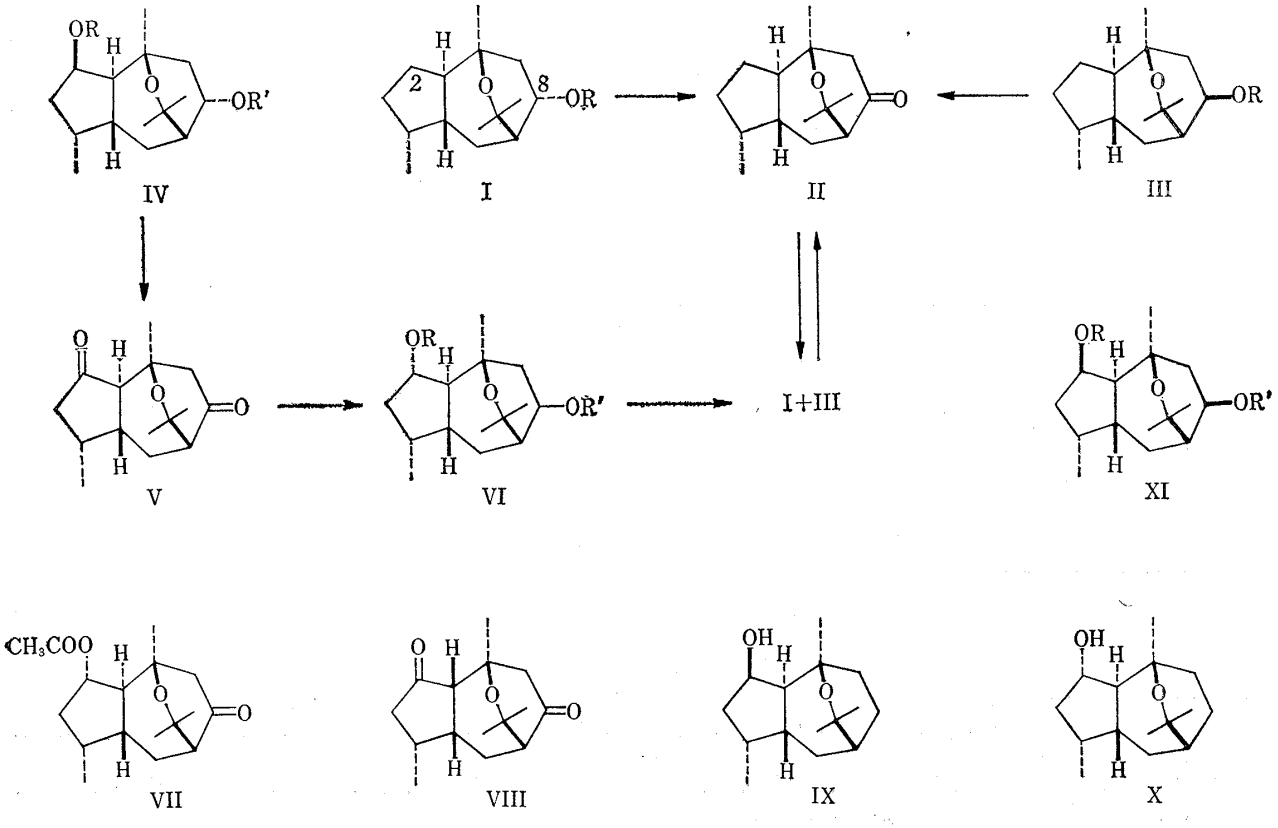
2) H. Hikino, M. Ono, Y. Takeshita, T. Takemoto : Unpublished data.

8.85, and 8.73 or 8.97, 8.76, and 8.76τ) on carbons attached to the ethereal oxygen, and a hydrogen (5.70 or 4.88τ) which is attached to the carbon atom bearing the hydroxyl or acetoxyl group. The last signal indicates that the hydroxyl group of kessanol is secondary. One of the three double-bond equivalents of the molecule is associated with the oxide bridge. The remaining two are attributed to two carbocyclic rings since no indication can be found for the presence of unsaturation of any sort colorimetrically or spectroscopically.

8-*epi*-Kessanol was isolated as the crystalline acetate (Ⅲ; R=$COCH_3$) which on alkaline hydrolysis afforded the crystalline 8-*epi*-kessanol (Ⅲ;R=H). The alcohol and its acetate have the similar properties to those of their 8-epimers in the infrared and NMR spectra; the presence of a secondary methyl (9.24 or 9.13τ), three tertiary methyls on carbons bearing the oxidic oxygen (1100 cm^{-1}, 8.95, 8.82, and 8.70τ or 1106 cm^{-1}, 8.89, 8.77, and 8.70τ), and a secondary hydroxyl (3490 cm^{-1}, 5.98τ) or acetoxyl group (1740 and 1240 cm^{-1}, 5.07τ) being indicated.

On chromic acid oxidation, both kessanol and 8-*epi*-kessanol gave the same ketone (Ⅱ), kessan-8-one, a fact which established the epimeric relationship of both the alcohols with respect to the carbon bearing the hydroxyl group. This relation was further confirmed by the following observations. Lithium aluminum hydride reduction of kessan-8-one (Ⅱ) gave a mixture of kessanol and 8-*epi*-kessanol in the approximate ratio of 3:2. On reduction of kessan-8-one with sodium and ethanol afforded 8-*epi*-kessanol together with a small amount of kessanol.

The optical rotatory dispersion curve of the ketone (Ⅱ) showing a positive Cotton effect (a=+72) is essentially the same as that (a=+53) of 2β-acetoxykessan-8-one (Ⅶ). This observation suggests that the carbonyl group of the former (Ⅱ) is in the same environment as the latter (Ⅶ). Although the carbonyl group in the ketone (Ⅱ) is situated in a six-membered ring, its stretching vibration appears at 1730 cm^{-1} which is more compatible with that of a five-membered ring ketone. The same shift towards



higher wave numbers of the C-8 carbonyl in the kessane skeleton can also be observed in some other instances: *e.g.*, 2-acetoxykessan-8-one (Ⅶ) (1730 cm^{-1}), kessane-2,8-dione (Ⅴ) (1724 cm^{-1}), and isokessane-2,8-dione (Ⅷ) (1730 cm^{-1}). This anomaly may be rationalized in terms of ring strain of some sort.

These results and in particular those of the NMR study may suggest kessanol and 8-*epi*-kessanol to be the 2-deoxy-derivatives of kessyl glycol (Ⅳ; R=H, R′=H) and 8-*epi*-kessyl glycol (Ⅺ; R=H, R′=H), respectively. This assumption has been proved by the evidence described below.

The transformation of kessyl glycol (Ⅳ) into the 2-deoxy-derivative was thus designed. A promising approach was suggested by the following observations. It has been found that the 2β-hydroxyl group in the kessane skeleton (*viz.*, α-kessyl alcohol (Ⅸ)) resists tosylation while the epimeric 2α-hydroxyl (*viz.*, 2-*epi*-α-kessyl alcohol (Ⅹ)) is tosylated in the usual manner and can subsequently be reduced to give a deoxy-derivative.[3] On the other hand, the resistance of the 8α-hydroxy group to tosylation is now observed in kessyl glycol 2-acetate (Ⅳ; R=$COCH_3$, R′=H). Therefore, tosylation followed by lithium aluminum hydride reduction of kessane-2α,8β-diol could be expected to give kessan-8α-ol.

Kessyl glycol (Ⅳ; R=H, R′=H) was oxidized with chromic acid to give kessane-2,8-dione (Ⅴ) which on reduction with lithium aluminum hydride afforded a diol. By analogy with the results of lithium aluminum hydride reduction of α-kessyl ketone[4] and kessan-8-one, the diol is reasonably regarded as a mixture (Ⅵ; R=H, R′=H) of epimers at C-8 of 2-*epi*-kessyl glycol. This mixture was tosylated and successively reduced with lithium aluminum hydride to yield, together with a fairly large amount of kessane (bisdeoxykessyl glycol), an alcohol, in a poor yield, which was proved to be the mixture of kessanol and 8-*epi*-kessanol that was previously derived from kessan-8-one (Ⅱ) by lithium aluminum hydride reduction. Therefore, tosylation of the C-8 hydroxyl group in this case seemed to have taken place to a considerable extent. Further on chromic acid oxidation this mixture of the two epimeric alcohols furnished kessan-8-one (Ⅱ). The above interconversion achieved the object of showing kessanol and 8-*epi*-kessanol to be 8-hydroxykessanes.

In their NMR spectra, the C-8 hydrogens of kessanol, kessyl glycol, and their acetates are found to appear at lower field by 0.24~0.32 p.p.m. than those of the

Table I. Chemical Shifts of the C-8 Hydrogens of the Kessan-8-ols

Substance	Solvent	Line position (τ)
kessanol (I; R=H)	CCl_4	5.70
8-*epi*-kessanol (Ⅲ; R=H)	〃	5.97
kessyl glycol (Ⅳ; R=R′=H)	$CHCl_3$	5.62
8-*epi*-kessyl glycol (Ⅺ; R=R′=H)	〃	5.92
kessanyl acetate (I; R=$COCH_3$)	CCl_4	4.88
8-*epi*-kessanyl acetate (Ⅲ; R=$COCH_3$)	〃	5.12
kessyl glycol diacetate (Ⅳ; R=R′=$COCH_3$)	〃	4.85
8-*epi*-kessyl glycol diacetate (Ⅺ; R=R′=$COCH)_3$	〃	5.17

corresponding 8-epimers (Table I) indicating the identity of the configuration at C-8 of kessanol and kessyl glycol and of 8-*epi*-kessanol and 8-*epi*-kessyl glycol. On application

3) H. Hikino, Y. Hikino, Y. Takeshita, K. Shirata, T. Takemoto: This Bulletin, **11**, 547 (1963); *Ibid.*, **15**, 321 (1967).

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

of the "benzoate rule"[5] to kessyl glycol and 8-*epi*-kessyl glycol, the absolute configuration at C-8 of kessyl glycol has already been suggested to be *R*, *i.e.*, the hydroxyl group being α-disposed.[4] In confirmation, this rule was also applied to the pair of kessanol and 8-*epi*-kessanol. The benzoylation shift was found to be dextrorotatory ($\Delta[M]_D$ +22°) in the kessanol series and laevorotatory ($\Delta[M]_D$ −115°) in the 8-*epi*-kessanol series. Therefore, the same conclusion about the absolute configuration at C-8 of kessanol (*i.e.*, *R*) and 8-*epi*-kessanol (*i.e.*, *S*) can be deduced as that of kessyl glycol and 8-*epi*-kessyl glycol.

Since the structure and absolute configuration of kessyl glycol as shown in formula Ⅳ (R=H, R′=H) have already been elucidated,[4] kessanol and 8-*epi*-kessanol have thus been established to be represented by stereoformulae Ⅰ (R=H) and Ⅲ (R=H), respectively.

Experimental*4

Kessanyl Acetate——$C_{17}H_{28}O_3$, d_4^{25} 1.051, n_D^{25} 1.488, $[\alpha]_D$ −15.6°(c=10.2), IR (liquid) cm^{-1} : 1736, 1234 (acetoxyl), 1080 (oxide), NMR : doublet (3H) at 9.19 τ (J=6.1, C<u>H</u>$_3$-CH), singlets (3H and 6H, respectively) at 8.97 and 8.76 τ (C<u>H</u>$_3$-C-O-), singlet (3H) at 7.98 τ (C<u>H</u>$_3$-CO-O-), multiplet (1H) at 4.88 τ (<u>H</u>-C-OCOCH$_3$).

Hydrolysis of Kessanyl Acetate——Kessanyl acetate (100 mg.) was refluxed under N_2 with 2*N* ethanolic KOH solution (3 ml.) for 2 hr. Removal of the solvent and addition of H_2O deposited the product (83 mg.) which was crystallized from light petroleum to give kessanol (Ⅰ; R=H) as colorless needles, m.p. 121~122°, $[\alpha]_D$ +11.4°(c=10.2), mol. wt. 238 (mass spec.), *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found : C, 75.75; H, 10.94. IR (KBr) cm^{-1} : 3378 (hydroxyl), 1096 (oxide). NMR : doublet (3H) at 9.18 τ (J=5.4, C<u>H</u>$_3$-CH<), singlets (3H, respectively) at 8.97, 8.85, 8.73 τ (C<u>H</u>$_3$-C⩽O-), multiplet (1H) at 5.70 τ (<u>H</u>-C⩽OH), tetranitromethane test : negative.

8-*epi*-Kessanyl Acetate——$C_{17}H_{28}O_3$, m.p. 60.5~61.5°, $[\alpha]_D$ −19.4° (c=8.7), IR (KBr) cm^{-1} : 1739, 1240 (acetoxyl), 1106 (oxide), NMR : doublet (3H) at 9.13 τ (J=5.7, C<u>H</u>$_3$-CH), singlets (3H, respectively) at 8.89, 8.77, 8.70 τ (C<u>H</u>$_3$-C⩽O-), singlet (3H) at 8.00 τ (CH$_3$-CO-O-), triplet (1H) at 5.07 τ (J=9.0, <u>H</u>-C⩽OCOCH$_3$).

Hydrolysis of 8-*epi*-Kessanyl Acetate——8-*epi*-Kessanyl acetate (1.39 g.) was set aside with *N* ethanolic KOH solution (15 ml.) at room temperature overnight. Upon isolation, the product (1.06 g.) was crystallized from light petroleum to afford 8-*epi*-kessanol (Ⅲ; R=H) as colorless needles, m.p. 142.5~143°, $[\alpha]_D$ −6.8° (c=5.9), *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found : C, 75.51; H, 11.18. IR (KBr) cm^{-1} : 3490 (hydroxyl), 1100 (oxide). NMR : doublet (3H) at 9.24 τ (J=5.3, C<u>H</u>$_3$-CH<), singlets (3H, respectively) at 8.95, 8.82, 8.70 τ (C<u>H</u>$_3$-C⩽O-), triplet (1H) at 5.98 τ (J=8.7, <u>H</u>-C⩽OH).

Oxidation of Kessanol with Chromic Acid——Kessanol (0.83 g.) in ether (10 ml.) was stirred with $Na_2Cr_2O_7 \cdot 2H_2O$ (0.4 g.) and H_2SO_4 (0.5 g.) in H_2O (2 ml.) at room temperature for 3 hr. Isolation of the product (0.75 g.) by ether extraction and distillation under reduced pressure gave kessan-8-one (Ⅱ) as a colorless oil, d_4^{25} 1.038, n_D^{25} 1.496, $[\alpha]_D$ +100.6° (c=9.8), ORD (c=0.301, MeOH) : $[M]_{326}^{peak}$ +3960°, $[M]_{321}^{trough}$ +3730°, $[M]_{315}^{peak}$ +4260°, $[M]_{277}^{trough}$ −2900°,*5 *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found : C, 76.01; H, 10.19. IR (liquid) cm^{-1} : 1730 (carbonyl), 1406 (methylene next to carbonyl), 1045 (oxide). NMR : doublet (3H) at 9.17 τ (J=6.1, C<u>H</u>$_3$-CH<), singlets (3H, respectively) at 8.97, 8.85, 8.73 τ (C<u>H</u>$_3$-C<O-).

Oxidation of 8-*epi*-Kessanol with Chromic Acid——8-*epi*-Kessanol (Ⅲ; R=H) (1.12 g.) in ether (10 ml.) was stirred with $Na_2Cr_2O_7 \cdot 2H_2O$ (0.5 g.) and H_2SO_4 (0.7 g.) in H_2O (3 ml.) at room temperature for 3 hr. After isolation, the product (1.08 g.) was distilled under reduced pressure to yield kessan-8-one (Ⅱ) as a colorless oil, IR (liquid) cm^{-1} : 1730 (carbonyl), 1404 (methylene α to carbonyl), 1044 (oxide). The identity was established by identical behavior upon VPC (silicone SE 30) and superimposable IR spectra.

Reduction of Kessan-8-one with Lithium Aluminum Hydride——Kessan-8-one (Ⅱ) (1.20 g.) in ether (20 ml.) was treated with $LiAlH_4$ (0.3 g.) at room temperature for 3 hr. Isolation in the customary manner yielded the product (1.20 g.), m.p. 120°, which was shown to be the mixture of kessanol (Ⅰ; R=H) and 8-*epi*-kessanol (Ⅲ; R=H) by TLC, IR and NMR spectra.

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*4 Mc.p.s. are uncorrected. Rotations were determined in $CHCl_3$ solution. NMR measurements were carried out at 60 Mc.p.s. for CCl_4 solution with $(CH_3)_4Si$ as internal standard. Chemical shifts are expressed in τ-values and coupling constants (J) in c.p.s. Thin-layer chromatography (TLC) was done on silica gel plate using benzene-AcOEt (10:3) as a solvent.

*5 cf. 2β-acetoxykessan-8-one (Ⅶ), ORD (c=0.233, MeOH) : $[M]_{326}^{peak}$ +2170°, $[M]_{323}^{trough}$ +1920°, $[M]_{317}^{peak}$ +2340°, $[M]_{278}^{trough}$ −2950°.

5) J. H. Brewster : Tetrahedron, **13**, 106 (1961).

The mixture was chromatographed over silica gel (35 g.).

Elution with benzene gave a crystalline material (0.60 g.) crystallized from light petroleum afforded kessanol (I; R=H) as colorless needles, m.p. 120~121°, which was identified in the usual criteria.

Successive elution with benzene yielded a crystalline mass (0.13 g.) which was shown by TLC to be a mixture of kessanol (I; R=H) and 8-*epi*-kessanol (III; R=H).

Further elution with benzene and benzene-ether (1:1) gave a crystalline substance (0.46 g.) which on crystallization from light petroleum afforded 8-*epi*-kessanol as colorless needles, m.p. 142~143°, identified in the usual criteria.

Reduction of Kessan-8-one with Sodium and Ethanol——Metallic Na (0.2 g.) was added portionwise to a refluxed solution of kessan-8-one (II) (50 mg.) in EtOH (3 ml.) and the mixture was kept at 100° for 3 hr. The product was precipitated by the addition of H_2O, collected by filtration, and dried to give the mixture of 8-*epi*-kessanol (III; R=H) and a minute amount of kessanol (I; R=H), m.p. 134°, $[\alpha]_D$ 0° (c=8.8). The heterogeneous nature was confirmed by TLC, IR and NMR spectra.

The mixture was separated by preparative TLC and crystallized from light petroleum to give 8-*epi*-kessanol (III; R=H) as colorless needles, m.p. 141~142°, identified by the usual criteria.

Attempted Tosylation of Kessyl Glycol 2-Acetate——Kessyl glycol 2-acetate (IV; R=$COCH_3$, R'=H) (107 mg.) in pyridine (2 ml.) was treated with TsCl (111 mg.) at room temperature for 1 day. Working up in the usual manner gave the product (91 mg.) crystallized from light petroleum to yield the recovered diol monoacetate (IV; R=$COCH_3$, R'=H) as colorless needles, m.p. 102~104°, undepressed when mixed with the starting material. The IR spectra were also identical.

Reduction of Kessane-2,8-dione with Lithium Aluminum Hydride——Kessane-2,8-dione (V) (200 mg.) and excess $LiAlH_4$ in ether (10 ml.) were stirred at room temperature for 2 hr. Isolation of the product (155 mg.) in the usual way and crystallization from AcOEt gave the kessane-2α,8-diols (VI; R=H, R'=H, configuration at C-2 tentative) as colorless needles, m.p. 200~201°, IR (KBr) cm^{-1}: 3290 (hydroxyl).

Tosylation of the Kessane-2α,8-diols——The kessane-2α,8-diols (VI; R=H, R'=H) (0.20 g.) in pyridine (2.5 ml.) was treated overnight at room temperature with TsCl (0.6 g.). The reaction mixture was poured into crushed ice and extracted with ether. The ethereal solution was worked up in the customary manner to give a mixture of the crude tosylates (VI; R=$SO_2C_6H_4CH_3$, R'=H and $SO_2C_6H_4CH_3$) of the kessane-2α,8-diols as an colorless viscous oil (0.30 g.), IR (liquid) cm^{-1}: 3425 (hydroxyl), 1600, 1358, 1173 (tosylate).

Reduction of the Tosylates with Lithium Aluminum Hydride——The crude tosylates (306 mg.) above obtained in ether (20 ml.) was stirred with excess $LiAlH_4$ at room temperature for 3.5 hr. The product (185 mg.) was isolated by ether extraction and placed on a column of alumina (10 g.).

Elution with light petroleum afforded an oil (58 mg.) distilled under reduced pressure to yield kessane as colorless mobile oil, identified by VPC (silicone SE 30) and IR comparison.

Benzene eluted a crystalline fraction (20 mg.) which on crystallization from light petroleum afforded the mixture of kessanol (I; R=H) and 8-*epi*-kessanol (III; R=H) as colorless needles, m.p. 124~125°, IR (KBr) cm^{-1}: 3436 (hydroxyl), 1096, 1037 (oxide) (the spectrum was indistinguishable from that of the mixture obtained from kessan-8-one by $LiAlH_4$ reduction).

Oxidation of the Kessan-8-ols with Chromic Acid——The kessan-8-ols (15 mg.) above obtained was oxidized in a similar manner to that described previously for oxidation of kessanol (I; R=H). The product (12 mg.) was purified in the usual way to give kessan-8-one (II) as a colorless oil, which was identified by TLC, VPC, and IR spectrum.

Benzoylation of Kessanol——Kessanol (98 mg.) and BzCl (210 mg.) in pyridine (1 ml.) were left standing at room temperature for 1 day. Isolation in the usual manner gave the product (119 mg.) which was crystallized from light petroleum to afford kessanyl benzoate (I; R=COC_6H_5) as colorless prisms, m.p. 66~67°. $[\alpha]_D$ +14.3°(c=6.4), *Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.46; H, 8.78. IR (KBr) cm^{-1}: 1718, 1277 (ester), 1605, 1112, 713 (phenyl).

Benzoylation of 8-*epi*-Kessanol——8-*epi*-Kessanol (45 mg.) in pyridine (1 ml.) was kept at room temperature with BzCl (130 mg.) for 2 days. After isolation, the product was crystallized from light petroleum to give 8-*epi*-kessanyl benzoate (IV; R=COC_6H_5) as colorless prisms, m.p. 103~104°. $[\alpha]_D$ −38.6°(c=5.1), *Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.43; H, 8.73. IR (KBr) cm^{-1}: 1715, 1277 (ester), 1604, 1111, 718 (phenyl).

We are grateful to Prof. W. A. Ayer, University of Alberta, and Research Laboratories, Takeda Chemical Industries, Ltd., for the NMR spectra, to Research Laboratory, Shionogi & Co., Ltd., for the optical rotatory dispersion curves, to Hitachi, Ltd., for the mass spectra, and to Analytical Laboratories, this Institute, for microanalyses and the infrared spectra.