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STRUCTURE AND ABSOLUTE CONFIGURATION OF α-KESSYL ALCOHOL AND KESSYL GLYCOL*

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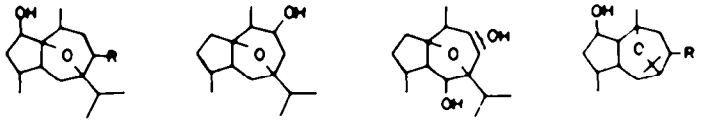
Abstract—The structures and absolute configuration of α-kessyl alcohol (I) and kessyl glycol (II), sesquiterpenic constituents of Japanese valerian roots, have been established on the basis of chemical and spectroscopic data.

STRUCTURAL studies on the sesquiterpenoid alcohols, α-kessyl alcohol, $C_{15}H_{26}O_2$, and kessyl glycol, $C_{15}H_{26}O_3$, from several kinds of Japanese valerian[1] were initiated by Asahina and his school and continued by Kaneoka and Ukita. Their work has demonstrated that (i) both alcohols possess the guaiane carbon skeleton with an additional oxide ring, (ii) both alcohols have a hydroxyl located at C-2 of guaiane, and (iii) an additional hydroxyl group is at C-8 in kessyl glycol.[2] Structures IIa and Ia were accordingly proposed in 1944 and 1945 for kessyl glycol[3] and α-kessyl alcohol[4] respectively, although structure IIb[5] for the former had been proposed earlier. In 1950 Treibs independently advanced Ib[6] as the structure of the latter. In 1956, however,



Ia : R = H
IIa : R = OH

Ib

IIb

Ic : R = H
IIc : R = OH

a careful reconsideration of the evidence provided, led de Mayo to propose structures Ic and IIc for these alcohols.[7] With the intention of establishing the constitution and the stereochemistry of these alcohols, the present authors undertook a reinvestigation of these substances culminating in the proposal of the structures I and II.†

* This paper forms Part VII in the Medical School series on Sesquiterpenoids. Part VI, H. Hikino K. Meguro, G. Kusano and T. Takemoto, *Yakugaku Zasshi* in press.

† A part of this work has been outlined in a preliminary communication: *Tetrahedron Letters* No. 26, 1787 (1963) and also presented at the IUPAC International Symposium on the Chemistry of Natural Products, Kyoto (1964).

[1] [a] H. Hikino, Y. Hikino, H. Kato, Y. Takeshita and T. Takemoto, *Yakugaku Zasshi* **83**, 219 (1963);
[b] 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* Vol. V; pp. 564 and 568. Cambridge Univ. Press, London (1957).

[3] T. Ukita, *Yakugaku Zasshi* **64**, 285 (1944).

[4] T. Ukita, *Yakugaku Zasshi* **65**, 458 (1945).

[5] K. Kaneoka, *Yakugaku Zasshi* **61**, 123 (1941).

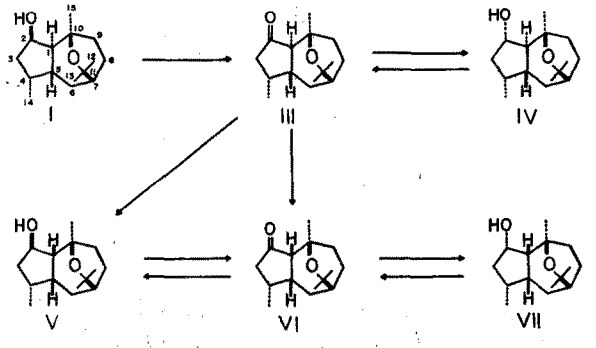
[6] W. Treibs, *Liebigs Ann.* **570**, 165 (1950).

[7] P. de Mayo, *Perfumery and Essent. Oil Record* **48**, 18 (1957).

Structure of α-kessyl alcohol (I) *and kessyl glycol* (II)

The NMR spectra of I and II disclosed the presence of four methyl groups, only one of which is attached to a tertiary carbon (doublet at 0·77 ppm; J = 6·0 c/s) for I and at 0·84 ppm (J = 6·1 c/s) for II, the other three methyl groups being attached to quaternary carbons (singlets at 1·19 (3H), 1·22 (3H), 1·29 ppm (3H) for I and at 1·16 (3H), and 1·33 ppm (6H) for II). This observation, when coupled with the results of chemical degradations,[2] demonstrates the correctness of structure Ic for kessyl alcohol and IIc for kessyl glycol.

Stereochemistry at C-2. α-Kessyl alcohol (I) gave on chromic acid oxidation the known α-kessyl ketone (III),[8] which has its carbonyl group in a five-membered ring (ν^{chf} 1735 cm^{-1}). On LAH reduction, III afforded the isomeric alcohol,2-*epi*-α-kessyl alcohol (IV) which is epimeric with I only at the 2-position, since the same ketone (III) was obtained on oxidation. Compound III, however, gave another isomeric alcohol, isokessyl alcohol (V) when reduced with sodium in ethanol.[9] This alcohol (V) has also been obtained by a similar reduction of isokessyl ketone (VI),[9] a base-catalysed isomerization product of α-kessyl ketone. The course of isomerization from III to VI can only be explained by an epimerization at the α position of the carbonyl, since the reaction takes place even during alumina chromatography. The ketone VI gave a fourth isomer, 2-*epi*-isokessyl alcohol (VII), on LAH reduction. Since both V and VII can be oxidized by chromic acid to VI, they can only differ in



their configuration at C-2. With all diastereoisomers at C-1 and C-2 at hand, the absolute configuration of the hydroxyl group in α-kessyl alcohol was determined by applying the "benzoate rule".[10] Thus benzoates were prepared both from I and IV and their $\Delta[M]_D$ values (= $[M]_{D\ benzoate} - [M]_{D\ alcohol}$) were compared. In the α-kessyl alcohol series, the $\Delta[M]_D$ value was −192°, whereas in the 2-*epi*-α-kessyl alcohol series the value was +298°. From these values, C-2 was concluded to have an R-configuration (2β-OH) in I and an S-configuration (2α-OH) in IV.

Stereochemistry at C-1. In view of the mild conditions employed for the conversion of α-kessyl ketone (III) to isokessyl ketone (VI), the only likely change for isomerization is the epimerization at the α-position of the carbonyl group in the five-membered ring. The ORD curves shown in Fig. 1 disclosed that the change from III to VI is associated with an inversion of the Cotton effect from positive to negative. From an

[8] Y. Asahina and G. Hongo, *Yakugaku Zasshi* **44**, 227 (1924).
[9] Y. Asahina and S. Nakanishi, *Yakugaku Zasshi* **46**, 828 (1926).
[10] J. H. Brewster, *Tetrahedron* **13**, 106 (1961).

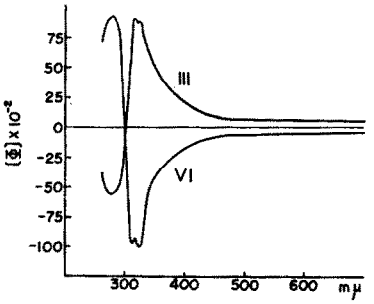
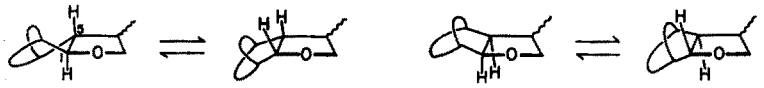


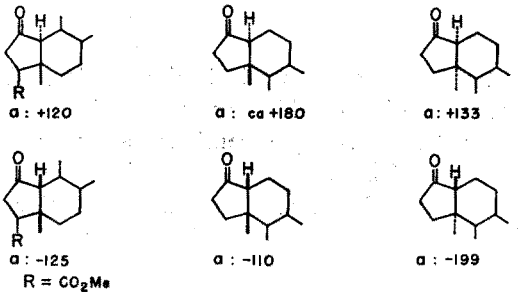
FIG. 1. ORD curves of α-kessyl ketone (III) and isokessyl ketone (VI).

examination of scale models, such a change in Cotton effect can only be explained when the epimerization of the C-1 hydrogen is from α orientation to β, regardless of the orientation of the hydrogen at C-5. Thus the epimerization is schematically presented by the change from A to B or from C to D.*



Confirmatory chemical evidence for the relative configurations at C-1 and C-2 was obtained by the following sequence of reactions: 2-Acetoxykessan-8-one (VIII)[11], obtained by the chromic acid oxidation of kessyl glycol 2-acetate (IX), was further oxidized by permanganate to the acetoxydicarboxylic acid (X), which, on being heated in acetic acid, underwent cleavage of the oxide bridge and simultaneous decarboxylation to give the unsaturated acetoxy-hydroxy-monocarboxylic acid (XI).[12] The structure of XI is supported by its NMR spectrum which shows the presence of a secondary methyl, a tertiary methyl, an acetoxyl and an isopropylidene group and by the IR spectrum of its methyl ester which discloses the presence of a hydroxy

* A similar situation has been found in the steroid and triterpenoid series; the ORD data reported by Djerassi (*Tetrahedron* **13**, 13 (1961)) and Klyne (*Ibid.* **13**, 29 (1961)) for the following three pairs of the compounds are in agreement with our assumption.

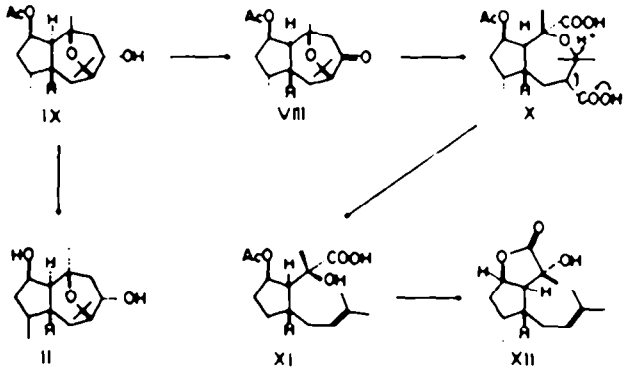


Corresponding changes in the CD curves have been reported by W. O. Godtfredsen, W. von Daehne, S. Vangedal, A. Marquet, D. Arigoni and A. Melera, *Ibid.* **21**, 3505 (1965).

[11] K. Kaneoka and U. Tutida, *Yakugaku Zasshi* **61**, 6 (1941).

[12] K. Kaneoka and S. Kurosaki have obtained this acid in different ways. *Yakugaku Zasshi* **61**, 9 (1941).

group. The monocarboxylic acid (XI) was submitted to alkaline hydrolysis to afford



directly the hydroxy-γ-lactone (XII), the NMR of which still exhibits the presence of an isopropylidene group. Since the ring junction in the γ-lactone must be *cis*,[13] the relative stereochemistry of the hydroxyl at C-2 and the hydrogen at C-1 in XII and thence in I is *trans*, which is in accord with the conclusions described earlier.

Stereochemistry at C-4. Relative configuration of the hydroxyl at C-2 and the methyl group at C-4 must be *cis* in α-kessyl alcohol (I) and *trans* in 2-*epi*-α-kessyl alcohol (IV) or *vice versa*. In an NMR study[14] of 15-hydroxypregnanes containing methyl and hydroxyl groups in quasi-1,3-diaxial relationship, it has been shown that (i) the 18-methyl proton signal shows a noticeable down-field shift (0·23 ppm), whereas in the corresponding *trans* isomer only a small down-field shift (0·03 ppm) is seen compared to the unsubstituted compound, and (ii) this down-field shift decreases in going from the alcohol to its acetate if the hydroxyl is *cis* to the methyl group, but increases slightly if they are *trans*. This general rule was applied to the present series and the chemical shifts of the doublets due to the 14-methyl protons in the four epimeric alcohols and their acetates are listed in Table 1 together with those in the two parent compounds, kessane (XIII) and isokessane (XIV), both of which were derived from kessyl ketone (III) and isokessyl ketone (VI).[15]

As is clear from the Table, an appreciable down-field shift ($\Delta_{\alpha OH-\beta OH}$) of the methyl signal is observed both in α- and iso-series, those in IV and VII being in lower field; the effect of acetylation (Δ_{OAc-OH}) mentioned above is also clearly exhibited. Thus the methyl group at C-4 is *trans* to the 2β-hydroxyl in kessyl alcohol and α-oriented. From the behaviour of the methyl signals in the isokessane series, isokessyl alcohol (V) is concluded to have a 2β-hydroxyl and 2-*epi* isokessyl alcohol (VII) a 2α-hydroxyl.

[13] Cf. P. Crabbé, L. M. Guerrero, J. Rome and F. Sánches-Viesca, *Tetrahedron* **19**, 25 (1963).

[14] Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto and K. Tsuda, *Chem. Pharm. Bull.* **10**, 338 (1962).

[15] H. Hikino, Y. Hikino, Y. Takeshita, K. Shirata and T. Takemoto, *Chem. Pharm. Bull.* **11**, 547 (1963), and the experimental details to be published.

TABLE 1. CHEMICAL SHIFT OF 14-METHYL PROTONS*

Series	alcohol	Δ_{OH-H}	acetate	Δ_{OAc-H}	Δ_{OAc-OH}
Kessane (XIII)	0·78 (6·0)				
α-kessyl alcohol (I)	0·77 (6·0)	- 0·01	0·81 (6·4)	0·03	0·04
2-*epi*-α-Kessyl alcohol (IV)	0·91 (6·7)	0·13	0·90 (6·8)	0·12	-0·01
$\Delta_{\alpha OH-\beta OH}$		0·14		0·09	
Isokessane (XIV)	0·89 (6·2)				
Isokessyl alcohol (V)	0·87 (6·7)	- 0·02	0·90 (6·5)	0·01	0·03
2-*epi*-Isokessyl alcohol (VII)	0·97 (6·5)	0·08	0·95 (6·4)	0·06	- 0·02
$\Delta_{\alpha OH-\beta OH}$		0·10		0·05	

* Chemical shift is expressed in ppm from internal TMS, positive values meaning down-field shift, Coupling constant in parentheses is in c/s.

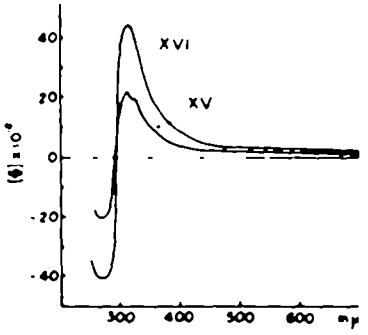
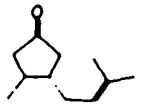
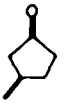


FIG. 2. ORD curves of 3-isopentenyl-4-methylcyclopentanone (XV) and (+)-3-methylcyclopentanone (XVI).

Stereochemistry at C-5. The ORD curve of 3-isopentenyl-4-methylcyclopentanone (XV) supplied by Ukita[4] is shown in Fig. 2 together with that[16] of (+)-3-methylcyclopentanone (XVI). Apparently, both curves exhibit a positive Cotton effect but



XV

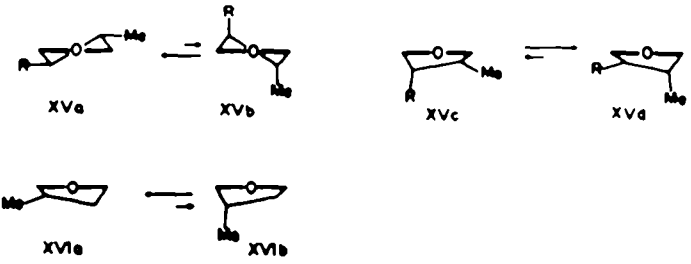


XVI

the amplitude of the former (*a:* 4330) is about a half of that (*a:* 8570) of the latter. Compound XV, which has the same part structure as XVI but is epimeric at C_4, would be expected to exhibit an enhanced negative Cotton effect if the isopentenyl group is *trans* to the methyl group; this is predicted from the assumption that the two substituents would adopt the preferred quasi-equatorial orientation resulting in the conformation XVa rather than XVb. On the other hand, if the two substituents are *cis* to each other, the same assumption leads to the prediction that the amplitude in the case of XV would be smaller than that of XVI and probably with a positive Cotton effect, since the preferred conformation in this case would be XVd rather than XVc because of the comparatively great bulkiness of the isopentenyl group; however, the predominance of XVd over XVc in this conformational equilibrium would be

[16] C. Djerassi, L. A. Mitcher and B. J. Mitcher, *J. Amer. Chem. Soc.* **81**, 947 (1959).

smaller than that of XVIa over XVIb in 3-methylcyclopentanone. Thus the above discussion indicates the relative stereochemistry at C-4 and C-5 to be *cis*.



If all of the assumptions described are correct, the hydrogens at C-1 and C-5 should be in a *trans* relationship in α-kessyl alcohol (I). In order to confirm the stereochemistry at these centers, α-kessyl ketone (III) and isokessyl ketone (VI) were submitted to Baeyer-Villiger oxidation, during which the stereochemistry of the starting ketones is known to be retained in the resulting lactones.[17] Thus α-kessyl lactone (XVII) and isokessyl lactone (XVIII) respectively were obtained as the sole

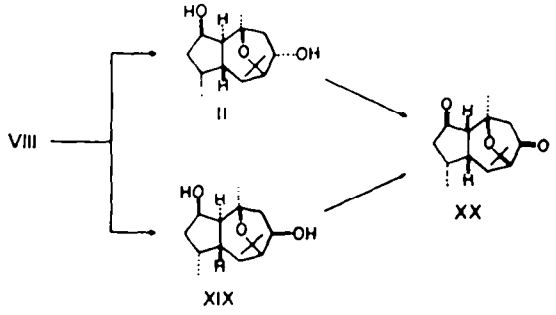
products. The NMR spectra of these lactones show doublets due to the hydrogens at C-1; δ 4·12 ppm (J = 10·2 c/s) for XVII and δ 4·31 ppm (J = 4·0 c/s) for XVIII. The stereochemical relationship between the dihedral angle of two hydrogens attached to adjacent carbons and the coupling constant[18] was applied directly to these values of the coupling constant and a *trans* configuration of the hydrogens at C-1 and C-5 was deduced for XVII and a *cis* stereochemistry for XVIII. From this result, a *trans* relationship at the ring juncture of III and *cis* relationship for VI follows; the conclusion obtained up to this point is consistent for all asymmetric centers in the five-membered ring.

Stereochemistry at C-7 (*and* C-10). Inspection of Dreiding models with the stereochemistry established so far for α-kessyl alcohol (I), 2-*epi*-α-kessyl alcohol (IV), isokessyl alcohol (V), and 2-*epi*-isokessyl alcohol (VII), suggests the possible formation of intramolecular hydrogen bonding in I or in VII, depending on whether the oxide bridge is oriented β or α, respectively. IR measurements on these four epimeric alcohols at 0·001–0·2 M concentration in carbon tetrachloride revealed a concentration-independent band at 3570 cm^{-1} only for I; the other three showed two bands at 3625 cm^{-1} and 3430 cm^{-1}, the relative intensities of which vary with the change in the concentration of the alcohols. Consequently, the oxide bridge is disposed in such a direction that it forms an intramolecular hydrogen bond with 2β-hydroxyl in I, and thus in β orientation.

Stereochemistry at C-8. The above evidence establishes the absolute configuration I for α-kessyl alcohol; the orientation of the C-8 hydroxyl group in kessyl glycol

[17] C. H. Hassel in *Organic Reactions* (Edited by R. Adams), Vol. IX; p. 73. Wiley, New York (1957).
[18] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959); R. J. Abraham and J. S. E. Folker, *J. Chem. Soc.* 806 (1963); K. Kuriyama, E. Kondo and K. Tori, *Tetrahedron Letters* 1485 (1963).

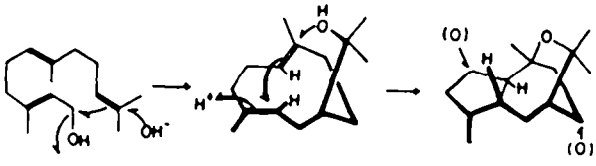
remains to be established. This problem was solved by application of the "benzoate rule". 2-Acetoxykessan-8-one (VIII) was reduced with LAH to give 8-*epi*-kessyl glycol (XIX) together with kessyl glycol (II). Chromic acid oxidation of both glycols furnished, after epimerization at C-1 by alumina, the same diketone XX.



Comparison of the molecular rotation difference $\Delta[M]_D$ of kessyl glycol and its benzoate, with that of 8-*epi*-kessyl glycol and its benzoate, after subtraction of the effect of benzoylation at the C-2 hydroxyl group (−192°, *vide supra*), clearly indicated that the benzoylation effect at the C-8 hydroxyl group is dextrorotatory (+8°) in the kessyl glycol series and laevorotatory (−145°) in the 8-*epi*-kessyl glycol series. Thus an R-configuration for II, and an S-configuration for XIX was deduced.*

Consideration of biogenetic pathway

Elucidation of the absolute configuration of α-kessyl alcohol (I) and kessyl glycol (II) confirmed the structures of kessane (XIII),[15] kessanol (XXI)[19] and 8-*epi*-kessanol (XXII)[19] all of which are congeners found in certain kinds of Japanese valerian root. The established structure for kessane and its corresponding alcohols implies their possible biogenetic pathway from *trans*-farnesol as shown below:



The ten-membered ring alcoholic intermediate[20] formed by the cyclization of *trans*-farnesol would be arranged in such a way that the two double bonds are facing each other in order to make overlap of π-electrons maximal and to undergo cyclization.

* A smaller dextrorotatory value (+22°) compared with the corresponding laevorotatory value (−115°) was also obtained for the respective $\Delta[M]_D$ values in XXI and XXII isolated from certain kinds of Japanese valerian root.[19]

[19] H. Hikino, Y. Hikino, Y. Takeshita and T. Takemoto, *Chem. Pharm. Bull.* **11**, 952 (1963) and the experimental detail to be published.

[20] J. B. Hendrickson, *Tetrahedron* **7**, 82 (1959).

Among several such arrangements, the one depicted is particularly suited for the formation of the kessane skeleton;[21] the *anti*-Markownikoff protonation of one of the double bonds followed by two concerted cyclizations would give rise to kessane with the correct stereochemistry.

EXPERIMENTAL

M.ps are uncorrected; $[\alpha]_D$s were measured in chf unless otherwise stated. NMR spectra were recorded at 60 Mc/s for CCl_4 soln unless otherwise stated. Chemical shift and coupling constant (in parentheses) are expressed in ppm from internal TMS and in c/s, respectively.

α-Kessyl alcohol.[8] Colorless prisms (from light petroleum), $C_{15}H_{26}O_2$, m.p. 85–86°, $[\alpha]_D$ −38·4° (*c* 10·1), IR ν_{max}^{KBr}: 3425 cm^{-1} (OH), $\nu_{max}^{CS_2}$: 3590 cm^{-1} (OH), $\nu_{max}^{CCl_4}$ (0·21–0·001 M): 3595 cm^{-1} (intramolecularly assoc. OH). NMR δ_{ppm}: 0·77 (3H, d, J = 6·5), 1·19 (3H, s), 1·21 (3H, s), 1·28 (3H, s), 3·94 (1H, t, J = 3·5). MS *m/e*: 238 (M$^+$), 223, 205, 177, 159, 149, 126 (base peak), 108, 97.

Acetate:[8] Colorless oil, d_4^{25} 1·053, n_D^{25} 1·486, $[\alpha]_D$ −75·1° (*c* 11·7). IR ν_{max}^{liq}: 1733, 1248 cm^{-1} (acetoxyl). NMR δ_{ppm}: 0·81 (3H, d, J = 6·4), 1·10 (3H, s), 1·23 (6H, s), 2·00 (3H, s), 4·95 (1H, broad t). (Found: C, 72·37; H, 9·76. Calc. for $C_{17}H_{28}O_3$: C, 72·82; H, 10·06%.)

Hydrate:[22] Colorless needles (from light petroleum), m.p. 56–57·5°.

Benzoate: Colorless prisms, m.p. 100–101°, $[\alpha]_D$ −82·7° (*c* 9·2). (Found: C, 76·79; H, 8·89. Calc. for $C_{22}H_{30}O_3$: C, 77·15; H, 8·83%.)

Kessyl glycol diacetate.[22] Colorless prisms (from light petroleum), m.p. 114°, $[\alpha]_D$ −78·5° (*c* 10·4). IR $\nu_{max}^{CHCl_3}$: 1720 cm^{-1} (acetoxyl). NMR δ_{ppm}: 0·85 (3H, d, J = 6·3), 1·12 (3H, s), 1·25 (3H, s), 1·32 (3H, s), 4·92 (1H, t, J = 4), 5·20 (1H, t, J = 8·5). (Found: C, 67·76; H, 8·77. Calc. for $C_{19}H_{30}O_5$: C, 67·43; H, 8·94%.)

Hydrolysis of kessyl glycol diacetate. Kessyl glycol diacetate (310 mg) in ether (20 ml) was added dropwise to LAH (200 mg) in ether (20 ml) under stirring. After 2 more hr stirring at room temp, the excess LAH was decomposed and organic material extracted with ether, which was then washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent left a yellow oil (208 mg) which was distilled *in vacuo* to give II[23] as a colorless oil (191 mg), b.p. 130–135°/4 mm, $[\alpha]_D$ −19·3° (*c* 3·4). IR $\nu_{max}^{CHCl_3}$: 3676, 3472 cm^{-1} (OH). NMR δ_{ppm}: 0·84 (3H, d, J = 6·1), 1·16 (3H, s), 1·33 (6H, s), 3·95 (1H, t, J = 4), 4·27 (1H, t, J = 8). MS *m/e*: 254 (M$^+$), 236, 221, 203, 176, 142, 127, 97, 53 (base peak). (Found: C, 70·50; H, 10·19. Calc. for $C_{15}H_{26}O_3$: C, 70·83; H, 10·30%.)

Dibenzoate: Colorless plates (from cyclohexane), m.p. 189·5–190·5°, $[\alpha]_D$ −50·5° (*c* 3·3). (Found: C, 75·57; H, 7·11. $C_{29}H_{34}O_6$ requires: C, 75·30; H, 7·41%.)

Oxidation of α-kessyl alcohol with chromic acid. Chromic acid soln, prepared from $Na_2Cr_2O_7 \cdot 2H_2O$ (213 mg) and H_2SO_4 (280 mg) in H_2O (1·3 ml) was added to a stirred soln of I (500 mg) in ether (10 ml) over 15 min at 25°. After 3 hr, the ether layer was washed with $NaHCO_3$aq and then H_2O, dried over Na_2SO_4 and evaporated to leave a colorless solid (493 mg) which was crystallized from light petroleum giving III[8] as colorless needles, m.p. 101·5–103°, $[\alpha]_D$ +239° (*c* 10·0). ORD (in MeOH, *c* 0·0726): $[\phi]_{600}$ +590, $[\phi]_{400}$ +1860, $[\phi]_{338}^{peak}$ +8830, $[\phi]_{323}^{trough}$ −8730, $[\phi]_{317}^{peak}$ +9060, $[\phi]_{278}^{trough}$ −5780 $[\phi]_{330}$ −1580. IR ν_{max}^{KBr}: 1730 (cyclopentanone), 1406 cm^{-1} (methylene adjacent to carbonyl). NMR δ_{ppm}: 0·88 (3H, d, J = 6·4), 1·19 (6H, s), 1·25 (3H, s). (Found: C, 76·41; H, 10·14. Calc. for $C_{15}H_{24}O_2$: C, 76·22; H, 10·24%.)

Semicarbazone:[8] Colorless silky needles (from EtOH), m.p. 225° (dec). (Found: C, 65·47; H, 9·27; N, 14·65. Calc. for $C_{16}H_{27}O_2N_3$: C, 65·49; H, 9·28; N, 14·32%.)

Reduction of α-kessyl ketone with lithium aluminum hydride. To a soln of III (50·0 mg) in ether (5 ml), LAH (ca. 10 mg) in ether (10 ml) was added dropwise with stirring at 20–25° and stirring was continued for 4 hr. The reaction mixture was washed with dil. H_2SO_4 and H_2O, and dried over Na_2SO_4. After evaporation of the solvent, the residual product (50·5 mg) was crystallized from light petroleum to give 2-*epi*-*α*-*kessyl alcohol* (IV) as colorless silky needles, m.p. 107–108·5°, $[\alpha]_D$ −37·8° (*c* 10·5). IR ν_{max}^{KBr}: 3425, 3340 cm^{-1} (assoc. OH), $\nu_{max}^{CCl_4}$ (0·21 M): 3627 (free OH), 3430 cm^{-1} (assoc. OH), $\nu_{max}^{CCl_4}$ (0·005 M): 3627 cm^{-1} (free OH). NMR δ_{ppm}: 0·91 (3H, d, J = 6·7), 1·15 (3H, s), 1·21

[21] C. Kaneko and S. Nozoe also discussed the importance of the conformer in biogenesis of certain sesquiterpenes. Abstract of the 9th Symposium on the Chemistry of Natural Products, Osaka, p. 143 (1965).

[22] Y. Asahina and S. Nakanishi, *Yakugaku Zasshi* **49**, 135 (1929).

(6H, s), 3·98 (1H, sextet, J = 6·0, 8·5, 8·5). MS *m/e*: 238 (M^+), 205, 177, 163, 147, 126 (base peak), 109, 97. (Found: C, 75·69; H, 11·13. $C_{16}H_{30}O_3$ requires: C, 75·58; H, 11·00%.)

Acetate: Colorless needles (from EtOH), m.p. 77–78°, b.p. 121–123°/5 mm, d_4^{25} 1·052, n_D^{25} 1·488, $[\alpha]_D$ +85·1° (*c* 4·2). IR ν_{max}^{KBr}: 1724, 1246 cm^{-1} (acetoxyl). NMR δ_{ppm}: 0·90 (3H, d, J = 6·8), 1·05 (3H, s), 1·16 (3H, s), 1·20 (3H, s), 1·93 (3H, s), 4·85 (1H, m). (Found: C, 72·70; H, 10·07. $C_{17}H_{30}O_3$ requires: C, 72·82; H, 10·06%.)

Benzoate: Colorless prisms (from light petroleum), m.p. 91·5–93°, $[\alpha]_D$ +113·4° (*c* 5·5). IR ν_{max}^{KBr}: 1715, 1285 cm^{-1} (ester). (Found: C, 76·94; H, 8·65. $C_{23}H_{34}O_3$ requires: C, 77·15; H, 8·83%.)

Oxidation of 2-epi-α-*kessyl alcohol with chromic acid.* Compound IV (40·0 mg) was oxidized with CrO_3 in the manner above to give colorless crystals (37·8 mg), which after recrystallization from light petroleum gave III as colorless needles, m.p. 102–103°. (Found: C, 76·35; H, 10·26. Calc. for $C_{16}H_{28}O_3$: C, 76·22; H, 10·24%.) The identity was established by mixed m.p. and comparison of IR spectra.

Reduction of α-*kessyl ketone with sodium and ethanol.* Compound III (0·5 g) in EtOH (15 ml) was heated under reflux and small pieces of metallic Na (1·3 g) were gradually added. The mixture was kept on a steam bath for 4 hr, diluted with H_2O (15 ml), and extracted with ether. The product crystallized from light petroleum as colorless needles of V,[9] m.p. 117–118°, $[\alpha]_D$ −13·8° (*c* 10·1). IR ν_{max}^{KBr}: 3425 cm^{-1} (OH), $\nu_{max}^{CCl_4}$ (0·21 M): 3627 (free OH), 3430 cm^{-1} (assoc. OH), $\nu_{max}^{CCl_4}$ (0·005 M): 3627 cm^{-1} (free OH). NMR δ_{ppm}: 0·87 (3H, d, J = 6·3), 1·16 (3H, s), 1·19 (6H, s), 4·11 (1H, m) MS *m/e*: 238 (M^+), 223, 205, 187, 177, 159, 126 (base peak), 108, 97. (Found: C, 75·49; H, 11·04. Calc. for $C_{16}H_{30}O_3$: C, 75·58; H, 11·00%.)

Acetate: Colorless oil, d_4^{25} 1·040, n_D^{25} 1·486, $[\alpha]_D$ −30·0° (*c* 10·3). IR ν_{max}^{liq}: 1727, 1222 cm^{-1} (acetoxyl). NMR δ_{ppm}: 0·90 (3H, d, J = 6·5), 1·05 (3H, s), 1·20 (6H, s), 1·96 (3H, s), 5·1 (1H, m). (Found: C, 72·20; H, 10·04. $C_{17}H_{30}O_3$ requires: C, 72·82; H, 10·06%.)

Oxidation of isokessyl alcohol with chromic acid. Compound V (1·39 g) in ether (10 ml) was stirred with CrO_3 soln, prepared from $Na_2Cr_2O_7 \cdot 2H_2O$ (0·66 g), H_2SO_4 (0·87 g), and H_2O (3·5 ml), at room temp for 3 hr. After being washed and dried, the product (1·30 g) was crystallized from light petroleum to give VI[9] as colorless plates, m.p. 51–52°, $[\alpha]_D$ −171° (*c* 4·6). ORD (in MeOH, *c* 0·0604): $[\phi]_{600}$ −200, $[\phi]_{400}$ −680, $[\phi]_{338}^{through}$ −10100, $[\phi]_{316}^{peak}$ −9200, $[\phi]_{313}^{trough}$ −9840, $[\phi]_{300}^{peak}$ +9300, $[\phi]_{266}$ +6630. IR ν_{max}^{KBr}: 1730 (cyclopentanone), 1407 cm^{-1} (methylene adjacent to carbonyl). NMR δ_{ppm}: 1·04 (3H, d, J = 5·6), 1·26 (9H, s). (Found: C, 75·70; H, 10·19. Calc. for $C_{16}H_{28}O_3$: C, 76·22; H, 10·24%.)

Isomerization of α-*kessyl ketone with alkali.* Compound III (1·0 g) was heated with 10% KOH (5 ml) on a water bath for 12 hr. Extraction with ether gave the product (1·0 g) which on crystallization from light petroleum gave VI as colorless plates, m.p. 51°, $[\alpha]_D$ −170·8° (*c* 10·0). Identity was established by mixed m.p. measurement and comparison of the IR spectra. The same product (VI) was also obtained from α-kessyl ketone by filtering its benzene soln through alumina (alkaline).

Reduction of isokessyl ketone with lithium aluminum hydride. To a soln of VI (0·7 g) in ether (20 ml), was added an excess of LAH in ether (10 ml), and the mixture was stirred for 1 hr. The product obtained was crystallized from light petroleum to give 2-epi-*isokessyl alcohol* (VII) as colorless prisms, m.p. 84–86°, $[\alpha]_D$ +39·1° (*c* 4·1). IR ν_{max}^{KBr}: 3378 cm^{-1} (OH), $\nu_{max}^{CCl_4}$ (0·1 M): 3626 (free OH), 3430 cm^{-1} (assoc. OH), $\nu_{max}^{CCl_4}$ (0·003 M): 3627 cm^{-1} (free OH). NMR δ_{ppm}: 0·97 (3H, d, J = 6·5), 1·16 (3H, s), 1·23 (6H, s), 4·1 (1H, broad m). MS *m/e*: 238 (M^+), 223, 205, 187, 177, 163, 147, 126 (base peak), 109, 108, 97. (Found: C, 75·45; H, 10·93. $C_{16}H_{30}O_3$ requires: C, 75·82; H, 11·00%.)

Acetate: Colorless oil, d_4^{25} 1·051, n_D^{25} 1·490, $[\alpha]_D$ +52·0° (*c* 10·0). IR ν_{max}^{liq}: 1738, 1239 cm^{-1} (acetoxyl). NMR δ_{ppm}: 0·95 (3H, d, J = 6·4), 1·15 (3H, s), 1·23 (6H, s), 1·98 (3H, s), 5·04 (1H, m). (Found: C, 73·30; H, 10·07. $C_{17}H_{30}O_3$ requires: C, 72·82; H, 10·06%.)

Oxidation of 2-epi-*isokessyl alcohol with chromic acid.* Compound V (56 mg) in ether (10 ml) was stirred with CrO_3 soln, prepared from $Na_2Cr_2O_7 \cdot 2H_2O$ (31 mg), H_2SO_4 (35 mg), and H_2O (2 ml), for 3 hr at room temp. Crystallization of the product from light petroleum gave VI as colorless plates, m.p. 50–51°.

Partial hydrolysis of kessyl glycol diacetate. Kessyl glycol diacetate (5·00 g) and KOH (820 mg, 1 eq.) in 80% EtOH (75 ml) was allowed to stand overnight at room temp. After neutralization of alkali with AcOH, the reaction mixture was concentrated to 20 ml and poured into water. Extraction with chf followed by washing with H_2O and drying with Na_2SO_4 and evaporation of the solvent afforded an oil (4·5 g) which was crystallized from ether and then from light petroleum to afford IX[11] as colorless prisms, m.p. 101–103°, $[\alpha]_D$ 65·7° (*c* 9·9). IR $\nu_{max}^{CHCl_3}$: 3636, 3448 (OH), 1724 cm^{-1}

(acetoxyl). NMR δ_{ppm}: 0·85 (3H, d, J = 6·1), 1·03 (3H, s), 1·13 (3H, s), 1·30 (3H, s), 2·00 (3H, s) 4·29 (1H, t, J = 8), 4·88 (1H, t, J = 4). (Found: C, 65·38; H, 9·50. Calc. for $C_{17}H_{28}O_4 \cdot H_2O$: C, 64·94; H, 9·62%.)

Oxidation of kessyl glycol 2-acetate with chromic acid. To the soln of IX (237 mg) in AcOH (15 ml), CrO_3 (100 mg) in AcOH (20 ml) was added dropwise at room temp. After being allowed to stand overnight, the reaction mixture was diluted with H_2O and neutralized with $NaHCO_3$ and extracted with ether, the extract was washed with H_2O and dried over Na_2SO_4. After evaporation of the solvent yellow crystals (178 mg) were obtained and purified by alumina chromatography. The colorless needles (126 mg) eluted with CCl_4 were crystallized from light petroleum–ether to afford VIII,[11] as colorless needles, m.p. 138·5–139·5°, $[\alpha]_D$ +8·9° (*c* 4·9). ORD (in MeOH, *c* 0·198): $[\phi]_{600}$ +40, $[\phi]_{400}$ +220, $[\phi]_{336}^{peak}$ +2140, $[\phi]_{313}^{trough}$ +1910, $[\phi]_{310}^{peak}$ +2320, $[\phi]_{300}^{trough}$ −2720, $[\phi]_{344}$ −1630. IR ν_{max}^{Chf}: 1726 cm^{-1} (acetoxyl and six-membered ketone). NMR δ_{ppm}: 0·79 (3H, d, J = 6·9), 1·20 (3H, s), 1·25 (3H, s), 1·37 (3H, s), 2·02 (3H, s), 4·99 (1H, t, J = 4·5). (Found: C, 68·70; H, 8·98. Calc. for $C_{17}H_{26}O_4$: C, 69·36; H, 8·90%.)

Oxidation of 2-acetoxykessan-8-one with potassium permanganate. The ketone VIII (4·655 g) was suspended in 4% NaOHaq (60 ml) and 6% $KMnO_4$aq (150 ml) was added under stirring at room temp. After 2 hr MnO_2 was filtered off and the filtrate was extracted with ether and the extracts were dried over Na_2SO_4. Evaporation of the solvent gave a yellow oil (0·524 g) (neutral fraction). The water layer was acidified with 2N H_2SO_4 and extracted with ether. After the usual treatment, a yellow oil (3·460 g) was obtained, which was crystallized from ether to afford the *acetoxy-dicarboxylic acid* (X) as colorless prisms, m.p. 175–177°, $[\alpha]_D$ −68·6° (*c* 7·4). IR $\nu_{max}^{CHCl_3}$: 3300–2800 (broad), 1733, 944 cm^{-1} (carboxyl and acetoxyl). (Found: C, 59·70; H, 7·70. $C_{17}H_{26}O_7$ requires: C, 59·63; H, 7·65%.) The dimethyl ester was formed by the action of diazomethane; colorless oil, IR ν_{max}^{Chf}: 1727 cm^{-1} (acetoxyl and ester).

The neutral fraction* mentioned above (524 mg) was further oxidised with 30% H_2O_2 (10 ml) on a water bath for a short time. Working up in the usual way gave the starting material VIII (210 mg) and the X (190 mg).

Decarboxylation of the acetoxy-dicarboxylic acid. The acid X (465 mg) was heated under reflux in AcOH for 3 hr. The reaction mixture was concentrated under red. press., diluted with H_2O, neutralized with $NaHCO_3$, and extracted with chf. The extracts were dried over Na_2SO_4. Evaporation of the solvent gave a brown oil (124 mg). The water layer was acidified with 2N H_2SO_4 and extracted with chf. The same treatment as above gave colorless crystals (307 mg), which were recrystallized from benzene to give XI[12] as colorless prisms, m.p. 159–160°, $[\alpha]_D$ −41·1° (*c* 3·0). IR ν_{max}^{Chf}: 3571, 3436 (OH), 3300–2800 (broad), 1724, 956 cm^{-1} (carboxyl and acetoxyl). NMR $\delta_{ppm}^{CDCl_3}$: 0·91 (3H, d, J = 6·2), 1·51 (3H, s), 1·53 (3H, s), 1·69 (3H, s), 4·8–5·6 (2H, m). (Found: C, 64·44; H, 8·59. Calc. for $C_{16}H_{26}O_5$: C, 64·40; H, 8·78%.)

Methyl ester: Colorless oil, IR ν_{max}^{Chf}: 3571 (OH), 1727 (acetoxyl and ester), 1640 cm^{-1} (double bond).

Hydrolysis of the acetoxy-carboxylic acid. The acid XI (1·833 g) was allowed to stand overnight at room temp with KOH (2·0 g) in 80% EtOH (20 ml). The reaction mixture was concentrated to about 10 ml under red. press., diluted with H_2O and extracted with ether. After being washed with H_2O, the extract was dried over Na_2SO_4. Evaporation of the solvent gave pale yellow crystals (982 mg), which were recrystallized from light petroleum to give XII[13] as colorless plates, m.p. 63–65°. IR ν_{max}^{Chf}: 3597 (OH), 1770 cm^{-1} (γ-lactone). NMR $\delta_{ppm}^{CHCl_3}$: 0·93 (3H, d, J = 6·3), 1·28 (3H, s), 1·62 (3H, s), 1·73 (3H, s), 5·1 (2H, m). (Found: C, 70·42; H, 8·95. Calc. for $C_{14}H_{24}O_3$: C, 70·55; H, 9·31%.)

ORD curve of 3-isopentenyl-4-methylcyclopentanone.[4] Solvent; MeOH (*c* 0·20). $[\phi]_{600}$ +80, $[\phi]_{400}$ +330, $[\phi]_{330}$ +1330, $[\phi]_{313}^{peak}$ +2190, $[\phi]_{273}^{trough}$ −2130, $[\phi]_{260}$ +1740.

Oxidation of α-kessyl ketone with perbenzoic acid. Compound III (406 mg) was allowed to react with perbenzoic acid (551 mg) in chf (15 ml) at 25° for 30 days. The reaction mixture was washed

* Although the neutral fraction was crystallized from ether to give yellow needles, recrystallization from light petroleum failed to give any pure compound with a sharp m.p. and consistent analytical values. IR spectrum of the product was superimposable with that of the "acetylchinon"[13] kindly provided by Professor Ukita. A similar H_2O_2 oxidation of the Kaneoka's sample gave exactly the same result with our product, showing the "acetylchinon" to be a mixture of the 2-acetoxykessane-8,9-dione and the starting material (VIII).

[13] K. Kaneoka and S. Yoshikura, *Yakugaku Zasshi* 61, 8 (1941).

with $NaHCO_3$aq and then with H_2O and dried over Na_2SO_4. Evaporation of the solvent gave an oil (357 mg), which was heated under reflux with 1N ethanolic KOH (13 ml) for 1 hr. The soln was concentrated under red. press., diluted with H_2O (50 ml), and extracted with ether. After acidification with 10% HCl, the aqueous layer was extracted with ether. Ether soln was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent gave the hydroxy-carboxylic acid (168 mg) as a crystalline solid which was heated in Ac_2O (3 ml) for 2 hr. After addition of H_2O, the reaction mixture was neutralized with $NaHCO_3$, and extracted with ether. The residue (135 mg) from the ether soln was chromatographed on alumina (10 g); the benzene eluate (36 mg) afforded a solid which on recrystallization from light petroleum gave *α-kessyl lactone* (XVII) as colorless prisms, m.p. 140·5–141·5°, $[\alpha]_D$ +25·7° (*c* 4·2). IR ν_{max}^{KBr}: 1727 cm^{-1} (δ-lactone). NMR δ_{ppm}: 1·01 (3H, d, J = 6·4), 1·20 (3H, s), 1·23 (6H, s), 4·12 (1H, d, J = 10·2). (Found: C, 71·16; H, 9·54. $C_{18}H_{34}O_3$ requires: C, 71·39; H, 9·59%.)

Oxidation of isokessyl ketone with perbenzoic acid. Isokessyl ketone (304 mg) was oxidized with perbenzoic acid (489 mg) in chf (10 ml) as described in the preceding section. After removal of acidic materials and evaporation, an oil (267 mg) was obtained, which was passed through a silica gel (30 g) column. Besides some recovery of the starting material, a fraction eluted with benzene afforded a crystalline material, which was recrystallized from light petroleum to give *isokessyl lactone* (XVIII; 42·1 mg) as colorless plates, m.p. 115–116°, $[\alpha]_D$ +25·4° (*c* 10·0). IR ν_{max}^{KBr}: 1724 cm^{-1} (δ-lactone). NMR $\delta_{ppm}^{CDCl_3}$: 1·00 (3H, d, J = 5·8), 1·27 (3H, s), 1·30 (6H, s), 4·31 (1H, d, J = 4·0). (Found: C, 72·28; H, 9·36. $C_{18}H_{34}O_3$ requires: C, 71·39; H, 9·59%.)

Reduction of 2-acetoxykessan-8-one with lithium aluminum hydride. Compound VIII (500 mg) in ether (20 ml) was reduced with LAH (750 mg) in ether (20 ml) under stirring for 2 hr at room temp. Working up gave a mixture of II and XIX as a colorless semicrystalline paste (450 mg), in which the latter predominates (determined by NMR). Recrystallization of the mixture from ether and ether–isooctane (1:2) afforded 8-epi-*kessyl glycol* (XIX) as colorless prisms, m.p. 171–173°, $[\alpha]_D$ −35·0° (*c* 4·1). IR $\nu_{max}^{CHCl_3}$: 3558, 3424 cm^{-1} (OH). NMR δ_{ppm}^{Chf}: 0·81 (3H, d, J = 6·9), 1·32 (3H, s), 1·40 (3H, s), 1·44 (3H, s), 4·08 (1H, t, J = 4·5), 4·08 (1H, t, J = 9). MS *m/e*: 254 (M^+), 236, 221, 203, 161, 142, 127, 97, 43 (base peak). (Found: C, 70·18; H, 9·95. $C_{18}H_{34}O_3$ requires: C, 70·83; H, 10·30%.)

Diacetate: Colorless oil, $[\alpha]_D$ −29·2° (*c* 8·2). NMR δ_{ppm}: 0·88 (3H, d, J = 6·3), 1·16 (3H, s), 1·27 (6H, s), 1·97 (3H, s), 1·98 (3H, s), 4·83 (1H, t, J = 9), 4·95 (1H, t, J = 4·5). (Found: C, 67·57; H, 9·12. $C_{18}H_{30}O_5$ requires: C, 67·43; H, 8·94%.)

Dibenzoate: Colorless glassy material, $[\alpha]_D$ −92·2° (*c* 2·7). (Found: C, 75·49; H, 7·41. $C_{32}H_{34}O_5$ requires: C, 75·30; H, 7·16%.)

Oxidation of kessyl glycol with chromic acid. To a soln of II (570 mg) in AcOH (10 ml), an AcOH soln (15 ml) of CrO_3 (600 mg) was added dropwise at room temp and the mixture was allowed to stand overnight at room temp. The reaction mixture was diluted with H_2O, neutralized with $NaHCO_3$ and extracted with chf. After washing with H_2O, and drying over Na_2SO_4, the solvent was evaporated to give a yellow oil (433 mg), which was chromatographed on alumina. Elution with benzene yielded colorless crystals (350 mg). Recrystallization from light petroleum afforded XX[11] as colorless needles m.p. 87–89°, $[\alpha]_D$ −21·9° (*c* 4·9). IR $\nu_{max}^{CHCl_3}$: 1733 cm^{-1} (five- and six-membered ketone). (Found: C, 72·01; H, 8·92. Calc. for $C_{18}H_{32}O_3$: C, 71·97; H, 8·86%.)

Oxidation of 8-epi-*kessyl glycol with chromic acid.* Compound XIX (129 mg) was oxidized with CrO_3 (300 mg) in AcOH as described. The yellow oil (98 mg) obtained was chromatographed on alumina and crystals (73 mg) were eluted by benzene–ether. Recrystallization from light petroleum gave colorless needles, m.p. 91–92°. This was identical with XX.[11]

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