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Structure and Absolute Configuration of Kobusone and Isokobusone[1]

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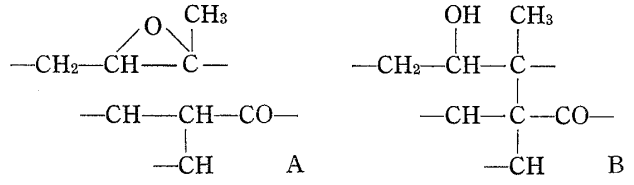
Two norsesquiterpenoids, kobusone and isokobusone, have been newly isolated from nutgrass, *Cyperus rotundus* (Cyperaceae), and shown to have the stereostructures I and VII, respectively, by the spectral properties of them and their derivatives and by transformation of caryophyllene oxide (VI) to the oxido-ketone (I) which has further been converted into the keto-alcohol (VII).

Recently we have been undertaking a chemical study of the essential oil of nutgrass, *Cyperus rotundus* Linné (Cyperaceae), of Japanese origin and hitherto isolated a number of new sesquiterpenoids such as cyperotundone,[3] sugeonol,[4] sugetriol,[5] cyperol, isocyperol,[6] and cyperolone.[7] Continuation of our work has resulted in the further isolation of two norsesquiterpenoids for which the names kobusone and isokobusone are proposed. In the present paper, the stereostructures I and VII for kobusone and isokobusone, respectively, are discussed.

Kobusone has the molecular formula $C_{14}H_{22}O_2$. The infrared (IR) spectrum shows the presence of a carbonyl in a six- or larger-membered ring (1692 cm^{-1}) and geminal dimethyl groups (1384 and 1363 cm^{-1}). In the nuclear magnetic resonance (NMR) spectrum, signals due to two tertiary methyls (8.98 τ), a tertiary methyl on carbon bearing oxygen function (8.75 τ), and a methine adjacent to carbonyl (quartet 7.03 τ) are evident. Therefore, it is concluded that the two oxygens in kobusone are involved in a carbonyl and an oxide function.

Baeyer-Villiger oxidation of kobusone with pertrifluoroacetic acid yielded the lactone (II) which showed an IR band at 1738 cm^{-1} (six- or larger-membered ring lactone). The NMR spectrum exhibits the retention of the three tertiary methyls (9.00, 8.91, and 8.91 τ), the disappearance of the methine next to carbonyl, and the formation of a methine attached to a lactonic oxygen (quartet 5.11 τ).

Kobusone was reduced with lithium aluminum hydride to give the oxido-alcohol (III) whose IR and NMR spectra showed that the carbonyl in kobusone was converted into a secondary hydroxyl (3645, 3480 cm^{-1}, and 6.16 τ). Since the alcohol (III) on oxidation with chromium trioxide-pyridine complex regenerated the parent ketone kobusone, the oxide function in kobusone remained unchanged in the alcohol (III). Signals due to hydrogens on carbons



A

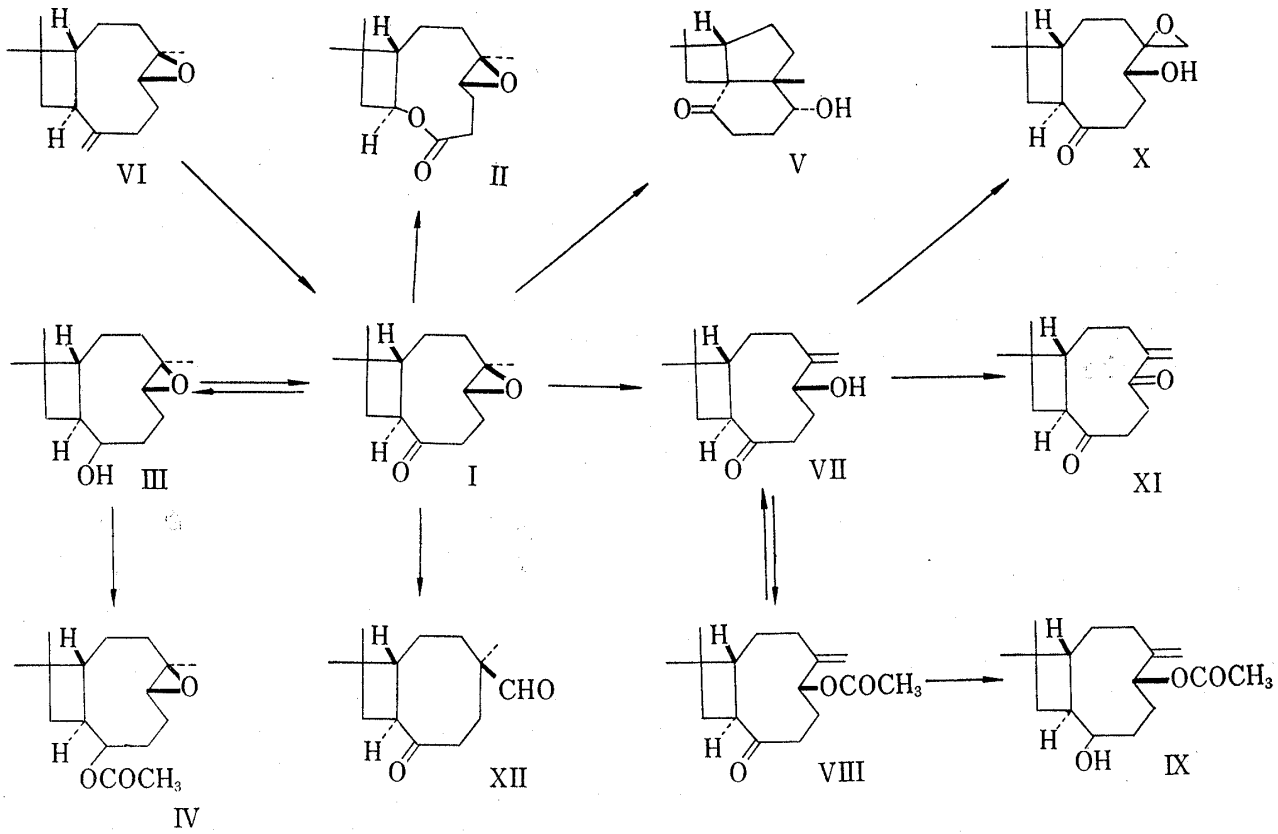
B

1) This paper constitutes Part XXXIII in the series on Sesquiterpenoids. Preceding paper, Part XXXII: H. Hikino, K. Agatsuma, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 959 (1969).
2) Location: *Aobayama, Sendai.*
3) H. Hikino, K. Aota, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 628 (1965); **14**, 890 (1966).
4) H. Hikino, K. Aota, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 52 (1968).
5) H. Hikino, K. Aota, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1433 (1967); **16**, 1900 (1968).
6) H. Hikino, K. Aota, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1929 (1967).
7) H. Hikino, K. Aota, Y. Maebayashi, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **14**, 1439 (1966); **15**, 1349 (1967).

carrying ethereal oxygens in the alcohol (III) and its acetate (IV) appear as quartets at 6.96 and 7.21 τ, respectively. These line positions suggest that the ethereal oxygen in kobusone constitutes an epoxide ring.

Therefore, kobusone has the partial structure as shown in A. Furthermore, since there is no other center of unsaturation, kobusone is bicarbocyclic.

Alkali treatment of kobusone gave two products. The IR and NMR spectra of the main product showed the presence of a secondary hydroxyl (3655, 3510 cm^{-1}, and quartet 6.16 τ), a carbonyl in a six- or larger-membered ring (1698 cm^{-1}), a methylene α to carbonyl (1428 cm^{-1}), and three tertiary methyls (9.18, 9.11, and 9.01 τ). Since there is no other point of unsaturation, the product is consequently tricarbocyclic. Based on the above evidence, it may be concluded that transannular rearrangement from the partial structure A to B has taken place during alkali treatment of kobusone. This transformation suggests that kobusone has an eight- or larger-membered ring in which the carbonyl group and the epoxide are situated.



Meanwhile, we noticed that during the structural elucidation of caryophyllene Barton, *et al.*[8] had obtained a norketone from caryophyllene oxide by permanganate oxidation. The physico-chemical properties and the reactions of the norketone resembled those of kobusone. Then, caryophyllene oxide (VI) was ozonized to give the norketone which was identified as kobusone.

Whereupon it follows that the stereostructure of kobusone is represented by formula I.

Isokobusone also analyzed for $C_{14}H_{22}O_2$. The IR and NMR spectra indicate the presence of a secondary hydroxyl (3420 cm^{-1} and quartet 5.88 τ), a carbonyl in a six- or larger-membered ring (1687 cm^{-1}), a methylene adjacent to carbonyl (1411 cm^{-1}), a methine α to

8) D.H.R. Barton and A.S. Lindsey, *J. Chem. Soc.*, **1951**, 2988; D.H.R. Barton, T. Bruun, and A.S. Lindsey, *ibid.*, **1952**, 2210; A. Aebi, D.H.R. Barton, A.W. Burgstahler, and A.S. Lindsey, *ibid.*, **1954**, 4659; D.H.R. Barton and A. Nickon, *ibid.*, **1954**, 4665.

carbonyl (quartet 6.96 τ), a vinylidene (3075, 920 cm^{-1}, 5.07, and 5.01 τ), and geminal dimethyls (1373, 1357 cm^{-1}, and 9.00 τ). The methine quartets are observed in the NMR spectra of isokobusone acetate (VIII) and other derivatives (X, XII) (*vide infra*) as in the spectrum of kobusone, but not in the spectrum of the diol monoacetate (IX) prepared from the ketol acetate (VIII) by sodium borohydride reduction. That isokobusone contains only one double bond (vinylidene) was shown by its perbenzoic acid oxidation giving the monoepoxide (X).

On oxidation with chromium trioxide–pyridine complex isokobusone gave the dione (XI). The presence of an α,β-unsaturated ketone system was confirmed by the following facts: the UV spectrum exhibited a maximum at 225 mμ, the IR spectrum showed bands at 1680 and 1623 cm^{-1}, and the NMR spectrum displayed a 2H vinyl proton signal at 4.37 τ. The secondary hydroxyl in isokobusone is, therefore, situated at the α-position of the vinylidene group.

Now, the fact that certain spectral properties of isokobusone are similar to those of kobusone (*vide supra*) and that isokobusone coexists with kobusone in the one plant suggests that isokobusone is most probably the isomerized kobusone (VII).

In order to confirm this assignment, direct conversion of kobusone into isokobusone was attempted. Treatment of kobusone with boron trifluoride etherate in benzene gave isomerization products. The main product has the molecular formula $C_{14}H_{22}O_2$ and shows the spectral properties suggestive of the presence of an aldehyde (2710, 1723 cm^{-1}, and singlet 0.62 τ), a carbonyl in a six- or larger-membered ring (1690 cm^{-1}), a methylene adjacent to carbonyl (1419 cm^{-1}), a methine α to carbonyl (quartet 6.80 τ), and three tertiary methyls (9.00, 8.96, and 8.90 τ). Consequently the product was concluded to have the structure XII. Kobusone was next treated with trifluoroacetic acid in methanol to give an isomerized product which was identified as the natural isokobusone.

On the basis of the above evidence, isokobusone is represented by formula VII.

Experimental[9]

Isolation of Kobusone and Isokobusone——The crude drug "Ko-bushi", the dried rhizomes of *Cyperus rotundus* Linné (Japanese name: Hama-suge), was steam distilled to give the essential oil as a pale brown liquid in 0.6% yield.

The oil was chromatographed over alumina and separated roughly into hydrocarbon, ketone, acetate, and alcohol fractions.

The acetate fractions which were submitted to rechromatography on silica gel. Elution with benzene and crystallization from light petroleum yielded kobusone (I) as colorless needles, mp 60—61°, $[\alpha]_D$ −142.2° (c=3.6), MS m/e: 222 (M^+). *Anal.* Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.82; H, 10.08. IR (KBr) cm^{-1}: 1692 (cyclononanone), 1384, 1363 (*gem*-dimethyls). NMR: 6H s at 8.98 ($C\underline{H}_3)_2C<$), 3H s at 8.75 ($C\underline{H}_3$–C<O>CH–), 1H dd at 7.03 (J=9, 17, –CO–C$\underline{H}$(CH–)–CH_2–).

The alcohol fractions which were combined and chromatographed over silica gel. Elution with benzene–AcOEt (2:1) followed by crystallization from ether gave isokobusone (VII) as colorless needles, mp 108—109°, $[\alpha]_D$ −40.1° (c=3.1). *Anal.* Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.48; H, 9.99. IR (KBr) cm^{-1}: 3420 (hydroxyl), 3075, 920 (vinylidene), 1687 (cyclononanone), 1411 (methylene adjacent to carbonyl), 1373, 1357 (*gem*-dimethyls). NMR ($CHCl_3$): 6H s at 9.00 (($C\underline{H}_3)_2C<$), 1H dd at 6.96 (J=9,17, –CO–C$\underline{H}$(CH–)–CH_2–), 1H dd at 5.88 (J=7,8, CH_2=C–C$\underline{H}$(OH)–CH_2–), two 1H unresolved s at 5.07, 5.01 ($C\underline{H}_2$=C<).

Baeyer-Villiger Oxidation of Kobusone with Pertrifluoroacetic Acid——A solution of pertrifluoroacetic acid was prepared by dropwise addition of $(CF_3CO)_2O$ (0.3 ml) to 90% H_2O_2 (0.5 ml) in CH_2Cl_2 (3 ml). The solution was added to a mixture of kobusone (249 mg) and Na_2HPO_4 (1.5 g) in CH_2Cl_2 (3 ml) and the mixture stirred at room temperature for 30 min. After filtering off the salt, the mixture was diluted with water and

9) Melting points are uncorrected. Specific rotations were measured in $CHCl_3$ solution. NMR spectra were recorded at 60 MHz in CCl_4 solution using Me_4Si as internal standard unless otherwise indicated. Chemical shifts are indicated in τ-values and coupling constants (J) in Hz units. Abbreviations: s=singlet, d=doublet, and dd=doublet of doublets.

extracted with CH_2Cl_2. After working up in the usual manner, the product (230 mg) was filtered through silica gel (5 g). Elution with light petroleum–benzene (1:1) gave a crystalline mass (97 mg) which was crystallized from light petroleum to give the lactone (II) as colorless needles, mp 95—96°, $[\alpha]_D$ −47.6° (c=3.7). *Anal.* Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 71.00; H, 9.31. IR (CCl_4) cm^{-1}: 1738 (θ-lactone), 1426 (methylene α to carbonyl), 1382, 1364 (*gem*-dimethyls). NMR: 3H s at 9.00 ($C\underline{H}_3$–C⩽), 6H s at 8.91 ($C\underline{H}_3$–C⩽, $C\underline{H}_3$–C<O>CH–), 1H dd at 5.11 (J=9,17, –CO–O–C$\underline{H}$(CH–)–CH_2–).

Reduction of Kobusone with Lithium Aluminum Hydride——Kobusone (91 mg) was stirred with excess of $LiAlH_4$ in ether (5 ml) at room temperature for 30 min. After isolation in the customary way, the product (100 mg) was crystallized from ether to give the oxido-alcohol (III) as colorless needles, mp 140.5—141°, $[\alpha]_D$ −117.8° (c=3.6). *Anal.* Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.81; H, 10.62. IR ($CHCl_3$) cm^{-1}: 3645, 3480 (hydroxyl), 1380, 1363 (*gem*-dimethyls). NMR ($CHCl_3$): 6H s at 9.03 (($C\underline{H}_3)_2$C<), 3H s at 8.74 ($C\underline{H}_3$–C<O>CH–), 1H dd at 6.96 (J=5,9, –CH_2–C$\underline{H}$<O>C<), 1H unresolved d at 6.16 (J=10, –CH_2–C$\underline{H}$ (OH)–CH<).

Oxidation of the Oxido-alcohol with Chromium Trioxide-Pyridine Complex——The oxido-alcohol (III) (32 mg) in pyridine (0.5 ml) was added to CrO_3 (46 mg) in pyridine (0.5 ml) and left standing at room temperature for 1 day. The product (27 mg), isolated in the usual manner, was crystallized from light petroleum to furnish kobusone (I) as colorless needles, mp 60—61°, identified by the usual criteria.

Acetylation of the Oxido-alcohol——The oxido-alcohol (III) (19 mg) in pyridine (0.5 ml) was treated with Ac_2O (0.2 ml) at room temperature for 1 day. The product (31 mg) isolated in the customary way, was crystallized from light petroleum to give the oxido-acetate (IV) as colorless needles, mp 86—87°, $[\alpha]_D$ −98.4° (c=3.1). *Anal.* Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.01; H, 9.72. IR (CCl_4) cm^{-1}: 1737, 1233 (acetoxyl), 1376, 1363 (*gem*-dimethyls). NMR: 6H s at 9.05 (($C\underline{H}_3)_2$C<), 3H s at 8.78 ($C\underline{H}_3$ –C<O>CH–), 3H s at 7.95 ($C\underline{H}_3$–CO–O–), 1H dd at 7.21 (J=5, 10, –CH_2–C$\underline{H}$<O>C<), 1H unresolved d at 5.25 (J=9, –CH_2–C$\underline{H}$(OCOCH$_3$)–C<).

Alkali Treatment of Kobusone——Kobusone (106 mg) was refluxed under N_2 with ethanolic KOH solution (10%; 8 ml) for 5.5 hr. After working up in the customary manner, the product (118 mg), shown by TLC (silica gel, benzene: AcOEt=10: 3) to be a mixture, was chromatographed over silica gel (5 g).

Elution with benzene yielded a crystalline mass (71 mg) which was crystallized from ether to give the isomeric keto-alcohol (V) as colorless needles, mp 149.5—150°, $[\alpha]_D$ −33.3° (c=3.5), MS m/e: 222 (M^+). IR (CCl_4) cm^{-1}: 3655, 3510 (hydroxyl), 1698 (cyclohexanone), 1428 (methylene next to carbonyl), 1374, 1357 (*gem*-dimethyls). NMR ($CHCl_3$): 3H s at 9.18 ($C\underline{H}_3$–C⩽), 3H s at 9.11 ($C\underline{H}_3$–C⩽), 3H s at 9.01 ($C\underline{H}_3$–C⩽), 1H dd at 6.16 (J=6, 10, –CH_2–C$\underline{H}$(OH)–C⩽).

Successive elution with benzene–AcOEt (5:1) afforded a crystalline mass (24 mg) which was crystallized from ether to give a keto-alcohol as colorless needles, mp 151—152°, $[\alpha]_D$ +75.3° (c=3.7), MS m/e: 222 (M^+), IR ($CHCl_3$) cm^{-1}: 3630, 3480 (hydroxyl), 1703 (carbonyl in six- or larger-membered ring), 1409 (methylene adjacent to carbonyl). NMR ($CHCl_3$): 6H s at 9.04 (($C\underline{H}_3)_2$C<), 3H s at 8.97 ($C\underline{H}_3$–C⩽), 1H multiplet at∼6.9 ($\underline{H}$–C⩽O–).

Ozonolysis of Caryophyllene Oxide——Caryophyllene oxide (VI) (170 mg) in AcOEt (8 ml) was ozonized at 0° for 1 hr. The reaction mixture was stirred with PtO_2 (50 mg) under H_2 for 30 min. After working up in the usual way, the product was chromatographed on alumina (5 g). Ether eluted a crystalline mass (123 mg) which was crystallized from light petroleum to give the oxido-ketone as colorless needles, mp 60—61°, $[\alpha]_D$ −138.9° (c=3.6). IR (CCl_4) cm^{-1}: 1698 (cyclononanone), 1380, 1366 (*gem*-dimethyls). NMR: 6H s at 8.98 (($C\underline{H}_3)_2$C<), 3H s at 8.75 ($C\underline{H}_3$–C<O>CH–), 1H dd at 7.03 (J=9, 17, –CO–C$\underline{H}$(CH–)–CH_2–), identified as the natural kobusone (I) by mixed melting point and comparison of IR and NMR spectra.

Acetylation of Isokobusone——Isokobusone (20 mg) in pyridine (0.5 ml) was treated with Ac_2O (0.3 ml) at room tempetature for 1 day. Upon isolation, the product (25 mg) was crystallized from light petroleum to give isokobusone acetate (VIII) as colorless needles, mp 124—125°, *Anal.* Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.45; H, 9.20. IR (CCl_4) cm^{-1}: 3100, 1645, 914 (vinylidene), 1740, 1230 (acetoxyl), 1705 (cyclononanone), 1413 (methylene α to carbonyl), NMR: 6H s at 8.90 (($C\underline{H}_3)_2$C<), 3H s at 8.03 ($C\underline{H}_3$–CO–O–), 1H dd at 7.08 (J=9, 17, –CO–C$\underline{H}$(CH–)–CH_2–), two 1H unresolved s at 5.07, 4.98 ($C\underline{H}_2$=C<), 1H broad peak at *ca.* 4.95 (CH_2=C–C$\underline{H}$(OCOCH$_3$)–CH_2–).

Hydrolysis of Isokobusone Acetate——Isokobusone acetate (VIII) (30 mg) in EtOH (0.5 ml) was hydrolyzed in ethanolic KOH solution (10 mg/0.3 ml) at room temperature for 30 min. After isolation in the usual manner, the product (25 mg) on crystallization from ether yielded isokobusone as colorless needles, mp 108—109°, identified by the usual criteria.

Reduction of Isokobusone Acetate with Sodium Borohydride——Isokobusone acetate (VIII) (27 mg) and excess of $NaBH_4$ were stirred in MeOH (1 ml) at room temperature for 2 hr. The product (28 mg) isolated by AcOEt extraction was crystallized from ether to give the diol monoacetate (IX) as colorless needles, mp 142—143°. *Anal.* Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.01; H, 9.72. IR (KBr) cm^{-1}: 3510 (hydroxyl), 3060, 1650, 881 (vinylidene), 1716, 1258 (acetoxyl). NMR ($CDCl_3$): 6H s at 9.03 (($C\underline{H}_3)_2$C<), 3H s at 8.95 ($C\underline{H}_3$–CO–O–), 1H broad peak at 6.38 (–CH_2–C$\underline{H}$(OH)–CH<), 2H unresolved single peak at

4.96 ((CH_2=C<), 1H broad peak at 4.78 (CH_2=C–C<u>H</u>(OCOCH$_3$)–CH_2–).

Epoxidation of Isokobusone with Perbenzoic Acid——Isokobusone (34 mg) and BzO_2H (25 mg) in $CHCl_3$ (1.5 ml) was kept at room temperature for 3 days. The reaction mixture was washed with 10% NaOH solution and then with water, and evaporated. The residue (38 mg) was crystallized from AcOEt to give epoxy-isokobusone (X) as colorless needles, mp 166—167°, $[\alpha]_D$ −32.0° (c=2.5). *Anal.* Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.32; H, 9.21. IR ($CHCl_3$) cm^{-1}: 3610, 3425 (hydroxyl), 1693 (cyclononanone), 1416 (methylene next to carbonyl), 1380, 1363 (*gem*-dimethyls), NMR ($CDCl_3$): 3H s at 9.00 (C<u>H</u>$_3$–C<), 3H s at 8.98 (C<u>H</u>$_3$–C<), 2H s at 7.35 (C<u>H</u>$_2$<O>C<), 1H dd at 6.82 (J=7, 9, –CH_2–C<u>H</u>(OH)–C<).

Oxidation of Isokobusone with Chromium Trioxide-Pyridine Complex——Isokobusone (26 mg) in pyridine (0.8 ml) was added to Cr_3O (35 mg) in pyridine (0.5 ml) and left standing at room temperature for 1 day. Upon isolation with ether, the product (22 mg) was crystallized from light petroleum to give the dione (XI) as colorless needles, mp 44—45°. *Anal.* Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.15; H, 9.02. UV_{max}^{EtOH} mμ (log ε): 255 (3.77). IR (CCl_4) cm^{-1}: 1695 (cyclononanone), 1680, 1623 (α-vinylidene cyclononanone), 1410 (methylene α to carbonyl). NMR: 3H s at 9.05 (C<u>H</u>$_3$–C<), 3H s at 9.02 (C<u>H</u>$_3$–C<), 2H unresolved peak at 4.37 (C<u>H</u>$_2$=C–CO–).

Treatment of Kobusone with Boron Trifluoride Etherate——Kobusone (189 mg) was treated with BF_3–ether (0.5 ml) in benzene (1 ml) at room temperature for 15 min. The mixture was worked up in the customary manner and the product (190 mg) was chromatographed over silica gel (10 g). Elution with benzene gave a crystalline mass (90 mg) which was crystallized from ether to yield the keto–aldehyde (XII) as colorless needles, mp 117—118°, $[\alpha]_D$ +54.3° (c=4.2). *Anal.* Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.58; H, 10.04. IR ($CHCl_3$) cm^{-1}: 2710, 1723 (aldehyde), 1690 (cyclooctanone), 1419 (methylene adjacent to carbonyl). NMR ($CHCl_3$): 3H s at 9.00 (C<u>H</u>$_3$–C<), 3H s at 8.96 (C<u>H</u>$_3$–C<), 3H s at 8.90 (C<u>H</u>$_3$–C<), 1H dd at 6.80 (J=9, 17, –CO–C<u>H</u>(CH–)–CH_2–), 1H s at 0.62 (O<u>H</u>C–C<).

Treatment of Kobusone with Trifluoroacetic Acid——Kobusone (240 mg) in MeOH (1 ml) was stirred with CF_3COOH (0.3 ml) at room temperature for 5 hr. The reaction mixture was diluted with water and extracted with AcOEt. The product (243 mg) was chromatographed over silica gel (6 g). Elution with light petroleum–benzene (1:1) yielded a crystalline mass (181 mg) which on crystallization from light petroleum gave the starting kobusone (I) as colorless needles, mp 60—61°, identified in the usual criteria. Successive elution with benzene–AcOEt (10:3) afforded a crystalline mass (27 mg) which was crystallized from ether furnished the isomerized kobusone (VII) as colorless needles, mp 108—109°, $[\alpha]_D$ −41.3° (c=3.5). IR ($CHCl_3$) cm^{-1}: 3635, 3450 (hydroxyl), 3090, 910 (vinylidene), 1690 (cyclononanone), 1409 (methylene next to carbonyl), 1373, 1359 (*gem*-dimethyls). NMR ($CHCl_3$): 6H s at 9.00 ((C<u>H</u>$_3$)$_2$C<), 1H dd at 6.96 (J=9, (C<u>H</u>$_3$)$_2$C<17, –CO–C<u>H</u>(CH–)–CH_2–), 1H dd at 5.88 (J=7, 8, CH_2=C–C<u>H</u>(OH)–CH_2–), two 1H unresolved s at 5.07, 5.01 (C<u>H</u>$_2$=C–CH(OH)–), identified as the natural isokobusone by mixed melting point and comparison of IR and NMR spectra.

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