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Structure and Absolute Configuration of Sugeonol[1]

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From nutgrass, *Cyperus rotundus* (Cyperaceae), a new sesquiterpenic ketol has been isolated as the acetate and named sugeonol whose stereostructure I has been deduced from the following evidence. Spectral determinations of sugeonol and its acetate (II) indicate the presence of a 2-methyl-3-substituted-cyclopent-2-enone system. Chemical and physico-chemical properties of its derivatives (III and IV) have established that the hydroxyl group of sugeonol is situated at the γ-position of the α,β-unsaturated ketone system and in another cyclopentane ring. Oxidation of sugeonol with selenium dioxide has given the trione (VI) derived from cyperotundone (V) establishing the skeleton of sugeonol. The coupling constant between the C-6 and C-7 hydrogens shows the C-6 hydroxyl to be α-oriented.

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Our recent studies on the essential oil of nutgrass, *Cyperus rotundus* Linné (Cyperaceae), of Japanese origin have led to the isolation and structural elucidation of various sesquiterpenic constituents such as α-cyperone, cyperotundone,[3] cyperolone,[4] cyperol, and isocyperol.[5] We have further undertaken the investigation of acetate fractions and isolated an acetate of a new sesquiterpenoid ketol for which the name sugeonol is proposed. It will be shown in the present paper that sugeonol is represented by stereoformula I.

Sugeonol is present in nature as its acetate (II) which possesses formula $C_{17}H_{24}O_3$. The infrared spectrum showed bands at 1704 and 1674 cm^{-1} attributed to a cyclopentenone moiety, and a characteristic band at 1418 cm^{-1} due to a methylene adjacent to carbonyl as well as bands at 1735 and 1231 cm^{-1} associated with an acetoxyl group. The ultraviolet spectrum exhibited a maximum at 246.5 mμ (log ε 4.14) suggestive of a fully substituted α,β-unsaturated ketone. The nuclear magnetic resonance (NMR) spectrum indicated the presence of four methyls, *i.e.*, one being secondary, two tertiary, and one vinylic, but no vinylic hydrogen. The line position (1.74 ppm) of the vinylic methyl signal indicated it to be situated at the α-position of an α,β-unsaturated ketone in S-*trans* configuration.[6] From these spectral characteristics, it is clear that the substance (II) has a 2-methyl-3-substituted-2-cyclopentenone system with a methylene grouping next to the carbonyl.

On alkaline hydrolysis the acetate (II) gave the free ketol (I), sugeonol, which showed essentially the same infrared and NMR properties to those of its acetate (II) described above, except for the differences caused by replacement of the acetoxyl by a hydroxyl group.

We next examined the nature and environment of the hydroxyl (or acetoxyl) group. The NMR spectra of both substances (I and II) recorded 1H signals for hydrogens on carbons bearing oxygen functions at 4.98 and 5.76 ppm, respectively. Therefore, the hydroxyl group in sugeonol is secondary. The deshielded chemical shifts of these signals suggested that they should be α to unsaturated systems. This assignment was further verified by double

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[1] This paper is Part XIX in the series on Sesquiterpenoids. Preceding paper, Part XVIII: H. Hikino, K. Ito, K. Aota, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 43 (1968).

[2] Location: *Kita-4-bancho, Sendai.*

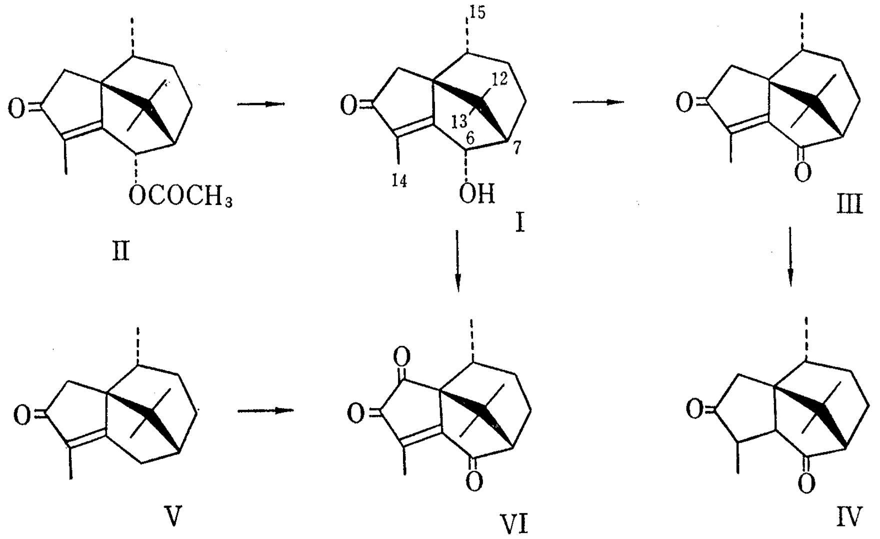
[3] H. Hikino, K. Aota, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 628 (1965); **14**, 890 (1966).

[4] H. Hikino, K. Aota, Y. Maebayashi, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **14**, 1439 (1966); **15**, 1349 (1967).

[5] H. Hikino, K. Aota, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1929 (1967).

[6] cf. W. von E. Doering, M.R. Willcott, III, and M. Jones, Jr., *J. Am. Chem. Soc.*, **84**, 1224 (1962).

resonance experiments of the acetate (II) which revealed that the olefinic methyl protons and the proton on carbon attached to the acetoxyl were long-range coupled (J=1.1 cps) with each other. In order to confirm the location of the hydroxyl group, oxidation of sugeonol with chromium trioxide-pyridine complex was carried out. The diketone (III) thus obtained exhibited an ultraviolet maximum at 272 mμ (log ε 4.03). The observed bathochromic shift (+21—25 mμ) of the maximum as compared with those of the original ketol (I) and its acetate (II) demonstrated that the newly formed carbonyl group became conjugated with the α,β-unsaturated ketone system at the γ-position. Therefore, it follows that the hydroxyl group in sugeonol is situated γ to the α,β-unsaturated ketone system. The infrared spectrum of the dione (III) showed bands at 1724 and 1713 cm^{-1}. Therefore, the newly formed ketonic group must also be located in a five membered ring. Thus, as can be expected, the ene-dione (III) had to be easily reduced with zinc and acetic acid, as indeed was the case. The infrared spectrum of the resulting saturated dione (IV) exhibited band at 1740 cm^{-1} assigned to cyclopentanones but no band ascribable to a cyclohexanone. Since the infrared and NMR spectra of the diones (III and IV) excluded that the two carbonyl groups were oriented in the same cyclopentane ring, sugeonol must contain two five-membered rings fused with each other.



Now, the evidence so far obtained together with the fact that sugeonol coexists with cyperotundone (V) in the same plant suggests that sugeonol is 6-hydroxycyperotundone. The spectral features described below also fit eminently in the framework of cyperotundone (V). 1) The ultraviolet spectra of sugeonol and the acetate (II) are practically identical with that (λ_{max} 245 mμ (log ε 3.96)) of cyperotundone (V). Moreover, the circular dichroism curves exhibited the negative Cotton effect ($[\theta]_{321}$ -89×10^2 and $[\theta]_{324}$ -74×10^2, respectively) and are similar to that ($[\theta]_{314}$ -54×10^2) of cyperotundone.[7] The differences in these curves may be ascribable to the contributions of the substitutents at the γ-positions of the α,β-unsaturated ketone systems.[8] 2) The NMR spectra of sugeonol and its acetate (II) resemble that of cyperotundone (V). Thus, the chemical shifts of the signals originating from the methyl groups of sugeonol and its acetate (II) differ only very slightly from those of cyperotundone (V)(see Table I).

Rigorous proof for the carbon skeleton of sugeonol has been obtained as follows. Thus, a direct conversion of cyperotundone (V) to sugeonol or its derivatives was next tried. An

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[7] H. Hikino, K. Ito, K. Aota, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 44 (1968).

[8] This will be discussed in detail in our forthcoming paper.

TABLE I

Compounds	Solvents	Chemical shifts of the methyl protons (in ppm from TMS)			
		C–12	C–13	C–15(α)	C–14
Sugeonol (I)	$CHCl_3$	1.12	0.76	0.62	1.88
Sugeonyl acetate (II)	CCl_4	1.13	0.87	0.65	1.74
Cyperotundone (V)	CCl_4	1.17	0.75	0.61	1.67

attempt to oxidize cyperotundone (V) with *tert*–butyl chromate to the dione (III), however, resulted in the recovery of the starting material (V). Attempted oxidation of cyperotundone (V) with mercuric acetate to sugeonyl acetate also failed recovering the original ketone (V). With the objective of obtaining sugeonol, cyperotundone (V) was oxidized with selenium dioxide yielding not the desired ketol but a trione whose structure was elucidated as VI by a a molecular weight determination and spectral analyses. Then, sugeonol was also treated with the same reagent to give a trione. Both triones were identical and the carbon skeleton of sugeonol was thus established.

The hydroxyl group must consequently be situated at C–6. After the establishment of the cyperotundone skeleton for sugeonol, it is predicted that a coupling constant between C–6α and C–7 hydrogens (dihedral angle: 20—30°) is fairly large, while that between C–6β, and C–7 hydrogens (dihedral angle: 100—90°) is very small, judging by inspection of Dreiding models, and from a Karplus type relationship between the coupling constant and the dihedral angle between vicinal protons. In reality, the observed coupling constants measured for the slightly multiplying doublets arising from the C–6 hydrogens in sugeonol and the acetate (II) were both 6 cps indicating the C–6 hydroxyl group to be oriented in the α–configuration.

Based on the above evidence, sugeonol is concluded to have the stereostructure I.

Experimental[9]

Isolation of Sugeonyl Acetate——The crude drug "Kō–bushi," the dried rihzomes 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.[3]

The oil was chromatographed on alumina. After percolation of ketone fractions with benzene, successive elution with the same solvent afforded acetate fractions which were combined and chromatographed on silica gel. When eluted with benzene, a crystalline substance was obtained which was crystallized from light petroleum to give sugeonyl acetate (II) as colorless needles, mp 94—94.5°, $[\alpha]_D$ +63.2°(c=4.2), CD (c=0.0502, dioxane): $[\theta]_{324}$ -74×10^2, *Anal.* Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.85; H, 8.87, UV λ_{max}^{EtOH} mμ (log ε): 246.5 (4.14), IR (KBr) cm^{-1}: 1735, 1231 (acetoxyl), 1704, 1674 (cyclopentenone), 1418 (methylene adjacent to carbonyl), NMR (CCl_4): doublet (3H) at 0.65 (J=7, $C\underline{H}_3$–CH⟨), singlet (3H) at 0.87 ($C\underline{H}_3$–C⋖), singlet (3H) at 1.13 ($C\underline{H}_3$–C⋖), doublet (3H) at 1.74 (J=1.1, $C\underline{H}_3$–C=C–CH⟨), singlet (3H) at 2.10 ($C\underline{H}_3$–CO–O–), slightly splitting doublet (1H) at 5.76 (J=6, ⟩C=C–C$\underline{H}$($OCOCH_3$)–CH⟨).

Hydrolysis of Sugeonyl Acetate——Sugeonyl acetate (II)(83 mg) was hydrolyzed in ethanolic NaOH solution (22 mg/1ml) for 2 hr. The mixture was diluted with H_2O and extracted with ether. The extract (79 mg) on crystallization from ether yielded sugeonol (I) as colorless needles, mp 181—182.5°, $[\alpha]_D$ +87.5° (c=3.8), CD (c=0.0603, dioxane): $[\theta]_{321}$ -89×10^2, *Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.76; H. 9.47, UV λ_{max}^{EtOH} mμ (log ε): 251 (4.10), IR ($CHCl_3$) cm^{-1}: 3640,3430 (hydroxyl), 1696, 1660 (cyclopentenone), 1416 (methylene α to carbonyl), IR (KBr) cm^{-1}: 3380 (hydroxyl), 1685, 1647 (cyclopentenone), 1416 (methylene α to carbonyl), NMR ($CHCl_3$): doublet (3H) at 0.62 (J=7, $C\underline{H}_3$–CH–), singlet (3H) at 0.76 ($C\underline{H}_3$–C⋖), singlet (3H) at 1.12 ($C\underline{H}_3$–C⋖), doublet (3H) at 1.88 (J=1, $C\underline{H}_3$–C=C–CH⟨), slightly multiplying doublet (1H) at 4.98 (J=6, ⟩C=C–C$\underline{H}$(OH)–CH⟨).

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[9] Melting points are uncorrected. Specific rotations were measured for $CHCl_3$ solution. NMR spectra were determined at 60 Mcps. Chemical shifts are given in ppm units from Me_4Si as internal standard and coupling constants (J) in cps.

Oxidation of Sugeonol with Chromium Trioxide–Pyridine Complex——Sugeonol (33 mg) in pyridine (0.8 ml) was added to CrO_3 (41 mg) in pyridine (0.3 ml) and kept at room temperature for 4 hr. Upon isolation in the usual manner, the product (31 mg) was sublimed *in vacuo* to give the ene–dione (III) as pale yellow needles, mp 43.5—44°, CD ($c=0.0601$, dioxane): $[\theta]_{400}$ -22×10^2, $[\theta]_{352}$ $+17\times10^2$, UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ ($\log\varepsilon$): 272 (4.03), IR (CCl_4) cm^{-1}: 1713 (conjugated five membered ring ketones), 1415 (methylene next to carbonyl), NMR (CCl_4): doublet (3H) at 0.68 ($J=6$, $\mathrm{C\underline{H}_3{-}CH}\langle$), singlet (3H) at 0.88 ($\mathrm{C\underline{H}_3{-}C}\mathrel{-\!\!\!<}$), singlet (3H) at 1.17 ($\mathrm{C\underline{H}_3{-}C}\mathrel{-\!\!\!<}$), singlet (3H) at 2.00 ($\mathrm{-CO{-}C(C\underline{H}_3){=}C{-}CO{-}}$).

Reduction of the Ene–dione with Zinc and Acetic Acid——The ene–dione (III) (17 mg) in AcOH (0.5 ml) was heated at 100° with Zn dust (0.1 g) for 1 hr. The solids were removed by filtration and the product was isolated by diluting the filtrate with H_2O followed by extraction with ether. The combined extracts were evaporated to afford the γ–dione (IV) as a colorless oil (16 mg), IR (CCl_4) cm^{-1}: 1740 (cyclopentanones), 1411 (methylene α to carbonyl).

Attempted Oxidation of Cyperotundone with *tert*–Butyl Chromate——To cyperotundone (V) (75 mg) in CCl_4 (1ml) was added a mixture of $CrO_2(O\text{-}tert\text{-}Bu)_2$ solution (solution B,[10] 1 ml), AcOH (0.3 ml), and Ac_2O (1.2 ml) dropwise with stirring at 70—80° over a period of 30 min and the stirring was continued for a further 3 hr. Isolation in the customary way gave the unchanged cyperotundone (V), identified in the usual criteria.

Attempted Oxidation of Cyperotundone with Mercuric Acetate——Cyperotundone (V) (52 mg) in AcOH (4 ml) was heated with $(AcO)_2Hg$ (160 mg) at 60—70° for 4 hr. Dilution with H_2O and extraction with ether followed by evaporation of the organic solvent afforded the recovered cyperotundone (V), identified in the usual criteria.

Oxidation of Cyperotundone with Selenium Dioxide——Cyperotundone (V) (38 mg) in AcOH (2 ml) was heated under reflux for 5 hr with SeO_2 (42 mg). After dilution with H_2O and isolation of the product with ether a red oil was obtained on evaporation of the solvent. Percolation through alumina (1 g) and elution with ether yielded a crystalline mass (40 mg) which was crystallized from light petroleum to furnish the trione (VI) as pink needles,[11] mp 106—108°, mol. wt. 246 (mass spec.), IR (CCl_4) cm^{-1}: 1766, 1713 (1,2–dione, conjugated five–membered ring ketone), NMR: doublet (3H) at 0.70 ($J=7$, $\mathrm{C\underline{H}_3{-}CH}\langle$), singlet (3H) at 0.87 ($\mathrm{C\underline{H}_3{-}C}\mathrel{-\!\!\!<}$), singlet (3H) at 1.38 ($\mathrm{C\underline{H}_3{-}C}\mathrel{-\!\!\!<}$), singlet (3H) at 2.21 ($\mathrm{-CO{-}C(C\underline{H}_3){=}C{-}CO{-}}$).

Oxidation of Sugeonol with Selenium Dioxide——Sugeonol (56 mg) was oxidized with SeO_2 in the same procedure described above to give a red oil which was dissolved in ether and filtered through alumina (1 g). Evaporation of the filtrate gave a crystalline mass (51 mg) which on crystallization from light petroleum afforded the trione (VI) as pink needles,[11] mp 108—109°, identified as the trione (VI) derived from cyperotundone (V) by mixed mp and comparison of IR and NMR spectra.

Acknowledgement Thanks are due to Analytical Laboratory, Department of Chemistry, this University, for the mass spectrum, and to Analytical Laboratories, this Institute, for the NMR spectra and microanalyses.

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[10] R.V. Oppenauer and H. Oberrauch, *Anales asoc. quim. argentina*, **37**, 246 (1949) (*C.A.*, **44**, 3909 (1950)).

[11] A trace amount of colloidal Se could not be removed by chromatography, sublimation, crystallization, and treatment with precipitated Ag.