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STRUCTURE AND ABSOLUTE CONFIGURATION OF α-ROTUNOL AND β-ROTUNOL, SESQUITERPENOIDS OF *CYPERUS ROTUNDUS**

H. HIKINO, K. AOTA, D. KUWANO and T. TAKEMOTO
Pharmaceutical Institute, Tohoku University, Aoba-yama, Sendai, Japan

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Abstract—Two novel sesquiterpenic keto-alcohols, α-rotunol and β-rotunol, have been isolated from nutgrass, *Cyperus rotundus* ;Cyperaceae). The stereostructure II of β-rotunol is based on spectral properties and by transformation to the dienone (V) which has also been derived from hinesol (VI). α-Rotunol has been given the stereostructure I based on its physico-chemical properties.

NUTGRASS, *Cyperus rotundus* Linné (Cyperaceae), a perennial herb of tropical and temperate zones. In Japan, it is called "Ko-bushi" and used as a Chinese medicine for the treatment of women's diseases.

From the crude drug collected in Japan, we have hitherto isolated a number of sesquiterpenoids, cyperotundone,[1] sugeonol,[2] sugetriol,[3] cyperol, isocyperol,[4] kobusone, isokubosone,[5] and cyperolone.[6] Continuation of our work has resulted in the further isolation of two novel sesquiterpenic keto-alcohols for which the terms α-rotunol and β-rotunol are given. The present study has led to the elucidation of the structures and absolute configurations of these two sesquiterpenoids as represented by formulas I and II, respectively. The evidence will now be discussed in this paper.†

β-Rotunol analysed for $C_{15}H_{22}O_2$ which was confirmed by a mass-spectrometic determination (Fig 1). It was disclosed as a conjugated ketone by its UV absorption (λ_{max} 235 nm (log ε 4·13)) whilst its IR absorption (ν_{max} 1640 cm^{-1}) suggests that the chromophore is situated in a six- or larger-membered ring. A vinyl Me signal (δ 1·99 ppm; NMR) is coupled to a vinyl hydrogen signal (δ 5·89 ppm; NMR), indicating the presence of a triply substituted ethylenic linkage. Further the line positions of both signals, coupled with the UV and IR spectral evidence, demonstrate that a β-methyl-α,β-unsaturated ketone system is present. In the NMR spectrum, there are two doublets at 2·07 and 2·71 ppm (J = 17 Hz) in an AB system, in which the former is coupled to the vinyl hydrogen signal at 5·89 ppm. These signals along with an IR band at 1410 cm^{-1} are consistent with the presence of a methylene grouping which is next to the CO and also adjacent to a quaternary carbon. Furthermore, the IR and NMR spectra indicate the presence of a tertiary Me (δ 1·15 ppm), a vinyl Me (δ 1·74 ppm) and a vinylidene group (ν_{max} 3100, 890 cm^{-1}, δ 4·75 ppm). The latter two functions are inserted in an isopropenyl group, since platinum catalysed partial hydrogenation of β-rotunol yielded the dihydroderivative (III) whose NMR spectrum shows the disappearance of the signals due to these functions in β-rotunol and instead the forma-

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† A preliminary account of this work has been announced; H. Hikino, K. Aota, D. Kuwano and T. Takemoto, *Tetrahedron Letters* 2741 (1969).

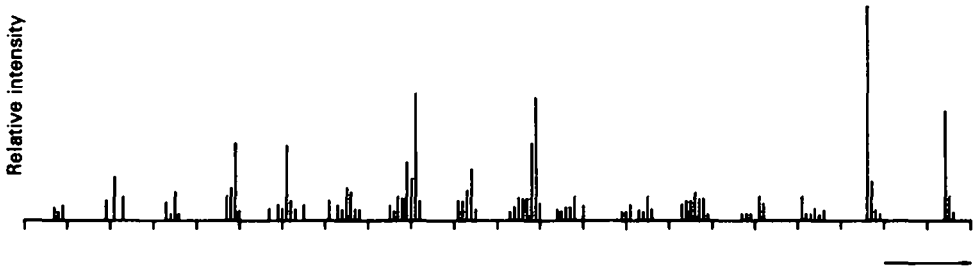


FIG. 1. Mass spectrum of β-rotunol (70 ev) *m/e*

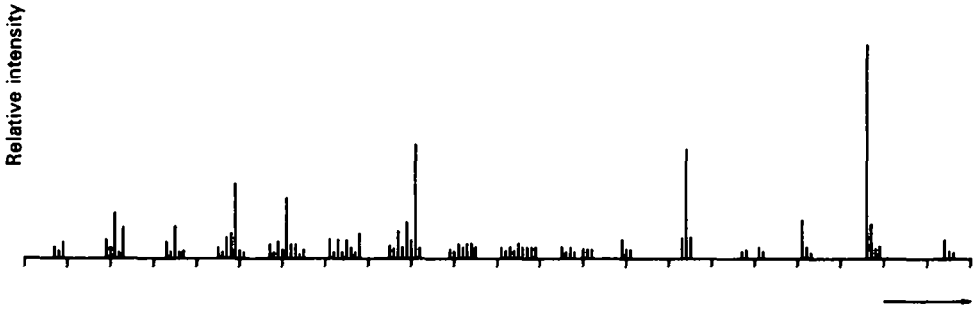


FIG. 2. Mass spectrum of α-rotunol (70 ev) *m/e*

tion of a 6H doublet for an isopropyl group. On the other hand, β-rotunol shows in the IR spectrum an OH absorption (ν_{max} 3450 cm^{-1}) but it exhibits in the NMR spectrum no signal due to a hydrogen on a hydroxyl-carrying carbon, a fact which indicates that the OH group is tertiary. The presence in β-rotunol of two ethylenic bonds, one trisubstituted and one disubstituted, was shown by its complete hydrogenation to a saturated tetrahydro derivative, the keto-alcohol IV.

In order to establish the environment of the OH group, β-rotunol on treatment with $POCl_3$ in pyridine gave a dehydration product whose spectral properties indicate the formation of a cross-conjugated dienone system having two Me groups at β- and β′-positions (ν_{max} 1660, 1630 cm^{-1}, δ 2·04 (6H), 5·84 ppm (2H)) as well as the retention of the isopropenyl group (ν_{max} 3090, 890 cm^{-1}, δ 1·77 (3H), 4·71 ppm (2H)). Based on these observations, we formulated the dehydration product as V and, consequently, the original β-rotunol as II, the location of the isopropenyl group at C-7 being tentatively assigned on the assumption that β-rotunol is derived from a normally constructed isoprenoid, an eudesmane.

To substantiate these conclusions the dienone (V) was synthesised. A convenient starting point was hinesol, one of the main constituents of *Atractylodes lancea* De Candolle (Compositae),[7] whose structure has been the subject of protracted controversy and recently elucidated as shown in formula VI except for the configuration at C-7[8] which has more recently been assigned to be *R* as depicted.[9, 10] When hinesol (VI) was oxidized with *t*-butyl chromate, hinesolone (VII) was obtained. Oxidation of the enone (VII) with 2,3-dichloro-5,6-dicyano-benzoquinone afforded a dienone which on the basis of the spectroscopic data must be formulated as VIII. Thus it shows the spectral properties indicating the presence of a β,β′-dimethyl-dienone (ν_{max} 1660,

1615 cm^{-1}, δ 2·08 (6H), 6·01 ppm (2H)) and a hydroxy-isopropyl (ν_{max} 3645, 3430 cm^{-1}, δ 1·26 (3H), 1·29 ppm (3H)). The dienone (VIII) was also obtained by selenium dioxide oxidation of the keto-alcohol (VII) but in a lower yield. On dehydration with $POCl_3$ in pyridine the hydroxy-dienone (VIII) gave a dehydration product which appeared to be heterogenous. Separation of the isomeric mixture by means of chromatography furnished the isopropylidene derivative (IX) (δ 1·70 ppm (6H)) and the isopropenyl derivative (V) (ν_{max} 887 cm^{-1}, δ 1·78 (3H), 4·72 ppm (2H)).

Direct comparison of the dienones (V) derived from β-rotunol and hinesol confirmed the identity, establishing the structure and absolute configuration of β-rotunol as II but exclusive of stereochemistry at the ring junctions.

The genesis of the dienone (V) (systematically spirovetiva-1(10),3,11-trien-2-one)‡ on the treatment of β-rotunol with $POCl_3$in pyridine may be rationalized by the following mechanism. Thus, the C-9:C-10 bonding is migrated upon the electron-deficient center at C-5 initially formed by elimination of the OH group. This indicated that the C-9:C-10 bond is located in the antiparallel position to the O:C-5 bond. Such a conformational feature is only possible if the C-5 OH and the C-10 Me are both β-oriented, since the C-7 isopropenyl has already been established to be β.

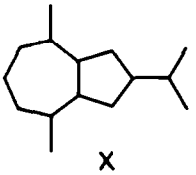
The formation of the dienone (V) from β-rotunol clearly bears some analogy to the rearrangement of a 4β,5β-epoxy-eudesmane which initiated with ring contraction to give an intermediate cation of the spirovetivane skeleton, but the retention of the oxygen function at C-4 in this case facilitates cleavage of the C-4:C-5 bond to give a further rearranged product.[12] Therefore, we suggested that dehydration of an eudesmane derivative having a 5β-OH might be expected to form a spirovetivane derivative.[12] The rearrangement of β-rotunol to the dienone (V) now constitutes one of the examples.

The proposed stereochemistry was further substantiated by the CD curve of β-rotunol (Fig 3) showing a negative Cotton effect for the n-π^* transition which is almost identical with that of the reference substance but having no OH group at the allylic position, 5β-spirost-3-en-2-one.[13] The CD curve exhibits a positive Cotton effect for the π-π^* transition whose sign is opposite to that of the reference substance. This reversion is due to the OH function located at the γ-position of the α,β-unsaturated ketone.[14]

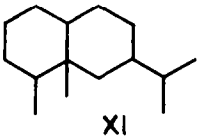
On the basis of the above evidence, β-rotunol is established to have the stereostructure II.

α-Rotunol possesses the same composition $C_{15}H_{22}O_2$ and has the same structural features as β-rotunol: a β-methyl-α,β-unsaturated ketone (λ_{max} 235 nm (log ε 4·03),

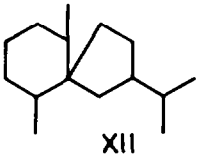
‡ The name vetivane was originally proposed for the hydrocarbon (X) which was considered to be the parent substance of α- and β-vetivones. However, both ketones were later elucidated not to have such a carbon skeleton, *i.e.*, α-vetivone has the elemophilane skeleton (XI)[11] while β-vetivone possesses the skeleton (XII) presently in question.[8] Since vetivazulene is a derivative of the hydrocarbon (X), the name vetivane is retained for it. Recently, the new name spirovetivane has been proposed for the parent hydrocarbon (XII).[10]



X



XI



XII

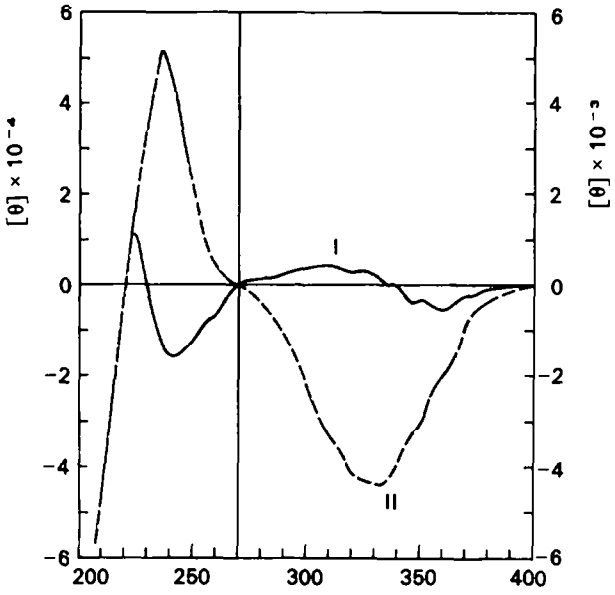
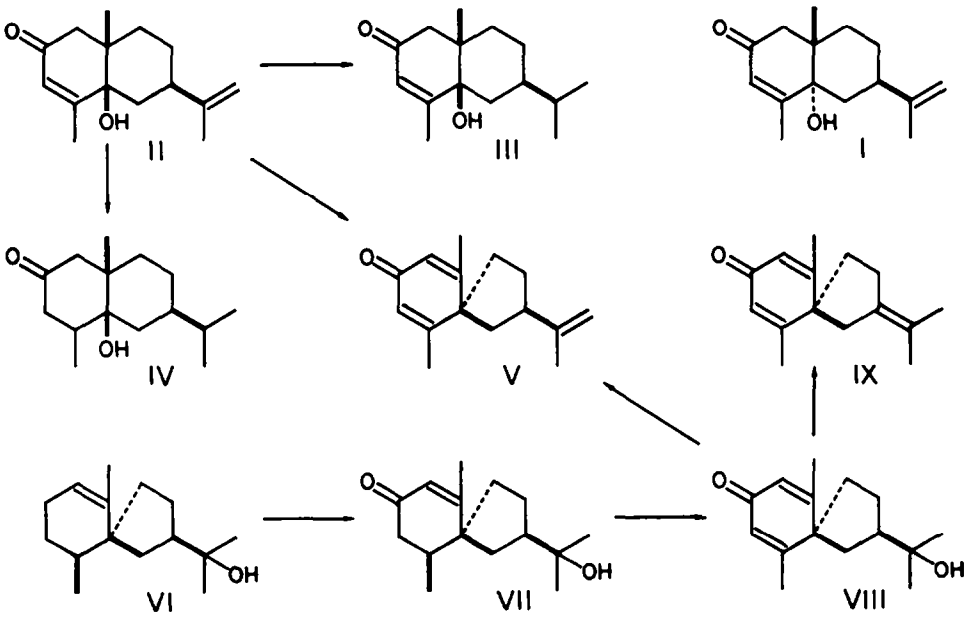


FIG. 3. CD curves λ (nm) of α-rotunol (I) and β-rotunol (II)



ν_{max} 1663, 1623 cm^{-1}, δ 1·95 (3H) and 5·83 ppm (1H) mutually coupled), a methylene adjacent to the CO and next to a quaternary carbon (ν_{max} 1411 cm^{-1}, δ 2·72 ppm (1H)). a tertiary Me (1·04 ppm (3H)). a tertiary OH (ν_{max} 3450 cm^{-1}), and an isopropenyl (ν_{max} 3090, 891 cm^{-1}, δ 1·76 (3H), 4·77 ppm (2H)). The mass spectrum is essentially identical with that of β-rotunol but there are minor differences in the relative intensities in certain peaks (Figs 1, 2). These observations demonstrate that α-rotunol is a

stereoisomer of β-rotunol. In the NMR spectrum of α-rotunol, one hydrogen of the methylene group α to the CO group (δ 2·72 ppm) is a long-range coupled to the tertiary Me protons (δ 1·04 ppm). This result and the known stereochemical requirements for a coupling through 4σ-bonds ("W arrangement"), indicated the *trans* ring fusion of α-rotunol. Further, the CD curve of α-rotunol (Fig 3) shows a negative Cotton effect with a fine structure for the n-π^* transition which is essentially superimposable, including the fine structure, on that of the reference substance but possessing no OH group at the allylic position, 17β-acetoxy-5α-androst-3-en-2-one.[13] The change in sign of the Cotton effects for the π-π^* transition of the α,β-unsaturated CO's due to the difference of the γ-functions was again observed in α-rotunol and the reference substance.

The accumulated data have led to the conclusion that α-rotunol is represented by stereoformula I.

EXPERIMENTAL

M.ps are uncorrected. Specific rotations refer to $CHCl_3$ soln. NMR spectra were determined at 60 MHz unless otherwise indicated. Chemical shifts are given in ppm from internal TMS and coupling constants (J) in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quadruplet and br = broad.

Isolation of α-rotunol and β-rotunol. 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 on alumina. Percolation with benzene yielded ketone fractions followed by acetate fractions and successive elution with the same solvent afforded alcohol fractions which, upon combination, were submitted to rechromatography on silica gel.

Elution with benzene-AcOEt (10:1) followed by crystallization from ether afforded *β-rotunol* (II) as colorless needles, m.p. 118–119°; $[\alpha]_D$ + 44·8° (*c* 5·8), CD (dioxan): $[\theta]_{334}$ − 3460 (*c* 0·117), $[\theta]_{236}$ + 51200 (*c* 0·0117); UV λ_{max} nm (log ε): 232 (4·11); IR ν_{max}^{KBr} cm^{-1}: 4350 (OH), 3100, 890 (vinylidene), 1640 (enone); NMR (100 MHz, $CDCl_3$): 3H s at 1·15 ($C_{(15)}H_3$), 3H t at 1·74 (J = 1, $C_{(13)}H_3$), 3H d at 1·99 (J = 1, $C_{(14)}H_3$), two 1H d's at 2·07, 2·71 (J = 17, $C_{(1)}H_2$), 2H q at 4·75 (J = 1, $C_{(12)}H_2$), 1H q at 5·89 (J = 1, $C_{(3)}H$). (Found: C, 76·72; H, 9·50. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%).

Further elution with the same solvent followed by crystallization from ether yielded *α-rotunol* (I) as colorless needles, m.p. 87·5–88·5°; CD (dioxan): $[\theta]_{372}$ − 260, $[\theta]_{361}$ − 530, $[\theta]_{352}$ − 360, $[\theta]_{347}$ − 400 (*c* 0·112), $[\theta]_{242}$ − 15300 (*c* 0·00170); UV λ_{max} nm (log ε): 235 (4·03); IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 3090, 891 (vinylidene), 1663, 1623 (enone); NMR (100 MHz, $CDCl_3$): 3H d at 1·04 (J = 1, $C_{(15)}H_3$), 3H t at 1·76 (J = 1, $C_{(13)}H_3$), 3H d at 1·95 (J = 1, $C_{(14)}H_3$), 1H dq at 2·72 (J = 17, 1, $C_{(1\alpha)}H$), 2H q at 4·77 (J = 1, $C_{(12)}H_2$), 1H q at 5·83 (J = 1, $C_{(3)}H$), (Found: C, 76·63; H, 9·41, $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%).

Partial hydrogenation of β-rotunol over Adams' catalyst in ethyl acetate. β-Rotunol (23 mg) in AcOEt (5 ml) was hydrogenated using PtO_2 (5 mg) at room temp. After the consumption of 1 mole of H_2, the catalyst was filtered off and the solvent distilled off. The product on distillation under reduced pressure gave *dihydro-β-rotunol* (III) as a colorless oil (20 mg), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640, 3420 (OH), 1660 (cyclohexenone); NMR (CCl_4): 6H d at 0·93 (J = 6, $C_{(12)}H_3$, $C_{(13)}H_3$), 3H s at 1·00 ($C_{(15)}H_3$), 3H s at 1·96 ($C_{(14)}H_3$), 1H s at 5·70 ($C_{(3)}H$).

Complete hydrogenation of β-rotunol over Adams' catalyst in ethyl acetate. β-Rotunol (35 mg) in AcOEt (5 ml) was hydrogenated over PtO_2 (30 mg) at room temp. After the absorption of 2 moles of H_2, the catalyst was filtered off and the solvent removed. The product was chromatographed over silica gel (2 g). Elution with benzene and distillation under diminished pressure afforded *tetrahydro-β-rotunol* (IV) as a colorless oil, MS (*m/e*): 238 (M^+); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3645, 3450 (OH), 1720 (cyclohexanone); NMR (CCl_4): 3H s at 0·92 ($C_{(15)}H_3$), 6H d at 0·93 (J = 6, $C_{(12)}H_3$, $C_{(13)}H_3$), 3H d at 0·97 (J = 6, $C_{(14)}H_3$).

Dehydration of β-rotunol with phosphorus oxychloride in pyridine. β-Rotunol (53 mg) in pyridine (0·8 ml) was treated with $POCl_3$ (0·05 ml) at room temp for 1 day. Upon isolation in the usual manner, the product (27 mg) was chromatographed over silica gel (3 g). Elution with benzene-AcOEt (10:1) gave *anhydro-β-rotunol* (V) as a colorless oil (19 mg), CD (*c* 0·106, MeOH): $[\theta]_{322}$ − 920; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1660, 1630 (dienone),

890 (vinylidene); NMR (CCl_4): 3H s at 1·77 ($C_{(13)}H_3$), 6H s at 2·04 ($C_{(14)}H_3$, $C_{(15)}H_3$), 2H br s at 4·71 ($C_{(12)}H_2$), 2H s at 5·84 ($C_{(1)}H$, $C_{(3)}H$).

Oxidation of hinesol with t-butyl chromate. To hinesol (VI; 2·0 g) in CCl_4 (20 ml) was added a mixture of *t*-butyl chromate soln (solution B,[15] 16 ml), AcOH (5 ml), and Ac_2O (2 ml) with stirring at 80° during 30 min. Stirring was continued for a further 1·5 hr at 80°. The mixture was cooled at 0°, oxalic acid soln (10%, 30 ml) added, and oxalic acid (2·3 g) added. The product (1·93 g) was applied to a silica gel column (30 g) in benzene. The fraction (1·22 g) eluted with benzene-AcOEt (10:3) was crystallized from light petroleum to give VII as colorless prisms, m.p. 72–73°; $[\alpha]_D$ − 105·7° (*c* 5·0); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640, 3430 (OH), 1665, 1617 (cyclohexenone); NMR (CCl_4): 3H d at 1·01 (J = 6, $C_{(14)}H_3$), 6H s at 1·18 ($C_{(12)}H_3$, $C_{(13)}H_3$), 3H s at 1·96 ($C_{(15)}H_3$), 1H s at 5·60 ($C_{(1)}H$). (Found: C, 76·08; H, 10·28. Calc. for $C_{15}H_{24}O_2$: C, 76·22; H, 10·24%).

Oxidation of hinesolone with 2,3-dichloro-5,6-dicyano-benzoquinone. Hinesolone (VII; 570 mg) in AcOEt (3 ml) was heated on a steam-bath with DDQ (560 mg) for 9 hr. Isolation in the usual manner afforded the product (448 mg) which was chromatographed over silica gel (8 g). Elution with benzene-AcOEt (2:1) gave 11-*hydroxy-spirovetiva*-1(10),3-*dien*-2-*one* (VIII) as a colorless oil (270 mg), CD (*c* 0·160, dioxan): $[\theta]_{359}$ −260; IR $\nu_{max}^{HCl_3}$ cm^{-1}: 3645, 3430 (OH), 1660, 1615 (dienone); NMR ($CDCl_3$): two 3H s's at 1·26, 1·29 ($C_{(12)}H_3$, $C_{(13)}H_3$), 6H s at 2·08 ($C_{(14)}H_3$, $C_{(15)}H_3$), 2H s at 6·01 ($C_{(1)}H$, $C_{(3)}H$).

Oxidation of hinesolone with selenium dioxide. Hinesolone (VII; 400 mg) and SeO_2 (580 mg) in *t*-BuOH (5 ml) and AcOH (4 ml) were kept under N_2 at 90° for 7 hr. After isolation, the product (360 mg) was chromatographed over silical gel (5 g). Elution with benzene-AcOEt (10:1) yielded VIII as a colorless oil (90 mg), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3645, 3430 (OH), 1660, 1615 (dienone); NMR ($CDCl_3$): two 3H s's at 1·25, 1·28 ($C_{(12)}H_3$, $C_{(13)}H_3$), 6H s at 2·07 ($C_{(14)}H_3$, $C_{(15)}H_3$), 2H s at 5·95 ($C_{(1)}H$, $C_{(3)}H$). Identification with VIII above obtained by the usual criteria.

Dehydration of the dienone with phosphorus oxychloride in pyridine. The dienone VIII (270 mg) in pyridine (1·5 ml) was allowed to react with $POCl_3$ (0·3 ml) at 0°. After 48 hr, the product (70 mg) was isolated and chromatographed over $AgNO_3$-inpregnated silica gel (10%, 1 g).

Elution with benzene gave *spirovetiva*-1(10),3,7(11)-*trien*-2-*one* (IX) as a colorless oil (11 mg), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1666, 1632 (dienone); NMR (CCl_4): 6H s at 1·70 ($C_{(12)}H_3$, $C_{(13)}H_3$), 6H s at 1·99 ($C_{(14)}H_3$, $C_{(15)}H_3$), 2H s at 5·86 ($C_{(1)}H$, $C_{(3)}H$).

Successive elution with benzene-AcOEt (20:1) furnished V as a colorless oil (7 mg), CD (*c* 0·0889, MeOH) $[\theta]_{322}$ − 840; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1660, 1631 (dienone), 890 (vinylidene); NMR (CCl_4): 3H s at 1·78 ($C_{(13)}H_3$), 6H s at 2·02 ($C_{(14)}H_3$, $C_{(15)}H_3$), 2H br s at 4·72 ($C_{(12)}H_2$), 2H s at 5·88 ($C_{(1)}H$, $C_{(3)}H$). The identity with V derived from β-rotunol was confirmed by the usual criteria.

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REFERENCES

[1] H. Hikino, K. Aota and T. Takemoto, *Chem. Pharm. Bull.* **13**, 628 (1965); **14**, 890 (1966)
[2] H. Hikino, K. Aota and T. Takemoto, *Ibid.* **16**, 52 (1968)
[3] H. Hikino, K. Aota and T. Takemoto, *Ibid.* **15**, 1433 (1969); **16**, 1900 (1968)
[4] H. Hikino, K. Aota and T. Takemoto, *Ibid.* **15**, 1929 (1967)
[5] H. Hikino, K. Aota and T. Takemoto, *Ibid.* **17**, 1390 (1969)
[6] H. Hikino, K. Aota, Y. Maebayashi and T. Takemoto, *Ibid.* **14**, 1439 (1966); **15**, 1349 (1967)
[7] I. Yosioka, S. Takahashi, H. Hikino and Y. Sasaki, *Ibid.* **7**, 319 (1959)
[8] J. A. Marshall and P. C. Johnson, *J. Amer. Chem. Soc.* **89**, 2750 (1697); *J. Org. Chem.* **35**, 192 (1970)
[9] I. Yosioka and T. Kimura, *Chem. Pharm. Bull.* **17**, 856 (1969)
[10] J. A. Marshall and S. F. Brady, *Tetrahedron Letters* 1387 (1969)
[11] K. Endo and P. de Mayo, *Chem. Commun.* 89 (1967); *Chem. Pharm. Bull.* **17**, 1324 (1969
[12] H. Hikino, T. Kohama and T. Takemoto, *Tetrahedron* **25**, 1037 (1969)
[13] K. Kuriyama, *Tennen-butsu Kagaku* '67 (*Chemistry of Natural Products* '67), p. 159. Nankodo, Tokyo
[14] K. Kuriyama, private communication
[15] R. V. Oppenauer and H. Oberrauch, *Anales Asoc. Quim. Arg.* **37** 246 (1949); *Chem. Abstr.* **44**, 3909 (1950)