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# Terpenoids. IX.[1] The Structure and Absolute Configuration of Isodocarpin, a New Diterpenoid from *Isodon trichocarpus* Kudo and *I. japonicus* Hara

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The chemical and spectral evidence led to a conclusion that isodocarpin, a new diterpenoid from the leaves of *Isodon trichocarpus* Kudo and *I. japonicus* Hara, has the structure and absolute configuration VII.

We have been studying the constituents in *Isodon trichocarpus* Kudo (Japanese name "Kurobana-hikiokoshi") and *I. japonicus* Hara ("Hikiokoshi"), and have published the preliminary communications[3,4] and some full papers[5,6] on the isolation and structure of several new diterpenoids. This paper deals with the details of the structure elucidation of isodocarpin.

The methanolic extract of the dried leaves of *Isodon trichocarpus* Kudo was treated as shown in the experimental section to give a new diterpenoid from the filtrate from enmein.

This is the crystal having mp 270—273° (decomp.) and $[\alpha]_D^{17}$ −172°, and its molecular formula was found to be $C_{20}H_{26}O_5$, which has one less oxygen than enmein. As the substance was a new natural product, it was named isodocarpin. The presence of a five-membered ring ketone which was conjugated with an exocyclic methylene group was supported from the infrared (IR) absorption bands at 1750 and 1640 $cm^{-1}$ as well as the ultraviolet (UV) absorption maximum at 232 mμ (ε 4800), and the nuclear magnetic resonance (NMR) spectral data.[7] The NMR spectrum closely resembles

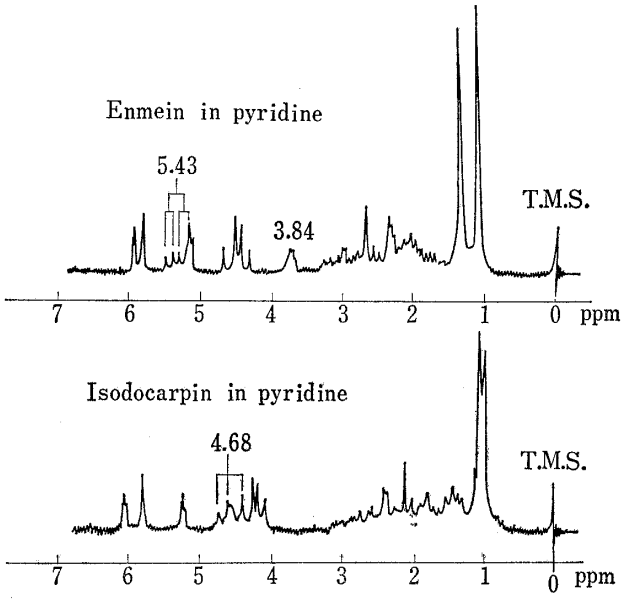


Fig. 1. The Nuclear Magnetic Resonance Spectra of Enmein and Isodocarpin

1) Part VIII: E. Fujita, T. Fujita, and N. Ito, *Yakugaku Zasshi*, **87**, 1150 (1967).
2) Location: *Uji, Kyoto-fu.*
3) E. Fujita, T. Fujita, and M. Shibuya, *Chem. Commun.*, **1966**, 297.
4) E. Fujita, T. Fujita, and M. Shibuya, *Tetrahedron Letters*, **1966**, 3153.
5) E. Fujita, T. Fujita, and M. Shibuya, *Yakugaku Zasshi*, **87**, 1076 (1967).
6) E. Fujita, T. Fujita, and M. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **16**, 509 (1968).
7) See experimental section.

that of enmein (I)[8] whose structure[9] and absolute configuration[10] have been established. Hence, the presence of a five-membered ring hemiacetal and a $\delta$-lactone like enmein was expected. The IR spectrum also showed the absorption bands at 3455 $cm^{-1}$ (OH) and 1695 $cm^{-1}$ ($\delta$-lactone carbonyl). As shown in Fig. 1.[11] the proton signal of the hydrogen at C-3 which appeared at $\delta$ 3.84 ppm in enmein, is absent in the NMR spectrum of isodocarpin. Moreover, the C-1 proton signal appeared at $\delta$ 4.68 ppm in the NMR spectrum of isodocarpin, while it appeared at $\delta$ 5.43 ppm in enmein because of a deshielding effect by the C-3 $\beta$-axial hydroxyl group. These observations led to a postulation that isodocarpin might be 3-deoxyenmein.

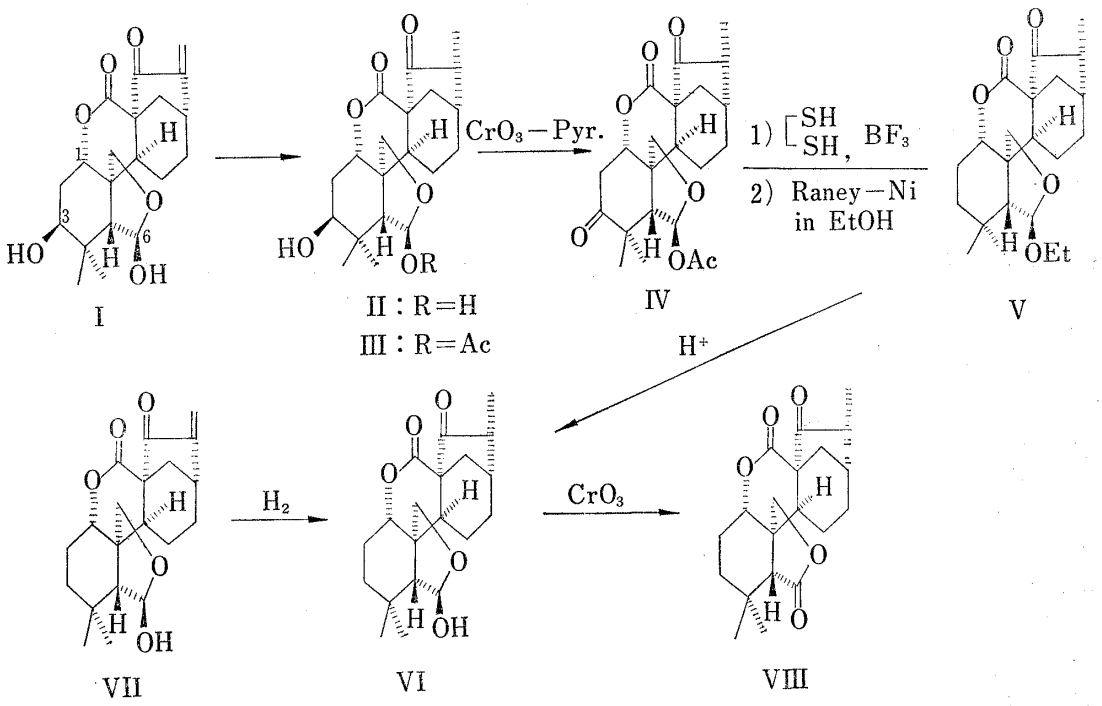


Chart 1

Now, dihydroenmein (II) was partially acetylated with acetic acid to give dihydroenmein 6-acetate (III),[9a] which was oxidized with chromic acid-pyridine complex to afford dihydroenmeinone acetate (IV). The latter on thioketalization followed by desulfurization with Raney nickel in ethanol yielded 3-deoxy acetal V. Subsequent acid-catalyzed hydrolysis of the product V gave a compound VI which proved to be identical with dihydroisodocarpin.

Thus, the structure of isodocarpin was established as 3-deoxyenmein (VII). Dihydroisodocarpin (VI) on chromic acid oxidation gave dehydrodihydroisodocarpin (VIII), which was identified with the authentic sample of 3-deoxydehydrodihydroenmein (VIII)[9b] derived from enmein (I).

Isodocarpin was isolated also from *Isodon japonicus* HARA by the authors.

8) T. Ikeda and S. Kanatomo, *Yakugaku Zasshi*, **78**, 1128 (1958).
9) *a*) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, M. Takahashi, H. Irie, A. Numata, T. Fujita, T. Okamoto, M. Natsume, Y. Kawazoe, K. Sudo, T. Ikeda, M. Tomoeda, S. Kanatomo, T. Kosuge, and K. Adachi, *Tetrahedron Letters*, **1964**, 1243; *b*) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, H. Irie, A. Numata, T. Fujita, and T. Suzuki, *Tetrahedron*, **22**, 1659 (1966).
10) *a*) Y. Iitaka and M. Natsume, *Tetrahedron Letters*, **1964**, 1257, *Acta Cryst.*, **20**, 197 (1966); *b*) K. Shudo, M. Natsume, and T. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 1019 (1965); *c*) E. Fujita, T. Fujita, K. Fuji, and N. Ito, *Chem. Pharm. Bull.* (Tokyo), **13**, 1023 (1965); *d*) E. Fujita, T. Fujita, K. Fuji, and N. Ito, *Tetrahedron*, **22**, 3423 (1966).
11) Taken in pyridine.

## Experimental[12]

**Isolation of Isodocarpin (VII)**——The dried leaves (100 kg) of *Isodon trichocarpus* Kudo which was collected at Kanazawa district in August, 1964 was extracted with MeOH (300 liters) under refluxing for 54 hr. The extract was evaporated to 100 liters *in vacuo* and left standing for 2 weeks at room temperature to give crystals (600 g). To the filtrate (500 ml) was added MeOH (500 ml) and refluxed for 1 hr with added charcoal (20 g), then filtered. The green color got yellow, when the treatment was repeated for three times. Methanol was distilled off to give a residue (200 g), which was dissolved in AcOEt. The solution was washed with 0.5% $Na_2CO_3$ and 0.1 N HCl. After washing with $H_2O$ and drying over anhydrous $Na_2SO_4$, the solvent was distilled off to give a syrupy residue (100 g). The syrup (20 g) was chromatographed on silica gel (800 g) column. The eluate with the mixture of $CHCl_3$ and acetone (8:2) yielded isodocarpin (VII) (50 mg) as plates, mp 270—273° (decomp.), $[\alpha]_D^{17}$ −172° ($c$=1, $CHCl_3$). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3455 (OH), 1750, 1695 (C=O), 1640 (double bond). UV $\lambda_{max}$: 232 m$\mu$ ($\varepsilon$=4800), NMR ($\delta$): 0.98 (3H, singlet), 1.03 (3H, singlet), 4.02 (2H, singlet), 4.41 (1H, quartet, $J$=7.0, 10.0 cps), 5.36 (1H, singlet), 5.50 (1H, singlet), 6.10 (1H, singlet). NMR ($\delta$) (pyridine): 0.97 (3H, singlet), 1.02 (3H, singlet), 4.36 (2H, AB-type, $J$=9.0 cps), 4.68 (1H, triplet, $J$=8.0 cps), 5.28 (1H, singlet), 5.73 (1H, singlet) and 5.98 (1H, singlet). *Anal.* Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.60; H, 7.63.

**Dihydroenmeinone Acetate (IV)**——A solution of dihydroenmein 6-acetate (III) (1 g) in pyridine (10 ml) was added under stirring to a complex prepared from $CrO_3$ (3 g) and pyridine (30 ml). After standing overnight, $H_2O$ (120 ml) was added. The mixture was extracted with $CHCl_3$ and the extract was washed with $H_2O$. After drying over anhydrous $Na_2SO_4$, the solvent was distilled off to give a crystalline residue (750 mg). It was chromatographed on silica gel, and the eluate with $CHCl_3$ yielded the needles, mp 191—193° (decomp.), after recrystallization from MeOH. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1755, 1720 (C=O). *Anal.* Calcd. for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.04; H, 7.19.

**3-Deoxydihydroenmein 6-Acetal (V)**——A mixture of dihydroenmeinone acetate (IV) (240 mg), ethanedithiol (1 ml) and $BF_3$-etherate (0.5 ml) was allowed to stand for 1 hr at room temperature, and then poured into saturated $Na_2CO_3$ aq. (20 ml). The mixture was extracted with $CHCl_3$. The extract, after washing with $H_2O$ and drying, was evaporated to dryness under reduced pressure. The residue was refluxed in EtOH (30 ml) with Raney Ni W-2 (6 g) for 10 hr and the reaction mixture was filtered while hot. The solvent was evaporated to give the residue (200 mg), which was chromatographed on silica gel column. The elution with $CHCl_3$ gave 3-deoxydihydroenmein 6-acetal (V) (76 mg) as crystals. mp 169—170°, $[\alpha]_D^{17}$ −159° ($c$=1, $CHCl_3$),. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1760, 1720 (C=O). NMR ($\delta$): 0.97, 1.00 (each 3H, singlet), 1.08 (3H, triplet, $-OCH_2\underline{CH_3}$), 1.14 (3H, doublet, $C\underline{H_3}$ at C-16), 3.50 (2H, multiplet, $-OC\underline{H_2}CH_3$), 3.97 (2H, AB type, $J$=9.0 cps, $-OC\underline{H_2}-$), 4.38 (1H, triplet, C-1-$\underline{H}$), 4.88 (1H, singlet, C-6-$\underline{H}$). *Anal.* Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.21; H, 8.87.

**Acid-catalyzed Hydrolysis of (V)**——A mixture of 3-deoxydihydroenmein 6-acetal (V) (20 mg), AcOH (1 ml) and $H_2O$ (0.5 ml) was heated on a water bath for 2 hr. After cooling, $H_2O$ (3 ml) was added. The mixture was extracted with $CHCl_3$ and the extract, after washing and drying, was evaporated to give a residue (18 mg). Crystallization and purification from MeOH afforded needles (12 mg), mp 225—230° (decomp.), which proved to be identical with dihydroisodocarpin (VI) by mixture melting point determination and IR spectral comparison.

**Dihydroisodocarpin (VI)**——A solution of isodocarpin (VII) (20 mg) in MeOH (5 ml) was hydrogenated in the presence of Adams' catalyst (5 mg) for 1.5 hr. The catalyst was filtered off and the solvent was evaporated to give crystals (20 mg). mp 224—230° (decomp.). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3500 (OH), 1750, 1695 (C=O). NMR ($\delta$): 1.14 (3H, doublet, $C\underline{H_3}$ at C-16). *Anal.* Calcd. for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.85; H, 8.16.

**Dehydrodihydroisodocarpin (VIII)**——To a solution of dihydroisodocarpin (VI) (20 mg) in AcOH (1 ml) was added a solution of $CrO_3$ (10 mg) in a mixture of AcOH (0.5 ml) and $H_2O$ (0.1 ml). After standing at room temperature for 3 hr, excess MeOH was added, then the mixture was allowed to stand overnight. The precipitated crystalline product was recrystallized from MeOH to yield VIII (7 mg) as needles, mp 295—300°. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1760, 1750, 1715 (C=O). *Anal.* Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.17; H, 7.67. It proved to be identical with the authentic sample VIII derived from enmein.

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12) All melting points were determined by a micro melting point apparatus (Yanagimoto) and were uncorrected. UV spectra were recorded in EtOH on a Hitachi model EPS-3 spectrophotometer, IR spectra on a Hitachi model EPI-S2 spectrophotometer and NMR spectra in $CDCl_3$, unless otherwise stated, with TMS as an internal standard on a Varian A-60 spectrometer.