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DITERPENOID CONSTITUENTS OF *Isodon trichocarpus* AND *Isodon japonicus* (TERPENOIDS IV)[1]

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Recently, we isolated enmein(I) and its 3-acetate(II) from *Isodon japonicus* Hara ("Hikiokoshi")(Labiatae).[1] A further investigation on the bitter principles from the dried leaves of *I. japonicus* Hara and *I. trichocarpus* Kudo ("Kurobana-hikiokoshi") has led to the isolation of eight bitter principles including enmein and its 3-acetate. Table 1 shows the names of the new components, the constitutions, the physical constants and their sources.

The molecular formula of isodocarpin [λ_{max} 232 mμ (ε 4800), ν_{max}^{KBr} 3455, 1750, 1695, and 1640 cm^{-1}] corresponds to des-O enmein. The N.M.R. spectra of isodocarpin and enmein closely resemble each other except that the latter has a proton signal at δ^{pyr} 3.84 ppm (H at C-3, HO-C<u>H</u>⟨) which is absent in the former. These observations led to the postulation that

isodocarpin may be 3-desoxyenmein. Thus, thioketalization and desulfurization with Raney nickel of dihydroenmeinone acetate (XI), $C_{22}H_{28}O_7$, m.p. 191-193°(dec.) which was prepared by oxidation of dihydroenmein 6-acetate(X),[2b] gave desoxy acetal XII, $C_{22}H_{32}O_5$, m.p. 169-170°(dec.). The product from acid-catalyzed hydrolysis of the latter proved to be identical with dihydroisodocarpin(IX), $C_{20}H_{28}O_5$, m.p. 224-230°(dec.).

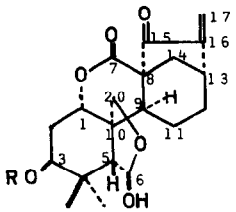
TABLE 1

name	molecular formula	m.p.*	$[\alpha]_D^{17}$	source**
enmein(I)	$C_{20}H_{26}O_6$	308-312°(dec.)	-136°	t,j
enmein 3-acetate(II)	$C_{22}H_{28}O_7$	267-271°(dec.)	-112°	j
isodocarpin(III)	$C_{20}H_{26}O_5$	270-273°(dec.)	-172°	t
nodosin(IV)	$C_{20}H_{26}O_6$	275-280°(dec.)	-203°	t,j
isodotricin(V)	$C_{21}H_{30}O_7$	240-245°(dec.)	-114°	t
trichodonin(VI)	$C_{20}H_{30}O_7$ (28)	234-237°(dec.)	+ 32°	t
ponicidin(VII)	$C_{20}H_{28}O_6$	238-241°(dec.)	-118°	j
oridonin(VIII)	$C_{20}H_{28}O_6$	248-250°(dec.)	- 46°	t,j

* The melting points were determined on a micro m.p. apparatus (Yanagimoto) and were uncorrected.

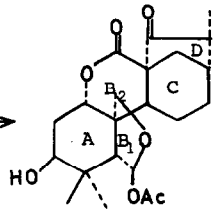
** t : Isodon trichocarpus Kudo, j : I. japonicus Hara

Moreover, the keto lactone XIII, $C_{20}H_{26}O_5$, m.p. 290-300° (dec.) was prepared from dihydroisodocarpin(IX) by oxidation with chromic acid ; subsequently acid XIV, m.p. 260-265°(dec.) was derived from XIII by treatment with alkali. Compounds XIII, XIV, and XV (methyl ester of the acid XIV) were identified with authentic samples[2] prepared from enmein. Thus, the structure of isodocarpin was established as 3-desoxyenmein(III).



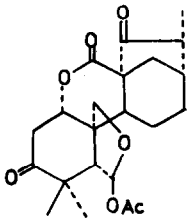
(I) ; R=H
(II); R=Ac

1) H_2/Pt
2) AcOH



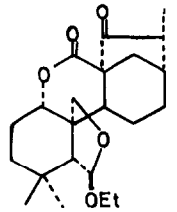
(X)

CrO_3/Pyr.



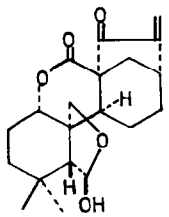
(XI)

1) $\left[\begin{matrix}SH\\SH\end{matrix}\right]BF_3$
2) Ra-Ni in EtOH



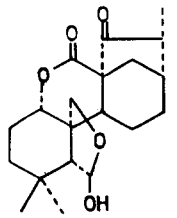
(XII)

H^+
(AcOH-H_2O)



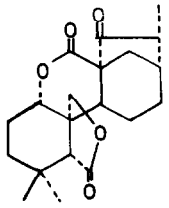
(III)

H_2 / Pt



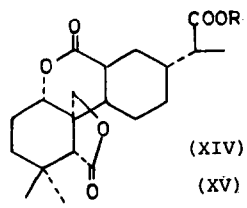
(IX)

CrO_3/AcOH



(XIII)

5 % KOH

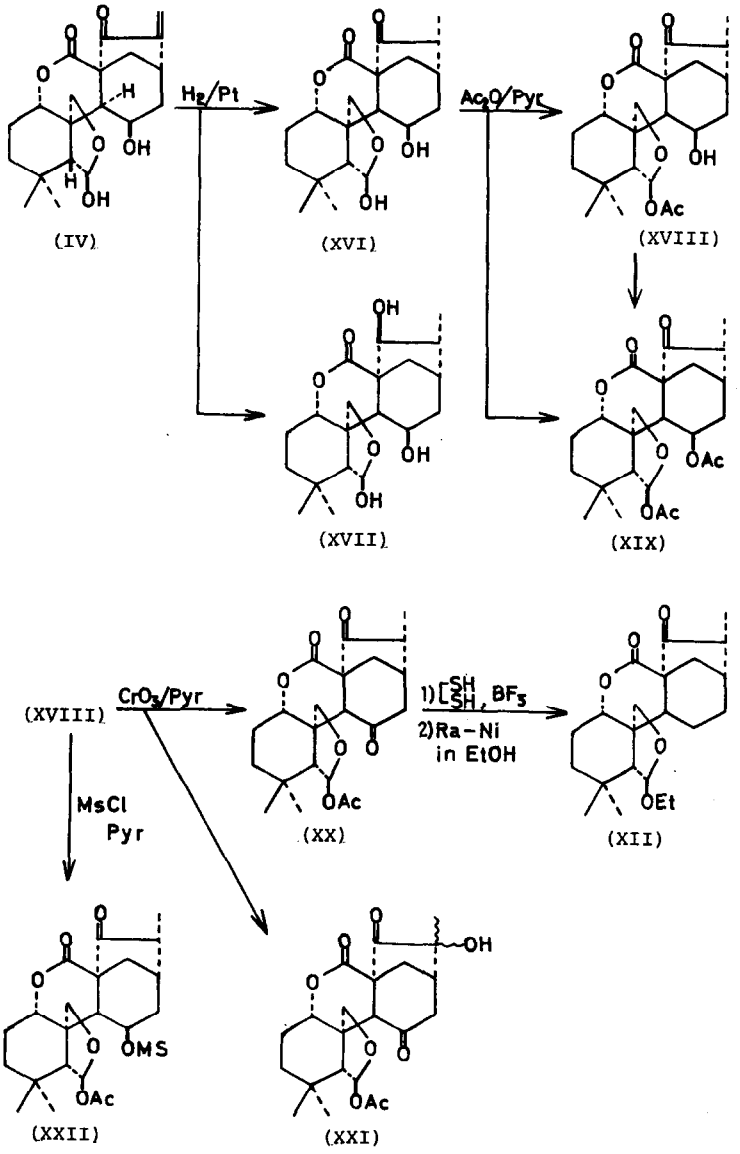


(XIV); R = H
(XV); R = Me

Nodosin has the same molecular formula with enmein, as shown in Table 1. Similarly to enmein, it contains a five-membered hemiacetal [ν_{max}^{KBr} 3500 and 3350 cm^{-1} δ^{pyr} 5.79(singlet, H at C-6) and 4.43 ppm (AB type, J = 9.0 c/s, 2H at C-20)], a δ-lactone (ν_{max}^{KBr} 1690 cm^{-1}), and a five-membered ketone conjugated to an exocyclic methylene group [λ_{max} 233 mμ (ε 8000), ν_{max}^{KBr} 1740 and 1640 cm^{-1} δ^{pyr} 5.32 and 5.97 ppm (methylene protons at C-17)] in the molecule. The spectral data of nodosin show the presence of a further secondary hydroxyl group [ν_{max}^{KBr} 3500 and 3350 cm^{-1} $\delta^{pyr\cdot D_2O}$ 5.16 ppm (triplet, J = 4.0 c/s) >CH-OH : cf. δ^{pyr} 3.84 ppm (broad), H at C-3 of enmein].

Nodosin on hydrogenation in the presence of Adams' catalyst gave dihydronodosin(XVI), $C_{20}H_{28}O_6$, m.p. 245-248°(dec.), and tetrahydronodosin(XVII), $C_{20}H_{30}O_6$, m.p. 225-228°(dec.). Dihydronodosin(XVI) on treatment with acetic anhydride and pyridine at room temperature for 2 hours gave a monoacetate $C_{22}H_{30}O_7$, m.p. 290-300°(dec.), to which the 6-acetate structure XVIII, excepting the location of the secondary hydroxyl group, was assigned on the basis of the N.M.R. evidence [$\delta^{C_5D_5N}$ 6.46 ppm (singlet, H at C-6)]. Although the secondary hydroxyl group at C-3 in enmein was completely acetylated by leaving overnight with acetic anhydride and pyridine at room temperature, the acetylation of the remaining secondary hydroxyl group of nodosin required more prolonged treatment.[3]

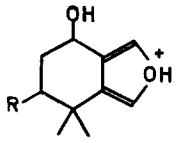
Dihydronodosin monoacetate(XVIII) on oxidation with

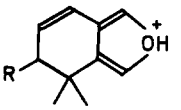

H2/Pt
Ac2O/Pyr
(IV)
(XVI)
(XVIII)
(XVII)
(XIX)
CrO3/Pyr
1)[SH SH, BF3
2)Ra-Ni in EtOH
MsCl Pyr
(XVIII)
(XX)
(XII)
(XXII)
(XXI)

chromic acid-pyridine complex yielded a keto derivative XX, $C_{22}H_{28}O_7$, m.p. 200-202°(dec.) as a major product, and a tertiary alcohol XXI, $C_{22}H_{28}O_8$, m.p. 217-221°(dec.)[ν_{max}^{KBr} 3350 cm^{-1} δ^{CDCl_3} 1.51 (3H, singlet, $C\underline{H}_3$ at C-16) and 3.45 ppm (singlet, $\underline{HO}$-C_{16})] as a minor product. The compound XX on thioketalization with ethanedithiol followed by desulfurization of the resulting thioketal with Raney nickel in ethanol, gave an acetal, which was identified with the aforementioned compound XII. The conversion confirmed that nodosin corresponds to a hydroxyisodocarpin, accordingly that nodosin is an isomer of enmein differing in the location of a secondary hydroxyl group.

A more hindered hydroxyl group than the C-3 β-axial hydroxy in enmein could be α-axial at C-2, β-quasi axial at C-11, α-quasi axial at C-12, or β-quasi axial at C-14.[4] In the N.M.R. spectrum of compound XX, a quartet (J = 6.5 and 9.0 c/s) due to a proton at C-1 appeared at δ^{CDCl_3} 4.54 ppm. The fact denied the presence of an α-axial hydroxyl group at C-2 in nodosin. The mass spectral data also excluded the possibility of a hydroxyl group on the A-ring ; peaks at m/e 183 and 165 appeared in the mass spectrum of dihydroenmein, while the corresponding fragments appeared at m/e 167 and 149 in the mass spectra of dihydroisodocarpin(IX) and dihydronodosin. Structures XXIII-XXVI can be assigned to these fragments.[5]

In the N.M.R. spectrum of keto acetate XX, sharp singlet signals(each 1H) were observed at δ^{CDCl_3} 3.13 and 3.02 ppm. One of them is due to a proton at C-5, and another one to a





(XXIII) ; R = OH (m/e 183) (XXIV) ; R = OH (m/e 165)

(XXV) ; R = H (m/e 167) (XXVI) ; R = H (m/e 149)

proton on a carbon next to the newly formed carbonyl. The appearance of the sharp singlet discards the possibility of the carbonyl group being at C-12, that is, the possibility of the original hydroxyl group being at C-12.

The N.M.R. signal of a proton on the carbon to which the secondary hydroxyl group was attached appeared as a triplet in nodosin as described above, while it appeared as a quartet at $\delta^{C_5D_5N \cdot D_2O}$ 5.07 ppm (J = 3.0 and 4.5 c/s) in dihydronodosin (XVI), and as a quartet at δ^{CDCl_3} 5.39 ppm (J = 3.5 and 4.0 c/s) in mesylate XXII. These observations exclude the location of the hydroxyl group at C-14.

From these facts, it was concluded that the secondary hydroxyl group is located at C-11. The coupling constants reasonably explain the assignment of a β-quasi axial conformation to this hydroxyl group. The considerable paramagnetic shift of the proton signal at C-5 in compound XX (see above) can be reasonably interpreted as the anisotropic effect of the carbonyl group at C-11 on the basis of the investigation with a stereo model. Moreover, in the N.M.R. spectra of

nodosin, dihydronodosin(XVI), monoacetate XVIII, diacetate XIX and mesylate XXII, a one-proton doublet appeared at δ^{pyr} 3.72 ppm (J = 11.5 c/s), $\delta^{C_5D_5N}$ 3.87 ppm (J = 11 c/s), $\delta^{C_5D_5N}$ 3.78 ppm (J = 11.5 c/s), $\delta^{C_5D_5N}$ 3.14 ppm (J = 11.5 c/s) and δ^{CDCl_3} 2.97 ppm (J = 12.0 c/s), respectively. In compound XX, in which the secondary alcohol had been converted to a ketone, no proton signal excepting the afore-mentioned two sharp singlets at δ 3.02 and 3.13 ppm was observed in the range of δ2.9-3.9 ppm. On the basis of spin decoupling experiments on the proton at δ 3.78 ppm in compound XVIII, the signal could be assigned to a β-H at C-14, which is deshielded by the anisotropic effect of the β-OH at C-11.

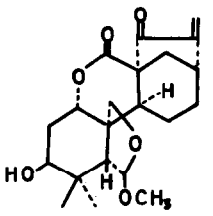
As a result of the aforegoing experiments, the structural formula IV including its absolute configuration is proposed for nodosin.

The assignment of the β-orientation to the new hydroxyl group at C-15 of tetrahydronodosin(XVII) was based on the coupling constant value (J = 3.5 c/s)[6] of the proton signal on C-15 at δ^{pyr} 3.71 ppm (doublet).

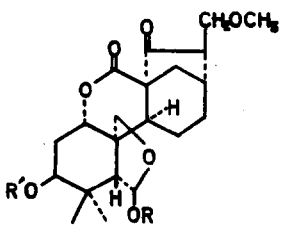
The spectral investigation of isodotricin shows no exocyclic methylene group, but proves the presence of a five-membered ketone (ν_{max}^{KBr} 1755 cm^{-1}), a δ-lactone (ν_{max}^{KBr} 1705 cm^{-1}), a same environment as hemiacetal moiety in enmein [δ^{pyr} 5.89 ppm (singlet, H at C-6)], and a hydroxyl group at C-3 [ν_{max}^{KBr} 3400 cm^{-1} $\delta^{C_5D_5N}$ 6.72 (doublet, J = 4 c/s, HO at C-3), and 3.82 ppm (broad, H at C-3)] in the molecule. The compound on acetylation gave a diacetate, m.p. 110-120°(dec.), $C_{25}H_{34}O_9$, XXVII. Isodotricin also contains a $>CH-CH_2-O-CH_3$ group [δ^{pyr}

3.15 (3H, singlet] and 3.58 ppm (AB part of ABX type)].

From the aforegoing data, the substance was expected to have a structure in which a methoxymethyl group is attached to C-16 instead of the exocyclic methylene in enmein(I). Hence, enmein in methanol was allowed to reflux for 4 hours in the presence of conc. sulfuric acid to give a monomethyl ether XXVIII, m.p. 235-239°(dec.), $C_{21}H_{28}O_6$ [λ_{max} 233 mμ (ε 7500), δ^{CDCl_3} 3.26 (3H, singlet), 6.08 and 5.50 ppm ($C\underline{H}_2$=C<)], and a dimethyl ether XXIX, $C_{22}H_{32}O_7$, m.p. 200-203° (dec.)[δ^{CDCl_3} 3.27 (3H, singlet), 3.55 (3H, singlet), and ca. 3.70 ppm (2H at C-17 overlapping with H at C-3)]. The latter was hydrolyzed with dil. acetic acid to give another monomethyl ether V, which proved to be identical with the natural compound, isodotricin. The more stable β-orientation can be assigned to the substituent at C-16.[7] Thus, the structure of 17-methoxy-16-epi-dihydroenmein(V) is proposed for isodotricin.



(XXVIII)



(XXVII) ; R = R'= Ac

(XXIX) ; R = Me, R'= H

(V) ; R = R'= H

Subsequently, we isolated a substance which was identified with a sample, m.p. 231°(dec.), $[\alpha]_D^{17}$+32.0°, reported by Takahashi et al.[8], and gave it a new name "trichodonin". The investigations on trichodonin(VI), ponicidin(VII), and oridonin(VIII) are in progress.

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[2] The samples were kindly supplied by Prof. S. Uyeo.
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[3] Even a reaction for 16 days did not complete diacetylation, but a little monoacetate was recovered.

[4] The C-ring is present as a boat form : see, Y. Iitaka and M. Natsume, Tetrahedron Letters, 1257 (1964).

[5] The detailed mass spectra on a series of enmein derivatives will be published elsewhere.

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