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A NEW BITTER PRINCIPLE OF ISODON JAPONICUS HARA

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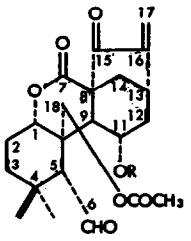
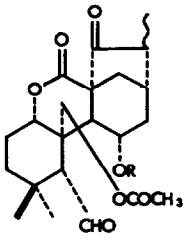
Recently six compounds were isolated from Isodon japonicus Hara (Labiatae) and their structural elucidations were made by Fujita and his collaborators (1-3). From the same plant we have isolated a new bitter compound, provisionally named isodonal, of which structural elucidation will be stated here.

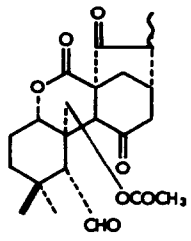
Isodonal (1), $C_{22}H_{28}O_7$, m.p. 245-247° (decomp.), $[\alpha]_D^{20}$ +91.8° (c =1.0, pyridine) shows λ_{max}^{EtOH} 230.5 mμ (log ε 3.75) in UV spectrum, and ν_{max} 3540 (hydroxyl), 1740 (six membered lactone and ester), 1710 (five membered ketone), 1240 (ester), 1640 and 820 cm^{-1} (double bond; disappears on hydrogenation) in IR spectrum. Catalytic hydrogenation of 1 on Pd-charcoal yielded dihydroisodonal (2), $C_{22}H_{30}O_7$, m.p. 252-253° (decomp.), $[\alpha]_D^{20}$ +103° (c = 1.0,pyridine), which exhibits no UV and IR bands due to double bond. On acetylation with acetic anhydride and pyridine 1 yielded acetylisodonal (3), $C_{24}H_{30}O_8$, m.p. 228-229° (decomp.), $[\alpha]_D^{20}$ +117.7° (c = 1.0, pyridine), which has no hydroxyl band in IR. The acetoxyl group in 3 could not be hydrolyzed with oxalic acid, in contrast to the case of acetylenmein (4). Hydrogenation of 3 on Pd-charcoal gave acetyldihydroisodonal (4), $C_{24}H_{32}O_8$, m.p. 200-202° (decomp.), which was obtainable, in turn, by acetylation of 2. The presence of an aldehyde group and two acetoxyl groups and the absence of hemiacetal ring in 3 and 4 were revealed by NMR spectrum (TABLE I). When 2 was submitted to oxidation with Jones' reagent an aldehydeketone (5), $C_{22}H_{28}O_7$, m.p. 205-206° (decomp.), and a hydroxycarboxylic acid (6), $C_{22}H_{28}O_8$, m.p. 263-267° (decomp.) were obtained. In IR spectrum of 5 the hydroxyl band which had been observed in 2 disappeared and a new band due to six membered ring ketone (1710 cm^{-1}) appeared. In NMR spectrum of 5 the signal due to the methine proton in $CH_2\underline{CH}(OAc)$ group of 3 disappeared but the band of aldehyde group (0.12 τ, d, J = 3 cps, 1H) was retained. The formation of 5 indicates that the hydroxyl group in 1 is secondary one. 5 and 12 were strongly positive in Zimmermann test and this suggest the presence of, at least, a methylene group adjacent to the



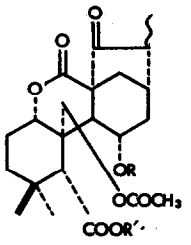
(1) R-H
(3) R-$COCH_3$



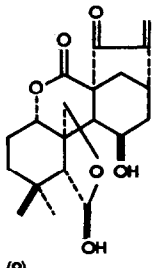
(2) R-H
(4) R-$COCH_3$



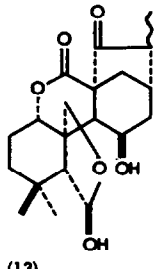
(5)



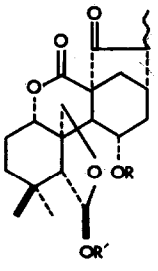
(6) R-R′-H
(7) R′-CH_3
(8) R-$COCH_3$, R′-CH_3



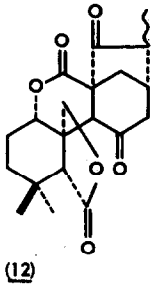
(9)



(13)



(10) R-R′-H
(11) R-R′-$COCH_3$



(12)

ketone group. Furthermore the presence of an acetoxyl group in isodonal was established from the signal (7.92 τ, s, 3H) in NMR spectrum of 5. In contrast to 5, 6 showed the IR band due to hydroxyl (3400 cm^{-1}) and carboxylic acid (3200, 2800–2500 and 1690 cm^{-1}) and gave a monomethyl ester (7), $C_{23}H_{30}O_8$, m.p. 240–243° (decomp.) and an acetyl monomethyl ester (8), $C_{25}H_{32}O_9$, m.p. 208–211° (decomp.) which has a signal due to a carbomethoxyl group (6.31 τ, s, 3H) but not the one due to aldehyde group in NMR spectrum. The foregoing results including the NMR data in the TABLE I showed the presence of CHCHO, $CH_2CHOHCH$, CCH_2OCOCH_3, $COC{=}CH_2$, $(CH_3)_2C$ groups and a six membered lactone in isodonal and this, in conjunction with the postulate of enmein skeleton in it, led to its formulation as 1.

TABLE I
NMR-Spectra for some Derivatives of Isodonal (τ-value, $CDCl_3$, TMS)

	$(CH_3)_2C$	CH_3CH	$COC{=}CH_2$	CCH_2O	$CHCHO$	$CHCHO$
(3)	8.82(s)	---	3.85(s) 4.37(s)	4.90(s)	6.96(d, J=3)	0.12(d, J=3)
(4)	8.82(s)	8.78(d, J=7)	---	4.80(s)	7.15(d, J=3)	0.12(d, J=3)
(5)	8.83(s)	8.73(d, J=7)	---	5.10(s)	6.65(d, J=3)	0.13(d, J=3)
(8)	9.00(s) 8.81(s)	8.75(d, J=7)	---	4.85(s)	---	---
(12)	8.90(s) 8.71(s)	8.69(d, J=7)	---	5.75(d, J=3)	---	---

	$OCOCH_3$	$CHOAc$	$COOCH_3$
(3)	7.89(s) 8.00(s)	5.12(dd, J_{ax}=7 and J_{bx}=15)	---
(4)	7.08(s) 7.92(s)	5.12(dd, J_{ax}=7 and J_{bx}=15)	---
(5)	7.98(s)		---
(8)	7.95(s) 7.74(s)	5.02(m)	6.31(s)
(12)	---	---	---

To prove this assignment isodonal was correlated with nodosin (9) by the following procedure. Acetyldihydroisodonal 4 was hydrolysed with 0.02 N 50% methanolic potassium hydroxide in cold to give the compound (10), $C_{20}H_{28}O_6$, m.p. 225–228° (decomp.) which had IR bands due to hydroxyl group and gave a diacetate (11), $C_{24}H_{32}O_8$, m.p. 223–227° (decomp.). The formulation of 10 as a hemiacetal was substatiated by its NMR spectrum. 10 showed a signal at 3.57 τ due to C_6-methine proton instead of aldehyde proton in 1. Appearance of C_6-methine proton as singlet indicates the same β-configuration of the hemiacetal proton as in enmein and nodosin (1 and 4). Oxidation of 10 with Jones' reagent afforded the

diketolactone (12), $C_{20}H_{24}O_6$, m.p. 198-200°, the IR spectrum and NMR of which were indistinguishable with those of bisdehydrodihyronodosin which was obtained from dihydronodosin (13) by oxidation with Jones' reagent. However, 10 and its acetate (11) were not identical with dihydronodosin and acetyldihyronodosin respectively. Therefore, it may be concluded that 10 and 11 is the C_{11}-epimer of dihydronodosin and acetyldihydronodosin respectively. Since the configuration of C_{11}-hydroxyl in nodosin was determined to be β by Fujita that of C_{11}-hydroxyl in 10, 11 and isodonal itself should be α-configuration. This was supported by the observation in NMR spectrum of 3 where the signal of a proton attached to C_{11} appeared at 5.27 τ (dd, $J_{\alpha x}$ = 7 cps and $J_{\beta x}$ = 15 cps) as compared with 4.84 τ (t, J = 4 cps) in nodosin.

Isodonal is the first example in natural enmein-type diterpenes which has a C_{18}-acetoxymethyl and C_6-aldehyde groups instead of hemiacetal ring.

We thank Professor E. Fujita for the identification of dihydronodosin and the diketolactone (12).

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