[Chem. Pharm. Bull. 18(5) 871—883 (1970)]

UDC 581.19 : 615.322.011.5 : 582.949.2 : 547.597.02

Studies on the Constituents of *Isodon trichocarpus* KUDO. I. Isolation of the Constituents and the Structures of Isodonol, Enmedol, and Enmenol

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(Received November 6, 1969)

Enmein (I) and 12 new constituents were isolated from *Isodon trichocarpus* KUDO. Among them, isodonol, enmedol, and enmenol, new diterpenoids having full (−)-kauran type carbon skeleton, were examined and V, VI, and VII were assigned respectively to isodonol, enmedol and enmenol from chemical and physical data.

From *Isodon trichocarpus* KUDO (Japanese name: Kurobana-hikiokoshi), a bitter priciple, enmein has been isolated by three Japanese groups.[2-4] Its chemical structure was investigated by many researchers[2-7] and finally elucidated as (I) by co-operative studies of three Japanese groups,[8] X-ray diffraction study,[9] and interconversion into (−)-kaurane[10] (III). Enmein is a diterpene, possessing (−)-kaurane type carbon skeleton, whose ring B is cleaved to form δ-lactone and a 5-membered hemiacetal.

In addition to enmein, Kanatomo reported the isolation of a compound, $C_{25}H_{34}O_8$, mp 263—265°.[2]

Recently, we found that *Isodon trichocarpus* KUDO contained many minor components, and we were able to isolated 13 constituents, including enmein, the main product, and isodonol, which might be identical with the compound of mp 263—265° obtained by Kanatomo. The outline of the isolation procedure[11] is as follows. Dry leaves of *Isodon trichocarpus* KUDO were extracted with hot water according to Kanatomo's method, and the extract was adsorbed with activated charcoal. Subsequent extraction of the adsorbate with hot methanol, and concentration of the extract afforded a crystalline precipitate of enmein. After removal of enmein by filtration, the mother liquid was extracted with ethyl acetate, and the extract was chromatographed over silica gel with a mixed solvent system (chloroform–ethyl acetate). All of the compounds thereby showed good analytical data and molecular weights as C_{20} compounds or their acetates, except enmedol (compound D), which was an ethylydene derivative of isodonol. Molecular formulae and some physical properties are shown in Table I.

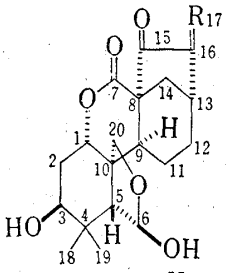
1) Location: *Hongo 7-3-1, Bunkyo-ku, Tokyo, 113, Japan.*
2) T. Ikeda and S. Kanatomo, *Yakugaku Zasshi*, **78**, 1128 (1958).
3) K. Naya, *Nippon Kagaku Zasshi*, **79**, 885 (1958).
4) M. Takahashi, T. Fujita, and Y. Koyama, *Yakugaku Zasshi*, **78**, 699 (1958).
5) T. Ikeda, T. Kosuge, and S. Kanatomo, *Yakugaku Zasshi*, **78**, 947 (1958).
6) M. Takahashi, T. Fujita, and Y. Koyama, *Yakugaku Zasshi*, **80**, 594, 696 (1960).
7) *a*) S. Kanatomo, *Chem. Pharm. Bull.* (Tokyo), **6**, 680 (1958); *b*) S. Kanatomo, *Yakugaku Zasshi*, **81**, 1049, 1437 (1961).
8) *a*) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, M. Takahashi, H. Irie, A. Numata, T. Fujita, T. Okamoto, M. Natsume, Y. Kawazoe, K. Shudo, 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, *ibid.*, **1966**, 1659.
9) Y. Iitaka and M. Natsume, *Tetrahedron Letters*, **1964**, 1257.
10) *a*) K. Shudo, M. Natsume, and T. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 1019 (1965); *b*) E. Fujita, T. Fujita, K. Fuji, and N. Ito, *Tetrahedron*, **1966**, 3423.
11) Details concerning the isolation procedure will be stated elsewhere in future.

Table I. Constituents of *Isodon trichocarpus* Kudo

		mp (°C)	Formula	$[\alpha]_D$
Ememonin	(compound A)	>300		−89
Enmenin	(compound B)	162—163	$C_{24}H_{34}O_7$	−84
	(compound C)	239—240	$C_{22}H_{28}O_7$	+25
Enmedol	(compound D)	297—299	$C_{22}H_{30}O_6$	−45
Enmein			$C_{20}H_{26}O_6$	
Ememofin	(compound F)	293—295	$C_{22}H_{30}O_7$	+27
Ememogin	(compound G)	>297	$C_{20}H_{26}O_7$	−126
Isodonol		248—249	$C_{20}H_{28}O_6$	−47
Enmenol	(compound I)	240—242	$C_{20}H_{30}O_6$	−29
Emejin	(compound J)	282—285	$C_{20}H_{28}O_7$	−180
Ememosin	(compound K)	255—259	$C_{22}H_{30}O_8$	−122
Enmelol	(compound L)	263—265	$C_{20}H_{30}O_5$	−48
Ememodin	(compound D′)	237—239	$C_{20}H_{26}O_6$	−131

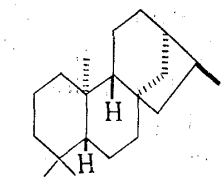
Simultaneously with this isolation, we took up structural investigation of the constituents of *Isodon trichocarpus* Kudo and found that they could be classified into two groups in respect to their structures. The first group has a full (−)-kaurane type skeleton and the second has an incomplete (−)-kaurane type skeleton like enmein. In this paper, we wish to report the structures of isodonol, enmedol (compound D), and enmenol (compound I), which are new diterpenoids belonging to the first group.

Now, we propose structure (V), (VI), and (VII) respectively for isodonol,[12] enmedol,[13] and enmenol.[13]

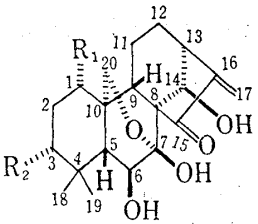


I : R = =<H H

II : R = H CH3

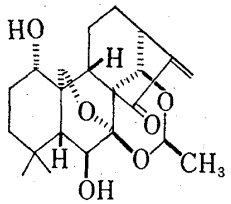


III

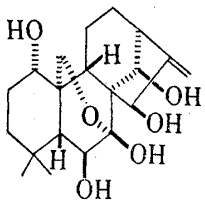


IV : R1 or R2 = OH

V : R1 = OH, R2 = H



VI



VII

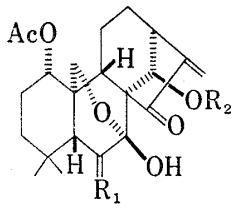
Chart 1

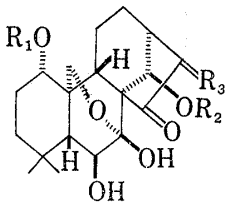
12) The authors presented the structure of isodonol as IV at the 10th Symposium on the Chemistry of Natural Products in Tokyo, 1966 (Symposium Papers, 192 (1966)). Independently, E. Fujita, T. Fujita, and shibuya reported the structure of oridonin as V, which was identical with isodonol, at the same Symposium (Symposium Papers, 224 (1966), and *Chem. Commun.*, **6**, 252 (1967)).

13) The structures of enmedol and enmenol were presented by the present authors at the 24th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April 1967 (Abstracts of Papers, 459).

Structure of Isodonol

Isodonol (V), prisms, mp 248—249°, has a molecular formula of $C_{20}H_{28}O_6$ (M^+, *m/e* 364). Its infrared (IR) spectrum (KBr) shows the presence of C=O (1712 cm^{-1}), C=C (1645 cm^{-1}), and OH (3600—2800 cm^{-1}), while its ultraviolet (UV) spectrum (95% ethanol) shows the absorption bands at 237.5 mμ (ε 7530), 332 mμ (ε 77), slightly different from those of enmein.[14] Acetylation of isodonol with acetic anhydride–pyridine afforded a noncrystalline diacetate (VIII) having residual hydroxyl groups. Heating of mixture of isodonol and acetic acid in a sealed tube afforded a monoacetate (IX), which was also obtained by the hydrolysis of VIII with oxalic acid. Isodonol diacetate (VIII) was oxidized with chromium trioxide–acetic acid to yield δ-ketone (X), unstable to silica gel chromatography. Absorption band at 3440 cm^{-1} in its IR spectrum (CCl_4) shows the presence of a tertiary hydroxyl group, while the bands at 1746 and 1742 cm^{-1} (sh.) and the same UV (95% ethanol) absorption band at 233 mμ as enmein, suggest the presence of a 5-membered exocyclic α,β-conjugated ketone,[15] and an interaction between one secondary hydroxyl and a carbonyl group of conjugated ketone in isodonol.





VIII : R_1=  , R_2=Ac

IX : R_1=  , R_2=H

X : R_1= =O, R_2=Ac

XI : R_1=H, R_2=H, R_3=

XII : R_1=H, R_2=H, R_3=

XIII : R_1=Ac, R_2=Ac, R_3=

Chart 2

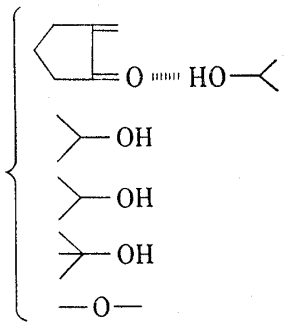


Chart 3

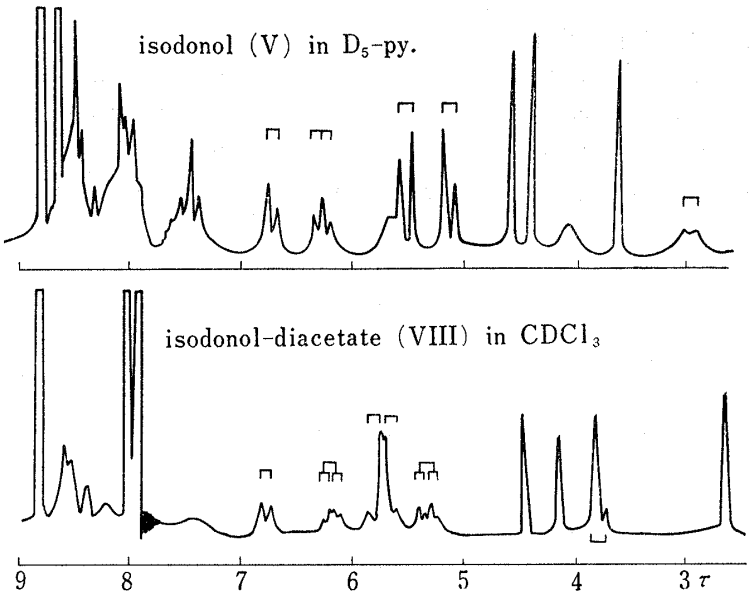


Chart 4

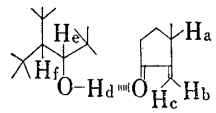
14) Enmein has its UV (95% ethanol) absorption maximum at 233 mμ (ε 6000).

15) Absorption maximum calculated for this 5-membered exocyclic α,β-conjugated ketone is 230 mμ according to the "Interpretation of the Ultraviolet Spectra of Natural Products," (A.I. Scott, Pergamon Press, London, 1964, p. 60).

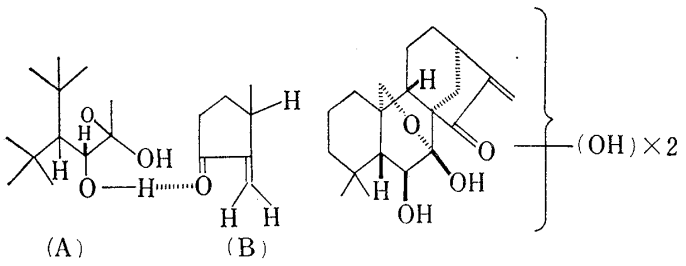
Catalytic hydrogenation of isodonol over palladium–charcoal afforded dihydroisodonol (XI), containing a trace of impurity which was removed by recrystallization and was thought to be C-15 epimer (XII) of XI. Acetylation of XI gave dihydroisodonol diacetate (XIII) which was also obtained by catalytic hydrogenation of VIII over palladium–charcoal. These observations indicate the presence of functional groups shown in Chart 3, and isodonol is presumed to be pentacyclic.

The nuclear magnetic resonance (NMR) spectra of isodonol and its diacetate (VIII) clarify the environments of the functional groups shown in Chart 3, and exhibit the presence of partial structures (XIV), (XV), (XVI), (XVII), (XVIII), and (XIX). The spectra and spectral data are shown in Chart 4 and in Table II.

Table II. Partial Structures in Isodonol (V) and Its Diacetate (VIII)

	V (D_5-py.)	VIII ($CDCl_3$)
 (XIV)	Ha 6.83τ, d, J=9 cps Hb, Hc 4.47, 3.70 τ, each 1H, s Hd 3.07 τ, d, J=10 cps He	6.81 τ, d, J=9 cps 4.36, 3.71 τ, each 1H, s 3.68 τ, d, J=11 cps 6.18 τ, d of d, J=6 and 11 cps
$\times\!\begin{matrix}CH_3\\CH_3\end{matrix}$ (XV)	8.87, 8.72 τ, each 3H, s	8.87 τ, 6H, s
$>CH_gOH$ (XVI)	6.32 τ, 1H, t, 1H, t, J=8—9 cps	6.18 τ, 1H, q, J=6 and 11 cps
$H\!+\!CH_hOH$ (XVII)	4.66 τ, 1H, s	4.16 τ, 1H, s
$+\!\hat{O}H$ (XVIII)	4.17 τ, 1H, s	
$+CH_2O-$ (XIX)	5.58, 5.28 τ, each 1H, d, J=10 cps	5.80, 5.64 τ, each 1H, d, J=10 cps

Quartet-doublet signal of $C\underline{H}_e$–$O\underline{H}_d$ in partial structure (XIV) was confirmed by the decoupling method. The chemical shift of $O\underline{H}_d$ signal was dependent on acid and thermal changes. In addition, $C\underline{H}_e$ signal of VIII changes from a quartet to a doublet (J=7 cps) by the addition of deuterium oxide. Signals due to H_d and H_e are absent in the NMR spectrum of δ-ketone (X). Further, XIII afforded an aldehyde-lactone (XXI) by oxidation with sodium periodate acetic acid, showing an AB-type quartet signal of $\geqslant$–CH_fCH_eO (H_f, 8.14 τ; H_e, 0.05 τ; each 1H, doublet, J=7 cps) in its NMR spectrum ($CDCl_3$). These data lead to an extension of the partial structure (XIV) to XX. The NMR (D_5-pyridine) spectrum of dihydroisodonol (XI) showed the presence of newly produced system $>CH–CH_3$, instead of $>=<^{H}_{H}$ recognized in isodonol. Besides, that the 1H signal at 6.67 τ in the NMR spectrum of XI changes from a quintet to AB_3 quartet (J=7 cps) by irradiation of methylene region, confirms the presence of only one proton in the allyl position of exo-methylene.



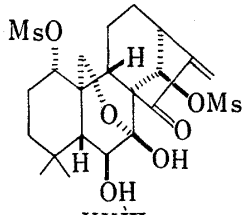
XX XXII

Chart 5

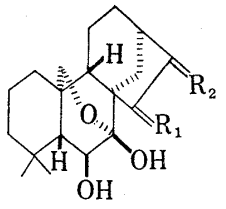
Now, it is clear that isodonol has partial structures of XV—XX, and all of these could be satisfied only by a kaurane-type skeleton among the known skeletal types of diterpenes. If (—)-kaurane type skeleton is assumed for isodonol, then (B) part of the partial structure XX would be best placed at ring D, (A) part of XX at ring B, and hydrogen-bonded hydroxyl group should be situated at C-6 and β-oriented. The coupling constant between C-5 and C-6 protons is 5—7

cps[16] in isodonol derivatives, and a Dreiding model shows that α-OH at C-6 is unable to form hydrogen bonding with C-15 carbonyl group. Thus, isodonol is represented by the structure shown by XXII.

The fundamental carbon skeleton of isodonol was deduced by converting it in the following way into a triol (XXIV), which was also obtained from the known derivative (XLVIII)[17] of enmein. Mesylation of isodonol afforded a dimesylate (XXIII), which was submitted to hydrogenation over Raney Nickel to the triol (XXIV).



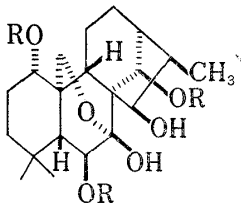
XXIII



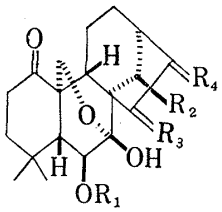
XXIV : R_1=  , R_2= 

XXV : R_1=, R_2= 

XXVI : R_1=  , R_2= 



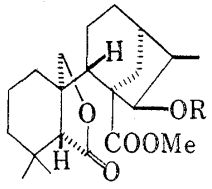
XXVII : R=H
XXVIII : R=Ac



XXIX : R_1=H, R_2=OH, R_3= =O, R_4=

XXX : R_1=Ac, R_2=H, R_3=, R_4= = 

XXXI



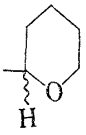
XLVIII : R=H
XLIX, L : R= 

Chart 6

Oxidation of dihydroisodonol (XI) with sodium periodate-acetic acid gave δ-lactone hemiacetal (XXXII) (IR (KBr): 1750, 1716 cm^{-1}), which was proved to be a 5-membered hemiacetal by further oxidation with chromium trioxide-acetic acid into γ,δ-di-lactone (XXXIII) (IR (KBr): 1775, 1740 (br.)). This suggests the presence of hydroxyl at C-1 or C-3 position of ring A. In the NMR spectra of isodonol derivatives, the proton at the foot of this hydroxyl group often appears as a quartet signal and this hydroxyl is thought to be α-oriented. We have no decisive proof concerning the position of this hydroxyl group in ring A, though the IR spectrum of δ-lactone hemiacetal (XXXII) resembles that of dihydroenmein (II), and dehydro-dihydroisodonol (XXIX), obtained by chromium trioxide-pyridine complex oxidation of XI, exhibits a positive Cotton curve[18] same as known keto-lactam[19] (XXXI) and dehydroenmein[20] (XXX),

16) Dreiding model shows that the dihedral angle between C-5β-H and C-6α-H in XXII, having a boat-formed B ring, is about 120°, which corresponds to the coupling constant of 2.1 and 4 cps by "Karplus' equation" and modified "Williamson and Johnson's equation," respectively. On the contrary, coupling constant between C-5β-H and C-6β-H is 8.5 and 16 cps by the equation of Karplus and Williamson, respectively (N.S. Bhacca and D.H. Williams, "Application of NMR Spectroscopy in Organic Chemistry." Holden-Day, Inc., San Francisco, London, Amsterdam, 1964, p. 49).

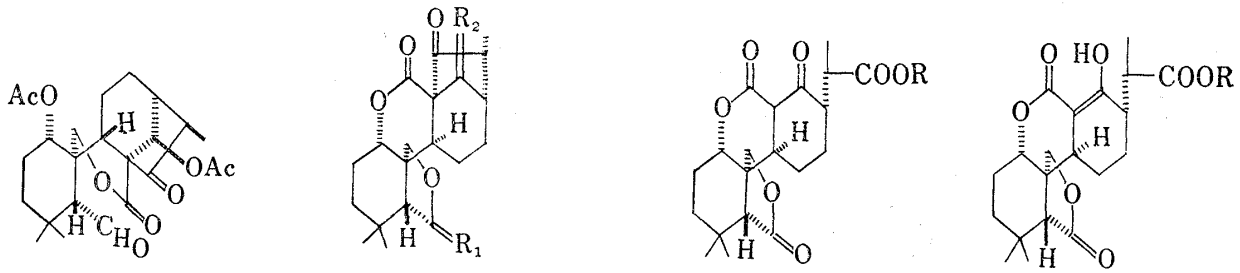
17) K. Shudo, M. Natsume, and T. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 1019 (1965).

18) From the octant prospect, 3-keto group is preferable for XXIX if ring A is chair formed, and 1-keto, if boat formed.

19) T. Sugasawa, *Chem. Pharm. Bull.* (Tokyo), **9**, 897 (1961).

20) S. Mori, T. Koizumi, K. Shudo, and T. Okamoto, *Chem. Pharm. Bull.* (Tokyo), Submitted.

which have C-1 keto group and are structurally closely related to XXIX. Concerning the hydroxyl group in ring A, Fujita, *et al.* proved it to be 1α-OH.[12]



XXI

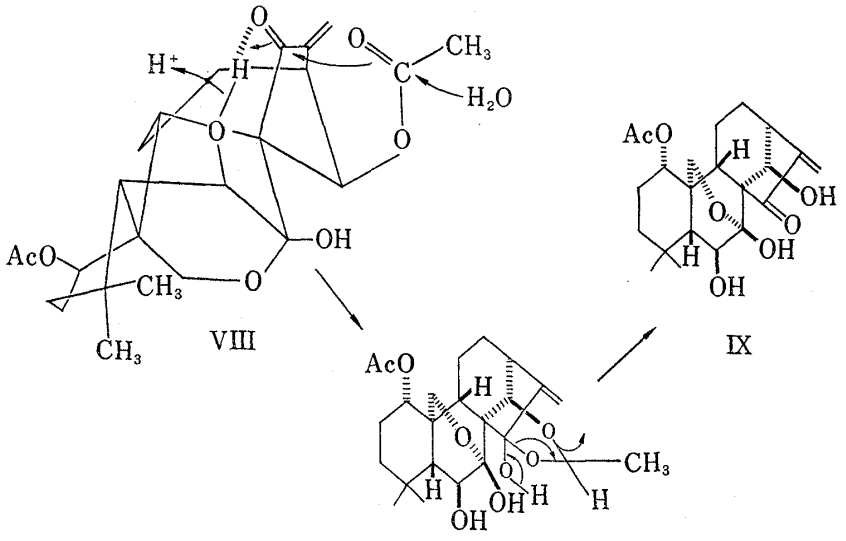
XXXII : R_1=⟨OH/H, R_2=⟨H/OH
XXXIII : R_1, R_2=O

XXXIV : R=H
XXXVI : R=Me

XXXV : R=H
XXXVII : R=Me

Chart 7

The last remaining hydroxyl group should be C-14β-OH because in the NMR spectra of isodonol derivatives, the proton on the carbon bearing this hydroxyl group always appears as a 1H singlet, for instance at 4.66 τ in isodonol (V) (D_5-pyridine), 4.63 τ in dihydroisodonol (D_5-pyridine), and so forth. This observation is explainable only by considering C-14β-OH. Namely, the dihedral angle between C-14α-H and C-13-H is nearly rectangular and there would be no coupling between them. This situation is the same as that found in grayanotoxin and its derivatives.[21-22] The lower chemical shift of C-14α-H is due to the anisotropic effect of C-15 carbonyl group. In the selective hydrolysis reaction of is odonol diacetate (VIII) to monoacetate (IX), the intramolecular catalysis shown in Chart 8 is well explained by considering C-14β-OAc.[23] Moreover, unstability of γ,δ-di-lactone (XXXIII) is easily understood by assuming C-14β-OH for isodonol. Thus, XXXIII contains an unstable β-diketone system which is cleaved by silica gel to form keto-acid (XXXIV) or enol-acid (XXXV). It is not clear what factor controls the inclination to keto-acid or to enol-acid, but keto-acid (XXXIV)



VIII

IX

Chart 8

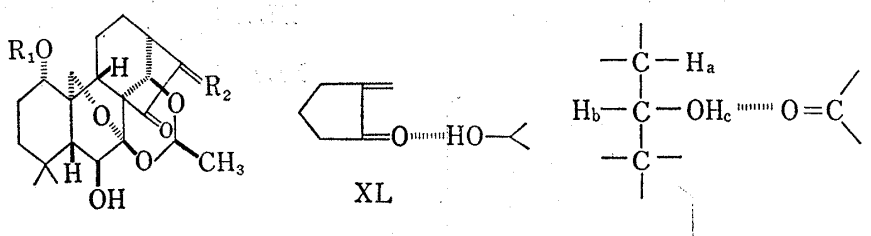
21) T. Kozima, K. Nakanishi, M. Yanai, and H. Kakisawa, *Tetrahedron Letters*, **1964**, 1329.
22) Nagata, *et al.* reported the synthesis of 3β,5β-ethanocholestan-4β-ol-3a-one, which contained similar circumstances as found in C/D ring of grayanotoxin (*Chem. Pharm. Bull.* (Tokyo), **16**, 875 (1968)).
23) That the position of hydrolyzed acetoxyl group was C-14 was proved by convertion of IX into enmedol monoacetate (XXXIX).

was enolized to enol-acid (XXXV) by refluxing in acetic acid. On the other hand, enol-acid methyl ester (XXXVII) was converted into keto-acid methyl ester (XXXVI) in the mesylation condition. Lastly, the presence of C-14β-OH was confirmed by the easy formation of ethylidene compound, enmedol (VI).

Catalytic hydrogenation of exo-methylene and carbonyl group in D ring of isodonol derivatives provides interesting problems. As mentioned before, desulfurization of isodonol dimesylate (XXIII) with Raney nickel afforded a triol (XXIV) having C-15β-OH and C-16β-Me. Catalytic hydrogenation of isodonol (V) over palladium-charcoal and subsequent mesylation and desulfurization afforded a complicated mixture from which a triol (XXV) was obtained. Because of the reasons to be stated below, this triol (XXV) is thought to be derived from a minor C-15 epimer of dihydroisodonol (XI), namely, (XII). Reduction of dihydroisodonol (XI), a major product from catalytic hydrogenation of isodonol (V), with sodium borohydride gave tetrahydroisodonol (XXVII), which was also obtained by direct sodium borohydride reduction of isodonol, and whose C-15-OH and C-16-Me were *cis* to each other (NMR: C-15-H, 4.71 τ, 1H, doublet, J=10 cps). Acetylation of XXVII afforded tetrahydroisodonol triacetate (XXVIII). This fact is explained by considering β-orientation for C-15-OH and steric hindrance due to C-9β-H and C-11β-H on its acetylation. Therefore, tetrahydroisodonol (XXVII) should have C-15β-OH and C-16β-Me, and hence dihydroisodonol (XI) should have C-16β-Me. Coincidence of XXVII and dihydroenmenol, obtained by catalytic hydrogenation of enmenol (VII) which has β-oriented C-15-OH, inevitably supports this conclusion.

Structure of Enmedol

Enmedol (VI), $C_{22}H_{30}O_6$ (M^+, *m/e* 390), was obtained as prisms, mp 297—299°. Its spectral data (IR ν_{max}^{KBr} cm^{-1}: 3600—2800, 1715, UV $\lambda_{max}^{95\%\ EtOH}$ mμ: 236, $[\alpha]_D$ −45°) resemble closely those of isodonol (V) and this fact suggests the presence of a partial structure, XL. Enmedol afforded dihydroenmedol (XXXVIII) by catalytic hydrogenation, monoacetate (XXXIX) by treatment with acetic anhydride-pyridine, but enmedol was recovered by sodium periodate-acetic acid oxidation. The NMR (D_5-pyridine) spectrum of XXXIX exibits the presence of two tertiary methyls (8.82 τ, 6H, singlet), one acetoxyl (8.05 τ, 3H, singlet), ether methine >CHO– (5.42 τ, 1H, singlet), an exo-methylene (4.52 τ, 3.90 τ, each 1H, singlet), an ether methylene >$-CH_2O-$(5.83 τ, 2H, singlet), and partial structure of XLI (H_b, 6.13 τ, doublet of doublets, J=7 and 12 cps; H_c, 4.16 τ, doublet, J=12 cps), which were also recognized in isodonol derivatives. In addition, AB_3-type signals at 4.61 τ, (1H, quartet, J=5 cps) and 8.72 τ, (3H, doublet, J=5 cps) in the NMR spectrum of XXXIX and molecular formula $C_{22}H_{30}O_6$ of enmedol indicate that enmedol might be an ethylidene derivative of isodonol (V). This deduction was confirmed by the fact that hydrolysis of enmedol with hydrogen chloride in aqueous MeOH affoded isodonol. Considering the observation that enmedol is recovered by sodium periodate-acetic acid oxidation, and the presence of a partial structure XLI in enmedol, one of the two hydroxyl groups which forms dioxorane ring should be C-7β-OH. Additionally, this inference leads to the conclusion that the remaining hydroxyl group is at C-14



XXXVIII : R_1=H, R_2=$\langle^{CH_3}_{H}$

XXXIX : R_1=Ac, R_2=$\langle^{H}_{H}$

Chart 9

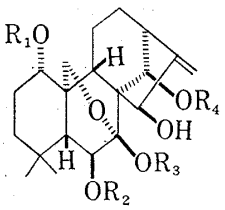
and is β-oriented, and no other hydroxyl group is suitable for ethylidene formation. Furthermore, the observation that condensation reaction between isodonol and acetaldehyde afforded enmedol as a sole product means that enmedol has the most energetically stable dioxorane ring and methyl orientation. Dreiding model shows that dioxorane ring is chair formed and the methyl group of ethylidene is β-oriented. Thus enmedol has structure represented by VI.

Structure of Enmenol

Enmenol (VII), $C_{20}H_{30}O_6$ (M^+, *m/e* 366), prisms, mp 240—242°, exhibits no carbonyl band in its IR spectrum (KBr). In the NMR spectrum (D_5-pyridine) of enmenol, presence of two tertiary methyls (8.80, 8.77 τ, each 3H, singlet), one exo-methylene (4.37 τ, 2H, singlet), and a partial structure of $\geqslant$-CH_2O-(5.62, 5.20 τ, each 1H, doublet, J=10 cps) was confirmed. Therefore, enmenol should have five hydroxyl groups, if we assume (—)-kaurane type skeleton for enmenol. Enmenol consumed 1 mole of sodium periodate and afforded a triacetate (XLII) by treatment with acetic anhydride–pyridine,and XLII did not consume sodium periodate. Enmenol has vicinal hydroxyl groups, at least one of which is acetylable. Environments of hydroxyl groups, in enmenol were deduced from its NMR spectrum (D_5-pyridine), in which 1H doublet (J=5 cps) at 5.77 τ was assigned to C-6α-H, 1H singlet at 4.92 τ to C-15-H, and 1H singlet at 4.68 τ to C-14α-H. We can anticipate structure (XLIV) for enmenol. Enmenol was proved to be VII by correlation with isodonol in two different ways.

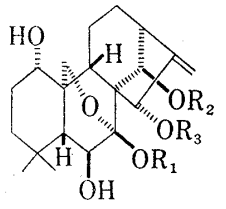
(i) Enmenol was catalytically hydrogenated to afford dihydroenmenol which was identical with tetrahydroisodonol (XXVII).

(ii) Enmenol was converted into dioxorane compound (XLIII) by condensation reaction with acetaldehyde, and then XLIII was oxidized with manganese dioxide to afford enmedol (VI), which was already correlated with isodonol (V), as mentioned before. In the dioxorane ring formation reaction, a mixture of dioxoranes XLV, XLVI, and XLVII is expected to be formed if C-15-OH is α-oriented because its Dreiding model shows that two of the hydroxyl groups in C-7β-OH, C-14β-OH, and C-15α-OH are in the same 1,3-diaxial relationship with each other. The fact that only one species is produced by condensation reaction means that the hydroxyl group at C-15 is β-oriented. Moreover, formation of triacetate (XII), in which C-15-OH is recovered nonacetylated by steric hindrance of C-9β-H and C-11β-H, supports β-orientation of C-15-OH. Thus enmenol is elucidated as VII.



XLII : R_1, R_2, R_4=Ac, R_3=H

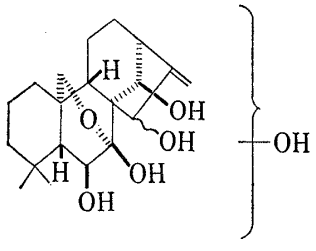
XLIII : R_1, R_2=H, $\begin{matrix}R_3\\R_4\end{matrix}$=$\diagdown\!\!\diagup^{CH_3}_{H}$



XLV : $\begin{matrix}R_1\\R_2\end{matrix}$=$\diagdown\!\!\diagup^{CH_3}_{H}$, R_3=H

XLVI : $\begin{matrix}R_2\\R_3\end{matrix}$=$\diagdown\!\!\diagup^{CH_3}_{H}$, R_1=H

XLVII : $\begin{matrix}R_1\\R_3\end{matrix}$=$\diagdown\!\!\diagup^{CH_3}_{H}$, R_2=H



XLIV

Chart 10

Experimental[24]

Isodonol (V)——Isodonol was recrystallized from MeOH as needles, mp 248—249°. $[\alpha]_D^{24}$ −47° ($c=1.017\times10^{-1}$, 95% EtOH). ORD ($c=1.017\times10^{-1}$, 95% EtOH) $[M]^{31}$ (mμ): 818 (312) (peak), −1340 (360) (trough). UV $\lambda_{max}^{95\%\ EtOH}$ 237.5 mμ (ε 7530), 332 mμ (ε 77). IR ν_{max}^{KBr} cm^{-1}: 3600—2800, 1712, 1645. NMR τ (D_5-py.): 8.87, 8.72 (each 3H, singlet), 6.83 (1H, doublet, $J=9$ cps, C-13-H), 6.32 (1H, triplet, $J=8$—9 cps, C-1β-H), 5.70 (1H, broad, singlet, C-6α-H), 5.58, 5.25 (each 1H, doublet, $J=10$ cps, C-20-H×2), 4.66 (1H, singlet, C-14α-H), 4.47, 3.70 (each 1H, singlet, =CH$_2$), 4.17 (1H, broad, singlet, OH), 3.07 (1H, doublet, $J=10$ cps, C-6β-OH). Mass Spectrnm M^+, *m/e* 364. *Anal.* Calcd. for $C_{20}H_{28}O_6$: C, 66.28; H, 7.23. Found: C, 66.03; H, 7.48.

Isodonol Diacetate (VIII)——Ac_2O (1 ml) was added to a solution of V (200 mg) in pyridine (2 ml). After standing over night at room temperature, the reaction mixture was concentrated to give an oil (260 mg), which was chromatographed on silica gel (5 g). The $CHCl_3$ elution afforded pure VIII (212 mg) as a thick oil. IR ν_{max}^{KBr} cm^{-1}: 3560, 3380, 1740, 1722 (sh.), 1645. NMR τ ($CDCl_3$): 8.87 (6H, singlet), 7.99, 7.93 (each 3H, singlet, –OCOCH$_3$), 6.81 (1H, doublet, $J=9$ cps, C-13-H), 6.18 (1H, doublet of doublets, $J=6$ and 11 cps, C-6α-H), 5.80, 5.64 (each 1H, doublet, $J=10$ cps, C-20-H×2), 5.33 (1H, X part of ABX, $J=5$ and 8 cps, C-1β-H), 4.36 (1H, singlet, C-14α-H), 4.16, 3.71 (each 1H, singlet, =CH$_2$), 3.68 (1H, doublet, $J=11$ cps).

Isodonol Monoacetate (IX)——(i) VIII (118 mg) was added to a solution of oxalic acid (258 mg) in H_2O (10 ml) and the mixture was refluxed for 45 min. The reaction mixture was extracted with $CHCl_3$, which was dried and evaporated leaving a yellow gum (98 mg). The residue was chromatographed on silica gel to afford starting meterial VIII (25 mg), thoroughly hydrolyzed V (5 mg), and partially hydrolyzed monoacetate (IX) (21 mg), which was recrystallized from MeOH as prisms, mp 238—239°.

ii) A mixture of V (53 mg) and Ac_2O (10 mg) in a sealed tube was heated in an oil bath at 180—190° for 4 hr. Evaporation and silica gel chromatography of the amorphous residue afforded unreacted V (23 mg) and monoacetate (22 mg), which was identical with IX by mixed mp, and in IR and NMR spectra; mp 235—236°. IR ν_{max}^{KBr} cm^{-1}: 3360, 3330, 3190, 1738, 1718, 1640. NMR τ ($CDCl_3$): 8.87 (6H, singlet), 8.00 (3H, singlet), 6.85 (1H, doublet, $J=9$ cps, C-13-H), 6.23 (1H, broad, singlet, C-6-H), 5.67 (2H, triplet, $J=11$ cps), 5.28 (X part of ABX, quartet, $J=6$ and 9 cps, C-1β-H), 5.03 (1H, singlet, C-14α-H), 4.02, 3.61 (each 1H, singlet).

Oxidation of Isodonol Diacetate (VIII) to δ-Ketone (X)——A mixture of CrO_3 (100 mg), AcOH (4 ml), and H_2O (0.5 ml) was added to a solution of VIII (100 mg) in AcOH (7 ml). The mixture was allowed to stand for 13 hr in an ice box. After destruction of excess oxidant with MeOH, the solvent was evaporated *in vacuo*. The residue was diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to give X as thin-layer chromatographically pure oil (75 mg), which was further purified by silica gel chromatography, but did not crystallize. UV $\lambda_{max}^{95\%\ EtOH}$ 233 mμ. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3440, 1746, 1742 (sh.), 1645. NMR τ ($CDCl_3$): 8.90, 8.50 (each 3H, singlet), 7.88 (6H, singlet), 7.84 (1H, singlet, C-5-H), 6.81 (1H, doublet, $J=10$ cps, C-13-H), 5.64, 5.42 (each 1H, doublet, $J=11$ cps), 5.25 (2H), 4.35 (1H, singlet, C-14α-H), 3.78 (2H, singlet, =CH$_2$).

Dihydroisodonol (XI)——V (450 mg) in MeOH (20 ml) was hydrogenated in the presence of 15% Pd–C, and 1 mole of H_2 was absorbed rapidly. Treatment in an usual manner afforded a crystalline precipitate which contained slight impurity. Recrystallization from MeOH afforded XI (378 mg) as needles, mp 226—232°. ORD ($c=0.584\times10^{-1}$, 95% EtOH) $[M]^{27}$ (mμ): +2420 (279) (peak), −4940 (316) (trough). IR ν_{max}^{KBr} cm^{-1}: 3600—2900, 1713. NMR τ(D_5-py.): 8.92, 8.80 (each 3H, singlet), 8.89 (3H, doublet, $J=7$ cps), 6.67 (1H, quintet), 5.89 (1H, doublet of doublets, $J=6$ and 12 cps), 5.69, 5.29 (each 1H, doublet, $J=10$ cps), 4.71 (1H, singlet), 4.31 (1H, broad singlet), 3.48 (1H, doublet, $J=12$ cps).

Dihydroisodonol Diacetate (XIII)——i) VIII (104 mg) in MeOH was hydrogenated over 10% Pd–C. Usual treatment and subsequent silica gel chromatography afforded XIII (95 mg) as a thick oil. IR ν_{max}^{KBr} cm^{-1}: 3560, 3400, 1740 (broad). NMR τ ($CDCl_3$): 8.86 (6H, singlet), 6.34 (1H, doublet of doublets, $J=6$ and 12 cps, C-6α-H), 5.80 (2H, singlet), 5.35 (1H, X part of ABX, $J=5$ and 8 cps), 4.24 (1H, doublet, $J=12$ cps, C-6-OH), 4.08 (1H, singlet, C-14α-H).

ii) A solution of XI (103 mg) in pyridine (1 ml) was treated with Ac_2O (1 ml) for 13 hr at room temperature. Purification of the product by silica gel chromatography gave a colorless oil (112 mg), which was identical with XIII by IR and TLC.

Periodate Oxidation of XIII to Aldehyde-lactone (XXI)——A mixture of $NaIO_4$ (40 mg), H_2O (3 ml), and EtOAc (1 drop) was added to a solution of XIII (57 mg) in AcOH (1 ml), and the mixture was left for 36 hr at 50—55.° After additional heating on a water bath at 50° for 20 min, the solvent was evaporated under reduced pressure. The residue was diluted with H_2O and extracted with EtOAc. The organic layer was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to give an oil. Purification by silica gel chromatography afforded XXI as a thick oil, quantitatively. NMR τ ($CDCl_3$): 9.08, 8.70 (each 3H, singlet),

24) All melting points were measured by Yanagimoto's Micro–Melting Point Apparatus and are not corrected.

8.88 (3H, doublet, $J=7$ cps), 8.14 (1H, doublet, $J=5$ cps, C-5-H), 7.95, 7.85 (each 3H, singlet), 7.00 (1H, quintet), 5.30 (2H), 5.06, 4.86 (each 1H, doublet, $J=11$ cps, C-20-H×2), 4.09 (1H, singlet), 0.05 (1H, doublet, $J=7$ cps).

Isodonol Dimesylate (XXIII)——To a solution of V (392 mg) in pyridine (2 ml), MsCl (30 drops) was added under cooling in an ice bath. After standing over night at room temperature, the reaction mixture was diluted with H_2O and left standing for 1 hr. The mixture was concentrated and the residue was extracted with CH_2Cl_2 and then with EtOAc. Each organic layer was washed with H_2O and dried over anhyd. Na_2SO_4. Evaporation of the EtOAc gave amorphous XXIII (69 mg) in almost pure state and the CH_2Cl_2 gave an oil (127 mg), which was chromatographed on silica gel (5 g). Fr. 8—12 of 5% EtOAc–$CHCl_3$ elution afforded pure amorphous XXIII (36 mg). IR ν_{max}^{KBr} cm^{-1}: 3375, 1715, 1350 (br.), 1173. NMR τ ($CDCl_3$): 8.86 (6H, singlet), 6.98 (3H, singlet), 6.88 (3H, singlet), 5.78 (2H, singlet), 4.42 (1H, singlet), 4.36 (1H, singlet), 4.05 (1H,), 3.78 (1H, singlet).

Desulfurization of XXIII to Triol (XXIV)——To a solution of XXIII (160 mg)in abs. EtOH (20 ml), Rany Ni W-4 catalyst (15 g) was added and the mixture was heated in an autoclave in H_2 atmosphere (primary pressure 43 atm) for 17.5 hr at 55—65° with stirring. Then the mixture was centrifuged and the supernatant fluid was decanted. The precipitate was washed repeatedly with EtOH. Washings were combined with the supernatant fluid, and the solvent was evaporated to leave a solid, which was chromatographed on silica gel (5 g). Fr. 2—5 of EtOAc elution afforded a crystalline triol (XXIV) (81 mg) which was recrystallized from MeOH–EtOAc to give needles, mp 206.5—208°. $[\alpha]_D^{33}$ −51° ($c=1.082\times10^{-1}$, 95% EtOH). IR ν_{max}^{KBr} cm^{-1}: 3460, 3400, 1165, 1080, 1060. (Mass. Calcd. for $C_{20}H_{32}O_4$: 336. Found: M^+, *m/e* 336.) By mixed mp, IR, TLC, and $[\alpha]_D$, the triol (XXIV) was identified with an authentic sample, mp 204—210°, obtained from (XLVIII).[15]

Triol (XXV)——V (342 mg) was catalytically hydrogenated over Pd–C in a usual manner to give solid (340 mg), which was treated with MsCl (30 drop)–pyridine (10 ml). After standing over night at room temperature, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over anhyd. Na_2SO_4, and concentrated to give an oil (461 mg), which was chromatographed on silica gel (12 g). Fr. 7—12 of $CHCl_3$ elution afforded an amorphous residue (305 mg), which showed two spots very closely with each other on thin-layer plate. IR ν_{max}^{KBr} cm^{-1}: 3580, 3400 (br.), 1730, 1350 (br.), 1175, 930. The mesylated mixture was dissolved in abs. EtOH (20 ml), and Raney Ni W-4 was added to the solution. The mixture left in an autoclave in H_2 atmosphere for 2 months (primary pressure 40 atm.) with occasional stirring. The same work-up as in the case of desufurization of XXIII to triol (XXIV) gave a complicated mixture, which was chromatographed on silica gel. Fr. 8—10 of 20% EtOAc–$CHCl_3$ elution gave a partially crystalline oil (31 mg). Crystallization from CH_3COCH_3 afforded XXV (4 mg) as needles, mp 208—211°. IR ν_{max}^{KBr} cm^{-1}: 3400 (br.), 1080. *Anal.* Calcd. for $C_{20}H_{32}O_4\cdot\frac{1}{2}H_2O$: C, 69.56; H, 9.57. Found: C, 69.22; H, 9.37. (Mass. Calcd. for $C_{20}H_{32}O_4$: 336. Found: M^+, *m/e* 336.) This triol (XXV) was not identified either of the triols[25] (XXIV), (XXVI).

Tetrahydroisodonol (XXVII)——i) To a solution of XI (100 mg) in MeOH (5 ml), $NaBH_4$ (110 mg) was added with cooling in an ice bath and the mixture was left over night at room temperature. Evaporation of MeOH under reduced pressure gave a colorless residue, which was extracted with EtOAc. Usual work-up of the extract gave only a small quantity of amorphous solid (10 mg), therefore, the residue was diluted with H_2O and again extracted with EtOAc. The organic layer was washed with H_2O, dried over anhyd. Na_2SO_4, and concentrated to give an amorphous solid (98 mg). Since the two lots of solids were identical by TLC, they were combined and recrystallized from MeOH to give XXVII(58 mg) as needles, mp 225—230°. IR ν_{max}^{KBr} cm^{-1}: 3400, 3340, 1055, 1025.

ii) To a solution of V (80 mg) in MeOH (5 ml), $NaBH_4$ (90 mg) in MeOH (3 ml) was added and the mixture was left over night at room temperature. The same work-up as in the case of $NaBH_4$ reduction of XI to XXVII afforded a crystalline precipitate, which was recrystallized from CH_3COCH_3–MeOH to give XXVII as fine needles (34 mg), mp 234—237°. Its identity with $NaBH_4$ reduction product of XI was proved by IR and mixed mp. NMR τ (D_2-py.): 8.85 (6H, singlet), 8.72 (3H, doublet, $J=7$ cps), 6.24 (1H, triplet, $J=8$ cps, C-1β-H), 5.86 (1H, doublet, $J=5$ cps, C-6α-H), 5.63, 5.23 (each 1H, doublet, $J=10$ cps, C-20-H×2), 4.92 (1H, singlet, C-14α-H), 4.71 (1H, doublet, $J=10$ cps, C-15α-H).

Tetrahydroisodonol Triacetate (XXVIII)——Ac_2O (1 ml) was added to a solution of XXVII (38 mg) in pyridine (2 ml). The mixture was heated at 80—90° for 3 hr and left over night at room temperature. Evaporation *in vacuo* gave an oily residue (49 mg), which was chromatographed on silica gel (4 g). Fr. 2—4 of $CHCl_3$ elution gave a thick oil, which was crystallized from ether hexane to give XXVIII as prisms, mp 163—165° (>120°: became opaque). IR ν_{max}^{KBr} cm^{-1}: 3590, 3550, 3480, 3410, 1745 (sh.), 1723, 1704, 1648, 1245, 1220, 1050, 1025. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1755, 1745, 1220 (br.), 1060, 1025. NMR τ ($CDCl_3$): 9.16, 8.84 (each 3H, singlet), 9.02 (3H, doublet, $J=7$ cps), 8.00, 7.94, 7.89 (each 3H, singlet,–OCOCH$_3$×3), 5.85 (2H, singlet, C-20-H×2), 5.62 (1H, singlet, OH), 5.58 (1H, doublet, $J=10$ cps, C-15α-H), 5.32 (1H,

25) M. Somei, K. Shudo, T. Okamoto, and M. Natsume, Abstracts of Papers, 24th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April 1967, p. 460.

quartet, $J=6$ and 9 cps, C-1β-H), 4.82 (1H, doublet, $J=5$ cps, C-6α-H), 4.62 (1H, singlet, C-14α-H). *Anal.* Calcd. for $C_{26}H_{28}O_9 \cdot H_2O$: C, 60.94; H, 7.81. Found: C, 61.31; H, 7.79.

Dehydrodihydroisodonol (XXIX)——To a solution of XI (100 mg) in pyridine (1.5 ml), CrO_3 (100 mg)–pyridine (3 ml) complex was added and left over night at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with H_2O dried over anhyd. Na_2SO_4, and evaporated to give amorphous solid, which was chromatographed on silica gel (5 g). Fr. 7—14 of 6—8% EtOAc–$CHCl_3$ elution afforded XXIX as needles (62.5 mg), a part of which was recrystallized from acetone to show mp 191—194°. ORD ($c=0.595\times10^{-1}$, 95% EtOH) $[M]^{29}$ (mμ): −5870 (275) (trough), 7850 (322) (peak). IR ν_{max}^{KBr} cm^{-1}: 3400 (br.), 1725 (sh.), 1710. NMR τ ($CDCl_3$): 9.00, 8.82 (each 3H, singlet), 8.80 (3H, doublet, $J=7$ cps), 6.89 (1H, quintet), 6.32 (1H, doublet of doublets, $J=7$ and 12 cps, C-6α-H), 5.99, 5.72 (each 1H, doublet, $J=10$ cps, C-20-H×2), 5.07 (1H, singlet, C-14α-H), 4.38 (1H, doublet, $J=12$ cps, C-6β-OH). *Anal.* Calcd. for $C_{20}H_{28}O_6 \cdot \frac{1}{2}H_2O$: C, 64.34; H, 7.75. Found: C, 64.33; H, 7.29.

Keto-lactam (XXXI)——A mixture of didesoxo–isosongorin (52 mg) in pyridine (3 ml) and CrO_3 (80 mg)–pyridine (2 ml) complex was allowed to stand over night at room temperature. After treating of excess oxidant with EtOH, the mixture was concentrated, diluted with H_2O, and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried, and evaporated to leave an oily residue, which was chromatographed on silica gel. Benzene elution afforded crystalline XXXI (18 mg), mp 113—118°. ORD ($c=0.806\times10^{-1}$, 95% EtOH) $[M]^{33}$ (mμ): 850 (310) (peak), −24700 (245) (trough). IR ν_{max}^{KBr} cm^{-1}: 1705, 1630.

Periodate Oxidation of XI to δ-Lactone Hemiacetal (XXXII)——To XI (550 mg) in AcOH (20 ml), a mixture of $NaIO_4$ (540 mg), H_2O (14 ml), and EtOAc (6 drops) was added. After standing over night at 50°, excess oxidant was reduced with $Na_2S_2O_3$. The reaction mixture was concentrated and diluted with H_2O. Extraction with $CHCl_3$, and its drying with anhyd. Na_2SO_4 and evaporation *in vacuo* gave an amorphous powder. By silica gel chromatographic purification, XXXII was obtained as fine needles (235 mg), mp 219—221°. IR ν_{max}^{KBr} cm^{-1}: 3480 (br.), 1750, 1716. NMR τ (D_5-py.): 9.08, 9.00 (each 3H, singlet), 8.90 (3H, doublet, $J=7$ cps), 7.00 (1H, quintet, C-13-H), 6.03 (2H, singlet, C-20-H×2), 5.60 (1H, triplet, C-1β-H), 5.20 (1H, singlet), 4.73 (1H, singlet). *Anal.* Calcd. for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 66.09; H, 7.73.

Dihydroenmein (II)——I (1440 mg) in MeOH was hydrogenated in the presence of 10% Pd–C. Usual treatment afforded a crystalline precipitate (1409 mg), which was recrystallized from MeOH to give II as needles,mp 268.5—269.5°. IR ν_{max}^{KBr} cm^{-1}: 3470, 1758, 1713. NMR τ (py.): 9.03 (3H, doublet, $J=7$ cps), 8.97, 8.70 (each 3H, singlet), 6.20 (1H, br. singlet), 6.15, 5.97 (each 1H, doublet, $J=9$ cps), 4.65 (1H, quartet, $J=7$ and 10 cps), 4.16 (1H, singlet).

Oxidation of XXXII to γ,δ-Dilactone (XXXIII) and Subsequent β-Diketocleavage to γ-Lactone-enolacid (XXXV)——A solution of XXXII (84 mg) in AcOH (10 ml) was treated with a mixture of CrO_3 (77 mg), AcOH (5 ml), and H_2O (2 drops) for 2 days at room temperature. After destruction of excess oxidant with EtOH, the mixture was concentrated at below 50°, diluted with H_2O, and extracted with $CHCl_3$. The organic layer was washed with water, dried over anhyd. Na_2SO_4, and evaporated to give an oily XXXIII, which contained slight impurity. IR ν_{max}^{KBr} cm^{-1}: 1775, 1740 (br.). Oily XXXIII was chromatographed on silica gel (5 g) and elution with 5% EtOAc–$CHCl_3$ afforded XXXV (36 mg) as needles, mp 221—225°, after recrystallization. IR ν_{max}^{KBr} cm^{-1}: 3400 (br.), 1780, 1740, 1710 (sh.), 1640, 1600. ORD: no Cotton effect, UV $\lambda_{max}^{95\%\ EtOH}$: 270 m$\mu$ (ε 9250), 275 mμ (sh.). $FeCl_3$ (+). *Anal.* Calcd. for $C_{20}H_{26}O_7$: C, 63.48; H, 6.93. Found: C, 63.55; H, 6.90.

Oxidation of XXXII to γ-Lactone-ketoacid (XXXIV)——To a solution of XXXII (38 mg) in AcOH (5 ml), a mixture of CrO_3 (37 mg), AcOH (3 ml), and H_2O (4 drops) was added. After standing overnight at room temperature, the reaction mixture was concentrated *in vacuo* at below 50°. The same work-up as above for XXXV afforded an amorphous powder, which was chromatographed on silica gel (5 g) to give needles (16 mg) by 40% EtOAc–$CHCl_3$ elution. Recrystallization from MeOH afforded XXXIV, mp 225.5—227°. IR ν_{max}^{KBr} cm^{-1}: 1770, 1710. ORD ($c=0.592\times10^{-1}$, 95% EtOH) $[M]^{24}$ (mμ): −6130 (315) (trough), 3710 (274) (peak). (Mass Calcd. for $C_{20}H_{26}O_7$: 378. Found: M$^+$, *m/e* 378).

Enolization of XXXIV to XXXV——A solution of XXXIV (65 mg) in AcOH (5 ml) was refluxed for 3 hr. Evaporation to dryness and subsequent silica gel chromatographic purification of the residue afforded an enol–acid (2 mg), mp 210—215°, which was identical with XXXV by mixed mp and IR spectra.

Enol-acid Methyl Ester (XXXVII)——To XXXV (29 mg) in MeOH, ether solution of excess CH_2N_2 was added with chilling at 0°. After 5 min, excess CH_2N_2 was decomposed by addition of 10% AcOH and the solvent was evaporated *in vacuo*. Crystallization of the residue from hexane–EtOH afforded XXXVII (19 mg) as needles, mp 231—233°. IR ν_{max}^{KBr} cm^{-1}: 1775, 1735, 1640, 1600.

Keto-acid Methyl Ester (XXXV)——A solution of XXXVII (11 mg) in $CHCl_3$ (2 ml) and pyridine (0.7 ml) was treated with MsCl (2 ml) for 3 days in an ice box. After dilution with H_2O, the mixture was left standing for 1 hr. Evaporation *in vacuo* gave an oil and powdery XXXV, which was washed with EtOH to show mp 224—226°. ORD ($c=0.513\times10^{-1}$, 95% EtOH) $[M]^{29.5}$ (mμ): −7650 (318) (trough), 3450 (274) (peak). IR ν_{max}^{KBr} cm^{-1}: 1780, 1765, 1745, 1715. $FeCl_3$ (−). (Mass Calcd. for $C_{21}H_{28}O_7$: 392. Found: M$^+$/*e* 392).

Enmedol (VI)——Enmedol (VI) was crystallized form EtOH as fine needles, mp 297—299°. $[\alpha]_D^{27.5}$ −45° ($c=1.147\times10^{-1}$, MeOH) $[M]^{27.5}$: 980 (354) (trough). UV $\lambda_{max}^{95\%\ EtOH}$ 237 mμ. IR ν_{max}^{KBr} cm^{-1}: 3600—

2800, 1715, 1650. NMR τ (D_5-py.): 8.84, 8.71 (each 3H, singlet), 8.71 (3H, doublet, $J=5$ cps, $\overset{-O}{-O}\!>\!CH\text{-}C\underline{H}_3$), 6.94 (1H, doublet, $J=7$ cps, C-13-$\underline{H}$), 6.44 (1H, triplet, $J=8$ cps, C-1β-$\underline{H}$), 5.82 (1H, doublet, $J=7$ cps, C-6α-$\underline{H}$), 5.71, 5.34 (each 1H, doublet, $J=10$ cps), 5.34 (1H, singlet, C-14α-$\underline{H}$), 4.58, 3.86 (each 1H, singlet, $=\!<\!\underline{H}\!>$), 4.38 (1H, quartet, $J=5$ cps, $\overset{-O}{-O}\!>\!C\underline{H}\text{-}CH_3$). *Anal.* Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.64; H, 7.68. (Mass Calcd. for $C_{22}H_{30}O_6$: 390. Found: M^+, *m/e* 390).

Dihydroenmedol (XXXVIII)——VI (70 mg) in MeOH (5 ml) was hydrogenated in the presence of 10% Pd–C. Usual treatment gave a solid, which was crystallized from EtOAc–MeOH to XXXVIII as leaflets, mp 272—275°. IR ν_{max}^{KBr} cm^{-1}: 3460, 3400, 1725. *Anal.* Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 66.93; H, 8.05.

Enmedol Monoacetate (XXXIX)——i) A solution of VI (62 mg) in pyridine (1 ml) and Ac_2O (1 ml) was left over night at room temperature. Evaporation of the solvent *in vacuo*, dilution of residue with H_2O extraction with $CHCl_3$, and subsequent concentration gave an amorphous powder. The $CHCl_3$ elution of silica gel chromatography gave a solid which was crystallized from ether to afford XXXIX as needles, mp 197—198°. IR ν_{max}^{KBr} cm^{-1}: 3340, 1740, 1725, 1712. NMR τ ($CDCl_3$): 8.82 (6H, singlet), 8.72 (3H, doublet, $J=5$ cps), 8.05 (3H, singlet), 6.94 (1H, doublet, $J=8$ cps), 6.13 (1H, doublet of doublets, $J=7$ and 12 cps, C-6α-$\underline{H}$), 5.83 (2H, triplet, $J=12$ cps), 5.42 (1H, singlet), 4.61 (1H, quartet, $J=5$ cps), 4.52, 3.90 (each 1H, singlet), 4.16 (1H, doublet, $J=12$ cps). *Anal.* Calcd. for $C_{24}H_{32}O_7$: C, 71.25; H, 7.97. Found: C, 71.18; H, 8.01.

ii) IX (63 mg) was dissolved in freshly prepared MeCHO (5 ml), and anhyd. $CuSO_4$ (1 g) was added to this solution. After stirring for 5 hr, $CuSO_4$ was filtered off and washed well with EtOAc. The filtrate and washings were combined and concentrated to give a solid, which was purified by silica gel chromatography. Elution of the product with 50% CH_2Cl_2–benzene gave an oil, crystallization of which from ether–hexane afforded XXXIX as needles, mp 199—200°. The identity of XXXIX obtained by two different ways (i) and (ii) was confirmed by mixed mp and IR spectra.

Hydrolysis of Enmedol (VI) to Isodonol (V)——A solution of VI (37 mg) in MeOH (8 ml) and 2N HCl (1 ml) was refluxed for 2 hr. The reaction mixture was concentrated and diluted with H_2O. Extraction of the product with $CHCl_3$, and drying of the solution over anhyd. Na_2SO_4 and its evaporation gave a solid, which was chromatographed on silica gel to afford unreacted crystalline VI and an amorphous powder (16 mg). Recrystallization of the latter from MeOH–EtOAc was repeated to give fine needles, mp 243—247°, which were identical with V by mixed mp and IR spectra.

Condensation of Isodonol (V) and MeCHO to Enmedol (VI)——Anhyd. $CuSO_4$ (2.5 g) was added to a suspension of V (88 mg) in freshly prepared MeCHO (10 ml). The mixture was stirred at room temperature for 1.5 hr and $CuSO_4$ was filtered off. The filtrate, combined with EtOAc washings of $CuSO_4$, was evaporated. The residue was purified by silica gel chromatography to give an amorphous powder, crystallization of which afforded fine needles, mp 293—295°, which were proved to be identical with VI by mixed mp and IR spectra.

Enmenol (VII)——VII was recrystallized from EtOAc as prisms, mp 240—242°, and consumed 1 mole of $NaIO_4$. $[\alpha]_D^{30.5}$ −29° ($c=1.370\times10^{-1}$, 95% EtOH). IR ν_{max}^{KBr} cm^{-1}: 3320, 1100—1000. NMR τ (D_5-py.): 8.80, 8.77 (each 3H, singlet), 7.4—7.1 (2H), 6.27 (1H, triplet, $J=7$ cps), 5.77 (1H, doublet, $J=5$ cps), 5.62, 5.20 (each 1H, doublet, $J=10$ cps, C-20-$\underline{H}\times2$), 4.92 (1H, singlet, C-14α-$\underline{H}$), 4.68 (1H, singlet, C-15α-$\underline{H}$), 4.37 (2H, singlet, $=\!<\!\underline{H}$).

Enmenol Triacetate (XLII)——A solution of VII (28 mg) in pyridine (1 ml) and Ac_2O (1 ml) was allowed to stand for 66 hr at room temperature. The solvent was evaporated and the residue was chromatographed on silica gel to give an oily XLII (20 mg), which did not consume $NaIO_4$. IR ν_{max}^{KBr} cm^{-1}: 3530, 1740, 1230. NMR τ ($CDCl_3$): 9.15, 8.80 (each 3H, singlet), 8.06, 7.96; 7.87 (each 3H, singlet), 5.87 (2H, singlet).

Hydrogenation of Enmenol (VII) to Tetrahydroisodonol (XXVII)——VII (38 mg) in MeOH (3 ml) was hydrogenated in the presence of Pt (prepared from (20 mg) of PtO_2). Usual treatmet gave a crystalline precipitate. Its recrystallization from MeOH–acetone afforded dihydroenmenol as needles, mp 227—230°, which was identical with tetrahydroisodonol (XXVII) by mixed mp, TLC, and IR spectra.

Condensation of VII and MeCHO to XLIII——A mixture of VII (165 mg) and anhyd. $CuSO_4$ (1 g) in MeCHO (10 ml) was stirred for 2.5 hr at room temperature. The same work-up as in the condensation of V to VI, gave a crystalline precipitate (172 mg). Recrystallization from MeOH–EtOAc afforded unreacted VII (48 mg) as needles. The mother liquid was chromatographed on silica gel (5 g) and Fr. 3—10 (EtOAc elution) gave crystalline XIII (75 mg), a part of which was recrystallized to show mp 156—158°. IR ν_{max}^{KBr} cm^{-1}: 3410 (br.), 1165, 1068. *Anal.* Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 68.90; H, 8.19.

Oxidation of XLIII with MnO_2 to Enmedol (VI)——To a solution of XLIII (39 mg) in $CHCl_3$ (5 ml), freshly prepared MnO_2 (200 mg) was added. After stirring for 27.5 hr, MnO_2 was removed by centrifugation and subsequent decantation. MnO_2 was washed repeatedly with $CHCl_3$ and $CHCl_3$ washings were combined with the supernatant. The solution was concentrated to give a powder (35 mg), which was purified by silica gel chromatography. The elution of the product with 20% EtOAc–$CHCl_3$ afforded needles (28 mg), a part of which was recrystallized to show mp 293—295°. The identity of this sample with VI

was confirmed by TLC, mixed mp, and IR spectra. No product other than VI was detected by TLC of this oxidation reaction.

XLVIII to Triol (XXIV)——A mixture of XLVIII (1.175 g), dihydropyrane (1.5 ml), TsOH (130 mg) in THF (15 ml) was left overnight at room temperature. A mixture of two kinds of pyrane compounds was produced, which were isolated by silica gel (100 ml) chromatography (solvent hexane–$CHCl_3$) to give oily XLIX (837 mg) and L (700 mg). A solution of XLIX (727 mg) in xylene (7 ml) and THF (11 ml) was added dropwise into a boiling mixture of Na-xylene (Na 600 mg, xylene 15 ml). After refluxing for 3 min with vigorous stirring, Na was removed and then MeOH (1 ml) and H_2O were added to the reaction mixture in that order. The mixture was extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to give an oil (300 mg), a part of which was chromatographed on silica gel to afford XXIV as needles, mp 204—210°. $[\alpha]_D^{13}$ −52° ($c=0.890\times10^{-1}$, 95% EtOH). IR ν_{max}^{KBr} cm^{-1}: 3460, 3400, 1165, 1080, 1060. *Anal.* Calcd. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.65; H, 9.41. (Mass Calcd. for $C_{20}H_{32}O_4$: 336. Found: M^+, *m/e* 336).

Acknowledgement We are indebted to Dr. S. Kanatomo of Kanazawa University for providing us some of the samples.