Chemical Constitution of Enmein a Bitter Principle from Isodon trichocarpus Kudo

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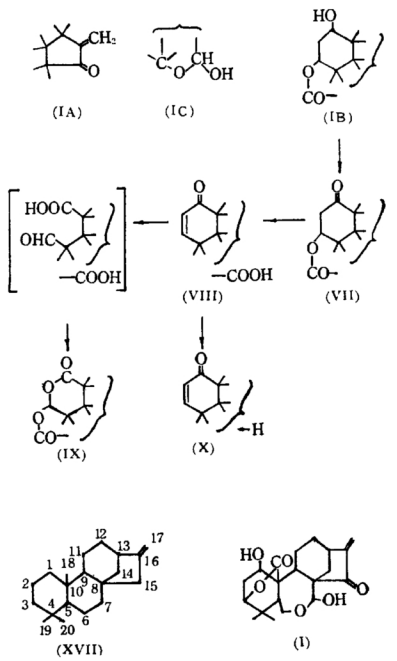
The partial structure IA was suggested by Takahashi, Fujita and Koyama[1] for enmein[2] (isodonin[3]), $C_{20}H_{26}O_6$, m. p. 274~275°C, $[\alpha]_D$ −156° (acetone). We now wish to propose the structure I for enmein from the following evidences.

Reduction reactions, carried out by us and by other investigators[1,2], of enmein are summarized as follows. Catalytic hydrogenation of enmein (λ_{max}^{EtOH} 232.5 mμ (ε 7400)) affords a mixture of dihydroenmein-a (IIa), $C_{20}H_{28}O_6$, m.p. 256~257°C (decomp.) (λ_{max}^{EtOH} 297 mμ (ε 36); ν_{max} 2.90, 5.72, 5.87 μ), and dihydroenmein-b (IIb), $C_{20}H_{28}O_6$, m. p. 215~216°C (decomp.) (ν_{max} 2.82, 5.72, 5.82 μ). On mild treatment with sodium borohydride IIb is epimerized to IIa. Dihydroenmein-a is also obtained by the sodium borohydride reduction of enmein in methanol at room temperature. Both dihydroenmeins give the same diacetate (III), $C_{24}H_{32}O_8$, m. p. 231~232°C (decomp.), which is obtained also by the reduction of diacetylenmein (IV), $C_{24}H_{30}O_8$, m. p. 221~223°C (decomp.). Both enmein and dihydroenmein are reduced with sodium borohydride in ethanol at 60°C to yield tetrahydroenmein (V), $C_{20}H_{30}O_6$, m. p. 260°C (decomp.) (ν_{max} 2.91, 5.86 μ), (triacetate (VI), $C_{26}H_{36}O_9$, m. p. 193°C (ν_{max} 5.78 μ, no hydroxyl)). Since dihydroenmein-a (IIa) (ν_{max} 5.87 μ; exalted δ-lactone) is recovered unchanged after consuming one mole of alkali on hydrolysis, it is suggested that enmein has a δ-lactone group.

The partial structure IB is deduced from following results. Chromium trioxide-oxidation of dihydroenmein-a (IIa) affords bisdehydrodihydroenmein (VII), $C_{20}H_{24}O_6$, m. p. 251~253°C (decomp.), (monosemicarbazone, $C_{21}H_{27}O_6N_3$, m. p. 225~226°C). Bisdehydrodihydroenmein consumes one mole of dilute alkali (1/60 N) on hydrolysis to yield an acid (VIII),



$C_{20}H_{24}O_6 \cdot 1/3H_2O$, m. p. 233°C (decomp.) (ν_{max} 5.64, 5.75, 5.86, 6.01 μ), (monomethylester, $C_{21}H_{26}O_6$, m.p. 245~246°C, monosemicarbazone, $C_{21}H_{27}O_6N_3$, m. p. 265~267°C (decomp.). Inspection of the ultraviolet spectra of VIII (λ_{max}^{EtOH} 225 mμ (ε 9600)) and its monosemicarbazone (λ_{max}^{EtOH} 278 mμ (ε 14300)) shows that the acid VIII possesses an α,β-unsaturated

1) M. Takahashi, T. Fujita and Y. Koyama, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **78**, 699(1958); **80**, 594, 696(1960).
2) T. Ikeda and S. Kanatomo, ibid., **78**, 1123 (1958).
3) K. Naya, *J. Chem. Soc. Japan, Pure Chem. Soc.* (*Nippon Kagaku Zasshi*), **79**, 885 (1958). In comparison of infrared spectra, isodonin was identical with enmein which was kindly supplied by Dr. S. Kanatomo, Kanazawa University.

ketone group, –CO–CH=CH–. Ozonolysis of VIII affords a crystalline neutral substance (IX), $C_{19}H_{22}O_7$, m. p. 249~251°C (decomp.), which consumes two moles of dilute alkali (1/50 N) on hydrolysis, gives positive color reactions for an aldehyde and shows no more absorption of the enone group in its ultraviolet spectrum. On pyrolysis VIII is decarboxylated to yield a neutral substance (X), $C_{19}H_{24}O_4$, m. p. 169~172°C (λ_{max}^{EtOH} 225 mμ (ε 8500)).

Bisdehydrodihydroenmein (VIII) consumes two moles of alkali (1/5 N) to yield an amorphous acid, while the neutral substance X is recovered unchanged after consuming one mole of alkali on hydrolysis. Therefore it is suggested that a lactone group is newly formed in oxidation of IIa to VII. On the other hand, treatment of dihydroenmein-a (IIa) with ethanolic sulfuric acid affords an *O*-ethyl derivative (XI), $C_{22}H_{32}O_6$, m. p. 193~195°C, (monoacetate, $C_{24}H_{34}O_7 \cdot 1/2C_6H_6$, m. p. 103~105°C, (no hydroxyl in its infrared spectrum)). Treatment of IIa with methanolic hydrogen chloride affords *O*-methyldihydroenmein(XII), $C_{21}H_{30}O_6$, m. p. 192~193°C, which reverts to dihydroenmein-a (IIa) on acid-catalyzed hydrolysis. The presence of a methoxyl group in XII was confirmed by the Zeisel analysis and the NMR spectrum (τ 6.68; three protons) of dehydro-*O*-methyldihydroenmein (XIII), $C_{21}H_{28}O_6$, m. p. 218~220°C, which is obtained from XII by chromium trioxide-oxidation. On hydrolysis XIII consumes one mole of alkali to yield a crystalline acid (XIV), $C_{21}H_{28}O_6 \cdot H_2O$, m. p. 190~192°C (decomp.) (λ_{max}^{EtOH} 230 mμ (ε 9700); ν_{max} 5.75, 5.85, 5.97, 6.17 μ), (monomethyl ester $C_{22}H_{30}O_6$, m. p. 189~192°C (λ_{max}^{EtOH} 228 mμ (ε 10400)), monosemicarbazone $C_{22}H_{31}O_6N_3 \cdot H_2O$, m. p. 205°C (decomp.) (λ_{max}^{EtOH} 277.5 mμ (ε 14900)). Conversion of XII to XIV (via XIII) is easily recognized as the transformation, IB→VII→VIII, of the part IB in XII. From these results, it is concluded that the remaining oxygen atoms in the enmein molecule exist as a cyclic hemi-acetal group IC.

Recently two important degradation products were isolated by Kanatomo[4], namely 1-ethyl-4-(3, 3-dimethylcyclohexyl)benzene (XV) on dry distillation of enmein with baryta and retene (XVI) on selenium dehydrogenation of the lithium aluminum hydride-reduction product of dihydroenmein. Kanatomo suggested that enmein has the carbon skeleton of phyllocladene (XVII) and the ketonic and lactonic carbonyl groups exist at the C_{15}- and C_{18}-positions of XVII, respectively.

4) S. Kanatomo, *J. Pharm. Soc. Japan.* (*Yakugaku Zasshi*), 81, 1049 (1961).

However, from the molecular formula and the partial structure, IA, IB and IC, of enmein, it is apparent that enmein must have a tricarbocyclic ring. Our proposed structure I for enmein is supported by the following evidences. The NMR spectra of diacetyldihydroenmein (III) and dehydro-*O*-methyldihydroenmein (XIII) show that the number of protons attached to the carbon atom, to which one or two oxygen atoms are bonded, is five (at the C_1-, C_3-, C_6- and C_7-positions) in III and four (at the C_3-, C_6- and C_7-positions) in XIII. Furthermore a sharp singlet (τ 3.80; one proton equivalent) attributed to the C_7-proton of the hemiacetal acetate[5] in III shows that the carbon atom adjacent to the hemiacetal group in enmein must have no hydrogen atom. From the biogenetic point of view, it is suggested that the hemiacetal group in the ring B may be formed from a 7-ketoditerpene by the Bayer-Villiger type oxidation followed by the reduction of a lactone formed.

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5) J. A. Pople, W. G. Schneider and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance", McGraw-Hill Book Comp., Inc., New York (1959), p. 395.