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Synthesis of Gibbane Derivatives from Enmein

In continuation of our work aimed at correlating enmein[1] (I) to kaurenoid diterpenes, *e.g.* aconite alkaloids and gibberellins, conversion of enmein to compounds having gibbane structure (II) will be described in this paper.

In order to construct the B ring of gibberellins, the Favorskii-type of rearrangement was first planned to a mesylate of the hemiketal (IV), which can be obtained by the acyloin condensation of the ester lactone (III), and whose structure has been established by relating to (−)-kaurane.[2,3] However, the mesylation of IV with mesyl chloride in pyridine resulted in the formation of a rearranged ketone (V) as a major product, m.p. 147~148°, ν_{max}^{KBr} 1705 cm^{-1}, NMR : τ 6.23 (2H, AB quartet, J=9 c.p.s., $\geqslant$C-$\underline{CH}_2$-O-), 5.87 (1H, singlet, $\rangle$$\underline{CH}$-O-) (*Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found : C, 79.48; H, 9.98) and V was reduced with sodium borohydride to an alcohol, m.p. 152~153.5° (*Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found : C, 79.15; H, 10.55), indicating the ketone function in V.

An alternative route to extrude one carbon atom with the formation of the ring B carboxylic acid is the benzylic acid rearrangement of the ketohemiketal (VI), m.p. 166~171° (*Anal.* Calcd. for $C_{20}H_{30}O_3$; C, 73.43; H, 9.50. Found : C, 75.13; H, 9.51), obtained by Sarett oxidation of IV. Infrared absorption spectrum of VI (ν_{max}^{KBr} cm^{-1} : 1726, 3440) shows that it possesses the keto-hemiketal form, and VI was converted back to IV with sodium borohydride in the yield of 8%, accompanied with an epimeric alcohol (VII) (84% yield), m.p. 131~136° (*Anal.* Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found : C, 75.39; H, 10.31), the latter being formed by sterically favored attack of the reagent. Therefore, VI is proved to be 6-keto-7-hemiketal and retain the *trans* A/B ring juncture.

When VI was heated in alkaline ethylene glycol, a crystalline acid (VIII), m.p. 182~

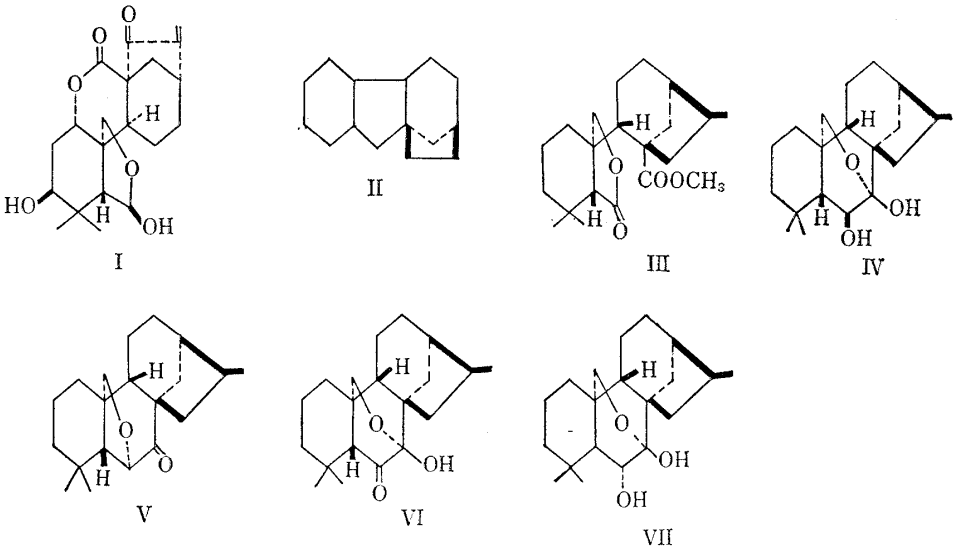

Chart 1.

1) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, M. Takahashi, H. Irie, A. Numata, T. Okamoto, M. Natsume, Y. Kawazoe, K. Shudo, T. Ikeda, M. Tomoeda, S. Kanatome, T. Kosuge, K. Adachi : Tetrahedron Letters, **1964**, 1243. Y. Iitaka, M. Natsume : *Ibid.*, **1964**, 1257.
2) K. Shudo, M. Natsume, T. Okamoto : This Bulletin, **13**, 1019 (1965).
3) E. Fujita, T. Fujita, K. Fuji, N. Ito : *Ibid.*, **13**, 1023 (1965).

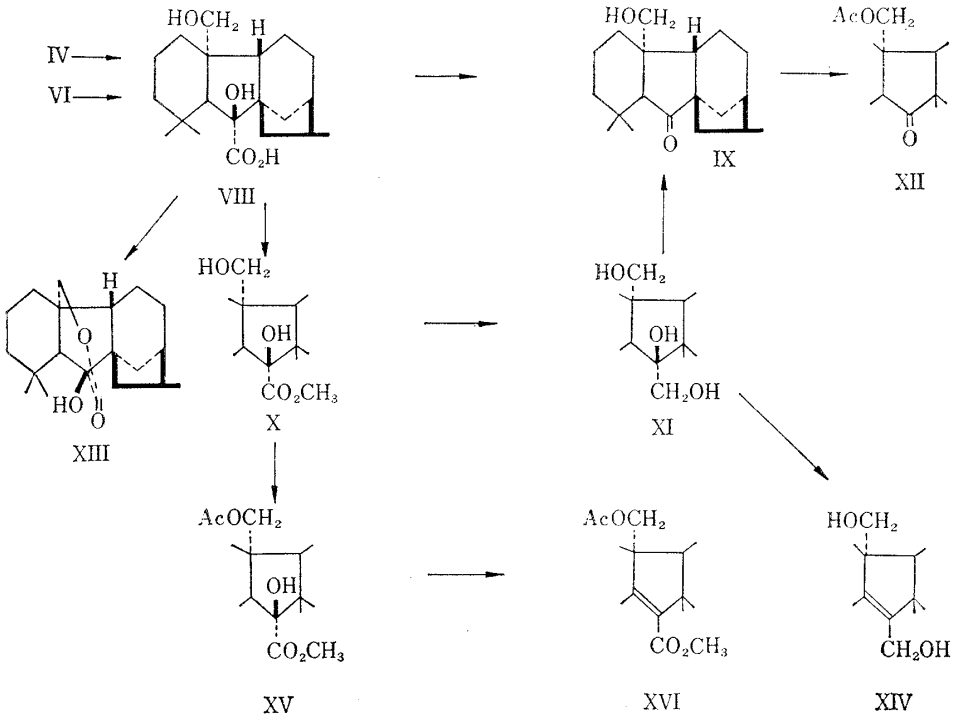

Chart 2.

186°, ν_{max}^{KBr} cm^{-1} : 1690, 2400~3550 (*Anal.* Calcd. for $C_{20}H_{32}O_4 \cdot \frac{1}{3}H_2O$: C, 70.14; H, 9.61. Found : C, 70.54, 70.58, 69.96; H, 9.78, 9.57, 9.52) was isolated in moderate yields. The formation of Ⅷ was also observed as an acidic product of Huang-Minlon reaction of Ⅳ in a low yield and Ⅷ was conveniently obtained by the alkali treatment of Ⅳ. The α-hydroxy acid function on a five-membered ring in the acid (Ⅷ), was proved by oxidation using lead tetracetate to a ketone (Ⅸ), m.p. 110~111° or 137~137.5° (*Anal.* Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found : C, 78.85; H, 10.44) and by lithium aluminum hydride reduction of the ester (Ⅹ), m.p. 98~100° (*Anal.* Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found : C, 72.15; H, 9.74) to a triol (Ⅺ), m.p. 144~145°, NMR : τ 6.28 (2H, AB quartet, J=12 c.p.s., $\geqslant$C-C$\underline{H}_2$OH), 6.22 (2H, AB quartet, J=12 c.p.s., $\geqslant$C-C$\underline{H}_2$OH) (*Anal.* Calcd. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found : C, 74.73; H, 10.86), followed by sodium periodate oxidation of Ⅺ to the same ketone (Ⅸ). The ketonic band in the infrared absorption spectrum of Ⅸ is 1725 cm^{-1} (in CS_2), but its acetate (Ⅻ), m.p. 72~73°(*Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found : C, 76.22; H, 9.70) exhibits absorption bands at 1750 and 1733 cm^{-1} (CS_2), and the former is assignable to a five-membered ring ketone.

Since Ⅷ readily formed a lactone (XIII), m.p. 139~141.5°, ν_{max}^{KBr} cm^{-1} : 1725 (δ-lactone), 3400, NMR : τ 5.92 (AB quartet, J=11 c.p.s., $\geqslant$C-C$\underline{H}_2$-O-) (*Anal.* Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found : C, 75.61; H, 9.44) catalized by *p*-toluenesulfonic acid, the carboxylic acid has the α-side configuration. A Dreiding model experiment suggests that the lactonisation from an assumed A/B *cis*-fused acid generates new serious non-bonded interactions, while no such interaction operates in the lactonisation of *trans*-fused acid. Observed ease of lactonisation of the acid (Ⅷ) may be possible when A/B ring juncture is *trans*-fused. The acid (Ⅷ) is therefore represented to be 4aα-hydroxymethyl-10β-hydroxy-1,1,8β-trimethylgibbane-10α-carboxylic acid.

Several attempts for removing the tertiary hydroxyl group are in progress. Dehydrated alcohol (XIV), m.p. 152~155°, NMR : τ 6.51 (quartet, $\geqslant$C-C$\underline{H}_2$-O-), 5.77 (quartet, $\rangle$C=C-C$\underline{H}_2$-O-) (*Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found : C, 78.61; H, 10.42)

was prepared from a diacetate of triol (XI) by treatment with thionyl chloride followed by hydrolysis. The ester acetate (XV), m.p. 105~106° (*Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.48; H, 9.11) was treated with thionyl chloride in pyridine to give an unsaturated ester (XVI), but XVI resisted to the catalytic hydrogenation.

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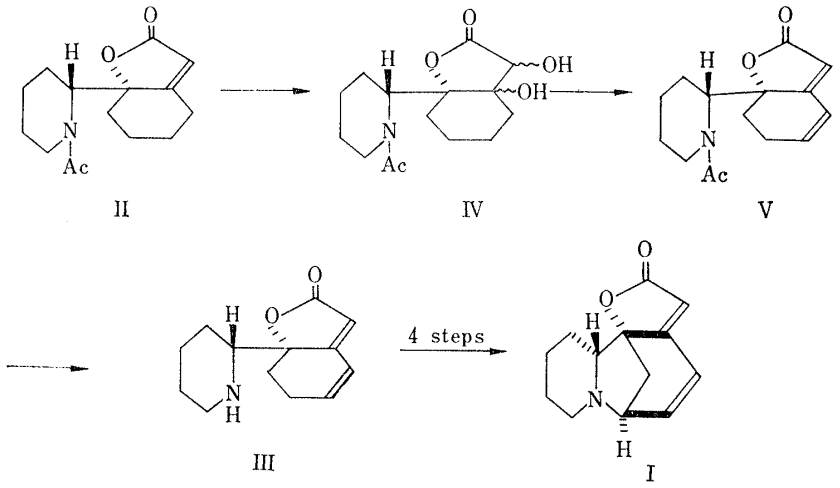
Total Synthesis of Securinine

The conversion of a degradation product (II)[1] of securinine (I),[1,2,3] an alkaloid of *Securinega suffruticasa* REHD., into another degradation product (III)[1] is now described. This work constitutes a total synthesis of securinine, since the synthesis[4] of *rac*-II, the partial synthesis[5] of securinine from III, and the resolution of *rac*-securinine[6] have been achieved.



Hydroxylation of II with potassium permanganate in aqueous acetone at 19° for 3 days gave a diol (IV), m.p. 257~258° from ethanol, IR ν_{max}^{Nujol} cm^{-1}: 3257, 1789, 1637, in 33% yield. Dehydration of IV with thionyl chloride in anhydrous pyridine at 60° for 15 min. and then at room temperature for 2 days, followed by chromatographical purification on alumina and benzene as eluent, gave an acetate, m.p. 157~159° from ethyl acetate, in 2.3% yield. The acetate was identical with the degradation product (V),

1) S. Saito, K. Kotera, N. Shigematsu, A. Ide, N. Sugimoto, Z. Horii, M. Hanaoka, Y. Yamawaki, Y. Tamura: Tetrahedron, **19**, 2085 (1963).
2) Z. Horii, M. Ikeda, Y. Yamawaki, Y. Tamura, S. Saito, K. Kotera: *Ibid.*, **19**, 2101 (1963).
3) S. Imado, M. Shiro, Z. Horii: This Bulletin, **13**, 643 (1965).
4) Z. Horii, M. Hanaoka, Y. Tamura, S. Saito, N. Sugimoto: Chem. & Ind.(London), **1964**, 664.
5) S. Saito, N. Shigematsu, H. Yoshikawa, Z. Horii, Y. Tamura: This Bulletin, **11**, 1219 (1963).
6) S. Saito, T. Tanaka, T. Iwamoto, C. Matsumura, N. Sugimoto, Z. Horii, M. Makita, M. Ikeda, Y. Tamura: Yakugaku Zasshi, 84, 1126 (1964); A dextro-rotatory enantiomer of securinine is named virosecurinine. Therefore, *rac*-securinine means an equimolecular mixture of securinine and virosecurinine.