Treatment of the diketo-ester (I) or α,β-keto-enol (Ⅲ) with 20% potassium hydroxide solution in the boiling water bath for 10~11 hours afforded 1,9-dicarboxy-1,11-dimethyl-1,2,3,4,10,11-hexahydrofluoren-9-ol (Ⅳ) as colorless prisms, m.p. 131~134°, from methanol with addition of water, $[\alpha]_D^{8.5}$ −32.0(EtOH). UV λ_{max}^{EtOH} mμ(log ε): 264(2.84), 272(2.87). IR ν_{max}^{KBr} 1710 cm^{-1} (*Anal.* Calcd. for $C_{17}H_{20}O_5 \cdot H_2O$: C, 63.34; H, 6.88. Found: C, 63.45; H, 7.11).

Proof of the structure of (Ⅳ) was obtained by the oxidation of (Ⅳ) with chromic acid under a mild condition to 1,11-dimethyl-1-carboxy-1,2,3,4,10,11-hexahydrofluorenone (Ⅴ), whose melting point, mixed melting point, and infrared spectrum were identical with those of Ohta's authentic sample.[6]

The author is indebted to Professor Eiji Ochiai for his valuable advice and encouragement, and also to Dr. M. Ohta for the donation of his specimens.

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[6] M. Ohta: This Bulletin, **5**, 256 (1957).

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On the Alkaloid of *Fritillaria verticillata* Willd. var. *Thunbergii* Baker. (I). On the Position of the Secondary Hydroxyls and Skeleton of Verticine[*1]

Investigation by Fukuda[1] on the alkaloidal constituents of corms of *Fritillaria verticillata* Willd. var. *Thunbergii* Baker has resulted in isolation of four alkaloids; verticine, m.p. 224~224.5°, fritillarine, m.p. 130~131°, verticilline, m.p. 148~150°, and another amorphous base. Some preliminary structural survey was later reported on the principal constituent, verticine.[2] Attention to these alkaloids was directed by Dr. Fukuda who very kindly provided his specimens for the first two of the alkaloids isolated in 1931, together with some crude material.

Verticine (I), $C_{27}H_{45}O_3N$,[*2] m.p. 223~224°, purified by counter-current distribution (pH 5.4, phosphate buffer), is a saturated (UV $\lambda_{max}^{HCl-EtOH}$ 215 mμ(ε 10)) tertiary amine (complete recovery on nitrosation) of pKa′ 9.5, with no carbonyl group. Thiocyanate, m.p. 263~265° (decomp.). Hydrochloride, m.p. 310~312°(decomp.). Perchlorate, m.p. 279°(decomp.).

Hydroxylic nature of the oxygen functions was indicated by the following experiments. Chromic acid oxidation of (I) at 60° affords, after counter-current distribution (pH 3.8), two ketones, verticinone (Ⅱ), $C_{27}H_{43}O_3N$, m.p. 212~213°(UV λ_{max}^{EtOH} 288 mμ(ε 38). IR ν_{max}^{KBr} 1705, 1425 cm^{-1}(sh))(Periodate, m.p. 199°(decomp.)), and verticinedione (Ⅲ), $C_{27}H_{41}O_3N$, m.p.

[*1] Presented at the Ibaragi District Meeting of the Chemical Society of Japan, at Hitachi, October 10, 1960.

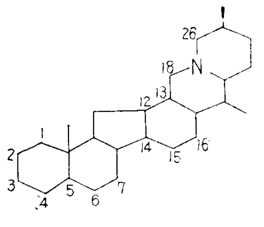
[*2] All analytical values are in good agreement with the molecular formula shown. Reported formula,[2] $C_{18}H_{33}O_2N$ or $C_{19}H_{35}O_2N$.

[1] M. Fukuda: Nippon Kagaku Zasshi, **50**, 74 (1929); Sci. Repts. Tohoku Univ., Ser. A, **18**, 323 (1929).

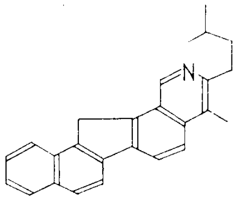
[2] *Idem*: Nippon Kagaku Zasshi, **69**, 165, 167 (1948).

167~168°(UV λ_{max}^{EtOH} 285 mμ(ε 58), IR ν_{max}^{KBr} 1705, 1428 cm^{-1}, pKa′ 9.3), in 15% and 60% yield, respectively. (II), identical (mixed m.p. and IR spectra) with purifired fritillarine,[*3] m.p. 212~213°, gives (III) in a good yield on chromic acid oxidation, whereas (III) is resistant to further oxidation. Presence of bands due to tertiary hydroxyl group, i.e. IR ν_{max}^{KBr} 3550, 1290, 1126 cm^{-1} in (III) and also IR $\nu_{max}^{CHCl_3}$ 3650, 1124 cm^{-1} in verticine diacetate [hydrochloride, m.p. 292°(decomp.)] reveals all of three oxygens in verticine (I) to be hydroxyls, two secondary and one tertiary. Both (II) and (III) could be converted to (I) by reduction with sodium and ethanol (low yield from (III)), eliminating the possibility of skeletal rearrangement during the oxidation.

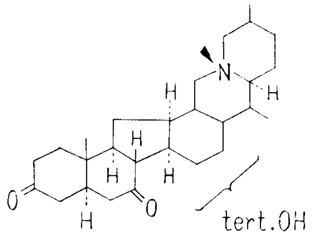
From all of these data, there is little doubt about the identity of verticine, as has been pointed out,[3] with peimine, m.p. 223°, first isolated by Chou and Chen[4] from *Fritillaria Roylei* Hook, and extensively studied by groups of Chinese chemists[*4] and also recently isolated as a glycoside, peiminoside, by Morimoto and Kimata[5] from *Fritillaria Thunbergii* Miq.[*5] Although direct comparison has not been realized,[*6] it may be appropriate to adopt cevane skeleton (IV) to these compounds following the result of dehydrogenation experiments of peimine carried out by Chu and Loh[6] who obtained veranthridine[7] (V) as well as 2,5-lutidine and 8-methyl-1,2-benzofluorene.[8] The problem, therefore, remains to locate the oxygen functions into the well-established frame-work of steroidal alkaloid.



(IV)



(V)



(A)

An oxygen can be placed in C-3 from the following evidences in addition to those recently provided by Morimoto and Kimata[5,9] on isolation of peiminoside and formation of α,β-unsaturated ketone (λ_{max} 224 mμ) by selenium oxide oxidation: 1) The diketone (III) gives a positive Zimmermann reaction (λ_{max} 520 mμ) whereas the monoketone (II) is negative. 2) (II) gives, on Huang-Minlon reduction, deoxoverticinone (VI), $C_{27}H_{45}O_2N$, m.p. 157~158.5°, which is, in turn, converted by chromic acid to the corresponding ketone, dehydrodeoxoverticinone (VII), $C_{27}H_{43}O_2N$, m.p. 169.5~170.5°, IR $\nu_{max}^{CHCl_3}$ 3450, 1704, 1124 cm^{-1}. Optical rotatory dispersion (RD) curve[*7] of (VII) has a positive Cotton effect ($[M]_{315}$ +2120°,

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[*3] Reported formula,[2] $C_{19}H_{33}O_2N$.

[*4] An account of these investigations was presented briefly in reference (5).

[*5] Identity of the two peimines obtained independently has not yet been established (Private communication from Dr. H. Morimoto).

[*6] Identity of verticine (I) and verticinedione (III) respectively with peimine and peiminone obtained by Morimoto and Kimata was established by the courtesy of Dr. Y. Kuwada, Takeda Chemical Industries, Ltd.

[*7] Optical rotatory dispersions in this paper were measured by Dr. T. Goto, Nagoya University, to whom the authors' deep gratitude is expressed.

3) K. J. Morgan, J. A. Barltrop: Quart. Revs., **12**, 34 (1958).

4) T. Q. Chou, K. K. Chen: Chinese J. Physiol., **6**, 265 (1932).

5) H. Morimoto, S. Kimata: This Bulletin, 8, 302 (1960).

6) T. T. Chu, J. Y. Loh: Acta Chim. Sinica, **21**, 227 (1955); T. T. Chu, W. K. Hwang, J. Y. Loh: *Ibid.*, **21**, 232 (1955) (C. A., **51**, 444 (1957)).

7) W. A. Jacobs, S. W. Pelletier: J. Org. Chem., **18**, 765 (1953).

8) M. E. Gross, H. P. Lankelma: J. Am. Chem. Soc., **73**, 3439 (1951).

9) H. Morimoto, S. Kimata: This Bulletin, **8**, 871 (1960).

$[M]_{265.5}$ −4150°) in accord with that of cholestan-3-one[10] ($[M]_{307}$ +3710°, $[M]_{267}$ −2860°). Configurational change during the reduction is not likely to occur since (II) is recovered unchanged on refluxing with alkali in diethylene glycol. RD curve of (VII) also confirms α-orientation of the C-5 hydrogen in cevane skeleton.

For the site of the other secondary hydroxyl, which is more easily oxidized, positions 1, 2, 4, 18 and 26 are excluded from the infrared spectra and pK values of the above-mentioned compounds as well as from the resistance of (I) and (II) toward periodate. Of the remaining positions, C-6 is definitely eliminated from the sign and shape of RD curve of the monoketone (II) ($[M]_{315}$ −2720°, $[M]_{285}$ −155°). The curve, similar to that of 3-acetoxycholestan-7-one[10] ($[M]_{310}$ −1530°, $[M]_{274}$ +67°),[*8] implies the position 7 as the site of the carbonyl group and *trans*-fused B/C ring juncture in (II),[*9] although the other positions cannot be completely excluded and further evidences are needed.

cis-Fusion of C/D ring juncture is understood from the biogenesis of C-nor-D-homo-steroid skeleton, which may have been derived from 12-oxygenated steroid by bond migration from 13-14 to 12-14 as has been effected by Hirshmann and others[12] in the case of steroidal sapogenin. *cis*-Configuration of the juncture is found widely in veratrum alkaloids[3,11,13] and in steroidal glycosides of Asclepiadaceae.[14]

Alkali-stable *trans* B/C ring juncture with carbonyl at C-7 in (II) and (III), rather unusual for hydrindan-4-one system, could be explained by considerable increase of steric interaction in *cis* B/C ring system between hydrogens in ring D and the methyl at C-10 and the carbonyl group at C-7, as is clearly shown by scale model.[*10]

Presence of *trans*-quinolizidine system is indicated by a small but clear band at 2760 cm^{-1} in infrared spectra of all of the compounds mentioned in this paper and its disappearance in that of verticine N-oxide diacetate, $C_{31}H_{49}O_6N \cdot H_2O$, m.p. 229~230°, formed from (I) by action of perbenzoic acid in acetic acid and sulfuric acid.

Summing up all these data, the diketone (III) may best be represented by the partial formula (A) with reservation that the tertiary hydroxyl may be at C-12.

A deep gratitude is expressed to Dr. Masao Fukuda, Research Director of Tekkosha Co., for his generous gift of the alkaloids with which the investigation was and will be carried out, and to Drs. Hiroshi Morimoto and Yutaka Kuwada for their kind comparison of their specimens with the present ones.

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[*8] Larger amplitude in this case may be ascribed to the conformational change due to the ring contraction of C-ring. Similar changes in amplitude have been observed between 7-oxocholanic acid derivatives and protoverine derivatives and between cholestan-3-one and coprostan-3-one and their B-nor analogs (C. Djerassi, *et al.* : J. Am. Chem. Soc., **78**. 3761 (1956), **80**, 4853 (1958); S. M. Cupchan, *et al.* : *Ibid.*, **82**, 2616 (1960); W. G. Dauben, *et al.*, Bull. soc. chim. France, **1960**, 1338).

[*9] In this argument, chair form of D-ring is assumed in analogy with cevine on which sufficient evidences are provided.[11] If it is the case, octant rule predicts positive cotton effect for both C-15 and C-16 ketones.

[*10] This is particularly the case in the model with D-ring in chair form.

10) C. Djerassi, W. Closson, A. E. Lippman : J. Am. Chem. Soc., **78**, 3163 (1956).

11) S. M. Kupchan, W. S. Johnson, S. Rajagopalan : Tetrahedron, **7**, 47 (1959); W. T. Eeles : Tetrahedron Letters, **No. 7**, 24 (1960).

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14) J. W. Cornforth : Chem. & Ind. (London), **1959**, 602; H. Mitsuhashi, Y. Shimizu, I. Nishi, T. Nomura : Abstract, 4th Symposium on Chemistry of Natural Products, Kyoto, October 1960. 139.