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Yoshio Ban and Ichizo Inoue: The Synthesis of β-Carboline Derivatives. VI.*1 A Synthesis of 3-Ethyl-10-methoxy-12*H*-indolo[2,3-*a*]quinolizinium Salt (10-Methoxy-flavopereirine).

(*Faculty of Pharmaceutical Sciences, School of Medicine, Hokkaido University**2)

Numerous indole alkaloids containing the various ring systems occur in the botanical kingdom, and some of them carry a methoxyl group at 6 position ("indole" numberring) of the indole part in the molecule.[1] It is interesting, however, that some indoloquinolizine alkaloids possessing an aromatized C-ring such as flavopereirine (I)[2], sempervirine (II),[3] and flavocarpine (III)[4], don't have any methoxyl group at A-ring. These alkaloids were synthesized according to the method developed in this laboratory, which is suitable for a synthesis of some indolo[2,3-*a*]quinolizinium salts.[5]

In this paper, we wish to report that 3-ethyl-10-methoxy-12*H*-indolo[2,3-*a*]quinolizinium chloride (VII) which might be called "10-methoxy-flavopereirine hydrochloride," was synthesized by the same method with some expectation that this compound would at some time be found in nature, based upon the biogenetic consideration.

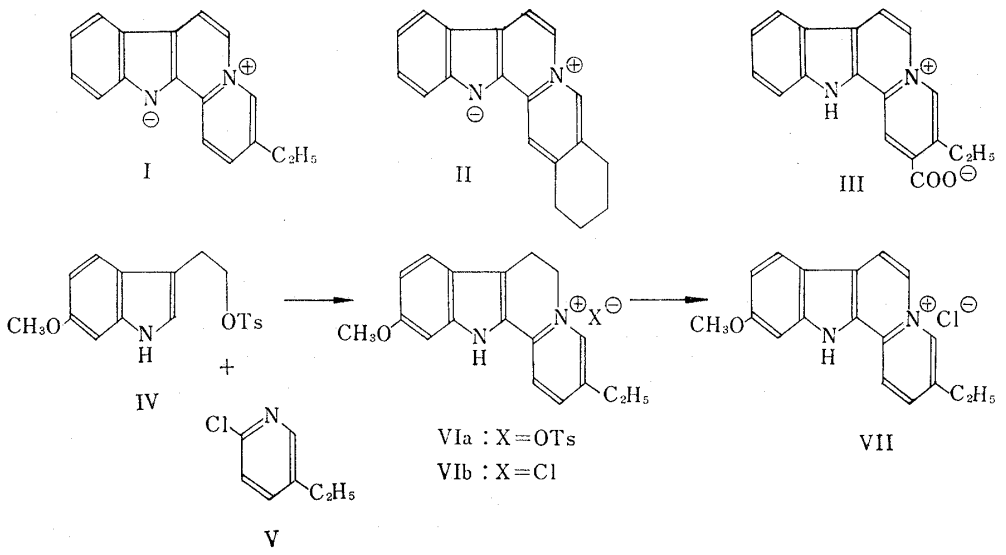

Chart 1.

A condensation of 2-(6-methoxyindol-3-yl)ethyl *p*-toluenesulfonate (IV)[5d] with 2-chloro-5-ethyl-pyridine (V)[5b,6] was carried out by heating at 60~70° for 9 hr., during which time

*1 Part V. Y. Ban, M. Seo: This Bulletin, **12**, 1378 (1964).

*2 Kita-12-jo, Nishi-5-chome, Sapporo, Hokkaido (伴 義雄, 井上一三).

1) Cf. M. Hesse: "Indolealkaloide in Tabellen," (1964), Springer-Verlag, Berlin.

2) *a*) O. Bejar, R. Goutarel, M. M. Janot, A. Le Hir: Compt. rend. hebd. Seances Acad. Sci., **244**, 2066 (1957). *b*) N. A. Hughes, H. Rapoport: J. Am. Chem. Soc., **80**, 1604 (1958).

3) R. B. Woodward, B. Witkop: *Ibid.*, **71**, 379 (1949); R. B. Woodward, W. M. McLamore: *Ibid.*, **71**, 379 (1949).

4) G. Büchi, R. E. Manning, F. A. Hochstein: *Ibid.*, **84**, 3393 (1962).

5) Y. Ban, M. Seo: *a*) Chem. & Ind. (London), **1960**, 235; *b*) Tetrahedron, **16**, 5, 11 (1961); *c*) J. Org. Chem., **27**, 3380 (1962); *d*) This Bulletin, **11**, 1193 (1963); *e*) *Ibid.*, **12**, 1378 (1964).

6) Cf. S. Sugasawa, M. Kirisawa: Pharm. Bull. (Tokyo), **4**, 139 (1956); *Ibid.*, **3**, 190 (1955).

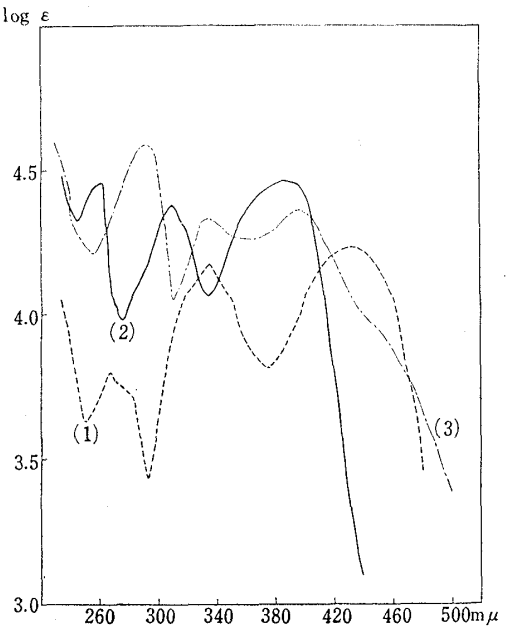

Fig. 1.

(1) ------ 3-Ethyl-10-methoxy-6,7-dihydro-12*H*-indolo[2,3-*a*]quinolizinium chloride (Ⅵb) in EtOH.
(2) ———— 3-Ethyl-10-methoxy-12*H*-indolo[2,3-*a*]quinolizinium chloride (Ⅶ) in EtOH.
(3) —•—•— Ⅶ in 0.015*N* KOH-EtOH.

the yellow brownish powder deposited. This was purified as orange yellow needles (Ⅵa), m.p. 191~194°, and converted into the chloride (Ⅵb), orange yellow needles, d.p. 280~285°, whose ultraivolet absorption spectrum is shown Fig. 1.

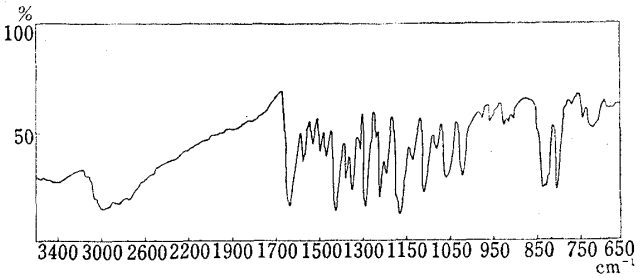

Fig. 2. 3-Ethyl-10-methoxy-12*H*-indolo[2,3-*a*]-quinolizinium Chloride (Ⅶ·H_2O) in KBr Disk

The chloride (Ⅵb) was oxidized with tetrachloro-*o*-benzoquinone in acetic acid[7] to afford 10-methoxy-flavopereirine hydrochloride (Ⅶ), pale yellow needles, m.p. 290~291°, in 77% yield. The ethanolic solution of this compound indicated a remarkably strong blue fluorescence as well as flavopereirine.

The ultraviolet and infrared absorption spectra are shown in Fig. 1 and Fig. 2, respectively.

Experimental*3

3-Ethyl-10-methoxy-6,7-dihydro-12*H*-indolo[2,3-*a*]quinolizinium Salts (Ⅵ)——A mixture of 2-(6-methoxyindol-3-yl)ethyl *p*-toluenesulfonate (Ⅳ; 568 mg., 1.6 mmoles) and 2-chloro-5-ethylpyridine (Ⅴ; 2.0 g.) was heated at 60~70° under a stream of N_2 for 9 hr., during which time yellow brownish crystals deposited. On cooling, ether was added and the precipitate was triturated, collected by filtration, and recrystallized from EtOH twice to afford 230 mg. (31%) of Ⅵa as orange yellow needles, m.p. 191~194°. *Anal.* Calcd. for $C_{25}H_{26}O_4N_2S\cdot H_2O$: C, 64.09; H, 6.02; N, 5.98. Found: C, 63.84; H, 5.85; N, 6.19. The foregoing tosylate (Ⅵa) was dissolved in MeOH and passed through the anion exchange resin (IRA-410) substituted by chlorine ion. The MeOH was removed *in vacuo* to leave the residual crystals, which were recrystallized from EtOH to afford 154 mg. of orange yellow needles (Ⅵb), d.p. 280~285°. *Anal.* Calcd. for $C_{18}H_{19}ON_2Cl$: C, 68.67; H, 6.08; N, 8.89. Found: C, 68.71; H, 6.15; N, 9.17. UV λ_{max}^{EtOH} mμ (log ε): 268 (3.80), 335 (4.18), 433 (4.24); λ_{min}^{EtOH} mμ (log ε): 254 (3.63), 293 (3.43), 374 (3.82).

3-Ethyl-10-methoxy-12*H*-indolo[2,3-*a*]quinolizinium Chloride (Ⅶ)——A mixture of the foregoing chloride (Ⅵb; 63 mg., 0.2 mmole) and tetrachloro-*o*-benzoquinone (62 mg., 0.25 mmole) in AcOH (0.8 ml.) was heated in a boiling water bath for 6 hr. On cooling, the mixture was diluted with ether to dissolve the ether-soluble tetrachlorocatechol. The ether-insoluble product was collected by filtration, and recrystallized from EtOH (2 ml.) to afford 48 mg. (77%) of pale yellow needles, m.p. 290~291° (decomp.). The ethanolic solution of this compound (Ⅶ) showed a remarkably strong blue fluorescence. *Anal.* Calcd. for $C_{18}H_{17}ON_2Cl\cdot H_2O$: C, 65.35; H, 5.79; N, 8.47. Found: C, 65.29; H, 5.82; N, 8.66. UV λ_{max}^{EtOH} mμ (log ε): 262 (4.46), 312 (4.38), 384 (4.47); λ_{min}^{EtOH} mμ (log ε): 245.5 (4.33), 276 (3.98), 335 (4.07). UV $\lambda_{max}^{0.015N\ KOH\ in\ EtOH}$ mμ (log ε): 293 (4.59), 335 (4.34), 398 (4.37); $\lambda_{min}^{0.015N\ KOH\ in\ EtOH}$ mμ (log ε): 256 (4.21), 309 (4.06), 364 (4.27).

*3 All melting points are uncorrected.

7) G. A. Swan: J. Chem. Soc., **1958**, 2039.

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Summary

3-Ethyl-10-methoxy-12*H*-indolo[2,3-*a*]quinolizinium chloride might be called "10-methoxy-flavopereirine hydrochloride," which was synthesized by the method developed in this laboratory with some expectation that this compound would at some time be found in nature.

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