ferrocene is delayed when columns E and F were used, and these are not suitable for the separation.

From the results hitherto mentioned, it was shown that the mixture of several ferrocene derivatives shown in Fig's. 1, 2, and 4 could be separated by any of columns A~H in Table I, but the separation of mixture of ferrocene derivatives in Fig. 3 could be achieved only by column H.

The authors wish to express their hearty thanks to Dr. S. Mizushima of this laboratory who always encouraged them to conduct this work. The authors also thank to H. Ochi and N. Ishibashi who helped the synthetic experiments, to Dr. K. Yamakawa of Tokyo College of Science who discussed with them on many problems.

Summary

The satisfactory results were obtained to separate the mixture of several ferrocene derivatives by gas chromatography using column H (2.5% Apiezon-L on chromosorb-W, column length 1.4 m. × 4 mm., column temperature 200° and flow rate of He 50 ml./min.).

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121. Yoshio Ban, Reiji Sakaguchi, and Masako Nagai (née Seo): The Synthesis of β-Carboline Derivatives. VII*1. The Isolation of the Possible Intermediate in the Condensation of 3-(2-Bromoethyl)indole and 2-Halogenopyridine.

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In the previous papers of this series,[1] it was reported that the possible intermediates in the new method for the synthesis of β-carboline derivatives developed in this laboratory are isolated only in specific cases. For instane, on condensation of 3-(2-bromoethyl)indole (I) with 3-chloro-5,6,7,8-tetrahydroisoquinoline (II), there was obtained 2-[2-(3-indolyl)ethyl]-3-chloro-5,6,7,8-tetrahydroisoquinolinium bromide (III) as an intermediate, which was treated with phosphoryl chloride to afford the indoloquinolizinium salt (IV).

Nevertheless, in the general procedure which I is heated with 2-halogenopyridine (Va, b) on a water bath for 4~10 hr., 6,7-dihydro-12*H*-indolo [2,3-*a*]quinolizinium salt (VI) is the sole product although careful search for the possible intermediate (VII) has been made.[2] In this paper, it is reported that such an intermediate (VII) has been actually isolated and characterized.

A solution of I and 2-bromopyridine (Va) in ethanol was allowed to stand at room temperature for one week to produce a quaternary salt as yellow prisms, m.p. 121~122°

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*1 Part VI. Y. Ban, I. Inoue: This Bulletin, **12**, 1381 (1964).

*2 Kita-12-jo, Nishi-5-chome, Sapporo, Hokkaido (伴 義雄, 坂口礼司, 永井雅子(旧姓瀬尾)).

1) *a*) Y. Ban, M. Seo: Tetrahedron, **16**, 11 (1961). *b*) Y. Ban, M. Seo: This Bulletin, **12**, 1378 (1964).

2) Y. Ban, M. Seo: Tetrahedron, **16**, 5 (1961).

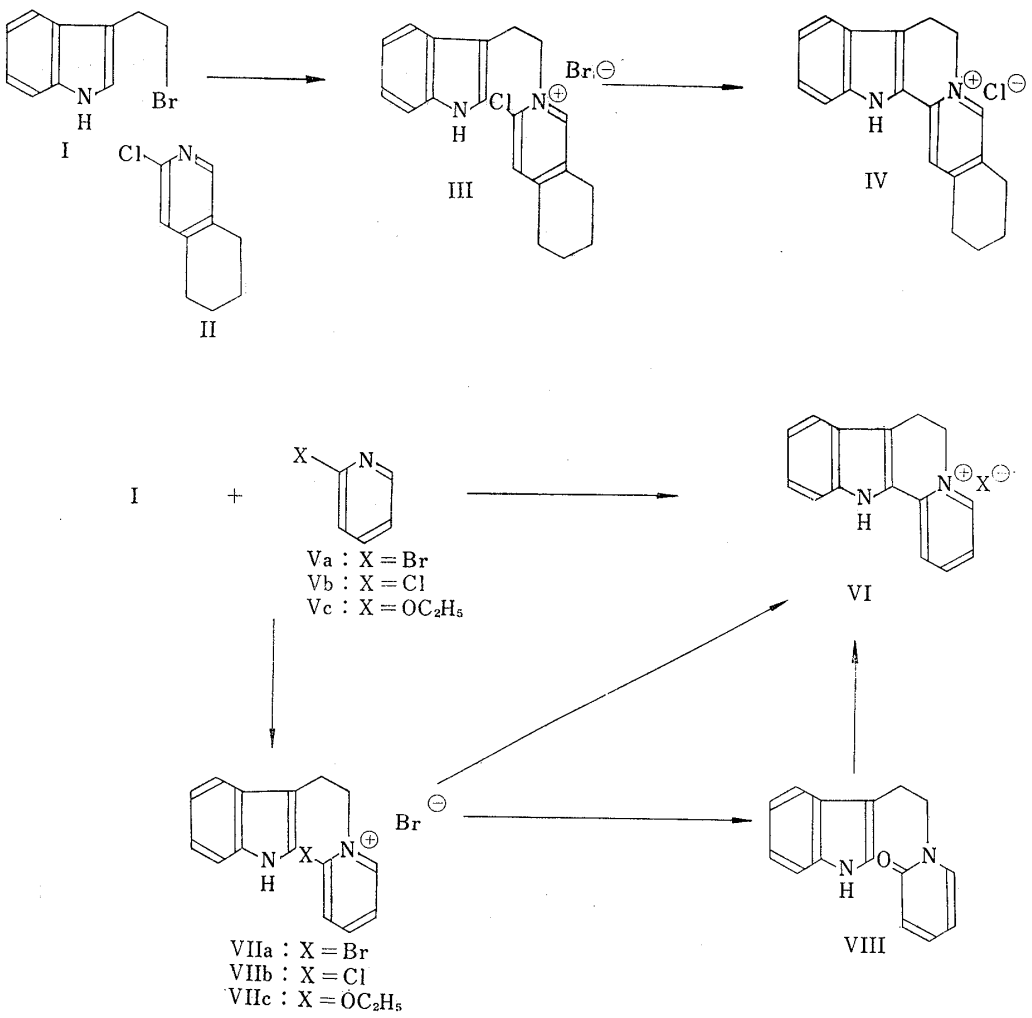

Chart 1.

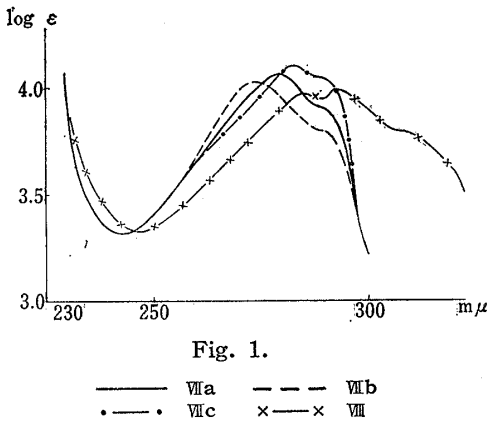

Fig. 1.

(decomp.), whose ultraviolet spectrum is compatible with the assignment of Ⅶa as is shown in Fig. 1, since that absorption is equal to the summation of those of I and 1-alkyl-2-chloropyridinium salt,[3] and the elemental analyses also support this composition.

In conformity with this assignment, the quaternary salt (Ⅶa) was treated with sodium hydroxide solution on warming to yield readily the corresponding pyridone (Ⅷ) as colorless prisms, m.p. 170~171°, which was proved by its ultraviolet absorption spectrum, infrared spectrum and elemental analyses. The pyridone (Ⅷ) was refluxed with phosphoryl chloride for 6 hr. to afford Ⅵ (X=Cl), orange yellow needles, m.p. 305° (decomp.), which were identified with an authentic specimen[2]. The bromide (Ⅵ, X=Br) was also prepared by fusion of Ⅶa in an oil bath kept at 140~150° under a diminished pressure for three minutes.

3) Y. Ban, O. Yonemitsu, T. Oishi, S. Yokoyama, M. Nakagawa : This Bulletin, **7**, 609 (1959).

Similarly, a methanolic solution of I and 2-chloropyridine (Vb) was gently refluxed for 3 hr. in a current of nitrogen to afford the quaternary salt (VIIb), the structure of which was also assigned particularly by its ultraviolet spectrum (Fig. 1). According to elemental analyses, the compound (VIIb) which was dried at 60° *in vacuo* overnight, was assumed to contain one molar crystalline methanol. Therefore, the above sample was kept about 90° *in vacuo* for 2 days in order to eliminate the crystalline methanol. But, the resulting material was found to be already mixed with the cyclized product (VI) judging from its ultraviolet spectrum. Under the above conditions, the halogen atoms at 2-position seemed to remain unreacted with alcohol.

With an auxiliary interest about the reactivity of an iminoether system (EtO–C(=N–)–) as an electrophilic reagent in connection with other problems, the condensation of I with 2-ethoxypyridine (Vc)[4] was attempted. Thus, an ethanolic solution of I and Vc was allowed to stand at room temperature for one week to afford the quaternary salt (VIIc) in a poor yield (10%). Accordingly, the improvement of a yield of this salt (VIIc) is now being investigated.

A series of the above reactions strongly suggests the following plausible mechanism of one step synthesis of an indoloquinolizinium salt (VI) from I and Va or Vb, which further confirms our previous proposal on this subject[1].

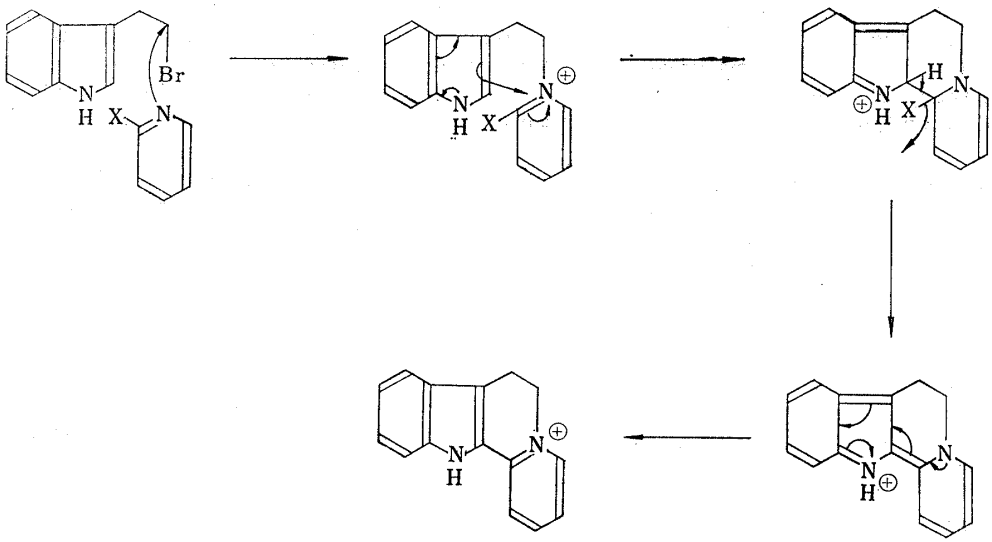

Chart 2.

Experimental

1-[2-(3-indolyl)ethyl]-2-bromopyridinium Bromide (VIIa)——A solution of the bromide (I, 3 g.) and 2-bromopyridine (Va, 2.4 g.) in EtOH (3 ml.) was allowed to stand at room temperature for one week, to which ether was added. The precipitated yellow crystals were collected and recrystallized from EtOH to afford 2 g. (40%) of yellow prisms, m.p. 121~122° (decomp.). *Anal.* Calcd. for $C_{15}H_{14}N_2Br_2$: C, 47.12; H, 3.67; N, 7.33. Found: C, 47.33; H, 4.02; N, 7.29. UV λ_{max}^{EtOH} mμ (log ε): 279.5 (4.06), λ_{min}^{EtOH} mμ (log ε): 243 (3.31), $\lambda_{shoulder}^{EtOH}$ mμ (log ε): 289 (3.90).

1-[2-(3-Indolyl)ethyl]-2-chloropyridinium Bromide (VIIb)——A solution of the bromide (I, 448 mg.) and 2-chloropyridine (Vb, 278 mg.) in MeOH (2 ml.) was gently refluxed for 3 hr. in a current of nitrogen. To the mixture was added ether, and the precipitated yellow crystals were collected and recrystallized from MeOH to afford 245 mg. (36.3%) of yellow needles, m.p. 157~160° (not definite and gradually decomposed). *Anal.* Calcd. for $C_{15}H_{14}N_2BrCl \cdot CH_3OH$: C, 51.95; H, 4.87; N, 7.58. Found: C, 51.88; H, 4.84; N, 7.35. UV λ_{max}^{EtOH} mμ (log ε): 274.5 (4.03), λ_{min}^{EtOH} mμ (log ε): 242 (3.31), $\lambda_{shoulder}^{EtOH}$ mμ (log ε): 289 (3.79).

4) H. J. den Hertog, J. P. Wibaut, F.R. Schepman, A.A. van der Wal: Rec. Trav. Chim., 69, 700 (1950).

1-[2-(3-Indolyl)ethyl]-2-ethoxypyridinium Bromide (VIIc)——A solution of the bromide (I, 560 mg.) and 2-ethoxypyridine (Vc, 310 mg.) in EtOH (3 ml.) was allowed to stand at room temperature. The solvent was evaporated and the residual gum was washed with hexane to remove the unreacted material. The dark green gum thus obtained was dissolved in a small amount of EtOH, to which ether was added to deposit crystals, which were recrystallized from EtOH-ether to afford 87 mg. (10%) of colorless needles, m.p. 134~135°. *Anal.* Calcd. for $C_{17}H_{19}ON_2Br$: C, 58.79; H, 5.47; N, 8.07. Found: C, 58.86; H, 5.53; N, 8.23. UV λ_{max}^{EtOH} mμ (log ε): 282.5 (4.10), λ_{min}^{EtOH} mμ (log ε): 242 (3.30), $\lambda_{shoulder}^{EtOH}$ mμ (log ε): 289 (4.04).

1-[2-(3-Indolyl)ethyl]-2(1*H*)-pyridone (VIII)——To a suspension of 1-[2-(3-indolyl)ethyl]-2-bromopyridinium bromide (VIIa, 130 mg.) in H_2O (10 ml.) was added a solution of NaOH (290 mg.) in H_2O (3 ml.), and the whole mixture was heated on a water bath for 2 hr. After cooling, the mixture was extracted with $CHCl_3$ (10 ml. × 4), the extract was washed with water, dried over $CaCl_2$ and the solvent was evaporated to leave a pale brown gum which crystallized on standing for several minutes. After recrystallizations from benzene, the pyridone (VIII) was obtained as colorless prisms, 64 mg. (80%). m.p. 170~171°. *Anal.* Calcd. for $C_{15}H_{14}ON_2$: C, 75.62; H, 5.85; N, 11.76. Found: C, 75.63; H, 5.97; N, 12.08. UV λ_{max}^{EtOH} mμ (log ε): 285 (3.97), 292 (3.99), λ_{min}^{EtOH} mμ (log ε): 247 (3.32), 289 (3.95), $\lambda_{shoulder}^{EtOH}$ mμ (log ε): 308 (3.79). IR cm^{-1}: $\nu_{C=O}$ 1650.

On substituting VIIb for VIIa in the above hydrolysis, the same pyridone (VIII) was obtained in 80% yield.

6,7-Dihydro-12*H*-indolo[2,3-*a*]quinolizinium Salts (VI)——a) 1-[2-(3-indolyl)ethyl]-2-bromopyridinium bromide (VIIa, 100 mg.) was fused in an oil bath kept at 140~150° under a diminished pressure for 3 min. After cooling, the crude product was recrystallized from MeOH to afford 56 mg. (71%) of yellow needles, m.p. 325° (decomp.), which was identified with the authentic sample (VI, X=Br), m.p. 325~330° (decomp.), by IR and UV spectral comparison.

b) A suspension of 1-[2-(3-indolyl)ethyl]-2(1*H*)-pyridone (VIII, 70 mg.) in $POCl_3$ (2.5 g.) was refluxed for 6 hr. and the excess of $POCl_3$ was evaporated to leave a yellow residue, which was dissolved in MeOH. Ether was added to deposit yellow crystals which were recrystallized from MeOH to give 38 mg. (50%) of the quaternary chloride (VI, X=Cl), m.p. 305° (decomp.), which was identified with the authentic specimen, m.p. 305° (decomp.), by UV and IR spectral comparison.

The authors are grateful to Prof. Em. S. Sugasawa for his valuable advice and to Mrs. S. Toma and Miss A. Maeda of the Central Analysis Room of this Faculty for elemental analyses. It is a pleasure to express appreciations to the Abbott Research Grant Committee, and to the District Government of Hokkaido for financial support of this work.

Summary

The possible intermediates in the condensation of 3-(2-bromoethyl)indole and 2-halogenopyridines constituting the new method for the synthesis of β-carboline derivatives developed in this laboratory, have been isolated and characterized, which confirms our previous proposal on the mechanism of this reaction.

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