in an ice bath. To this solution was added bis(chloroethyl)amine derivative (0.05 mole) in EtOH, and the mixture was kept at 0° for 3~7 days. The separated crystals were collected and recrystallized from appropriate solvent (see Table I).

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Summary

Aromatic nitrogen mustards containing an azo group (Ⅶ~XV), a nitrogen mustard with a carrier and masking group, were synthesized in one step starting from *p*-amino-phenylalanine or aliphatic *p*-amino-phenyl acid.

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Yoshio Ban and Masako Seo: The Synthesis of β-Carboline Derivatives. V.*1 A Synthesis of 1-Methyl-1,2,3,4,7,8-hexahydro-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium Salts.

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In the preceding paper*1, the total synthesis of alstoniline (I), an alkaloid of *Alstonia constricta* F. MUELL was described. In the course of this work, the intermediate, 5-methyl-5,6,7,8-tetrahydro-3(2*H*)isoquinolone (Ⅱ) was brominated with phosphoryl bromide in a sealed tube to afford the fully aromatized compound, 3-bromo-5-bromomethyl-isoquinoline (Ⅲ). Also, when the similar bromination was carried out in an open vessel, there was obtained a mixture of 3-bromo-5-methylisoquinoline (Ⅳ) and the above dibromo-base (Ⅲ).*1

It is described in this paper that the same intermediate (Ⅱ) was subjected to chlorination with phosphoryl chloride to afford the partially aromatized product, 3-chloro-5-methyl-5,6,7,8-tetrahydroisoquinoline (Va), in contrast to the foregoing bromination reactions, from which compound (Va) 1-methyl-1,2,3,4,7,8-hexahydro-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium salts (Ⅷa and b) were synthesized.

The results of the above halogenation reactions are parallel to those briefly described by Swan who halogenated 5,6,7,8-tetrahydro-3(2*H*)isoquinolone with phosphoryl chloride and with phosphoryl bromide.[1] The structures of the products were readily distinguished by their ultraviolet absorption spectra as are shown in Fig. 1. The spectrum of Ⅴ is similar to that of 2-chloropyridine which is quite different from those of Ⅲ and Ⅳ. As for the latters, reference was made to 3-fluoroisoquinoline.[2]

Meanwhile, it has been already reported that Vb was condensed with Ⅵ to afford Ⅶb, which was cyclized with phosphoryl chloride or aluminum chloride to furnish Ⅷc,

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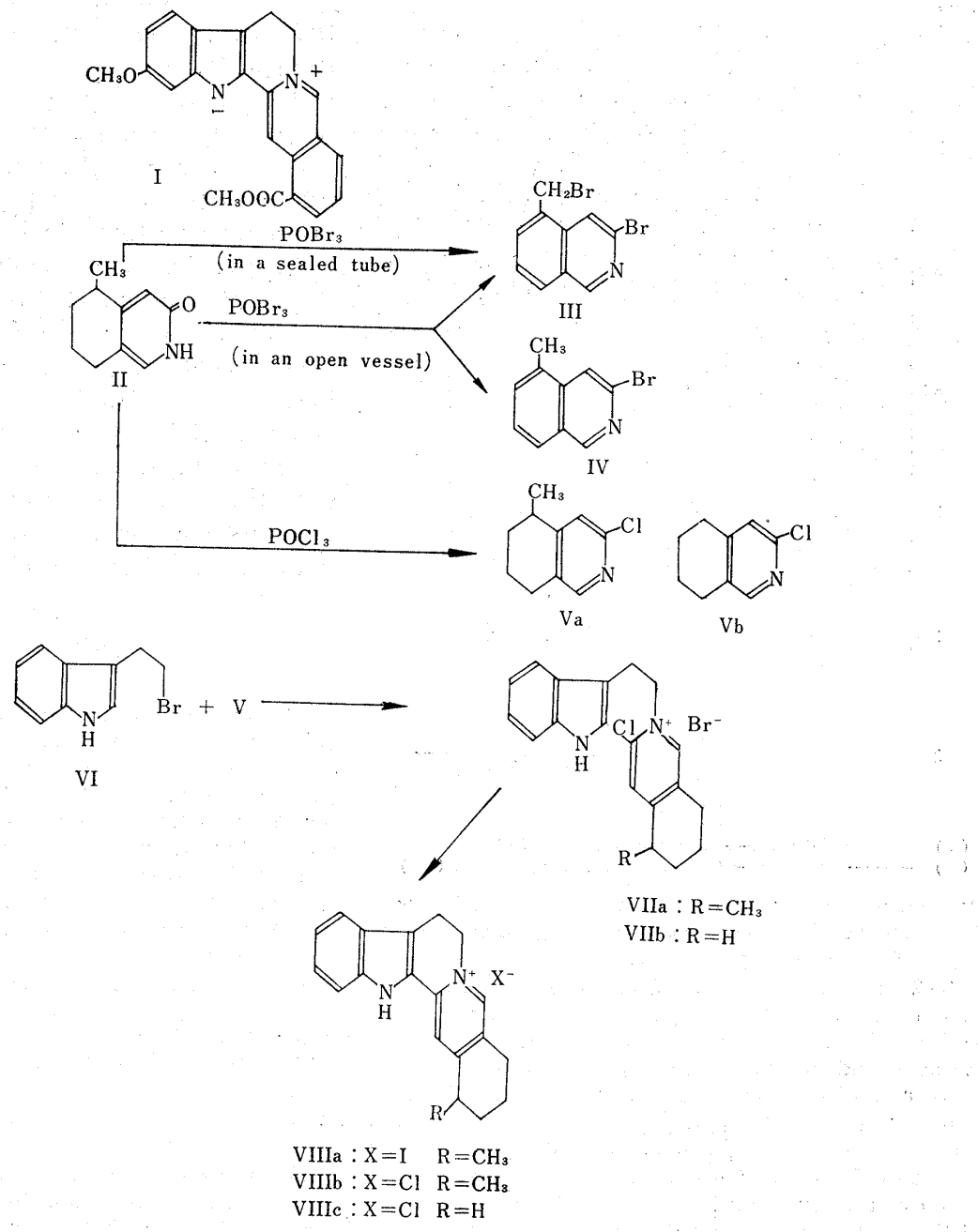
*1 Part Ⅳ: This Bulletin, **12**, 1296 (1964).

*2 Kita-12-jo, Nishi-5-chome, Sapporo, Hokkaido (伴 義雄, 瀬尾雅子).

1) G. A. Swan: J. Chem. Soc., **1958**, 2038.

2) S. B. Knight, W. K. Miller, A. Roe: J. Am. Chem. Soc., **74**, 1599 (1952).



and then Ⅷc was dehydrogenated to sempervirine nitrate, an alkaloid of *Gelsemium sempervirens*, Ait.[3]

Since Va corresponds to a homo-derivative of Vb, a similar condensation of Ⅵ with Va was attempted to survey the reaction path in this type of synthesis.

The condensation was carried out by refluxing in benzene for 14 hr., and the crude product was found to be mainly a quaternary isoquinolinium bromide (Ⅶa) in 50% yield, contaminated with a small amount of the by-product, which was deduced by the ultraviolet absorption spectrum. The substance was purified from ethanol-ether to afford the pure bromide (Ⅶa), orange yellow needles, m.p. 188°. The concentration of the mother liquor yielded a brown oil, which was not characterized on account of scarcity of the material.

3) Y. Ban, M. Seo : Tetrahedron, **16**, 11 (1961).

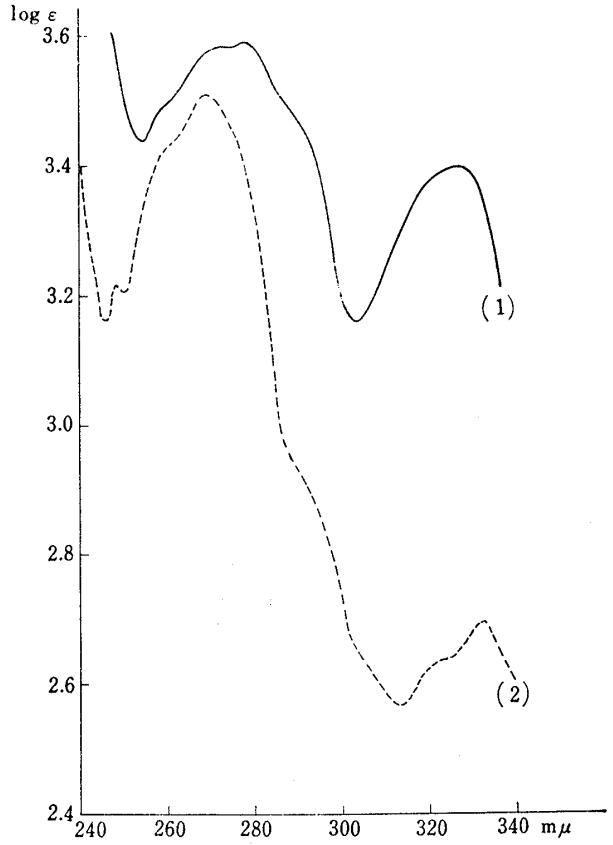


Fig. 1.

(1) ———— 3-Bromo-5-methylisoquinoline (Ⅳ)
(2) – – – – 3-Chloro-5,6,7,8-tetrahydroisoquinoline (Va)

This result was parallel to that of the condensation for a synthesis of sempervirine. The reason why the intermediates (Ⅶa and b) were isolated only in these cases of this series of syntheses, is not clear still at present. But, it seems obvious that the hydroaromatic ring fused at 4 and 5 positions of the pyridine nucleus might deactivate the chlorine atom at 2 position.

The foregoing quaternary salt (Ⅶa) was heated with aluminum chloride in xylene to afford the quinolizinium chloride (Ⅷb), yellow needles, m.p. 260°, which might be called a "homodihydrosempervirine," showing an identical ultraviolet absorption with that of dihydrosempervirine (Ⅷc).[3]

Experimental

3-Chloro-5-methyl-5,6,7,8-tetrahydroisoquinoline (Va)——A solution of 5-methyl-5,6,7,8 tetrahydro-3 (2*H*) isoquinolone (1 g.) in $POCl_3$ (13 g.) was heated at 180~190° in a sealed tube for 12 hr. After standing overnight, the reaction mixture was poured into cold water, filtered and the filtrate was made alkaline with KOH, extracted with ether, then the extract was dried over K_2CO_3. The solvent was evaporated, the residual oil was purified by distillation to give 1 g. of pale yellow liquid, b.p$_8$ 141~142°. UV : λ_{max}^{EtOH} 269 mμ (log ε 3.52); λ_{min}^{EtOH} 246 mμ (log ε 3.16).

2-(2-Indol-3-yl) ethyl-3-chloro-5-methyl-5,6,7,8-tetrahydroisoquinolinium Bromide (VIIa)——An equimolar mixture of 3-(2-bromoethyl)indole (672 mg.) and 3-chloro-5-methyl-5,6,7,8-tetrahydroisoquinoline (544.5 mg.) in abs. benzene (3 ml.) was heated on a steam bath for 14 hr. On cooling, abs. ether was added, triturated, and the insoluble orange yellow solid was collected by filtration. Yield, 600 mg. or 50%. This was recrystallized from EtOH-ether to afford 420 mg. (35%) of orange yellow needles, m.p. 188°. *Anal.* Calcd. for $C_{20}H_{22}N_2BrCl$: C, 59.18; H, 5.42; N, 6.90. Found : C, 59.48; H, 5.36; N, 6.90. UV : λ_{max}^{EtOH} 280 mμ (log ε 4.01); λ_{min}^{EtOH} 254 mμ (log ε 3.77).

1-Methyl-1,2,3,4,7,8-hexahydro-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium Chloride (VIIIb)——To a suspension of the foregoing bromide (Ⅶa, 380 mg.) in xylene (10 ml.) was added aluminum chloride (133.5 mg.) and the mixture was refluxed with stirring for 10 hr. On cooling, 30 ml. of hot water was added and the aqueous layer was separated, and saturated with solid KI. The precipitate (Ⅶa) was collected by filtration, dried, and treated with freshly prepared AgCl in MeOH to yield the corresponding chloride (Ⅷb) which was recrystallized from EtOH to afford 50 mg. (15.2%) of yellow needles, m.p. 260°. *Anal.* Calcd. for $C_{20}H_{21}N_2Cl \cdot H_2O$: C, 70.07; H, 6.71; N, 8.17. Found : C, 70.29; H, 7.04; N, 8.63. UV λ_{max}^{EtOH} mμ (log ε) : 386 (4.10), 317 (4.23), 223 (4.35); λ_{max}^{EtOH} mμ (log ε) : 346 (4.00), 275 (3.63).

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Summary

1-Methyl-1,2,3,4,7,8-hexahydro-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium salt (Ⅷ, R=CH_3) was synthesized from 3-chloro-5-methyl-5,6.7,8-tetrahydroisoquinoline (Va), in which case the intermediary quaternary bromide (Ⅶa) was isolated.

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