acetone. mp 241—243° [alone and mixed with the sample prepared from III (R=CH_3, R'=OH)]. The crude crystalline residue obtained from III (R=R'=H) was recrystallized from benzene. mp 218—221° [alone and mixed with III (R=CH_3, R'=H) prepared by Beckmann rearrangement].

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Hofmann Degradation of Quinolizidine (Synthesis of Quinolizine Derivatives. XXII[1])

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In the work reported earlier,[3] the Hofmann degradation of sparteine was tried and des-N-methyloxysparteine (II) was obtained as the sole product from 17-oxysparteine methiodide (I), and α-des-N-methylsparteine (IV) and β-des-N-methylsparteine (V) in approximately 2:1 ratio from sparteine methiodide (III). Since the A—B ring juncture of sparteine is *trans* and C—D ring juncture is *cis*, the degradation of I corresponds to the Hofmann degradation of *trans*-quinolizidine methiodide (VI) and that of III to *cis*-quinolizidine methiodide (VII). Schofield[4] reported that the Hofmann degradation of VI afforded a large amount of N-methylazocyclodecene (VIII) and a small amount of N-methylpiperidylbutene (IX) in approximately 90:5 ratio, and that a small amount of VIII and a large amount of IX in approximately 5:90 ratio were obtained from VII.

Comparison of this result with the degradation of I and III shows that the formation of II alone from I is in parallel with the degradation of VI, but the formation of a large amount of IV and a small amount of V from III is rather a reverse of the degradation of VII.

In order elucidate this problem, Hofmann degradation of *trans*- (VI) and *cis*-quinolizidine methiodide (VII) was reexamined to compare its result with that of Schofield.

The starting compound, quinolizidine methiodide was synthesized by the method of Clemo and others[5] for the *trans* compound (VI) and by that of Moynehan and others[6] for the *cis* compound (VII). Authenticity of these compounds was proved by the analytical values and the data of their derivatives agreeing with those listed in the literature.

Hofmann degradation of VI and VII was carried out under identical condition by treatment with silver oxide and an oily product was obtained in 81.8 and 16.7% yield, respectively. These two substances were separated into two sharp peaks each in gas chromatogram but

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1) Part XXI: S. Ohki and M. Akiba, *Chem. Pharm. Bull.* (Tokyo), **17**, 2484 (1969).
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3) K. Sugimoto, N. Shibata, and S. Ohki, *Yakugaku Zasshi*, **88**, 903 (1968).
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5) G.R. Clemo, G.R. Ramage, and R. Raper, *J. Chem. Soc.*, **1932**, 2959.
6) T.M. Moynehan, K. Schofield, R.A.Y. Jones, and A.R. Katritzky, *J. Chem. Soc.*, **1962**, 2637.

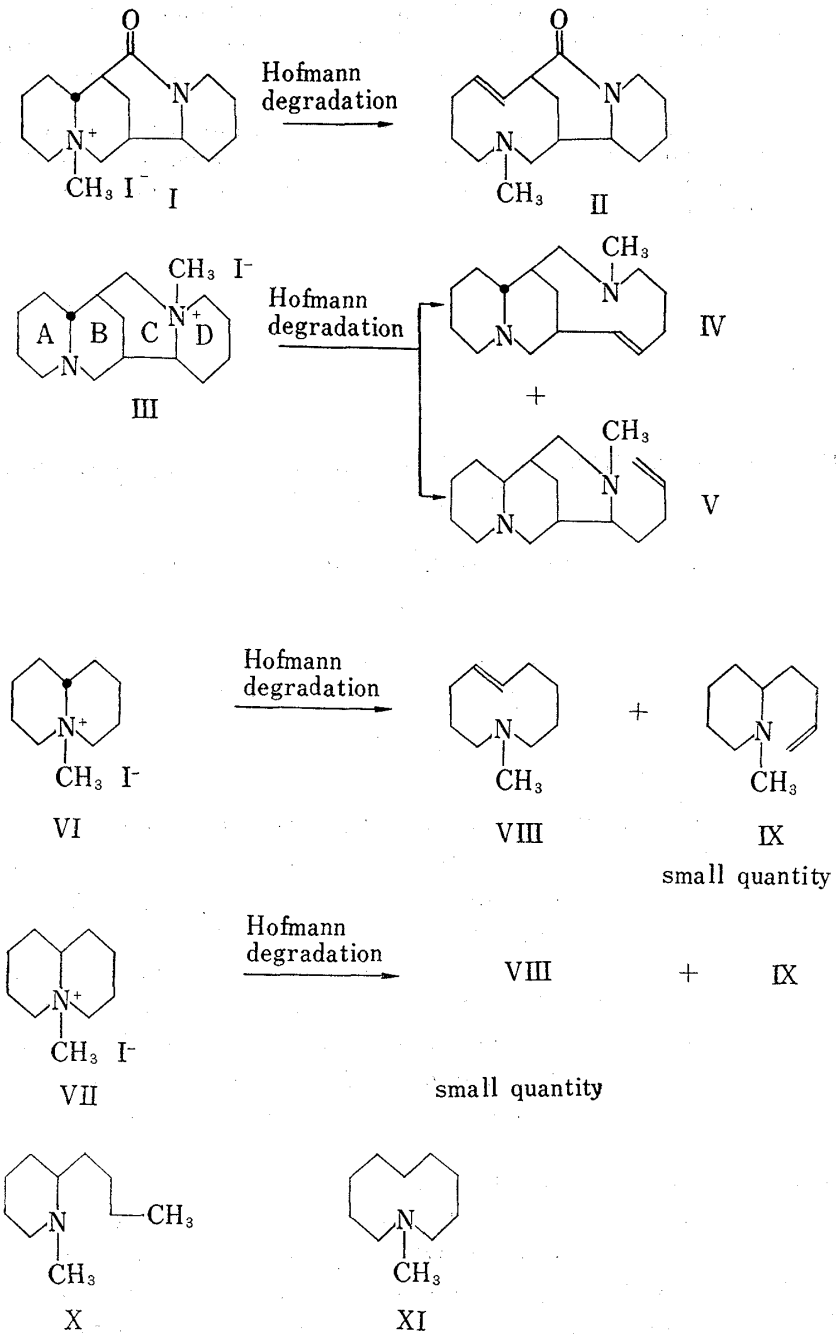

Chart 1

each of the peaks overlapped completely (formation ratio about 50:50). The degradation products from IV was submitted to catalytic reduction without separation, using 5% rhodium carbon as the catalyst, and the oily product thereby obtained was converted to a methiodide, by which crystals of mp 242.5° and crystals of mp 160—163° were obtained. The former methiodide and its methopicrate, mp 142.5°, were found to be identical with the methiodide, mp 242°, and methopicrate, mp 142.5°, of N-methylazacyclodecane (X), synthesized by the modified method of Prelog and others.[7] X had recently been derived from quinolizidine by an elegant method by Arata and others[8] and their identity was also confirmed.[9] The latter

7) V. Prelog and R. Seiwerth, *Ber.*, **72**, 1638 (1939).
8) Y. Arata, S. Yoshifuji, and Y. Yasuda, *Chem. Pharm. Bull.* (Tokyo), **16**, 569 (1968).
9) Grateful acknowledgement is made to Professor Yoshiro Arata for the donation of this sample.

methiodide agreed entirely with 1-methyl-2-butylpiperidine methiodide (XI), synthesized by the method of Clemo and others[5] with a slight modification.

Reaction of the degradation products from VI with methyl iodide gave a methiodide, mp 245—247° and a methiodide, mp 142—145°. The nuclear magnetic resonance (NMR) spectrum of the latter methiodide showed a signal for *endo*-methylene. This methiodide was converted to a methochloride which was reduced and then converted again to the methiodide by treatment with potassium iodide by which a methiodide, mp 160—163°, was obtained. This substance agreed entirely with 1-methyl-2-butylpiperidine methiodide (XI).

From the foregoing results, it became clear that the Hofmann degradation of VI and VII affords VIII and IX in both cases in approximately 50:50 ratio and that the result is contrary to the report of Schofield[4] that VIII or IX is obtained selectively.

The Hofmann degradation is a kind of the so-called fragmentation reaction and the *anti*-elimination with β-hydrogen far more easily proceeds over *syn*-elimination.[10] Consequently, *anti*-elimination of C_1–$H_{(eq)}$ (or C_9–$H_{(eq)}$), situated on the same plane as the C_{10}–N bond in VI, and *anti*-elimination of C_3–$H_{(eq)}$ (or C_7–$H_{(eq)}$) situated on the same plane as the C_4–N (or C_6–N) bond should occure with same facility, and this fact endorses the formation of VIII and IX in equal amounts. The same relationship can also be applied to C_1–$H_{(eq)}$ (or C_9–$H_{(eq)}$) against C_{10}–N and C_3–$H_{(eq)}$ (or C_7–$H_{(eq)}$) against C_4–N (or C_6–N) in VII. The poor yield of the product from VII is assumed to be due in part to the presence of an equilibrium between VIIa and VIIb (Chart 2).

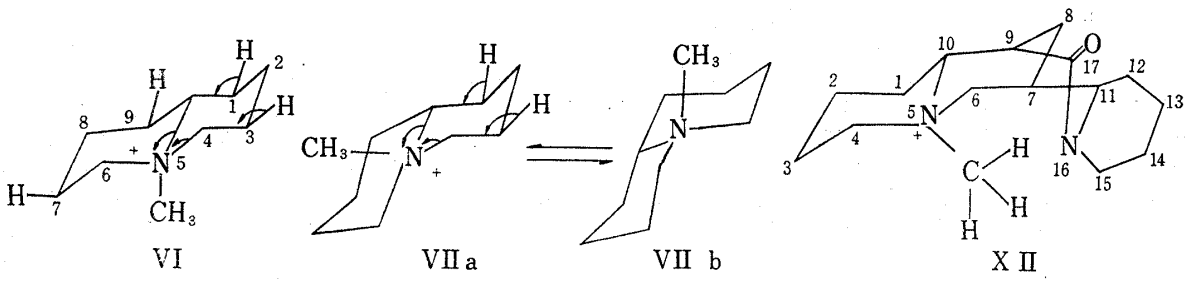

Chart 2

Application of the present result on VI and VII to the case of I and III show that the formation of II alone from I is inconsistent with the above theory. It is assumed that this is due to the steric hindrance resulting from the introduction of a methyl group into N(5) giving a strain to the *trans*-quinolizidine ring (*cf.* XII) and the above steric relation cannot be maintained.

There is an argument[11] of whether the C-ring in sparteine is in chair or boat form but when a methyl group is introduced into N(16), C-ring would not be able to take the boat form by steric hindrance. Consequently, there would be *anti*-elimination between C_{11}–N and C_{12}–$H_{(eq)}$, and between C_{15}–N and C_{14}–$H_{(eq)}$, resulting in the formation of IV and V.

Experimental

Hofmann Degradation of *trans*-Quinolizidine Methiodide (VI)——A solution of 4 g of VI dissolved in 100 ml of H_2O and added with 4 g of Ag_2O was allowed to stand at room temperature with stirring for 4 hr the reaction mixture was filtered, and the filtration residue was extracted with hot water. Water was

10) J. Sicher, J. Závada, and J. Krupička, *Tetrahedron Letters*, **1966**, 1619; M. Pánkova, J. Sicher, and J. Závada, *Collection Czech. Chem. Commun.*, **1967**, 394.

11) L. Marion and N.J. Leonard, *Can. J. Chem.*, **29**, 355 (1951); F. Bohlmann, D. Shumann, and C. Arndt, *Tetrahedron Letters*, **1965**, 2705; I. Ribas, J.L. Castedo, and A. Galcfa, *Tetrahedron Letters*, **1965**, 3181; P.J. Krueger and J. Skolik, *Tetrahedron*, **23**, 1799 (1965); P. Baranowsky, J. Skolik, and M. Wiewiorowski, *Tetrahedron*, **20**, 2383 (1964).

evaporated from this solution and the oily residue was heated in an oil bath at 180—200° at a reduced pressure (10 mmHg) to effect degradation. The distillate was collected to 1.8 g (81.8%) of a colorless oil.

Hofmann Degradation of *cis*-Quinolizidine Methiodide (VII)——A solution of 2.2 g of VII dissolved in 60 ml of H_2O and added with 2.2 g of Ag_2O was stirred for 4 hr at room temperature, the reaction mixture was filtered, and the filtration residue was extracted with hot water. Water was evaporated from this extract solution under a reduced pressure and the residual oily substance was heated in an oil bath at 180—200° at a reduced pressure (10 mmHg) to effect degradation. This distillate of colorless oil was collected. Yield, 0.2 g (16.7%). Gas chromatographic analysis showed the product to be the same as that from the Hofmann degradation of *trans*-quinolizidine.

Des-N-methylquinolizidine Methiodide——A solution of 1 g of colorless oily des-N-methylquinolizidine (VIII and IX) dissolved in 10 ml of acetone and added 2 g of MeI was allowed to stand at room temperature for 12 hr, the crystals formed were collected, and recrystallized from EtOH to colorless crystals, mp 245—247°. Yield, 0.4 g (21.0%). *Anal.* Calcd. for $C_{11}H_{22}NI$: C, 44.78; H, 7.52; N, 4.75. Found: C, 44.84; H, 7.46; N, 4.54. Methopicrate, mp 149.5°.

Ether was added to the mother liquor left removal of the crystals of mp 245—247° and the crystals that precipitated out were collected and recrystallized to colorless crystals, mp 142—145°. Yield, 0.7 g (36.8%). *Anal.* Calcd. for $C_{11}H_{22}NI$: C, 44.78; H, 7.52; N, 4.75. Found: C, 44.70; H, 7.62; N, 4.68.

Reduction of Des-N-methylquinolizidine Methiodide (mp 142—145°)——A suspension of 1 g of des-N-methylquinolizidine methiodide (mp 142—145°) and AgCl freshly prepared from 2 g of $AgNO_3$ in *ca.* 50 ml of H_2O was stirred at room temperature for 4 hr. The mixture wsa filtered, the residue on the filter was washed with hot water, and the combined filtrate and washing was evaporated under a reduced pressure. The residual oily substance was dissolved in EtOH and submitted to catalytic reduction with 0.1 g of Adams PtO_2: The reduction mixture was filtered, 1 g of KI was added to the filtrate, and the mixture was reflexed on a water bath for 2 hr. The reaction mixture was filtered while hot, the filtrated, and ether was added to residual solution. The crystals that precipitated out were collected and recrystallized from acetone to colorless crystals, mp 160—163°, which showed no depression on admixture with 1-methyl-2-butylpiperidine methiodide synthesized by another route.

Dihydro-des-N-methylquinolizidine Methiodide——A solution of 2 g of des-N-methylquinolizidine, a colorless oily substance without being separation, dissolved in 100 ml of AcOH was submitted to catalytic reduction over 200 mg of 5% Rh-C. The catalytic mixture was filtered, AcOH was evaporated from the filtrate, and the residue was basified with H_2O and 10% NaOH. This alkaline solution was extracted with ether and the solvent was evaporated from the ether layer. The oily residue was dissolved in 10 ml of acetone, 4 g of MeI was added, and the mixture was allowed to stand for 12 hr. The crystals that precipitated out were collected and recrystallized from EtOH to colorless crystals, mp 242.5°. Yield, 0.4 g (10.3%). Methopicrate, mp 142.5°. Ether was added to the mother liquor left after separation of the crystals of mp 242.5° and the crystals that precipitated out were collected and recrystallized from EtOH–$(C_2H_5)_2O$ to colorless crystals, mp 160—163°. Yield, 1.8 g (46.2%).

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Studies on the Constituents of *Euphorbia ebracteolata* Hayata

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According to many old documents of Chinese orthodox medicine and Japanese phytologists, it is known that chinese antiphlogistic and skin disease drug, Lüju (閭茹) is originated

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