Quinolizidines. I. : Quaternization of the Quinolizidine System : Effect of β, γ -Unsaturation on Stereoselectivity in Methiodide Formation

[Chem. Pharm. Bull. 23(1) 144—156 (1975)] UDC 547.898.04

Quinolizidines. I. Quaternization of the Quinolizidine System: Effect of β,γ-Unsaturation on Stereoselectivity in Methiodide Formation[1]

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(Received July 1, 1974)

Quaternization of benzo[*a*]quinolizidine (Ib) with methyl iodide gave a 3.6: 1 mixture of the *cis*- (IIb: X=I) and the *trans*-methiodide (IIIb: X=I). The 9,10-dimethoxy derivative (Ia) also gave the corresponding *cis*- (IIa: X=I) and *trans*-methiodide (IIIa: X=I) in a ratio of 3.3 to 1. Treatment of enamines Va,b with methyl iodide furnished the N-methylated product (VIa,b) and the C-methylated product (VIIa,b) in a ratio of 1.2: 1. Catalytic hydrogenation of VIa,b produced a mixture of the *cis*- (IIa,b) and the *trans*-methosalt (IIIa,b) in a rough ratio of 2.8: 1, whereas that of VIIa,b gave the 1-methylated benzo[*a*]quinolizidine (VIIIa,b). Compound VIIIa was alternatively prepared from piperidone IX by the Bischler-Napieralski cyclization and subsequent hydrogenation. In the case of the simple quinolizidine system with the simplest β,γ-unsaturation (XV), the quaternization with methyl iodide produced the *cis*- (XVI) and the *trans*-methiodide (XVII) almost equally. Repetition of the known methiodide formation of XXVI and hydrogenation of enamine methiodide XIX confirmed their reported high stereoselectivity, and factors responsible for the difference in stereoselectivity between these reactions of the β,γ-unsaturated system and the saturated system have been discussed. At 250° the *cis*-methiodides (IIa,b, XX) isomerized to the corresponding *trans*-fused salts (IIIa,b, XXI) to some extent and one may roughly compare the susceptibilities of IIa, IIb, and XX, which decrease in that order.

As part of our recent study on the synthesis of the benzo[*a*]quinolizidine system from piperidine derivatives,[3] we had occasion to examine the quaternization of 9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine (Ia) with methyl iodide. The first and most detailed study of this quaternization to date is that of Child and Pyman,[4] who separated the reaction product by fractional recrystallization from water into the sparingly soluble β-methiodide, mp 244—245°, and the more soluble α-methiodide, mp 228°, largely convertible into the former at 250°, but failed to interpret these observations. In this paper we present the evidence that the α- and the β-methiodide are the *cis* (IIa: X=I) and *trans* (IIIa: X=I) isomers, respectively, as well as the results of quaternization studies of 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine (Ib) and 1,3,4,6,7,9a-hexahydro-2*H*-quinolizine (XV) with particular emphasis on the effect of β,γ-unsaturation (with respect to the nitrogen) in the quinolizidine system on stereoselectivity in the methiodide formation. It is hoped that the studies will further help to unravel the factors responsible for the formation of methiodide isomers in

1) Presented in part at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April 4, 1974.
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3) *a*) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **20**, 1451 (1972); *b*) T. Fujii, S. Yoshifuji, K. Michishita, M. Mitsukuchi, and K. Yoshida, *ibid.*, **21**, 2695 (1973).
4) R. Child and F.L. Pyman, *J. Chem. Soc.*, **1931**, 36.

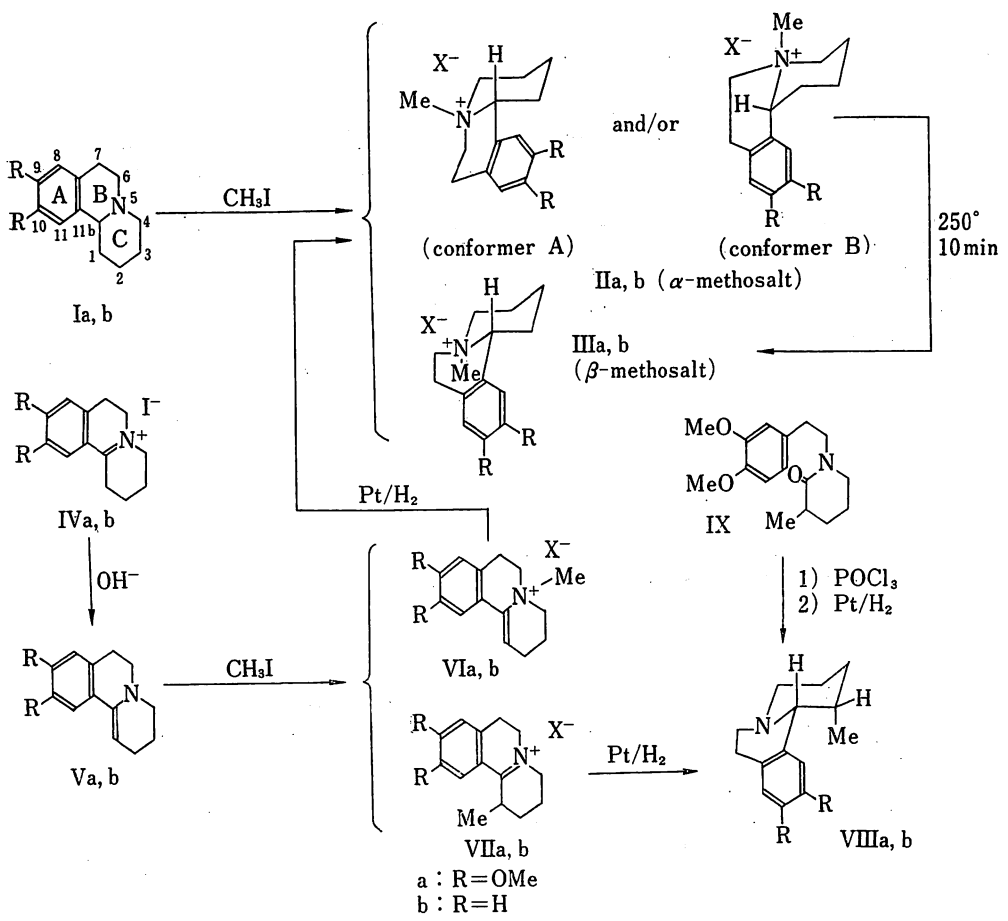


Chart 1

similar heterocyclic systems such as tetrahydroprotoberberine,[5] canadine,[6] and octahydropyrido[1,2-*a*]pyrazin-1-one (XXV).[7]

The reaction of free base Ia with methyl iodide was carried out according to the published procedure[4] and it brought about the results consistent with those reported.[4] The resulting α- and β-methiodide salts were further converted into the corresponding perchlorates and picrates to confirm the distinctions between them. The almost complete thermal conversion of the α-methiodide into the β-methiodide, realized also in our hands, suggested that the former is probably the thermodynamically less stable *cis* isomer (IIa: X=I) and the latter, the more stable *trans* isomer (IIIa: X=I).[8]

To examine this question, the nuclear magnetic resonance (NMR) spectra of these methiodides and methoperchlorates were measured in deuterated dimethyl sulfoxide or trifluoro-

5) *a*) S.N. Chakravarti, R.D. Haworth, and W.H. Perkin, Jr., *J. Chem. Soc.*, **1927**, 2275; *b*) A.L. Margni, D. Giacopello, and V. Deulofeu, *J. Chem. Soc.* (C), **1970**, 2578; *c*) C. Tani, S. Takao, and K. Tagahara, *Yakugaku Zasshi*, **93**, 197 (1973).
6) C. Tani, K. Ishibashi, and M. Wada, *Yakugaku Zasshi*, **74**, 315 (1954), and references cited.
7) Y. Arata and Y. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 1248 (1973). This ring system (XXV) (Chart 3) also may be regarded as the one carrying β,γ-unsaturation considering the partial double bond character of the central C—N bond of the amide group.
8) N.L. Allinger and J.L. Coke, *J. Am. Chem. Soc.*, **81**, 4080 (1959), and references cited.

TABLE I. Difference in Chemical Shift for Isomeric N-Methyl Groups of Quaternary Salts

Compound	B/C ring stereochemistry	Chemical shift (τ)[a] In $(CD_3)_2SO$ N-CH_3	$\tau(trans)-\tau(cis)$	In CF_3CO_2H N-CH_3	$\tau(trans)-\tau(cis)$
IIa (X=I) (α-methiodide)	*cis*	6.94		6.76	
IIIa (X=I) (β-methiodide)	*trans*	7.15	0.21	6.98	0.22
IIa (X=ClO_4)	*cis*	6.95		—	
IIIa (X=ClO_4)	*trans*	7.15	0.20	—	—
IIb (X=I)	*cis*	6.91		6.76	
IIIb (X=I)	*trans*	7.12	0.21	6.98	0.22
XVI	*cis*	6.87		6.75	
XVII	*trans*	7.12	0.25	6.97	0.22
XX	*cis*	6.81		6.74 (6.85)[b]	
XXI	*trans*	7.01	0.20	6.93 (7.04)[b]	0.19 (0.19)[b]

a) Measured on 5% (w/v) solution.
b) The value obtained in D_2O by Moynehan, *et al.*[10]

acetic acid and the chemical shifts of quaternary N-methyl signals were directly compared[9] with those of a set of *cis*- (XX)[10,11] and *trans*-N-methylquinolizidinium iodide (XXI).[10] The principle of this approach is based on the generalization[12] that in the methiodides of quinolizidine (XXVI)[10] and related ring systems[13] the quaternary N-methyl resonance of a *cis*-fused salt occurs at lower field than that of its *trans*-fused isomer. It may be seen from Table I that in both solvents the quaternary N-methyl protons of the α- and the β-methiodide resonated at the positions quite close to those of the isomeric pair, XX and XXI, respectively. Furthermore, replacement of the counter anion by perchlorate ion also gave similar results, permitting the assignment of B/C *cis*-fused structure (IIa) to the α-methosalts and the *trans*-fused structure (IIIa) to the β-methosalts. Comparison of the area of two quaternary N-methyl resonances observed for a crude product sample from the reaction of Ia and methyl iodide led to an estimation that in the mixture the *cis*-methiodide (IIa: X=I) is dominant over the *trans*-methiodide (IIIa: X=I) in a ratio of 3.3 to 1.

9) A recent paper by M. Tsuda, Ma. Tsuda, Y. Kawazoe, A.F. Casy, and M.M.A. Hassan [*Chem. Pharm. Bull.* (Tokyo), **22**, 809 (1974)] has accentuated that due consideration of solvent should be made in the interpretation of the spectra of cyclic quaternary ammonium salts especially if comparison between spectra recorded in polar and non-polar solvents are being made.

10) T.M. Moynehan, K. Schofield, R.A.Y. Jones, and A.R. Katritzky, *J. Chem. Soc.*, **1962**, 2637.

11) *a*) K. Schofield and R.J. Wells, *Chem. Ind.* (London), **1963**, 572; *b*) *Idem*, *Australian J. Chem.*, **18**, 1423 (1965).

12) T.A. Crabb, R.F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971); *b*) A.T. Bottini, "Selective Organic Transformations," Vol. 1, ed. by B.S. Thyagarajan, Wiley-Interscience, New York, 1970, pp. 89—142; *c*) J. McKenna, "Topics in Stereochemistry," Vol. 5, ed. by E.L. Eliel and N.L. Allinger, Wiley-Interscience, New York, 1970, pp. 275—308.

13) *a*) C.D. Johnson, R.A.Y. Jones, A.R. Katritzky, C.R. Palmer, K. Schofield, and R.J. Wells, *J. Chem. Soc.*, **1965**, 6797; *b*) M.F. Bartlett, B. Korzun, R. Sklar, A.F. Smith, and W.I. Taylor, *J. Org. Chem.*, **28**, 1445 (1963); *c*) M. Shamma and J.M. Richey, *J. Am. Chem. Soc.*, **85**, 2507 (1963); *d*) W.L. Meyer and N. Sapianchiay, *ibid.*, **86**, 3343 (1964); *e*) M. Skvortsov and J.A. Elvidge, *J. Chem. Soc.* (B), **1968**, 1589; *f*) J.D. England, D. Temple, and J. Sam, *J. Med. Chem.*, **11**, 353 (1968); *g*) I. Matsuo, K. Sugimoto, and S. Ohki, *Chem. Pharm. Bull.* (Tokyo), **16**, 1680 (1968); *h*) S. Ohki, M. Akiba, H. Shimada, and K. Kunihiro, *ibid.*, **16**, 1889 (1968).

TABLE II. Angular Proton Resonances of Quaternary Salts

Salt	B/C stereochemistry	$C_{(11b)}$-Proton[a]				
		Chemical shift (τ)	$\tau(cis)-\tau(trans)$	Multiplicity[b]	Coupling constant (J, Hz)	Half-height width (Hz)
IIa (X=I) (α-methiodide)	*cis*	5.57	0.31	t or d-d	—	18
IIIa (X=I) (β-methiodide)	*trans*	5.26		d-d	10 and 4	17
IIa ($X=ClO_4$)	*cis*	5.62	0.29	t or d-d	—	18
IIIa ($X=ClO_4$)	*trans*	5.33		d-d	10 and 4	18
IIb (X=I)	*cis*	5.35	0.25	t	*ca.* 7	17
IIIb (X=I)	*trans*	5.10		d-d	10 and 3	17

a) Measured in $(CD_3)_2SO$ at *ca.* 5% (w/v) concentration.
b) The letter t refers to triplet; d-d, doublet-of-doublets.

It has previously been reported by other workers that the parent benzo[*a*]quinolizidine system (Ib) gave a single methiodide of mp 133°[14] or of mp 226—229°,[15] but without making any reference to its stereochemistry. In our study, however, we found that this quaternization also gave a 3.6: 1 mixture of the *cis*- (IIb: X=I) and the *trans*-methiodide (IIIb: X=I), from which only the former, mp 188—189°, could be isolated in a pure state. An analytical sample of the latter, mp 201—202.5° (decomp.), was separately obtained *via* an alternative route as described later. The difference in chemical shift for the isomeric quaternary N-methyl groups of these two salts is also assembled in Table I.

The assignment of stereochemistry with respect to B/C ring juncture was further checked by examining the angular proton resonance. It may be seen from Table II that in all cases the $C_{(11b)}$–H signal of the *cis*-fused salt appeared approximately 0.3 ppm upfield from that of the *trans*-counterpart. This presents a sharp contrast to the reverse observed for conformational isomers of the free bases of certain benzo[*a*]quinolizidines.[16] If analogies can be drawn with carbocyclic systems[17a,18] as to the effect of the methyl group on the chemical shifts of ring protons, the difference in the present case may be attributed to that the introduction of the axial N-methyl group into the *trans*-fused ring causes a deshielding of the adjacent axial angular proton even after removing a shielding due to the antiparallel axial lone pair[19] originally present in the free base, whereas the axial or equatorial angular proton in the *cis*-fused salt enjoys the loss of a deshielding by the lone pair *gauche* to it and the gain of a shielding by the adjacent equatorial or axial N-methyl group. Another criterion for distinguishing between both isomeric salts would be the splitting pattern of the angular proton, which has been successfully utilized in studies of conformational isomers of certain benzo[*a*]-quinolizidine bases.[16] Each of the angular protons of all the salts assigned *trans* B/C stereochemistry in Table II showed a doublet-of-doublets with large *trans* diaxial (J=10 Hz) and small *gauche* (J=3—4 Hz) splittings due to coupling with the methylene protons at the 1-

14) *a*) S. Akaboshi, T. Kutsuma, and K. Achiwa, *Chem. Pharm. Bull.* (Tokyo), **8**, 14 (1960); *b*) D. Herbst, R. Rees, G.A. Hughes, and H. Smith, *J. Med. Chem.*, **9**, 864 (1966).
15) D.W. Brown, S.F. Dyke, M. Sainsbury, and W.G.D. Lugton, *Tetrahedron*, **26**, 4985 (1970).
16) *a*) M. Uskoković, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3364 (1964); *b*) G. Van Binst and J.C. Nouls, *J. Chem. Soc.* (C), **1970**, 150; *c*) J.W. Van Dyke, Jr., H.J. Havera, R.D. Johnson, H. Vidrio, and A. Viveros, *J. Med. Chem.*, **15**, 91 (1972); *d*) A. Buzas, F. Cossais, J.P. Jacquet, L. Novák, and C.S. Szántay, *J. Heterocyclic Chem.*, **11**, 175 (1974).
17) *a*) L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed., Pergamon Press, Oxford, 1969, p. 237; *b*) *Idem, ibid.*, p. 288.
18) T.A. Crabb and E.R. Jones, *Tetrahedron*, **26**, 1217 (1970), and references cited.
19) *a*) H.P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Letters*, **1964**, 2553; *b*) J.B. Lambert and R.G. Keske, *ibid.*, **1969**, 2023.

position. In the cases of the *cis*-fused salts, however, the angular proton showed only a poorly resolved triplet or doublet-of-doublets, which did not permit further discrimination between two possible conformers, A and B. The half-height width of this signal was found to be comparable to that of the *trans*-counterpart, hence it also failed to answer the question of the orientation[17b] of the angular proton in the B/C *cis*-fused system. These observations suggest that the *cis*-fused salt in hand may be a mixture of conformers A and B or that even if it is in either form the quinolizidine moiety may be so distorted by the influence of both the aromatic ring and the angular N-methyl group that the angular proton is no longer exactly axial or equatorial with respect to ring C.

The *cis*-methiodide (IIb: X=I) also could be converted into the *trans*-methiodide (IIIb: X=I) on being heated at 250°. The rate of the isomerization appeared to be slower than that of the 9,10-dimethoxy derivative (IIa: X=I) on the assumption that both isomerizations would attain similar *trans*/*cis* equilibrium states. If the isomerization proceeds by the heterolytic bond cleavage between $N_{(5)}$ and $C_{(11b)}$ and subsequent recyclization, one logical explanation for the apparent retardation is that the postulated intermediate 10-membered cyclic carbonium ion derived from IIb (X=I), being a benzyl cation lacking the methoxyl group at the *p*-position, is less stabilized than that derived from the 9,10-dimethoxy derivative (IIa: X=I). In addition, we found that *cis*-N-methylquinolizidinium iodide (XX) itself also undergoes isomerization to the *trans*-methiodide (XXI) at 250°, but at an apparently slower rate than that of IIb (X=I). This finding may support the assumed importance of the role of the aromatic ring played in the isomerization described above.

Next we tried to prepare *cis*-methiodide IIa (X=I) after the analogy of the catalytic hydrogenation of 1,3,4,6,7,8-hexahydro-5-methyl-2*H*-quinolizinium iodide (XIX) leading to *cis*-N-methylquinolizidinium iodide (XX).[11] Treatment of enamine Va,[20a] prepared from quaternary iodide IVa,[3a,4,15,20b] with methyl iodide yielded a 1.2: 1 mixture of the N-methylated product (VIa: X=I) and the C-methylated product (VIIa: X=I), from which only the former could be separated by recrystallization. Catalytic hydrogenation of the N-methylated product (VIa: X=I) over Adams catalyst gave a 2.8: 1 mixture of the *cis*- (IIa: X=I) and the *trans*-methiodide (IIIa: X=I).

The mother liquor from the recrystallization of VIa (X=I), containing the C-methylated product (VIIa: X=I) as the major component, was also hydrogenated similarly to give the 1-methylbenzo[*a*]quinolizidine derivative (VIIIa), which was identical with a sample prepared from piperidone IX[3b] by the Bischler-Napieralski cyclization and subsequent catalytic reduction. The infrared (IR) spectrum of free base VIIIa in chloroform showed Bohlmann bands[21] in the 2700—2800 cm^{-1} region, indicative of B/C *trans* stereochemistry. On the analogy of the catalytic hydrogenation of 1-methyldehydroquinolizidinium perchlorate,[10] the hydrogens at the 11b- and 1-positions would be expected to be *cis* with respect to each other. It follows that the C-methyl group is probably in the axial position as depicted in Chart 1. This view was supported by inspection of molecular models and the NMR spectra of VIIIa and related compounds. It may be seen from Table III that the C-methyl protons of VIIIa resonated at 9.21 τ while those of compounds XI—XIV resonated at lower field by *ca.* 0.1—0.3 ppm. In free base VIIIa with *trans*-fused ring, the axial C-methyl group lies below the plane of the neighboring aromatic ring and is, therefore, shielded. This may be paralleled by the experience of other workers with some 13-methyltetrahydroprotoberberines.[5c,22] The coupling constant

20) *a*) Y. Ban and O. Yonemitsu, *Chem. Pharm. Bull.* (Tokyo), **8**, 653 (1960); *b*) Y. Ban, O. Yonemitsu, and M. Terashima, *ibid.*, **8**, 183 (1960).

21) *a*) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); *b*) E. Wenkert and D.K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).

22) *a*) M. Shamma, C.D. Jones, and J.A. Weiss, *Tetrahedron*, **25**, 4347 (1969); *b*) C.K. Yu, D.B. MacLean, R.G.A. Rodrigo, and R.H.F. Manske, *Can. J. Chem.*, **48**, 3673 (1970); *c*) P.W. Jeffs, *Experientia*, **21**, 690 (1965); *d*) S. Naruto and H. Kaneko, *Yakugaku Zasshi*, **92**, 1017 (1972).

TABLE III. Comparison of C-Methyl Proton Resonances

Compound	B/C stereochemistry	C-Methyl group		
		Orientation	Chemical shift (τ)[a]	Coupling constant (J, Hz)[a]
VIIIa	*trans*	axial	9.21	7.0
VIIIb	*trans*	axial	9.21	7.2
XI[b]	—	equatorial	9.12	5.7
XI (diastereomer)[b]	—	equatorial	9.10	5.7
XII[b]	—	equatorial	9.07	6.0
XII (diastereomer)[b]	—	equatorial	9.05	6.0
XIII[b]	—	equatorial	9.06	6.0
XIV	*cis, trans*	axial	8.94	7.0
XIV	*cis, trans*	equatorial	9.10	5.9

a) Measured in $CDCl_3$ at 10% (w/v) concentration: doublet.
b) from ref. 3*b*

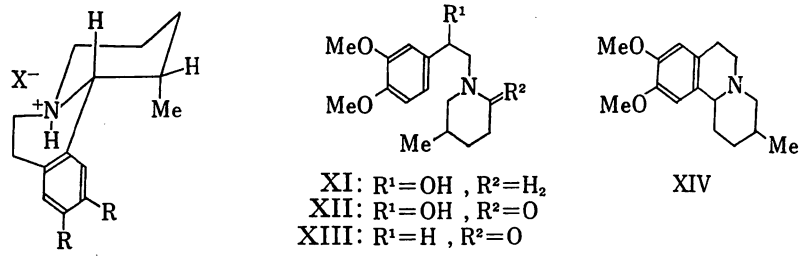
of the C-methyl doublet observed for VIIIa was larger than those of the equatorial C-methyl groups in Table III, in general agreement with the finding of Moynehan, *et al.*[10]

Of the reference compounds in Table III, free base XIV was synthesized from piperidone XIII[3b] by the Bischler-Napieralski reaction followed by catalytic reduction. That this free base is possibly a mixture of B/C *cis*- and B/C *trans*-conformers with the equatorial or axial C-methyl group was suggested by the Bohlmann's IR criterion[21] and the NMR spectrum in deuterated chloroform. It displayed a small signal (*ca.* 0.1H), heavily overlapped with those of the O-methyl protons, in the 6.0—6.2 τ region, a region where the angular protons of the *cis*-conformers may resonate.[16] The spectrum also showed the presence of two kinds of methyl groups as shown in Table III. Assignment of the orientation was based on the same criteria as those utilized by Moynehan, *et al.*[10] for monomethylquinolizidines. Comparison of the peak area of the two methyl groups indicated that conformers carrying the equatorial methyl group is predominant over those with the axial methyl group in a rough ratio of 7: 1.

The unsubstituted benzo[α]quinolizidine enamine (Vb) was similarly prepared from IVb[14a] and methylated to yield a 1.2: 1 mixture of the N-methylated product (VIb: X=I) and the C-methylated product (VIIb: X=I). The occurrence of the C-methylation in enamines Va and Vb to a greater extent than that[23] of the simple quinolizidine enamine (XVIII) may be ascribed to the effect of the rigid, planar aromatic ring by the analogy with the exclusive C-methylation of dihydroberberine.[23b] Catalytic hydrogenation of a mixture of VIb (X=ClO_4) and VIIb (X=ClO_4), obtained from the mixture of the iodide salts, over Adams catalyst and after-treatment of the reduced products gave a 2.7: 1 mixture of the *cis*- (IIb: X=I) and the *trans*-methiodide (IIIb: X=I), from which the latter could be isolated in a pure state, together with the 1-methyl derivative (VIIIb) whose spectral data (Table III) were similar to those of VIIIa. The NMR spectrum of the perchlorate (Xb: X=ClO_4) of VIIIb in deuterated dimethyl sulfoxide revealed a doublet-of-doublets (J=10.5 and 3 Hz, $C_{(11b)}$–H) at 5.37 τ, which turned a doublet with J=3 Hz on addition of D_2O, indicating that N^+–H and $C_{(11b)}$–H are *trans* diaxial to each other and that $C_{(1)}$–H is *gauche* to the latter, hence the C-methyl group is axial as depicted in Chart 2. If the protonation does not alter the B/C ring stereochemistry originally present in free base VIIIb, this finding would serve as an additional evidence for the stereostructures assigned to VIIIa and VIIIb.

As an aid in our efforts to account for the observed inversion or decrease in stereoselectivity of the quaternization or the hydrogenation in the benzo[*a*]quinolizidine series, the reactions

23) *a*) N.J. Leonard, A.S. Hay, R.W. Fulmer, and V.W. Gash, *J. Am. Chem. Soc.*, 77, 439 (1955); *b*) M.G. Reinecke and L.R. Kray, *J. Org. Chem.*, **30**, 3671 (1965), and references cited.



Xa : R=OMe
Xb : R=H

XI: $R^1=OH$, $R^2=H_2$
XII: $R^1=OH$, $R^2=O$
XIII: $R^1=H$, $R^2=O$

XIV

Chart 2

were extended to the simple quinolizidine system as shown in Chart 3. In the quaternization of base XXVI with methyl iodide, the previously reported exclusive formation[10] of the *trans*-fused methiodide (XXI) was confirmed also in our hands. Repetition of the known reaction sequence XVIII→XIX→XX revealed that the catalytic reduction at the second step is also highly stereoselective as reported previously,[11] but with the formation (10%) of the *trans*-fused salt (XXI). The result was interpreted in terms of hydrogenation of XIX at the least hindered face.[11] The same may be applied to the corresponding step (VI→II+III) in the

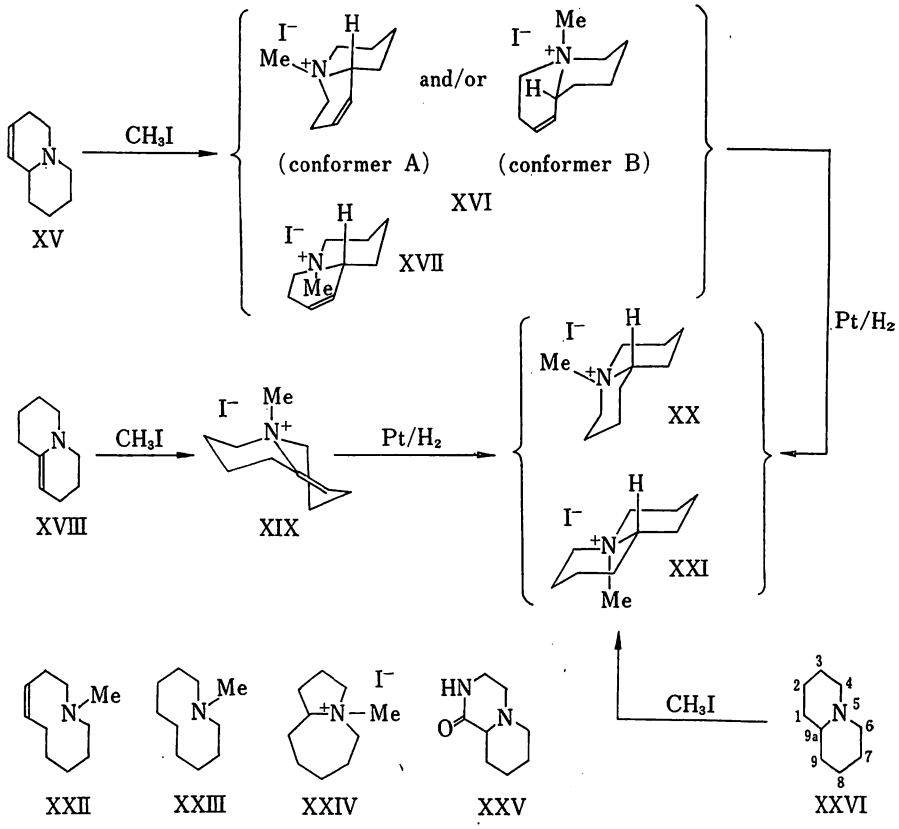


Chart 3

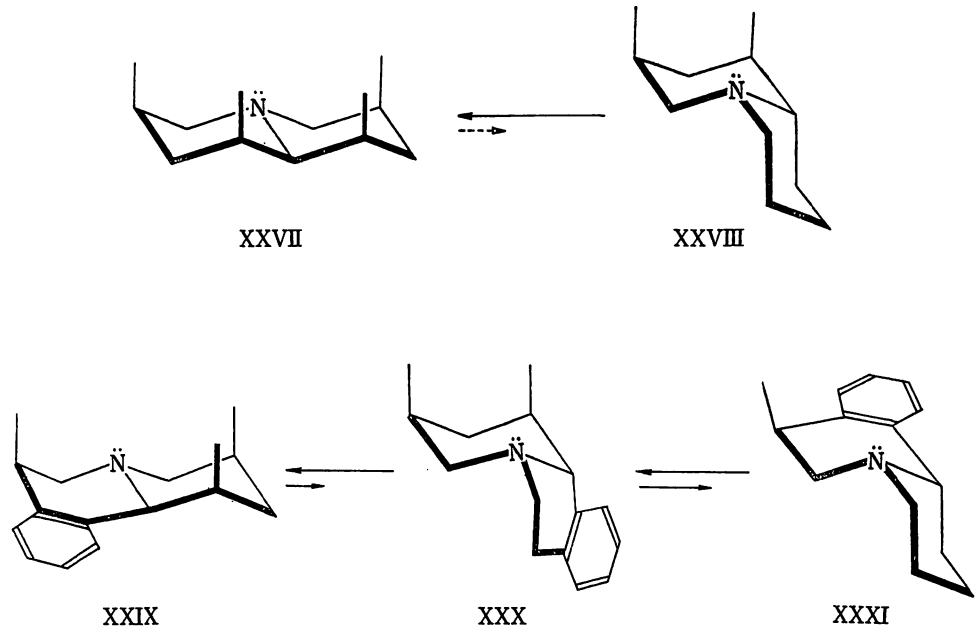


Chart 4

benzo[*a*]quinolizidine series. In this case, however, the fusion of the aromatic ring results in the removal of the stereochemically important axial $C_{(2)}$-hydrogen of the original ring system (XIX) and causes ring B to become flatter than the corresponding ring of XIX. This may be the reason for the lowered stereoselectivity, *e.g.*, IIa (X=I): IIIa (X=I)=2.8: 1, in the hydrogenation of VI.

When treated with methyl iodide, the β,γ-unsaturated quinolizidine (XV)[23a,24] gave a 1:1 mixture of the *cis*- (XVI) and the *trans*-methiodide (XVII), from which the former could be isolated but only in a state not completely free from the latter. Although the assignment of their B/C ring stereochemistry shown in Table I was based on the argument described before, it was further assured by the catalytic hydrogenation of a sample of XVII containing a little XVI, which led to a mixture of XXI and XX. In this reduction, the possibly competitive hydrogenolysis of the methiodides at the central C–N bond appeared not to occur to any appreciable extent since none of the possible by-products, XXII·HI, XXIII·HI, and XXIV, were NMR spectroscopically detectable in the reaction mixture.

Probably the most striking aspect of the quaternization of the quinolizidine system is that the stereoselectivity is profoundly influenced by β,γ-unsaturation with respect to the nitrogen in favor of the formation of the *cis*-fused quaternary salt. Although all free bases (Ia,b, XV) exhibit Bohlmann bands[21] in their IR spectra, that alone does not disprove the coexistence of the two possible *cis*-conformers with which the *trans*-conformer equilibrates by very rapid inversion[12b] as illustrated in Chart 4. In the case of quinolizidine (XXVI) itself the equilibrium constant, K=[XXVII]/[XXVIII], has been estimated to be 1600 at 25°,[13a] hence even the faster methiodide formation of the *cis*-conformer (XXVIII) than that of the *trans*-conformer (XXVII)[13a] can not produce any measurable amount of the *cis*-fused methiodide (XX). In the cases of the unsaturated systems (Ia,b, XV), however, the ring into which the unsaturation is introduced becomes flatter and loses 1,3-diaxial repulsion between the lone pair and the axial hydrogen originally present at the 1-position, and this

24) T. Miyadera and Y. Kishida, *Tetrahedron*, 25, 397 (1969).

would increase the population of the two *cis*-conformers (types XXX and XXXI) and facilitate especially the methiodide formation of the *cis*-conformer of a XXXI-type.

It is also particularly noteworthy that the stereoselectivity in the methiodide formation of the benzo[*a*]quinolizidine system (I) is rather higher than that of the simply unsaturated system (XV). At present it is as yet uncertain whether this is attributed purely to the capability of the rigid, planar aromatic ring in reducing the flexibility of the quinolizidine moiety more than the simple double bond, and further work is needed to define kinetically the role of such unsaturation.

Experimental[25]

***cis*- and *trans*-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-5-methyl-2*H*-benzo[*a*]quinolizinium Iodide [IIa (X=I) and IIIa (X=I)]**——i) By Quaternization: A mixture of free base Ia[3a,4,15,20b] (2.24 g, 9.06 mmoles) and methyl iodide (18.2 g, 128 mmoles) was heated under reflux for 5 hr. The excess of methyl iodide was removed by evaporation under diminished pressure. The resulting yellowish solid was washed with ether and dried to give the crude methiodide (3.49 g, 99%), mp 227—231° (decomp.) (lit.[4] mp 236°), which was shown to be a 3.3: 1 mixture of IIa (X=I) and IIIa (X=I) by NMR spectroscopy (see Theoretical part). The crude salt was triturated with H_2O (50 ml) and an insoluble solid was collected by filtration. Eight recrystallizations of the sparingly soluble solid from H_2O yielded the *trans*-methiodide (IIIa: X=I) (*β*-methiodide[4]) as colorless rosettes of needles, mp 247—247.5° (decomp.) [lit.[4] mp 244—245° (corr.)]; UV $\lambda_{max}^{H_2O}$ nm (ε): 227 (20500), 283 (3300); NMR (see Tables I and II). *Anal.* Calcd. for $C_{16}H_{24}O_2NI$: C, 49.37; H, 6.21; N, 3.60. Found: C, 49.50; H, 6.28; N, 3.64.

The mother liquor from the trituration of the crude salt with H_2O was evaporated *in vacuo* to dryness, and the resulting solid was recrystallized four times from H_2O, giving the *cis*-methiodide (IIa: X=I) (*α*-methiodide[4]) as colorless scales, mp 229—230° (decomp.) [lit.[4] mp 228° (corr.)]; UV $\lambda_{max}^{H_2O}$ nm (ε): 227 (20700), 283 (3500); NMR (see Tables I and II). *Anal.* Found: C, 49.24; H, 6.21; N, 3.64.

When determined UV spectrophotometrically, the *cis*-methiodide (IIa: X=I) was 3.38 times more soluble in H_2O at 20° than the *trans*-methiodide (IIIa: X=I).

ii) By Hydrogenation of VIa (X=I): A solution of VIa (X=I) (500 mg, 1.29 mmoles) in H_2O (160 ml) was hydrogenated over Adams catalyst (180 mg) at room temperature and atmospheric pressure for 50 hr. Removal of the catalyst by filtration and evaporation of the filtrate left a pale yellowish solid, which was shown NMR spectroscopically to be a 2.8: 1 mixture of IIa (X=I) and IIIa (X=I). Repeated recrystallizations of the solid from H_2O produced colorless needles, mp 247° (decomp.), identical (by mixed melting-point test and UV, IR, and NMR spectra) with the sample of IIIa (X=I) obtained by method-(i).

***cis*- and *trans*-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-5-methyl-2*H*-benzo[*a*]quinolizinium Perchlorate [IIa (X=ClO_4) and IIIa (X=ClO_4)]**——Prepared by dissolving a small sample of IIa (X=I) or IIIa (X=I) in warm H_2O and adding 15% aq. NH_4ClO_4. The resulting precipitates were filtered off and recrystallized from H_2O. The *cis*-methoperchlorate (IIa: X=ClO_4) was obtained as colorless prisms, mp 222.5—223° (decomp.); NMR (Tables I and II). *Anal.* Calcd. for $C_{16}H_{24}O_6NCl$: C, 53.11; H, 6.69; N, 3.87. Found: C, 52.90; H, 6.73; N, 3.92. The *trans*-methoperchlorate (IIIa: X=ClO_4) crystallized in colorless needles, mp 194.5—195.5° (decomp.); NMR (Tables I and II). *Anal.* Found: C, 53.43; H, 6.79; N, 3.97.

***cis*- and *trans*-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-5-methyl-2*H*-benzo[*a*]quinolizinium Picrate {IIa [X=2,4,6-$(NO_2)_3C_6H_2O$] and IIIa [X=2,4,6-$(NO_2)_3C_6H_2O$]}**——Each of IIa (X=I) and IIIa (X=I) was dissolved in H_2O with slight warming, and a saturated solution of picric acid in H_2O was added. The resulting precipitates were filtered off and recrystallized from H_2O. The *cis*-methopicrate crystallized in yellow needles, mp 207—207.5° (decomp.). *Anal.* Calcd. for $C_{22}H_{26}O_9N_4$: C, 53.87; H, 5.34; N, 11.42. Found: C, 53.69; H, 5.25; N, 11.63. The *trans*-methopicrate was produced as yellow needles, mp 189—191° (decomp.). *Anal.* Found: C, 53.81; H, 5.46; N, 11.24.

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25) All melting points are corrected; boiling points, uncorrected. Spectra reported herein were determined with a Hitachi EPS-2U UV spectrophotometer, a JASCO-DS-402G or a JASCO-IRA-2 IR spectrophotometer, a JEOL-JMS-01SG mass spectrometer, or a Varian HA-100, a JEOL-JNM-PS-100, or a JEOL-JNM-C-60H NMR spectrometer using tetramethylsilane as an internal standard. For gas–liquid chromatography (GLC) a Shimadzu GC-3AH gas chromatograph, equipped with a 1.5 m×3 mm column containing 1.5% SE-30 (methyl silicone) on Chromosorb W, was used. The following abbreviations are used: b=broad, d=doublet, DMSO=dimethyl sulfoxide, m=multiplet, q=quartet, s=singlet, t=triplet.

We are indebted to Mr. Y. Itatani and Misses S. Toyoshima, T. Tsuji, and H. Hyuga at Kanazawa University for microanalyses and NMR and mass spectral data.

***cis*-1,3,4,6,7,11b-Hexahydro-5-methyl-2*H*-benzo[*a*]quinolizinium Iodide (IIb: X=I)**——A solution of base Ib[14,15] (1.93 g, 10.3 mmoles) and methyl iodide (9.31 g, 65.6 mmoles) in methanol (5 ml) was refluxed for 5 hr. The excess of methyl iodide and methanol were evaporated to dryness *in vacuo*, and the resulting light brown solid was washed with ether and dried to yield the crude methiodide (3.36 g, 99%), mp 149—175°, which was shown to be a 3.6: 1 mixture of IIb (X=I) and IIIb (X=I) by NMR spectroscopic determination similar to that employed for the crude methiodide derived from Ia. The IR spectrum of this solid in chloroform was virtually identical with that of a sample prepared by mixing pure samples of IIb (X=I) and IIIb (X=I) in a ratio of 3.6: 1. Recrystallization of the crude product from ethanol afforded the *cis*-methiodide (IIb: X=I) as colorless, minute needles, mp 188—189°; NMR (Tables I and II). *Anal.* Calcd. for $C_{14}H_{20}NI$: C, 51.08; H, 6.12; N, 4.25. Found: C, 50.88, H, 5.98; N, 3.97. Efforts to isolate the *trans*-fused salt (IIIb: X=I) from the mother liquor from the first recrystallization of the crude product were in vain.

Thermal Conversion of IIa (X=I) into IIIa (X=I)——A small sample (100 mg) of IIa (X=I) was heated in a stream of nitrogen in an oil bath kept at 245—253° for 10 min. After cooling, the resulting brown solid was dissolved in trifluoroacetic acid. In the NMR spectrum of this solution, the quaternary N-methyl signal of IIa (X=I) at 6.76 τ almost completely disappeared and a large singlet at 6.98 τ attributable to the N-methyl signal of IIIa (X=I) became visible. In a separate experiment, the crude product was recrystallized from H_2O to give colorless needles, mp 247° (decomp.), undepressed upon mixture with a sample of the *trans*-methiodide (IIIa: X=I). The IR spectra of both samples were also identical.

Thermal Conversion of IIb (X=I) into IIIb (X=I)——A small sample of IIb (X=I) was heated as described above for the isomerization of IIa (X=I). After cooling, the resulting dark solid was dissolved in DMSO-d_6 and the NMR spectrum of the solution was measured. Comparison of the area of two N-methyl singlets at 6.91 and 7.12 τ disclosed that the reaction mixture contained IIb (X=I) and IIIb (X=I) in a ratio of 2.7: 1.

9,10-Dimethoxy-5-methyl-3,4,6,7-tetrahydro-2*H*-benzo[*a*]quinolizinium Iodide (VIa: X=I)——First, quaternary iodide IVa[3a,4,15,20b] was directly converted into Va[20a] following a modified literature procedure:[20a] salt IVa (5.0 g, 13.4 mmoles) was dissolved in H_2O (65 ml) with application of heat. After cooling, 15% aq. NaOH was added under cooling until no further precipitates appeared. The resulting, faintly yellowish crystals (Va) were collected by filtration, washed with H_2O, and used immediately in the following methylation experiment.

The total amount of Va above was dissolved in ethanol (50 ml) and the solution was heated with stirring at 60—65° (bath temperature) for 1 hr with methyl iodide (10 g, 70 mmoles). Removal of the excess of methyl iodide and ethanol by vacuum distillation left a mixture of a brown oil and a yellow solid, which was shown NMR spectroscopically to contain VIa (X=I), NMR (DMSO-d_6) 6.81 τ (s, $N_{(5)}$–CH_3), and VIIa (X=I), NMR (DMSO-d_6) 8.71 τ (d, J=7 Hz, $C_{(1)}$–CH_3), in a ratio of 1.2: 1. The mixture was triturated with a little ethanol and an insoluble solid was collected by filtration to give the crude N-methylated product (3.27 g). Recrystallizations from 70% aq. ethanol furnished an analytical sample of VIa (X=I) (524 mg, 10% based on the salt IVa used) as colorless scales, mp 203—204° (decomp.); UV $\lambda_{max}^{H_2O}$ nm (ε): 219 (30500), 263 (14800), 300 (6100); IR ν_{max}^{Nujol} 1665 cm^{-1} (weak, C=C); NMR (DMSO-d_6) τ: 6.81 (3H, s, $N_{(5)}$–CH_3), 6.20 (6H, s, two CH_3O's), 3.30 (1H, unresolved q, $C_{(1)}$–H), 3.15 and 2.92 (1H each, s, aromatic protons). *Anal.* Calcd. for $C_{16}H_{22}O_2NI$: C, 49.62; H, 5.73; N, 3.62. Found: C, 49.83; H, 5.82; N, 3.84.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-1-methyl-2*H*-benzo[*a*]quinolizine (VIIIa)——i) From Va through VIIa (X=I): A stirred solution of Va,[20a] prepared from IVa[3a,4,15,20b] (1.31 g, 3.51 mmoles) as described above, and methyl iodide (15 g, 106 mmoles) in ethanol (40 ml) was heated in an oil bath kept at 50—60° for 2 hr. After evaporation of the excess of methyl iodide and ethanol, 30% aq. ethanol (80 ml) was added to the residue. An insoluble solid (VIa: X=I) was removed by filtration and the filtrate, which contained VIIa (X=I), was hydrogenated over Adams catalyst (150 mg) at room temperature and atmospheric pressure for 7.5 hr. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo* to leave a colorless solid, which was dissolved in H_2O (70 ml). The aq. solution was made strongly alkaline with NaOH pellets and extracted with ether. The ethereal extracts were concentrated, after being dried over KOH and anhyd. K_2CO_3, to dryness to leave a viscous, brown oil (465 mg), shown to be a mixture by three spots on a thin-layer chromatography (TLC) plate. The oil was chromatographed on a 50-g alumina column using hexane–ethyl acetate (3: 1, v/v) as eluent. Evaporation of the solvents from the earliest fractions left VIIIa (147 mg, 16% based on the salt IVa used) as colorless needles, mp 74—77°, identical (by TLC, IR spectrum, and mixed melting-point test) with an authentic sample obtained by method-(ii).

ii) From Piperidone IX: A solution of IX[3b] (2.0 g, 7.21 mmoles) and $POCl_3$ (15 ml) in abs. benzene (20 ml) was heated in an oil bath kept at 80—90° for 3 hr. The excess of $POCl_3$ and benzene were removed by evaporation under vacuum and the residue, after being washed with hexane, was dissolved in H_2O (80 ml). The aq. solution was washed with benzene, filtered through wet filter paper, and hydrogenated over Adams catalyst (200 mg) at room temperature and atmospheric pressure for 5 hr. When the filtered reaction mixture was concentrated to dryness *in vacuo*, a thick, brown oil was obtained. The oil was dissolved in H_2O (40 ml), and the aq. solution was made strongly alkaline with NaOH pellets and extracted with ether. The ethereal solution was dried over KOH and anhyd. K_2CO_3 and evaporated to leave VIIIa (1.34 g, 71% based on the piperidone IX used) as a colorless solid, mp 69—73°. It crystallized from hexane in colorless needles, mp

77—79°; UV $\lambda_{max}^{99\%EtOH}$ 285 nm (ε 3500); IR ν_{max}^{Nujol} 2745 cm^{-1}; IR $\nu_{max}^{CHCl_3}$ 2760 cm^{-1} (*trans*-quinolizidine ring);[21] NMR ($CDCl_3$) τ: 9.21 (3H, d, J=7 Hz, $C_{(1)}$–CH_3), 6.17 (6H, s, two CH_3O's), 3.49 and 3.39 (1H each, s, aromatic protons); Mass Spectrum *m/e*: 261 (M^+). *Anal.* Calcd. for $C_{16}H_{23}O_2N$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.76; H, 8.89; N, 5.61.

The hydriodide (Xa: X=I) of VIIIa was obtained as colorless scales (from H_2O), mp 217—220° (decomp.); NMR (DMSO-d_6) τ: 9.15 (3H, d, J=7 Hz, $C_{(1)}$–CH_3), 6.23 (6H, two CH_3O's), 5.35 (1H, b, $C_{(11b)}$–H), 3.17 (2H, aromatic protons). *Anal.* Calcd. for $C_{16}H_{24}O_2NI$: C, 49.37; H, 6.21; N, 3.60. Found: C, 49.30; H, 6.26; N, 3.66.

3,4,6,7-Tetrahydro-2*H*-benzo[*a*]quinolizine (Vb)——To a chilled solution of IVb[14a] (3.24 g, 10.3 mmoles) in H_2O (12 ml) was added 15% aq. NaOH (*ca.* 5 ml) until no further separation of an oil was observed. The mixture was extracted with benzene, and the benzene solution was dried over anhyd. Na_2SO_4 for a while and concentrated to dryness *in vacuo* to leave an unstable, brownish oil, which was immediately used in the following methylation.

Methylation of Vb——A stirred solution of the total amount of Vb above and methyl iodide (24 g, 169 mmoles) in methanol (25 ml) was heated in an oil bath kept at 55—60° for 5 hr. The mixture was concentrated to dryness *in vacuo* and the residue was dissolved in H_2O (40 ml). After being washed with benzene, the aq. solution was evaporated to dryness *in vacuo* to give an oily methylated product (2.94 g), presumed to contain VIb (X=I) and VIIb (X=I). The crude product resisted hydrogenation using Adams catalyst.

Hydrogenation of VIb and VIIb: Isolation of *trans*-1,3,4,6,7,11b-Hexahydro-5-methyl-2*H*-benzo[*a*]-quinolizinium Iodide (IIIb: X=I) and 1,3,4,6,7,11b-Hexahydro-1-methyl-2*H*-benzo[*a*]quinolizine (VIIIb)——A portion (1.21 g) of the crude mixture of VIb (X=I) and VIIb (X=I) described above was dissolved in H_2O (50 ml) and a solution of $AgClO_4$ (920 mg, 4.44 mmoles) in H_2O (5 ml) was added. The precipitates (AgI) that resulted were collected by filtration and washed with hot H_2O (80 ml). The filtrate and washings were combined and hydrogenated over Adams catalyst (100 mg) at room temperature and atmospheric pressure for 6 hr. The catalyst was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The residue was dried to give an oily mixture of perchlorates (1.18 g), whose NMR spectrum in DMSO-d_6 [τ: 9.17 (d, J=7.5 Hz, $C_{(1)}$–CH_3), 7.14 (s, *trans*-$N_{(5)}$–CH_3), 6.90 (s, *cis*-$N_{(5)}$–CH_3)] suggested that it contained the two N-methylated products [IIb (X=ClO_4) and IIIb (X=ClO_4)] and the C-methylated product (Xb: X=ClO_4) in a ratio of 1.2: 1 and that the ratio of IIb (X=ClO_4) to IIIb (X=ClO_4) was approximately 2.7 to 1.

The hydrogenation product (3.49 g) from repeated preparations on the scale shown above was dissolved in H_2O (220 ml) and 10% aq. NaOH (8 ml) was added. The resulting oil was extracted with benzene and the benzene solution was dried over anhyd. Na_2SO_4 and evaporated to dryness *in vacuo* to leave a brown oil (1.32 g), shown to be a mixture by two spots on a TLC plate. The oil was chromatographed on a 130-g alumina column using hexane–benzene (2: 1, v/v) as eluent. An oil (707 mg) from earlier fractions was further purified by vacuum distillation to furnish VIIIb (623 mg) as a pale yellowish oil, bp 97—98° (1 mm Hg); IR ν_{max}^{film} 2752 cm^{-1}; IR $\nu_{max}^{CHCl_3}$ 2759 cm^{-1} (*trans*-quinolizidine ring);[21] NMR (Table III); Mass Spectrum *m/e*: 201 (M^+), 186 (M^+-CH_3).

The perchlorate (Xb: X=ClO_4) was prepared by dissolving a small sample (186 mg) of the free base (VIIIb) in ethanol (10 ml) and adding 70% aq. $HClO_4$ (250 mg) followed by ether (40 ml). Recrystallization from ethanol gave almost colorless prisms, mp 145—146°; NMR (DMSO-d_6) τ: 9.16 (3H, d, J=7.5 Hz, $C_{(1)}$–CH_3), 8.15 (4H, m, $C_{(2)}$- and $C_{(3)}$-protons), 6.2—7.3 (m, $C_{(1)}$–H, $C_{(4)}$–, $C_{(6)}$–, and $C_{(7)}$–protons), 5.37 (1H, d–d, J=10.5 and 3 Hz, turned d with J=3 Hz on addition of D_2O, $C_{(11b)}$–H), 2.75 (4H, m, aromatic protons), 0.9—1.6 (1H, very b, disappeared on addition of D_2O, $N_{(5)}$–H).

On the other hand, the aq. layer from the extraction of free base VIIIb, described above, was acidified with 10% aq. HCl (10 ml) and evaporated to dryness *in vacuo*. The residue was triturated with ethanol (70 ml) and an insoluble solid was removed by filtration. The filtrate was concentrated to dryness *in vacuo* and the residue was dissolved in H_2O (150 ml) with warming (50°). The aq. solution was saturated with KI and extracted with chloroform. The chloroform solution was dried over anhyd. Na_2SO_4 and evaporated to dryness *in vacuo* to yield an orange oil, which solidified on trituration with ether, giving crude IIIb (X=I) (1.49 g), mp 176—189° (decomp.). An analytical sample crystallized from ethanol in colorless, minute needles, mp 201—202.5° (decomp.); NMR (Tables I and II). *Anal.* Calcd. for $C_{14}H_{20}NI$: C, 51.08; H, 6.12; N, 4.25. Found: C, 51.18; H, 5.95; N, 4.38.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-3-methyl-2*H*-benzo[*a*]quinolizine (XIV)——This base was prepared from piperidone XIII[3b] in 83% yield following a procedure similar to that described under method (ii) in the preparation of VIIIa and obtained as a colorless oil, IR $\nu_{max}^{CHCl_3}$ 2762 cm^{-1} (*trans*-quinolizidine ring);[21] NMR (Table III); Mass Spectrum *m/e*: 261 (M^+). The oil was unstable and turned reddish brown on standing

Quaternization of XXVI with Methyl Iodide——The reaction was carried out in a similar manner to that reported:[10] a solution of quinolizidine (XXVI)[26] (100 mg, 0.72 mmole) and methyl iodide (1 ml) in ethanol (2 ml) was heated at 52—58° (bath temperature) for 30 min. The excess of methyl iodide and ethanol were

26) *a*) V. Boekelheide and S. Rothchild, *J. Am. Chem. Soc.*, 71, 879 (1949); *b*) S. Ohki and Y. Noike, *Yakugaku Zasshi*, 72, 490 (1952); *c*) Y. Arata, T. Shioda, J. Yamada, and Y. Hayashi, *ibid.*, 89, 389 (1969)

removed by evaporation under diminished pressure, leaving a straw-colored solid (190 mg, 94%). The NMR spectrum of this crude product in DMSO-d_6 showed a singlet at 7.01 τ (*trans*-$N_{(5)}$-CH_3) and a very small singlet at 6.81 τ (possibly *cis*-$N_{(5)}$-CH_3). The area of the latter was only 2—3% of the former. Recrystallization of the crude solid from ethanol yielded an analytical sample of XXI as colorless prisms, mp 314—315° (decomp.) [lit.[10] mp 320° (decomp.)]; NMR (Table I). *Anal.* Calcd. for $C_{10}H_{20}NI$: C, 42.72; H, 7.17; N, 4.98. Found: C, 42.89; H, 7.14; N, 5.15.

Hydrogenation of XIX——The procedure used here followed that of Schofield and Wells:[11b] methiodide XIX[11b,23a] (380 mg, 1.35 mmoles), mp 229—230° (decomp.) [lit.[11b] mp 230—232° (decomp.)]; NMR (DMSO-d_6) τ: 6.69 (3H, s, $N_{(5)}$-CH_3), 4.18 (1H, b, $C_{(9)}$-H), was hydrogenated in ethanol (25 ml) over Adams catalyst (50 mg) at room temperature and atmospheric pressure for 8.5 hr. When the filtered solution was concentrated to dryness *in vacuo*, a slightly yellowish solid (379 mg, 99%), mp 293—294° (decomp.), was obtained. The NMR spectrum of this sample in DMSO-d_6 indicated that it was a 9: 1 mixture of the *cis*- (XX) and the *trans*-methiodide (XXI). Recrystallization of the crude solid from ethanol gave an analytical sample of XX as colorless needles, mp 322—323° (decomp.) [lit.[11b] mp 332—336° (decomp.)]; NMR (Table I). *Anal.* Calcd. for $C_{10}H_{20}NI$: C, 42.72; H, 7.17; N, 4.98. Found: C, 42.85; H, 7.20; N, 5.00.

Thermal Isomerization of XX and XXI——A small sample of the *cis*-methiodide (XX) was heated in a sealed tube at 250° for 20 min. The NMR spectrum of the resulting, dark solid in DMSO-d_6 showed two N-methyl resonances at 6.81 τ (XX) and 7.01 τ (XXI). The relative area of both signals was 5.7 to 1. Under the same conditions the *trans*-methiodide (XXI) gave a 12.3: 1 mixture of XXI and XX.

1,3,4,6,7,9a-Hexahydro-2*H*-quinolizine (XV)——Prepared in 32% yield by the pyrolysis of 1-acetoxyquinolizidine according to the directions of Leonard, *et al.*,[23a] but the pyrolysis temperature was lowered to *ca.* 510°. For further purification, the free base (XV), bp 70—74° (18 mmHg), was converted into the picrate, which was recrystallized from ethanol to produce yellow flakes, mp 181—181.5° (decomp.) (lit. mp 178—179°;[23a] mp 182—183°[24]); NMR (pyridine-d_5) τ: 6.0—9.0 (13H, m, CH_2's and $C_{(9a)}$-H), 4.49 (1H, bd, J= 10.5 Hz, $C_{(9)}$-H), 4.21 (1H, d-m, J=10.5 Hz, $C_{(8)}$-H). *Anal.* Calcd. for $C_{15}H_{18}O_7N_4$: C, 49.18; H, 4.95; N, 15.30. Found: C, 49.32; H, 5.18; N, 15.24.

The purified picrate (1.22 g, 3.33 mmoles) was powdered and warmed at 50—60° for a while with 10% aq. HCl (30 ml). After cooling, the mixture was filtered to remove picric acid that deposited. The filtrate was thoroughly washed with benzene and concentrated to dryness *in vacuo*. The residue was dissolved in H_2O (10 ml) and 10% aq. NaOH (10 ml) was added. After being saturated with K_2CO_3, the mixture was extracted with benzene. The benzene solution was dried over anhyd. K_2CO_3 for 1 hr and evaporated *in vacuo* to leave XV (250 mg, 55%) as a slightly brownish oil, shown by GLC to be homogeneous; IR ν_{max}^{film} cm^{-1}: 3040 (HC=CH), 2750 (*trans*-quinolizidine ring),[21] 1660 (weak, C=C); NMR ($CDCl_3$) identical with that recorded.[24] The oil was immediately used in the next quaternization reaction.

The starting 1-acetoxy derivative was prepared by the reaction sequence described below. Condensation of ethyl 2-piperidinecarboxylate, prepared in 83% yield by the hydrogenation of ethyl 2-pyridinecarboxylate[27] in ethanol over Raney Ni at 100 atmospheric pressure and 60—70°,[28] with ethyl 4-bromobutyrate[29] was accomplished in a manner similar to that reported[30] but in benzene instead of acetone, giving ethyl 2-ethoxycarbonyl-1-piperidinebutyrate in 81% yield. The Dieckmann condensation of the diester and subsequent decarboxylation also followed the published procedure,[30] but sodium ethoxide for the cyclization was replaced by two equivalents of powdered sodium as employed earlier[31] and ether for extracting the product, by benzene. The resulting 1-ketoquinolizidine[23a,30,31] (68% yield) was reduced with $LiAlH_4$[23a] to produce 1-hydroxyquinolizidine (85%) as a mixture of two epimers.[13f,32] Treatment of the 1-hydroxy derivative with acetic anhydride[23a] gave 1-acetoxyquinolizidine[23a] (95%) as a mixture of two epimers,[13f] which was subjected to the pyrolysis described above.

Quaternization of XV with Methyl Iodide——A solution of base XV (250 mg, 1.82 mmoles) and methyl iodide (1.66 g, 11.7 mmoles) in methanol (1.2 ml) was heated at 50—60° (bath temperature) for 5 hr. The reaction mixture was evaporated to dryness *in vacuo* and the resulting orange solid was triturated with ether. An insoluble solid was collected by filtration to afford the crude product (492 mg, 97%), shown by NMR spectroscopy to be a 1: 1 mixture of the *cis*- (XVI) and the *trans*-methiodide (XVII). Recrystallizations from 2-propanol gave colorless prisms (XVI) having indefinite melting point, which were as yet contam-

27) R. Camps, *Arch. Pharm.*, **240**, 345 (1902).
28) The reaction conditions employed here were kindly suggested by Professor S. Yamada and Dr. T. Kunieda, University of Tokyo.
29) J. Lavety and G.R. Proctor, "Organic Syntheses," Coll. Vol. V, ed. by H.E. Baumgarten, John Wiley and Sons, New York, 1973, p. 545.
30) T. Kunieda, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 337 (1967).
31) G.R. Clemo and G.R. Ramage, *J. Chem. Soc.*, **1931**, 437.
32) *a*) H.S. Aaron, G.E. Wicks, Jr., and C.P. Rader, *J. Org. Chem.*, **29**, 2248 (1964); *b*) C.P. Rader, G.E. Wicks, Jr., R.L. Young, Jr., and H.S. Aaron, *ibid.*, **29**, 2252 (1964).

inated with a very small amount of XVII. NMR (Table I). *Anal.* Calcd. for $C_{10}H_{18}NI$: C, 43.02; H, 6.50; N, 5.02. Found: C, 42.90; H, 6.35; N, 5.26.

The mother liquor from the first recrystallization of XVI was concentrated to dryness. Recrystallizations of the residue from ethanol or 2-propanol failed to give a pure sample of XVII, but provided only a mixture of XVII and XVI in a variable ratio.

Hydrogenation of XVI and XVII——A 1.5: 1 mixture (55.6 mg, 0.199 mmole) of XVII and XVI was hydrogenated in ethanol (12 ml) over Adams catalyst (8.4 mg) at room temperature and atmospheric pressure for 10 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo* to leave a slightly yellowish solid (55 mg). Its NMR spectrum in DMSO-d_6 was virtually superimposable on that of a 1.5: 1 mixture of authentic XXI and XX. Any other peaks attributable to those of XXII·HI, XXIII·HI, and XXIV were undetected. The IR spectra of both mixtures were also identical.

Decahydro-1-methylazecine Hydriodide (XXIII·HI)——Prepared from the corresponding picrate[33] in the following manner: a mixture of the picrate (192 mg, 0.5 mmole) and 10% aq. HCl (10 ml) was shaken vigorously for 10 min. The mixture was extracted with benzene to remove picric acid. The aq. layer was saturated with KI and extracted with chloroform. The chloroform solution was dried over anhyd. Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was dissolved in ethanol (3 ml) and ether (15 ml) was added. The precipitates that resulted were filtered off and recrystallized in the same way as before, affording XXIII·HI (109 mg, 77%) as colorless scales, mp 156—158°; NMR (DMSO-d_6) τ: 8.0—8.7 (14H, m, C-CH_2-C's), 7.21 (3H, b s, HN^+-CH_3), 6.5—7.0 (b, NCH_2's), 6.70 (s, N^+-H). *Anal.* Calcd. for $C_{10}H_{22}NI$: C, 42.41; H, 7.83; N, 4.95. Found: C, 42.20; H, 7.65; N, 4.97.

1-Azabicyclo[5.3.0]decane Methiodide (XXIV)——The free base of 1-azabicyclo[5.3.0]decane required for this experiment was prepared by the method of Clemo and Ramage[31] and obtained as a pale yellow, unstable oil, bp 82° (18 mm Hg) [lit.[31] bp 43° (0.5 mm Hg); bp 75° (14 mm Hg)]; IR ν_{max}^{film} 2780 cm^{-1} (Bohlmann band[21]). The picrate from this oil crystallized from ethanol in yellow needles, mp 215—216° (decomp.) [lit. mp 213° (decomp.);[31] mp 216—217°[33]], identical with an authentic sample.[33]

To the free base (181 mg, 1.3 mmoles) above was added methyl iodide (2.28 g, 16 mmoles) with stirring under ice-cooling. After 30 min, the mixture was heated at reflux for 2 hr. The excess of methyl iodide was removed by evaporation under vacuum, and the resulting light brown solid was washed with ether to furnish the crude methiodide (352 mg, 96%), mp 233—238° (decomp.). Its NMR spectrum in DMSO-d_6 showed a small singlet at 7.12 τ (0.36H, tentatively attributable to *trans*-$N_{(1)}$-CH_3) and a large singlet at 6.92 τ (2.64H, tentatively attributable to *cis*-$N_{(1)}$-CH_3). Recrystallization of the crude product from acetone provided methiodide XXIV, presumed to have *cis*-fused ring, as colorless needles, mp 279—280° (decomp.) (lit. mp 283°;[31] mp 279—280°[34]); NMR (DMSO-d_6) τ: 7.45—8.72 (12H, m, C-CH_2-C's), 6.92 (3H, s, $N_{(1)}$-CH_3), 6.14—6.60 (5H, m, $N_{(1)}$-CH, $N_{(1)}$-CH_2's). When a small sample of XXIV was heated in a sealed tube at 250° for 10 min and the NMR spectrum of the resulting dark solid was measured in DMSO-d_6, a singlet at 7.12 τ was visible besides the $N_{(1)}$-CH_3 signal of XXIV. The relative area of the two signals was 1: 1.6. The appearance of the singlet at 7.12 τ is probably owing to the isomerization of XXIV to the *trans*-fused methiodide.

Acknowledgement We are pleased to acknowledge the support of our work by a Grant-in-Aid for Scientific Research (A-843031, to Professor Y. Yamamoto) from the Ministry of Education of Japan. We are also grateful to Emeritus Professor Dr. S. Sugasawa, University of Tokyo, and Professor Y. Ban, Hokkaido University, for their interest and warm encouragement and to Professor Y. Arata, Kanazawa University, for a generous gift of decahydro-1-methylazecine picrate and 1-azabicyclo[5.3.0]decane picrate.

33) Y. Arata, Y. Oda, S. Yasuda, and M. Hanaoka, *Chem. Pharm. Bull.* (Tokyo), 21, 2672 (1973).
34) N.J. Leonard and W.E. Goode, *J. Am. Chem. Soc.*, 72, 5404 (1950).