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Studies on 1-Azabicyclo Compounds. XXIV.¹⁾ Synthesis and Stereochemistry of 10-Ethyl-, 10-Vinyl-, and 10-Ethynyl-quinolizidine Methiodides

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On quaternization of 10-ethyl-, 10-vinyl-, and 10-ethynyl-quinolizidine with methyl iodide, the formation of the *cis* methiodide *vs.* the corresponding *trans* methiodide increased according to the order of the bulkiness of the 10-substituent as $\text{CH}_3\text{CH}_2 > \text{CH}_2=\text{CH} > \text{CH}\equiv\text{C}$. The stereochemistry of the above methiodides was established. The N^+ -methyl signals of the *cis* 10-substituted quinolizidine methiodides were confirmed to appear at higher field than those of the corresponding *trans* methiodides except for the 10-ethynyl methiodides in their nuclear magnetic resonance spectra.

It has been reported that the bulkier the 10-substituent became, the more the formation of the *cis* methiodide *vs.* the corresponding *trans* methiodide increased on quaternization of the 10-substituted quinolizidines such as 10-cyano-, 10-methyl-, 10-hydroxymethyl-, and 10-nitromethyl-quinolizidine with methyl iodide.³⁾ The present paper deals with the stereochemistry of the quaternization product of 10-ethyl-, 10-vinyl-, and 10-ethynyl-quinolizidine (III, V, and IV).

Reaction of $\Delta^{1,10}$ -dehydroquinolizidine perchlorate⁴⁾ (I) with ethynylmagnesium bromide⁵⁾ gave in 70% yield 10-ethynylquinolizidine (IV), which showed bands at 3160 ($\equiv\text{CH}$), 2760, 2670 (Bohlmann bands), and 2075 cm^{-1} ($\text{C}\equiv\text{C}$) in its infrared (IR) spectrum and a peak at m/e 163 (M^+) in its mass spectrum. The product (IV) was also obtained in 90% yield from 10-cyanoquinolizidine⁴⁾ (II) with ethynylmagnesium bromide.⁶⁾ Catalytic hydrogenation of IV with the Lindlar catalyst⁷⁾ in the presence of quinoline afforded 10-vinylquinolizidine (V) in 75% yield. The product showed bands at 2800, 2750, 2675 (Bohlmann bands), and 1625 cm^{-1} ($\text{C}=\text{C}$) in its IR spectrum and signals at 3.75 (d-d, $J=18$; 11.5 Hz, $\text{CH}=\text{CH}_2$), 4.70 (d-d, $J=11.5$; 1.5 Hz, $\text{H}^>\text{C}=\text{C}<\frac{\text{H}}{\text{H}}$), and 4.92 τ (d-d, $J=18$; 1.5 Hz, $\text{H}^>\text{C}=\text{C}<\frac{\text{H}}{\text{H}}$) in its nuclear magnetic resonance (NMR) spectrum.

The quaternization product of 10-ethylquinolizidine⁴⁾ (III), IR $\nu_{\text{max}}^{\text{liq}}$ cm^{-1} : 2790, 2750 (Bohlmann bands), with methyl iodide exhibited N^+ -methyl signals at 6.74 and 6.94 τ in its NMR spectrum. The measurement of the areas of both signals indicated that the product is a mixture of two isomeric methiodides (VI and VII) in the 2:9 ratio. Recrystallization of the product from ethanol gave the major methiodide (VII), mp 293–295° (decomp.), NMR τ : 6.94 (N^+-CH_3). The minor methiodide (VI) could not be isolated in a pure form. Quaternization of V with methyl iodide afforded a mixture of two isomeric methiodides (X and XI), NMR τ : 6.74 and 6.98 (N^+-CH_3), in the 4:9 ratio calculated from its NMR spectrum, from which the major methiodide (XI), mp 294–295° (decomp.), NMR τ : 6.98, was isolated by

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3) Y. Arata, T. Aoki, M. Hanaoka, and M. Kamei, *Chem. Pharm. Bull.* (Tokyo), **23**, 333 (1975).4) N.J. Leonard and A.S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956).5) E.R.H. Jones, L. Skattebøl, and M.C. Whiting, *J. Chem. Soc.*, **1956**, 4765.6) *cf.*, M.G. Reinecke and R.F. Francis, *J. Org. Chem.*, **37**, 3494 (1972).7) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

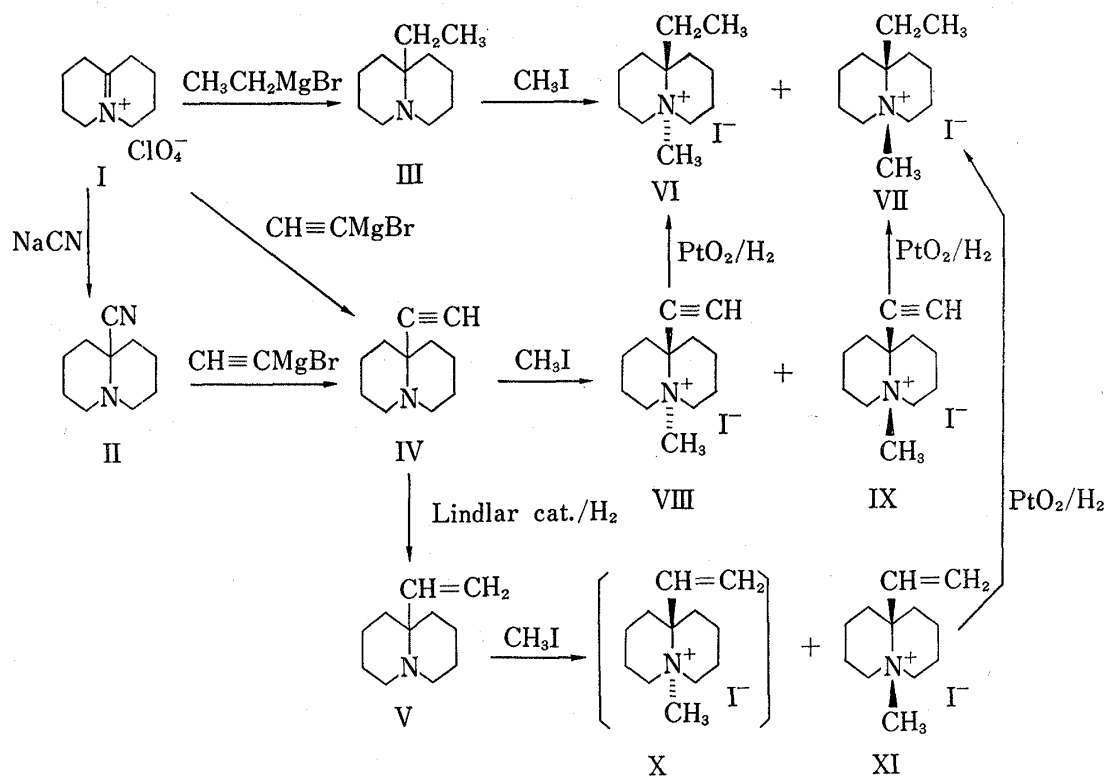


Chart 1

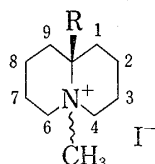
recrystallization from ethanol. Catalytic hydrogenation of XI gave 10-ethylquinolizidine methiodide which was identical with VII in IR spectra.

The N^+ -methyl signals of *cis* 10-substituted quinolizidine methiodides were previously found to appear at higher field than those of the corresponding *trans* methiodides except for the 10-cyano methiodides in their NMR spectra.³⁾ Therefore, the methiodides (VII and XI) could be assigned to be *cis* and the methiodides (VI and X), *trans* by comparison of the chemical shift of their N^+ -methyl signals.

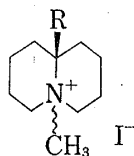
The product obtained by quaternization of IV with methyl iodide was fractionally recrystallized to afford two isomeric methiodides in the 15:2 ratio: the methiodide (VIII), mp 265–267° (decomp.), NMR τ : 6.81 (N^+-CH_3), and the methiodide (IX), mp 276–278° (decomp.), NMR τ : 6.66 (N^+-CH_3). Contrary to the other 10-substituted quinolizidine methiodides, the N^+ -methyl signal of the *trans* 10-ethynyl methiodide would be expected to appear at higher field than that of the *cis* methiodide because of the anisotropy of the ethynyl group similar to that of the cyano group.^{3,8)} The methiodide (VIII) would be, therefore, *trans* and the methiodide (IX), *cis*. In order to prove the above assignment, both the methiodides (VIII and IX) were hydrogenated over platonic oxide to provide the methiodide (VI), NMR τ : 6.74 (N^+-CH_3), and the methiodide (VII), NMR τ : 6.94 (N^+-CH_3), respectively. The methiodide (VII) thus obtained was identified with the *cis* methiodide derived from III by IR and NMR spectra.

The stereochemistry of all the methiodides assigned above was unequivocally established to be correct by the ^{13}C -NMR spectra³⁾ of VII and VIII as shown in Table I. The *trans* methiodide (VIII) exhibited four signals due to the ring carbons besides C-10 in its ^{13}C -NMR spectrum, as VIII has a plane of symmetry included $\text{HC}\equiv\text{C}-\text{C}^{10}-\text{N}^+-\text{CH}_3$ in its molecule.

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TABLE I. ^{13}C -NMR Spectral Data of *cis*-10-Ethyl- and *trans*-10-Ethynyl-quinolizidine Methiodide (VII and VIII)

Compound R	Chemical shift (ppm from TMS, in $\text{CF}_3\text{CO}_2\text{D}$)							Other signal
	C_1, C_9	C_2, C_8	C_3, C_7	C_4, C_6	C_{10}	N^+-CH_3		
VII CH_3CH_2 (<i>cis</i>)	27.33	19.02	21.66	59.02	74.39	47.99	18.71	(CH_2CH_3)
	31.60	21.66	26.01	63.21			27.33	(CH_2CH_3)
VIII $\text{CH}\equiv\text{C}$ (<i>trans</i>)	33.49	19.95	20.82	64.07	71.64	41.35	78.34	$(\text{C}\equiv\text{CH})$
							84.80	$(\text{C}\equiv\text{CH})$

TABLE II. NMR Spectral Data of N^+ -Methyl Signals of 10-Substituted Quinolizidine Methiodides and Their Quaternization Ratio of *trans* and *cis* Methiodides

Compound R	Chemical shift (τ , in D_2O)		Ratio <i>trans</i> : <i>cis</i>
	<i>trans</i>	<i>cis</i>	
CH_3CH_2	6.74	6.94	2:9
$\text{CH}_2=\text{CH}$	6.74	6.98	4:9
$\text{CH}\equiv\text{C}$	6.81	6.66	15:2
CH_3	6.83	6.97	1:1 ⁹⁾

As summarized in Table II, the formation of the *cis* methiodides *vs.* the corresponding *trans* methiodides increased according to the order of the bulkiness of the 10-substituent as $\text{CH}_3\text{CH}_2 > \text{CH}_2=\text{CH} > \text{CH}\equiv\text{C}$. And it was further confirmed that the N^+ -methyl signals of the *cis* 10-substituted quinolizidine methiodides appeared at higher field than those of the corresponding *trans* methiodides except for the methiodides with the 10-substituent having directly a triple bond.

Experimental⁹⁾

10-Ethynylquinolizidine (IV)—1) From I: To a solution of ethynylmagnesium bromide⁵⁾ (prepared from Mg (1.6 g), ethyl bromide (7.0 g) and acetylene) in tetrahydrofuran (THF) (45 ml) was added 1^{1,10}-dehydroquinolizidine perchlorate⁴⁾ (I, 3.0 g) in small portions and the reaction mixture was heated at 60–70° for 4 hr with stirring. The mixture was treated with H_2O (20 ml) and extracted with ether. The extract was dried over Na_2SO_4 and evaporated. The residue was distilled to give IV (1.4 g (70%)) as a colorless oil, bp 57–60°/25 mmHg, which was solidified on standing, mp 58–59°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3160 ($\equiv\text{CH}$), 2760, 2670 (Bohlmann bands), 2075 ($\text{C}\equiv\text{C}$). Mass Spectrum m/e : 163 (M^+), 162 ($\text{M}-1$), 134 (base peak).

9) Melting points and boiling points are uncorrected. All melting points were measured with a Yanagimoto Micro Melting Point Apparatus. IR spectra were measured with a Spectrophotometer IR-G, Japan Spectroscopic Co., NMR spectra with PS-100, Japan Electron Lab. Co., using sodium 2,2,3,3-tetradeutero-3-trimethylsilylpropionate (in D_2O) and tetramethylsilane (TMS) (in CDCl_3) as an internal standard, ^{13}C NMR spectra with PS-100-PF-100, Japan Electron Lab. Co., at 25.1 MHz using TMS as an internal standard in $\text{CF}_3\text{CO}_2\text{D}$, and mass spectra with JMS-01SG, Japan Electron Lab. Co.

2) From II: To a solution of ethynylmagnesium bromide⁵⁾ (prepared from Mg (1.2 g), ethyl bromide (7.0 g) and acetylene) in THF (45 ml) was added dropwise a solution of 10-cyanoquinolizidine⁴⁾ (II, 1.5 g) in THF (15 ml) and the reaction mixture was heated at 70–80° for 6 hr with stirring and treated in the same procedure as that described in 1) to give IV (1.3 g (90%)) which was identical with that obtained in 1) in IR spectra and thin-layer chromatographic behaviour.

10-Vinylquinolizidine (V)—10-Ethynylquinolizidine (IV, 150 mg) was hydrogenated in *n*-hexane (15 ml) over the Lindlar catalyst⁷⁾ (60 mg) in the presence of quinoline (60 mg) at atmospheric pressure and room temperature. After the theoretical amount of H₂ was uptaken, the catalyst was filtered off. The filtrate was evaporated and the residue was dissolved in 10% aq. NaH₂PO₄. The solution was washed with ether, made alkaline with 20% aq. NaOH and extracted with ether. The extract was dried over Na₂SO₄ and evaporated. The residue was distilled to give V (113 mg (74.5%)) as a colorless oil, bp 120–125° (bath temperature)/20 mmHg. IR $\nu_{\text{max}}^{\text{liq}}$ cm⁻¹: 2800, 2750, 2675 (Bohlmann bands), 1625 (C=C). NMR (CDCl₃) τ : 3.75 (1H, d-d, $J=18$; 11.5 Hz, CH=CH₂), 4.70 (1H, d-d, $J=11.5$; 1.5 Hz, $\text{H}^{\text{H}}\text{C}=\text{C}\langle\frac{\text{H}}{\text{H}}\rangle$), 4.92 (1H, d-d, $J=18$; 1.5 Hz, $\text{H}^{\text{H}}\text{C}=\text{C}\langle\frac{\text{H}}{\text{H}}\rangle$).

trans- and cis-10-Ethylquinolizidine Methiodide (VI and VII)—1) From III: A solution of 10-ethylquinolizidine⁴⁾ (III, 500 mg) and MeI (2.5 g) in MeOH (2 ml) was kept standing in a refrigerator for 24 hr. The precipitate was collected by filtration and recrystallized from EtOH to give the *cis* methiodide (VII, 499 mg), mp 293–295° (decomp.), as colorless cubes, NMR (D₂O) τ : 6.94 (3H, s, N⁺-CH₃), 7.78 (2H, broad, CH₂CH₃), 9.09 (3H, t, $J=8$ Hz, CH₂CH₃). Anal. Calcd. for C₁₂H₂₄NI: C, 46.60; H, 7.82; N, 4.52. Found: C, 46.81; H, 7.83; N, 4.80.

The filtrate and mother liquor of recrystallization were combined and evaporated *in vacuo* to give a mixture of the *trans* and *cis* methiodides (VI and VII, 453 mg), in the 5: 8 ratio, as a pale brown solid. NMR (D₂O) τ : 6.74 (15/13 H, s, N⁺-CH₃), 6.94 (24/13 H, s, N⁺-CH₃).

2) From VIII: The methiodide (VIII, 100 mg) was hydrogenated in MeOH (10 ml) over PtO₂ (35 mg) at atmospheric pressure and room temperature. After the theoretical amount of H₂ was uptaken, the catalyst was filtered off. The filtrate was evaporated *in vacuo* and the residue (96 mg) was recrystallized from EtOH to give the *trans* methiodide (VI, mp >300° (decomp.)), as a colorless cubes. NMR (D₂O) τ : 6.74 (3H, s, N⁺-CH₃), 7.76 (2H, q, $J=7$ Hz, CH₂CH₃), 9.09 (3H, t, $J=7$ Hz, CH₂CH₃). Anal. Calcd. for C₁₂H₂₄NI: C, 46.60; H, 7.82; N, 4.52. Found: C, 46.27; H, 7.68; N, 4.81.

3) From IX: The methiodide (IX, 100 mg) was hydrogenated in MeOH (10 ml) over PtO₂ (35 mg) at atmospheric pressure and room temperature. The reaction mixture was treated in the same procedure as that described in 2) to give the *cis* methiodide (VII, 95 mg), which was identical with VII obtained in 1) in IR and NMR spectra.

4) From XI: The methiodide (XI, 10 mg) was hydrogenated in MeOH (5 ml) over PtO₂ (10 mg) at atmospheric pressure and room temperature. The reaction mixture was treated in the same procedure as that described in 2) to give the *cis* methiodide (VII, 9 mg), which was identical with VII obtained in 1) in IR spectra.

trans- and cis-10-Ethynylquinolizidine Methiodide (VIII and IX)—A solution of IV (500 mg) and MeI (4.5 g) in MeOH (4 ml) was refluxed for 5 hr and evaporated *in vacuo*. The residue was recrystallized from H₂O to give the *cis* methiodide (IX, 106 mg), mp 276–278° (decomp.), as colorless plates. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3190 ($\equiv\text{CH}$), 2100 (C \equiv C). NMR (D₂O) τ : 6.66 (3H, s, N⁺-CH₃). Anal. Calcd. for C₁₂H₂₀NI: C, 47.22; H, 6.60; N, 4.58. Found: C, 47.13; H, 6.47; N, 4.55.

The mother liquor was evaporated *in vacuo* and the residue was recrystallized from H₂O to give the *trans* methiodide (VIII, 795 mg), mp 265–267° (decomp.), as colorless plates. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3180 ($\equiv\text{CH}$), 2100 (C \equiv C). NMR (D₂O) τ : 6.81 (3H, s, N⁺-CH₃). Anal. Calcd. for C₁₂H₂₀NI: C, 47.22; H, 6.60; N, 4.58. Found: C, 47.21; H, 6.40; N, 4.80.

trans- and cis-10-Vinylquinolizidine Methiodide (X and XI)—A solution of V (265 mg) and MeI (2 g) in MeOH (1 ml) was kept standing in a refrigerator for 20 hr. The reaction mixture was evaporated *in vacuo* to give a mixture of the *trans* and *cis* methiodides (X and XI, 456 mg), in the 4: 9 ratio, as a pale brown solid. NMR (D₂O) τ : 6.74 (12/13 H, s, N⁺-CH₃), 6.98 (27/13 H, s, N⁺-CH₃). The mixture was recrystallized from EtOH to give the *cis* methiodide (XI, 251 mg), mp 294–295° (decomp.), as colorless needles. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1635 (C=C). NMR (D₂O) τ : 6.98 (3H, s, N⁺-CH₃), 4.48 (1H, d, $J=17$ Hz, $\text{H}^{\text{H}}\text{C}=\text{C}\langle\frac{\text{H}}{\text{H}}\rangle$), 4.40 (1H, d, $J=11$ Hz, $\text{H}^{\text{H}}\text{C}=\text{C}\langle\frac{\text{H}}{\text{H}}\rangle$), 3.40 (1H, d-d, $J=17$; 11 Hz, CH=CH₂). Anal. Calcd. for C₁₂H₂₂NI: C, 46.92; H, 7.22; N, 4.56. Found: C, 46.87; H, 7.18; N, 4.61.

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