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Studies on Antispasmodics. I. Synthesis and Anticholinergic Activity of 1-, 2-, and 3-Diarylmethylenequinolizidine Quaternary Ammonium Salts[1]

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As part of a search for new antispasmodic agents, we have synthesized 1-, 2-, and 3-diarylmethylenequinolizidine quaternary ammonium salts (**4**—**15**), which can be regarded as conformationally rigid derivatives of diphemanil methylsulfate (**1**) or timepidium bromide (**2**). The Grignard reaction of ethoxycarbonylquinolizidines (**16**, **21**, and **30**) with phenyllithium or 2-thienylmagnesiumbromide, followed by dehydration, afforded diarylmethylenequinolizidines (**19**, **20**, **24**, **25**, **33**, and **34**). Quaternization of the 1-substituted derivatives (**19** and **20**) with methyl bromide afforded only the *cis* methobromides (**4** and **6**). On similar treatment, the 2-substituted derivatives (**24** and **25**) each afforded two isomeric methobromides, the *trans* (**8a** and **9a**) and *cis* (**8b** and **9b**), and the 3-substituted derivatives also afforded *trans* (**12a** and **13a**) and *cis* methobromides (**12b** and **13b**). The stereochemistry of these methobromides was confirmed by thermal isomerization experiments and the chemical shifts of N^+-methyl signals in the ^1H- and ^{13}C-nuclear magnetic resonance spectra. The quaternary ammonium salts (**4**—**15**) exhibited more potent anticholinergic activity than **1** and **2**, and the activities of several compounds (**8**, **9**, and **13**) were equal to or greater than that of atropine. The structure–activity relationships of these compounds are discussed.

Keywords——antispasmodics; anticholinergic activity; conformationally rigid derivatives; diarylmethylenequinolizidine; diarylmethylenequinolizidine quaternary salts; stereochemistry; ^{13}C-NMR; structure–activity relationships

A number of synthetic antispasmodics have so far been developed and used clinically. These drugs are characterized by their structures, which contain a quaternary nitrogen connected through a suitable length of methylene chain with a functional group such as an ester, a ketal, an olefin, an alcohol, or an amide, with aromatic rings in the vicinity. Agents possessing an ester group have been found to be labile, due to ester hydrolysis.[3a-e]

In order to develop new and chemically stable antispasmodics, studies of compounds containing a double bond seem promising. As compounds of this type, diphemanil methylsulfate (**1**),[4] timepidium bromide (**2**),[5] and prifinium bromide (**3**),[6a] are already on the

1) A part of this work was presented at the 98th Annual Meeting of Pharmaceutical Society of Japan, Okayama, April 1978.

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3) *a*) H. Nogami, M. Horioka, S. Awazu, and H. Yamada, *Chem. Pharm. Bull.* (Tokyo), **6**, 277 (1958); *b*) H. Nogami and N. Nakajima, *ibid.*, **6**, 283 (1958); *c*) M. Horioka, T. Aoyama, K. Takano, T. Maeda, and K. Shirahama, *Yakuzaigaku*, **34**, 16 (1974); *d*) T. Aoyama, T. Maeda, and M. Horioka, *Chem. Pharm. Bull.* (Tokyo), **25**, 3376 (1977); *e*) M. Horioka, T. Aoyama, and H. Karasawa, *ibid.*, **25**, 175 (1977).

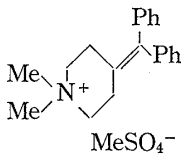
4) N. Sperber, *J. Am. Chem. Soc.*, **73**, 5010 (1951).

5) N. Kawazu, T. Kanno, S. Saito, and H. Tamaki, *J. Med. Chem.*, **15**, 914 (1972).

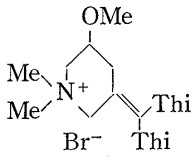
6) *a*) S. Ohki, Japan. Patent 22462 (1965); *b*) S. Ohki, F. Hamaguchi, T. Yanagi, and M. Yoshino, *Chem. Pharm. Bull.* (Tokyo), **14**, 187 (1966); *c*) M. Hitomi, H. Nojima, and S. Uchida, *Nippon Yakurigaku Zasshi*, **62**, 427 (1966); *d*) S. Ohki and M. Yoshino, *Chem. Pharm. Bull.* (Tokyo), **16**, 269 (1968); *e*) S. Ohki, M. Yoshino, and F. Hamaguchi, *ibid.*, **16**, 320 (1968); *f*) S. Ohki, *Yuki Gosei Kagaku Kyokai Shi*, **30**, 1 (1972); *g*) S. Ohki, N. Ozawa, Y. Yabe, and H. Matsuda, *Chem. Pharm. Bull.* (Tokyo), **24**, 1362 (1976); *h*) N. Ozawa, H. Matsuda, Y. Yabe, and S. Ohki, *ibid.*, **24**, 1371 (1976); *i*) S. Ohki, Y. Yabe, N. Ozawa, and F. Hamaguchi, *Yakugaku Zasshi*, **96**, 952 (1976).

market, and all of them possess a monocyclic hetero ring, *i.e.* piperidine or pyrrolidine, substituted with a diarylmethylene group. The structure-activity relationships of **3** have been studied in detail by Ohki *et al.*[6b-i] They reported that the introduction of alkyl groups into the pyrrolidine ring of **3** often enhanced its anticholinergic activity; these substituents affect the conformation of the pyrrolidine ring and therefore change the distance between the nitrogen and the diphenylmethylene group in **3**. The introduction of substituents may act to fix the conformation of the pyrrolidine ring to some extent, resulting in the maintenance of a constant distance between the two functional groups.

On the basis of this assumption, compounds possessing a bicyclic hetero ring substituted with a diarylmethylene group would be expected to exhibit a more potent anticholinergic activity due to their conformational rigidity. Initially, a quinolizidine ring was selected as a bicyclic hetero ring system for conformational fixation of the piperidine ring of **1** and **2**. This paper deals with the synthesis and anticholinergic activity of 1-, 2-, and 3-diarylmethylenequinolizidine quaternary ammonium salts (**4**—**15**).



1



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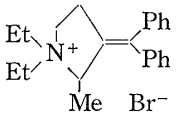

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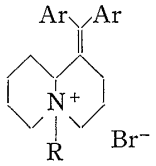
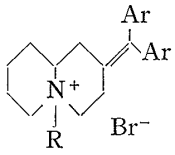
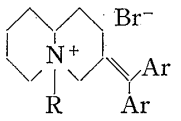


4: Ar=Ph, R=Me
5: Ar=Thi, R=Me
6: Ar=Ph, R=Et
7: Ar=Thi, R=Et



8: Ar=Ph, R=Me
9: Ar=Thi, R=Me
10: Ar=Ph, R=Et
11: Ar=Thi, R=Et



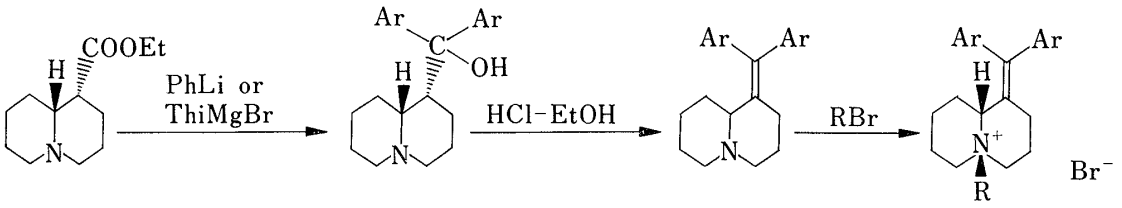
12: Ar=Ph, R=Me
13: Ar=Thi, R=Me
14: Ar=Ph, R=Et
15: Ar=Thi, R=Et

Ph=phenyl, Thi=2-thienyl

Chart 1

5-Alkyl-1-diarylmethylenequinolizidinium Bromide (4—7)

The reaction of 1-ethoxycarbonylquinolizidine (**16**)[7] with phenyllithium (PhLi) afforded the diphenylmethanol (**17**),[8] mp 143—145°, in 84% yield. The infrared (IR) spectrum



16

17 : Ar=Ph
18 : Ar=Thi

19 : Ar=Ph
20 : Ar=Thi

4 : Ar=Ph, R=Me
5 : Ar=Thi, R=Me
6 : Ar=Ph, R=Et
7 : Ar=Thi, R=Et

Ph=phenyl, Thi=2-thienyl

Chart 2

7) *a*) F. Bohlmann and O. Schmidt, *Chem. Ber.*, **97**, 1354 (1964); *b*) Y. Arata, M. Hanaoka, H. Kato, E. Koshinaka, and T. Nishikawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 2381 (1975).
8) K. Winterfeld and J. Augstein, *Chem. Ber.*, **90**, 863 (1957).

showed bands at *ca.* 3100 cm^{-1} due to the hydroxyl group hydrogen-bonded with the nitrogen, and at 2780 cm^{-1} due to the Bohlmann band in dilute chloroform solution. The compound exhibited a peak at *m/e* 321 (M^+) in its mass spectrum (MS). Similar treatment of **16** with 2-thienylmagnesiumbromide (ThiMgBr) afforded the dithienylmethanol (**18**), mp 186—187°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: *ca.* 3100 (bonded OH), 2770 (Bohlmann band), *m/e* 333 (M^+), in 53% yield. Heating of **17** and **18** in an ethanolic solution saturated with hydrogen chloride (HCl–EtOH) effected dehydration to give 1-diphenylmethylenequinolizidine (**19**), mp 75—77°, *m/e* 303 (M^+), and 1-dithienylmethylenequinolizidine (**20**), *m/e* 315 (M^+), the hydrochloride, mp 194—197°, in 94% and 97% yields, respectively.

The *cis*-fused conformations of the quinolizidines (**19** and **20**) were supported by the absence of the Bohlmann bands in their IR spectra. Inspection of Dreiding models of **19** and **20** revealed the presence of strong steric interaction between one of the aromatic rings and the C_9-methylene in the *trans*-fused conformation.

Quaternization of **19** and **20** with methyl bromide produced only the *cis* methobromide (**4**), mp>300°, and the *cis* methobromide (**5**), mp 294—297° (dec.), respectively. Similarly, quaternization of **19** and **20** with ethyl bromide also provided the *cis* ethobromide (**6**), mp >300°, and the *cis* ethobromide (**7**), mp 286—288° (dec.), respectively.

5-Alkyl-2-diarylmethylenequinolizidinium Bromide (8—11)

The reaction of 2-ethoxycarbonylquinolizidine (**21**)[9] with PhLi or ThiMgBr afforded the diphenylmethanol (**22**), mp 194—196°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 2770 (Bohlmann band), *m/e* 321 (M^+), in 93% yield, or the dithienylmethanol (**23**), mp 149—150°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590 (OH), 2760 (Bohlmann band), *m/e* 333 (M^+), in 93% yield. On treatment with HCl–EtOH, **22** and **23** gave 2-diphenylmethylenequinolizidine (**24**), mp 112—112.5°, IR ν_{max}^{KBr} cm^{-1}:

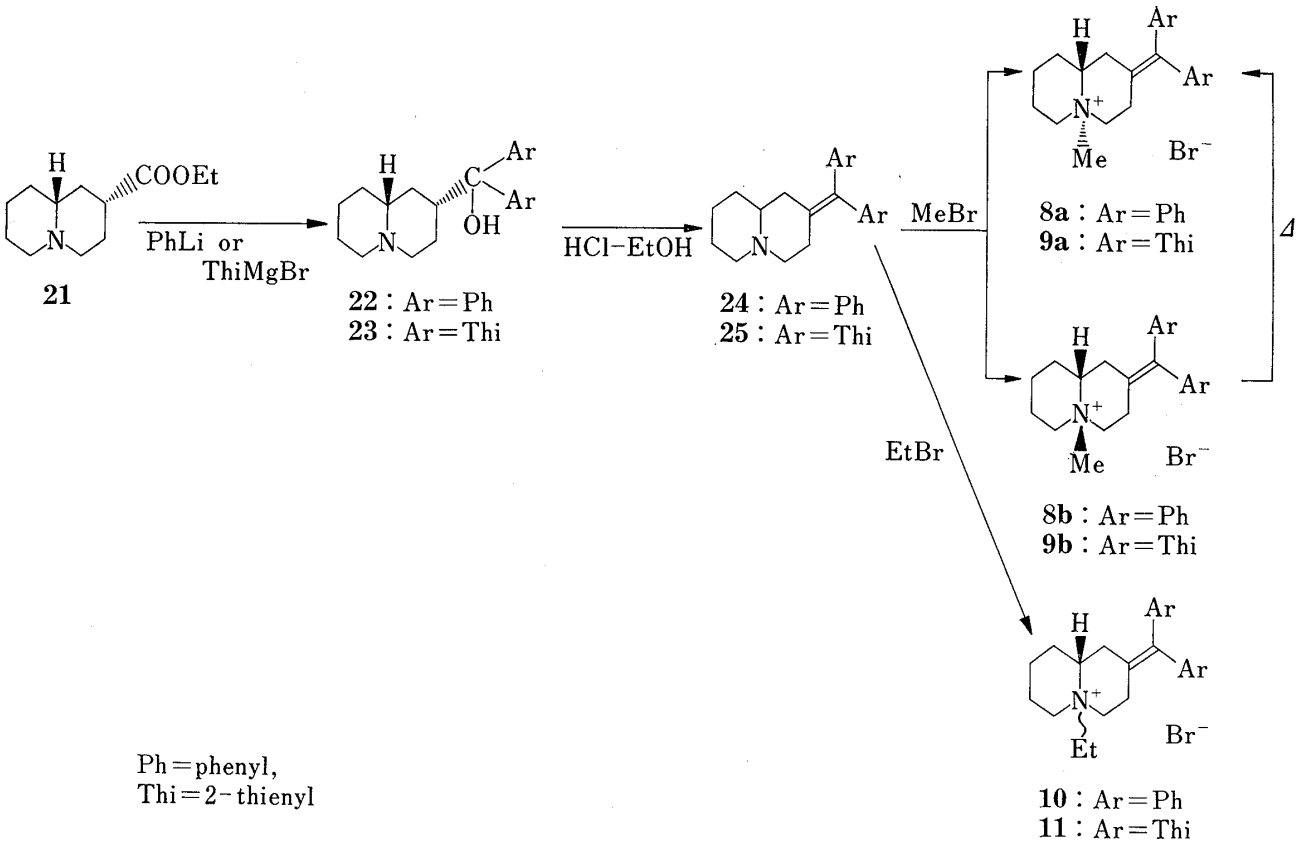


Chart 3

9) N.J. Leonard, K. Conrow, and R.W. Fulmer, *J. Org. Chem.*, **22**, 1445 (1957).

2800, 2750 (Bohlmann bands), 1635 (C=C), *m/e* 303 (M^+), and the 2-dithienylmethylenequinolizidine (**25**), mp 88—90°, IR ν_{max}^{KBr} cm^{-1}: 2800, 2750 (Bohlmann bands), *m/e* 315 (M^+), in 95% and 83% yields, respectively.

Quaternization of **24** with methyl bromide afforded two isomeric methobromides, **8a**, mp 263—265°, NMR δ: 3.33 (N^+–Me), and **8b**, mp 238—239°, NMR δ: 3.67 (N^+–Me), in a 5:1 ratio. On similar treatment, **25** also afforded two isomeric methobromides, **9a**, mp 246—248° (dec.), NMR δ: 3.42 (N^+–Me), and **9b**, mp 239—241° (dec.), NMR δ: 3.76 (N^+–Me), in a 4:1 ratio. On the basis of the report[10] that the N^+-methyl signal of *cis* quinolizidine methiodide generally appears at lower field than that of the corresponding *trans* methiodide in the ^{1}H-NMR spectrum, the stereochemistries of **8a** and **9a** were assigned as *trans* and those of **8b** and **9b** as *cis*. These assignments were supported by the observed thermal isomerization of **8b** to **8a** at 250°. The ethobromides (**10**), mp 233—234°, and (**11**), mp 217—218°, were obtained on quaternization of **24** and **25**, respectively, with ethyl bromide. Attempts to isolate other isomeric ethobromides were unsuccessful and the stereochemistries of **10** and **11** remained undetermined.

5-Alkyl-3-diarylmethylenequinolizidinium Bromide (12—15)

As the previously reported synthesis of 3-ethoxycarbonylquinolizidine (**30**)[11] from 2-vinylpyridine *via* 5 steps was inconvenient and gave a low yield, an alternative and convenient synthesis of **30** was sought.

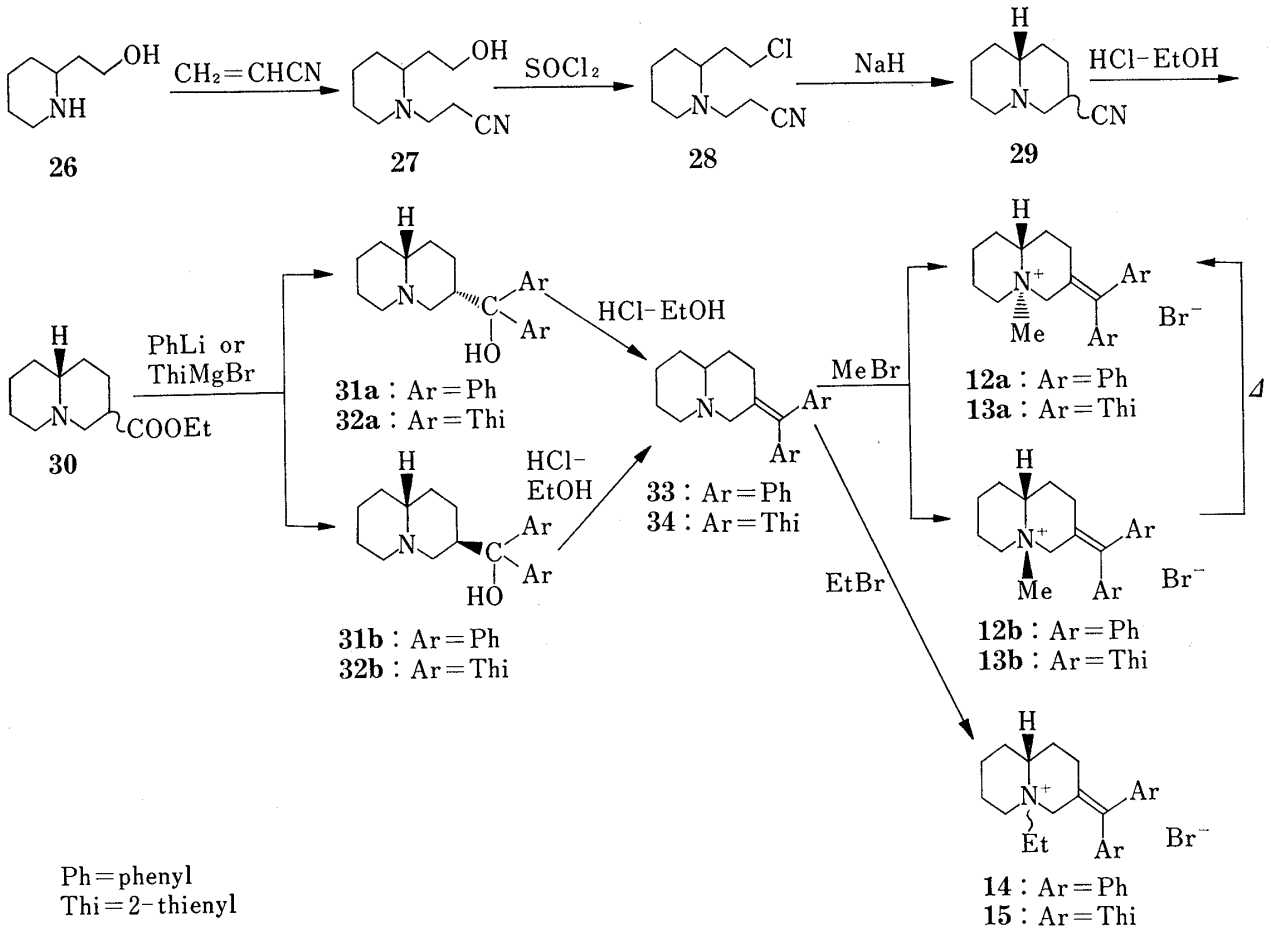


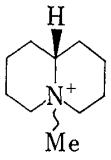
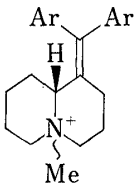
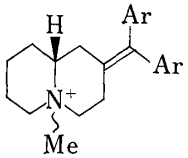
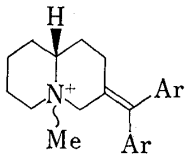
Chart 4

10) T.M. Moynehan, K. Schofield, R.A.Y. Jones, and A.R. Katritzky, *J. Chem. Soc.*, **1962**, 2637.
11) *a*) J. Ratusky, A. Reiser, and F. Sorm, *Chem. Listy*, **48**, 1794 (1954); *b*) S. Ohki and Y. Noike, *Chem. Pharm. Bull.* (Tokyo), **7**, 708 (1959); *c*) Y. Arata, H. Kato, and T. Shioda, *Yakugaku Zasshi*, **88**, 614 (1968).

The addition product (**27**) of 2-piperidineethanol (**26**) to acrylonitrile was chlorinated with thionyl chloride to afford the chloronitrile (**28**), bp_2 135—136°, in 84% overall yield from **26**. Treatment of **28** with sodium hydride (NaH) effected cyclization to give a 90% yield of 3-cyanoquinolizidine (**29**), bp_2 103—106°, IR $\nu_{max}^{liq.}$ cm^{-1}: 2250 (CN), *m/e* 164 (M^+), which was shown to be a mixture of two diastereoisomers in a 1:1 ratio by gas chromatograph–mass spectroscopy (GC–MS). Heating of **29** in ethanolic hydrogen chloride gave an 81% yield of the desired ester (**30**), bp_2 95—97° (lit.[11c] bp_3 95—97°), IR $\nu_{max}^{liq.}$ cm^{-1}: 1730 (CO), which was shown to be a mixture of two diastereoisomers in a 4:5 ratio by GC–MS. Thus, the ester (**30**) could be obtained in 4 steps from **26** in 61% overall yield by simple procedures. The separation of diastereoisomers, the stereochemistries of the nitrile (**29**) and the ester (**30**), and the details of the ring closure reaction will be reported elsewhere.

The product obtained from **30** on treatment with PhLi was fractionally recrystallized to give two isomeric alcohols, **31a**, mp 188—189.5°, *m/e* 321 (M^+), and **31b**, mp 166—167°, *m/e* 321 (M^+). The IR spectrum of **31a** in dilute chloroform solution showed bands at *ca.* 3100 (hydrogen-bonded OH) and 2770 cm^{-1} (Bohlmann band), while that of **31b** showed bands at 3600 (free OH) and 2780 cm^{-1} (Bohlmann band). Therefore, the stereochemistries of **31a** and **31b** were established to be *trans*-fused quinolizidine, having an axial and an equatorial diphenylhydroxymethyl group, respectively. Similar treatment of **30** with ThiMgBr followed by fractional recrystallization gave the axial dithienylmethanol (**32a**), mp 147—148°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: *ca.* 3100 (hydrogen-bonded OH), 2780 (Bohlmann band), *m/e* 333 (M^+), and the equatorial dithienylmethanol (**32b**), mp 176—177°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590 (free OH), 2770

Table I. ^1H- and ^{13}C-NMR N^+-Methyl Signals of Diarylmethylenequinolizidine Methobromides and the Quaternization Ratio of *trans*- and *cis*-Methobromides

Compd.		Ar	^1H-NMR Chemical Shift of N^+-Me (δ in $CDCl_3$)		^{13}C-NMR Chemical Shift of N^+-Me (δ in $CDCl_3$)		Ratio
			trans	*cis*	*trans*	*cis*	*trans* : *cis*
	X⁻		2.96[a] (X=I)	3.15[a] (X=I)	38.63[b] (X=I)	51.02[b] (X=Cl)	
	Br⁻	Ph	—	3.38	—	51.07	0 : 1
		Thi	—	3.36	—	51.17	0 : 1
	Br⁻	Ph	3.33	3.67	37.84	50.34	5 : 1
		Thi	3.42	3.76	37.52	50.53	4 : 1
	Br⁻	Ph	2.97	3.40	39.14	50.30	8 : 1
		Thi	2.92	3.43	38.89	50.34	8 : 1

a) in D_2O.
b) in CD_3OD.

(Bohlmann band), *m/e* 333 (M^+). On treatment with HCl–EtOH, both alcohols (**31a** and **31b**) were dehydrated to give 3-diphenylmethylenequinolizidine (**33**), mp 118—120°, IR ν_{max}^{KBr} cm^{-1}: 2800, 2750 (Bohlmann bands), 1640 (C=C), *m/e* 303 (M^+), and both alcohols (**32a** and **32b**) gave 3-dithienylmethylenequinolizidine (**34**), mp 128—130°, IR ν_{max}^{KBr} cm^{-1}: 2800, 2750 (Bohlmann bands), *m/e* 315 (M^+), in excellent yields.

Quaternization of **33** with methyl bromide afforded the *trans* methobromide (**12a**), mp 259—261°, NMR δ: 2.97 (N^+–Me), and the *cis* methobromide (**12b**), mp 256—259°, NMR δ: 3.40 (N^+–Me), in an 8:1 ratio. On similar treatment, **34** gave the *trans* methobromide (**13a**), mp 278—281° (dec.), NMR δ: 2.92 (N^+–Me), and the *cis* methobromide (**13b**), mp 269—270° (dec.), NMR δ: 3.43 (N^+–Me), in an 8:1 ratio. The stereochemistries of **12a**, **12b**, **13a** and **13b** were assigned on the basis of the chemical shifts of the N^+-methyl signals in their ^1H–NMR spectra, as described in the case of 2-substituted quinolizidinium bromides. These assignments were supported by the observed thermal isomerization of **12b** to **12a** at 250°. The ethobromides (**14**), mp 225—228°, and (**15**), mp 226—228° (dec.) were isolated on quaternization of **33** and **34**, respectively, with ethyl bromide. Attempts to isolate other isomeric ethobromides were unsuccessful and the stereochemistries of **14** and **15** remained undetermined.

The sterochemistries of all the methobromides assigned above were confirmed by their ^{13}C–NMR spectra. As shown in Table I, the N^+-methyl groups of the *trans* methobromides appeared at higher field (37.5—39.5 ppm) than those of the *cis* methobromides (50.0—51.5 ppm). These observations are compatible with the data for quinolizidine methohalides[12] (see Table I) and for 9a-substituted quinolizidine methiodides (N^+-methyl signals of the *trans* form appeared at 41—45 ppm and those of the *cis* form at 48—50 ppm).[13]

Pharmacology

Diarylmethylenequinolizidine quaternary ammonium salts (**4**—**15**) prepared in this study were tested for anticholinergic activity by the Magnus method using isolated ileum from quinea pigs. The results are shown in Table II.

Table II. Anticholinergic Activities of the Synthesized Compounds

Compd.	Anti-Ach[a] ED_{50} (g/ml)	Relative Potency (Atropine=1)	Compd.	Anti-Ach[a] ED_{50} (g/ml)	Relative Potency (Atropine=1)
4	3.8×10^{-8}	0.18	**5**	2.5×10^{-8}	0.26
6	3.5×10^{-8}	0.19	**7**	6.8×10^{-8}	0.10
8a	7.6×10^{-9}	1.05	**9a**	1.0×10^{-8}	1.10
8b	8.6×10^{-9}	0.91	**9b**	1.4×10^{-8}	0.79
10	3.1×10^{-8}	0.22	**11**	2.6×10^{-8}	0.27
12a	1.2×10^{-8}	0.53	**13a**	8.6×10^{-9}	1.28
12b	1.1×10^{-8}	0.57	**13b**	1.2×10^{-8}	0.92
14	1.5×10^{-8}	0.45	**15**	1.8×10^{-8}	0.33
19	1.2×10^{-6}	0.01	**20**	3.2×10^{-7}	0.02
24	5.8×10^{-8}	0.09	**25**	3.0×10^{-8}	0.22
33	5.0×10^{-8}	0.14	**34**	1.6×10^{-8}	0.38
1	6.3×10^{-8}	0.11	**2**	4.0×10^{-8}	0.15
3	1.8×10^{-8}	0.34			

a) Protective activity against the action of acetylcholine (1×10^{-7} g/ml) on isolated ileum from guinea pigs.

Compounds **4**—**15** showed significant inhibition of the constriction induced by acetylcholine; they appeared to have more potential than the monocyclic compounds (**1**, **2**).

12) M. Sugiura, N. Takano, and Y. Sakaki, *Chem. Pharm. Bull.* (Tokyo), **25**, 960 (1977).
13) *a*) Y. Arata, T. Aoki, M. Hanaoka, and K. Kamei, *Chem. Pharm. Bull.* (Tokyo), **23**, 333, (1975); *b*) Y. Arata, M. Hanaoka, and S.K. Kim, *ibid.*, **23**, 1142 (1975).

Among the compounds tested, the activities of **8**, **9**, and **13** were equal to or greater than that of atropine, and **12** showed one-half of the activity of atropine. The pA_2 values of **8a**, **9a**, **12a**, **13a**, and atropine were 9.07, 9.45, 8.69, 9.05, and 8.92, respectively, and these compounds antagonized acetylcholine competitively.

Based on the above results, some structure-activity relationships of alkyl diarylmethylenequinolizidinium bromides can be summarized as follows.

(1) Quaternization of the tertiary amine enhanced its anticholinergic activity.
(2) The anticholinergic activity increased according to the substitution position of quinolizidine in the order 2->3->1-.
(3) The thienyl group tended to produce a more potent effect than the phenyl group.
(4) Among the substituents on the quaternary nitrogen atom, a methyl group was more effective than an ethyl group.
(5) The *trans* methobromides tended to be more effective than the corresponding *cis* derivatives, though no marked difference was noted.

The potent anticholinergic activities of the quinolizidine derivatives (**4**—**15**) compared to **1** or **2** might be due to the rigidity of their conformation compared to that of **1** or **2**, as anticipated. Furthermore, the distance between the two functional groups in the 2-substituted derivatives would be most appropriate for the acetylcholine receptor. The differences of activity between the 1- and 3-substituted derivatives and between phenyl and thienyl substituents might be due to differences of steric effects and affinity for the receptor, respectively.

Thus, conformationally rigid bicyclic hetero ring systems with a diarylmethylene group were found to have potent anticholinergic activity.

Investigations of the synthesis and structure-activity relationships of related bicyclic hetero ring compounds are in progress.

Experimental[14]

***cis*(1*H*, 9a*H*)-1-Diphenylhydroxymethylquinolizidine (17)**——A solution of *cis*(1*H*, 9a*H*)-1-ethoxycarbonylquinolizidine (**16**,[7] 3.00 g) in abs. ether (20 ml) was added dropwise to a stirred solution of PhLi in abs. ether (30 ml) (prepared from Li (0.59 g) and PhBr (6.69 g)) with cooling. The reaction mixture was stirred at room temperature for 30 min, decomposed by addition of H_2O, and extracted with ether. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was recrystallized from hexane to give **17** (3.81 g, 84%) as colorless needles, mp 143—145°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} (2×10^{-1} M solution): *ca.* 3100 (bonded OH), 2780 (Bohlmann band). ^{1}H-NMR ($CDCl_3$) δ: 7.05—7.80 (10H, m, aromatic protons), 8.25 (1H, br, OH, disappeared on addition of D_2O). MS *m/e*: 321 (M^+). *Anal.* Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.03; H, 8.41; N, 4.52.

***cis*(1*H*, 9a*H*)-1-(Di-2-thienylhydroxymethyl)quinolizidine (18)**——A solution of **16**[7] (3.00 g) in abs. tetrahydrofuran (THF, 20 ml) was added dropwise to a stirred solution of ThiMgBr in abs. THF (80 ml) (prepared from Mg (1.42 g) and ThiMgBr (9.26 g)), and the reaction mixture was refluxed for 1 hr, decomposed by addition of saturated aq. NH_4Cl under cooling, and evaporated *in vacuo*. The residue was diluted with H_2O and extracted with ether. The ether layer was shaken with 10% aq. HCl. The aq. layer was made alkaline with aq. K_2CO_3 and extracted with ether. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was recrystallized from $(iso\text{-}Pr)_2O$ to give **18** (2.53 g, 53%) as colorless prisms, mp 186—187°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} (2×10^{-1} M solution): *ca.* 3100 (bonded OH), 2770 (Bohlmann band). ^{1}H-NMR ($CDCl_3$) δ: 6.76—7.16 (6H, m, aromatic protons), 9.29 (1H, br, OH, disappeared on addition of D_2O). MS *m/e*: 333 (M^+). *Anal.* Calcd. for $C_{18}H_{23}NOS_2$: C, 64.82; H, 6.95; N, 4.20. Found: C, 64.94; H, 7.05; N, 3.82.

14) All melting points were measured with a Yanagimoto micro melting point apparatus. Melting points and boiling points are uncorrected. The extracts were dried over anhydrous Na_2SO_4. IR spectra were measured with an IRA-2 spectrophotometer, Japan Spectroscopic Co. ^{1}H-NMR spectra were measured with Hitachi R-20B and JEOL FX-100 spectrometers, using TMS as an internal standard, ^{13}C-NMR spectra were obtained with a JEOL FX-100 unit at 25.05 MHz, using TMS as an internal standard. MS and GC-MS were carried out with a Hitachi RMU-6M machine, and GC with a Hitachi 063 unit employing a 2% QF-1 column. The following abbreviations are used: br=broad, d=doublet, d-d=doublet of doublets, m=multiplet, s=singlet.

1-Diphenylmethylenequinolizidine (19)——A solution of **17** (3.50 g) in EtOH (20 ml) saturated with HCl was refluxed for 1 hr and evaporated *in vacuo*. The residue was made alkaline with aq. NaOH and extracted with ether. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was recrystallized from hexane to give **19** (3.11 g, 94%) as colorless needles, mp 75—77°. ^{1}H-NMR ($CDCl_3$) δ: 7.21, 7.25 (10H, each s, aromatic protons). MS *m/e*: 303 (M^+). *Anal.* Calcd. for $C_{22}H_{25}N$: C, 87.08; H, 8.30; N, 4.62. Found: C, 86.97; H, 8.52; N, 4.11.

1-(Di-2-thienylmethylene)quinolizidine (20)——A solution of **18** (1.40 g) in EtOH (10 ml) saturated with HCl was treated by the procedure described for **19** to give **20** (1.28 g, 97%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 6.76—7.08 (4H, m, aromatic protons), 7.16—7.36 (2H, m, aromatic protons). MS *m/e*: 315 (M^+). Hydrochloride: slightly brownish prisms, mp 194—197° (iso-PrOH–$(iso\text{-}Pr)_2O$). *Anal.* Calcd. for $C_{18}H_{21}NS_2\cdot HCl$: C, 61.43; H, 6.30; N, 3.98. Found: C, 61.13; H, 6.64; N, 3.84.

1-Diphenylmethylene-5-methyl-*cis*-quinolizidinium Bromide (4)——A solution of **19** (2.0 g) and MeBr (5 ml) in acetone (50 ml) was left to stand at room temperature for 10 min. The precipitate was collected by filtration to give **4** (2.5 g, 95%). ^{1}H-NMR ($CDCl_3$) δ: 3.38 (N^+-CH_3). Recrystallization from EtOH gave colorless plates, mp>300°. ^{13}C-NMR ($CDCl_3$) δ: 51.07 (N^+-CH_3). *Anal.* Calcd. for $C_{23}H_{28}BrN$: C, 69.34; H, 7.08; N, 3.52. Found: C, 69.29; H, 7.19; N, 3.27.

1-(Di-2-thienylmethylene)-5-methyl-*cis*-quinolizidinium Bromide (5)——A solution of **20** (2.0 g) and MeBr (5 ml) in acetone (50 ml) was treated by the procedure described for **4** to give **5** (2.4 g, 92%). ^{1}H-NMR ($CDCl_3$) δ: 3.36 (N^+-CH_3). Recrystallization from EtOH-$(iso\text{-}Pr)_2O$ gave colorless scales, mp 294—297° (dec.). ^{13}C-NMR ($CDCl_3$) δ: 51.17 (N^+-CH_3). *Anal.* Calcd for $C_{19}H_{24}BrNS_2$: C, 55.60; H, 5.89; N, 3.41. Found: C, 55.18; H, 6.11; N, 3.54.

1-Diphenylmethylene-5-ethyl-*cis*-quinolizidinium Bromide (6)——A solution of **19** (0.50 g) and EtBr (1 ml) in acetone (20 ml) was left to stand at room temperature for 1.5 hr. The precipitate was collected by filtration to give **6** (0.61 g, 90%). Recrystallization from EtOH gave colorless plates, mp>300°. *Anal.* Calcd. for $C_{24}H_{30}BrN\cdot 1/2H_2O$: C, 68.40; H, 7.41; N, 3.32. Found: C, 68.61; H, 7.31; N, 3.24.

1-(Di-2-thienylmethylene)-5-ethyl-*cis*-quinolizidinium Bromide (7)——A solution of **20** (0.30 g) and EtBr (1 ml) in acetone (10 ml) was treated by the procedure described for **6** to give **7** (0.35 g, 88%). Recrystallization from EtOH–$(iso\text{-}Pr)_2O$ gave colorless needles, mp 286—288° (dec.). *Anal.* Calcd. for $C_{20}H_{26}BrNS_2$: C, 56.59; H, 6.17; N, 3.30. Found: C, 56.79; H, 6.54; N, 3.13.

***cis*(2*H*, 9a*H*)-2-Diphenylhydroxymethylquinolizidine (22)**——A solution of *cis*(2*H*, 9a*H*)-2-ethoxycarbonylquinolizidine (**21**,[9] 1.95 g) in abs. ether (20 ml) was added dropwise to a stirred solution of PhLi in abs. ether (50 ml) (prepared from Li (0.39 g) and PhBr (4.79 g)). The reaction mixture was refluxed for 30 min, decomposed by addition of H_2O, and evaporated *in vacuo*. A small amount of hexane was added to the residue and the precipitate was collected by filtration to give **22** (2.77 g, 93%), which was recrystallized from benzene to give colorless prisms, mp 194—196°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} (2×10^{-1} M solution): 3600 (OH), 2770 (Bohlmann band). ^{1}H-NMR ($CDCl_3$) δ: 2.28 (1H, s, OH, disappeared on addition of D_2O), 7.10—7.75 (10H, m, aromatic protons). MS *m/e*: 321 (M^+). *Anal.* Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.23; H, 8.53; N, 4.25.

***cis*(2*H*, 9a*H*)-2-(Di-2-thienylhydroxymethyl)quinolizidine (23)**——Compound **29**[9] (3.80 g) was treated with a solution of ThiMgBr in abs. THF (100 ml) (prepared from Mg (1.35 g) and ThiBr (8.80 g)) by the procedure described for **18** to give **23** (5.58 g, 93%), which was recrystallized from benzene–$(iso\text{-}Pr)_2O$ to give colorless prisms, mp 149—150°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} (2×10^{-1} M solution): 3590 (OH), 2760 (Bohlmann band). ^{1}H-NMR ($CDCl_3$) δ: 2.97 (1H, s, OH, disappeared on addition of D_2O), 6.82—7.26 (6H, m, aromatic protons). MS *m/e*: 333 (M^+). *Anal.* Calcd. for $C_{18}H_{23}NOS_2$: C, 64.82; H, 6.95; N, 4.20. Found: C, 64.99; H, 6.96; N, 3.85.

2-Diphenylmethylenequinolizidine (24)——Compound **22** (4.76 g) in EtOH (30 ml) saturated with HCl was treated by the procedure described for **19** to give **24** (4.27 g, 95%) as colorless needles, mp 112—112.5° (benzene–$(iso\text{-}Pr)_2O$). IR ν_{max}^{KBr} cm^{-1}: 2800, 2750 (Bohlmann bands), 1635 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 7.18 (10H, s, aromatic protons). MS *m/e*: 303 (M^+). *Anal.* Calcd. for $C_{22}H_{25}N$: C, 87.08; H, 8.30; N, 4.62. Found: C, 87.21; H, 8.21; N, 4.59.

2-(Di-2-thienylmethylene)quinolizidine (25)——Compound **23** (3.03 g) in EtOH (20 ml) saturated with HCl was treated by the procedure described for **19** to give **25** (2.38 g, 83%) as colorless needles, mp 88—90° ($(iso\text{-}Pr)_2O$). IR ν_{max}^{KBr} cm^{-1}: 2800, 2750 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 6.74—7.03 (4H, m, aromatic protons), 7.13—7.30 (2H, m, aromatic protons). MS *m/e*: 315 (M^+). *Anal.* Calcd. for $C_{18}H_{21}NS_2$: C, 68.53; H, 6.71; N, 4.44. Found: C, 68.34; H, 6.72; N, 4.26.

2-Diphenylmethylene-5-methyl-*trans*-quinolizidinium Bromide (8a) and 2-Diphenylmethylene-5-methyl-*cis*-quinolizidinium Bromide (8b)——A solution of **24** (5.50 g) and MeBr (10 ml) in MeOH (50 ml) was left to stand at room temperature for 2 days, evaporated *in vacuo*, and washed with ether to give a mixture of **8a** and **8b** (7.14 g, 99%) in a 5:1 ratio. ^{1}H-NMR ($CDCl_3$) δ: 3.33 (5/2H, s, N^+-CH_3), 3.67 (1/2H, s, N^+-CH_3). The mixture was recrystallized from MeOH–acetone to give **8a** (5.34 g) as colorless prisms, mp 263—265°. ^{1}H-NMR ($CDCl_3$) δ: 3.33 (N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 37.84 (N^+-CH_3). *Anal.* Calcd. for $C_{23}H_{28}BrN$: C, 69.34; H, 7.08; N, 3.52. Found: C, 69.08; H, 7.16; N, 3.26.

The mother liquor was evaporated *in vacuo* and the residue was recrystallized three times from MeOH–acetone to give **8b** (1.12 g) as colorless prisms, mp 238—239°. ^{1}H-NMR ($CDCl_3$) δ: 3.67 (N^+-CH_3). ^{13}C-

NMR ($CDCl_3$) δ: 50.34 (N^+-CH_3). *Anal.* Calcd. for $C_{23}H_{28}BrN$: C, 69.34; H, 7.08; N, 3.52. Found: C, 69.21; H, 7.16; N, 3.34.

Thermal Conversion of 8b into 8a——The methobromide (**8b**, 50 mg) was heated in an oil bath at 250° for 10 min. After cooling, a brownish solid was obtained and was found to be a mixture of **8a** and **8b** in a 2:1 ratio. ^{1}H-NMR ($CDCl_3$) δ: 3.33 (2H, s, N^+-CH_3), 3.67 (1H, s, N^+-CH_3).

2-(Di-2-thienylmethylene)-5-methyl-*trans*-quinolizidinium Bromide (9a) and 2-(Di-2-thienylmethylene)-5-methyl-*cis*-quinolizidinium Bromide (9b)——A solution of **25** (6.04 g) and MeBr (10 ml) in MeOH (100 ml) was treated by the procedure described for **8** to give a mixture of **9a** and **9b** (7.78 g, 98%) in a 4:1 ratio. ^{1}H-NMR ($CDCl_3$) δ: 3.42 (12/5H, s, N^+-CH_3), 3.76 (3/5H, s, N^+-CH_3)

The mixture was recrystallized from EtOH to give **9a** (4.60 g) as colorless prisms, mp 246—248° (dec.). ^{1}H-NMR ($CDCl_3$) δ: 3.42 (3H, s, N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 37.52 (N^+-CH_3). *Anal.* Calcd. for $C_{19}H_{24}BrNS_2$: C, 55.60; H, 5.89; N, 3.41. Found: C, 55.31; H, 5.88; N, 3.10.

The mother liquor was evaporated *in vacuo* and the residue was recrystallized four times from iso-PrOH–ether to give **9b** (0.21 g) as colorless scales, mp 239—241° (dec.). ^{1}H-NMR ($CDCl_3$) δ: 3.76 (N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 50.53 (N^+-CH_3). *Anal.* Calcd. for $C_{19}H_{24}BrNS_2\cdot H_2O$: C, 53.26; H, 6.12; N, 3.27. Found: C, 53.14; H, 6.17; N, 3.16.

2-Diphenylmethylene-5-ethylquinolizidinium Bromide (10)——A mixture of **24** (0.5 g) and EtBr (20 ml) in a sealed tube was heated at 70—80° for 2 days then evaporated *in vacuo*. The residue was recrystallized from acetone to give **10** (0.2 g, 29%) as colorless needles, mp 233—234°. *Anal.* Calcd for $C_{24}H_{30}BrN$: C, 69.90; H, 7.33; N, 3.40 Found: C, 69.58; H, 7.42; N, 3.26.

2-(Di-2-thienylmethylene)-5-ethylquinolizidinium Bromide (11)——A mixture of **25** (0.6 g) and EtBr (10 ml) was treated by the procedure described for **10** to give **11** (0.2 g, 25%) as colorless prisms, mp 217—218° (iso-PrOH). *Anal.* Calcd. for $C_{20}H_{26}BrNS_2$: C, 56.59; H, 6.17; N, 3.30. Found: C, 56.31; H, 6.17; N, 3.37.

3-[2-(2-Chloroethyl)piperidin-1-yl]propionitrile (28)——A mixture of 2-piperidineethanol (**26**, 50 g) and acrylonitrile (25 g) was heated at 70—80° for 2 hr, then the excess acrylonitrile was evaporated off *in vacuo*. The residue (**27**) was dissolved in $CHCl_3$ (100 ml) and $SOCl_2$ (50.8 g) was added dropwise. After refluxing for 1 hr, the solvent was evaporated off *in vacuo*. The residue was made alkaline with aq. K_2CO_3 and extracted with ether. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was distilled to give **28** (65.3 g, 84%) as a colorless oil, bp 135—136° (2 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 2250 (CN). MS *m/e*: 200, 202 (3:1, M^+).

3-Cyanoquinolizidine (29)——Compound **28** (33.0 g) was added dropwise to a suspension of 50% NaH (14.2 g) in a solution of EtOH (1 ml) and DMF (200 ml) with stirring. The reaction mixture was heated at 50—60° for 1 hr, then poured into ice-water, and extracted with ether. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The residue was distilled to give **29** (24.3 g, 90%) as a colorless oil, bp 103—106° (2 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 2250 (CN). The product (**29**) showed two peaks on GC (column temperature, 130°, retention times: 1.56 and 2.36 min) in a 1:1 ratio. GC–MS of both fractions *m/e*: 164 (M^+).

3-Ethoxycarbonylquinolizidine (30)——A solution of **29** (37.5 g) in abs. EtOH (100 ml) was saturated with HCl gas, refluxed for 2 hr, then evaporated *in vacuo*. The residue was made alkaline with aq. K_2CO_3 and extracted with ether. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residue was distilled to give **30** (39.2 g, 81%) as a colorless oil, bp 95—97° (2 mmHg) (lit.[11c] bp 95—97° (3 mm Hg)). IR $\nu_{max}^{liq.}$ cm^{-1}: 1730 (CO). The product (**30**) showed two peaks on GC (column temperature, 110°, retention times: 1.89 and 2.84 min) in a 4:5 ratio. GC–MS of both fractions *m/e*: 211 (M^+).

***cis*(3*H*, 9a*H*)-3-Diphenylhydroxymethylquinolizidine (31a) and *trans*(3*H*, 9a*H*)-3-Diphenylhydroxymethylquinolizidine (31b)**——Compound **30** (17.4 g) was treated with a solution of PhLi in abs. ether (150 ml) (prepared from Li (3.4 g) and PhBr (32.4 g)) by the procedure described for **22** to give **31** (22.8 g, 86%). Recrystallization from iso-PrOH gave **31a** (8.7 g) as colorless needles, mp 188—189.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} (2×10^{-1} M solution): *ca.* 3100 (bonded OH), 2770 (Bohlmann band). ^{1}H-NMR ($CDCl_3$) δ: 7.73 (1H, s, OH, disappeared on addition of D_2O), 7.10—7.75 (10H, m, aromatic protons). MS *m/e*: 321 (M^+). *Anal.* Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.07; H, 8.53; N, 4.49.

The mother liquor was evaporated *in vacuo* and the residue was recrystallized twice from iso-PrOH to give **31b** (6.8 g) as colorless plates, mp 166—167°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} (2×10^{-1} M solution): 3600 (OH), 2780 (Bohlmann band). ^{1}H-NMR ($CDCl_3$) δ: 2.23 (1H, s, OH, disappeared on addition of D_2O), 7.10—7.68 (10H, m, aromatic protons). MS *m/e*: 321 (M^+). *Anal.* Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.24; H, 8.62; N, 4.40.

***cis*(3*H*, 9a*H*)-3-(Di-2-thienylhydroxymethyl)quinolizidine (32a) and *trans*(3*H*, 9a*H*)-3-(Di-2-thienylhydroxymethyl)quinolizidine (32b)**——A solution of **30** (19.3 g) in abs. ether (300 ml) was added dropwise to a stirred solution of ThiMgBr in abs. ether (300 ml) (prepared from Mg (8.9 g) and ThiBr (59.7 g)), and the reaction mixture was left to stand for 1 hr at room temperature, then decomposed by addition of saturated aq. NH_4Cl with cooling. The ether layer was separated and the aq. layer was extracted with ether. The ether layer and extract were combined, washed with H_2O, dried and evaporated *in vacuo*. The residue **32** (26.8 g, 88%) was recrystallized from benzene to give **32b** (3.49 g) as colorless needles, mp 176—177°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} (2×10^{-1} M solution): 3590 (OH), 2770 (Bohlmann band). ^{1}H-NMR ($CDCl_3$) δ: 3.04 (1H, s, OH,

disappeared on addition of D_2O), 6.82—7.28 (6H, m, aromatic protons). MS *m/e*: 333 (M^+). *Anal.* Calcd. for $C_{18}H_{23}NOS_2$: C, 64.82; H, 6.95; N, 4.20. Found: C, 64.55; H, 6.92; N, 4.01.

The mother liquor was evaporated *in vacuo* and the residue was recrystallized three times from $(iso\text{-}Pr)_2O$ to give **32a** (3.63 g) as colorless needles, mp 147—148°. IR $\nu_{max}^{CHCl_3}$ cm^{-1} (2×10^{-1} M solution): *ca.* 3100 (bonded OH), 2780 (Bohlmann band). ^{1}H-NMR ($CDCl_3$) δ: 6.80—7.24 (6H, m, aromatic protons), 8.87 (1H, s, OH, disappeared on addition of D_2O). MS *m/e*: 333 (M^+). *Anal.* Calcd. for $C_{18}H_{23}NOS_2$: C, 64.82; H, 6.95; N, 4.20. Found: C, 64.91; H, 7.04; N, 3.96.

3-Diphenylmethylenequinolizidine (33)——1) From **31a**: A solution of **31a** (3.0 g) in EtOH (20 ml) saturated with HCl was treated by the procedure described for **19** to give **33** (2.8 g, 99%) as colorless needles, mp 118—120° (hexane). IR ν_{max}^{KBr} cm^{-1}: 2800, 2750 (Bohlmann bands), 1640 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 2.60 (1H, d, J=12 Hz, C_4–H_{ax}), 3.57 (1H, d-d, J=12, 2 Hz, C_4–H_{eq}), 7.19 (10H, s, aromatic protons). MS *m/e*: 303 (M^+). *Anal.* Calcd. for $C_{22}H_{25}N$: C, 87.08; H, 8.30; N, 4.62. Found: C, 87.30; H, 8.33; N, 4.48.

2) From **31b**: A solution of **31b** (3.0 g) in EtOH (20 ml) saturated with HCl was treated by the procedure described for **19** to give **33** (2.8 g, 99%) as colorless needles, mp 118—120° (hexane), which were identical with those obtained from **31a** (IR and NMR spectra and mixed melting point).

3-(Di-2-thienylmethylene)quinolizidine (34)——1) From **32a**: A solution of **32a** (3.0 g) in EtOH (20 ml) saturated with HCl was treated by the procedure described for **19** to give **34** (2.53 g, 89%) as colorless needles, mp 128—130° ($(iso\text{-}Pr)_2O$). IR ν_{max}^{KBr} cm^{-1}: 2800, 2750 (Bohlmann bands). ^{1}H-NMR ($CDCl_3$) δ: 2.60 (1H, d, J=12 Hz, C_4–H_{ax}), 3.80 (1H, d-d, J=12, 2 Hz, C_4-H_{eq}), 6.78—7.05 (4H, m, aromatic protons), 7.14—7.30 (2H, m, aromatic protons). MS *m/e*: 315 (M^+). *Anal.* Calcd. for $C_{18}H_{21}NS_2$: C, 68.53; H, 6.71; N, 4.44. Found: ,C 68.36; H, 6.75; N, 4.36.

2) From **32b**: A solution of **32b** (3.0 g) in EtOH (20 ml) saturated with HCl was treated by the procedure described for **19** to give **34** (2.64 g, 93%) as colorless needles, mp 128—130° ($(iso\text{-}Pr)_2O$), which were identical with those obtained from **32a** (IR and NMR spectra and mixed melting point).

3-Diphenylmethylene-5-methyl-*trans*-quinolizidinium Bromide (12a) **and 3-Diphenylmethylene-5-methyl-*cis*-quinolizidinium Bromide** (12b)——A solution of **33** (15.0 g) and MeBr (30 ml) in MeOH (200 ml) was treated by the procedure described for **8** to give a mixture of **12a** and **12b** (19.5 g, 99%) in an 8: 1 ratio. ^{1}H-NMR ($CDCl_3$) δ: 2.97 (8/3H, s, N^+-CH_3), 3.40 (1/3H, s, N^+-CH_3)

The mixture was washed with acetone (200 ml) and recrystallized from MeOH–acetone to give **12a** (11.7 g) as colorless needles, mp 259—261°. ^{1}H-NMR ($CDCl_3$) δ: 2.97 (3H, s, N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 39.14 (N^+-CH_3). *Anal.* Calcd. for $C_{23}H_{28}BrN$: C, 69.34; H, 7.08; N, 3.52. Found: C, 69.60; H, 7.29; N, 3.26.

The acetone washing was evaporated *in vacuo* and the residue was recrystallized three times from MeOH–ether to give **12b** (0.63 g) as colorless prisms, mp 256—259°. ^{1}H-NMR ($CDCl_3$) δ: 3.40 (3H, s, N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 50.30 (N^+-CH_3). *Anal.* Calcd. for $C_{23}H_{28}BrN$: C, 69.34; H, 7.08; N, 3.52. Found: C, 69.06; H, 7.20; N, 3.48.

Thermal Conversion of 12b into 12a——The methobromide (**12b**, 50 mg) was treated by the procedure described for the conversion of **8b** into **8a** to give a mixture of **12a** and **12b** in a 3: 1 ratio. ^{1}H-NMR ($CDCl_3$) δ: 2.97 (9/4H, s, N^+-CH_3), 3.40 (3/4H, s, N^+-CH_3).

3-(Di-2-thienylmethylene)-5-methyl-*trans*-quinolizidinium Bromide (13a) **and 3-(Di-2-thienymethylene)-5-methyl-*cis*-quinolizidinium Bromide** (13b)——A solution of **34** (15.6 g) and MeBr (30 ml) in MeOH (300 ml) was treated by the procedure described for **8** to give a mixture of **13a** and **13b** (19.5 g, 95%) in an 8: 1 ratio. ^{1}H-NMR ($CDCl_3$) δ: 2.92 (8/3H, s, N^+-CH_3), 3.43 (1/3H, s, N^+-CH_3).

The mixture was washed with hot acetone (150 ml) and recrystallized from MeOH–acetone to give **13a** (13.6 g) as colorless needles, mp 278—281° (dec.). ^{1}H-NMR ($CDCl_3$) δ: 2.92 (3H, s, N^+–CH_3). ^{13}C-NMR ($CDCl_3$) δ: 38.89 (N^+–CH_3). *Anal.* Calcd. for $C_{19}H_{24}BrNS_2$: C, 55.60; H, 5.89; N, 3.41. Found: C, 55.55; H, 5.91; N, 3.38.

The acetone washing was evaporated *in vacuo* and the residue was recrystallized twice from MeOH–acetone to give **13b** (0.15 g) as colorless scales, mp 269—270° (dec.). ^{1}H-NMR ($CDCl_3$) δ: 3.43 (3H, s, N^+-CH_3). ^{13}C-NMR ($CDCl_3$) δ: 50.34 (N^+-CH_3). *Anal.* Calcd. for $C_{19}H_{24}BrNS_2$: C, 55.60; H, 5.89; N, 3.41. Found: C, 55.60; H, 5.96; N, 3.26.

3-Diphenylmethylene-5-ethylquinolizidinium Bromide (14)——A mixture of **33** (1.0 g) and EtBr (20 ml) was treated by the procedure described for **10** to give **14** (0.43 g, 32%) as coloress plates, mp 225—228° (acetone). *Anal.* Calcd. for $C_{21}H_{30}BrN$: C, 69.90; H, 7.33; N, 3.40. Found: C, 69.87; H, 7.36; N, 3.27.

3-(Di-2-thienylmethylene)-5-ethylquinolizidinium Bromide (15)——A mixture of **34** (0.6 g) and EtBr (10 ml) was treated by the procedure described for **10** to give **15** (0.27 g, 33%) as pale yellow prisms, mp 226—228° (dec.) (iso-PrOH–acetone). *Anal.* Calcd. for $C_{20}H_{26}BrNS_2\cdot1/5H_2O$: C, 56.12; H, 6.22; N, 3.27. Found: C, 56.13; H, 6.18; N, 3.04.

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