IR ν_{max}^{cap} cm^{-1}: 2980, 2950, 1710, 1600, 755, 695. This IR spectrum was identical with that of the authentic (±)-VIII[10] in the same state. This acid was further confirmed as its (±)-anilide. (±)-Hydratropanilide mp 132—133°, showed no depression on mixed melting point measurement with the authentic sample,[17] mp 132—133°. IR ν_{max}^{KBr} cm^{-1}: 3300, 1680, 1600, 1540, 760, 700. This IR spectrum was also identical with that of the authentic sample[17] in the same state.

***S*(+)-Hydratropic Acid (*S*(+)-VIII)**——Treatment of *S*(−)-VII (α_D^{13} −0.616° (*l*=0.1, neat), bp 88—89° (5—6 mmHg)) (1.00 g, 7.6 mmole) in a manner similar to the case of (±)-VII afforded crude *S*(+)-VII as a pale yellow oil (1.2 g), which was purified by fractional distillation to give pure *S*(+)-VIII as a colorless oil (0.58 g, 51%), bp 121° (5 mmHg), $[\alpha]_D^{12}$ +36.2° (*c*=11.7, benzene). IR spectrum of this sample was identical with that of the authentic (±)-VIII in the same state. The optical purity of this sample was assumed to be 39%, based on the assumption that *S*(+)-VIII showing $[\alpha]_D$ +92.5° (*c*=3.4825, benzene)[11] was 100% optically pure.

The same treatment of *S*(−)-VII (α_D^8 −0.812° (*l*=0.1, neat) bp 93—98° (11 mmHg) (1.09 g, 8.3 mmole) as that described above, afforded pure *S*(+)-VIII as a colorless oil (0.58 g, 46%), bp 127° (7 mmHg), $[\alpha]_D^{12}$ +44.5° (*c*=11.6, benzene). IR spectrum of this sample was identical with that of the authentic (±)-VIII in the same state. The optical purity of this acid was calculated to be 48% based on the assumption described above.

When *S*(−)-VII (α_D^{10} −0.041° (*l*=0.1, neat), bp 82—84° (4 mmHg)) (1.95 g, 0.015 mole) was treated in a manner similar to that described above, *S*(+)-VIII showing bp 132° (9 mmHg), $[\alpha]_D^{11}$ +1.12° (*c*=28.8, benzene) (optical purity 1.2%) was obtained in 61% yield.

Racemization of *S*(+)-Hydratropic Acid (*S*(+)-VIII) under the Hydrolysis Condition of *S*(−)-Hydratropanitrile (*S*(−)-VII)——Treatment of *S*(+)-VIII showing $[\alpha]_D^{17}$ +64.3° (*c*=9.49, benzene) (1.05 g, 7.6 mmole) was treated under the same reaction condition as that employed for the hydrolysis of *S*(−)-VII. Extractive isolation followed by fractional distillation afforded the pure *S*(+)-VIII as a colorless oil (0.42 g, 40%), bp 125° (10 mmHg), $[\alpha]_D^{17}$ +55.4° (*c*=8.40, benzene). Based on the above experiment, extent of racemization of *S*(+)-VIII under the hydrolysis condition was calculated to be 13.8%.

Acknowledgement The authors are indebted to the members of the Central Analysis Room of this Faculty for elemental analyses and spectra measurements.

17) S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 1001 (1965).

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Synthesis of 1-Carbethoxyindolizines *via* Intramolecular 1,5-Cyclization of Ylides

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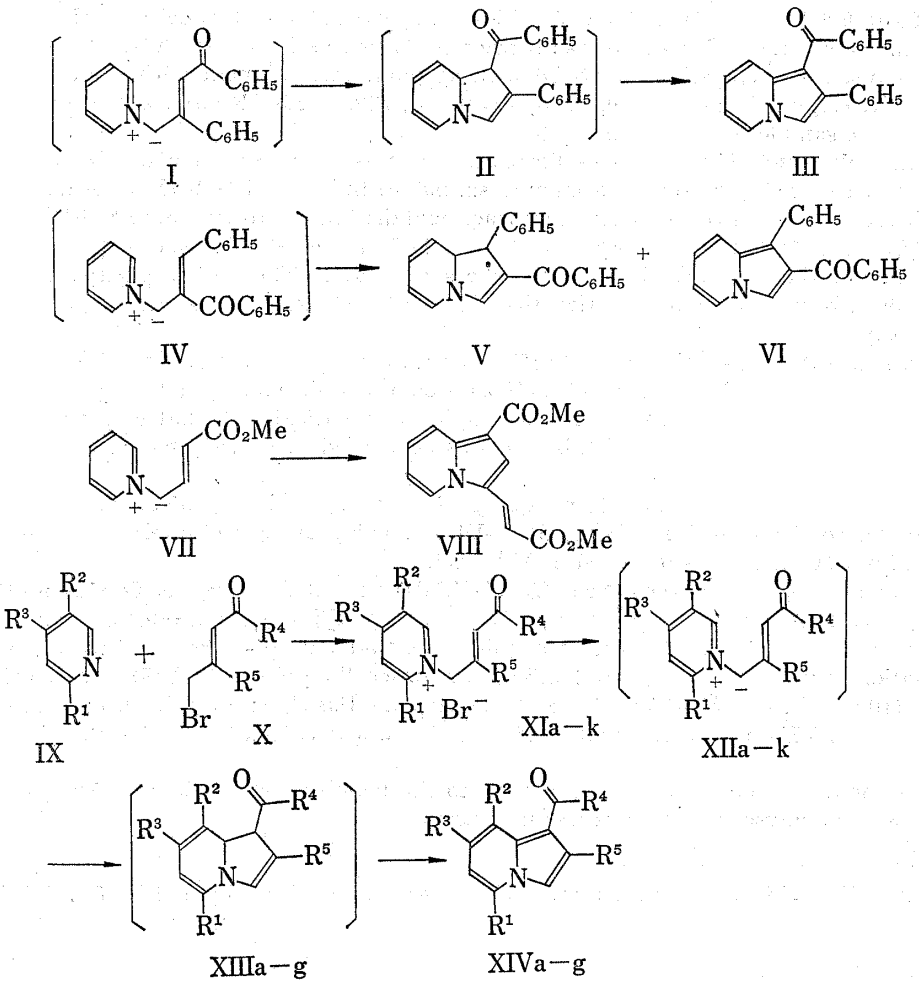
Previously we described that the pyridinium ylide (I) readily undergoes intramolecular 1,5-cyclization followed by dehydrogenation of the intermediate (II) to give the indolizine (III).[2] Later Pohjala[3] showed that the closely related pyridinium ylide (IV) also cyclizes to give a mixture of the dihydroindolizine (V) and the indolizine (VI). In contrast, the ylide (VII) was shown to give a rather unusual product (VIII) presumably by an intermolecular 1,3-dipolar cycloaddition reaction.[4] These results prompted us to examine the scope of the

1) Location: *Toneyama, Toyonaka, Osaka.*
2) Y. Tamura, N. Tsujimoto, Y. Sumida, and M. Ikeda, *Tetrahedron*, **28**, 21 (1972).
3) E. Pohjala, *Tetrahedron Letters*, **1972**, 2585.
4) Y. Tamura, Y. Sumida, and M. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **20**, 1058 (1972).



	R^1	R^2	R^3	R^4	R^5		R^1	R^2	R^3	R^4	R^5
a:	H	H	H	OEt	Me	**f**:	Me	H	H	OEt	C_6H_5
b:	Me	H	H	OEt	Me	**g**:	H	Me	H	OEt	C_6H_5
c:	H	Me	H	OEt	Me	**h**:	H	H	H	OMe	CO_2Me
d:	H	H	Me	OEt	Me	**i**:	H	H	Me	OMe	CO_2Me
e:	H	H	H	OEt	C_6H_5	**j**:	H	H	Me		$-(CH_2)_3-$

Chart 1

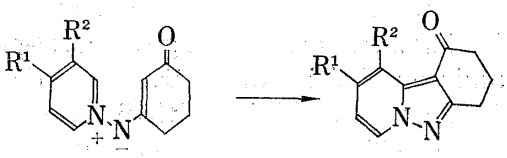
intramolecular 1,5-cyclization reaction, in particular, the effect of the nature of substituents at 2′-position of the readily accessible pyridinium 1-(3′-carbalkoxy)allylides (XII).

1-(3′-Carbalkoxyallyl)pyridinium bromides (XIa—i) were obtained in high yields by treatment of pyridines (IX) with the corresponding bromo esters (Xa—i) in ether at room temperature. The structures of the salts were proved by the spectral evidence, the details of which are given in the Experimental.

The pyridinium salts (XIa—g) thus obtained were treated with potassium carbonate in ethanol at room temperature for 5 hr. After filtration of the inorganic material, the filtrate was concentrated under vacuum. The residual mixture was separated from tarry substance by passing through a short column of alumina to give indolizines (XIVa—g). The results are summarized in Table I.

The structures of the new indolizines (XIVb—d,f,g) were determined by the elemental analysis and comparison of the spectral data (Table II) with those of the known indolizines (XIVa and XIVe), which were identified by direct comparison with authentic samples pre-

pared by the method of Bragg and Wibberly.[5] The formation of these indolizines is explained in terms of the intermediacy of XII and XIII. It should be noted that the 3-methylpyridinium salts (XIc and XIg) afforded almost exclusively XIVc and XIVg. This result parallels the behavior of XV (R^1=H, R^2=Me) which gives XVI (R^1=H, R^2=Me) and is explained by a similar discussion previously presented.[2]



XV XVI

Chart 2

Table I. Indolizines (XIVa—g)

Starting material	Product	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XIa	XIVa	41 — 42[a]	18	$C_{12}H_{13}O_2N$						
XIb	XIVb	68 — 70	26	$C_{13}H_{15}O_2N$	71.86	6.96	6.45	71.88	6.97	6.33
XIc	XIVc	56 — 57	21	$C_{13}H_{15}O_2N$	71.86	6.96	6.45	71.87	6.86	6.37
XId	XIVd	61 — 62	14	$C_{13}H_{15}O_2N$	71.86	6.96	6.45	71.76	6.92	6.41
XIe	XIVe	107 —108[b]	38	$C_{17}H_{15}O_2N$						
XIf	XIVf	71 — 72	34	$C_{18}H_{17}O_2N$	77.39	6.13	5.02	77.49	6.29	4.93
XIg	XIVg	66.5— 67.5	18	$C_{18}H_{17}O_2N$	77.39	6.13	5.02	77.46	6.16	4.92

a) lit.[5] mp 43—44° *b*) lit.[5] mp 106—107°

Table II. Spectral Data of Indolizines (XIVa—g)

Compd. No.	M^+ *m/e*	IR ν_{max}^{KCl} cm^{-1}	UV λ_{max}^{EtOH} mμ (log ε)	NMR (in $CDCl_3$) τ
XIVa	203	1665,1630	230sh(4.42),235.5(4.43), 260(3.94),269(3.97), 296sh(3.85),308.5(4.05), 334(3.91),346sh(3.90)	1.90(1H, d, J=9 cps, H_8), 2.18(1H, d, J=7 cps, H_5), 2.85—3.25(1H, m, H_7), 3.00(1H, s, H_3),3.42 (1H, t, J=7 cps, H_6), 5.68(2H, q, J=7 cps, $-C\underline{H}_2CH_3$), 7.58(3H, s, $-CH_3$), 8.64(3H, t, J=7 cps, $-CH_2C\underline{H}_3$)
XIVb	217	1670,1635	230sh(4.30),234(4.32), 257(3.76),265.5(3.73), 296sh(3.61),310(3.82), 325sh(3.86),337.5(3.92), 354sh(3.71)	1.90(1H, d, J=9 cps, H_8), 3.03(1H, dd, J=7, 9 cps, H_7), 3.04(1H, s, H_3), 3.50(1H, d, J=7 cps, H_6),5.64(2H, q, J=7 cps, $-C\underline{H}_2CH_3$), 7.61, 7.65 (2×3H, 2×s, 2×$-CH_3$), 8.62(3H, t, J=7 cps, $-CH_2C\underline{H}_3$)
XIVc	217	1675,1625	232sh(4.33),237(4.34), 260(3.74),268.5(3.71), 297sh(3.71),311.5(3.89), 329(3.85),343sh(3.82)	2.35(1H, bd, J=7 cps, H_5), 3.03(1H, s, H_3), 3.20 —3.80 (2H, m, H_6, H_7), 5.72(2H, q, J=7 cps, $-C\underline{H}_2CH_3$), 7.50, 7.68 (2×3H, 2×s, 2×$-CH_3$), 8.66(3H, t, J=7 cps, $-CH_2C\underline{H}_3$)
XIVd	217	1665,1640	234.5sh(4.45),238(4.47), 261(3.89),269.5(3,88), 299sh(3.87),312(4.05), 330.5(3.89),345sh(3.84)	2.1(1H, bs, H_8), 2.27(1H, d, J=7 cps, H_5), 3.06 (1H, s, H_3), 3.55(1H, dd, J=2, 7 cps, H_6), 5.68 (2H, q, J=7 cps, $-C\underline{H}_2CH_3$), 7.60, 7.70(2×3H, 2×s, 2×$-CH_3$), 8.62(3H, t, J=7 cps, $-CH_2C\underline{H}_3$)
XIVe	265	1670,1600	237.5(4.88),257sh(4.81), 298sh(3.41),308.5(3.24), 334sh(3.95),346.5(3.97)	1.78(1H, d, J=9.5 cps, H_8), 2.07(1H, dd, J=1.5, 6.5 cps, H_5), 2.3—2.8(6H, m, C_6H_5, H_3), 2.98(1H, ddd, J=1.5, 6.5, 9.5 cps, H_7), 3.33(1H, t, J=6.5 cps, H_6), 5.80 (2H, q, J=7 cps, $-C\underline{H}_2CH_3$), 8.83 (3H, t, J=7 cps, $-CH_2C\underline{H}_3$)
XIVf	279	1670,1635 1605	237.5(4.40),257sh(4.24), 300sh(3.81),312(3.92), 328sh(3.98),340(4.04), 355sh(3.91)	1.80(1H, d, J=9 cps, H_8), 2.3—3.1(7H, m, C_6H_5, H_3, H_7), 3.42(1H, d, J=7.5 cps, H_6), 5.78(2H, q, J=7 cps, $-C\underline{H}_2CH_3$), 7.5(3H, s, $-CH_3$), 8.82(3H, t, J=7 cps, $-CH_2C\underline{H}_3$)
XIVg	279	1675,1635 1600	237(4.46),258sh(4.29), 296sh(3.83),311(3.98), 325sh(4.02),340(4.10), 356sh(3.95)	2.24(1H, d, J=7cps, H_8), 2.50—2.75(5H, m, C_6H_5), 2.79(1H, s, H_3), 3.25—3.65(2H, m, H_6, H_7), 5.88 (2H, q, J=7 cps, $-C\underline{H}_2CH_3$), 7.52 (3H, s, $-CH_3$), 8.98(3H, t, J=7 cps, $-CH_2C\underline{H}_3$)

5) D.R. Bragg and D.G. Wibberly, *J. Chem. Soc.*, **1962**, 2627.

In sharp contrast to the cases of XIa—g, attempts to cyclize the pyridinium salts (XIh,i) having a carbomethoxyl group at 2′-position, resulted in the formation of black tarry material and no indolizine derivatives were detected. Attempts to trap a possible intermediate XIIh through cycloaddition with dimethyl acetylenedicarboxylate were also unsuccessful. Finally, when 1-(3′-oxocyclohexen-1′-ylmethyl)pyridinium bromide (XIj) prepared from 4-methylpyridine and 3-bromomethyl-2-cyclohexen-1-one,[6] was treated with base, again no indolizine derivative was obtained. The last example is contrasted to the case of XV (R^1=Me, R^2=H) which, upon heating, gives the pyrazolo[1,5-*a*]pyridine derivative (XVI) (R^1=Me, R^2=H).[2] At present time we have no ready explanation which satisfactorily accounts for the differences noted. We will postpone further discussion until a more thorough study can be undertaken.

Experimental[7]

1-(3′-Carbethoxy-2′-phenylallyl)-3-methylpyridinium Bromide (XIg)——The general procedure used is illustrated by this example. A solution of 3-methylpyridine (172 mg) and ethyl 3-bromomethylcinnamate[8] (500 mg) in ether was allowed to stand at room temperature for 3 days. A white precipitate was filtered and recrystallized from acetone to give white needles of XIg (624 mg, 93%), mp 153—156°. IR ν_{max}^{KCl} cm^{-1}: 1705 and 1635. NMR (in $CDCl_3$) τ: 0.61 (1H, s, H_2), 0.81 (1H, bd, J=7 cps, H_6), 1.72 (1H, bd, J=8 cps, H_4), 1.9—2.8 (6H, m), 3.22 (2H, s, $-CH_2-$), 3.60 (1H, s, $-C=CH-$), 5.75 (2H, q, J=7 cps, $-CH_2CH_3$), 7.53 (3H, s, $-CH_3$), and 8.67 (3H, t, J=7 cps, $-CH_2CH_3$). *Anal.* Calcd. for $C_{18}H_{20}O_2NBr$: C, 59.81; H, 5.58; N, 3.88. Found: C, 60.01; H, 5.43; N, 3.83.

1-(3′-Carbethoxy-2′-phenylallyl)-2-methylpyridinium Bromide (XIf)——From 2-methylpyridine (186 mg) and ethyl 3-bromomethylcinnamate (500 mg) there was obtained XIf (156 mg, 23%) as white needles, mp 159—163° (from acetone). IR ν_{max}^{KCl} cm^{-1}: 1700 and 1630. NMR (in $CDCl_3$) τ: 0.24 (1H, bd, J=7 cps, H_6), 1.70 (1H, d, J=7 cps, H_4), 1.9—2.9 (7H, m), 3.17 (2H, s, $-CH_2-$), 3.72 (1H, s, $-C=CH-$), 5.78 (2H, q, J=7 cps, $-CH_2CH_3$), 7.10 (3H, s, $-CH_3$), and 8.71 (3H, t, J=7 cps, $-CH_2CH_3$). *Anal.* Calcd. for $C_{18}H_{20}O_2NBr$: C, 59.81; H, 5.58; N, 3.88. Found: C, 59.61; H, 5.37; N, 3.74.

1-(2′,3′-Dicarbomethoxyallyl)pyridinium Bromide (XIh)——From pyridine (655 mg) and dimethyl bromomethylmaleate[9] (2.0 g) there was obtained XIh (2.45 g, 92%) as white needles, mp 87—88° (from acetone). IR ν_{max}^{KCl} cm^{-1}: 1740sh, 1720, and 1630. NMR (in $CDCl_3$) τ: 0.52 (2H, d, J=7 cps, H_2 and H_6), 1.33 (1H, d, J=cps, H_4), 1.74 (2H, dd, J=7 and 8 cps, H_3 and H_5), 2.23 (1H, s, $-C=CH-$), 3.80 (2H, s, $-CH_2-$), 6.11 and 6.19 (2×3H, 2×s, 2× $-OCH_3$). *Anal.* Calcd. for $C_{12}H_{14}O_4NBr$: C, 45.49; H, 4.46; N, 4.43. Found: C, 45.28; H, 4.53; N, 4.56.

1-(2′,3′-Dicarbomethoxyallyl)-4-methylpyridinium Bromide (XIi)——From 4-methylpyridine (465 mg) and dimethyl bromomethylmaleate (1.2 g) there was obtained XIi (1.4 g, 90%) as white needles, mp 136—137° (from acetone). IR ν_{max}^{KCl} cm^{-1}: 1740sh, 1720, and 1635. NMR (in $CDCl_3$) τ: 0.73 (2H, d, J=6.8 cps, H_2 and H_6), 2.02 (2H, d, J=6.8 cps, H_3 and H_5), 2.74 (1H, s, $-C=CH-$), 3.91 (2H, s, $-CH_2-$), 6.10 and 6.19 (2×3H, 2×s, 2×$-OCH_3$), and 7.32 (3H, s, $-CH_3$). *Anal.* Calcd. for $C_{13}H_{17}O_4NBr$: C, 47.29; H, 4.89; N, 4.24. Found: C, 47.28; H, 4.53; N, 4.56.

1-(3′-Oxocyclohexen-1′-ylmethyl)-4-methylpyridinium Bromide (XIj)——From 4-methylpyridine (245 mg) and 3-bromomethyl-2-cyclohexen-1-one (497 mg) there was obtained XIj (348 mg, 47%) as white needles, mp 179—180° (from acetone). IR ν_{max}^{KCl} cm^{-1}: 1670 and 1640. NMR (in $CDCl_3$) τ: 0.57 (2H, d, J=6.5 cps, H_2 and H_6), 2.09 (2H, d, J=6.5 cps, H_3 and H_5), 3.94 (2H, s, $-CH_2-$), 4.53 (1H, s, $-C=CH-$), 7.34 (3H, s, $-CH_3$), and 7.2—8.2 (6H, m). *Anal.* Calcd. for $C_{13}H_{16}ONBr\cdot H_2O$: C, 52.01; H, 6.05; N, 4.67. Found: C, 52.48; H, 6.23; N, 4.98.

In a similar manner the pyridinium salts (XIa, XIb, XIc, XId, and XIe), were obtained as an oil in 62, 98, 61, 81, and 83% yields, respectively, and used for further reaction after washing with dry ether.

General Procedure for Indolizines XIVa—g——To a solution of the salts (XIa—g) (2 mmole) in EtOH (6 ml) was added anhydrous K_2CO_3 (276 mg) and the mixture was stirred at room temperature for 5 hr. The reaction mixture was filtered and the solvent was evaporated under vacuum. The residue was chromatographed over alumina with C_6H_6–ligroin (1: 4). The first eluent was concentrated to give crystalline indolizine derivatives, which were recrystallized from aqueous EtOH. The results are summarized in Tables I and II.

6) Prepared from dimethyl-(3-oxo-1-cyclohexen-1-yl)methylsulfoxonium bromide. Unpublished data in our laboratory.
7) All melting points are uncorrected. The IR spectra were determined with a Hitachi-EPIG2 spectrophotometer, UV spectra with a Hitachi EPS-3T spectrophotometer and NMR spectra with a Hitachi R-20 instrument with tetramethylsilane as internal reference.
8) A.C. Moore, *J. Am. Chem. Soc.*, **71**, 2583 (1949).
9) H. Schaltegger, U.S. Patent 2790757 (1957) [*C. A.*, **52**, 1250a (1958)].