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Preparation of New Nitrogen-Bridged Heterocycles. 19.[1] Smooth Syntheses of Thieno[3,2-*a*]- and Thieno[2,3-*b*]indolizine Derivatives

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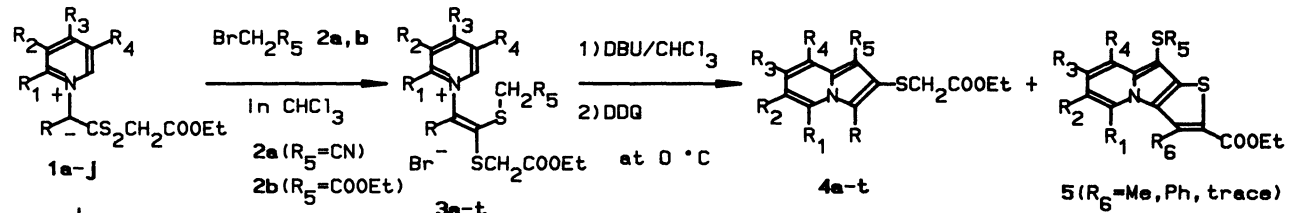
The reactions of 2-(ethoxycarbonylmethylthio)indolizines having an acyl and/or a cyano group at the 1- and 3-positions under several alkaline conditions were examined, and title compounds, thieno[3,2-*a*]- and thieno[2,3-*b*]indolizine derivatives were obtained in fairly good yields. The cyclization modes observed in these transformation reactions were in accord with those expected by the molecular orbital calculations using some model compounds and by the stereochemical consideration of starting indolizines. The alkylations of 3-hydroxythieno[3,2-*a*]- and 3-hydroxythieno[2,3-*b*]indolizines were also investigated and the corresponding *O*- and *C*-alkylated heterocycles were formed in good yields.

In our previous communication[2] we have reported the smooth intramolecular cyclizations of the indolizines possessing an ethoxycarbonylmethylthio group at the 2-position and a cyano or an ethoxycarbonyl group at 1- or 3-position to ethyl 3-aminothieno[3,2-*a*]indolizine-2-carboxylates or ethyl 3-hydroxythieno-[2,3-*b*]indolizine-2-carboxylates under alkaline conditions. The regiospecificity of the reactions and the high synthetic value for the preparations of new heterocyclic skeletons prompted us to investigate further these intramolecular cyclizations using various 2-(ethoxycarbonylmethylthio)indolizines from the theoretical and practical standpoints of view. In this paper we wish to describe the formation of some thieno[3,2-*a*]- and thieno[2,3-*b*]indolizine derivatives from the alkaline treatment of polyfunctionalized indolizines and the comparison of the cyclization modes observed in these reactions with those expected by the molecular orbital calculations using model compounds.

Results and Discussion

Preparations of 2-(Ethoxycarbonylmethylthio)indolizines. These 2-(ethoxycarbonylmethylthio)indolizine derivatives **4a—t** were prepared in moderate to good yields by the treatment of the pyridinium salts **3a—t**, readily obtainable from the *S*-alkylations of the corresponding pyridinium-*N*-methylides **1a—j** with bromoacetonitrile **2a** or ethyl bromoacetate **2b**, with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 0 °C followed by the addition of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as a dehydrogenating agent to the resulting reaction solutions. In the reactions of pyridinium salts **3e—j**, **o—t** possessing an acetyl or a benzoyl group, the formations of tricyclic thieno[2,3-*b*]-indolizines **5**[3] were also formed, but their yields were very low (<3%) (Scheme 1).

The structures of indolizines **4a—t** were determined



Ylide	R_1	R_2	R_3	R_4	R
1a	H	H	H	H	COOEt
1b	Me	H	H	H	COOEt
1c	H	H	Me	H	COOEt
1d	H	Me	H	Me	COOEt
1e	H	H	H	H	COMe
1f	Me	H	H	H	COMe
1g	H	H	Me	H	COMe
1h	H	Me	H	Me	COMe
1i	H	H	H	H	COPh
1j	H	H	Me	H	COPh

Prod.	Salt	R_1	R_2	R_3	R_4	R_5	R
4a	3a	H	H	H	H	CN	COOEt
4b	3b	Me	H	H	H	CN	COOEt
4c	3c	H	H	Me	H	CN	COOEt
4d	3d	H	Me	H	Me	CN	COOEt
4e	3e	H	H	H	H	CN	COMe
4f	3f	Me	H	H	H	CN	COMe
4g	3g	H	H	Me	H	CN	COMe
4h	3h	H	Me	H	Me	CN	COMe
4i	3i	H	H	H	H	CN	COPh
4j	3j	H	H	Me	H	CN	COPh

Prod.	Salt	R_1	R_2	R_3	R_4	R_5	R
4k	3k	H	H	H	H	COOEt	COOEt
4l	3l	Me	H	H	H	COOEt	COOEt
4m	3m	H	H	Me	H	COOEt	COOEt
4n	3n	H	Me	H	Me	COOEt	COOEt
4o	3o	H	H	H	H	COOEt	COMe
4p	3p	Me	H	H	H	COOEt	COMe
4q	3q	H	H	Me	H	COOEt	COMe
4r	3r	H	Me	H	Me	COOEt	COMe
4s	3s	H	H	H	H	COOEt	COPh
4t	3t	H	H	Me	H	COOEt	COPh

Scheme 1.

Table 1. ^{1}H NMR Spectral Data of 2-(Ethoxycarbonylmethylthio)indolizines

Compd[a] No.	C-5	C-6	C-7	C-8	CH_2CO_2Et			R			R_5	
4a	9.54	7.00	7.35	7.70	4.01	1.22	4.19	1.43	4.47		—	
	br d	dt	br t	br d	s	t	q	t	q			
4b	2.58	6.79	7.26	7.63	3.81	1.20	4.15	1.47	4.48		—	
	s	br d	q	br d	s	t	q	t	q			
4c	9.31	6.77	2.38	7.37	3.94	1.19	4.15	1.40	4.40		—	
	d	dd	s	br s	s	t	q	t	q			
4d	9.28	2.34	6.97	2.74	3.86	1.22	4.17	1.47	4.47		—	
	br s	s	br s	s	s	t	q	t	q			
4e	10.02	7.12	7.49	7.82	3.96	1.19	4.17	2.94			—	
	br d	dt	br t	br d	s	t	q	s				
4f	2.38	6.83	7.32	7.66	3.81	1.17	4.10	2.92			—	
	s	br d	q	br d	s	t	q	s				
4g	9.83	6.89	2.47	7.49	3.91	1.18	4.13	2.89			—	
	d	dd	s	br s	s	t	q	s				
4h	9.67	2.33	7.03	2.71	3.83	1.15	4.11	2.90			—	
	br s	s	br s	s	s	t	q	s				
4i	9.33	7.02	b)	b)	3.63	1.10	4.05	7.3—8.0			—	
	br d	dt			s	t	q	m				
4j	9.25	6.87	2.48	b)	3.61	1.07	4.03	7.3—7.9			—	
	d	dd	s		s	t	q	m				
4k	9.52	6.99	7.33	8.38	3.79	1.10	4.07	1.44	1.44	4.47	4.49[c]	
	br d	dt	br t	br d	s	t	q	t	t	q	q	
4l	2.53	6.67	7.15	8.28	3.73	1.10	4.07	1.43	1.43	4.43	4.46[c]	
	s	br d	q	br d	s	t	q	t	t	q	q	
4m	9.37	6.79	2.43	8.12	3.74	1.09	4.05	1.44	1.44	4.45	4.45[c]	
	d	dd	s	br s	s	t	q	t	t	q	q	
4n	9.27	2.30	6.84	2.44	3.68	1.13	4.10	1.41	1.44	4.43	4.46[c]	
	br s	s	br s	s	s	t	q	t	t	q	q	
4o	9.90	6.98	7.37	8.39	3.86	1.13	4.07	3.00		1.47	4.47	
	br d	dt	br t	br d	s	t	q	s		t	q	
4p	2.36	6.80	7.31	8.39	3.84	1.14	4.09	2.98		1.46	4.49	
	s	br d	q	br d	s	t	q	s		t	q	
4q	9.82	6.82	2.44	8.15	3.83	1.11	4.05	2.96		1.46	4.45	
	d	dd	s	br s	s	t	q	s		t	q	
4r	9.75	2.34	6.98	2.48	3.76	1.18	4.14	2.96		1.44	4.50	
	br s	s	br s	s	s	t	q	s		t	q	
4s	9.26	7.01	b)	8.48	3.58	1.05	4.01	7.2—8.0		1.46	4.50	
	br d	dt		br d	s	t	q	m		t	q	
4t	9.22	6.89	2.50	8.28	3.58	1.08	4.02	7.4—8.0		1.48	4.51	
	d	dd	s	br s	s	t	q	m		t	q	

a) These coupling constants are as follows: $J_{5,6}=J_{6,7}=7.0$, $J_{7,8}=9.0$, $J_{6,8}=2.0$, and $J_{Et}=7.0$ Hz. b) Overlapped with the phenyl proton signals. c) The signals due to these two ethoxycarbonyl groups could not be assigned.

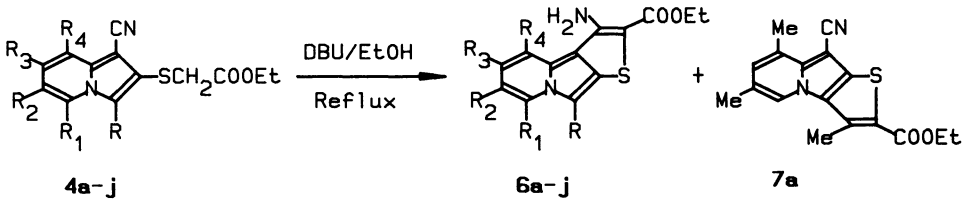
by the analyses of their physical and spectral data and by the comparisons of their ^{1}H NMR (Table 1) and IR spectra (Table 4) with those of other indolizine derivatives prepared earlier by us[1,4] and other investigators.[5] For example, the elemental analyses of indolizines **4a—t** were in good accord with the proposed compositions and their ^{1}H NMR spectra showed distinct proton signals at near δ 1.15 (t, 3H, J=7.0 Hz, $OCH_2\underline{CH_3}$), 3.61—4.01 (s, 2H, SCH_2), and near 4.10 (q, 2H, J=7.0 Hz, $O\underline{CH_2}CH_3$) due to the 2-ethoxycarbonylmethylthio group, together with other proton signals on the indolizine ring. The presence of a saturated ester carbonyl group in the 2-substituent could be also confirmed by the absorption bands appeared at 1720—1740 cm^{-1} in their IR spectra. Interestingly, the up-field shift (10—30 cm^{-1}) of the absorption band of the carbonyl group at the 1-position in indolizines **4n**, **r** or at the 3-position in indolizines **4b**, **f**, **l**, **p** was observed. These shifts must be caused by the steric crowding of the carbonyl group with the 2-ethoxycarbonylmethylthio and the 5- or 8-methyl groups.

Preparations of Thieno[3,2-*a*]- and Thieno[2,3-*b*]-indolizines. Since these indolizines **4a—t** have an active methylene group in the 2-substituent and an acyl and/or a cyano group at the 1- or 3-position, the intramolecular reactions between these group should lead to the indolizine derivatives fused with a thiophene ring. Thus, the reactions of indolizines **4a—t** were examined under alkaline conditions in which the carbanion formation from the active methylene group could be expected.

Table 2. ^{1}H NMR Spectral Data of Thieno[3,2-*a*]indolizines

Compd[a,b] No.	C-7	C-6	C-5	C-4	C-3	R		COOEt		
6a	9.63	7.01	7.29	7.78	6.08	1.38	1.46	4.34	4.43[c]	
	br d	dt	br t	br d	br s	t	t	q	q	
6b	2.89	6.95	7.35	7.71	6.07	1.41	1.51	4.40	4.47[c]	
	s	br d	q	br d	br s	t	t	q	q	
6c	9.40	6.78	2.39	7.33	5.95	1.38	1.44	4.34	4.41[c]	
	d	dd	s	br s	br s	t	t	q	q	
6d	9.36	2.32	6.83	2.74	6.30	1.39	1.47	4.35	4.44[c]	
	br s	s	br s	s	br s	t	t	q	q	
6f	2.61	6.87	7.33	7.49	6.12	2.56		1.37	4.36	
	s	br d	q	br d	br s	s		t	q	
6h	9.97	2.33	7.00	2.88	6.37	2.51		1.40	4.34	
	br s	s	br s	s	br s	s		t	q	
6i	10.38	7.20	d)	d)	6.13	7.3—8.1		1.31	4.29	
	br d	dt			br s	m		t	q	
6j	10.10	6.93	2.48	d)	6.03	7.3—8.0		1.29	4.25	
	d	dd	s		br s	m		t	q	
9a	9.27	2.33	6.88	2.74	10.99	1.41	1.47	4.40	4.40[c]	
	br s	s	br s	s	br s	t	t	q	q	
9b	9.89	2.40	7.03	2.83	10.95	2.53		1.42	4.42	
	br s	s	br s	s	br s	s		t	q	
13a	9.38	2.35	6.93	2.74	4.16	1.42	1.48	4.41	4.44[c]	
	br s	s	br s	s	s	t	t	q	q	
13b	9.42	2.37	6.96	2.80	1.42	1.49	1.49	4.41	4.41	4.44[c]
	br s	s	br s	s	t	t	t	q	q	q
14a	9.23	2.34	7.07	2.87	—	1.41	4.42	1.21	4.21	1.87[e]
	br s	s	br s	s		t	q	t	q	s

a) The coupling constants are as follows: $J_{6,7}=J_{5,6}=7.0$, $J_{4,5}=9.0$, $J_{4,6}=2.0$, $J_{Et}=7.0$ Hz. b) The spectra of compound **6e** and **6g** could not be measured because of their low solubility. c) The signals due to these ethoxycarbonyl groups could not be assigned. d) Overlapped with the phenyl proton signals. e) The methyl signal on the C-2 position.



Prod.	React.	R_1	R_2	R_3	R_4	R
6a	**4a**	H	H	H	H	COOEt
6b	**4b**	Me	H	H	H	COOEt
6c	**4c**	H	H	Me	H	COOEt
6d	**4d**	H	Me	H	Me	COOEt
6e	**4e**	H	H	H	H	COMe

Prod.	React.	R_1	R_2	R_3	R_4	R
6f	**4f**	Me	H	H	H	COMe
6g	**4g**	H	H	Me	H	COMe
6h(+**7a**)	**4h**	H	Me	H	Me	COMe
6i	**4i**	H	H	H	H	COPh
6j	**4j**	H	H	Me	H	COPh

Scheme 2.

The treatment of indolizines **4a—g, i, j** having the 1-cyano group with DBU in refluxing ethanol gave smoothly ethyl 3-aminothieno[3,2-*a*]indolizine-2-carboxylates **6a—g, i, j**, in 50—94% yields, respectively, while the similar reaction of indolizine **4h** afforded also ethyl 9-cyano-3,6,8-trimethylthieno[2,3-*b*]indolizine-2-carboxylate **7a** in ca. 65% yield, together with the expected ethyl 9-acetyl-3-amino-4,6-dimethylthieno[3,2-*a*]indolizine-2-carboxylate **6h** (ca. 18%). Apparently, the formation of amino compounds **6a—j** results from the nucleophilic addition of the carbanion generated in situ to the 1-cyano group of indolizines **4a—j**, and that of product **7a** from the nucleophilic attack of the same species to the 3-acetyl group (Scheme 2).

On the other hand, the reactions of diethyl 1,3-indolizinedicarboxylates **4k—n** with DBU did not afford any significant products, but their reactions

Table 3. ^{1}H NMR Spectral Data of Thieno[2,3-*b*]indolizines

Compd[a] No.	C-5	C-6	C-7	C-8	C-3[b]		COOEt				
7a	8.19	2.36	6.88	2.67	2.94		1.42	4.38			
	br s	s	br s	s	s		t	q			
7b	8.57	6.82	7.29	8.33	2.99		1.42	1.47	4.40	4.44[c]	
	br d	dt	br t	br d	s		t	t	q	q	
7c	2.97	6.63	7.21	8.37	3.04		1.43	1.49	4.41	4.49[c]	
	s	br d	q	br d	s		t	t	q	q	
7d	8.23	6.53	2.39	7.94	2.84		1.42	1.46	4.38	4.40[c]	
	d	dd	s	br s	s		t	t	q	q	
7e	8.18	2.31.	6.87	2.87	2.96		1.44	1.49	4.41	4.41[c]	
	br s	s	br s	s	s		t	t	q	q	
7f	d)	6.57	d)	8.39	7.0—7.9		1.17	4.22	1.49	4.49	
		dt		br d	m		t	q	t	q	
7g	d)	6.42	2.39	8.15	7.0—7.9		1.18	4.22	1.49	4.48	
		dd	s	br s	m		t	q	t	q	
8a	8.59	6.83	7.31	8.27	10.53		1.42	1.45	4.41	4.41	
	br d	dt	br t	br d	br s		t	t	q	q	
8b	3.00	6.63	7.21	8.22	11.44		1.41	1.46	4.41	4.41	
	s	br d	q	br d	br s		t	t	q	q	
8c	8.39	6.63	2.42	7.97	8.70		1.41	1.44	4.39	4.39[c]	
	d	dd	s	br s	br		t	t	q	q	
11a	8.72	6.90	7.34	8.33	4.31		1.43	1.48	4.43	4.47[c]	
	br d	dt	br t	br d	s		t	t	q	q	
11b	2.97	6.65	7.23	8.28	4.11		1.43	1.48	4.41	4.45[c]	
	s	br d	q	br d	s		t	t	q	q	
11c	8.55	6.70	2.45	8.08	4.29		1.43	1.47	4.40	4.43[c]	
	d	dd	s	br s	s		t	t	q	q	
11d	8.70	6.85	7.31	8.30	1.40	1.46	1.50	4.37	4.43	4.56[c]	
	br d	dt	br t	br d	t	t	t	q	q	q	
11e	3.01	6.67	7.25	8.32	1.42	1.47	1.49	4.40	4.40	4.49[c]	
	s	br d	q	br d	t	t	t	q	q	q	
11f	8.57	6.71	2.46	8.08	1.41	1.46	1.50	4.38	4.43	4.56[c]	
	d	dd	s	br s	t	t	t	q	q	q	
12a	8.93	7.04	7.50	8.24	—		1.23	4.23	1.41	4.38	1.90[e]
	br d	dt	br t	br d			t	q	t	q	s
12b	3.14	6.77	7.42	8.50	—		1.26	4.25	1.44	4.41	1.91[e]
	s	br d	q	br d			t	q	t	q	s
12c	8.81	6.90	2.49	8.05	—		1.23	4.23	1.41	4.38	1.91[e]
	d	dd	s	br s			t	q	t	q	s

a) The coupling constants are as follows: $J_{5,6}=J_{6,7}=7.0$, $J_{7,8}=9.0$, $J_{6,8}=2.0$, $J_{Et}=7.0$ Hz. b) The proton signal due to the hydroxyl, methyl, methoxyl, or ethoxyl group. c) The signals due to these ethoxycarbonyl groups could not be assigned. d) Overlapped with the phenyl proton signals. e) The methyl signal on the C-2 position.

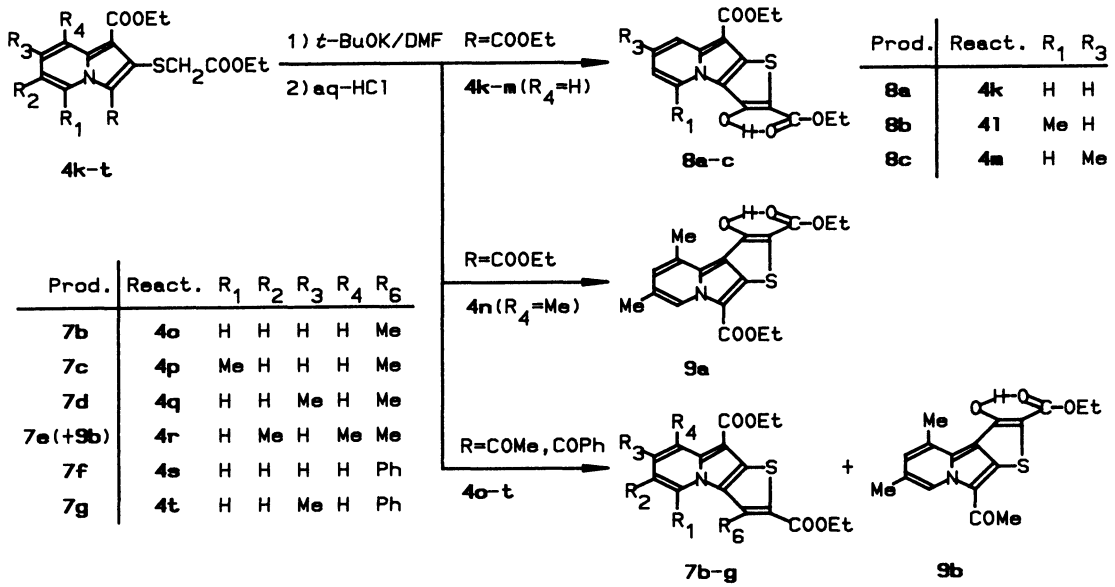
under the conditions for the Dieckmann reaction[6] gave the corresponding adducts: The treatment of indolizines **4k—m** with potassium *t*-butoxide in *N,N*-dimethylformamide (DMF) at room temperature followed by quenching the resulting mixture with diluted hydrochloric acid formed diethyl 3-hydroxythieno[2,3-*b*]indolizine-2,9-dicarboxylates **8a—c** in very good yields. Interestingly, similar reaction of compound **4n** did not give any compound of type **8**, but afforded only diethyl 3-hydroxy-4,6-dimethylthieno[3,2-*a*]indolizine-2,9-dicarboxylate **9a** in 89% yield. Analogously, the reactions of indolizines **4o—t** with potassium *t*-butoxide gave the corresponding cycloadducts **7b—d**, **7e+9b**, **7f**, and **7g**, respectively. Same products **7b**, **d**, **e**, were also obtained in 86, 74, and 59% yields by the reactions of indolizines **4o**, **q**, **r** with DBU. These results are shown in Scheme 3.

The structural assignments of thieno[3,2-*a*]indolizines **6a—j** and **9a**, **b** and thieno[2,3-*b*]indolizines **7a—g** and **8a—c** were accomplished mainly by their elemental and by ^{1}H NMR (Table 2 and 3) and IR (Table 5) spectral analyses. The structures of ethyl 3-aminothieno[3,2-*a*]indolizine-2-carboxylates **6a—j** could be easily decided by the appearances of two amino absorption bands (3300—3450 cm^{-1}) and the absence of the cyano band in their IR spectra and by the presence of amino proton signals (δ 5.95—6.37 (br s, 2H)) and the absence of the active methylene signals in their ^{1}H NMR spectra. Similarly, compounds **7a—g** were assigned to ethyl 3-methyl- or 3-phenylthieno[2,3-*b*]indolizine-2-carboxylates because the elimination of a water molecule from indolizines **4h**, **o—t** was confirmed by their elemental and by IR and ^{1}H NMR spectral analyses. On the other hand, the

Table 4. Some Data of 2-(Ethoxycarbonylmethylthio)indolizines

Compd No.	Salt(SM[a])	Method	Yield %	Mp θ_m/°C	$\nu^{KBr}_{CN\text{ and }CO}$/cm^{-1}			Formula[b]
4a	**3a** (**1a**, **2a**)	A	68	88—89	2208	1726	1676	$C_{16}H_{16}N_2O_4S$
4b	**3b** (**1b**, **2a**)	A	40	69—70	2208	1723	1716	$C_{17}H_{18}N_2O_4S$
4c	**3c** (**1c**, **2a**)	A	87	101—102	2200	1735	1670	$C_{17}H_{18}N_2O_4S$
4d	**3d** (**1d**, **2a**)	A	65	107—109	2211	1724	1680	$C_{18}H_{20}N_2O_4S$
4e	**3e** (**1e**, **2a**)	B	17	92—94	2218	1740	1630	$C_{15}H_{14}N_2O_3S$
4f	**3f** (**1f**, **2a**)	B	22	69—70	2210	1726	1661	$C_{16}H_{16}N_2O_3S$
4g	**3g** (**1g**, **2a**)	B	21	106—107	2201	1723	1634	$C_{16}H_{16}N_2O_3S$
4h	**3h** (**1h**, **2a**)	B	22	110—112	2217	1721	1626	$C_{17}H_{18}N_2O_3S$
4i	**3i** (**1i**, **2a**)	B	19	91—93	2200	1726	1610	$C_{20}H_{16}N_2O_3S$
4j	**3j** (**1j**, **2a**)	B	24	139—142	2201	1729	1612	$C_{21}H_{18}N_2O_3S$
4k	**3k** (**1a**, **2b**)	A	31	53	1729	1686	1670	$C_{18}H_{21}NO_6S$
4l	**3l** (**1b**, **2b**)	A	47	70—71	1720	1705	1675	$C_{19}H_{23}NO_6S$
4m	**3m**(**1c**, **2b**)	A	57	59—60	1726	1681	1670	$C_{19}H_{23}NO_6S$
4n	**3n** (**1d**, **2b**)	A	64	103—104	1725	1716	1671	$C_{20}H_{25}NO_6S$
4o	**3o** (**1e**, **2b**)	B	40	61—62	1720	1684	1617	$C_{17}H_{19}NO_5S$
4p	**3p** (**1f**, **2b**)	B	26	53—54	1723	1684	1652	$C_{18}H_{21}NO_5S$
4q	**3q** (**1g**, **2b**)	B	57	83—86	1720	1684	1620	$C_{18}H_{21}NO_5S$
4r	**3r** (**1h**, **2b**)	B	69	98—100	1734	1690	1639	$C_{19}H_{23}NO_5S$
4s	**3s** (**1i**, **2b**)	B	68	96—97	1723	1685	1620	$C_{22}H_{21}NO_5S$
4t	**3t** (**1j**, **2b**)	B	78	83—84	1721	1685	1608	$C_{23}H_{23}NO_5S$

a) Starting materials. b) Satisfactory analytical data (within 0.3% for C, H, and N) were obtained for all new compounds.



Scheme 3.

structures of products **8a**—**c** and **9a**, **b** could be determined by considering in detail the presence or absence of the anisotropic effect of the carbonyl group participating with the cyclizations: In the ^{1}H NMR spectra of compounds **8a**—**c**, for example, the chemical shifts (δ 7.97—8.27) due to the 8-proton were very similar to those (δ 8.12—8.38) of the starting indolizines **4k**—**m**, but the values (δ 8.59 and 8.39) for the 5-proton of cycloadducts **8a**, **c** were largely different from those (δ 9.52 and 9.37) of indolizine derivatives **4k** and **4m**. On the contrary, the chemical shifts (δ 9.27 and 9.89) owing to the 7-proton of compounds **9a**, **b** were almost same value (δ 9.27 and 9.75) with the 5-proton of indolizine **4n**, **r**. These facts mean that the 3-ester group was attacked in the formers (**4k**—**m**) and the 1-ester group in the latters (**4n**, **r**). That is to say, the cyclization modes can be decided clearly by the largely diminished anisotropic effect (δ ca. 1 ppm) for the protons at the position peri to the carbonyl group disappeared during the reactions. Furthermore, the presence of an enolic hydroxyl proton signal at δ 8.70—11.44 (1H, br s) shows definitely that these compounds **8a**—**c** and **9a**, **b** have an aromatic thiophene ring.

Table 5. Some Data of Thieno[3,2-*a*]- and Thieno[2,3-*b*]indolizines

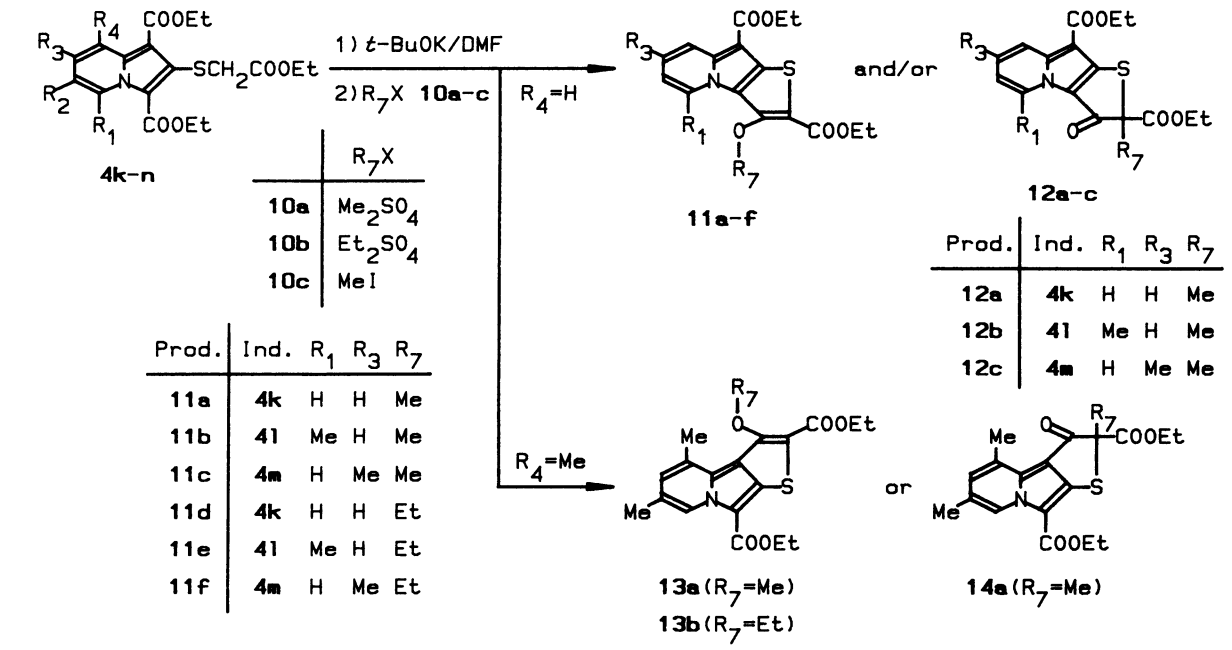
Compd	React.	Method	Yield %	Mp θ_m/°C	$\nu^{KBr}_{NH_2 \text{ and } CO}$/cm^{-1}				Formula[a]
6a	**4a**	A	94	211—213	3442	3330	1650		$C_{16}H_{16}N_2O_4S$
6b	**4b**	A	50	170—172	3398	3320	1652		$C_{17}H_{18}N_2O_4S$
6c	**4c**	A	75	198—200	3438	3333	1677		$C_{17}H_{18}N_2O_4S$
6d	**4d**	A	89	183—184	3520	3360	1691	1648	$C_{18}H_{20}N_2O_4S$
6e	**4e**	A	73	270—271	3439	3341	1644		$C_{15}H_{14}N_2O_3S$
6f	**4f**	A	83	190—191	3385	3301	1666		$C_{16}H_{16}N_2O_3S$
6g	**4g**	A	82	175—176	3445	3333	1652		$C_{16}H_{16}N_2O_3S$
7a(+**6h**)[b]	**4h**	A	ca. 65	157—160	2200[c]		1693		$C_{17}H_{16}N_2O_2S$
6i	**4i**	A	73	270—271	3439	3341	1644		$C_{20}H_{16}N_2O_3S$
6j	**4j**	A	61	235—236	3422	3320	1654		$C_{21}H_{18}N_2O_3S$
8a	**4k**	B	86	159—161	1674	1635	d)		$C_{16}H_{15}NO_5S$
8b	**4l**	B	87	190—192	1660		d)		$C_{17}H_{17}NO_5S$
8c	**4m**	B	84	139—140	1685		d)		$C_{17}H_{17}NO_5S$
9a	**4n**	B	89	156—158	1674	1633	d)		$C_{18}H_{19}NO_5S$
7b	**4o**	B(A)	78(86)	194—195	1690	1670			$C_{17}H_{17}NO_4S$
7c	**4p**	B	67	149—150	1684	1659			$C_{18}H_{19}NO_4S$
7d	**4q**	B(A)	90(74)	173—174	1680	1665			$C_{18}H_{19}NO_4S$
7e	**4r**	A	59	127—128	1690	1669			$C_{19}H_{21}NO_4S$
9b(+**7e**)	**4r**	B	34(49)	192—194	1647	1600	d)		$C_{17}H_{17}NO_4S$
7f	**4s**	B	91	118—119	1684	1665			$C_{22}H_{19}NO_4S$
7g	**4t**	B	84	159—160	1672	1662			$C_{23}H_{21}NO_4S$
11a	**4k**, **10a**	C	78	126—128	1685	1670			$C_{17}H_{17}NO_5S$
11b	**4l**, **10a**	C	76	133—134	1689	1661			$C_{18}H_{19}NO_5S$
11c	**4m**,**10a**	C	74	136—138	1689	1666			$C_{18}H_{19}NO_5S$
11d	**4k**, **10b**	C	77	98—99	1680	1667			$C_{18}H_{19}NO_5S$
11e	**4l**, **10b**	C	74	137—139	1680				$C_{19}H_{21}NO_5S$
11f	**4m**,**10b**	C	83	128—130	1686	1675			$C_{19}H_{21}NO_5S$
12a(+**11a**)	**4k**, **10c**	C	63(15)	146—148	1724	1677	1650		$C_{17}H_{17}NO_5S$
12b	**4l**, **10c**	C	68	139—140	1720	1700	1650		$C_{18}H_{19}NO_5S$
12c(+**11c**)	**4m**,**10c**	C	67(7)	122—124	1725	1675	1650		$C_{18}H_{19}NO_5S$
13a	**4n**, **10a**	C	81	135—136	1695	1675			$C_{19}H_{21}NO_5S$
13b	**4n**, **10b**	C	86	126—128	1688	1667			$C_{20}H_{23}NO_5S$
14a	**4n**, **10c**	C	87	152—153	1725	1700	1669		$C_{19}H_{21}NO_5S$

a) Satisfactory analytical data (within 0.3% for C, H, and N) were obtained for all new compounds except **6h**. b) Other physical and analytical data of compound **6h** (ca. 18%) could not be measured because of the inaccessibility of its pure sample. c) Cyano absorption band. d) Distinct hydroxyl absorption band did not appear in the range of 4000—3000 cm^{-1}.

Preparations of *O*- and *C*-Alkylated Thienoindolizines. Since facile and effective syntheses of 3-hydroxythieno[2,3-*b*]indolizines **8a—c** and 3-hydroxythieno[3,2-*a*]indolizine **9a** could be established, the preparations of some derivatives using them were examined. The treatment of indolizines **4k—n** with potassium *t*-butoxide in DMF at room temperature followed by the addition of dimethyl **10a** and diethyl sulfate **10b** yielded the corresponding *O*-methylated **11a—c** and **13a** and *O*-ethylated thienoindolizines **11d—f** and **13b** in 74—88% yields. On the other hand, the reactions of indolizines **4k—n** using methyl iodide **10c** as an alkylating agent gave compounds **11a**+**12a**, **12b**, **11c**+**12c**, and **14a** in good yields, and the *C*-methylated thienoindolizines **12a—c** and **14a** were major or exclusive (Scheme 4).

The structures of methoxy- and ethoxythienoindolizines **11a—f** and **13a, b** were determined by the presence of the methoxyl (δ 4.11—4.31 (3H, s)) or ethoxyl proton signals (δ near 1.40 (3H, t, J=7.0 Hz) and near 4.45 (2H, q, J=7.0 Hz)) in addition to other proton signals which were very similar to those of hydroxythienoindolizines **8a—c** and **9a, b** in their ^{1}H NMR spectra. On the other hand, compounds **12a—c** and **14a** were assigned by the indications of a methyl group (δ near 1.90 (3H, s)) and of an ethoxycarbonyl group (δ near 1.25 (3H, t, J=7.0 Hz) and near 4.25 (2H, q, J=7.0 Hz)) attached to the tetrahedral carbon and by the considerably increased down-field shift of the 5-proton signal (δ 8.93 (**12a**) and 8.81 (**12c**)) in their ^{1}H NMR spectra.

Reaction Mechanisms and Molecular Orbital (MO) Calculations. Possible mechanisms for these intramolecular cyclizations are shown in Scheme 5. As was expected, these thieno[3,2-*a*]- **6a—j** and **9a, b** and thieno[2,3-*b*]indolizine derivatives **7a—g** and **8a—c** must be formed via the nucleophilic attack of carbanion **15** generated in situ by the alkaline treatment of indolizines **4a—t** to the cyano or carbonyl group at the 1- or 3-position followed by the aromatizations through hydrogen shifts or with the elimination. The formations of *O*-alkylated **11a—f**

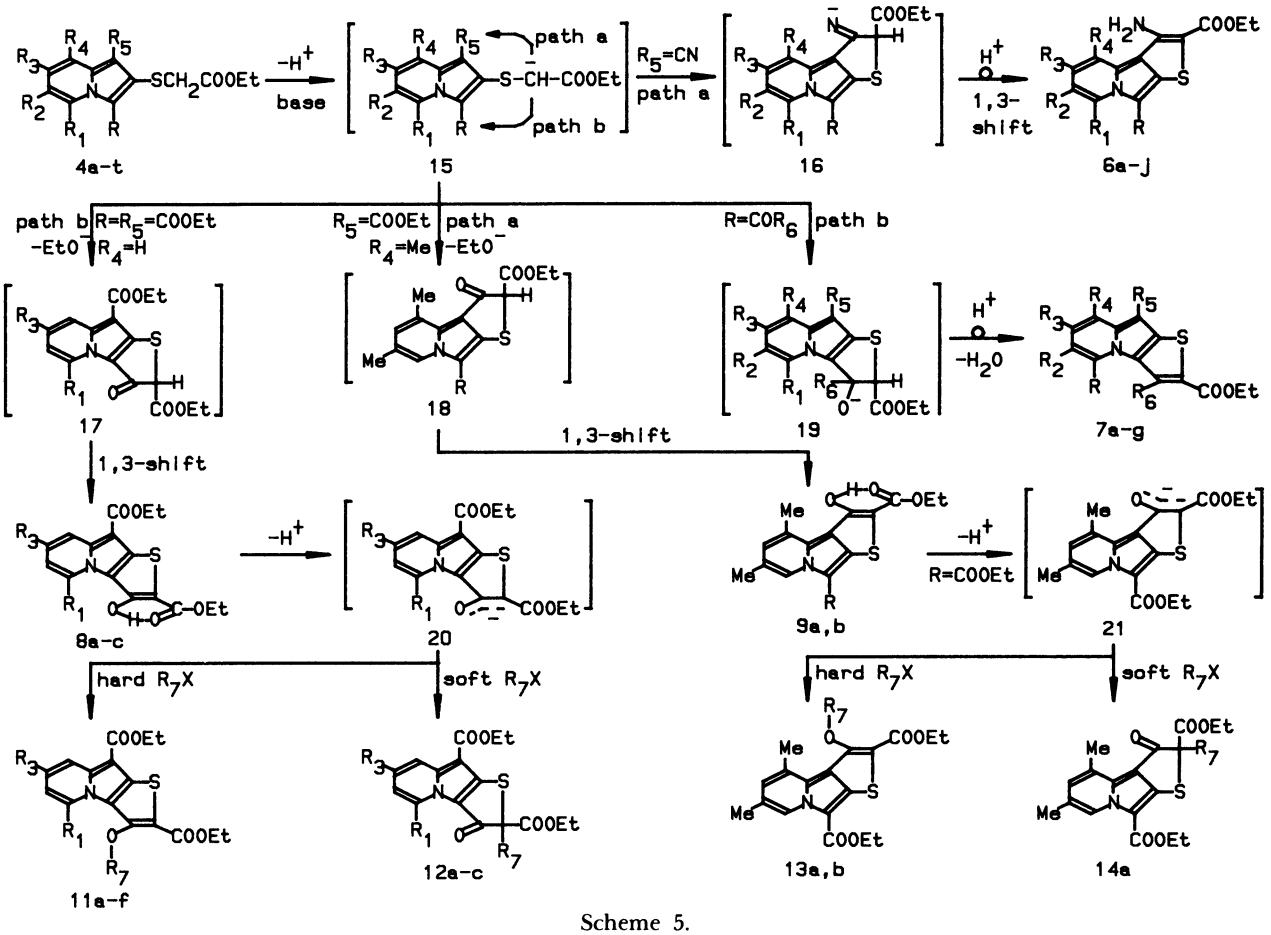


R_7X	
10a	Me_2SO_4
10b	Et_2SO_4
10c	MeI

Prod.	Ind.	R_1	R_3	R_7
11a	4k	H	H	Me
11b	4l	Me	H	Me
11c	4m	H	Me	Me
11d	4k	H	H	Et
11e	4l	Me	H	Et
11f	4m	H	Me	Et

Prod.	Ind.	R_1	R_3	R_7
12a	4k	H	H	Me
12b	4l	Me	H	Me
12c	4m	H	Me	Me

Scheme 4.



Scheme 5.

and **13a**, **b** and *C*-alkylated thienoindolizines **12a**—**c** and **14a** can be well-explained by the application of HSAB principle[7] to ambident anions **20** and **21**.

In order to obtain further information for the electrophilicity of the 1- and 3-substituents in the indolizine molecule, the MO calculations (PPP method)[8] of 1-cyano-3-indolizinecarboxylic acid **22a** and 1,3-indolizinedicarboxylic acid **22b** as models for

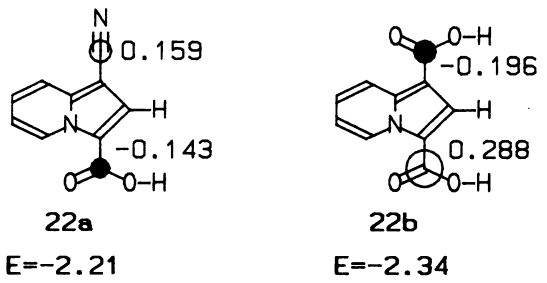


Fig. 1.

indolizines **4a, k** were carried out. The coefficients of the cyano and/or ester carbons at the 1- and 3-positions in the lowest unoccupied molecular orbitals (LUMO) of **22a, b** are shown in Fig. 1. Apparently, the order of the electrophilicity of the 1- and 3-substituent in these model compounds **22a,b** is 1-CN>3-COOH>1-COOH, and, except the cases of indolizines **4h, n, r**, parallel to that (1-CN>3-COMe or 3-COPh>3-COOEt>1-COOEt) observed. The formation of compound **7a** may be interpreted by considering the equilibrium (reversible) betweeen indolizine **4h** and 3-aminothieno[3,2-*a*]indolizine **6h** and an irreversible transformation of **4h** to **7a**. On the other hand, the nucleophilic attack leading to 3-hydroxythieno[3,2-*a*]indolizines **9a, b** can be explained in terms of the increased reactivity of the ester carbonyl carbon at the 1-position in indolizines **4n, r**, because the introduction of a 8-methyl group to the indolizine ring makes to shift the carbonyl absorption bands at the 1-position to considerably high (**4n**, 1716 cm^{-1}) and slightly high regions (**4r**, 1690 cm^{-1}).

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. The microanalyses were carried out on a Perkin-Elmer 240 elemental analyzer. The ^1H NMR spectra were determined with a Varian EM360A spectrometer in deuteriochloroform with tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. The IR spectra were taken with a Hitachi 260-10 infrared spectrophotometer.

Materials. Pyridinium ylides **1a—j** were prepared according to the procedure appeared in the literature.[3,9] Some physical and spectral data of new compounds are as follows: **1a**, 78%, yellow needles (from $CHCl_3$–ether), mp 131—132 °C, IR ν (KBr) 1740 and 1645 cm^{-1} (CO). Anal. ($C_{14}H_{17}NO_4S_2$) C, H, N. **1b**, 91%, yellow needles (from $CHCl_3$–ether), mp 136—137 °C, IR ν (KBr) 1720 and 1652 cm^{-1} (CO). Anal. ($C_{15}H_{19}NO_4S_2$) C, H, N. **1c**, 84%, yellow needles ($CHCl_3$–ether), mp 148—150 °C, IR ν (KBr) 1737 and 1650 cm^{-1} (CO). Anal. ($C_{15}H_{19}NO_4S_2$) C, H, N. **1d**, 85%, yellow needles ($CHCl_3$–ether), mp 178—179 °C, IR ν (KBr) 1724 and 1645 cm^{-1} (CO). Anal. ($C_{16}H_{21}NO_4S_2$) C, H, N. **1f**, 52%, yellow needles ($CHCl_3$–ether), mp 98—100 °C, IR ν (KBr) 1720 and 1590 cm^{-1} (CO). Anal. ($C_{14}H_{17}NO_3S_2$) C, H, N. **1h**, 81%, yellow needles ($CHCl_3$–ether), mp 171—172 °C, IR ν (KBr) 1721 and 1595 cm^{-1} (CO). Anal. ($C_{15}H_{19}NO_3S_2$) C, H, N.

Preparations of Indolizines. General Method A: A chloroform solution (20 ml) of pyridinium ylide **1a—d** (2 mmol) and bromoacetonitrile or ethyl bromoacetate (**2**, 2.2 mmol) was kept on standing until the ylide was completely alkylated (ca. 1—6 d). The resulting mixture was concentrated under reduced pressure at 50—55 °C and the residue was washed three times with ether to remove excess alkylating agents. Pyridinium salt thus obtained was again dissolved in chloroform (30 ml). To the solution DBU (0.38 g, 2.5 mmol) was added dropwise in an ice bath, and after stirring for additional 10 min, DDQ (0.45 g, 2 mmol) was added. The mixture was allowed to react for further 6—12 h in an ice bath and then concentrated under reduced pressure. The residue was separated by column chromatography (alumina) using chloroform as an eluent, and recrystallization from ethanol afforded the corresponding ethyl 2-(ethoxycarbonylmethylthio)indolizine-3-carboxylates **4a—d, k—n**.

Method B: A chloroform solution (30 ml) of ylide **1e—j** (2 mmol) and an alkylating agent (2.2 mmol) was kept on standing at room temperature until the ylide was completely disappeared. Without the removal of excess alkylating agent, the resulting solution was allowed to react with DBU (0.38 g, 2.5 mmol) and then with DDQ (0.45 g, 2 mmol) in an ice bath for 6—12 h. The similar work-ups of resulting mixtures gave other indolizine derivatives **4e—j, o—t**.

These results and some data are listed in Tables 1 and 4.

In the reactions of ylides **1e—j** ethyl 9-thiocyanato- and 9-(ethoxycarbonylthio)thieno[2,3-*b*]indolizine-2-carboxylates **5** were also obtained in below 3% yields but the preparations of pure samples could not be successful because of their low yields and of their thermal instability.

The application of Method A for the reactions of ylides **1e—j** having an acetyl or a benzoyl group gave complex mixtures and considerably diminished yields of the expected indolizines **4e—j, o—t** were observed. In these reactions indolizines and thieno[2,3-*b*]indolizines derived from pyridinium salts via the cis-trans-isomerization of the vinyl group were also detected.

Preparations of Thieno[3,2-*a*] and Thieno[2,3-*b*]indolizines. General Method A: An ethanolic solution (30 ml) of indolizine (1 mmol) was heated under the reflux temperature for 1—4 h. The solution was chilled overnight in a freezer and the precipitated substance was collected by filtration. Recrystallization from chloroform gave the corresponding thienoindolizines.

Method B: To a DMF solution (5 ml) of indolizine (1 mmol) potassium *t*-butoxide (0.14 g, 1.25 mmol) was added at room temperature and the mixture was kept on standing for an additional 1 h. After the acidification of the solution with diluted hydrochloric acid the precipitated substances were collected by filtration, washed with two portions (each 10 ml) of water, and dried in vacuum desiccator for 1 d. The separation of crude product by column chromatography (silica gel) using chloroform and recrystallization from ethanol provided the corresponding thienoindolizines.

These results and some physical and spectral data are summarized in Tables 2, 3, and 5.

Alkylations of Thienoindolizines. General Method: To a DMF solution (5 ml) of indolizine (1 mmol) potassium *t*-

butoxide (0.14 g, 1.25 mmol) was added at room temperature and the resulting mixture was kept on standing for an additional 1 h. An alkylating agent (2 mmol) was then added dropwise under stirring. After stirring for 1 h, the reaction solution was heated to 60—70 °C for further 10 min to complete the reaction. The work-ups gave the corresponding *O*-alkylated and/or *C*-alkylated thienoindolizine derivatives.

These results and some data are listed in Tables 2, 3, and 5.

References

1) For part 18 of this series, see A. Kakehi, S. Ito, N. Kinoshita, and Y. Abaka, *Bull. Chem. Soc. Jpn.*, **61**, 2055 (1988).

2) A. Kakehi, S. Ito, S. Matsumoto, and Y. Morimoto, *Chem. Lett.*, **1987**, 2043.

3) A. Kakehi, S. Ito, Y. Ohno, S. Shiba, and S. Kamata, *Bull. Chem. Soc. Jpn.*, **60** 3713 (1987).

4) A. Kakehi, S. Ito, S. Yonezu, K. Maruta, and K. Yuito, *Heterocycles*, **23**, 33 (1985); A. Kakehi, S. Ito, S. Yonezu, K. Maruta, K. Yuito, M. Shiohara, and K. Adachi, *Bull. Chem. Soc. Jpn.*, **60**, 1867 (1987).

5) C. Maseda, M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **94**, 839 (1974); Y. Tominaga, H. Fujito, K. Mizuyama, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.*, **25**, 1519 (1977); Y. Tominaga, Y. Miyake, H. Fujito, K. Kurata, H. Awaya, Y. Matsuda, and G. Kobayashi, *ibid.*, **25**, 1528 (1977).

6) W. S. Johnson, B. Bannister, and R. Pappo, *J. Am. Chem. Soc.*, **78**, 6331 (1956); H. Sugihara, H. Mabuchi, and Y. Kawamatsu, *Chem. Pharm. Bull.*, **35**, 1919 (1987).

7) T.-L. Ho "Hard and Soft Acids and Bases Principle in Organic Chemistry," Academic Press, New York (1977).

8) R. Pariser and R. G. Parr, *J. Chem. Phys.*, **21**, 466 (1953); **21**, 767 (1953); J. A. Pople, *Trans. Faraday Soc.*, **49**, 1375 (1953); H. O. Pritchard and H. A. Skinner, *Chem. Rev.*, **55**, 745 (1955).

9) Y. Tominaga, H. Fujito, H. Norisue, A. Ushirogochi, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, **99**, 1081 (1979).