Preparation of New Nitrogen-Bridged Heterocycles. XXII.[1] A New Approach to the Syntheses of Thienoindolizine Derivatives

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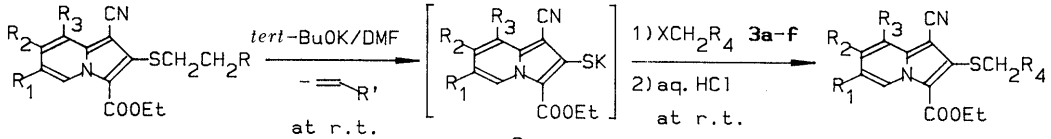
Ethyl 2-[(2-substituted ethyl)thio]-3-indolizinecarboxylates (1a—f and 5a—f) were deprotected with potassium *tert*-butoxide in *N,N*-dimethylformamide and the resulting potassium 2-indolizinethiolates were alkylated with various alkylating agents such as chloroacetone (3a), phenacyl bromides (3b—d), and nitrobenzyl bromides (3e, f) to afford smoothly the corresponding *S*-functionalized indolizine derivatives (4a—r and 6a—r) in considerable yields. On the other hand, the similar reactions of 3-acetyl-2-[(2-substituted ethyl)thio]indolizines (7a—f) provided 3-methylthieno[2,3-*b*]indolizine derivatives (8a—o), formed *via* the further intramolecular cyclizations of the initially generated *S*-alkylated indolizines under the reaction conditions employed here. The functionalized indolizines (4a—r and 6a—r) obtained above could also be transformed to the corresponding thieno[3,2-*a*]- (10a—r, 14a—d, and 15a, b) and thieno[2,3-*b*]indolizine derivatives (11a—h and 12a—d) under various alkaline conditions.

Keywords 2-[(substituted ethyl)thio]indolizine; deprotection; 2-[(substituted methyl)thio]indolizine; 2-indolizinethiol; thieno[3,2-*a*]indolizine; thieno[2,3-*b*]indolizine; alkylation

In our preceding paper[1] we described the preparations of some *S*-protected indolizines, 2-[(2-cyanoethyl)thio]- and 2-[(2-ethoxycarbonylethyl)thio]indolizine derivatives, and their smooth deprotections to the corresponding 2-indolizinethiol compounds with the elimination of acrylonitrile or ethyl acrylate. In addition, we also reported that the 2-indolizinethiols reacted with ethyl bromoacetate in the presence of base to afford 2-[(ethoxycarbonylmethyl)thio]indolizines which are well documented as potential precursors for thieno[3,2-*a*]- and thieno[2,3-*b*]indolizines.[2] These findings and pharmaceutical considerations[3] prompted us to study further the preparations of these heterocycles, though the indolizine derivatives having a functional group other than (alkoxycarbonylmethyl)thio at the 2-position were not accessible by our previous methods.[2,4] In this paper we wish to report the *S*-functionalizations of 2-indolizinethiol derivatives generated *in situ* by the alkaline treatment of the 2-[(2-cyanoethyl)thio]- and 2-[(2-ethoxycarbonylethyl)thio]indolizines and the transformations of the products thus obtained to thieno[3,2-*a*]- and thieno[2,3-*b*]indolizine derivatives.

Results and Discussion

***S*-Functionalizations of 2-Indolizinethiol Derivatives** When ethyl 1-cyano-2-[(2-cyanoethyl)thio]-3-indolizinecarboxylates (**1a—c**),[1] were allowed to react with potassium *tert*-butoxide and then with chloroacetone (**3a**) or phenacyl bromide (**3b**) in *N,N*-dimethylformamide (DMF) at room temperature, the corresponding 2-(acetonylthio)- (**4a—c**) or 2-(phenacylthio)indolizine derivatives (**4d—f**) were obtained in 38, 51, and 49%, or 91, 82, and 90% yields, respectively. The same products (**4a—f**) were also formed in 58, 63, 67, 77, 73, and 69% yields from the reactions of 1-cyano-2-[(2-ethoxycarbonylethyl)thio]indolizines (**1d—f**) with **3a, b**. The similar reactions of **1a—c** with *p*-chlorophenacyl bromide (**3c**), *p*-bromophenacyl bromide (**3d**), *p*-nitrobenzyl bromide (**3e**), and *o*-nitrobenzyl bromide (**3f**) in the presence of potassium *tert*-butoxide provided the *S*-functionalized indolizine derivatives (**4g—r**) in good yields (Chart 1). Analogously, the alkaline treatment of diethyl 2-[(2-substituted ethyl)thio]-1,3-indolizinedicarboxylates (**5a—f**) followed by the alkylations with the same reagents (**3a—f**) gave the corresponding *S*-functionalized



1	R_1	R_2	R_3	R
a	H	H	H	CN
b	H	Me	H	CN
c	Me	H	Me	CN
d	H	H	H	COOEt
e	H	Me	H	COOEt
f	Me	H	Me	COOEt

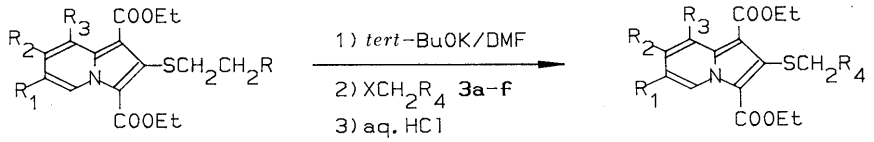
3	R_4
a	Ac
b	Bz
c	*p*-ClBz
d	*p*-BrBz
e	*p*-NO_2Ph
f	*o*-NO_2Ph

Bz : benzoyl

4	R_1	R_2	R_3	R_4
a	H	H	H	Ac
b	H	Me	H	Ac
c	Me	H	Me	Ac
d	H	H	H	Bz
e	H	Me	H	Bz
f	Me	H	Me	Bz
g	H	H	H	*p*-ClBz
h	H	Me	H	*p*-ClBz
i	Me	H	Me	*p*-ClBz

4	R_1	R_2	R_3	R_4
j	H	H	H	*p*-BrBz
k	H	Me	H	*p*-BrBz
l	Me	H	Me	*p*-BrBz
m	H	H	H	*p*-NO_2Ph
n	H	Me	H	*p*-NO_2Ph
o	Me	H	Me	*p*-NO_2Ph
p	H	H	H	*o*-NO_2Ph
q	H	Me	H	*o*-NO_2Ph
r	Me	H	Me	*o*-NO_2Ph

Chart 1



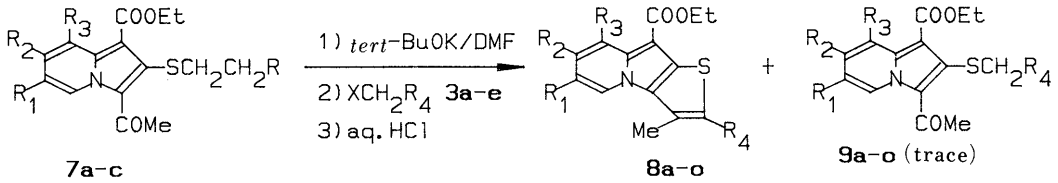
5a-f 6a-r

5	R_1	R_2	R_3	R
a	H	H	H	CN
b	H	Me	H	CN
c	Me	H	Me	CN
d	H	H	H	COOEt
e	H	Me	H	COOEt
f	Me	H	Me	COOEt

6	R_1	R_2	R_3	R_4
a	H	H	H	Ac
b	H	Me	H	Ac
c	Me	H	Me	Ac
d	H	H	H	Bz
e	H	Me	H	Bz
f	Me	H	Me	Bz
g	H	H	H	*p*-ClBz
h	H	Me	H	*p*-ClBz
i	Me	H	Me	*p*-ClBz

6	R_1	R_2	R_3	R_4
j	H	H	H	*p*-BrBz
k	H	Me	H	*p*-BrBz
l	Me	H	Me	*p*-BrBz
m	H	H	H	*p*-NO_2Ph
n	H	Me	H	*p*-NO_2Ph
o	Me	H	Me	*p*-NO_2Ph
p	H	H	H	*o*-NO_2Ph
q	H	Me	H	*o*-NO_2Ph
r	Me	H	Me	*o*-NO_2Ph

Chart 2



7a-c 8a-o 9a-o (trace)

7	R_1	R_2	R_3	R
a	H	H	H	CN
b	H	Me	H	CN
c	Me	H	Me	CN
d	H	H	H	COOEt
e	H	Me	H	COOEt
f	Me	H	Me	COOEt

8,9	R_1	R_2	R_3	R_4
a	H	H	H	Ac
b	H	Me	H	Ac
c	Me	H	Me	Ac
d	H	H	H	Bz
e	H	Me	H	Bz
f	Me	H	Me	Bz
g	H	H	H	*p*-ClBz
h	H	Me	H	*p*-ClBz

8,9	R_1	R_2	R_3	R_4
i	Me	H	Me	*p*-ClBz
j	H	H	H	*p*-BrBz
k	H	Me	H	*p*-BrBz
l	Me	H	Me	*p*-BrBz
m	H	H	H	*p*-NO_2Ph
n	H	Me	H	*p*-NO_2Ph
o	Me	H	Me	*p*-NO_2Ph

Chart 3

indolizine derivatives (**6a**—**r**) in good yields, respectively (Chart 2). On the other hand, the reactions of ethyl 3-acetyl-2-[(2-substituted ethyl)thio]-1-indolizinecarboxylates (**7a**—**f**) with **3a**—**e** in the presence of the same base at room temperature afforded ethyl 3-methylthieno[2,3-*b*]-9-indolizinecarboxylates (**8a**—**o**), together with trace amounts of the *S*-alkylated indolizines (**9a**—**o**). The reactions of **7a**—**f** with **3a**—**e** under heating gave exclusively tricyclic thienoindolizine derivatives (**8a**—**o**) (Chart 3).

The structures of these indolizines (**4a**—**r** and **6a**—**r**) and thieno[2,3-*b*]indolizines (**8a**—**o**) were mainly determined from the elemental analyses and proton nuclear magnetic resonance (^{1}H-NMR) and infrared (IR) spectral inspections. In particular, all of the elemental analyses of these compounds (**4a**—**r**, **6a**—**r**, and **8a**—**o**) were consistent with the proposed structures. The ^{1}H-NMR spectra (Table I) of the indolizines (**4a**—**r** and **6a**—**r**) always showed a singlet signal due to the active methylene group in the 2-substituent in the range of δ 3.73—4.81 and no proton signal[1] arising from the (2-cyanoethyl)thio or (2-ethoxycarbonylethyl)thio group of the starting indolizines (**1a**—**c** or **5a**—**c**) was detected. On the other hand, the ^{1}H-NMR spectra (Table II) of the thienoindolizines (**8a**—**o**) showed a markedly shifted 5-proton signal (appearing at *ca.* δ 8.1—8.7) compared with those (*ca.* δ 9.7—10.1) of the indolizines (**7a**—**f**),[1] and no proton signal attributable to the active methylene group was seen. The high-field shift of the 5-proton associated with the structural change from the bicyclic indolizine to the tricyclic thieno[2,3-*b*]indolizine has already been observed by us.[2] Similarly, the change of the IR absorption bands between the *S*-protected indolizines (**1a**—**f**, **5a**—**f**, and **7a**—**f**)[1] and the *S*-functionalized indolizines (**4a**—**r** and **6a**—**r**) or thienoindolizines (**8a**—**o**) (see Tables IV and V) were consistent with the alterations of the 2-substituents.

Preparations of Thieno[3,2-*a*]- and Thieno[2,3-*b*]indolizines from *S*-Functionalized Indolizines When ethyl 1-cyano-2-(acyl- and 2-[(arylmethyl)thio]-3-indolizinecarbox-

TABLE I. ^{1}H-NMR Spectral Data for 2-(Substituted Methylthio)indolizines

Compd.[a] No.	δ (CDCl$_3$) C-5	C-6	C-7	C-8	SCH_2	R_4	COOEt			
4a	9.52	7.02	7.34	7.69	4.09	2.34	1.42	4.43		
	brd	dt	brt	brd	s	s	t	q		
4b	9.43	6.81	2.38	7.41	4.06	2.32	1.41	4.40		
	d	dd	s	brs	s	s	t	q		
4c	9.29	1.97	6.95	2.67	3.88	2.04	1.42	4.42		
	brs	s	brs	s	s	s	t	q		
4d	9.60	7.00	[b]	[b]	4.79	7.3—8.3	1.37	4.38		
	brd	dt			s	m	t	q		
4e	9.42	6.85	2.44	[b]	4.81	7.2—8.3	1.38	4.39		
	d	dd	s		s	m	t	q		
4f	9.30	2.38	6.97	2.73	4.60	7.3—8.3	1.33	4.35		
	brs	s	brs	s	s	m	t	q		
4g	9.64	7.00	[b]	[b]	4.71	7.2—8.2	1.39	4.36		
	brd	dt			s	m	t	q		
4h	9.50	6.84	2.42	7.45	4.72	7.3—8.3	1.38	4.34		
	d	dd	s	brs	s	m	t	q		
4i	9.32	2.30	6.97	2.68	4.47	7.3—8.2	1.31	4.31		
	brs	s	brs	s	s	m	t	q		
4j	9.57	7.01	[b]	[b]	4.74	7.2—8.1	1.40	4.41		
	brd	dt			s	m	t	q		
4k	9.42	6.84	2.43	7.43	4.72	7.4—8.1	1.38	4.38		
	d	dd	s	brs	s	m	t	q		
4l	9.25	2.36	6.96	2.74	4.52	7.4—8.0	1.33	4.33		
	brs	s	brs	s	s	m	t	q		
4m	9.51	7.00	[b]	[b]	4.51	7.2—8.4	1.43	4.43		
	brd	dt			s	m	t	q		
4n	9.42	7.09	2.38	7.42	4.46	7.3—8.4	1.42	4.38		
	d	dd	s	brs	s	m	t	q		
4o	9.24	2.26	6.94	2.63	4.31	7.3—8.3	1.42	4.36		
	brs	s	brs	s	s	m	t	q		
4p	9.55	7.00	[b]	[b]	4.75	7.2—8.3	1.39	4.39		
	brd	dt			s	m	t	q		
4q	9.39	6.84	2.42	[b]	4.73	7.2—8.3	1.39	4.37		
	d	dd	s		s	m	t	q		
4r	9.23	2.31	6.94	2.68	4.61	7.2—8.1	1.36	4.30		
	brs	s	brs	s	s	m	t	q		
6a	9.51	6.98	7.34	8.37	3.83	2.24	1.46	1.46	4.48	4.50
	brd	dt	brt	brd	s	s	t	t	q	q
6b	9.39	6.81	2.43	8.33	3.80	2.23	1.44	1.44	4.47	4.47
	d	dd	s	brs	s	s	t	t	q	q
6c	9.26	2.29	6.84	2.42	3.73	2.22	1.40	1.43	4.43	4.45
	brs	s	brs	s	s	s	t	t	q	q
6d	9.40	6.88	[b]	8.28	4.39	7.0—8.0	1.21	1.37	4.20	4.33
	brd	dt		brd	s	m	t	t	q	q
6e	9.28	6.75	2.39	8.07	4.31	7.1—8.0	1.20	1.35	4.18	4.32
	d	dd	s	brs	s	m	t	t	q	q
6f	9.19	2.29	6.80	2.42	4.32	7.0—8.1	1.30	1.30	4.26	4.28
	brs	s	brs	s	s	m	t	t	q	q
6g	9.42	6.93	[b]	8.31	4.33	7.0—8.0	1.25	1.38	4.27	4.37
	brd	dt		brd	s	m	t	t	q	q
6h	9.34	6.81	2.43	8.32	4.33	7.1—8.0	1.26	1.39	4.27	4.38
	d	dd	s	brs	s	m	t	t	q	q
6i	9.20	2.30	6.83	2.42	4.27	7.1—8.0	1.31	1.43	4.27	4.33
	brs	s	brs	s	s	m	t	t	q	q
6j	9.45	6.97	7.33	8.33	4.33	7.4—8.0	1.27	1.39	4.27	4.36
	brd	dt	brt	brd	s	m	t	t	q	q
6k	9.34	6.80	2.43	8.11	4.32	7.4—8.0	1.27	1.39	4.29	4.38
	d	dd	s	brs	s	m	t	t	q	q
6l	9.21	2.31	6.85	2.43	4.28	7.4—8.0	1.31	1.34	4.28	4.34
	brs	s	brs	s	s	m	t	t	q	q
6m	9.39	6.92	[b]	8.29	4.28	7.0—8.0	1.39	1.44	4.38	4.44
	brd	dt		brd	s	m	t	t	q	q
6n	9.28	6.78	2.43	8.07	4.27	7.1—8.2	1.40	1.46	4.38	4.43
	d	dd	s	brs	s	m	t	t	q	q
6o	9.19	2.29	6.82	2.40	4.17	7.1—8.2	1.35	1.43	4.34	4.39
	brs	s	brs	s	s	m	t	t	q	q
6p	9.40	6.91	[b]	8.32	4.57	7.0—8.1	1.33	1.44	4.32	4.43
	brd	dt		brd	s	m	t	t	q	q
6q	9.27	6.73	2.40	8.09	4.53	7.0—8.1	1.31	1.43	4.28	4.41
	d	dd	s	brs	s	m	t	t	q	q
6r	9.20	2.31	6.82	2.41	4.47	6.9—8.2	1.34	1.38	4.34	4.34
	brs	s	brs	s	s	m	t	t	q	q

a) The coupling constants are as follows: $J_{5,6}=J_{6,7}=7.0$, $J_{7,8}=9.0$, $J_{6,8}=2.0$, and $J_{Et}=7.0$ Hz. *b*) Overlapped with the phenyl proton signals.

TABLE II. ^{1}H-NMR Spectral Data for Thieno[2,3-*b*]indolizines

Compd.[a] No.	δ (CDCl$_3$) C-5	C-6	C-7	C-8	COOEt		R_4	Me, OH, or OMe
8a	8.57	6.80	7.27	8.31	1.44	4.35	2.51	2.90
	brd	dt	brt	brd	t	q	s	s
8b	8.45	6.61	2.39	8.09	1.44	4.36	2.50	2.88
	d	dd	s	brs	t	q	s	s
8c	8.12	2.23	6.83	2.72	1.43	4.30	2.50	2.85
	brs	s	brs	s	t	q	s	s
8d	8.72	6.83	7.31	8.44	1.39	4.37	7.3—8.1	2.83
	brd	dt	brt	brd	t	q	m	s
8e	8.51	6.73	2.47	8.27	1.41	4.39	7.3—8.0	2.89
	d	dd	s	brs	t	q	m	s
8f	8.24	2.31	6.90	2.83	1.39	4.33	7.3—8.0	2.85
	brs	s	brs	s	t	q	m	s
8g	8.67	6.85	7.31	8.39	1.39	4.38	7.3—8.1	2.86
	brd	dt	brt	brd	t	q	m	s
8h	8.63	6.76	2.49	8.21	1.43	4.46	7.3—8.1	2.95
	d	dd	s	brs	t	q	m	s
8i	8.37	2.36	7.00	2.88	1.42	4.37	7.3—8.1	2.93
	brs	s	brs	s	t	q	m	s
8j	8.66	6.84	7.31	8.41	1.39	4.35	7.5—8.0	2.86
	brd	dt	brt	brd	t	q	m	s
8k	8.51	6.73	2.49	8.15	1.42	4.41	7.5—8.0	2.93
	d	dd	s	brs	t	q	m	s
8l	8.34	2.34	6.99	2.86	1.41	4.35	7.4—8.0	2.92
	brs	s	brs	s	t	q	m	s
8m	8.58	6.78	7.21	[b]	1.45	4.39	7.5—8.5	2.72
	brd	dt	brt		t	q	m	s
8n	8.43	6.61	2.42	8.11	1.47	4.39	7.4—8.6	2.68
	d	dd	s	brs	t	q	m	s
8o	8.25	2.29	6.81	2.83	1.44	4.34	7.5—8.6	2.68
	brs	s	brs	s	t	q	m	s
11a	8.71	6.95	7.41	8.27	1.44	4.42	2.38	*ca.* 10.0
	brd	dt	brt	brd	t	q	s	br
11b	8.53	6.76	2.46	8.01	1.45	4.42	2.36	*ca* 10.0
	d	dd	s	brs	t	q	s	br
11c	8.76	6.92	7.35	8.20	1.41	4.40	7.3—8.2	*ca.* 13.0
	brd	dt	brt	brd	t	q	m	br
11d	8.55	6.70	2.38	[b]	1.40	4.41	7.3—8.2	*ca.* 13.0
	d	dd	s		t	q	m	br
11e	8.71	6.92	7.35	8.18	1.40	4.39	7.3—8.2	*ca.* 12.5
	brd	dt	brt	brd	t	q	m	br
11f	8.60	6.75	2.43	7.94	1.41	4.40	7.3—8.2	*ca.* 13.7
	d	dd	s	brs	t	q	m	br
11g	8.75	6.93	7.37	8.20	1.40	4.38	7.4—8.0	*ca.* 10.6
	brd	dt	brt	brd	t	q	m	br
11h	8.62	6.78	2.43	[b]	1.41	4.39	7.3—8.1	*ca.* 10.0
	d	dd	s		t	q	m	br
12a	8.93	7.08	[b]	[b]	1.41	4.42	7.3—8.5	5.31[c]
	brd	dt			t	q	m	s
12b	8.77	6.86	2.48	[b]	1.40	4.40	7.3—8.5	5.27[c]
	d	dd	s		t	q	m	s
12c	9.01	7.10	[b]	8.33	1.42	4.42	7.3—8.3	5.96[c]
	brd	dt		brd	t	q	m	s
12d	8.87	6.91	2.51	[b]	1.40	4.39	7.3—8.3	5.93[c]
	d	dd	s		t	q	m	s
13a	8.57	6.90	7.37	8.32	1.46	4.43	2.63	4.16
	brd	dt	brt	brd	t	q	s	s
13b	8.45	6.75	2.46	8.10	1.44	4.42	2.61	4.13
	d	dd	s	brs	t	q	s	s
13c	8.75	6.91	7.40	8.37	1..43	4.43	7.4—8.2	3.97
	brd	dt	brt	brd	t	q	m	s
13d	8.60	6.73	2.47	[b]	1.41	4.41	7.3—8.2	3.94
	d	dd	s		t	q	m	s
13e	8.73	6.94	[b]	8.38	1.44	4.44	7.2—8.2	3.99
	brd	dt		brd	t	q	m	s
13f	8.61	6.78	2.50	8.16	1.43	4.44	7.3—8.1	3.99
	d	dd	s	brs	t	q	m	s
13g	8.69	6.89	7.38	8.32	1.42	4.42	7.4—8.1	3.97
	brd	dt	brt	brd	t	q	m	s
13h	8.57	6.74	2.47	8.10	1.42	4.41	7.4—8.1	3.96
	d	dd	s	brs	t	q	m	s
13i	8.53	6.87	7.26	[b]	1.46	4.43	7.7—8.5	3.90
	brd	dt	brt		t	q	m	s
13j	8.42	6.73	2.48	[b]	1.47	4.44	7.7—8.5	3.91
	d	dd	s		t	q	m	s
13k	8.53	6.80	7.23	8.30	1.44	4.42	7.4—8.1	3.72
	brd	dt	brt	brd	t	q	m	s
13l	8.39	6.62	2.41	8.06	1.43	4.40	7.4—8.1	3.70
	d	dd	s	brs	t	q	m	s

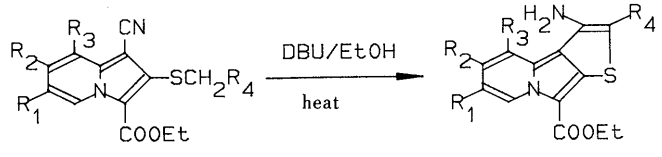
a) The coupling constants are as follows: $J_{5,6}=J_{6,7}=7.0$, $J_{7,8}=9.0$, $J_{6,8}=2.0$, and $J_{Et}=7.0$ Hz. *b*) Overlapped with the phenyl proton signals. *c*) The methine proton signal at the 2-position.

ylates (**4a—o, r**) were heated under reflux in ethanol in a water bath in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the expected ethyl 3-aminothieno[3,2-a]-9-indolizinecarboxylates (**10a—o,r**) were obtained in 21—90% yields, respectively. On the other hand, the reactions of indolizines (**4p, q**) with DBU under the same conditions gave only unidentified products,[5] but those at low temperature (40—50 °C) gave the expected 3-aminothienoindolizines (**10p, q**) in 50 and 78% yields (Chart 4).

The reactions of diethyl 2-[(acylmethyl)thio]-(**6a, b, d, e, g, h, j, k**) and 2-[(arylmethyl)thio]-1,3-indolizinedicarboxylates (**6m, n, p, q**) having no methyl group at the 8-position with potassium *tert*-butoxide in DMF at room temperature followed by the neutralization of the mixtures with aqueous hydrochloric acid gave the corresponding ethyl 3-hydroxythieno[2,3-*b*]-9-indolizinecarboxylates (**11a—h**) and the 3-oxo derivatives (**12a—d**) in very good yields, respectively. Furthermore, the addition of dimethyl sulfate to the reaction mixtures of the indolizines (**6a, b, d, e, g, h, j, k, m, n, p, q**) with potassium *tert*-butoxide yielded only the corresponding 3-methoxythieno[2,3-*b*]indolizine derivatives (**13a—l**) in moderate to good yields (Chart 5). On the other hand, the alkaline treatment of the indolizines (**6c, f, i, l, o, r**) possessing the 8-methyl group afforded ethyl 3-hydroxythieno[3,2-*a*]-9-indolizinecarboxylates (**14a—d**) and the 3-oxo isomers (**15a, b**) in 42—92% yields. However, further reactions of these thieno[3,2-*a*]indolizines (**14a—d** and **15a, b**) with dimethyl sulfate proved extremely difficult, and, even under heating, only trace amounts of the 3-methoxy derivatives (**16**) could be obtained (Chart 6).

The orientations observed in these cyclizations were completely regiospecific and coincided with our previous results obtained in the similar reactions of 2-[(ethoxycarbonylmethyl)thio]indolizines.[2]

The structures of these compounds (**10a—r, 11a—h, 12a—d, 13a—l, 14a—d,** and **15a, b**) were determined by their elemental analyses, ^{1}H-NMR and IR spectral inspections, and mechanistic considerations. In particular, the molecular compositions of all products were in good accord with our proposed structures, and the ^{1}H-NMR spectra (Tables II and III) of 3-amino- (**10a—r**) and 3-hydroxythieno[3,2-*a*]indolizines (**14a—d**), and 3-hydroxy- (**11a—h**) and 3-methoxythieno[2,3-*b*]indolizines (**13a—l**) were, except the proton signals due to the 2-substituents, quite similar to those of the thienoindolizines synthesized earlier by us, by the alkaline treatment of 2-(ethoxycarbonylmethylthio)indolizine derivatives.[2] On the other hand, the structures of

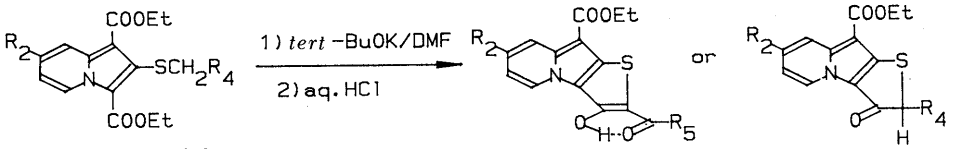


4a-r **10a-r**

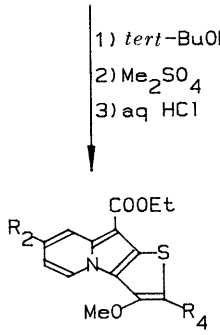
10	R_1	R_2	R_3	R_4
a	H	H	H	Ac
b	H	Me	H	Ac
c	Me	H	Me	Ac
d	H	H	H	Bz
e	H	Me	H	Bz
f	Me	H	Me	Bz
g	H	H	H	*p*-ClBz
h	H	Me	H	*p*-ClBz
i	Me	H	Me	*p*-ClBz

10	R_1	R_2	R_3	R_4
j	H	H	H	*p*-BrBz
k	H	Me	H	*p*-BrBz
l	Me	H	Me	*p*-BrBz
m	H	H	H	*p*-NO_2Ph
n	H	Me	H	*p*-NO_2Ph
o	Me	H	Me	*p*-NO_2Ph
p	H	H	H	*o*-NO_2Ph
q	H	Me	H	*o*-NO_2Ph
r	Me	H	Me	*o*-NO_2Ph

Chart 4



6a, b, d, e, g, h, j, k, m, n, p, q **11a-h** **12a-d**



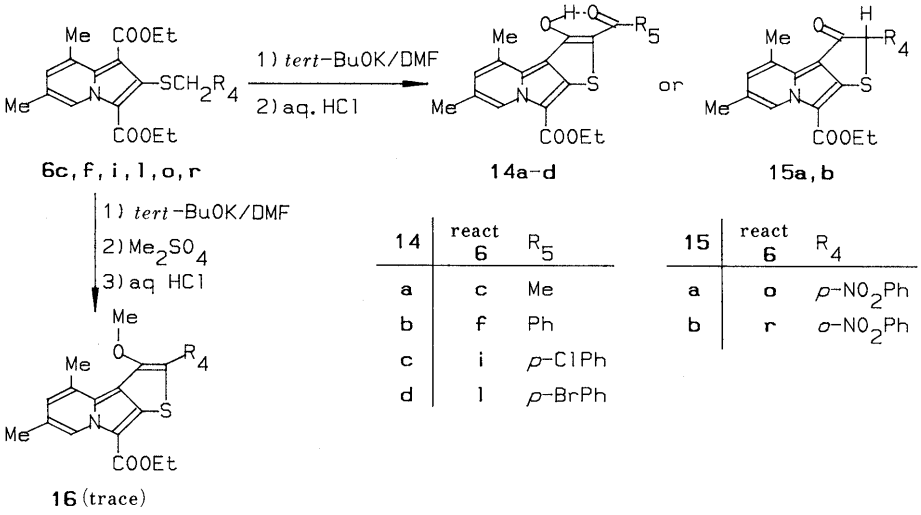
13a-l

13	react 6	R_2	R_4
a	a	H	Ac
b	b	Me	Ac
c	d	H	Bz
d	e	Me	Bz
e	g	H	*p*-ClBz
f	h	Me	*p*-ClBz
g	j	H	*p*-BrBz
h	k	Me	*p*-BrBz
i	m	H	*p*-NO_2Ph
j	n	Me	*p*-NO_2Ph
k	p	H	*o*-NO_2Ph
l	q	Me	*o*-NO_2Ph

11	react 6	R_2	R_5
a	a	H	Me
b	b	Me	Me
c	d	H	Ph
d	e	Me	Ph
e	g	H	*p*-ClPh
f	h	Me	*p*-ClPh
g	j	H	*p*-BrPh
h	k	Me	*p*-BrPh

12	react 6	R_2	R_4
a	m	H	*p*-NO_2Ph
b	n	Me	*p*-NO_2Ph
c	p	H	*o*-NO_2Ph
d	q	Me	*o*-NO_2Ph

Chart 5



14	react 6	R_5
a	c	Me
b	f	Ph
c	i	*p*-ClPh
d	l	*p*-BrPh

15	react 6	R_4
a	o	*p*-NO_2Ph
b	r	*o*-NO_2Ph

Chart 6

TABLE III. ^{1}H-NMR Spectral Data for Thieno[3,2-*a*]indolizines

Compd.[a,b] No.	δ ($CDCl_3$) C-7	C-6	C-5	C-4	COOEt	R_4	NH_2 or OH
10a	9.86	7.10	7.39	7.81	1.44 4.40	2.36	6.90
	brd	dt	brt	brd	t q	s	brs
10b	9.64	6.92	2.45	7.49	1.43 4.41	2.37	6.84
	d	dd	s	brs	t q	s	brs
10c	9.31	2.31	6.83	2.70	1.45 4.38	2.35	7.24
	brs	s	brs	s	t q	s	brs
10d	9.75	7.07	[c]	[c]	1.38 4.40	7.1—8.1	[c]
	brd	dt			t q	m	
10e	9.58	6.93	2.46	7.26	1.39 4.38	7.3—8.2	[c]
	d	dd	s	brs	t q	m	
10f	9.48	2.29	6.88	2.80	1.35 4.35	7.3—8.1	[c]
	brs	s	brs	s	t q	m	
10i	9.50	2.33	6.96	2.84	1.36 4.36	7.3—8.0	[c]
	brs	s	brs	s	t q	m	
10l	9.48	2.32	6.94	2.85	1.39 4.39	7.3—8.0	[c]
	brs	s	brs	s	t q	m	
10p	9.64	6.97	7.24	[c]	1.41 4.43	7.3—8.1	3.88
	brd	dt	brt		t q	m	brs
10q	9.42	6.73	2.34	7.38	1.42 4.36	7.4—8.2	3.87
	d	dd	s	brs	t q	m	brs
10r	9.52	2.29	6.85	2.78	1.41 4.33	7.2—8.3	3.80
	brs	s	brs	s	t q	m	brs
14a	9.31	2.38	7.02	2.82	1.48 4.44	2.38	[d]
	brs	s	brs	s	t q	s	
14b	9.22	2.29	6.94	2.83	1.41 4.40	7.4—8.2	15.95
	brs	s	brs	s	t q	m	brs
14c	9.30	2.35	7.03	2.88	1.42 4.41	7.3—8.1	*ca.* 16.0
	brs	s	brs	s	t q	m	br
14d	9.40	2.37	7.12	2.93	1.41 4.47	7.4—8.1	[d]
	brs	s	brs	s	t q	m	
15a	9.30	2.34	7.10	2.79	1.42 4.42	7.4—8.5	5.26[e]
	brs	s	brs	s	t q	m	s
15b	9.31	2.39	7.13	2.87	1.42 4.41	7.3—8.2	5.91[e]
	brs	s	brs	s	t q	m	s

a) The NMR spectra of compounds **10g**, **h**, **j**, **k**, **m**—**o** could not be measured because of low solubility. *b*) The coupling constants are as follows: $J_{5,6}=J_{6,7}=7.0$, $J_{4,5}=9.0$, $J_{4,6}=2.0$, and $J_{Et}=7.0$ Hz. *c*) Overlapped with the phenyl proton signals. *d*) The hydroxyl proton signal was not clearly seen. *e*) The methine proton signal at the 2-position.

the 3-oxo derivatives (**12a**—**d** and **15a**, **b**) were concluded based on the basis of the a singlet signal (δ 5.26—5.96) due to the 2-proton in their ^{1}H-NMR spectra. These compounds (**12a**—**d** and **15a**, **b**) may exist as a keto form owing to strain relief of the thiazapentalene structure and the absence of the hydrogen-bonding further stabilizing the aromatic thiophene structure. The failure of the preparations of 3-methoxythieno[3,2-*a*]indolizines (**16**) may be due to the steric hindrance of both the 4-methyl group and the 2-substituent with the 3-hydroxyl group.

In conclusion, it was shown that 2-indolizinethiol derivatives, readily obtainable by deprotecting 2-[(2-cyanoethyl)thio]- and 2-[(2-ethoxycarbonylethyl)thio]indolizines (**1a**—**f**, **5a**—**f**, and **7a**—**f**) possessing electron-withdrawing groups at the 1- and the 3-positions, are useful precursors of *S*-functionalized indolizines, thieno[3,2-*a*]- and thieno[2,3-*b*]indolizines which are not available by other methods.

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. The microanalyses were carried out on a Perkin-Elmer elemental analyzer. ^{1}H-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. IR spectra were taken with a Hitachi 260-10 infrared spectrophotometer.

***S*-Functionalizations of 2-Indolizinethiols. General Method** Potassium *tert*-butoxide (0.28 g, 2.5 mmol) was added at room temperature to a DMF solution (2 ml) of 2-[(2-substituted ethyl)thio]indolizine (2 mmol) which was prepared according to the procedure described in our preceding paper,[1] and, after sufficient stirring using a spatula, the resulting mixture was kept standing for an additional 15 min. An alkylating agent (**3**, 2.5 mmol) was added to the reaction mixture at room temperature and the resulting solution was allowed to react for 1 h with occasional stirring. The mixture was neutralized with dilute hydrochloric acid and the precipitate that separated was collected by filtration. It was dissolved in chloroform and the solution was filtered through phase-separating filter paper. The filtrate was concentrated and the residue was separated by column chromatography (alumina) using chloroform as an eluent. Recrystallizations from ethanol gave the corresponding *S*-alkylated indolizines (**4a**—**r** and **6a**—**r**) and 3-methylthieno[2,3-*b*]indolizines (**8a**—**o**).

The results and some physical and spectral data of the reactions of indolizines (**1a**—**f** and **5a**—**f**) with **3a**—**f** are shown in Tables I and IV; the products (**4a**, **b**, **n**, **p** and **6a**—**h**, **m**—**o**) were obtained as colorless needles, **4c**, **m** as colorless prisms, and **4d**—**l**, **o**, **q**, **r** and **6i**—**l**, **p**—**r** as pale yellow needles. The data for the reactions of the indolizines (**7a**—**f**) with **3a**—**e** are given in Tables II and V; **8a**—**l** were obtained as yellow needles and **8m**—**o** as red needles. The formations of the *S*-alkylated ethyl 3-acetyl-1-indolizinecarboxylates (**9a**—**o**) in these reactions at room temperature could sometimes be detected by means of ^{1}H-NMR spectral

TABLE IV. Some Data for 2-(Substituted Methylthio)indolizines

Compd. No.	React.		Yield (%)	mp (°C)	ν (KBr) cm^{-1} CO and CN	Formula	Analysis (%) Calcd (Found)		
							C	H	N
4a	**1a**	**3a**	38	93—94	1669 1704 2200	$C_{15}H_{14}N_2O_3S$	59.59	4.67	9.27
	1d	**3a**	58				(59.89	4.33	9.31)
4b	**1b**	**3a**	51	111—113	1665 1710 2200	$C_{16}H_{16}N_2O_3S$	60.74	5.10	8.85
	1e	**3a**	63				(60.79	5.05	8.85)
4c	**1c**	**3a**	49	124—126	1668 1715 2205	$C_{17}H_{18}N_2O_3S$	61.80	5.49	8.48
	1f	**3a**	67				(61.92	5.39	8.46)
4d	**1a**	**3b**	91	163—165	1672 1686 2200	$C_{20}H_{16}N_2O_3S$	65.92	4.43	7.69
	1d	**3b**	77				(65.71	4.55	7.77)
4e	**1b**	**3b**	82	158—161	1679 2200	$C_{21}H_{18}N_2O_3S$	66.65	4.79	7.40
	1e	**3b**	73				(66.57	4.77	7.49)
4f	**1c**	**3b**	90	128—130	1678 2204	$C_{22}H_{20}N_2O_3S$	67.33	5.14	7.14
	1f	**3b**	69				(67.36	5.05	7.21)
4g	**1a**	**3c**	72	165—167	1680 2200	$C_{20}H_{15}ClN_2O_3S$	60.23	3.79	7.02
							(60.10	3.74	7.20)
4h	**1b**	**3c**	67	161—163	1671 2200	$C_{21}H_{17}ClN_2O_3S$	61.09	4.15	6.78
							(61.05	4.04	6.93)
4i	**1c**	**3c**	70	201—203	1680 2210	$C_{22}H_{19}ClN_2O_3S$	61.89	4.49	6.56
							(61.88	4.40	6.66)
4j	**1a**	**3d**	57	174—176	1673 2200	$C_{20}H_{15}BrN_2O_3S$	54.19	3.41	6.32
							(54.19	3.24	6.49)
4k	**1b**	**3d**	70	162—164	1680 2200	$C_{21}H_{17}BrN_2O_3S$	55.15	3.75	6.13
							(55.18	3.79	6.08)
4l	**1c**	**3d**	86	200—202	1670 1690 2210	$C_{22}H_{19}BrN_2O_3S$	56.06	4.06	5.94
							(55.99	4.09	5.98)
4m	**1a**	**3e**	93	124—126	1672 2200	$C_{19}H_{15}N_3O_4S$	59.83	3.96	11.02
							(59.84	3.84	11.14)
4n	**1b**	**3e**	51	141—144	1670 2200	$C_{20}H_{17}N_3O_4S$	60.75	4.33	10.63
							(60.88	3.99	10.84)
4o	**1c**	**3e**	71	109—110	1670 2205	$C_{21}H_{19}N_3O_4S$	61.60	4.68	10.26
							(61.31	4.75	10.48)
4p	**1a**	**3f**	75	138—140	1679 2200	$C_{19}H_{15}N_3O_4S$	59.83	3.96	11.02
							(59.84	3.95	11.02)
4q	**1b**	**3f**	73	127—128	1674 2202	$C_{20}H_{17}N_3O_4S$	60.75	4.33	10.63
							(60.67	4.32	10.66)
4r	**1c**	**3f**	82	107—108	1676 2205	$C_{21}H_{19}N_3O_4S$	61.60	4.68	10.26
							(61.60	4.73	10.21)
6a	**5a**	**3a**	66	71—73	1680 1704	$C_{17}H_{19}NO_5S$	58.44	5.48	4.01
	5d	**3a**	69				(58.41	5.30	4.04)
6b	**5b**	**3a**	72	62—64	1677 1706	$C_{18}H_{21}NO_5S$	59.49	5.82	3.85
	5e	**3a**	76				(59.30	5.79	3.94)
6c	**5c**	**3a**	72	64—65	1678 1708	$C_{19}H_{23}NO_5S$	60.46	6.14	3.71
	5f	**3a**	81				(60.22	6.04	3.69)
6d	**5a**	**3b**	90	75—77	1671	$C_{22}H_{21}NO_5S$	64.22	5.14	3.40
	5d	**3b**	87				(64.16	5.01	3.44)
6e	**5b**	**3b**	94	102—103	1674	$C_{23}H_{23}NO_5S$	64.92	5.45	3.29
	5e	**3b**	86				(65.01	5.48	3.16)
6f	**5c**	**3b**	90	91—93	1676 1708	$C_{24}H_{25}NO_5S$	65.58	5.73	3.19
	5f	**3b**	93				(65.72	5.66	3.06)
6g	**5a**	**3c**	91	95—97	1674	$C_{22}H_{20}ClNO_5S$	59.26	4,52	3.14
							(59.26	4.48	3.18)
6h	**5b**	**3c**	91	115—117	1670	$C_{23}H_{22}ClNO_5S$	60.06	4,82	3.05
							(59.90	4.86	2.99)
6i	**5c**	**3c**	97	95—96	1672 1705	$C_{24}H_{24}ClNO_5S$	60.82	5.10	2.96
							(60.81	5.05	3.16)
6j	**5a**	**3d**	88	121—123	1674	$C_{22}H_{20}BrNO_5S$	53.89	4.11	2.86
							(53.72	3.94	2.70)
6k	**5b**	**3d**	96	112—114	1680	$C_{23}H_{22}BrNO_5S$	54.77	4.40	2.78
							(54.55	4.44	2.80)
6l	**5c**	**3d**	92	98—100	1675 1709	$C_{24}H_{24}BrNO_5S$	55.60	4.67	2.70
							(55.55	4.58	2.84)
6m	**5a**	**3e**	94	117—119	1678 1690	$C_{21}H_{20}N_2O_6S$	58.87	4.71	6.54
							(58.84	4.65	6.63)
6n	**5b**	**3e**	93	116—118	1675 1690	$C_{22}H_{22}N_2O_6S$	59.72	5.01	6.33
							(59.79	4.91	6.36)
6o	**5c**	**3e**	91	99—101	1671 1710	$C_{23}H_{24}N_2O_6S$	60.51	5.30	6.14
							(60.53	5.09	6.33)
6p	**5a**	**3f**	96	91—93	1671	$C_{21}H_{20}N_2O_6S$	58.87	4.71	6.54
							(59.02	4.44	6.32)
6q	**5b**	**3f**	92	90—92	1679 1694	$C_{22}H_{22}N_2O_6S$	59.72	5.01	6.33
							(59.75	4.84	6.47)
6r	**5c**	**3f**	94	110—112	1676 1715	$C_{23}H_{24}N_2O_6S$	60.51	5.30	6.14
							(60.59	5.19	6.18)

TABLE V. Some Data for 3-Methylthieno[2,3-*b*]indolizines

Compd. No.	React.		Yield (%)	mp (°C)	ν (KBr) cm^{-1} CO	Formula	Analysis (%) Calcd (Found)		
							C	H	N
8a	**7a**	**3a**	68	181—182	1636 1685	$C_{16}H_{15}NO_3S$	63.77	5.02	4.65
	7d	**3a**	95				(63.66	5.04	4.85)
8b	**7e**	**3a**	77	171—173	1633 1685	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44
							(64.65	5.57	4.67)
8c	**7f**	**3a**	69	161—164	1637 1702	$C_{18}H_{19}NO_3S$	65.63	5.81	4.25
							(65.70	5.87	4.52)
8d	**7a**	**3b**	75	201—202	1686	$C_{21}H_{17}NO_3S$	69.40	4.72	3.85
	7d	**3b**	88				(69.48	4.64	3.85)
8e	**7b**	**3b**	88	188—189	1690	$C_{22}H_{19}NO_3S$	70.00	5.07	3.71
	7e	**3b**	69				(69.87	5.05	3.86)
8f	**7c**	**3b**	54	157—159	1704	$C_{23}H_{21}NO_3S$	70.56	5.41	3.58
	7f	**3b**	79				(70.59	5.63	3.33)
8g	**7d**	**3c**	70	199—200	1675 1683	$C_{21}H_{16}ClNO_3S$	63.39	4.05	3.52
							(63.39	4.21	3.36)
8h	**7e**	**3c**	80	156—158	1685	$C_{22}H_{18}ClNO_3S$	64.15	4.40	3.40
							(53.86	4.57	3.68)
8i	**7f**	**3c**	96	176—178	1631 1711	$C_{23}H_{20}ClNO_3S$	64.86	4.73	3.29
							(64.57	4.80	3.51)
8j	**7d**	**3d**	97	194—195	1677 1684	$C_{21}H_{16}BrNO_3S$	57.02	3.65	3.17
							(57.10	3.67	3.08)
8k	**7e**	**3d**	67	164—166	1674	$C_{22}H_{18}BrNO_3S$	57.90	3.98	3.07
							(57.76	3.98	3.21)
8l	**7f**	**3d**	92	178—180	1630 1709	$C_{23}H_{20}BrNO_3S$	58.73	4.29	2.98
							(58.43	4.25	3.31)
8m	**7d**	**3e**	57	211—212	1657	$C_{20}H_{16}N_2O_4S$	63.15	4.24	7.36
							(63.14	4.25	7.42)
8n	**7e**	**3e**	53	220—223	1654	$C_{21}H_{18}N_2O_4S$	63.95	4.60	7.10
							(64.21	4.81	7.17)
8o	**7f**	**3e**	41	212—213	1689	$C_{22}H_{20}N_2O_4S$	64.69	4.94	6.86
							(64.73	4.94	6.82)

TABLE VI. Some Data for 1-Aminothieno[3,2-*a*]indolizines

Compd. No.	React.	Yield (%)	mp (°C)	ν (KBr) cm^{-1} CO and NH_2	Formula	Analysis (%) Calcd (Found)		
						C	H	N
10a	**4a**	73	262—263	1673 3300 3400	$C_{15}H_{14}N_2O_3S$	59.59	4.67	9.27
						(59.49	4.78	9.26)
10b	**4b**	70	261—264	1685 3260 3340	$C_{16}H_{16}N_2O_3S$	60.74	5.10	8.85
						(60.74	5.00	8.93)
10c	**4c**	80	215—218	1672 3240 3460	$C_{17}H_{18}N_2O_3S$	61.80	5.49	8.48
						(61.90	5.39	8.48)
10d	**4d**	84	225—228	1672 3350 3420	$C_{20}H_{16}N_2O_3S$	65.92	4.43	7.69
						(65.97	4.42	7.65)
10e	**4e**	58	251—253	1670 3290 3400	$C_{21}H_{18}N_2O_3S$	66.65	4.79	7.40
						(66.66	4.65	7.53)
10f	**4f**	90	203—204	1670 3420 3480	$C_{22}H_{20}N_2O_3S$	67.33	5.14	7.14
						(67.32	5.00	7.28)
10g	**4g**	55	265—268	1673 3290 3400	$C_{20}H_{15}ClN_2O_3S$	60.23	3.79	7.02
						(60.09	3.80	7.14)
10h	**4h**	57	295—298	1680 3290 3400	$C_{21}H_{17}ClN_2O_3S$	61.09	4.15	6.78
						(61.08	4.04	6.90)
10i	**4i**	63	239—242	1680 3380 3480	$C_{22}H_{19}ClN_2O_3S$	61.89	4.49	6.56
						(61.91	4.41	6.62)
10j	**4j**	39	273—236	1680 3300 3380	$C_{20}H_{15}BrN_2O_3S$	54.19	3.41	6.32
						(53.95	3.40	6.58)
10k	**4k**	49	297—300	1680 3300 3400	$C_{21}H_{17}BrN_2O_3S$	55.15	3.75	6.13
						(55.02	3.66	6.35)
10l	**4l**	55	236—238	1680 3380 3480	$C_{22}H_{19}BrN_2O_3S$	56.06	4.06	5.94
						(55.93	4.00	6.13)
10m	**4m**	76	278—280	1656 3340 3420	$C_{19}H_{15}N_3O_4S$	59.83	3.96	11.02
						(59.84	4.21	10.76)
10n	**4n**	88	218—220	1660 3350 3410	$C_{20}H_{17}N_3O_4S$	60.75	4.33	10.63
						(60.79	4.48	10.44)
10o	**4o**	76	235—237	1670 3340 3400	$C_{21}H_{19}N_3O_4S$	61.60	4.68	10.26
						(61.62	4.61	10.32)
10p	**4p**	50	165—168	1672 3345 3418	$C_{19}H_{15}N_3O_4S$	59.83	3.96	11.02
						(59.60	4.26	10.95)
10q	**4q**	78	190—192	1686 3340 3420	$C_{20}H_{17}N_3O_4S$	60.75	4.33	10.63
						(60.87	4.49	10.56)
10r	**4r**	21	193—196	1664 3340 3420	$C_{21}H_{19}N_3O_4S$	61.60	4.68	10.26
						(61.85	4.86	10.04)

TABLE VII. Some Data for 3-Hydroxy-, 3-Oxo-, and 3-Methoxythienoindolizines

Compd. No.	React.	Yield (%)	mp (°C)	ν (KBr) cm⁻¹	Formula	Analysis (%) Calcd (Found)		
						C	H	N
11a	**6a**	72	150—152	1690 [a]	$C_{15}H_{13}NO_4S$	59.39 (59.35)	4.32 4.31	4.62 4.86)
11b	**6b**	98	142—144	1685 [a]	$C_{16}H_{15}NO_4S$	60.55 (60.39	4.76 4.77	4.41 4.56)
11c	**6d**	73	171—173	1675 [a]	$C_{20}H_{15}NO_4S$	65.74 (65.65	4.14 4.14	3.83 3.83)
11d	**6e**	83	176—177	1676 [a]	$C_{21}H_{17}NO_4S$	66.48 (66.43	4.52 4.46	3.69 3.68)
11e	**6g**	89	173—176	1671 [a]	$C_{20}H_{14}ClNO_4S$	60.08 (59.90	3.53 3.66	3.50 3.27)
11f	**6h**	79	195—197	1670 [a]	$C_{21}H_{16}ClNO_4S$	60.94 (60.62	3.90 4.07	3.38 3.54)
11g	**6j**	92	187—189	1688 [a]	$C_{20}H_{14}BrNO_4S$	54.07 (53.75	3.18 3.23	3.15 3.42)
11h	**6k**	92	202—203	1690 [a]	$C_{21}H_{16}BrNO_4S$	55.03 (54.77	3.52 3.49	3.06 3.35)
12a	**6m**	92	220—222	1644 1690	$C_{19}H_{14}N_2O_5S$	59.68 (59.48	3.69 3.69	7.33 7.53)
12b	**6n**	84	233—235	1643 1687	$C_{20}H_{16}N_2O_5S$	60.60 (60.48	4.07 3.94	7.07 7.32)
12c	**6p**	97	168—169	1639 1696	$C_{19}H_{14}N_2O_5S$	59.68 (59.58	3.69 3.79	7.33 7.32)
12d	**6q**	95	198—200	1631 1696	$C_{20}H_{16}N_2O_5S$	60.60 (60.45	4.07 4.10	7.07 7.18)
13a	**6a** [b]	30	165—166	1685	$C_{16}H_{15}NO_4S$	60.55 (60.58	4.76 4.72	4.41 4.41)
13b	**6b** [b]	47	124—126	1685	$C_{17}H_{17}NO_4S$	61.62 (61.42	5.17 5.08	4.23 4.52)
13c	**6d** [b]	28	95—97	1690	$C_{21}H_{17}NO_4S$	66.48 (66.45	4.52 4.51	3.69 3.73)
13d	**6e** [b]	63	224—225	1685	$C_{22}H_{19}NO_4S$	67.33 (67.04	4.62 4.84	3.57 3.64)
13e	**6g** [b]	77	135—137	1685	$C_{21}H_{16}ClNO_4S$	60.94 (60.69	3.90 3.96	3.38 3.57)
13f	**6h** [b]	82	170—172	1674	$C_{22}H_{18}ClNO_4S$	61.75 (61.69	4.24 4.10	3.27 3.47)
13g	**6j** [b]	60	108—109	1689	[c]	52.95 (52.74	3.81 3.96	2.94 3.00)
13h	**6k** [b]	67	168—170	1690	$C_{22}H_{18}BrNO_4S$	55.94 (55.75	3.84 3.82	2.97 3.18)
13i	**6m** [b]	60	152—155	1687	$C_{20}H_{16}N_2O_5S$	60.60 (60.36	4.07 4.15	7.07 6.93)
13j	**6n** [b]	26	246—247	1692	$C_{21}H_{18}N_2O_5S$	61.45 (61.17	4.42 4.44	6.83 7.09)
13k	**6p** [b]	32	174—176	1673	[d]	57.96 (57.94	4.38 4.60	6.76 6.56)
13l	**6q** [b]	32	158—161	1672	$C_{21}H_{18}N_2O_5S$	61.45 (61.26	4.42 4.42	6.83 7.02)
14a	**6c**	91	122—124	1674 [a]	$C_{17}H_{17}NO_4S$	61.62 (61.55	5.17 4.94	4.23 4.14)
14b	**6f**	92	205—207	1671 [a]	$C_{22}H_{19}NO_4S$	67.16 (67.29	4.87 4.97	3.56 3.60)
14c	**6i**	45	238—239	1661 [a]	$C_{22}H_{18}ClNO_4S$	61.75 (61.51	4.24 4.27	3.27 3.48)
14d	**6l**	42	252—254	1659 [a]	$C_{22}H_{18}BrNO_4S$	55.94 (55.67	3.84 3.86	2.97 3.22)
15a	**6o**	92	195—197	1659 1687	$C_{21}H_{18}N_2O_5S$	61.45 (61.20	4.42 4.38	6.83 7.11)
15b	**6r**	81	178—180	1660 1690	$C_{21}H_{18}N_2O_5S$	61.45 (61.28	4.42 4.32	3.22 4.09)

a) The absorption bands due to the hydroxyl group were not clearly seen. *b*) Plus dimethyl sulfate. *c*) $C_{21}H_{16}BrNO_4S+H_2O$. *d*) $C_{20}H_{16}N_2O_5S+H_2O$.

inspections (on the basis of the presence of the methylene proton singlet in the range of δ 3.50—5.00) of the crude products, but these products could not be isolated because of their low yields. The reactions at 50—60 °C in a water bath for 3 h yielded only 3-methylthieno[2,3-*b*]indolizine derivatives (**8a—o**). The yields of **8a—o** listed in Table V are those obtained under the heating.

Preparations of 3-Aminothieno[3,2-*a*]indolizines. General Method An ethanolic solution (30 ml) of 1-cyanoindolizine (**4**, 0.15—0.20 g) and DBU

(0.40 g) was heated under reflux in a water bath until the indolizine (**4**) was no longer detectable on thin layer chromatography (*ca.* 3—12 h). The reaction solution was kept for 12 h in a freezer and the product that precipitated was collected by filtration. Recrystallizations from ethanol or chloroform gave the corresponding 3-aminothieno[3,2-*a*]indolizine derivatives (**10a—o, r**).

The corresponding 3-amino-2-(*o*-nitrophenyl)thienoindolizines (**10p, q**) could be formed from the reactions of the indolizines (**4p, q**) with DBU by lowering the reaction temperature to 40—50 °C, though they were not obtained under reflux.[5]

Compounds **10a, c—j, l** were obtained as yellow needles, **10b** as yellow prisms, **10k** as orange needles, **10m, o—r** as black needles, and **10n** as red needles. Some data for **10a—r** are listed in Tables III and VI.

Reactions of *S*-Functionalized Indolizines with Potassium *tert*-Butoxide. General Method A Potassium *tert*-butoxide (0.14 g, 1.25 mmol) was added to a DMF solution (2 ml) of the *S*-alkylated indolizine (**6**, 1 mmol) at room temperature and the resulting mixture was stirred well using a spatula. The suspension was kept standing for an additional 2 h and then neutralized with dilute hydrochloric acid. The product that precipitated was collected by filtration, dissolved again in chloroform (30 ml), and freed from water by filtration through a phase-separating filter paper. The filtrate was concentrated and the residue was separated by column chromatography (silica gel) using chloroform as an eluent. Recrystallizations from ethanol gave the thienoindolizine derivatives (**11a—h, 12a—d, 14a—d,** and **15a, b**).

General Method B Dimethyl sulfate (0.19 g, 1.5 mmol) was added to the reaction mixture including 3-hydroxy- (**11a—h**) or 3-oxothieno[2,3-*b*]indolizines (**12a—d**) prepared in General Method A, and the resulting solution was kept at room temperature for 2 h with occasional stirring. Usual work-up gave the corresponding 3-methoxythieno[2,3-*b*]indolizine derivatives (**13a—l**).

In the similar reactions of 3-hydroxy- (**14a—d**) and 3-oxothieno[3,2-*a*]indolizines (**15a, b**), however, these compounds were almost inert to dimethyl sulfate even under heating (70—80 °C) and only trace amounts of the 3-methoxy compounds (**16**) were detected by examination of the ^{1}H-NMR spectra. Compounds **12a, b, g, h, 13c, e—h,** and **14b—d** were obtained as yellow needles, **12c—f** and **13d** as orange needles, **12a—d, 13a, b,** and **15a, b** as pale yellow needles, **13i** as red needles, **13j** as black needles, **13k, l** as dark red needles, and **14a** as brown needles. These results and the physical and spectral data are summarized in Tables II, III, and VII.

References

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3) Some of these thieno[2,3-*b*]indolizine derivatives were recently found to show anti-HIV (human immuno deficiency virus) activity.
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); A. Kakehi, S. Ito, N. Kinoshita, and Y. Abaka, *ibid.*, **61**, 2055 (1988).
5) Although these unidentified compounds seem to be intermolecular condensation products of indolizines **4p, q** from their elemental and spectral analyses, their structures are still uncertain.