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MOLECULAR RECOGNITION OF 2-(ARYLMETHYLTHIO)-INDOLIZINE DERIVATIVES THROUGH AN INTRAMOLECULAR ARENE-π (CATION) INTERACTION[1]

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Abstract – Some 2-(arylmethylthio)indolizines bearing ethoxycarbonyl and/or cyano group(s) at the 1- and 3-positions were synthesized and their conformations were investigated by ^{1}H-NMR spectra and X-ray analyses. Interestingly, it was indicated that the sulfide linkages in 2-(1-naphthylmethylthio)indolizine derivatives in $CDCl_3$ solution are mainly present in gauche conformations and the intramolecular arene-π (cation) interactions reflect the electrophilic reactivity of the 1- and 3-substituents.

INTRODUCTION

In recent years, we reported interesting intramolecular arene-arene and arene-π interactions in some model compounds in which various aryl rings or double and triple bonds are combined with a thieno[3,4-*b*]indolizine ring at the 3-position through a sulfide spacer.[2-6] From these studies we made clear that the gauche forms of the sulfide linkage are more stable than the anti one and one gauche form having some favorable interaction as described above is predominant in the solution state, though the differences in the energies between these gauche and anti forms are small and these forms are capable of being present in their crystalline states. In a continuation of this work we are next interested in applying this type of interaction to molecular recognition, in particular, the discrimination between two functional groups which are similar. We selected diethyl indolizine-1,3-dicarboxylate and indolizine-1,3-carbonitriles as model compounds (See Figure 1) because their two ethoxycarbonyl and cyano groups are not distinguishable with ease by usual ^{1}H-NMR or IR spectra. In addition the pyrrole ring of the indolizine skeleton in the crystal structure did not indicate the distinct bond alteration as shown in form **B**

Dedicated to Professor Dr. Albert Padwa on his 75th birthday.

in Figure 1 and the 1- and 3-positions toward the 2-position has similar structural data.[7] However, the order (3-CN>1-CN>3-CO_2Et>1-CO_2Et) for the electrophilic reactivity of the ester carbonyl and cyano groups at the 1- and 3-positions in some reactions is evident except that of diethyl 6,8-dimethylindolizine-1,3-dicarboxylate in which the steric promotion to the 1-ethoxycarbonyl group by the 8-methyl one is present.[8-11] In general, a more reactive electron-withdrawing group in a molecule has a larger LUMO coefficient than a less reactive one and the intramolecular arene-π (cation) interaction between an aryl ring and the more reactive group should be larger than the other.

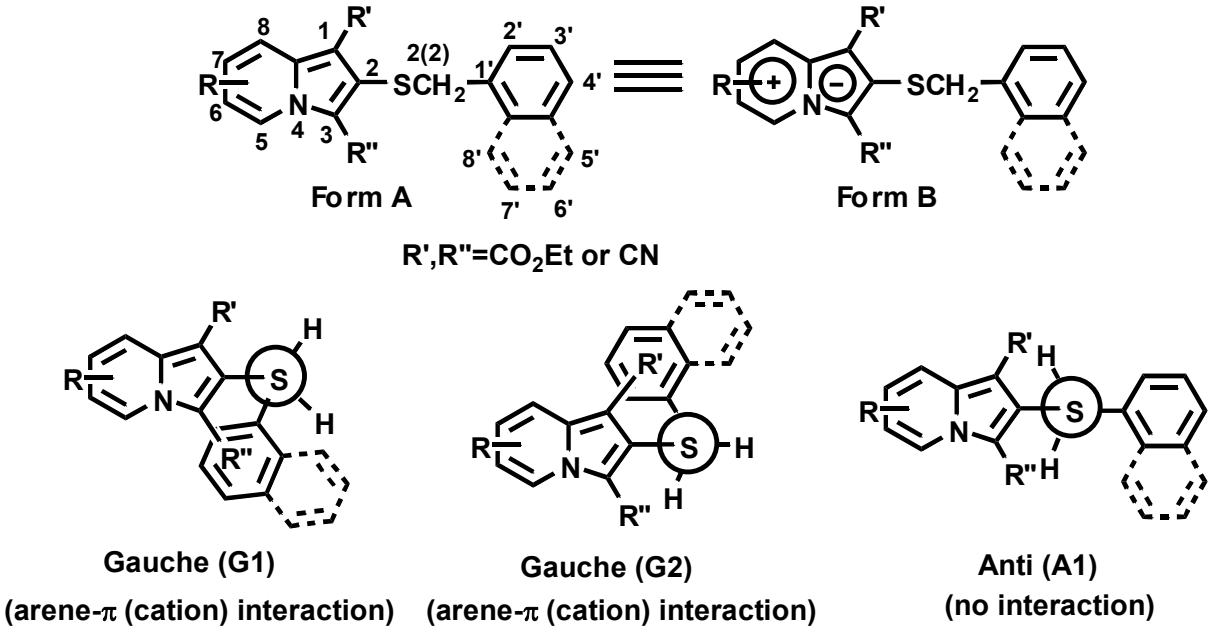


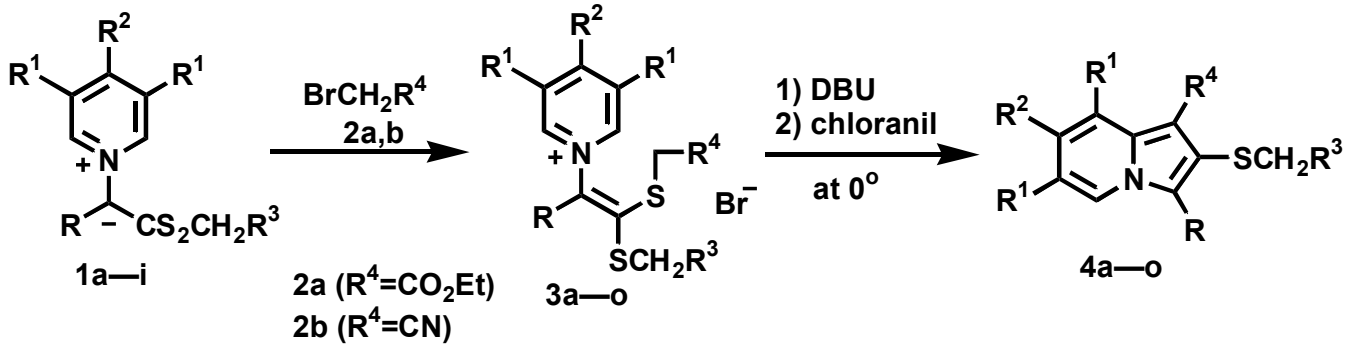
Figure 1

We expected that the gauche conformations (**G1** and **G2**) of title compounds would become more stable than the anti one (**A1**) in the solution state because of the presence of a favorable arene-π (cation) interaction and it can be easily detected by observing the shielding or deshielding effect of a proper aryl ring onto the 1- or 3-substituent and vice versa. In this paper we report the preparation of the title and related compounds and their conformational analyses by ^{1}H-NMR spectra and X-ray analyses.

RESULTS AND DISCUSSION

We selected phenyl and 1-naphthyl groups as the aryl group in the 2-substituent of the title compounds and examined the possibility of these shielding effects. From the consideration of these molecular structures using Dreiding models it was indicated that the overlap of the phenyl ring on the ethoxy group of the ester function at the 1- (**G2** form) or 3-position (**G1** form) is less effective but that of the 1-naphthyl ring is adequate. These models **4a—i**, and related compounds **4j—o** were prepared in 31—73% yields by the *S*-alkylations of pyridinium 1-(2-arylmethylthio-2-thioxo)ethylide (**1a—i**) with ethyl bromoacetate (**2a**) or bromoacetonitirile (**2b**), followed by alkaline treatment and dehydrogenation

of the corresponding pyridinium salts **3a—o**. (Scheme 1)



1	R	R^1	R^2	R^3
a	CO_2Et	H	H	Ph
b	CO_2Et	H	Me	Ph
c	CO_2Et	Me	H	Ph
d	CO_2Et	H	H	1-Naphthyl
e	CO_2Et	H	Me	1-Naphthyl
f	CO_2Et	Me	H	1-Naphthyl
g	CN	H	H	1-Naphthyl
h	CN	H	Me	1-Naphthyl
i	CN	Me	H	1-Naphthyl

a) Yield of 4 based on 1.

3,4	R	R^1	R^2	R^3	R^4	Yield[a] (%)
a	CO_2Et	H	H	Ph	CO_2Et	40
b	CO_2Et	H	Me	Ph	CO_2Et	52
c	CO_2Et	Me	H	Ph	CO_2Et	73
d	CO_2Et	H	H	1-Naphthyl	CO_2Et	54
e	CO_2Et	H	Me	1-Naphthyl	CO_2Et	41
f	CO_2Et	Me	H	1-Naphthyl	CO_2Et	40
g	CN	H	H	1-Naphthyl	CN	56
h	CN	H	Me	1-Naphthyl	CN	61
i	CN	Me	H	1-Naphthyl	CN	64
j	CO_2Et	H	H	1-Naphthyl	CN	34
K	CO_2Et	H	Me	1-Naphthyl	CN	49
l	CO_2Et	Me	H	1-Naphthyl	CN	38
m	CN	H	H	1-Naphthyl	CO_2Et	54
n	CN	H	Me	1-Naphthyl	CO_2Et	31
o	CN	Me	H	1-Naphthyl	CO_2Et	32

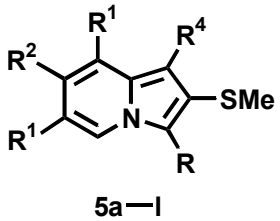
Scheme 1

Elemental analyses for products **4a—o** were in accord with our proposed compositions and their IR spectra exhibited characteristic aromatic ester carbonyl band(s) at 1676—1699 cm^{-1} or a cyano one at 2197—2213 cm^{-1}. In addition, the carbonyl band for the 1-ethoxycarbonyl group in compounds **4c**,**f**,**l** was observed at higher region (1705—1725 cm^{-1}).[8,9] The UV-VIS spectra of 2-(arylmethylthio)indolizines (**4a—o**) were nearly parallel to those for respect 2-(methylthio)indolizines and significant bathochromic shifts and an remarkable increase in their molar extinction coefficients were not observed.[12] The ^{1}H-NMR spectral data of 2-(arylmethylthio)- **4a—o** and the corresponding 2-(methylthio)indolizine derivatives **5a—l** (Figure 2) are shown in Table 1. In the ^{1}H-NMR and ^{13}C-NMR spectra of **4a—o** the signals for any other conformer could not be detected.[13] As expected, the shielding effect to one ethoxy group in the ^{1}H-NMR spectra of diethyl 2-(benzylthio)indolizine-1,3-

Table 1. ^{1}H-NMR spectral data for indolizine derivatives **4a**—**o** and **5a**—**l**

No[a]	C-5	C-6	C-7	C-8	R	R^4	SCH_2[b]	C-2'	C-3'	C-4'	C-5'	C-6'	C-7'	C-8'
4a	9.38	6.89	c)	8.25	1.41 4.39	1.46 4.45	4.20	7.11—7.28						
4b	9.26	6.72	2.40	8.04	1.41 4.37	1.46 4.44	4.18	7.11—7.23						
4c	9.19	2.29	6.78	2.42	1.39 4.38	1.44 4.39	4.11	7.16—7.27						
4d	9.36	6.90	7.26	8.29	1.18 4.11	1.43 4.42	4.64	7.15	7.24	7.70	7.81	7.46	7.51	8.22
4e	9.25	6.74	2.42	8.08	1.17 4.10	1.42 4.41	4.62	7.14	7.24	7.69	7.81	7.45	7.50	8.22
4f	9.17	2.30	6.80	2.42	1.28 4.17[c]	1.30 4.26[d]	4.55	7.15	7.27	7.74	7.84	7.48	7.52	8.21
4g	8.21	7.05	7.37	7.69	-----	-----	4.81	7.41	7.33	7.78	7.85	7.50	7.58	8.19
4h	8.06	6.86	2.45	7.47	-----	-----	4.79	7.40	7.32	7.78	7.85	7.50	7.58	8.19
4i	7.87	2.32	6.93	2.70	-----	-----	4.75	7.40	7.33	7.78	7.85	7.50	7.57	8.21
4j	9.47	6.99	7.34	7.69	1.27 4.27	-----	4.96	7.42	7.35	7.78	7.86	7.50	7.56	8.22
4k	9.35	6.82	2.45	7.46	1.26 4.25	-----	4.95	7.42	7.34	7.78	7.86	7.50	7.56	8.23
4l	9.16	2.31	6.90	2.73	1.22 4.15	-----	4.77	7.26—7.32		7.74	7.83	7.47	7.54	8.22
4m	8.26	7.00	7.33	8.23	-----	1.40 4.39	4.92	7.45	7.35	7.77	7.85	7.49	7.56	8.23
4n	8.10	6.81	2.44	8.03	-----	1.39 4.38	4.90	7.43	7.34	7.76	7.84	7.48	7.55	8.23
4o	7.88	2.30	6.84	2.49	-----	1.33 4.29	4.71	7.26—7.34		7.76	7.84	7.47	7.53	8.19
5a	9.44	6.92	7.26	8.24	1.47 4.48	1.45 4.44	2.54							
5b	9.33	6.76	2.42	8.03	1.47 4.46	1.46 4.44	2.53							
5c	9.20	2.29	6.79	2.42	1.46 4.46	1.42 4.43	2.46							
5d	8.28	7.09	7.39	7.68	-----	-----	2.77							
5e	8.14	6.90	2.47	7.44	-----	-----	2.75							
5f	7.95	2.35	6.95	2.70	-----	-----	2.72							
5g	9.49	6.98	7.33	7.65	1.47 4.46	-----	2.85							
5h	9.35	6.80	2.44	7.41	1.45 4.44	-----	2.84							
5i	9.21	2.31	6.89	2.71	1.47 4.45	-----	2.74							
5j	8.25	6.97	7.31	8.18	-----	1.44 4.41	2.79							
5k	8.11	6.80	2.44	7.97	-----	1.44 4.41	2.78							
5l	7.92	2.31	6.86	2.51	-----	1.42 4.40	2.67							

a) The coupling constants are as follows: $J_{5,6}$=$J_{6.7}$=6.9—7.1 Hz, $J_{5,7}$=1.2—2.0 Hz, $J_{7,8}$=8.8—9.0 Hz, $J_{2',3'}$=6.8—7.1 Hz, $J_{3'.4'}$=8.0—8.2 Hz, $J_{5',6'}$=7.8—8.1 Hz, $J_{6',7'}$=6.8—7.0 Hz, $J_{7',8'}$=8.0—8.3 Hz, $J_{2',4'}$=1.2 Hz, $J_{5',7'}$=1.0 Hz, $J_{6',8'}$=1.2 Hz, J_{Et}=7.1—7.2. b) Or SMe. c) Or 1.30 and 4.26. d) Or 1.28 and 4.17.



5a—l

5	R	R^1	R^2	R^4	5	R	R^1	R^2	R^4
a	CO_2Et	H	H	CO_2Et	g	CO_2Et	H	H	CN
b	CO_2Et	H	Me	CO_2Et	h	CO_2Et	H	Me	CN
c	CO_2Et	Me	H	CO_2Et	i	CO_2Et	Me	H	CN
d	CN	H	H	CN	j	CN	H	H	CO_2Et
e	CN	H	Me	CN	k	CN	H	Me	CO_2Et
f	CN	Me	H	CN	l	CN	Me	H	CO_2Et

Figure 2

dicarboxylates (**4a**—**c**) was considerably small (δ 0.06—0.09 ppm) in comparison to those of diethyl 2-(methylthio)indolizine-1,3-dicarboxylates (**5a**—**c**). On the other hand, the shielding effect to one ethoxy group in diethyl 2-(1-naphthylmethylthio)indolizine- 1,3-dicarboxylates (**4d**—**f**) was larger (δ 0.16—0.37 ppm) and the signals due to the C-2', C-3', and C-4' protons (see Figure 1) on the naphthyl ring also appeared at higher magnetic regions. Interestingly, both ethoxy proton signals in 6,8-dimethyl derivative **4f** changed significantly to indicate the coexistence of the **G1** and **G2** conformers. In the ^{1}H-NMR spectra of 2-(1-naphthylmethylthio)indolizine-1,3-dicarbonitriles (**4g**—**i**) the reduction or absence of the shielding effect to the C-2', C-3', and C-4' protons on the naphthyl ring in **4g**—**i** was observed. The fact that **4d**,**e** and **4g**—**i** have the **G1** conformation could be determined by the X-ray analyses of **4e**,**h** and the ORTEP drawing for **4e** is shown in Figure 3.[14] As seen in this figure the naphthyl moiety (arene) overlapped with the carbonyl function (π) in the 3-ethoxycarbonyl group. Similarly the naphthyl ring in **4h** faced to the 3-cyano group. The torsion angles (C2-S-C2(2)-C1') of **4e**,**h** were 56.8(4) and 59.5(3) ^{o}C respectively and these values closely resemble the ideal one (60 ^{o}C). The conformations of the ethyl 1-cyano-2-(1-naphthylmethylthio)indolizine-3-carboxylates **4j**—**l** and ethyl 3-cyano-2-(1-naphthylmethylthio)indolizine-1-carboxylates **4m**—**o** were deduced by comparing their ^{1}H-NMR spectra with those of **4d**,**e**,**g**—**i** and **5d**,**e**,**g**—**i**. For example, the signals of the 3-ethoxycarbonyl group in **4j**—**l** shifted to higher magnetic fields (δ 1.22—1.27 and 4.15—4.27) than those (δ 1.46—1.47 and 4.46—4.48) of **5g**—**i** to indicate the contribution of the **G1** form, but the shielding effect was smaller than that of **4d**,**e** and the high-field shifts to the C-2', C-3', and C-4' protons on the naphthyl ring of **4j**,**k** was almost not observed. All of the chemical shifts for the naphthyl ring protons of **4j**,**k** are parallel to those of **4g**—**i**. This fact seems to indicate the comparatively weak contribution of the **G1** form and the larger one of the **G2** form in **4j**,**k**. Similarly, the high-field shift to the 1-ethoxycarbonyl group of **4m**,**n** was almost not observed and the predominant presence of the **G1** form was suggested. However, the ^{1}H-NMR spectra of compounds **4l**,**o** exhibited significant high-field shifts of the C-2' proton and the ethoxyl protons, and the presence of the arene-π (cation) interaction

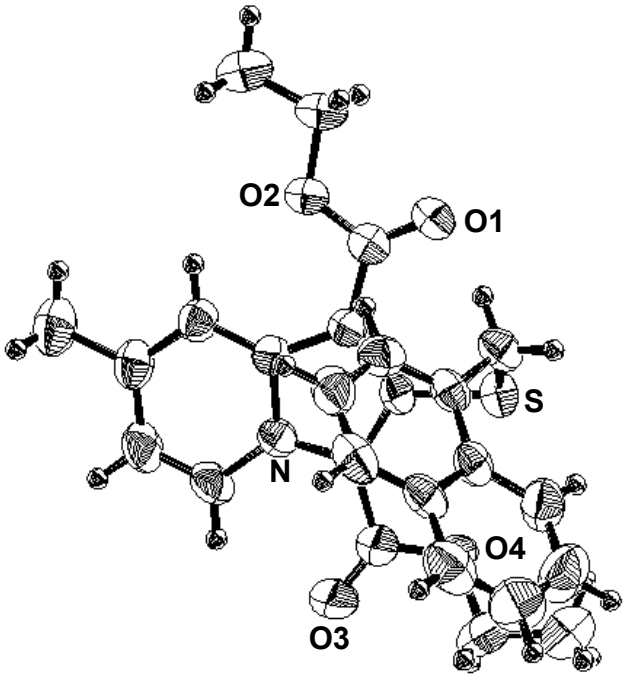


Figure 3. ORTEP drawing of 4e

between the 1-naphthyl ring and the ester carbonyl group was shown.

This trend (3-CN>1-CN>3-Es>1-Es) of the arene-π (cation) interaction shown here coincided well with the order of the electrophilic reactivity of indolizine derivatives bearing electron withdrawing groups at the 1- and 3-positions.[8,9] Furthermore, the increase in the reactivity of the 1-ethoxycarbonyl group by the 8-methyl group as seen in ethyl 6,8-dimethylindolizine-1-carboxylate derivatives **4f**,**o** was also in accord with our previous experimental results,[8,11] though it does not mean the exclusive nucleophilic attack on the 1-ethoxycarbonyl group in these molecules. The increased reactivity of the 3-ethoxycarbonyl group in ethyl 1-cyano-6,8-dimethylindolizine-3-carboxylate (**4l**) has not been observed until now but an example in which the 3-acetyl group of 3-acetyl-2-ethoxycarbonylmethylthio-6,8-dimethylindolizine-1-carbonitrile reacted under the alkaline conditions to provide the corresponding ethyl 9-cyano-3,6,8-trimethylthieno[2,3-*b*]indolizine-2-carboxylate was described.[8]

In summary, we have synthesized some 2-(1-naphthylmethylthio)indolizines having ethoxycarbonyl and/or cyano group(s) at the 1- and 3-positions and showed that the order of the reactivity of these substituents can be predicted by analyzing the intramolecular arene-π (cation) interaction.

EXPERIMENTAL

Melting points were measured with a Yanagimoto micromelting point apparatus and were not corrected. Microanalyses were carried out on a Perkin-Elmer 2400 elemental analyzer. The ^{1}H-NMR and ^{13}C-NMR spectra were determined with a JEOL JNM-LA400 (^{1}H: 400 MHz and ^{13}C: 100.4 MHz) spectrometer in deuteriochloroform[25] with tetramethylsilane used as the internal standard; the chemical shifts are expressed in δ values. The IR spectra were taken with JASCO FT/IR-5300 IR spectrophotometers.

Preparation of pyridinium 1-[2-(arylmethylthio)-2-thioxo]ethanides Pyridinium methylides employed here were prepared according to the procedure described by Tominaga *et al*.[15] The results and some properties of new pyridinium methylides (**1c**,**f**,**i**) are as follows:

3,5-Dimethylpyridinium 1-(1-ethoxycarbonyl-2-benzylthio-2-thioxo)ethanides (**1c**): 66% (from 1-ethoxycarbonylmethyl-3,5-dimethylpyridinium chloride, carbon disulfide, and benzyl bromide), yellow needles (from $CHCl_3$-Et_2O), mp 226—227 °C. IR (KBr) cm^{-1}: 1644. ^{1}H-NMR δ: 1.17 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 2.52 (6H, s, 3-, 5-Me), 4.14 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 4.57 (2H, s, SCH_2), 7.20 (1H, m, 4'-H), 7.27 (2H, m, 3'-H), 7.43 (2H, m, 2'-H), 7.92 (1H, br s, 4-H), 8.14 (2H, br s, 2-, 6-H). *Anal*. Calcd for $C_{19}H_{21}NO_2S_2$: C, 63.48; H, 5.89; N, 3.90. Found: C, 63.77; H, 5.71; N, 3.79.

3,5-Dimethylpyridinium 1-[1-ethoxycarbonyl-2-(1-naphthylmethylthio)-2-thioxo]ethanides (**1f**): 57% (from 1-ethoxycarbonylmethyl-3,5-dimethylpyridinium chloride, carbon disulfide, and

1-chloromethylnaphthalene), yellow needles (from $CHCl_3$- Et_2O), mp 234—235 °C. IR (KBr) cm^{-1}: 1640. ^{1}H-NMR δ: 1.11 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 2.53 (6H, s, 3-, 5-Me), 4.08 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 5.01 (2H, s, SCH_2), 7.38 (1H, q, *J*=7.1, 8.1 Hz, naphthyl-H), 7.45 (1H, m, naphthyl-H), 7.50 (1H, m, naphthyl-H), 7.60 (1H, (br d, *J*=6.8 Hz, naphthyl-H), 7.74 (1H, br d, *J*=8.5 Hz, naphthyl-H), 7.82 (1H, br d, *J*=7.6 Hz, naphthyl-H), 7.93 (1H, br s, 4-H), 8.17 (2H, br s, 2-, 6-H), 8.21 (1H, br d, *J*=8.3 Hz, naphthyl-H). *Anal*. Calcd for $C_{23}H_{23}NO_2S_2$: C, 67.45; H, 5.66; N, 3.42. Found: C, 67.44; H, 5.78; N, 3.31.

3,5-Dimethylpyridinium 1-[1-cyano-2-(1-naphthylmethylthio)-2-thioxo]ethanides (**1i**): 60% (from 1-cyanomethyl-3,5-dimethylpyridinium chloride, carbon disulfide, and 1-chloromethylnaphthalene), yellow needles (from $CHCl_3$- Et_2O), mp 203—204 °C. IR (KBr) cm^{-1}: 2166. ^{1}H-NMR δ: 2.51 (6H, s, 3-, 5-Me), 5.10 (2H, s, SCH_2), 7.40 (1H, q, *J*=7.1, 8.1 Hz, naphthyl-H), 7.49 (1H, m, naphthyl-H), 7.54 (1H, m, naphthyl-H), 7.63 (1H, (br d, *J*=7.1 Hz, naphthyl-H), 7.77 (1H, br d, *J*=8.3 Hz, naphthyl-H), 7.84 (1H, br d, *J*=7.6 Hz, naphthyl-H), 7.85 (1H, br s, 4-H), 8.19 (1H, br d, *J*=8.1 Hz, naphthyl-H), 8.58 (2H, br s, 2-, 6-H). *Anal*. Calcd for $C_{21}H_{18}N_2S_2$: C, 69.58; H, 5.01; N, 7.73. Found: C, 69.66; H, 5.01; N, 7.64.

Preparation of 2-(arylmethylthio)indolizine 4a—o and 2-(methylthio)indolizine derivatives 5a—l. **General method.** A mixture of pyridinium 1-(2-arylmethylthio-2-thioxo)ethanides (**1**, 2 mmol) or pyridinium 1-(2-methylthio-2-thioxo)ethanides (2 mmol), and ethyl bromoacetate **2a** or bromoacetonitrile **2b** (2.2 mmol) in $CHCl_3$ (20 mL) was kept at rt under occasional stirring until the disappearance of pyridinium methylide was detected by TLC monitoring (1-2 days). After *S*-alkylation was completed, the resulting solution was concentrated at reduced pressure and the residue was washed three times with 10 mL portions of ether to remove unaltered alkylating agent. Without further purification the resulting pyridinium salt was dissolved in $CHCl_3$ (30 mL) and the solution was treated with DBU (0.40 g, 2.6 mmol) under stirring in an ice bath for 10 min and then with chloranil (0.492 g, 2 mmol) under the same conditions for a further 4—6 h. The reaction mixture was concentrated at reduced pressure and the residue was separated by column chromatography on alumina using $CHCl_3$ as an eluent. The pale yellow $CHCl_3$ layers of product (**4**) were combined and concentrated at reduced pressure. Recrystallization of the crude product from EtOH afforded the corresponding 2-(arylmethylthio)indolizines **4** or 2-(methylthio)indolizines **5**. ^{1}H-NMR spectral data for products (**4a—o**) and (**5a—l**) are listed in Table 1, and the other data for new compounds (**4a—o**) and (**5c**,**f**,**i**,**l**) are as follows:

Diethyl 2-(benzylthio)indolizine-1,3-dicarboxylate (**4a**): 40% (from **1a** and ethyl bromoacetate (**2a**), colorless needles, mp 52—53 °C. IR (KBr) cm^{-1}: 1699, 1674. UV-Vis (nm (log ε), $CHCl_3$): 282

(4.18), 322 (3.94), 334 (3.95). ^{13}C NMR ($CDCl_3$) δ: 14.44, 14.60, 41.35, 60.15, 60.73, 107.97, 114.13, 117.53, 119.34, 125.40, 126.79, 127.45, 128.06, 128.78, 130.76, 138.00, 138.50, 161.27, 163.65. *Anal.* Calcd for $C_{21}H_{21}NO_4S$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.82; H, 5.48; N, 3.38.

Diethyl 2-benzylthio-7-methylindolizine-1,3-dicarboxylate (**4b**): 52% (from **1b** and **2a**), colorless needles, mp 114—115 °C. IR (KBr) cm^{-1}: 1699, 1676. UV-Vis (nm (log ε), $CHCl_3$): 285 (4.30), 324 (4.10), 336 (4.09). ^{13}C NMR ($CDCl_3$) δ: 14.41, 14.57, 41.35, 60.00, 60.55, 106.72, 116.63, 116.92, 117.89, 126.71, 126.88, 127.98, 128.72, 130.70, 136.69, 138.03, 139.02, 140.55, 161.27, 163.84. *Anal.* Calcd for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.52. Found: C, 66.48; H, 5.90; N, 3.46.

Diethyl 2-benzylthio-6,8-dimethylindolizine-1,3-dicarboxylate (**4c**): 73% (from **1c** and **2a**), colorless needles, mp 67—69 °C. IR (KBr) cm^{-1}: 1705, 1682. UV-Vis (nm (log ε), $CHCl_3$): 265 (4.31), 340 (4.05), 354 (4.02). ^{13}C NMR ($CDCl_3$) δ: 14.32, 14.51, 18.49, 19.42, 41.88, 60.43, 61.28, 114.16, 115.30, 123.19, 123.25, 125.82, 126.88, 127.90, 127.65, 128.14, 128.77, 132.96, 137.82, 161.20, 166.25. *Anal.* Calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 3.40. Found: C, 67.10; H, 6.29; N, 3.27.

Diethyl 2-(1-naphthylmethylthio)indolizine-1,3-dicarboxylate (**4d**): 54% (from **1d** and **2a**), colorless needles, mp 185—187 °C. IR (KBr) cm^{-1}: 1698. UV-Vis (nm (log ε), $CHCl_3$): 283 (4.41), 289 (shoulder), 335 (shoulder), 350 (shoulder). ^{13}C NMR ($CDCl_3$) δ: 14.21, 14.59, 39.32, 60.21, 60.65, 107.98, 114.17, 117.77, 119.41, 124.32, 125.03, 125.44, 125.51, 125.74, 127.00, 127.48, 127.88, 128.46, 130.82, 131.60, 133.77, 133.81, 138.54, 161.27, 163.74. *Anal.* Calcd for $C_{25}H_{23}NO_4S$: C, 69.26; H., 5.35; N, 3.23. Found: C, 69.17; H, 5.36; N, 3.31.

Diethyl 7-methyl-2-(1-naphthylmethylthio)indolizine-1,3-dicarboxylate (**4e**): 41% (from **1e** and **2a**), colorless prisms, mp 119—121 °C. IR (KBr) cm^{-1}: 1691, 1674. UV-Vis (nm (log ε), $CHCl_3$): 286 (4.41), 338 (shoulder), 353 (shoulder). ^{13}C NMR ($CDCl_3$) δ: 14.22, 14.61, 21.54, 39.37, 60.10, 60.52, 106.77, 116.72, 117.20, 118.01, 124.34, 125.03, 125.49, 125.71, 126.95, 127.84, 128.46, 130.84, 131.62, 133.78, 133.90, 136.75, 139.12, 161.32, 163.97 (one carbon is overlapping). *Anal.* Calcd for $C_{26}H_{25}NO_4S$: C, 69.78; H, 5.63; N, 3.13. Found: C, 69.81; H, 5.62; N, 3.10.

Diethyl 6,8-dimethyl-2-(1-naphthylmethylthio)indolizine-1,3-dicarboxylate (**4f**): 40% (from **1f** and **2a**), colorless needles, mp 138—140 °C. IR (KBr) cm^{-1}: 1725, 1671. UV-Vis (nm (log ε), $CHCl_3$): 277 (shoulder), 289 (shoulder), 340 (4.04), 354 (4.01). ^{13}C NMR ($CDCl_3$) δ: 14.21, 14.34, 18.48, 19.38, 39.70, 60.32, 61.26, 114.30, 115.49,123.16, 123.22, 124.20, 125.05, 125.48, 125.72, 125.76, 126.89, 127.01, 127.57, 127.87, 128.43, 131.50, 132.91, 133.57, 133.75, 161.14, 166.28. *Anal.* Calcd for $C_{27}H_{27}NO_4S$: C, 70.26; H, 5.90; N, 3.03. Found: C, 70.22; H, 6.01; N, 2.96.

2-(1-Naphthylmethylthio)indolizine-1,3-dicarbonitrile (**4g**): 54% (from **1g** and **2b**), colorless needles, mp

210—213 °C. IR (KBr) cm^{-1}: 2207. UV-Vis (nm (log ε), $CHCl_3$): 273 (4.36), 291 (shoulder), 320 (shoulder), 350 (shoulder). ^{13}C NMR ($CDCl_3$) δ: 37.68, 88.90, 100.37, 110.71, 113.46, 115.58, 117.65, 123.48, 125.01, 125.69, 125.90, 126.39, 126.80, 127.77, 128.64, 128.89, 131.04, 131.16, 134.36, 139.25. *Anal.* Calcd for $C_{21}H_{13}N_3S$: C, 74.31; H, 3.86; N, 12.38. Found: C, 74.21; H, 3.80; N, 12.32.

7-Methyl-2-(1-naphthylmethylthio)indolizine-1,3-dicarbonitrile (**4h**): 31% (from **1h** and **2b**), colorless needles, mp 214 °C. IR (KBr) cm^{-1}: 2211. UV-Vis (nm (log ε), $CHCl_3$): 274 (shoulder), 283 (4.14), 332 (shoulder). ^{13}C NMR ($CDCl_3$) δ: 21.48, 37.72, 87.44, 99.74, 111.05, 113.85, 116.30, 118.19, 123.59, 125.04, 125.11, 125.93, 126.45, 127.80, 127.81 ,128.69, 128.90, 131.20, 133.82, 134.31, 138.77, 139.78. *Anal.* Calcd for $C_{22}H_{15}N_3S$: C, 74.76; H, 4.28; N, 11.89. Found: C, 74.52; H, 4.46; N, 11.95.

6.8-Dimethyl-2-(1-naphthylmethylthio)indolizine-1,3-dicarbonitrile (**4i**): 32% (from **1i** and **2b**), colorless needles, mp 190—191 °C. IR (KBr) cm^{-1}: 2213. UV-Vis (nm (log ε), $CHCl_3$): 275 (4.35), 291 (shoulder), 329 (shoulder). ^{13}C NMR ($CDCl_3$) δ: 18.12, 18.19, 37.96, 88.61, 100.67, 111.11, 115.29, 121.72, 123.64, 125.06, 125.91, 126.38, 127.79, 128.45, 128.65, 128.83, 130.03, 131.29, 131.36, 133.84, 133.91, 137.32 (one carbon is overlapping). *Anal.* Calcd for $C_{23}H_{17}N_3S$: C, 75.18; H, 4.66; N, 11.44. Found: C, 75.39; H, 4.62; N, 11.26.

Ethyl 1-cyano-2-(1-naphthylmethylthio)indolizine-3-carboxylate (**4j**): 56% (from **1d** and **2b**), colorless needles, mp 155—157 °C. IR (KBr) cm^{-1}: 2209, 1680. UV-Vis (nm (log ε), $CHCl_3$): 273 (shoulder), 283 (4.51), 331 (3.98), 345 (shoulder). ^{13}C NMR ($CDCl_3$) δ: 14.30, 36.81, 60.87, 87.44, 114.44, 114.74, 115.52, 116.35, 123.86, 125.10, 125.71, 126.11, 126.16, 127.62, 128.13, 128.46, 128.55, 131.41, 131.86, 133.75, 134.28, 140.43, 160.39. *Anal.* Calcd for $C_{23}H_{18}N_2O_2S$: C, 71.48; H, 4.69; N, 7.25. Found: C, 71.62; H, 4.66; N, 7.14.

Ethyl 1-cyano-7-methyl-2-(1-naphthylmethylthio)indolizine-3-carboxylate (**4k**): 61% (from **1e** and **2b**), colorless needles, mp 147—149 °C. IR (KBr) cm^{-1}: 2209, 1680. UV-Vis (nm (log ε), $CHCl_3$): 275 (shoulder), 283 (4.51), 332 (shoulder), 345 (shoulder). ^{13}C NMR ($CDCl_3$) δ: 14.30, 21.19, 36.75, 60.71, 86.01, 113.79, 115.03, 117.23, 123.88, 125.08, 125.86, 126.08, 127.50, 127.59, 128.40, 128.52, 131.41, 131.92, 133.72, 134.17, 137.81, 140.89, 160.40. *Anal.* Calcd for $C_{24}H_{20}N_2O_2S$: C, 71.98; H, 5.03; N, 6.99. Found: C, 71.67; H, 5.09; N, 7.25.

Ethyl 1-cyano-6,8-dimethyl-2-(1-naphthylmethylthio)indolizine-3-carboxylate (**4l**): 64% (from **1f** and **2b**), colorless needles, mp 167—169 °C. IR (KBr) cm^{-1}: 2209, 1686. UV-Vis (nm (log ε), $CHCl_3$): 277 (4.40), 286 (4.40), 331 (shoulder), 347 (shoulder). ^{13}C NMR ($CDCl_3$) δ: 14.17, 18.44, 18.64, 38.02, 60.75, 88.90, 115.90, 117.04, 123.96, 124.09, 124.60, 125.00, 125.63, 125.97, 127.07, 127.32, 128.26, 128.49, 129.45, 131.39, 132.49, 132.79, 133.74, 137.66, 160.49. *Anal.* Calcd for $C_{25}H_{22}N_2O_2S$: C,

72.44; H, 5.35; N, 6.76. Found: C, 72.53; H, 5.45; N, 6.57.

Ethyl 3-cyano-2-(1-naphthylmethylthio)indolizine-1-carboxylate (**4m**): 34% (from **1g** and **2a**), colorless needles, mp 155—157 °C. IR (KBr) cm^{-1}: 2201, 1697. UV-Vis (nm (log ε), $CHCl_3$): 280 (4.46), 321 (shoulder), 352 (shoulder). ^{13}C NMR ($CDCl_3$) δ: 14.56, 36.78, 60.41, 98.83, 105.67, 112.95, 114.68, 119.95, 123.90, 124.96, 125.14, 125.79, 126.24, 126.47, 127.73, 128.53, 128.58, 131.54, 131.83, 133.79, 135.28, 138.29, 162.98. *Anal.* Calcd for $C_{23}H_{18}N_2O_2S$: C, 71.48; H, 4.69; N, 7.25. Found: C, 71.55; H, 4.74; N, 7.14.

Ethyl 3-cyano-7-methyl-2-(1-naphthylmethylthio)indolizine-1-carboxylate (**4n**): 49% (from **1h** and **2a**), colorless needles, mp 197—200 °C. IR (KBr) cm^{-1}: 2197, 1682. UV-Vis (nm (log ε), $CHCl_3$): 278 (4.52), 324 (shoulder). ^{13}C NMR ($CDCl_3$) δ: 14.58, 21.67, 36.73, 60.29, 98.09, 104.31, 113.24, 117.17, 118.54, 123.91, 124.32, 125.11, 125.76, 126.21, 127.69, 128.47, 128.54, 131.51, 131.86, 133.76, 135.25, 138.10, 138.72, 163.17. *Anal.* Calcd for $C_{24}H_{20}N_2O_2S$: C, 71.98; H, 5.03; N, 6.99. Found: C, 72.04; H, 4.89; N, 7.07.

Ethyl 3-cyano-6,8-dimethyl-2-(1-naphthylmethylthio)indolizine-1-carboxylate (**4o**): 38% (from **1i** and **2a**), colorless needles, mp 151—153 °C. IR (KBr) cm^{-1}: 2204, 1712. UV-Vis (nm (log ε), $CHCl_3$): 279 (4.34), 317 (shoulder), 331 (4.02). ^{13}C NMR ($CDCl_3$) δ: 14.34, 17.99, 20.28, 38.63, 61.24, 99.77, 111.01, 112.70, 120.91, 123.91, 124.39, 125.07, 125.70, 126.05, 127.547, 128.41, 128.54, 128.80, 129.35, 130.17, 131.41, 132.30, 133.81, 134.23, 164.01. *Anal.* Calcd for $C_{25}H_{22}N_2O_2S$: C, 72.44; H, 5.35; N, 6.76. Found: C, 72.43; H, 5.25; N, 6.87.

Diethyl 6,8-dimethyl-2-(methylthio)indolizine-1,3-dicarboxylate (**5c**): 81% (from 3,5-dimethylpyridinium 1-(1-ethoxycarbonyl-2-methylthio-2-thioxo)ethanide and **2a**), colorless needles, mp 51—52 °C. IR (KBr) cm^{-1}: 1719, 1669. UV-Vis (nm (log ε), $CHCl_3$): 267 (4.31), 338 (4.03), 354 (4.01). ^{13}C NMR ($CDCl_3$) δ: 14.30, 14.43, 18.47, 19.42, 19.89, 60.56, 61.38, 112.79, 114.36, 123.06, 123.26, 126.69, 127.76, 128.59, 133.03, 161.24, 166.58. *Anal.* Calcd for $C_{17}H_{21}NO_4S$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.90; H, 6.33; N, 4.13.

6,8-Dimethyl-2-(methylthio)indolizine-1,3-dicarbonitrile (**5f**): 66% (from 3,5-dimethylpyridinium 1-(1-cyano-2-methylthio-2-thioxo)ethanide and **2b**), colorless needles, mp 224—226 °C. IR (KBr) cm^{-1}: 2213. UV-Vis (nm (log ε), $CHCl_3$): 268 (4.50), 327 (4.03). ^{13}C NMR ($CDCl_3$) δ: 17.74, 18.12, 18.17, 86.73, 98.33, 111.71, 115.29, 121.73, 125.70, 128.26, 130.15, 137.11, 137.46. *Anal.* Calcd for $C_{13}H_{11}N_3S$: C, 64.71; H, 4.59; N, 17.41. Found: C, 64.61; H, 4.50; N, 17.60.

Ethyl 1-cyano-6,8-dimethyl-2-(methylthio)indolizine-3-carboxylate (**5i**): 60% (from 3,5-dimethylpyridinium 1-(1-ethoxycarbonyl-2-methylthio-2-thioxo)ethanide and **2b**), pale yellow needles, mp 123—125 °C. IR (KBr) cm^{-1}: 2207, 1686. UV-Vis (nm (log ε), $CHCl_3$): 274 (4.48), 283

(4.50), 332 (4.01). ^{13}C NMR ($CDCl_3$) δ: 14.39, 17.93, 18.42, 18.68, 60.87, 86.09, 113.80, 117.36, 124.08, 124.44, 126.76, 129.62, 136.15, 138.01, 160.53. *Anal.* Calcd for $C_{15}H_{16}N_2O_2S$: C, 62.48; H, 5.59; N, 9.71. Found: C, 62.39; H, 5.58; N, 9.68.

Ethyl 3-cyano-6,8-dimethyl-2-(methylthio)indolizine-1-carboxylate (**5l**): 73% (from 3,5-dimethylpyridinium 1-(1-cyano-2-methylthio-2-thioxo)ethanide and **2a**), colorless needles, mp 98—100 °C. IR (KBr) cm^{-1}: 2201, 1709. UV-Vis (nm (log ε), $CHCl_3$): 270 (4.53), 330 (4.04). ^{13}C NMR ($CDCl_3$) δ: 14.38, 17.94, 18.25, 20.63, 61.11, 96.89, 10869, 113.53, 12090, 124.11, 128.58, 129.93, 134.31, 134.73, 163.82. *Anal.* Calcd for $C_{15}H_{16}N_2O_2S$: C, 62.48; H, 5.59; N, 9.71. Found: C, 62.26; H, 5.45; N, 9.49.

Crystallography of diethyl 7-methyl-2-(1-naphthylmethylthio)indolizine-1,3-dicarboxylate (4e). A single crystal (1.00×0.22×0.14 mm) grown from EtOH was used for the unit-cell determinations and data collection by a Rigaku AFC5S four-circle diffractometer with graphite-monochromated MoK_α radiation (λ=0.71069 Å). Crystal data of **4e**: $C_{26}H_{25}NO_4S$; M=447.55; triclinic, space group P-1 (#2), Z=2 with a=10.628 (5) Å, b=14.634 (5) Å, c=8.435 (5) Å, α=95.36° (4), β=106.86° (4), γ=110.25° (2); V=1150.2 (9) Å^3, and $D_{calc.}$=1.292 g/cm^3. All calculations were performed using CrystalStructure.[16] The structure was solved by a direct method (SIR88).[17] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final R- and R_w-factors after full-matrix least-squares refinements were 0.062 and 0.049 for 2523 (I>2.00s(I)) observed reflections, respectively.

Crystallography of 7-methyl-2-(1-naphthylmethylthio)indolizine-1,3-dicarbonitrile (4h). A single crystal (0.68×0.24×0.20 mm) grown from EtOH was used for the unit-cell determinations and data collection by a Rigaku AFC5S four-circle diffractometer with graphite-monochromated MoK_α radiation (λ=0.71069 Å). Crystal data of **4h**: $C_{22}H_{15}N_3S$; M=353.44; monoclinic, space group $P2_1/c$ (#14), Z=4 with a=7.56 (4) Å, b=13.79 (4) Å, c=17.05 (5) Å, β=95.5° (5); V=1769.3 (122) Å^3, and $D_{calc.}$=1.327 g/cm^3. All calculations were performed using CrystalStructure.[16] The structure was solved by a direct method (SIR88).[17] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final R- and R_w-factors after full-matrix least-squares refinements were 0.058 and 0.041 for 1716 (I>2.00s(I)) observed reflections, respectively.

REFERENCES AND NOTES

1. Preparation of new nitrogen-bridged heterocycles. 74. For 73 of this series, see A. Kakehi, H. Suga, K. Ito, H. Kobayashi, and M. Shiro, *Heterocycles*, 2011, **81**, 175.

2. A. Kakehi, S. Ito, H. Suga, T. Miwa, T. Mori, and T. Kobayashi, *Heterocycles*, 2002, **57**, 17.
3. A. Kakehi, S. Ito, H. Suga, T. Miwa, T. Mori, T. Fujii, N. Tanaka, and T. Kobayashi, *Chem. Pharm. Bull.*, 2003, **51**, 75.
4. A. Kakehi, H. Suga, T. Kako, T. Fujii, N. Tanaka, and T. Kobayashi, *Chem. Pharm. Bull.*, 2003, **51**, 1246.
5. A. Kakehi, H. Suga, Y. Kaneko, T. Fujii, and N. Tanaka, *Chem. Pharm. Bull.*, 2005, **53**, 1430.
6. A. Kakehi, H. Suga, and H. Isogai, *Chem. Pharm. Bull.*, 2005, **55**, 95.
7. R. G. Pritchard, *Acta Cryst*., 1988, **C44**, 1150.
8. A. Kakehi, S. Ito, T. Fujii, Y. Morimoto, S. Matsumoto, and M. Shiohara, *Bull. Chem. Soc. Jpn*., 1989, **62**, 119.
9. A. Kakehi, S. Ito, N. Yamada, and K. Yamaguchi, *Chem. Pharm. Bull*., 1990, **38**, 1527.
10. A. Kakehi, S. Ito, T. Fujii, T. Ueda, and T. Hirata, *Chem. Pharm. Bull*., 1992, **40**, 2313.
11. H. Isawa, H. Suga, and A. Kakehi, *Heterocycles*, 2009, **78**, 319.
12. The UV-VIS spectra (nm (log ε), $CHCl_3$) for known indolizines **5a**,**b**,**d**,**e**,**g**,**h**,**j**,**k** are as follows: **5a**, 281 (4.40), 321 (shoulder), 333 (4.07), 347 (shoulder); **5b**, 285 (4.40), 321 (shoulder), 334 (4.11), 351 (shoulder); **5d**, 267 (4.45), 274 (shoulder), 323 (3.82), 350 (shoulder); **5e**, 267 (4.50), 275 (shoulder), 324 (3.94), 345 (shoulder); **5g**, 271 (4.52), 279 (4.53), 319 (shoulder), 330 (3.91), 343 (shoulder); **5h**, 270 (4.53), 280 (4.51), 317 (shoulder), 330 (3.95), 343 (shoulder); **5j**, 269 (4.55), 277 (shoulder), 322 (3.88), 348 (shoulder); **5k**, 268 (4.55), 276 (shoulder), 324 (3.99), 345 (shoulder).
13. In ^{1}H-NMR spectra of **4f**,**l** at -50 ^{o}C in $CDCl_3$ no signal for other conformers was detected.
14. C. K. Johnson, "ORTEO II, Report ORNL-5138," Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
15. Y. Tominaga, Y. Miyake, H. Fujito, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, 1977, **97**, 927.
16. CrystalStructure 3.8: Crystal Structure Analysis Package, Rigaku and Rigaku/MSC (2000—2006). 9009 New Trails Dr. The Woodlands TX 77381 USA.
17. SIR92: A. Altmare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polridori, and M. Camalli, *J. Appl. Cryst*., 1994, **27**, 435.