Preparation of New Nitrogen-Bridged Heterocycles. 51.[1] Syntheses and Structures of Compounds Having Two Indolizine Nuclei in a Molecule

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New compounds having two indolizine nuclei in a molecule were prepared in low to moderate yields from the reactions of potassium 2-indolizinethiolates with 1,ω-dihalides such as 1,2-diiodoethane, 1,3-dibromopropane, 1,4-dibromobutane, α,α′-dichloro-*o*-xylene, and α,α′-dichloro-*p*-xylene. Most of the products had the conformation in which the two indolizine rings in the molecule are as remote as possible, but only 1,2-bis[(2-indolizinyl)thio]methyl]benzene derivatives, prepared from potassium 2-indolizinethiolates and α,α′-dichloro-*o*-xylene, showed a weak attractive interaction between the two indolizine nuclei in the X-ray analysis and the nuclear Overhauser and exchange spectroscopy (NOESY) spectrum.

Key words indolizine; intramolecular interaction; stacked structure; X-ray analysis

We recently found a very interesting stacked structure for bis[1-cyano-9-(ethoxycarbonyl)thieno[3,4-*b*]indolizin-3-yl] disulfides (See B in Fig. 1), which were formed *via* the debenzylation of ethyl 3-benzylthio-1-cyanothieno[3,4-*b*]indolizine-9-carboxylates followed by the air oxidation of the resulting thieno[3,4-*b*]indolizine-3-thiols.[2] Although the origin of the superimposed structure is unclear, we proposed the presence of the ionic structure in the indolizine nucleus[3] and the favorable orientation through a disulfide linkage between the two thieno[3,4-*b*]indolizine rings in the molecule (see A and B in Fig. 1). Through-space interactions between two aromatic rings separated by an appropriate spacer are well known as a π–π or arene–arene interaction[4] and are potential candidates for some molecular switches and chiral auxiliaries, but this type of the interaction has scarcely been reported in such heterocyclic system. This finding largely prompted us to investigate the syntheses and their structures of compounds having two indolizine nuclei as a model compound for this phenomenon. In principle, single or double attractive interaction is possible for such indolizine derivatives (see C or D in Fig. 1). From this point of view we report here the preparation of the title compounds from the reactions of potassium 2-indolizinethiolates with 1,ω-dihalides and their conformational structures.

Results and Discussion

Preparations of 1,ω-Bis(2-indolizinylthio)alkanes and 1,2- and 1,4-Bis[(2-indolizinylthio)methyl]benzenes When potassium 2-indolizinethiolates (**2a**—**f**),[5] generated *in situ* from the reactions of ethyl 2-[(2-ethoxycarbonylethyl)thio]-indolizine-3-carboxylates (**1a**—**f**) with potassium *tert*-butoxide in *N*,*N*-dimethylformamide (DMF), were treated with 1,2-diiodoethane (**3a**) at room temperature or 80 °C for 2 d, the expected 1,2-bis[(3-ethoxycarbonyl-2-indolizinyl)thio]-ethanes (**4a**—**f**) were formed in 30—54% yields. (Chart 1)

Similar reactions for *S*-protected indolizines (**1a**—**f**) with potassium *tert*-butoxide and then 1,3-dibromopropane, or 1,4-dibromobutane gave the corresponding bissulfides (**4g**—**r**) in low to moderate yields. On the other hand, the reactions of **1a**—**f** with α,α′-dichloro-*o*-xylene did not afford the expected products under ordinary conditions. However, under more prolonged reaction time at 80 °C, only products **5c**, **f** were obtained in 38 and 30% yields, respectively. In contrast, the reaction of **1a**—**f** with α,α′-dichloro-*p*-xylene smoothly proceeded at the same temperature providing the expected products **5g**—**l** in 39—78% yields. These results are summarized in Charts 2 and 3.

Elemental analyses of products **4a**—**r** and **5c**, **f**—**l** were in good accord with our proposed structures and their IR spectra showed the characteristic cyano (2202—2216 cm^{-1}) and/or ester carbonyl band(s) (near 1670 and/or 1715 cm^{-1}). For the structures of these compounds, ^{1}H-NMR spectra of products **4a**—**r** and **5c**, **f**—**l** afforded two important informations: The first was the presence of the superimposed proton signals due to the two indolizine nuclei and the *S*-methylene group in the molecule, which suggested the presence of a factor of symmetry. The second was that the shielding effect for the pyridine protons anticipated for the stacked structure was not observed at all. For example, the ^{1}H-NMR spectrum of **4a** exhibited only a set of the 4 skeletal proton signals at δ 7.06 (2H, br t, *J*=7.0 Hz, 6-, 6′-H), 7.43 (2H, br dd, *J*=7.0, 9.0 Hz, 7-, 7′-H), 7.75 (2H, br d, *J*=9.0 Hz, 8-, 8′-H), and 9.60 (2H, d, *J*=7.0 Hz, 5-, 5′-H) and a singlet proton signal at δ 3.52 (4H, 2×SC$\underline{H}_2$), together with ethoxycarbonyl sig-

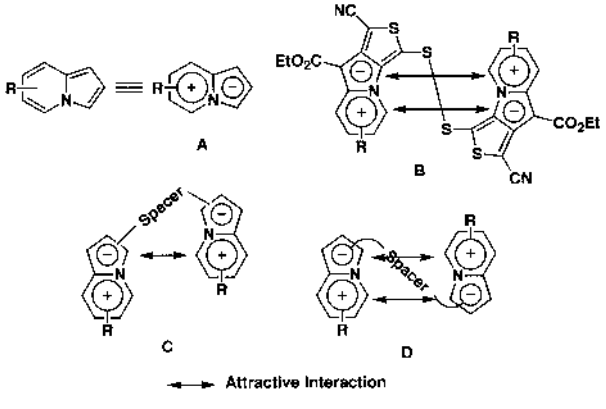

Fig. 1.

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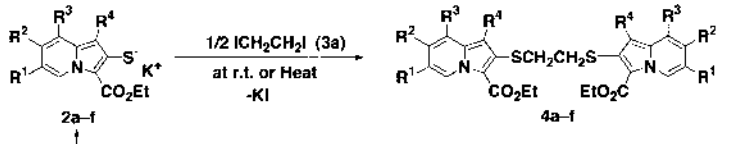
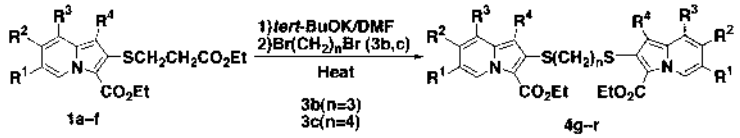


1,2	R^1	R^2	R^3	R^4	4	R^1	R^2	R^3	R^4	Yield (%)
a	H	H	H	CN	a	H	H	H	CN	30
b	H	Me	H	CN	b	H	Me	H	CN	36
c	Me	H	Me	CN	c	Me	H	Me	CN	34
d	H	H	H	CO_2Et	d	H	H	H	CO_2Et	53
e	H	Me	H	CO_2Et	e	H	Me	H	CO_2Et	33
f	Me	H	Me	CO_2Et	f	Me	H	Me	CO_2Et	54

4a–c: 2 days at r.t. 4d–f: 2 days at 80°C

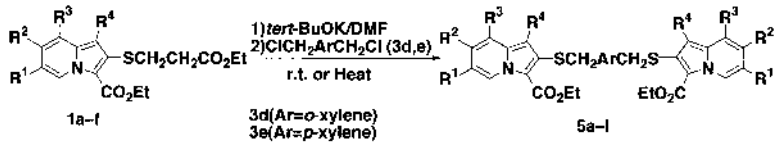
Chart 1



4	R^1	R^2	R^3	R^4	n	Yield (%)	4	R^1	R^2	R^3	R^4	n	Yield (%)
g	H	H	H	CN	3	22	m	H	H	H	CN	4	30
h	H	Me	H	CN	3	29	n	H	Me	H	CN	4	32
i	Me	H	Me	CN	3	21	o	Me	H	Me	CN	4	34
j	H	H	H	CO_2Et	3	22	p	H	H	H	CO_2Et	4	9
k	H	Me	H	CO_2Et	3	25	q	H	Me	H	CO_2Et	4	10
l	Me	H	Me	CO_2Et	3	6	r	Me	H	Me	CO_2Et	4	59

4g–r: 4 days at 80°C

Chart 2



5	R^1	R^2	R^3	R^4	Ar	Yield (%)	5	R^1	R^2	R^3	R^4	Ar	Yield (%)
a	H	H	H	CN	*o*-phenylene	0	g	H	H	H	CN	*p*-phenylene	78
b	H	Me	H	CN	*o*-phenylene	0	h	H	Me	H	CN	*p*-phenylene	66
c	Me	H	Me	CN	*o*-phenylene	38	i	Me	H	Me	CN	*p*-phenylene	41
d	H	H	H	CO_2Et	*o*-phenylene	0	j	H	H	H	CO_2Et	*p*-phenylene	39
e	H	Me	H	CO_2Et	*o*-phenylene	0	k	H	Me	H	CO_2Et	*p*-phenylene	48
f	Me	H	Me	CO_2Et	*o*-phenylene	30	l	Me	H	Me	CO_2Et	*p*-phenylene	46

5c: 4 days at 80°C. 5f: 10 days at 80°C. 5g–i: 1 day at 80°C. 5j–l: 2days at 80°C.

Chart 3

nals at δ 1.43 (6H, t, J=7.0 Hz, 2×$OCH_2C\underline{H}_3$) and 4.43 (4H, q, J=7.0 Hz, 2×$OC\underline{H}_2CH_3$). Any other signal for two different types of indolizine rings in this molecule could not be observed. These chemical shifts due to the indolizine moiety in compounds **4a** were very similar to those of the starting material **1a**.[5] Similar relations for the chemical shifts between the remaining products **4b**—**r** and **5c**, **f**—**l** and the *S*-protected indolizines **1a**—**f** were also observed. Interestingly, the nuclear Overhauser and exchange spectroscopy (NOESY) spectra of compounds **5c**, **f** bearing a *o*-phenylene moiety showed a weak correlation between the ester methyl and the 6- and 8-methyl groups (**5c**) or the 6-methyl group (**5f**), indicating the proximity of the two indolizine rings in the molecule. In the UV spectra for products **4b**—**r** and **5c**, **f**—**l**, furthermore, any absorption band suggesting the through-space interaction between the two indolizine ring could not be detected. From these spectral data and the considerations for their steric factors we presumed that these products except **5c**, **f** may take a conformation in which the two indolizine rings are as remote as possible. In order to confirm this inference, we carried out X-ray analyses for compounds **4d** and **5c** and compared their structures with those derived from MOPAC AM1 calculations.[6] The PLUTO drawings[7] and the optimized structures of **4d** and **5c** are shown in Figs. 2 and 3, respectively. As expected, the ORTEP drawing and the optimized structure for **4d** were similar to each other, and the former had a center of symmetry. On the other hand, the observed structure of **5c** was distinctly differ-

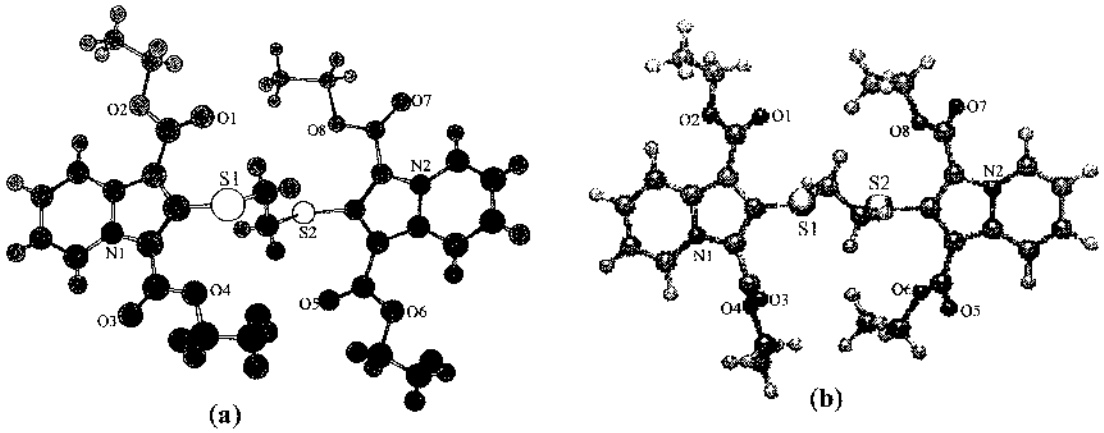


Fig. 2. PLUTO Drawing (a) from the X-Ray Analysis and the Optimized Structure (b) from AM1 Calculation for Compound **4d**

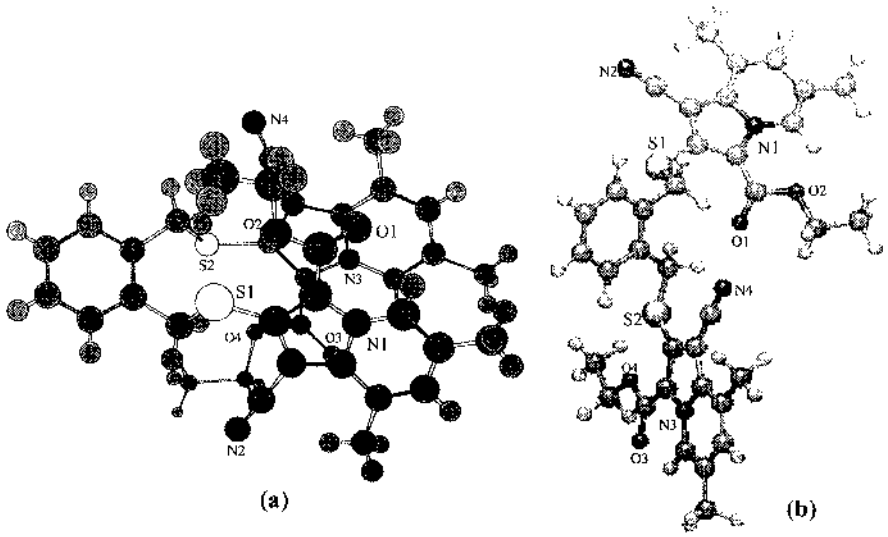


Fig. 3. PLUTO Drawing (a) from the X-Ray Analysis and the Optimized Structure (b) from AM1 Calculation for Compound **5c**

ent from the calculated one. In the solid structure of **5c** the two indolizine rings are much closer than those exhibited by AM1 calculation, though this approach might be still insufficient to overlap them. This fact indicates that the decrease or the loss of the eclipsed conformation of the methylene sequence in the spacer may promote largely an attractive interaction between two indolizine nuclei.

In conclusion, we prepared new compounds possessing two indolizine nuclei combined with various spacers and investigated their conformations. Most of the compounds had sterically favored structures, the two indolizine nuclei being as remote as possible, but those with the *o*-phenylene moiety in the spacer showed a considerable affinity between the two indolizine rings.

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are not corrected. Microanalyses were carried out on a Perkin-Elmer 2400 elemental analyzer. The ^{1}H-NMR spectra were determined with a Hitachi R-600 spectrometer (60 MHz) or JEOL JNM-LA400 (^{1}H: 400 MHz) spectrometer in deuteriochloroform with tetramethylsilane used as the internal standard; the chemical shifts are expressed in δ values. The IR and UV spectra were taken with a JASCO FT/IR-5300 IR and a SHIMADZU UV-2500PC spectrophotometers, respectively.

Preparation of Bissulfides. General Method After a DMF solution (2 ml) of ethyl 2-[(2-ethoxycarbonylethyl)thio]indolizine-3-carboxylate (**1**, 1 mmol)[5,8] was treated with potassium *tert*-butoxide (0.168 g, 1.5 mmol) in a water bath at 80 °C for 10 min, ethyl acrylate generated was completely removed under reduced pressure. The resulting potassium indolizine-2-thiolate (**2**) was then treated with the half equivalent of 1,ω-dihalides such as 1,2-diiodoethane (**3a**), 1,3-dibromopropane (**3b**), 1.4-dibromobutane (**3c**), α,α'-dichloro-*o*-xylene (**3d**), or α,α'-dichloro-*p*-xylene (**3e**) under the reaction conditions shown in Charts 1—3. After the reaction was completed, the reaction mixture was acidified with diluted hydrochloric acid (15 ml) and the oily material separated was extracted twice with 30 ml of chloroform. The chloroform solutions were combined, dried over anhydrous sodium sulfate and concentrated at reduced pressure. The residue was separated by column chromatography on alumina using ether and then chloroform. The chloroform solution was concentrated under reduced pressure. Recrystallization of the crude products from chloroform–hexane gave the corresponding bissulfides (**4a**—**r**, **5c**, **f**, **g**—**l**) as colorless crystals.

However, the reactions of **2a**, **b**, **d**, **e** with **3d** did not provide the corresponding bissulfides **5a**, **b**, **d**, **e** under these reaction conditions, and only 2-indorizinethiol derivatives were isolated.

Selected data for these products **4a**—**r**, and **5c**, **f**, **g**—**l** are as follows:

1,2-Bis[(1-cyano-3-ethoxycarbonyl-2-indolizinyl)thio]ethane (**4a**): 30% (from **1a** and 1,2-diiodoethane (**2a**)), mp 250 °C (dec.). IR (KBr) cm^{-1}: 2216, 1684. UV λ_{max} ($CHCl_3$) nm (log ε) 272 (4.65), 281 (4.60), 331 (4.17). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.43 (6H, t, J=7.0 Hz), 3.52 (4H, s), 4.43 (4H, q, J=7.0 Hz), 7.06 (2H, br t, J=7.0 Hz), 7.43 (2H, br dd, J=7.0, 9.0 Hz), 7.75 (2H, br d, J=9.0 Hz), 9.60 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{26}H_{22}N_4O_4S_2$: C, 60.22; H, 4.28; N, 10.80. Found: C, 60.50; H, 4.44; N, 10.52.

1,2-Bis[(1-cyano-3-ethoxycarbonyl-7-methyl-2-indolizinyl)thio]ethane (**4b**): 36% (from **1b** and 1,2-diiodoethane (**2a**)), mp 235—237 °C. IR (KBr) cm^{-1}: 2210, 1684. UV λ_{max} ($CHCl_3$) nm (log ε) 274 (4.75), 332 (4.31). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.43 (6H, t, J=7.0 Hz), 2.47 (6H, s), 3.51 (4H, s), 4.43 (4H, q, J=7.0 Hz), 6.90 (2H, dd, J=7.0, 2.0 Hz), 7.45 (2H, br s), 9.46 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{28}H_{26}N_4O_4S_2$: C, 61.52; H, 4.79; N, 10.25. Found: C, 61.37; H, 4.84; N, 10.45.

1,2-Bis[(1-cyano-3-ethoxycarbonyl-6,8-dimethyl-2-indolizinyl)thio]-ethane (**4c**): 34% (from **1c** and 1,2-diiodoethane (**2a**)), mp 235 °C (dec.). IR (KBr) cm^{-1}: 2214, 1680. UV λ_{max} ($CHCl_3$) nm (log ε) 275 (4.53), 333 (4.20). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.43 (6H, t, J=7.0 Hz), 2.31, 2.72 (each 6H, s), 3.31 (4H, s), 4.40 (4H, q, J=7.0 Hz), 6.99 (2H, br s), 9.29 (2H, br s). *Anal.* Calcd for $C_{30}H_{30}N_4O_4S_2$: C, 62.70; H, 5.26; N, 9.75. Found: C, 62.65; H, 5.40; N, 9.66.

1,2-Bis[[1,3-bis(ethoxycarbonyl)-2-indolizinyl]thio]ethane (**4d**): 53% (from **1d** and 1,2-diiodoethane (**2a**)), mp 142—146 °C. IR (KBr) cm^{-1}: 1672. UV λ_{max} (EtOH) nm (log ε) 236 (4.65), 279 (4.64), 332 (4.39). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.35 (12H, t, J=7.0 Hz), 3.12 (4H, s), 4.30, 4.32 (each 4H, q, J=7.0 Hz), 6.99 (2H, br t, J=7.0 Hz), 7.35 (2H, br dd, J=7.0, 9.0 Hz), 8.31 (2H, br d, J=9.0 Hz), 9.52 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{30}H_{32}N_2O_8S_2$: C, 58.81; H, 5.26; N, 4.57. Found: C, 58.91; H, 5.31; N, 4.42.

1,2-Bis[[1,3-bis(ethoxycarbonyl)-7-methyl-2-indolizinyl]thio]ethane (**4e**): 33% (from **1e** and 1,2-diiodoethane (**2a**)), mp 166—167 °C. IR (KBr) cm^{-1}: 1705, 1672. UV λ_{max} (EtOH) nm (log ε) 235 (4.66), 282 (4.62), 333 (4.41). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.35 (12H, t, J=7.0 Hz), 2.44 (6H, s), 3.12 (4H, s), 4.32 (8H, q, J=7.0 Hz), 6.84 (2H, dd, J=7.0, 2.0 Hz), 8.09 (2H, br s), 9.41 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{32}H_{36}N_2O_8S_2$: C, 59.98; H, 5.66; N, 4.37. Found: C, 59.77; H, 5.66; N, 4.25.

1,2-Bis[[1,3-bis(ethoxycarbonyl)-6,8-dimethyl-2-indolizinyl]thio]ethane (**4f**): 54% (from **1f** and 1,2-diiodoethane (**2a**)), mp 185—188 °C. IR (KBr) cm^{-1}: 1722, 1670. UV λ_{max} (EtOH) nm (log ε) 227 (4.44), 241 (4.42), 264 (4.42), 338 (4.16), 353 (4.15). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.29, 1.37 (each 6H, t, J=7.0 Hz), 2.34, 2.43 (each 6H, s), 3.01 (4H, s), 4.24, 4.43 (each 4H, q, J=7.0 Hz), 6.89 (2H, br s), 9.33 (2H, br s). *Anal.* Calcd for $C_{34}H_{40}N_2O_8S_2$: C, 61.06; H, 6.03; N, 4.19. Found: C, 61.16; H, 6.06; N, 4.06.

1,3-Bis[(1-cyano-3-ethoxycarbonyl-2-indolizinyl)thio]propane (**4g**): 22% (from **1a** and 1,3-dibromopropane (**2b**)), mp 129—132 °C (dec.). IR (KBr) cm^{-1}: 2202, 1680. UV λ_{max} (EtOH) nm (log ε) 233 (4.55), 270 (4.67), 329 (4.16). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.45 (6H, t, J=7.0 Hz), 1.8—2.4 (2H, m), 3.51 (4H, t, J=7.0 Hz), 4.49 (4H, q, J=7.0 Hz), 7.02 (2H, br t, J=7.0 Hz), 7.37 (2H, br dd, J=7.0, 9.0 Hz), 7.70 (2H, br d, J=9.0 Hz), 9.58 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{27}H_{24}N_4O_4S_2$: C, 60.88; H, 4.54; N, 10.52. Found: C, 60.96; H, 4.67; N, 10.31.

1,3-Bis[(1-cyano-3-ethoxycarbonyl-7-methyl-2-indolizinyl)thio]propane (**4h**): 29% (from **1b** and 1,3-dibromopropane (**2b**)), mp 165—167 °C. IR (KBr) cm^{-1}: 2208, 1672. UV λ_{max} (EtOH) nm (log ε) 234 (4.51), 270 (4.63), 329 (4.14). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.42 (6H, t, J=7.0 Hz), 1.8—2.4 (2H, m), 2.44 (6H, s), 3.47 (4H, t, J=7.0 Hz), 4.46 (4H, q, J=7.0 Hz), 6.77 (2H, dd, J=7.0, 2.0 Hz), 7.42 (2H, br s), 9.42 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{29}H_{28}N_4O_4S_2$: C, 62.12; H, 5.03; N, 9.99. Found: C, 61.97; H, 5.10; N, 10.07.

1,3-Bis[(1-cyano-3-ethoxycarbonyl-6,8-dimethyl-2-indolizinyl)thio]-propane (**4i**): 21% (from **1c** and 1,3-dibromopropane (**2b**)), mp 90—93 °C. IR (KBr) cm^{-1}: 2214, 1682. UV λ_{max} (EtOH) nm (log ε) 235 (4.58), 273 (4.54), 329 (4.16). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.47 (6H, t, J=7.0 Hz), 1.8—2.4 (2H, m), 2.33, 2.72 (each 6H, s), 3.36 (4H, t, J=7.0 Hz), 4.48 (4H, q, J=7.0 Hz), 6.94 (2H, br s), 9.26 (2H, br s). *Anal.* Calcd for $C_{31}H_{32}N_4O_4S_2$: C, 63.24; H, 5.48; N, 9.52. Found: C, 63.32; H, 5.61; N, 9.31.

1,3-Bis[[1,3-bis(ethoxycarbonyl)-2-indolizinyl]thio]propane (**4j**): 22% (from **1d** and 1,3-dibromopropane (**2b**)), mp 83—85 °C. IR (KBr) cm^{-1}: 1682. UV λ_{max} (EtOH) nm (log ε) 238 (4.56), 279 (4.48), 332 (4.23). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.40 (12H, t, J=7.0 Hz), 1.4—2.0 (2H, m), 3.13 (4H, t, J=7.0 Hz), 4.44 (8H, q, J=7.0 Hz), 6.97 (2H, br t, J=7.0 Hz), 7.36 (2H, br dd, J=7.0, 9.0 Hz), 8.32 (2H, br d, J=9.0 Hz), 9.51 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{31}H_{34}N_2O_8S_2$: C, 59.41; H, 5.47; N, 4.47. Found: C, 59.70; H, 5.23; N, 4.23.

1,3-Bis[[1,3-bis(ethoxycarbonyl)-7-methyl-2-indolizinyl]thio]propane (**4k**): 25% (from **1e** and 1,3-dibromopropane (**2b**)), mp 123—125 °C. IR (KBr) cm^{-1}: 1666. UV λ_{max} (EtOH) nm (log ε) 239 (4.60), 282 (4.56), 332 (4.27). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.39 (12H, t, J=7.0 Hz), 1.4—2.0 (2H, m), 2.44 (6H, s), 3.13 (4H, t, J=7.0 Hz), 4.48 (8H, q, J=7.0 Hz), 6.81 (2H, dd, J=7.0, 2.0 Hz), 8.11 (2H, br s), 9.42 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{33}H_{38}N_2O_8S_2$: C, 60.53; H, 5.85; N, 4.28. Found: C, 60.78; H, 5.97; N, 4.33.

1,3-Bis[[1,3-bis(ethoxycarbonyl)-6,8-dimethyl-2-indolizinyl]thio]propane (**4l**): 6% (from **1f** and 1,3-dibromopropane (**2b**)), mp 85—87 °C. IR (KBr) cm^{-1}: 1722, 1670. UV λ_{max} (EtOH) nm (log ε) 229 (4.44), 244 (4.43), 263 (4.38), 337 (4.13), 352 (4.12). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.39 (12H, t, J=7.0 Hz), 1.5—2.2 (2H, m), 2.32, 2.42 (each 6H, s), 3.02 (4H, t, J=7.0 Hz), 4.44 (8H, q, J=7.0 Hz), 6.86 (2H, br s), 9.32 (2H, br s). *Anal.* Calcd for $C_{35}H_{42}N_2O_8S_2$: C, 61.56; H, 6.20; N, 4.10. Found: C, 61.84; H, 6.10; N, 3.92.

1,4-Bis[(1-cyano-3-ethoxycarbonyl-2-indolizinyl)thio]butane (**4m**): 30% (from **1a** and 1,4-dibromobutane (**2c**)), mp 165—167 °C. IR (KBr) cm^{-1}: 2206, 1674. UV λ_{max} (EtOH) nm (log ε) 234 (4.52), 270 (4.74), 329 (4.20). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.46 (6H, t, J=7.0 Hz), 1.7—2.2 (4H, m), 3.37 (4H, br t, J=7.0 Hz), 4.49 (4H, q, J=7.0 Hz), 7.04 (2H, br t, J=7.0 Hz), 7.40 (2H, br dd, J=7.0, 9.0 Hz), 7.74 (2H, br d, J=9.0 Hz), 9.62 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{28}H_{26}N_4O_4S_2$: C, 61.52; H, 4.79; N, 10.25. Found: C, 61.79; H, 4.87; N, 10.01.

1,4-Bis[(1-cyano-3-ethoxycarbonyl-7-methyl-2-indolizinyl)thio]butane (**4n**): 32% (from **1b** and 1,4-dibromobutane (**2c**)), mp 191—194 °C. IR (KBr) cm^{-1}: 2206, 1674. UV λ_{max} (EtOH) nm (log ε) 237 (4.24), 271 (4.49), 328 (3.95). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.44 (6H, t, J=7.0 Hz), 1.5—2.0 (4H, m), 2.48 (6H, s), 3.35 (4H, br t, J=7.0 Hz), 4.46 (4H, q, J=7.0 Hz), 6.86 (2H, dd, J=7.0, 2.0 Hz), 7.49 (2H, br s), 9.45 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{30}H_{30}N_4O_4S_2$: C, 62.70; H, 5.26; N, 9.75. Found: C, 62.73; H, 5.49; N, 9.49.

1,4-Bis[(1-cyano-3-ethoxycarbonyl-6,8-dimethyl-2-indolizinyl)thio]butane (**4o**): 34% (from **1c** and 1,4-dibromobutane (**2c**)), mp 170—173 °C. IR (KBr) cm^{-1}: 2210, 1687. UV λ_{max} (EtOH) nm (log ε) 236 (4.63), 273 (4.63), 330 (4.23). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.46 (6H, t, J=7.0 Hz), 1.5—2.0 (4H, m), 2.34, 2.74 (each 6H, s), 3.20 (4H, br t, J=7.0 Hz), 4.46 (4H, q, J=7.0 Hz), 6.98 (2H, br s), 9.32 (2H, br s). *Anal.* Calcd for $C_{32}H_{34}N_4O_4S_2$: C, 63.76; H, 5.69; N, 9.29. Found: C, 64.01; H, 5.70; N, 9.01.

1,4-Bis[[1,3-bis(ethoxycarbonyl)-2-indolizinyl]thio]butane (**4p**): 9% (from **1d** and 1,4-dibromobutane (**2c**)), mp 83—85 °C. IR (KBr) cm^{-1}: 1693. UV λ_{max} (EtOH) nm (log ε) 237 (4.64), 280 (4.58), 332 (4.30). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.43 (12H, t, J=7.0 Hz), 1.2—1.9 (4H, m), 2.98 (4H, br t, J=7.0 Hz), 4.46 (8H, q, J=7.0 Hz), 6.98 (2H, br t, J=7.0 Hz), 7.35 (2H, br dd, J=7.0, 9.0 Hz), 8.35 (2H, br d, J=9.0 Hz), 9.56 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{32}H_{36}N_2O_8S_2$: C, 59.98; H, 5.66; N, 4.37. Found: C, 59.72; H, 5.72; N, 4.32.

1,4-Bis[[1,3-bis(ethoxycarbonyl)-7-methyl-2-indolizinyl]thio]butane (**4q**): 10% (from **1e** and 1,4-dibromobutane (**2c**)), mp 131—133 °C. IR (KBr) cm^{-1}: 1689. UV λ_{max} (EtOH) nm (log ε) 238 (4.60), 281 (4.55), 332 (4.29). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.43 (12H, t, J=7.0 Hz), 1.2—1.9 (4H, m), 2.42 (6H, s), 2.98 (4H, br t, J=7.0 Hz), 4.46 (8H, q, J=7.0 Hz), 6.81 (2H, dd, J=7.0, 2.0 Hz), 8.09 (2H, br s), 9.38 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{34}H_{40}N_2O_8S_2$: C, 60.87; H, 6.31; N, 4.18. Found: C, 60.71; H, 6.15; N, 4.12.

1,4-Bis[[1,3-bis(ethoxycarbonyl)-6,8-dimethyl-2-indolizinyl]thio]butane (**4r**): 59% (from **1f** and 1,4-dibromobutane (**2c**)), mp 105—108 °C. IR (KBr) cm^{-1}: 1714, 1676. UV λ_{max} (EtOH) nm (log ε) 229 (4.54), 244 (4.53), 262 (4.47), 337 (4.22). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.40, 1,42 (each 6H, t, J=7.0 Hz), 1.5—2.2 (4H, m), 2.33, 2.43 (each 6H, s), 2.90 (4H, br t, J=7.0 Hz), 4.43, 4.45 (each 4H, q, J=7.0 Hz), 6.86 (2H, br s), 9.30 (2H, br s). *Anal.* Calcd for $C_{36}H_{44}N_2O_8S_2$: C, 62.05; H, 6.36; N, 4.02. Found: C, 62.06; H, 6.37; N, 4.00.

1,2-Bis[(1-cyano-3-ethoxycarbonyl-6,8-dimethyl-2-indolizinyl)thiomethyl]-benzene (**5c**): 38% (from **1c** and α,α'-dchloro-*o*-xylene (**3d**)), mp 177—179 °C. IR (KBr) cm^{-1}: 2212, 1678. UV λ_{max} (EtOH) nm (log ε) 234 (5.00), 274 (4.37), 327 (1.54). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.41 (6H, t, J=7.2 Hz), 2.28, 2.65 (each 6H, s), 4.40 (4H, q, J=7.2 Hz), 4.65 (4H, s), 6.84 (2H, br s), 7.0—7.20 (4H, m), 9.09 (2H, br s). In this NOESY spectrum a weak correlation between the ester methyl group at the 3-position on the indolizine ring and the 6- and 8-methyl groups was observed. *Anal.* Calcd for $C_{36}H_{34}N_4O_4S_2$: C, 66.44; H, 5.27; N, 8.61. Found: C, 66.39; H, 5.35; N, 8.58.

1,2-Bis[[1,3-bis(ethoxycarbonyl)-6,8-dimethyl-2-indolizinyl]thiomethyl]-benzene (**5f**): 30% (from **1f** and α,α'-dichloro-*o*-xylene (**3d**)), mp 133—136 °C. IR (KBr) cm^{-1}: 1714, 1680. UV λ_{max} (EtOH) nm (log ε) 243 (4.53), 338 (1.68), 352 (1.53). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.33, 1.36 (each 6H, t, J=7.2 Hz), 2.29, 2.38 (each 6H, s), 4.24 (4H, s), 4.29 (4H, q, J=7.2 Hz), 4.32 (4H, q, J=7.2 Hz), 6.77 (2H, br s), 6.9—7.1 (4H, m), 9.16 (2H, br s). In this NOESY spectrum a weak correlation between the ester methyl group at

the 3-position on the indolizine ring and the 6-methyl group was observed. *Anal.* Calcd for $C_{40}H_{44}N_2O_8S_2$: C, 64.50; H, 5.95; N, 3.76. Found: C, 64.46; H, 5.96; N, 3.67.

1,4-Bis[(1-cyano-3-ethoxycarbonyl-2-indolizinyl)thiomethyl]benzene (**5g**): 78% (from **1a** and α,α'-dichloro-*p*-xylene (**3e**)), mp 190—192 °C. IR (KBr) cm^{-1}: 2210, 1682. UV λ_{max} (EtOH) nm (log ε) 237 (4.62), 271 (4.68), 279 (4.66), 330 (4.23). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.43 (6H, t, J=7.0 Hz), 4.46 (4H, q, J=7.0 Hz), 4.52 (4H, s), 7.04 (2H, br t, J=7.0 Hz), 7.39 (4H, s), 7.40 (2H, br dd, J=7.0, 9.0 Hz), 7.75 (2H, br d, J=9.0 Hz), 9.59 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{32}H_{26}N_4O_4S_2$: C, 64.63; H, 4.41; N, 9.42. Found: C, 64.89; H, 4.36; N, 9.21.

1,4-Bis[(1-cyano-3-ethoxycarbonyl-7-methyl-2-indolizinyl)thiomethyl]-benzene (**5h**): 66% (from **1b** and α,α'-dichloro-*p*-xylene (**3e**)), mp 223—225 °C. IR (KBr) cm^{-1}: 2208, 1682. UV λ_{max} ($CHCl_3$) nm (log ε) 274 (4.77), 282 (4.75), 332 (4.28). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.43 (6H, t, J=7.0 Hz), 2.45 (6H, s), 4.46 (4H, q, J=7.0 Hz), 4.52 (4H, s), 6.81 (2H, dd, J=7.0, 2.0 Hz), 7.34 (4H, s), 7.47 (2H, br s), 9.43 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{34}H_{30}N_4O_4S_2$: C, 65.57; H, 4.86; N, 9.00. Found: C, 65.59; H, 4.85; N, 8.99.

1,4-Bis[(1-cyano-3-ethoxycarbonyl-6,8-dimethyl-2-indolizinyl)thiomethyl]-benzene (**5i**): 41% (from **1c** and α,α'-dichloro-*p*-xylene (**3e**)), mp 235—237 °C. IR (KBr) cm^{-1}: 2212, 1734. UV λ_{max} (EtOH) nm (log ε) 239 (4.66), 274 (4.53), 330 (4.23). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.42 (6H, t, J=7.0 Hz), 2.33, 2.73 (each 6H, s), 4.35 (4H, s), 4.45 (4H, q, J=7.0 Hz), 6.97 (2H, br s), 7.29 (4H, s), 9.29 (2H, br s). *Anal.* Calcd for $C_{36}H_{34}N_4O_4S_2$: C, 66.44; H, 5.27; N, 8.61. Found: C, 66.26; H, 5.37; N, 8.68.

1,4-Bis[[1,3-bis(ethoxycarbonyl)-2-indolizinyl]thiomethyl]benzene (**5j**): 39% (from **1d** and α,α'-dichloro-*p*-xylene (**3e**)), mp 175—177 °C. IR (KBr) cm^{-1}: 1701, 1672. UV λ_{max} (EtOH) nm (log ε) 243 (4.68), 280 (4.53), 333 (4.31). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.40, 1.46 (each 6H, t, J=7.0 Hz), 4.20 (4H, s), 4.44, 4.49 (each 4H, q, J=7.0 Hz), 6.98 (2H, br t, J=7.0 Hz), 7.19 (4H, s), 7.35 (2H, br dd, J=7.0, 9.0 Hz), 8.36 (2H, br d, J=9.0 Hz), 9.55 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{36}H_{36}N_2O_8S_2$: C, 62.77; H, 5.27; N, 4.07. Found: C, 62.68; H, 5.30; N, 4.13.

1,4-Bis[[1,3-bis(ethoxycarbonyl)-7-methyl-2-indolizinyl]thiomethyl]benzene (**5k**): 48% (from **1e** and α,α'-dichloro-*p*-xylene (**3e**)), mp 280—284 °C. IR (KBr) cm^{-1}: 1684. UV λ_{max} (EtOH) nm (log ε) 243 (4.69), 283 (4.45), 321 (4.35). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.40, 1.45 (each 6H, t, J=7.0 Hz), 2.44 (6H, s), 4.19 (4H, s), 4.44, 4.49 (each 4H, q, J=7.0 Hz), 6.82 (2H, dd, J=7.0, 2.0 Hz), 7.18 (4H, s), 8.15 (2H, br s), 9.42 (2H, d, J=7.0 Hz). *Anal.* Calcd for $C_{38}H_{40}N_2O_8S_2$: C, 63.67; H, 5.62; N, 3.91. Found: C, 63.51; H, 5.72; N, 3.84.

1,4-Bis[[1,3-bis(ethoxycarbonyl)-6,8-dimethyl-2-indolizinyl]thiomethyl]-benzene (**5l**): 46% (from **1f** and α,α'-dichloro-*p*-xylene (**3e**)), mp 140 °C (dec.). IR (KBr) cm^{-1}: 1728, 1674. UV λ_{max} (EtOH) nm (log ε) 248 (4.59), 352 (4.15), 337 (4.16). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.39, 1.44 (each 6H, t, J=7.0 Hz), 2.32, 2.45 (each 6H, s), 4.13 (4H, s), 4.45 (8H, q, J=7.0 Hz), 6.87 (2H, br s), 7.21 (4H, s), 9.31 (2H, br s). *Anal.* Calcd for $C_{40}H_{44}N_2O_8S_2$: C, 64.50; H, 5.95; N, 3.76. Found: C, 64.47; H, 6.05; N, 3.69.

Crystallography of 1,2-Bis[[1,3-bis(ethoxycarbonyl)-2-indolizinyl]thio]-ethane (4d) A single crystals (0.42×0.54×1.00 mm) grown from $CHCl_3$–hexane was used for the unit-cell determinations and the data collection by Rigaku AFC5S four-circle diffractometer with graphite-monochromated Mo$K\alpha$ radiation (λ=0.71069 Å). Crystal data of these compounds are as follows: **4d**: $C_{30}H_{32}N_2O_8S_2$; M=612.71; triclinic, space group $P\bar{1}$ (#2), Z=1 with a=9.650 (2) Å, b=9.797 (5) Å, c=8.465 (4) Å, α=109.30° (3), β=96.20° (3), γ=83.66° (3); V=748.5 (6) Å^3, and D_{calc}=1.359 g/cm^3. All calculations were performed using the TEXSAN program.[9] The structure was solved by a direct method (MITHRIL).[10] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were refined isotropically. The final R- and R_w-factors after full-matrix least-squares refinements were 0.049 and 0.0581 for 3439 ($I>2.00\sigma(I>)$) observed reflections, respectively.

Crystallography of 1,2-Bis[(1-cyano-3-ethoxycarbonyl-6,8-dimethyl-2-indolizinyl)thiomethyl]benzene (5c) A single crystal (0.14×0.26×0.48 mm) grown from $CHCl_3$–hexane was used for the unit-cell determinations and the data collections by Rigaku AFC5S four-circle diffractometer with graphite-monochromated Mo$K\alpha$ radiation (λ=0.71069 Å). Crystal data of **5c**: $C_{30}H_{22}N_4O_4S_4$; M=630.77; triclinic, space group $P\bar{1}$ (#2), Z=2 with a=10.930 (4) Å, b=14.033 (4) Å, c=10.340 (4) Å, α=92.42° (3), β=108.11° (3), γ=72.18° (3); V=1432.6 (9) Å^3, and D_{calc}=1.462 g/cm^3. All calculations were performed using the TEXSAN program.[9] The structure was solved by a direct method (MITHRIL).[10] 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 0.065 and 0.065 for 3008 ($I>2.00\sigma(I)$) observed reflections, respectively.

References and Notes

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6) "WinMOPAC (Version 2.0)," Fujitsu Corporation.
7) Motherwell S., Clegg W., "PLUTO" program, Univ. of Cambridge, England (1978).
8) UV data for ethyl 2-[(2-ethoxycarbonylethyl)thio]indolizine-3-carboxylates are as follows: **1a**, λ_{max} (EtOH) nm (log ε) 233 (4.32), 269 (4.44), 329 (3.97); **1b**, λ_{max} (EtOH) nm (log ε) 234 (4.33), 271 (4.44), 330 (4.01); **1c**, λ_{max} (EtOH) nm (log ε) 236 (4.43), 273 (4.35), 330 (4.02); **1d**, λ_{max} (EtOH) nm (log ε) 237 (4.35), 279 (4.26), 332 (4.02); **1e**, λ_{max} (EtOH) nm (log ε) 239 (4.39), 282 (4.29), 332 (4.08); **1f**, λ_{max} (EtOH) nm (log ε) 230 (4.30), 241 (4.31), 262 (4.28), 336 (4.28), 352 (4.01).
9) "TEXSAN TEXRAY," Structure Analysis Package, Molecular Structure Corporation (1985).
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