Preparation of New Nitrogen-Bridged Heterocycles. XXVI.¹⁾ Crystal Structures of Thieno[3,2-*a*]- and Thieno[2,3-*b*]indolizine Derivatives

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Single crystal X-ray analyses of thieno[3,2-*a*]- and thieno[2,3-*b*]indolizine derivatives were carried out and their structures were definitively established. The tricyclic ring systems in both molecules were nearly planar and their deviations from the least-squares planes were less than 6.26°. The structural factors for their indolizine moieties were very similar to those for known aromatic indolizines, but those for the thiophene rings were somewhat different. The deviation from co-planarity and the deformation of the thiophene ring in thieno[3,2-*a*]indolizine were greater than those in thieno[2,3-*b*]indolizine.

Keywords thieno[3,2-*a*]indolizine; thieno[2,3-*b*]indolizine; indolizine; fused indolizine; fused thiophene; X-ray analysis

Recently, we reported simple and convenient methods for the preparations of several thieno[3,2-*a*]- and thieno[2,3-*b*]indolizine derivatives by alkaline treatment of the corresponding polyfunctionalized indolizine derivatives.²⁾ Since the syntheses were accomplished by reliable intramolecular addition or condensation processes at the final stage, there is little doubt that the products have the expected structures. However, it is still valuable to confirm their structures because they have new fused heterocyclic ring systems, and the structural information obtained by chemical and physical means is limited. In this paper we wish to report the results of X-ray single crystal analyses of thieno[3,2-*a*]- and thieno[2,3-*b*]indolizine derivatives.

Results and Discussion

A single crystal (approximately 0.6 × 0.5 × 0.8 mm) of ethyl 3-amino-2-benzoyl-4,6-dimethylthieno[3,2-*a*]indolizine-9-carboxylate (**1**) and a single crystal (0.4 × 0.4 × 1.0 mm) of ethyl 3,7-dimethyl-2-(*p*-methylbenzoyl)thieno[2,3-*b*]indolizine-9-carboxylate (**2**), prepared according to the procedure described in our previous paper,^{2c)} were used for the unit cell determinations and the data collections of a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated MoK α radiation ($\lambda = 0.71069$ Å). Both crystals were triclinic, space group $P\bar{1}$, $Z = 2$ with $a = 10.728(3)$ Å, $b = 12.070(2)$ Å, $c = 7.810(3)$ Å; $\alpha = 100.22(2)^\circ$, $\beta = 106.34(2)^\circ$, $\gamma = 95.56(2)^\circ$; $V = 943.4(5)$ Å³, and $D_{\text{calc}} = 1.381$ g/cm³ for **1**, and space group $P\bar{1}$, $Z = 2$, with $a = 10.548(1)$ Å, $b = 12.637(2)$ Å, $c = 7.458(1)$ Å; $\alpha = 97.27(1)^\circ$, $\beta = 101.03(1)^\circ$, $\gamma = 81.45(1)^\circ$, $V = 960.0(2)$ Å³, and $D_{\text{calc}} = 1.354$ g/cm³ for **2**.

The structures were solved by the direct method (MITHRIL),³⁾ and the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in the structure factor calculation in idealized positions. The final R -factors after the full-matrix least-squares refinements were 0.052 for 2376 observed reflections for **1** and 0.050 for 3157 observed reflections for **2**. The positional and thermal parameters with their standard deviations for compounds **1** and **2** are listed in Tables I and II. The bond distances and angles for non-hydrogen atoms and ORTEP drawings⁴⁾ of the structures are shown in Tables III and IV and Figs. 1 and 2, respectively.

The bond distances and angles for the indolizine moiety in compounds **1** and **2** are very similar to those for

1-acetoxy-2,3- and 3-acetoxy-1,2-diphenylindolizine reported by Wadsworth and his co-workers.⁵⁾ The proton nuclear magnetic resonance (¹H-NMR) spectral data for the indolizine ring protons and the methyl protons of **1**^{2c)} and **2** are in good agreement with those of known fully aromatic

Fig. 1. ORTEP Drawing of Thieno[3,2-*a*]indolizine **1** Showing the Atom Labeling Scheme and 50% Probability Thermal Ellipsoids

Fig. 2. ORTEP Drawing of Thieno[2,3-*b*]indolizine **2** Showing the Atom Labeling Scheme and 50% Probability Thermal Ellipsoids

TABLE I. Positional ($\times 10^4$) and Thermal Parameters ($\text{\AA}^2$) of Thieno[3,2-*a*]indolizine (**1**) for Non-hydrogen Atoms with Their Standard Deviations in Parentheses

Atom ^{a)}	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq}
S1	3214 (1)	2331.3 (8)	9110 (1)	3.68 (3)
O1	−3 (3)	3795 (3)	8248 (5)	6.4 (1)
O2	7789 (3)	2574 (2)	12031 (4)	5.7 (1)
O3	5962 (2)	1649 (2)	9823 (3)	4.2 (1)
N1	6232 (3)	4419 (2)	12685 (4)	3.7 (1)
N2	2057 (3)	5242 (3)	10608 (5)	5.4 (1)
C1	2079 (4)	3297 (3)	9280 (5)	3.9 (1)
C2	2699 (4)	4352 (3)	10417 (5)	3.8 (1)
C3	4072 (4)	4354 (3)	11288 (5)	3.4 (1)
C4	5201 (4)	5049 (3)	12609 (5)	3.6 (1)
C5	5469 (4)	6114 (3)	13844 (5)	4.2 (2)
C6	6715 (5)	6466 (3)	15027 (6)	5.1 (2)
C7	7748 (5)	5837 (4)	15035 (5)	4.9 (2)
C8	7482 (4)	4817 (3)	13866 (5)	4.5 (2)
C9	5801 (4)	3361 (3)	11458 (5)	3.5 (1)
C10	4470 (4)	3328 (3)	10633 (5)	3.3 (1)
C11	9101 (5)	6286 (4)	16326 (6)	6.6 (2)
C12	4418 (5)	6846 (3)	13886 (6)	5.8 (2)
C13	695 (4)	3025 (3)	8358 (6)	4.4 (2)
C14	23 (4)	1828 (4)	7501 (5)	4.1 (1)
C15	373 (4)	898 (4)	8240 (5)	4.5 (2)
C16	−314 (4)	−184 (4)	7444 (6)	5.3 (2)
C17	−1375 (5)	−344 (4)	5884 (7)	5.9 (2)
C18	−1750 (4)	570 (5)	5153 (6)	6.1 (2)
C19	−1067 (4)	1659 (4)	5964 (6)	5.2 (2)
C20	6641 (4)	2532 (3)	11191 (5)	3.7 (1)
C21	6694 (4)	762 (4)	9327 (6)	5.0 (2)
C22	5803 (5)	−82 (4)	7759 (6)	5.8 (2)

a) See Fig. 1 for the numberings of **1**.TABLE II. Positional ($\times 10^4$) and Thermal Parameters ($\text{\AA}^2$) of Thieno[2,3-*b*]indolizine (**2**) for Non-hydrogen Atoms with Their Standard Deviations in Parentheses

Atom ^{a)}	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq}
S1	7010.3 (6)	3749.8 (5)	7713 (1)	2.69 (3)
O1	5792 (2)	1923 (2)	8215 (4)	5.2 (1)
O2	8736 (2)	6831 (2)	6356 (3)	3.9 (1)
O3	6957 (2)	6045 (1)	6445 (3)	3.03 (8)
N1	10653 (2)	3798 (2)	8213 (3)	2.24 (8)
C1	7802 (2)	2575 (2)	8681 (4)	2.6 (1)
C2	9146 (2)	2480 (2)	8899 (3)	2.4 (1)
C3	9494 (2)	3401 (2)	8301 (3)	2.3 (1)
C4	11929 (3)	3358 (2)	8668 (4)	2.8 (1)
C5	12892 (2)	3907 (2)	8481 (4)	3.1 (1)
C6	12621 (2)	4933 (2)	7807 (4)	2.7 (1)
C7	11347 (2)	5366 (2)	7372 (3)	2.5 (1)
C8	10336 (2)	4817 (2)	7575 (3)	2.3 (1)
C9	8965 (2)	5069 (2)	7255 (3)	2.3 (1)
C10	8472 (2)	4169 (2)	7690 (3)	2.3 (1)
C11	6812 (3)	1890 (2)	9096 (4)	3.1 (1)
C12	7284 (3)	1233 (2)	10686 (4)	2.9 (1)
C13	6663 (3)	325 (2)	10669 (4)	3.4 (1)
C14	6863 (3)	−220 (2)	12218 (5)	3.8 (1)
C15	7662 (3)	121 (2)	13818 (5)	4.0 (1)
C16	8281 (3)	1017 (3)	13831 (4)	4.2 (1)
C17	8104 (3)	1555 (2)	12273 (4)	3.5 (1)
C18	7841 (5)	−451 (3)	15538 (6)	6.4 (2)
C19	10097 (3)	1538 (2)	9526 (4)	3.4 (1)
C20	13714 (3)	5515 (3)	7550 (4)	3.6 (1)
C21	8256 (2)	6069 (2)	6655 (4)	2.6 (1)
C22	6110 (3)	6982 (2)	5770 (4)	3.6 (1)
C23	5806 (3)	7802 (3)	7296 (5)	4.6 (2)

a) See Fig. 2 for the numberings of **2**.TABLE III. Bond Distances ($\text{\AA}$) and Angles ($^\circ$) of Thieno[3,2-*a*]indolizine (**1**) for Non-hydrogen Atoms with Their Standard Deviations in Parentheses

Bond distance ($\text{\AA}$)			
S1–C1	1.780 (4)	C5–C6	1.370 (6)
S1–C10	1.719 (4)	C5–C12	1.502 (6)
O1–C13	1.249 (4)	C6–C7	1.402 (6)
O2–C20	1.213 (4)	C7–C8	1.348 (5)
O3–C20	1.347 (4)	C7–C11	1.499 (6)
O3–C21	1.450 (4)	C9–C10	1.385 (5)
N1–C4	1.395 (4)	C9–C20	1.437 (5)
N1–C8	1.378 (5)	C13–C14	1.496 (5)
N1–C9	1.402 (4)	C14–C15	1.387 (5)
N2–C2	1.340 (4)	C14–C19	1.389 (5)
C1–C2	1.398 (5)	C15–C16	1.379 (6)
C1–C13	1.432 (5)	C16–C17	1.382 (6)
C2–C3	1.438 (5)	C17–C18	1.373 (7)
C3–C4	1.424 (5)	C18–C19	1.387 (6)
C3–C10	1.407 (5)	C21–C22	1.470 (6)
C4–C5	1.414 (5)		
Bond angle ($^\circ$)			
C1–S1–C10	90.1 (2)	C8–C7–C11	121.4 (5)
C20–O3–C21	116.4 (3)	N1–C8–C7	120.6 (4)
C4–N1–C8	122.4 (3)	N1–C9–C10	105.8 (3)
C4–N1–C9	110.8 (3)	N1–C9–C20	124.0 (3)
C8–N1–C9	126.8 (3)	C10–C9–C20	130.1 (3)
S1–C1–C2	112.0 (3)	S1–C10–C3	114.2 (3)
S1–C1–C13	124.0 (3)	S1–C10–C9	135.5 (3)
C2–C1–C13	124.0 (3)	C3–C10–C9	110.2 (3)
N2–C2–C1	122.3 (4)	O1–C13–C1	120.4 (4)
N2–C2–C3	125.6 (4)	O1–C13–C14	117.2 (4)
C1–C2–C3	112.1 (3)	C1–C13–C14	122.3 (3)
C2–C3–C4	141.8 (3)	C13–C14–C15	123.4 (4)
C2–C3–C10	111.2 (3)	C13–C14–C19	117.8 (4)
C4–C3–C10	107.0 (3)	C15–C14–C19	118.7 (4)
N1–C4–C3	106.2 (3)	C14–C15–C16	121.3 (4)
N1–C4–C5	117.4 (3)	C15–C16–C17	119.4 (4)
C3–C4–C5	136.3 (4)	C16–C17–C18	120.1 (4)
C4–C5–C6	118.4 (4)	C17–C18–C19	120.5 (4)
C4–C5–C12	121.3 (4)	C14–C19–C18	120.0 (4)
C6–C5–C12	120.2 (4)	O2–C20–O3	122.7 (4)
C5–C6–C7	123.2 (4)	O2–C20–C9	127.5 (4)
C6–C7–C8	118.0 (4)	O3–C20–C9	109.8 (3)
C6–C7–C11	120.6 (4)	O3–C21–C22	107.9 (3)

indolizine derivatives.⁶⁾ However, there are significant differences in the dihedral angles between the two least-squares planes of the indolizine ring. The dihedral angles between the pyridine and the pyrrole rings are 3.22° in **1** and 0.59° in **2**, and the indolizine ring of the latter is almost planar. On the other hand, the geometries of the thiophene rings in these molecules are considerably different from those of the parent thiophene⁷⁾ and benzo[*b*]thiophene derivatives.⁸⁾ First, there are large differences between the two sulfur–carbon (S–C) bond distances, and, second, the ring systems are not planar. The lengths of the S–C bonds (S1–C10) attached directly to the indolizine rings are 1.719 and 1.707 $\text{\AA}$ in **1** and **2**, respectively, and they are nearly the same as that (1.714 $\text{\AA}$) of the parent thiophene⁷⁾ but are shorter than those (average 1.744 $\text{\AA}$) of benzo[*b*]thiophenes.⁸⁾ This suggests that the S–C bonds have marked double-bond character due to the aromatic resonance structures, as expected in the parent thiophene.⁷⁾ On the other hand, the other S–C bonds (S1–C1, 1.780 $\text{\AA}$ in **1** and 1.759 $\text{\AA}$ in **2**) are longer than those of benzo[*b*]thiophenes,⁸⁾ and this is indicative of some reduction of the contribution of aromatic resonance structures at these bonds. The

Fig. 3. Probable Resonance Structures for Thieno[3,2-*a*]- and Thieno[2,3-*b*]indolizines

TABLE IV. Bond Distances (Å) and Angles (°) of Thieno[2,3-*b*]indolizine (2) for Non-hydrogen Atoms with Their Standard Deviations in Parentheses

Bond distance (Å)			
S1-C1	1.759 (3)	C6-C7	1.367 (4)
S1-C10	1.707 (3)	C6-C20	1.510 (4)
O1-C11	1.235 (3)	C7-C8	1.396 (3)
O2-C21	1.216 (3)	C8-C9	1.414 (3)
O3-C21	1.357 (3)	C9-C10	1.415 (3)
O3-C22	1.453 (3)	C9-C21	1.445 (3)
N1-C3	1.404 (3)	C11-C12	1.492 (4)
N1-C4	1.374 (3)	C12-C13	1.401 (4)
N1-C8	1.401 (3)	C12-C17	1.381 (4)
C1-C2	1.384 (3)	C13-C14	1.385 (4)
C1-C11	1.465 (4)	C14-C15	1.383 (5)
C2-C3	1.418 (3)	C15-C16	1.387 (4)
C2-C19	1.500 (4)	C15-C18	1.518 (5)
C3-C10	1.388 (3)	C16-C17	1.389 (4)
C4-C5	1.349 (4)	C22-C23	1.489 (5)
C5-C6	1.419 (4)		
Bond angle (°)			
C1-S1-C10	90.9 (1)	C8-C9-C10	106.0 (2)
C21-O3-C22	116.9 (2)	C8-C9-C21	125.3 (2)
C3-N1-C4	130.6 (2)	C10-C9-C21	128.7 (2)
C3-N1-C8	108.5 (2)	S1-C10-C3	110.7 (2)
C4-N1-C8	120.9 (2)	S1-C10-C9	139.4 (2)
S1-C1-C2	113.5 (2)	C3-C10-C9	109.9 (2)
S1-C1-C11	113.8 (2)	O1-C11-C1	119.6 (3)
C2-C1-C11	132.6 (2)	O1-C11-C12	118.8 (3)
C1-C2-C3	108.6 (2)	C1-C11-C12	121.3 (2)
C1-C2-C19	126.9 (2)	C11-C12-C13	119.1 (3)
C3-C2-C19	124.4 (2)	C11-C12-C17	122.2 (2)
N1-C3-C2	136.7 (2)	C13-C12-C17	118.2 (3)
N1-C3-C10	107.2 (2)	C12-C13-C14	120.3 (3)
C2-C3-C10	116.1 (2)	C13-C14-C15	121.3 (3)
N1-C4-C5	119.7 (2)	C14-C15-C16	118.4 (3)
C4-C5-C6	121.6 (2)	C14-C15-C18	121.3 (3)
C5-C6-C7	118.1 (2)	C16-C15-C18	120.4 (3)
C5-C6-C20	120.6 (2)	C15-C16-C17	120.7 (3)
C7-C6-C20	121.3 (3)	C12-C17-C16	121.1 (3)
C6-C7-C8	121.3 (2)	O2-C21-O3	123.6 (2)
N1-C8-C7	118.4 (2)	O2-C21-C9	125.8 (2)
N1-C8-C9	108.4 (2)	O3-C21-C9	110.6 (2)
C7-C8-C9	133.2 (2)	O3-C22-C23	111.8 (2)

least-squares plane of the thiophene ring intersect with those of the pyrrole and pyridine rings at 3.06 and 6.26° in **1** and at 2.99 and 2.41° in **2**, respectively, and, in particular, the deformation of the tricyclic ring system is greater in **1** than in **2**. These facts suggest that the major contributors to the resonance structures of the thieno[3,2-*a*]indolizine (**1**) and thieno[2,3-*b*]indolizine (**2**) are **1a** and **2a**, respectively, and the contributions of structures such as **1b** and **2b** are not

so large (see Fig. 3).

Experimental

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

Preparation of Thienoindolizines Ethyl 3-amino-2-benzoyl-4,6-dimethylthieno[3,2-*a*]indolizine-9-carboxylate (**1**) was prepared according to our recent paper,^{2c)} and a single crystal was grown from ethanol as a yellow needle. mp 204–205 °C (lit.^{2c)} 203–204 °C). On the other hand, ethyl 3,7-dimethyl-2-(*p*-methylbenzoyl)thieno[2,3-*b*]indolizine-9-carboxylate (**2**) was prepared freshly in 59% yield by the reaction of 3-acetyl-2-mercapto-7-methylindolizine-1-carboxylate with *p*-methylphenacyl bromide in the presence of alkali,^{2c)} since a suitable single crystal could not be obtained by the recrystallization of known derivatives.²⁾ A single crystal of **2** was grown from ethanol as yellow prism. mp 189–190 °C. IRν(KBr): 1673 (CO), 1587, 1281, 1230, 1058 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.37 (3H, t, *J* = 7.0 Hz, OCH₂CH₃), 2.42 (6H, s, 7-Me, tolyl-Me), 2.79 (3H, s, 3-Me), 4.33 (2H, q, *J* = 7.0 Hz, OCH₂CH₃), 6.62 (1H, dd, *J* = 7.0, 2.0 Hz, 6-H), 7.1–8.0 (4H, m, phenyl-H), 8.13 (1H, brs, 8-H), 8.49 (1H, d, *J* = 7.0 Hz, 5-H). Anal. Calcd for C₂₃H₂₁NO₃: C, 70.56; H, 5.41; N, 3.58. Found: C, 70.33; H, 5.47; N, 3.75.

Acknowledgement This work was supported in part by a Grant-in-Aid for Scientific Research (No. 02453085) from the Ministry of Education, Science and Culture.

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