HETEROCYCLES, Vol. 57, No. 1, 2002, pp. 17 - 20, Received, 16th November, 2001

A THROUGH-SPACE INTERACTION OF 3-BENZYLTHIOTHIENO-[3,4-*b*]INDOLIZINE DERIVATIVES COMBINED BY A HIGHLY FLEXIBLE SPACER[1]

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Abstract - Some ethyl 1-benzoyl-3-[(un)substituted benzylthio]thieno-[3,4-*b*]indolizine-9-carboxylates were prepared and their conformations were investigated. In the solid state and the chloroform solution they had stacked structures in which the phenyl ring and the pyridine moiety of theino[3,4-*b*]indolizine ring are partly overlapped.

It is well known that two aromatic rings separated by the appropriate spacer are attracted by the π-π or arene-arene interaction,[2] and the molecules having such function are potential candidates for a molecular switch and a chiral auxiliary.[3] We have recently reported an interesting stacked structure in bis[1-cyano-9-ethoxycarbonylthieno[3,4-*b*]-indolizin-3-yl] disulfides[4] and the unusual proximity of the two indolizine rings in 1,2-bis[[(2-indolizinyl)thio]-methyl]benzene derivatives,[1] and proposed the contribution of the unique ionic structure of the indolizine ring as a driving force for this through-space interaction. Furthermore, our recent development of a novel constructive method of a thieno[3,4-*b*]indolizine skeleton[5] prompted us to investigate the through-space interaction for various types of thieno[3,4-*b*]indolizine derivatives. The conformational analyses for some model molecules using Dreiding models showed that the phenyl ring and the pyridine moiety of the thieno[3,4-*b*]indolizine ring in the title compounds can considerably approach in the gauche form (**G**) in the relation to the exocyclic sulfide linkage, though they are largely remote in the anti one (**A**), as shown in Figure 1. In this communication we report a new efficient preparative method for ethyl 1-benzoyl-3-benzylthiothieno[3,4-*b*]indolizine-9-carboxylates and the through-space interaction.

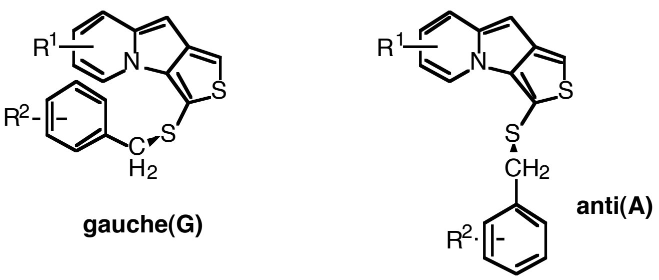
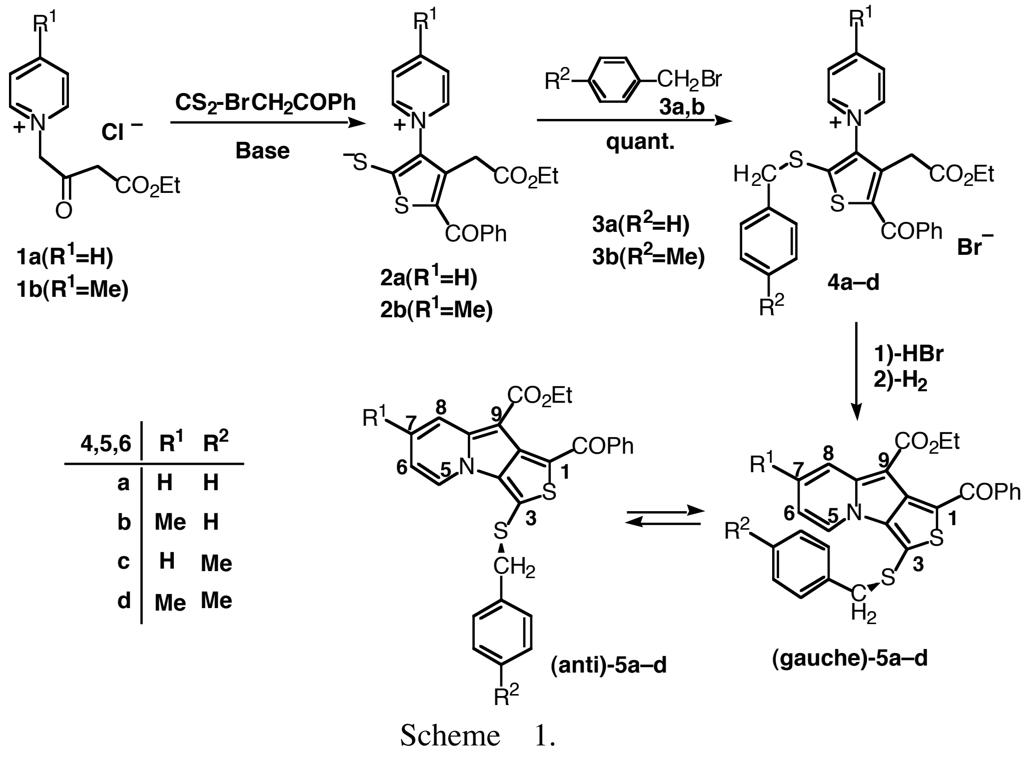


Figure 1

The title compounds, ethyl 1-benzoyl-2-(benzylthio)thieno[3,4-*b*]indolizine-9-carboxylates (**5a–d**),[6] were prepared by the S-alkylation of pyridinium betaines (**2a**,**b**),[6,7] readily obtainable from the reactions of 1-(ethoxycarbonylacetonyl)pyridinium chlorides (**1a**,**b**) with carbon disulfide and phenacyl bromide in the presence of triethylamine, with benzyl bromide (**3a**) and *p*-methylbenzyl bromide (**3b**), followed by the treatment of DBU and then chloranil (Scheme 1): (**5a**), 74%, mp 135–137 ° C (from $CHCl_3$-hexane), ν (CO) 1688 and 1589 cm^{-1}, UV λ_{max} ($CHCl_3$) nm (log e) 422 (3.91), 480 (3.80); **5b**, 67%, mp 144–147 °C (from $CHCl_3$-hexane), ν (CO) 1669, 1595 cm^{-1}, UV λ_{max} ($CHCl_3$) nm (log ε) 425 (4.18), 479 (3.58); (**5c**), 83%, mp 149–151 °C (from $CHCl_3$-hexane), ν (CO) 1674, 1597 cm^{-1}, UV λ_{max} ($CHCl_3$) nm (log e) 423 (3.90), 480 (3.84); **5d**, 65%, mp 110–111°C (from $CHCl_3$-hexane), ν (CO) 1674, 1591 cm^{-1}, UV λ_{max} ($CHCl_3$) nm (log ε) 428 (3.98), 476 (3.78).



4,5,6	R1	R2
a	H	H
b	Me	H
c	H	Me
d	Me	Me

Scheme 1.

The contribution of the gauche conformers (gauche-**5a–d**) in products (**5a–d**) was distinctly exhiibited by the observation of considerable shielding effects between the benzylic phenyl and the ring protons at the 5- and 6-positions in the H^1 NMR spectra and of the characteristic absorption bands at near 425 nm in the UV spectra. For example, the chemical shifts of the 5- and 6-protons in products (**5a–d**) were appeared at higher region (*ca.* 0.2 ppm) in the comparisons for those in ethyl 1-benzoyl-3-methylthiothieno[3,4-*b*]indolizine-9-carboxylate (**6a**) and its 7-methyl derivative (**6b**),[5] and those of the corresponding aromatic protons of 3-benzylthio group were also exhibited at higher magnetic field (δ 6.9–7.2). (Table 1)

Table 1. NMR Data of Ethyl 1-Benzoylthieno[3,4-*b*]indolizine-9-carboxylates (**5a–d**), and (**6a**,**b**)

No	C-5	C-6	C-7	C-8	RCH$_2$S	$\delta_{5\text{-H}}$	$\delta_{6\text{-H}}$	$\delta_{7\text{-H}}$	$\delta_{8\text{-H}}$
6a[a,b]	8.96	6.73	7.31	8.20	2.68	0.00	0.00	0.00	0.00
5a[a]	8.77	6.50	7.23	8.12	4.11 7.04–7.16[c]	0.19	0.23	0.08	0.08
5c[d]	8.77	6.49	7.26	8.15	2.21 4.11 6.97[c]	0.19	0.24	0.05	0.03
6b[a,e]	8.84	6.58	2.40	8.00	2.67	0.00	0.00	-----	0.00
5b[a]	8.67	6.36	2.35	7.93	4.11 7.05–7.20[c]	0.17	0.22	-----	0.07
5d[d]	8.65	6.35	2.37	7.96	2.21 4.09 6.97[c]	0.19	0.21	-----	0.03

a) 400 MHz (δ, CDCl$_3$). b) Standard to 7-unsubstituted compounds (**5a**,**c**). c) Benzylic phenyl protons. d) 60 MHz (δ, CDCl$_3$). e) Standard to 7-methyl compounds (**5b**,**d**).

Furthermore, a remarkabe absorption band owing to the through-space interaction between the phenyl ring and the pyridine moiety in their UV spectra appeared at 422–428 nm. The UV spectra of **5a** and **6a** are shown in Figure 3. Interestingly, the X-Ray analysis of one compound (**5c**) showed that it is the gauche conformer but not anti one.[8] As seen in the ORTEP drawing (Figure 3),[9] both the pyridine and phenyl moieties in this molecule are partly overlapped (the N$_1$-C$_{23}$ distance is 3.78(2) Å).

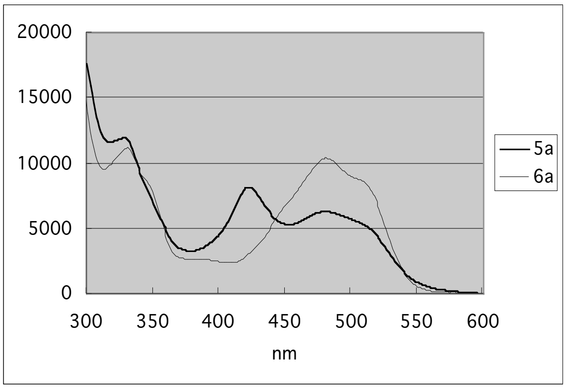


Figure 2. UV Spectra of of **5a** and **6a**

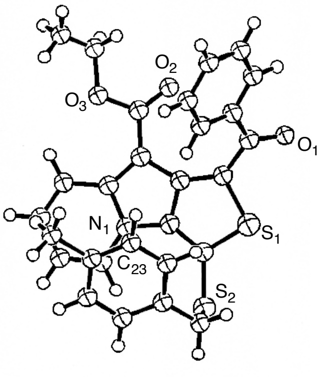


Figure 3. ORTEP drawing of **5c**

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6 All new compounds afforded satisfactory elemental analyses.

7 **2a**, 38%, mp 213–215 °C (from EtOH), ν (CO) 1730, 1599 cm^{-1}, δ (60 MHz, $CDCl_3$) 1.28 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 3.83 (2H, s, CH_2CO), 4.27 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.2–8.9 (5H, m, Py-H); **2b**, 42%, mp 174–177 °C (from EtOH), ν (CO) 1728, 1636 cm^{-1}, δ (60 MHz, $CDCl_3$) ,1.24 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 2.74 (3H, s, Py-$\underline{Me}$), 3.83 (2H, s, CH_2CO), 4.15 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.2–9.0 (4H, m, Py-H)

8 Crystallography of **5c:** A single crystal (0.38 x 0.46 x 0.86 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 MoK_a radiation (λ=0.71069 Å). Crystal data of these compounds are as follows: **5c**: $C_{28}H_{23}NO_3S_2$; M=485.61; monoclinic, space group $P2_1/a$ (#14), Z=4 with a=16.157 (1) Å, b=11.814 (3) Å, c=14.180 (1) Å, β=116.115° (5), γ=73.98° (3);V=2430.3 (5) $Å^3$, and $D_{calc.}$=1.327 g/cm^3. All calculation were performed using the TEXSAN program.[10] The structure was solved by a direct method (SIR).[11] 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 0.075 and 0.088 for 2137 (I>2. observed reflections), respectively.

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