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FIRST FORMATION OF THIEPINO[2,3-*b*]- AND THIEPINO[3,2-*a*]-INDOLIZINE DERIVATIVES[1]

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Abstract – The reactions of potassium 1,3-bis(ethoxycarbonyl)indolizine-2-thiolates with ethyl 4-bromocrotonate afforded the corresponding indolizine derivatives having (*E*)-(3-ethoxycarbonyl-2-propenyl)thio, (*E*)- and (*Z*)-(3-ethoxycarbonyl-1-propenyl)thio group at the 2-position. The alkaline treatment of these *S*-alkylated indolizines gave the title compounds in good yields.

We previously reported that potassium indolizine-2-thiolates bearing electron-withdrawing groups at the 1-, and 3-positions were useful precursors for the preparation of some novel nitrogen-bridged heterocycles such as thieno[2,3-*b*]-, thieno[3,2-*a*]-,[2,3] and thiino[2,3-*b*]indolizine derivatives.[4] The key step in above reactions was the intramolecular nucleophilic addition of the carbanion species generated in the 2-substituent onto a cyano or an acyl carbonyl group at the 1- or 3-position. Subsequent hydrogen transfer or elimination from the primary cycloadducts provided the corresponding heterocycles. As an extension of this reaction, we were interested in the behavior of indolizine derivatives having a vinylogous carbanion (allyl anion) in the 2-substituent, because species such as **Ia** should form 2-vinylthiophenes **II**, but those such as **Ib** should provide thiepins **III** which are not readily accessible (see Figure 1). In general, the route leading to five-membered heterocycles such as **II** is more favorable than that to provide seven-membered heterocycles such as **III** because of the smooth approach of the reaction sites in the transition state and of ready stabilization (aromatization) of the primary adducts. However, an example in which seven-membered products were exclusively formed is also known.[5] Here we describe the first formations of thiepino[2,3-*b*]- and thiepino[3,2-*a*]indolizine derivatives from the alkaline treatment of diethyl 1,3-indolizinedicarboxylates having an (*E*)-(3-ethoxycarbonyl-2-propenyl)thio, (*E*)- and (*Z*)-(3-ethoxycarbonyl-1- propenyl)thio group at the 2-position.

When potassium 1,3-bis(ethoxycarbonyl)indolizine-2-thiolate (**2a**), generated in situ by the reactions of diethyl 2-[(2-ethoxycarbonylethyl)thio]indolizine-1,3-dicarboxylate (**1a**) with potassium *tert*-butoxide in

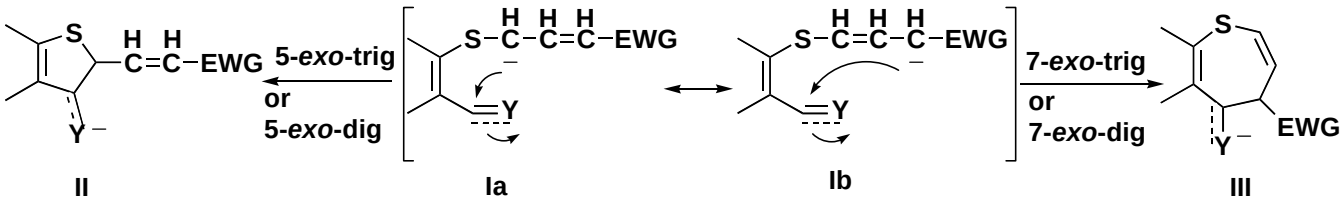
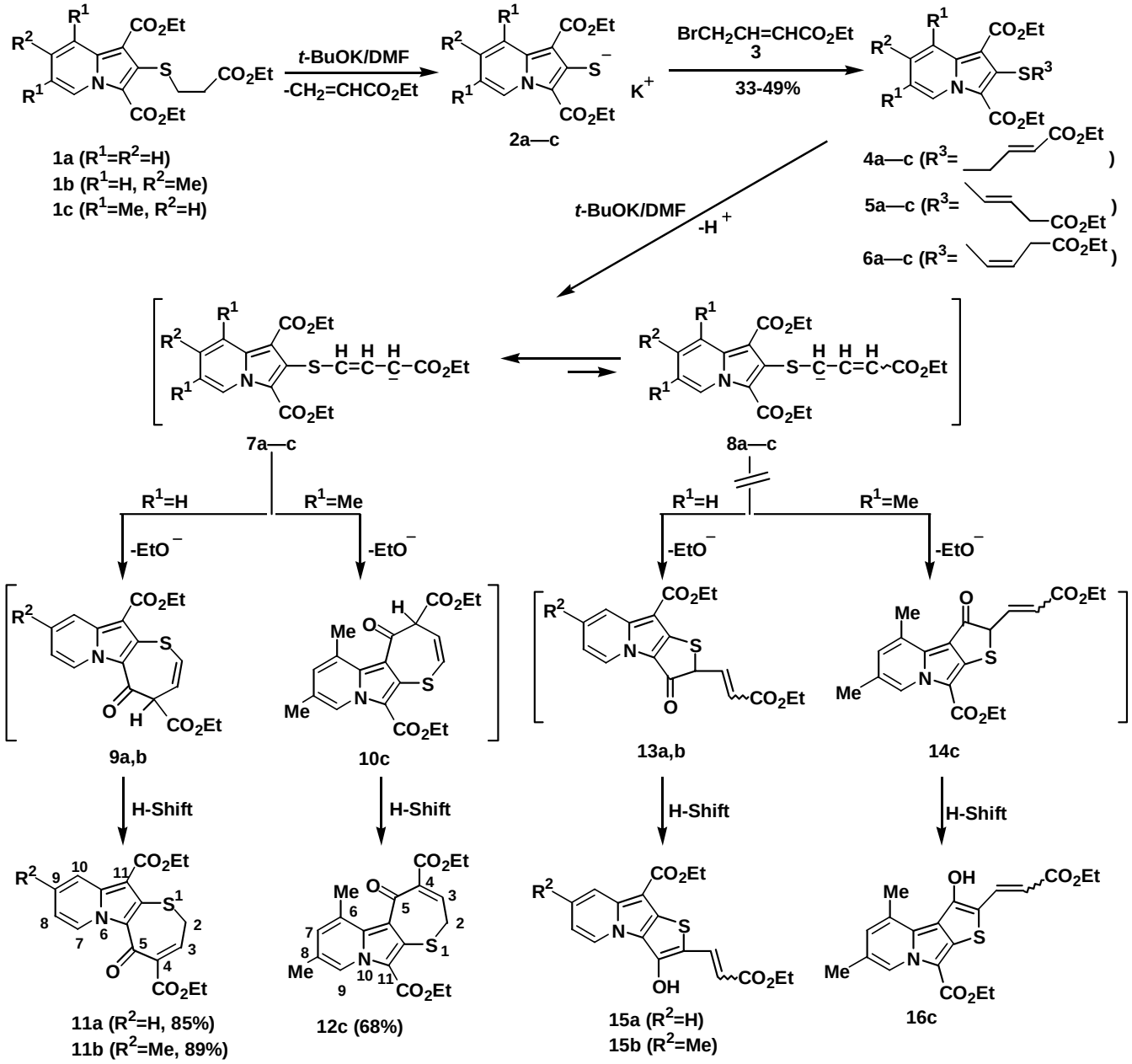


Figure 1

DMF, was treated with ethyl 4-bromocrotonate (**3**), a mixture of diethyl 2-[(*E*)-(3-ethoxycarbonyl-2-propenyl)thio]- (**4a**), diethyl 2-[(*E*)-(3-ethoxycarbonyl-1-propenyl)thio]- (**5a**), and diethyl 2-[(*Z*)-(3-ethoxycarbonyl-1-propenyl)thio]indolizine-1,3-dicarboxylates (**6a**) was obtained in a 49% yield as a pale yellow oil, and its ratio was 100:6:3.[6,7] Similar treatment of *S*-protected indolizines **1b**,**c** with **3** afforded the mixtures of the corresponding *S*-alkylated indolizines **4b**+**5b**+**6b** (its ratio is 100:4:2) and **4c**+**5c**+**6c** (its ratio is 50:11:9) in 40% and 33% yields.[6,7] Since all of indolizines **4a**—**c**, **5a**—**c**, and **6a**—**c** thus obtained are potential precursors for vinylogous carbanions such as **7a**—**c** and/or **8a**—**c**, we next examined their deprotonation. The reactions of **4a**+**5a**+**6a** and **4b**+**5b**+**6b** with potassium *tert*-butoxide in DMF at room temperature proceeded smoothly to give the corresponding products **11a**,**b** as unstable yellow powders in 85% and 89% yields.[8,9] These compounds were not diethyl 5-oxo-4,5-dihydrothiepino[2,3-*b*]indolizine-4,11-dicarboxylates (**9a**,**b**) which were initially expected from the nucleophilic attack of the carbanions **7a**,**b** on the ester carbonyl group at the 3-position of the indolizine ring followed by the elimination of an ethoxide ion, but were diethyl 5-oxo-2,5-dihydrothiepino[2,3-*b*]indolizine-4,11-dicarboxylates (**11a**) and its 9-methyl derivatives **11b** which were derived from the proton transfer of the cycloadducts **9a**,**b**. Similar reaction of **4c**+**5c**+**6c** provided diethyl 6,8-dimethyl-5-oxo-2,5-dihydrothiepino[3,2-*a*]indolizine-4,11-dicarboxylate (**12c**) in a 68% yield as an unstable yellow powder.[8,9] In these reactions, however, the alternative 2-vinylthieno[2,3-b]- (**9a**,**b**) or 2-vinylthieno[3,2-*a*]indolizine derivative (**10c**) which can be formed via the intermediate **8a**—**c** could not be obtained at all. These results are shown in Scheme 1.

The structural assignments for products **4a**—**c**, **5a**—**c**, **6a**—**c**, **11a**,**b**, and **12c** were performed mainly by ^{1}H-NMR spectral analyses. In particular, the structures of major *S*-alkylated indolizines **4a**—**c** could readily be determined by the presence of the *S*-methylene triplet (*J*=7.6 Hz) at δ 3.63—3.75 ppm and of the vinyl protons with a trans-coupling constant (15.4 Hz) near δ 5.7 and 6.9 ppm respectively, together with the signals of three ethoxycarbonyl and indolizine ring protons. Similarly, the structures of minor products **5a**—**c** and **6a**—**c** were assigned as the *E*- and *Z*-isomers of the 2-[(3-ethoxycarbonyl-1-propenyl)thio] group by the appearances of the methylene triplet (*J*=6.8—7.2 Hz) at higher magnetic regions (δ 3.08 (trans) and 3.32 or 3.33 (cis) ppm) and of the *S*-vinyl protons with a trans- (15.2—15.4 Hz) or cis-coupling constant (9.4 —9.6 Hz) near δ 5.8 and 6.2 ppm. On the other hand, ^{1}H-NMR spectra



Scheme 1

of thiepino[2,3-*b*]- **11a**,**b** and thiepino[3,2-*a*]indolizines **12c** exhibited the presence of only two ethoxy groups and the loss of an ethoxy group at lower magnetic regions. This is assignable to the ethoxycarbonyl group at the 1- or 3-position of the indolizine ring. This fact strongly suggested that carbanion **7** or **8** interacted with the ethoxycarbonyl group at the 1- or 3-position with the elimination of an ethoxide ion during these reactions. The absence of the AB type signals due to the exocyclic vinyl group as shown in 2-vinylthienoindolizines **15a**,**b** and **16c** and the presence of the AX_2 type signals (δ 3.39-3.43 (d, SCH_2) and 7.07-9.19 ppm (t, 3-H)) with a vicinal coupling constant (7.3 Hz) supported the thiepin structure for **11a**,**b** and **12c**. Furthermore, the comparisons of the chemical shifts of the protons on the indolizine ring in **11a**,**b** and **12c** with those in *S*-alkylated indolizines **4a**—**c** disclosed the orientation of these cyclizations. That is, the chemical shifts for each 7-proton in **11a**,**b** were shifted to a

higher magnetic region (ca. δ 0.5 ppm) in comparison with those of **4a**,**b**, while the chemical shifts of each 10-proton in **11a**,**b** and of the 9-proton in **12c** were grossly similar to those in **4a**—**c**. These facts indicate that the nucleophilic attacks of the anions on the 3-ester carbonyl carbon in **7a**,**b** and on the 1-ester one in **7c** occurred. The same orientation of the cyclization on the indolizine ring have already been observed in the transformation reactions from diethyl 2-(acylmethylthio)indolizine-1,3-dicarboxylates to the corresponding 2-acyltheino[2,3-*b*]- and 2-acylthieno[3,2-*a*]indolizine derivatives, and the electronic and steric effects leading to such orientations have been also described.[3] The reason for the exclusive formation of thiepino[2,3-*b*]- **11a**,**b** and thiepino[3,2-a]indolizine **12c** from the alkaline treatment of *S*-alkylated indolizines **4a**—**c**, **5a**—**c**, and **6a**—**c** is unclear, but the larger contribution of the allyl anions **7a**—**c**, which are stabilized by resonance and inductive effects, over the alternative anions **8a**—**c** may be considered. Further investigation of this reaction is now in progress.

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6. **4a**, ^{1}H NMR ($CDCl_3$) δ: 1.22, 1.46, and 1.47 (each 3H, t, *J*=7.1 or 7.2 Hz, 3xOCH$_2$C*H*$_3$), 3.75 (2H, dd, *J*=7.6, and 1,2 Hz, SC*H*$_2$), 4.11, 4.44, and 4.47 (each 2H, q, *J*=7.1 or 7.2 Hz, 3xOC*H*$_2$CH$_3$), 5.68 (1H, dt, *J*=15.4, 1.3, and 1.3 Hz, =C*H*CO$_2$Et), 6.91 (1H, dt, *J*=15.4, 7.6, and 7.6 Hz, SCH$_2$C*H*=CH), 6.93 (1H, dt, *J*=7.1, 7.1, and 1.2 Hz, 6-H), 7.27 (1H, ddd, *J*=9.2, 6.8, and 1.1 Hz, 7-H), 8.26 (1H, dt, *J*=9.3, 1.1, and 1.1 Hz, 8-H), and 9.42 (1H, dt, *J*=7.1, 1.1, and 1.1 Hz, 5-H).

   4b, ^{1}H NMR ($CDCl_3$) δ: 1.23, 1.46, and 1.47 (each 3H, t, *J*=7.1 Hz, 3xOCH$_2$C*H*$_3$), 2.43 (3H, d, *J*=1.0 Hz, 7-Me), 3.74 (2H, dd, *J*=7.6 and 1.2 Hz, SC*H*$_2$), 4.12, 4.44, and 4.46 (each 2H, q, *J*=7.1 or 7.2 Hz, 3xOC*H*$_2$CH$_3$), 5.67 (1H, dt, *J*=15.4, 1.3, and 1.3 Hz, =C*H*CO$_2$Et), 6.77 (1H, dd, *J*=7.3 and 1.9 Hz, 6-H), 6.91 (1H, dt, *J*=15.4, 7.6, and 7.6 Hz, SCH$_2$C*H*=CH), 8.06 (1H, quint, *J*=1.0 Hz, 8-H), and 9.32 (1H, d, *J*=7.2 Hz, 5-H).

   4c, ^{1}H NMR ($CDCl_3$) δ: 1.24, 1.42, and 1.47 (each 3H, t, *J*=7.1 Hz, 3xOCH$_2$C*H*$_3$), 2.30 (3H, s, 6-Me), 2.42 (3H, s, 8-Me), 3.63 (2H, dd, J=7.6 and 1.2 Hz, SC*H*$_2$), 4.14, 4.42, and 4.45 (each 2H, q, *J*=7.2 Hz, 3xOC*H*$_2$CH$_3$), 5.66 (1H, dt, *J*=15.4, 1.2, and 1.2 Hz, =C*H*CO$_2$Et), 6.80 (1H, br s, 7-Me), 6.93 (dt, J=15.4, 7.7, and 7.7 Hz, SCH$_2$C*H*=CH), 9.19 (1H, br s, 5-H).

   5a, ^{1}H NMR ($CDCl_3$) δ: 3.08 (2H, dd, *J*=7.2 and 1.3 Hz, C*H*$_2$CO$_2$Et), 5.80 (1H, dt, *J*=15.3, 7.2, and

7.2 Hz, SCH=C*H*CH_2), and 6.20 (1H, dt, *J*=15.3, 1.4, and 1.4 Hz, SC*H*=CH).[10]

5b, ^{1}H NMR ($CDCl_3$) δ: 3.08 (2H, dd, *J*=7.2 and 1.3 Hz, C*H*$_2$$CO_2$Et), 5.79 (1H, dt, *J*=15.2, 7.2, and 7.2 Hz, SCH=C*H*CH_2), and 6.20 (1H, dt, *J*=15.2, 1.3, and 1.3 Hz, SC*H*=CH).[10]

5c, ^{1}H NMR ($CDCl_3$) δ: 1.25, 1.39, and 1.41 (each 3H, t, *J*=7.1 or 7.2 Hz, 3x$CO_2CH_2CH_3$), 3.08 (2H, dd, *J*=7.1 and 1.5 Hz, C*H*$_2$$CO_2$Et), 4.13 and 4.35 (each 2H, q, *J*=7.2 Hz, 2x$CO_2CH_2CH_3$), 5.82 (1H, dt, *J*=15.3, 7.1, and 7.1 Hz, SCH=C*H*CH_2), and 6.21 (1H, dt, *J*=15.4, 1.2, and 1.2 Hz, SC*H*=CH).[10]

6a, ^{1}H NMR ($CDCl_3$) δ: 3.33 (2H, dd, *J*=6.8 and 1.7 Hz, C*H*$_2$$CO_2$Et), 5.79 (1H, dt, *J*=9.5, 6.8, and 6.8 Hz, SCH=C*H*CH_2), and 6.21 (1H, dt, *J*=9.5, 1.6, and 1.6 Hz, SC*H*=CH).[10]

6b, ^{1}H NMR ($CDCl_3$) δ: 3.33 (2H, dd, *J*=6.8 and 1.7 Hz, C*H*$_2$$CO_2$Et), 5.78 (1H, dt, *J*=9.6, 6.8, and 6.8 Hz, SCH=C*H*CH_2), and 6.21 (1H, dt, *J*=9.5, 1.7, and 1.7 Hz, SC*H*=CH).[10]

6c, ^{1}H NMR ($CDCl_3$) δ: 1.29, 1.37, and 1.40 (each 3H, t, *J*=7.0 or 7.1 Hz, 3x$CO_2CH_2CH_3$), 3.32 (2H, dd, *J*=6.9 and 1.7 Hz, C*H*$_2$$CO_2$Et), 4.18 and 4.34 (each 2H, q, *J*=7.2 Hz, 2x$CO_2CH_2CH_3$), 5.82 (1H, dt, *J*=9.4, 6.8, and 6.8 Hz, SCH=C*H*CH_2), and 6.26 (1H, dt, *J*=9.5, 1.6, and 1.6 Hz, SC*H*=CH).[10]

7. The separation of these indolizine mixtures **4a**+**5a**+**6a**, **4b**+**5b**+**6b**, and **4c**+**5c**+**6c** were unsuccessful, but they gave satisfactory elemental analyses.

4a+**5a**+**6a** (pale yellow oil). *Anal.* Calcd for $C_{20}H_{23}NO_6S$: C, 59.25; H, 5.72; N, 3.45. Found: C, 59.41; H, 5.66; N, 3.35.

4b+**5b**+**6b** (pale yellow oil). *Anal.* Calcd for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.01; N, 3.34. Found: C, 60.28; H, 5.98; N, 3.22.

4c+**5c**+**6c** (pale yellow oil). *Anal.* Calcd for $C_{22}H_{27}NO_6S$: C, 60.95; H, 6.28; N, 3.23. Found: C, 60.95; H, 6.35; N, 3.16.

8. **11a**: mp 134—137 °C, ν (KBr) cm^{-1} 1698 and 1747. ^{1}H NMR ($CDCl_3$) δ: 1.31 and 1.44 (each 3H, t, *J*=7.1 or 7.2 Hz, 2xOCH_2CH_3), 3.43 (2H, d, *J*=7.3 Hz, 2-H), 4.22 and 4.40 (each 2H, q, *J*=7.1 or 7.2 Hz, 2xOC*H*$_2$$CH_3$), 7.04 (1H, dt, *J*=6.8, 1.2, and 1.2 Hz, 8-H), 7.19 (1H, t, *J*=7.3 Hz, 3-H), 7.46 (1H, ddd, *J*=9.1, 7.0, and 1.2 Hz, 9-H), 8.23 (1H, dt, *J*=9.0, 1.2, and 1.2 Hz, 10-H), 8.95 (1H, dt, *J*=6.7, 1.2, and 1.2 Hz, 7-H). ^{13}C NMR ($CDCl_3$) δ: 14.19, 14.55, 35.86, 60.42, 61.45, 100.90, 114.92, 119.24, 121.41, 127.24, 127.59, 128.96, 141.50, 143.79, 145.50, 162.99, 169.17, 171.78. HRMS *m/z* calcd for $C_{18}H_{18}NO_5S$ (M^++H): 360.0900, found: 360.0898.

11b: mp 121—124 °C, ν (KBr) cm^{-1} 1664, 1701, 1748. ^{1}H NMR ($CDCl_3$) δ: 1.30 and 1.43 (each 3H, t, *J*=7.1 or 7.2 Hz, 2xOCH_2CH_3), 2.48 (3H, s, 9-Me), 3.41 (2H, d, *J*=7.3 Hz, 2-H), 4.22 and 4.39 (each 2H, q, *J*=7.1 or 7.2 Hz, 2xOC*H*$_2$$CH_3$), 8.00 (1H, br s, 10-H), 8.79 (1H, d, *J*=6.8 Hz, 7-H). ^{13}C NMR ($CDCl_3$) δ: 14.19, 14.57, 21.93, 35.87, 60.32, 61.43, 99.94, 117.23, 118.21, 121.02,

126.63, 127.18, 141.19, 141.69, 144.26, 145.90, 163.15, 169.24, 171.32. HRMS *m/z* calcd for $C_{19}H_{20}NO_5S$ (M^++H): 374.1057, found: 374.1025.

12c, mp 117—120 °C, ν (KBr) cm^{-1} 1668, 1692, and 1736. ^{1}H NMR ($CDCl_3$) δ: 1.30 and 1.45 (each 3H, t, *J*=7.1 or 7.2 Hz, 2xOCH$_2$C*H*$_3$), 2.35 (3H, s, 8-Me), 2.89 (3H, s, 6-Me), 3.39 (2H, d, *J*=7.3 Hz, 2-H), 4.21 and 4.41 (each 2H, q, *J*=7.0 or 7.1 Hz, 2xOC*H*$_2$CH$_3$), 7.03 (1H, br s, 9-H), 7.07 (1H, t, *J*=7.3 Hz, 3-H), 9.19 (1H, br s, 9-H). ^{13}C NMR ($CDCl_3$) δ: 14.20, 14.55, 18.32, 20.00, 36.17, 60.64, 61.34, 107.99, 113.60, 124.69, 125.57, 125.82, 129.55, 131.54, 135.47, 142.45, 144.73, 160.39, 169.47, 178.12. HRMS *m/z* calcd for $C_{20}H_{22}NO_5S$ (M^++H): 388.1232, found: 388.1191.

9. Because thiepinoindolizines **11a**,**b** and **12c** were considerably unstable, their compositions were confirmed by high resolution mass spectra.
10. Other proton signals were overlapped with those of major products **4a**—**c**.