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New isomers of 4,1-benzothiazepines. The first evidence for the desmotropy of seven-membered heterocycles

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Abstract—A novel procedure was developed for the preparation of 2,3-disubstituted 4,1-benzothiazepines, via the ring transformation of (2*R**,2a*S**)-2-chloro-2a-phenyl-2,2a-dihydro-2*H*,4*H*-azeto[1,2-*a*][3,1]benzothiazin-1-one (**1**) with sodium ethoxide in ethanol. The tautomeric products (*R**)-3-ethoxycarbonyl-2-phenyl-3,5-dihydro-4,1-benzothiazepine (**4**) and 3-ethoxycarbonyl-2-phenyl-1,5-dihydro-4,1-benzothiazepine (**5**) exhibit the rare phenomenon of desmotropy of the condensed seven-membered heterocycles. Surprisingly, these desmotropes could be separated by column chromatography. The products are unexpectedly stable in solution and their structures were proved by means of NMR and mass spectrometry.

Condensed 1,4-thiazepines are of considerable interest from both pharmaceutical and synthetic aspects.[1–3] Although 4,1-benzothiazepine derivatives have been much less studied, they also possess a wide variety of pharmacological effects (e.g., as antagonists for the mitochondrial sodium–calcium exchanger,[4–6] squalene synthetase inhibitors[7,8] and farnesyl transferase inhibitors[9]). We earlier prepared several 1,4-benzothiazepine derivatives.[10–13] For the synthesis of 2-methoxycarbonyl-3-aryl-4,5-dihydro-1,4-benzothiazepines, we devised a method starting from a monochloro-β-lactam which was condensed with 1,3-benzothiazines by ring transformation.[10,11,14]

As a continuation of our earlier investigations, the present aim was to extend the former ring enlargement reaction to the preparation of 2,3-disubstituted 4,1-benzothiazepines. When the monochloro-β-lactam derivative **1**, prepared by the Staudinger reaction of 2-phenyl-3,1-4*H*-benzothiazine with chloroacetyl chloride,[15] was treated with sodium ethoxide in dry ethanol at ambient temperature, two products were obtained (Scheme 1). These products gave two different spots on thin-layer chromatography. Careful column chromatography furnished the two compounds in relatively good yields.[16] However, it must be noted that under some circumstances (either basic or acidic treatment) the isolated pure products again formed an equilibrium mixture. Apparently, therefore, as might be expected, the compounds are able to interconvert.

The structures of prototropic annular tautomers **4** and **5** were established by means of NMR spectroscopy and mass spectrometry. In the proposed reaction mechanism, the first step is most probably ethanolysis of the β-lactam ring, providing the α-chloro-ester **2**, which gives the products through episulfonium salt **3** after the elimination of HCl.

Compounds **4** and **5** proved to be desmotropes. Desmotropy is a rare phenomenon; only a few examples are known in heterocyclic literature. After the pioneering work on substituted 2-thiohydantoins,[17] pyrazole,[18–20] tetrazole[21,22] and pyridoxal,[23] the derivatives were studied, mainly with the aid of solid-state NMR spectroscopy and/or X-ray crystallography, because of the instability of their desmotropes in solution.

Keywords: Desmotropy; 4,1-Benzothiazepine; β-Lactam; Ring transformation.
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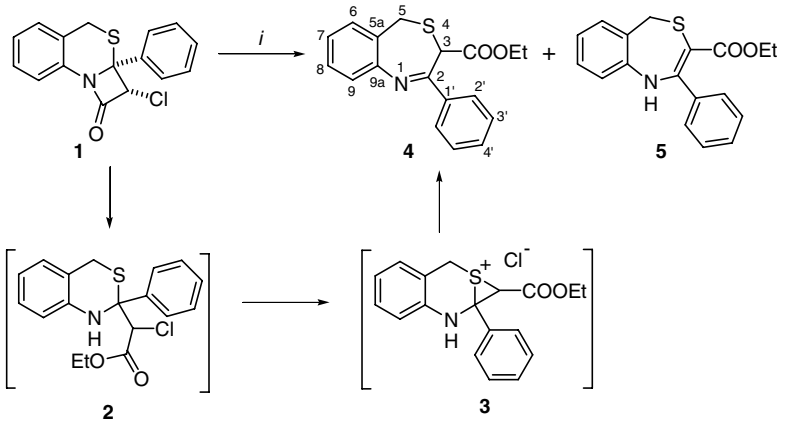

Scheme 1. (i) NaOEt, EtOH, rt, 15 min.

NMR spectroscopy. The structures of compounds **4** and **5** were confirmed by solution-state NMR spectroscopy.[24] Proton and carbon chemical shifts were assigned with the aid of DQF-COSY, HSQC and HMBC spectra.[25,26] The most distinctive signal for the desmotropes was that of C-3, the chemical shifts of which occurred at 46.64 and 101.68 ppm for compounds **4** and **5**, respectively, because of the different hybridizations of the carbons. Another clear difference between the desmotropes was the signal for H-5, which was a twofold singlet for compound **5**, but a pair of doublets for compound **4** (because in this case the H-5 protons were diastereotopic as a result of the asymmetric centre at C-3). For the final confirmation of the structures, ^{15}N chemical shifts were measured. As expected, a very large difference was observed in the shifts of N-1 (−51.4 ppm for **4** and −258.5 ppm for **5**), these values being in accordance with sp^2 and sp^3 nitrogen atoms.

The desmotropes were found to be very sensitive to the quality of the chloroform used as solvent. The stability of the individual desmotropes most probably depended on the acidity of the chloroform. In nonacidic pure chloroform, the compounds were stable for days. However, when they were dissolved in chloroform from another bottle, the other desmotrope was also observed immediately when the NMR spectrum was measured. After a few days, both NMR samples were found to display the same equilibrium, in which the ratio of **4** and **5** was 3:1, as in the crude product of the reaction.[16]

Mass spectrometry. The electron ionization (EI) mass spectra[27] of **4** and **5** were very similar,[28,29] as might be expected, especially since they possibly form an equilibrium mixture in the gas phase under EI conditions at 70 eV.

In conclusion, the ring transformation of **1** yielded a mixture of tautomeric **4** and **5**, which are new ring systems that could be separated by column chromatography. The separated desmotropes were relatively stable and exist in solution; their structures were proved by NMR spectroscopy. To the best of our knowledge, this is the first example of the desmotropy of condensed seven-membered heterocycles.

Further investigations (X-ray, NMR and MS) on the structures, conformations and stabilities of comparable compounds are under way.

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16. *Preparation of (R*)-3-ethoxycarbonyl-2-phenyl-3,5-dihydro-4,1-benzothiazepine* (**4**) *and 3-ethoxycarbonyl-2-phenyl-1,5-dihydro-4,1-benzothiazepine* (**5**). Azeto-3,1-thiazine **1** (200 mg, 0.66 mmol) was dissolved in dry ethanol (40 mL). To this stirred solution, sodium ethoxide (96 mg, 1.41 mmol) was added. The reaction mixture was stirred at room temperature for 15 min. After evaporation, the residue was dissolved in dichloromethane (20 mL). The organic phase was extracted with water (10 mL), dried (Na_2SO_4) and evaporated. The ^1H NMR spectrum of the crude product revealed a 3:1 mixture of **4** and **5**. The residue was subjected to column chromatography [Merck Silica gel 60 (0.063–0.100)] using *n*-hexane–ethyl acetate 9:1, followed by *n*-hexane–ethyl acetate 4:1 as eluent. In the initial fractions, **4** was obtained (122 mg, after trituration with *n*-hexane, as a pale-yellow crystalline powder, mp 114–115 °C, yield 59%); this was followed by mixed fractions, and then by **5** (29 mg, after trituration with *n*-hexane, as a white crystalline powder, mp 127–133 °C, yield 14%).
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24. *NMR experimental*. NMR spectra were acquired with a Bruker Avance 500 spectrometer (equipped with a BBI-5 mm-Zgrad-ATMM probe) operating at 500.13 MHz for ^1H and 125.77 MHz for ^{13}C. The spectra were recorded at 25 °C in $CDCl_3$ as a solvent, with a nonspinning sample in 5 mm NMR tubes. Proton and carbon spectra were referenced internally to the TMS signal at 0.00 ppm. Nitrogen spectra were referenced externally to nitromethane (standard sample, v/v 10/90 deuterated/nondeuterated) signal at 0.00 ppm. Besides the normal proton and carbon spectra, two-dimensional gradient selected DQF-COSY, HSQC and HMBC spectra were also recorded. Nitrogen shifts were determined from ^1H–^{15}N HSQC and ^1H–^{15}N HMBC spectra; their accuracy was approximately ±1 ppm. All spectra were measured by using the standard pulse programs installed by Bruker.
25. NMR results for compound **4**. δ_H ($CDCl_3$): 0.96 (3H, t, $J_{CH_2-CH_3} = 7.2$ Hz, –OCH_2–CH_3), 3.46 (1H, d, $J_{5x-5y} = 12.4$ Hz, H-5*x*), 3.68 (1H, d, $J_{5x-5y} = 12.4$ Hz, H-5*y*), 3.82 (2H, m, –OCH_2–CH_3), 4.53 (1H, s, H-3), 7.02 (1H, dd, $J_{8-9} = 7.8$ Hz, $J_{7-9} = 1.2$ Hz, H-9), 7.12 (1H, td, $J_{6-7} = J_{7-8} = 7.8$ Hz, $J_{7-9} = 1.2$ Hz, H-7), 7.26 (1H, dd, $J_{6-7} = 7.8$ Hz, $J_{6-8} = 1.2$ Hz, H-6), 7.32 (1H, td, $J_{7-8} = J_{8-9} = 7.8$ Hz, $J_{6-8} = 1.2$ Hz, H-8), 7.46–7.49 (3H, m, H-3′ and H-4′), 7.97 (2H, dd, $J_{2'-3'} = 7.5$ Hz, $J_{2'-4'} = 1.5$ Hz, H-2′). δ_C ($CDCl_3$): 13.70 (–OCH_2–*C*H_3), 30.33 (C-5), 46.64 (C-3), 62.19 (–O*C*H_2–CH_3), 122.67 (C-9), 125.68 (C-7), 126.21 (C-5a), 127.54 (C-2′), 128.59 (C-8), 128.67 (C-3′), 128.91 (C-6), 130.70 (C-4′), 137.88 (C-1′), 148.98 (C-9a), 164.49 (C-2), 168.33 (*C*=O). δ_N ($CDCl_3$): −51.4 (N-1).
26. NMR results for **5**. δ_H ($CDCl_3$): 0.87 (3H, t, $J_{CH_2-CH_3} = 7.0$ Hz, –OCH_2–CH_3), 3.86 (2H, q, $J_{CH_2-CH_3} = 7.0$ Hz, –OCH_2–CH_3), 4.06 (2H, s, H-5), 6.15 (1H, br s, N*H*), 6.77 (1H, dd, $J_{8-9} = 7.7$ Hz, $J_{7-9} = 1.2$ Hz, H-9), 6.90 (1H, td, $J_{6-7} = J_{7-8} = 7.7$ Hz, $J_{7-9} = 1.2$ Hz, H-7), 7.05 (1H, dd, $J_{6-7} = 7.7$ Hz, $J_{6-8} = 1.2$ Hz, H-6), 7.13 (1H, td, $J_{7-8} = J_{8-9} = 7.7$ Hz, $J_{6-8} = 1.2$ Hz, H-8), 7.41–7.43 (5H, m, H-2′, H-3′ and H-4′). δ_C ($CDCl_3$): 13.68 (–OCH_2–*C*H_3), 41.00 (C-5), 60.58 (–O*C*H_2–CH_3), 101.68 (C-3), 120.85 (C-9), 121.98 (C-7), 127.73 (C-8), 128.11 and 128.58 (C-2′ and C-3′), 129.16 and 129.19 (C-6 and C-4′), 132.24 (C-5a), 140.72 (C-9a), 141.28 (C-1′), 151.74 (C-2), 166.82 (*C*=O). δ_N ($CDCl_3$): −258.5 (N-1).
27. *Electron ionization mass spectra experimental.* The 70 eV low-resolution spectra were recorded on a VG ZABSpec instrument equipped with an OPUS V3.3 data system. The samples were introduced through a solid-inlet system without heating the probe. The accelerating voltage was 8 kV, the temperature of the source was 433 K, and the trap current was 200 μA. The accurate mass measurements were performed by voltage scanning at a resolution of 6000–10,000, using perfluorokerosene as reference compound.
28. MS results for **4**: $M^{+\cdot}(23) = C_{18}H_{17}NO_2S$: obsd 311.0980, calcd 311.0980, $[M-C_3H_5O_2]^+$: 238(5), $C_{14}H_{11}N^+$: 193(100), $C_{13}H_9^+$: 165(8.5), $C_7H_6^+$: 90(15), $C_7H_5^+$: 89(18), $C_6H_5^+$: 77(6).
29. MS results for **5**: $M^{+\cdot}(30) = C_{18}H_{17}NO_2S$: obsd 311.0978, calcd 311.0980, $[M-C_3H_5O_2]^+$: 238(7), $C_{14}H_{11}N^+$: 193(100), $C_{13}H_9^+$: 165(8), $C_7H_6^+$: 90(14), $C_7H_5^+$: 89(17), $C_6H_5^+$: 77(7).