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Synthesis of a novel heterocyclic ring system: 2-thia-3,5,6,7,9-pentaazabenz[*cd*]azulenes

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Abstract—Derivatives of 6,9-dihydro- and 6,7,8,9-tetrahydro-2-thia-3,5,6,7,9-pentaazabenz[*cd*]azulenes representing a new heterocyclic system have been prepared by the cyclocondensation reaction of ethyl 5-amino-4-(1-methylhydrazino)-2-methylthiothieno[2,3-*d*]-pyrimidine-6-carboxylate with ethyl orthoformate and various aldehydes. © 2002 Elsevier Science Ltd. All rights reserved.

Recently, it has been demonstrated that many thienopyrimidine and tri- and tetracyclic relatives as well as fused diazepines and triazepines possess diverse biological activity.[1] Seven-membered heterocyclic rings are also of considerable interest for conformational and theoretical investigations.[2] In this context and as part of our continuing program on the synthesis of *N*-heterocyclic compounds with potential pharmacological activities,[3] we have designed the synthesis of 2-thia-3,5,6,7,9-pentaazabenz[*cd*]azulenes, in which thienopyrimidine is *peri*-anellated with the 1,2,4-triazepine moiety. This report describes the synthesis and structural characterization of the first representatives of the title heterosystem.

The 5-amino-4-(1-methylhydrazino)thienopyrimidine **2**,[4] bearing suitable substituents for the formation of the triazepine ring in cyclization reactions with one

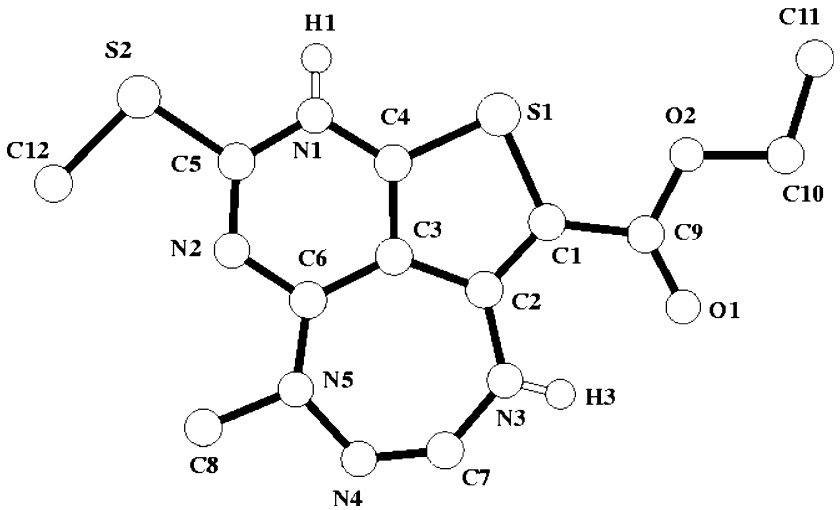

Figure 1. ORTEP drawing of compound **3b**.

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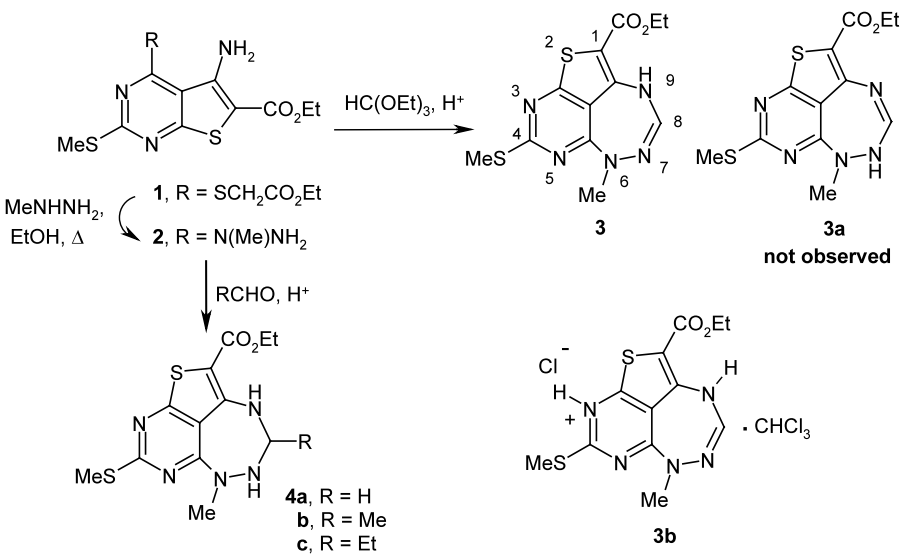
carbon reagents, was obtained by heating **1**[5] with an excess of methylhydrazine. When **2** was refluxed with triethyl orthoformate in the presence of sulfuric acid, a cyclocondensation reaction occurred to give 6,9-dihydro-2-thia-3,5,6,7,9-pentaazabenz[*cd*]azulene **3** in 92% yield as the only reaction product.[6] The formation of the isomeric triazepine **3a** was not observed. The structure elucidation of the product was based upon characteristic spectra and analytical data as well as by X-ray diffraction. The mass spectrum of the product shows the molecular ion peak with m/z 323. In the ^{1}H NMR spectrum along with the signals of COOEt, SMe and NMe groups, doublets at 6.42 and 9.03 ppm were observed due to the protons at C_8 and the NH group, respectively. The ^{13}C NMR spectrum of the product is in agreement with the proposed structure. Nevertheless, these data did not enable a choice to be made between structures **3** and **3a**. Only the absorption of the CO group in the IR spectrum at 1682 cm^{-1} and its insignificant shift to higher wavenumbers in comparison with the CO absorption at 1672 cm^{-1} of compound **2**, is in favor of structure **3**.

The structure of the product was unambiguously determined by single-crystal X-ray crystallography (Fig. 1). Slow crystallization from a chloroform solution provided single crystals suitable for X-ray crystallographic analysis. Compound **3** crystallised together with a molecule of $CHCl_3$ as a solvent of the hydrochloride **3b**.[7]

It should be quoted that the numbering system used for the ORTEP figure is different from that in Scheme 1. The bond lengths of N4–C7 and N3–C7 are 1.275 and 1.361 Å, respectively. These data suggested that the double bond is between N4 and C7. Summation of the three valence angles around N3 and N5 gave 360 and 359.8°, respectively, indicating the sp^2 character of these nitrogen atoms. The analogous result was also obtained for 1,3,4-benzotriazepinones.[2b] Thus, in the reaction of **2** with triethyl orthoformate, the 6,9-dihydro derivative **3** was formed.

This was a rather unexpected result because earlier it was shown that the analogous reaction of hydrazides of anthranilic acids with orthoformates led to the formation of the triazepine ring in which the double bond is conjugated with the aromatic system.[8] In order to understand why compound **3** is formed instead of **3a**, we were interested in the heats of formation of isomers **3** and **3a**. The conformations used for subsequent calculations were based on the lowest energy conformer of **3** and **3a**, calculated from rotation of the torsion angles around the C1–C9 bond (numbering of ORTEP drawing). We assumed that the formation of the product is determined by its thermodynamic stability. Indeed, the calculations performed by the semiempirical method PM3 using HyperChem 5.01 for Windows from HyperCube[9] showed different values. In agreement with experiment, **3** was calculated as being more stable (the means of ΔH_f are 19.8 and 32.1 kcal/mol for isomers **3** and **3a**, respectively).

Furthermore, we were interested in the synthesis of 2-thia-3,5,6,7,9-pentaazabenz[*cd*]azulenes using aldehydes as one carbon reagents. Heating **2** with a slight excess of the corresponding aliphatic aldehyde in the presence of a catalytic amount of hydrochloric acid afforded the 8-substituted 6,7,8,9-tetrahydro-2-thia-3,5,6,7,9-pentaazabenz[*cd*]azulenes (**4a**–**c**)[10] in 85–91% yields, respectively. Their analytical and spectral data are in accordance with the postulated structures.[11–13] Nevertheless, it should be mentioned that in the ^{1}H NMR spectra of **4**, broadened signals corresponding to the protons of triazepine ring are observed. This concerns not only the signals of the NH groups, but the signals of the 8-alkyl groups as well. This phenomenon is, probably, caused by an inversion of the triazepine ring and by a ring/open-chain (hydrazones) equilibrium



Scheme 1.

in solution.[14] A detailed NMR and computational study of these problems will be reported elsewhere.

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4. Procedure and physico-chemical data for compound **2**. A mixture of **1** (2.3 g, 5.94 mmol), ethanol (50 ml) and methylhydrazine (1.64 g, 35.7 mmol) was refluxed for 12 h. After cooling to room temperature, the precipitate was filtered off, the filtrate was evaporated to 1/3 of the initial volume, and the precipitate was filtered off, combined with the earlier obtained, and recrystallized to give 1.54 g (83%) of compound **2**, mp 215–217°C (from dioxane). δ_H (CF_3COOD): 1.08 (3H, t, $J=7.2$ Hz, CH_3), 2.41 (3H, s, SCH_3), 3.47 (3H, s, NCH_3) and 4.18 (2H, q, $J=7.2$ Hz, OCH_2); IR (Nujol) ν_{max}/cm^{-1} 3387, 3251, 3161, 3157 (NH_2), 1672 (CO). (Found: C, 42.5; H, 4.7; N, 22.5. $C_{11}H_{15}N_5O_2S_2$ requires C, 42.2; H, 4.8; N, 22.35%.)
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6. Procedure and physico-chemical data for compound **3**: A solution of **2** (1 g, 3.2 mmol) and ethyl orthoformate (15 ml) was heated to 100°C and a drop of conc. sulfuric acid was added. After the exothermic reaction had ceased the reaction mixture was refluxed for 1 h. After cooling to room temperature the precipitate was filtered off and recrystallized to give 0.95 g (92%) of compound **3**. Mp 181–182°C (from ethanol). δ_H ($CDCl_3$): 1.39 (3H, t, $J=7.2$ Hz, CH_3), 2.59 (3H, s, SCH_3), 3.57 (3H, s, NCH_3), 4.35 (2H, q, $J=7.2$ Hz, CH_2), 6.42 (1H, d, $J=4.8$ Hz, CH), 9.03 (1H, br.d, $J=4.8$ Hz, NH). δ_C ($CDCl_3$): 14.25 (CH_3), 14.32 (SCH_3), 41.16 (NCH_3), 61.51 (OCH_2), 101.13 (C_1 or C_{9b}), 102.20 (C_{9b} or C_1), 127.76 (C_8), 138.37 (C_{9a}), 154.18 (C_{5a}), 164.50 (C_4 or CO), 166.08 (CO or C_4), 170.17 (C_{2a}); IR (Nujol) ν_{max}/cm^{-1} 3310 cm^{-1} (NH), 1682 cm^{-1} (CO); MS m/z (%) 323 (M^+, 100); 295 (15), 278 (11), 277 (76), 249 (82). (Found: C, 44.7; H, 3.95; N, 21.8. $C_{12}H_{13}N_5O_2S_2$ requires C, 44.6; H, 4.05; N, 21.7%.)
7. X-Ray data for compound **3b**: crystal dimension, 0.4×0.4× 0.2 mm; crystal color, habit: colorless, needle; empirical formula, $C_{13}H_{15}Cl_4N_5O_2S_2$; formula weight, 479.22; crystal system, triclinic; lattice parameters $a=8.32(9)$ Å, $b=$ 9.20(10) Å, $c=13.73(14)$ Å; space group, $P1$ ($\#2$); $Z=2$. Crystallographic data for structure **3b** have been deposited at the Cambridge Crystallographic Data Centre (CCDC number 170959).
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9. HyperChem Release 5.0 for Windows, Hypercube, Inc.
10. Representative procedure for compounds **4a–c**: A mixture of compound **2** (0.6 g, 1.9 mmol), ethanol (20 ml) and 3 mmol of the corresponding aldehyde was heated to reflux temperature and a drop of conc. hydrochloric acid was added (in case of formaldehyde 32% formaline solution was used). The reaction mixture was refluxed for 1–3 h, then cooled to room temperature. The precipitate was filtered off, the filtrate was concentrated under reduced pressure to 1/3 of the initial volume. The collected precipitate was combined with the earlier obtained and recrystallized to give compounds **4a–c**.
11. Physico-chemical data for compound **4a**: Yield 91%, mp >250°C (from ethanol). δ_H ($CDCl_3$): 1.27 (3H, t, $J=7$ Hz, CH_3), 2.58 (3H, s, SCH_3), 3.36 (3H, s, NCH_3), 4.25 (2H, q, $J=7$ Hz, OCH_2), 4.7 (2H, s, CH_2), 5.7 (1H, br.s, NH), 7.92 (1H, br.s, NH); IR (Nujol) ν_{max}/cm^{-1} 3334 (NH); 1662 cm^{-1} (CO). (Found: C, 44.7; H, 4.5; N, 21.6. $C_{12}H_{15}N_5S_2O_2$ requires C, 44.3; H, 4.65; N, 21.5%.)
12. Physico-chemical data for compound **4b**: Yield 85%, mp 202–203.5°C (from ethyl acetate). δ_H (DMSO-d_6): 1.32 (3H, t, $J=7.2$ Hz, CH_3), 1.48 (3H, br.t, $J=7.2$ Hz, CH_3), 2.51 (3H, s, SCH_3), 3.35 (3H, s, NCH_3), 4.25 (2H, q, $J=7.2$ Hz, OCH_2), 4.45–4.58 (1H, br.m, CH), 5.7 (1H, br.s, NH), 7.88 (1H, br.s, NH); IR (Nujol) ν_{max}/cm^{-1} 3332 (NH); 3216 (NH); 1655 cm^{-1} (CO): MS m/z (%) 339 (M^+, 51); 325 (19); 324 (100); 296 (14); 278 (28); 251 (30). (Found: C, 46.3; H, 5.0; N, 20.7. $C_{13}H_{17}N_5O_2S_2$ requires C, 46.0; H, 5.05; N, 20.6%.)
13. Physico-chemical data for compound **4c**: Yield 86%, mp 174–176°C (from ethyl acetate). δ_H (DMSO-d_6): 1.15 (3H, br.t, $J=7$ Hz, CH_3), 1.36 (3H, t, $J=7.2$ Hz, CH_3), 1.67–1.84 (2H, m, CH_2), 2.52 (3H, s, SCH_3), 3.37 (3H, s, NCH_3), 4.12–4.25 (1H, br.m, CH), 4.25 (2H, q, $J=7.2$ Hz, OCH_2), 5.71 (1H, br.s, NH), 7.92 (1H, br.s, NH); IR (Nujol) ν_{max}/cm^{-1} 3319 (NH); 3232 (NH); 1659 cm^{-1} (CO); MS m/z (%) 353 (M^+, 38); 325 (13); 324 (19); 323 (100); 296 (16); 278 (30); 251 (16). (Found: C, 48.1; H, 5.45; N, 19.6. $C_{14}H_{19}N_5O_2S_2$ requires C, 47.6; H, 5.4; N, 19.8%.)
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