Synthesis of new heterocyclic sulfamides

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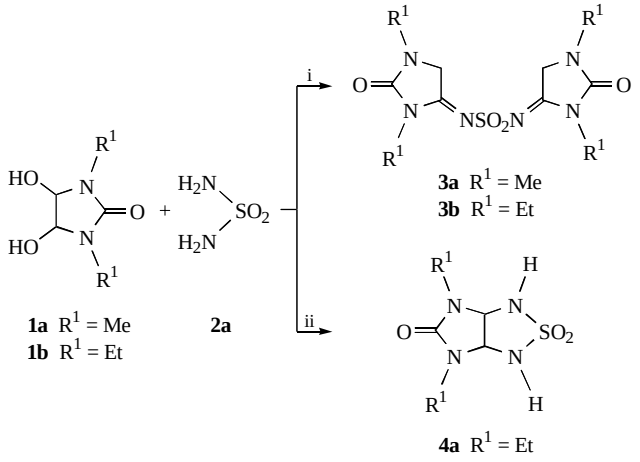
The synthetic approaches to novel N- and SO_2-containing bi-, tri- and tetracyclic systems, 6,8-di- and 2,4,6,8-tetraalkyl-7-oxo-3-thia-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,3-dioxides, 8,12-dioxo-9,11-dimethyl-4-thia-1,3,5,7,9,11-hexaazatricyclo[5.5.1.$0^{10,13}$]-tridecane-4,4-dioxide and 8,16-dioxo-3,5,11,13-tetramethyl-4,12-dithia-1,3,5,7,9,11,13,15-octaazatetracyclo[7.7.2.$0^{7,17}$.$0^{15,18}$]octadecane-4,4,12,12-tetraoxide, have been developed.

Sulfamides constitute a class of compounds among which are biologically active substances.[1–3] Here, we studied the condensation of sulfamides with 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones, 2,8-dihydroxymethyl-4,6-dimethyl- and 2,4,6,8-tetrahydroxymethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones.

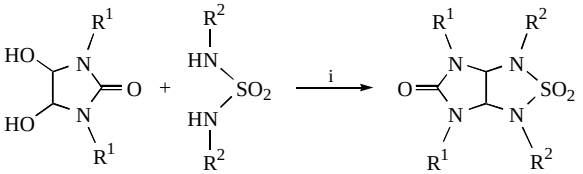
It was found previously that the interaction of 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones **1** with unsubstituted sulfamide **2a** at pH 1 leads to 4,4′-sulfonyldiiminobis(1,3-dialkylimidazolidine-2-ones)[4] **3** (Scheme 1). A study of the effect of acidity on the course of this reaction demonstrated that the yield of **3b** at pH < 1 increased from 5% reported earlier[4(b)] to 40%. A shift of pH towards the weakly acidic region resulted in the formation of a mixture of **3b** and 6,8-diethyl-7-oxo-3-thia-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,3-dioxide **4a**; however, only **4a** was formed at pH 5 (Scheme 1).



1a R^1 = Me
1b R^1 = Et
2a
3a R^1 = Me
3b R^1 = Et
4a R^1 = Et

Scheme 1 *Reagents and conditions*: i, H_2O, conc. HCl, 80 °C, 0.5–1.5 h; ii, H_2O, pH 5, 60 °C, 0.5 h.

Aran *et al.*[5] noted that most attention was focused on unsubstituted and monosubstituted sulfamides, whereas the reactivity of 1,3-disubstituted sulfamides is less well understood. The condensation of 1,3-dimethylsulfamide **2b** with **1** was found to form 2,4,6,8-tetraalkyl-7-oxo-3-thia-2,4,6,8-tetraazabicyclo[3.3.0]-octane-3,3-dioxides **4b**,**c** (Scheme 2).

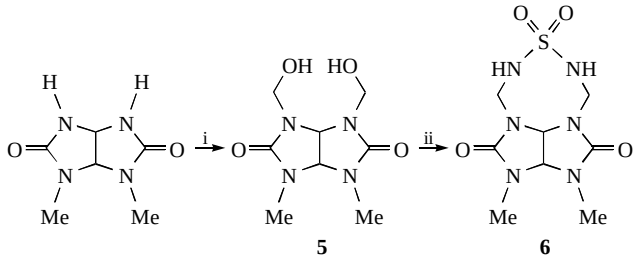


1a R^1 = Me
1b R^1 = Et
2b R^2 = Me
4b R^1 = R^2 = Me
4c R^1 = Et, R^2 = Me

Scheme 2 *Reagents and conditions*: i, H_2O, pH 1 (HCl), 80–90 °C, 1–2 h.

The combination of urea and sulfamide moieties allows us to suppose that these compounds exhibit high biological activity. This was supported by primary tests of the acute toxicity and the effect on the motional activity and orientation behaviour in mice (the results will be published elsewhere).

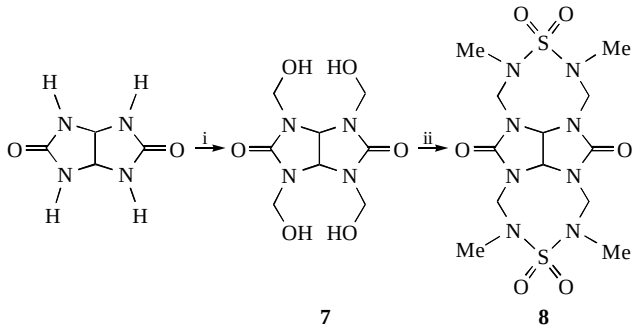
Recently, data on the inhibition of HIV-1 protease by seven- and eight-membered cyclic sulfamides and ureas were published.[2,3,6] Here, we developed the synthetic approaches to polycyclic systems including eight-membered rings with sulfamide and urea units. Thus, the condensation of **2a** with 2,8-dihydroxymethyl-4,6-dimethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione **5** in an acidic medium leads to 8,12-dioxo-9,11-dimethyl-4-thia-1,3,5,7,9,11-hexaazatricyclo[5.5.1.$0^{10,13}$]tridecan-4,4-dioxide **6** (Scheme 3).



5 **6**

Scheme 3 *Reagents and conditions*: i, MeOH, paraform, $NaHCO_3$, pH 8, 80 °C, 1 h; ii, MeOH, pH 1 (HCl), **2a**, boiling with stirring.

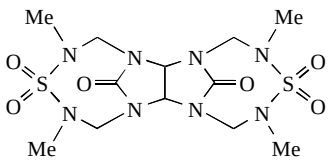
Analogously, the reaction of 1,3-dimethylsulfamide with 2,4,6,8-tetrahydroxymethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione **7** resulted in 8,16-dioxo-3,5,11,13-tetramethyl-4,12-dithia-1,3,5,7,9,11,13,15-octaazatetracyclo[7.7.2.$0^{7,17}$.$0^{15,18}$]octadecane-4,4,12,12-tetraoxide **8** (Scheme 4). We intend to prepare compounds like **6** and **8** bearing aryl substituents at a later time.



7 **8**

Scheme 4 *Reagents and conditions*: i, aqueous CH_2O solution, $NaHCO_3$, pH 8, 80 °C, 1 h; ii, H_2O, pH 1 (HCl), 80 °C, **2b**, stirring for 2 h.

The structure shown in Scheme 4 was attributed to compound **8**. Using NMR spectroscopy, it is impossible to validate or disprove the alternative structure **8′**.†



8′

We decided on the structure of **8** based on calculations of the conformational energies for two possible isomers using the MM2 program (107 and 349 kcal mol^{-1} for **8** and **8′**, respectively).

† NMR spectra were measured on AM 300 (300.13 MHz) and WM 250 (250.13 MHz) spectrometers (Bruker). Chemical shifts were measured with reference to residual protons of the deuterated solvents [$^2H_6$]DMSO (2.50 ppm) and D_2O (4.80 ppm).

4a: yield 58–60%, mp 198–199.5 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.05 (6H, Me), 3.05, 3.30 (4H, CH_2), 5.37 (2H, CH). IR (KBr, ν/cm^{-1}): 3448, 3144 (NH), 1656 (C=O), 1360, 1324, 1168 (SO_2). MS, *m*/*z*: 234 (M^+). Found (%): C, 36.02; H, 6.19; N, 24.01; S, 13.62. Calc. for $C_7H_{14}N_4O_3S$ (%): C, 35.89; H, 6.02; N, 23.91; S, 13.69.

4b: yield 51–53%, mp 177–179 °C. ^{1}H NMR (D_2O) δ: 2.90 (6H, Me), 2.96 (6H, Me), 5.31 (2H, CH). IR (KBr, ν/cm^{-1}): 1730 (C=O), 1345, 1140 (SO_2). MS, *m*/*z*: 234 (M^+). Found (%): C, 35.98; H, 6.13; N, 24.00; S, 13.74. Calc. for $C_7H_{14}N_4O_3S$ (%): C, 35.89; H, 6.02; N, 23.91; S, 13.69.

4c: yield 7–9%, mp 85–87 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.10 (6H, Me), 3.15, 3.35 (4H, CH_2), 5.25 (2H, CH). IR (KBr, ν/cm^{-1}): 1710 (C=O), 1345, 1150 (SO_2). MS, *m*/*z*: 262 (M^+). Found (%): C, 41.36; H, 7.02; N, 21.44; S, 12.35. Calc. for $C_9H_{18}N_4O_3S$ (%): C, 41.20; H, 6.92; N, 21.36; S, 12.22.

6: yield 58–60%, mp 237–239 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.82 (6H, Me), 4.30, 4.83 (4H, CH_2), 5.15 (2H, CH), 7.60 (2H, NH). IR (KBr, ν/cm^{-1}): 3336, 3272 (NH), 1704 (C=O), 1320, 1156 (SO_2). MS, *m*/*z*: 290 (M^+). Found (%): C, 32.93; H, 4.99; N, 29.10; S, 10.87. Calc. for $C_8H_{14}N_6O_4S$ (%): C, 33.10; H, 4.86; N, 28.95; S, 11.04.

8: yield 69–71%, mp > 300 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.92 (12H, Me), 4.80 (8H, CH_2), 5.50 (2H, CH). IR (KBr, ν/cm^{-1}): 1730 (C=O), 1355, 1160 (SO_2). MS, *m*/*z*: 374 ($M^+ - mSO_2$). Found (%): C, 32.75; H, 4.95; N, 25.32; S, 14.87. Calc. for $C_{12}H_{22}N_8O_6S_2$ (%): C, 32.87; H, 5.06; N, 25.55; S, 14.63.

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