A tandem of the Cornforth rearrangements of 4-(1,2,3-triazol-1-yl)iminomethyl-1,2,3-thiadiazole

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The method for the synthesis of 5-(2,6-dimethylmorpholino)-1,2,3-thiadiazole-4-carbaldehyde was proposed. Its reaction with sodium 1-amino-4-(*N*-methyl)carbamoyl-1,2,3-triazol-5-olate proceeds through a tandem of the Cornforth rearrangements. The initially formed azomethine isomerizes into sodium 4′-(2,6-dimethylmorpholino)thiocarbonyl-4-(*N*-methyl)carbamoyl-1,1′-bis[1,2,3]triazolyl-5-olate, which then rearranges to give sodium 4-{*N*-[4-(2,6-dimethylmorpholinothiocarbonyl)-1,2,3-triazol-1-yl]carbamoyl}-1-methyl-1,2,3-triazol-5-olate.

Key words: Cornforth rearrangement, diazomalonamide, 1,2,3-thiadiazole, 1,2,3-triazole.

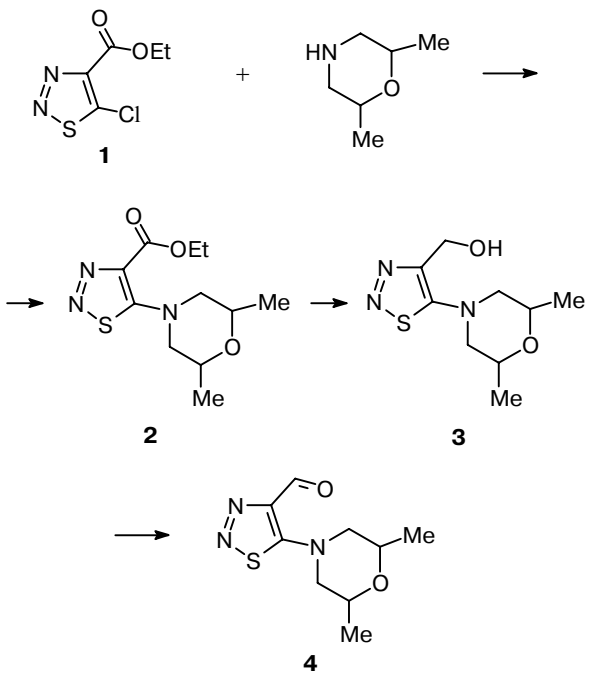
1,2,3-Thiadiazole and 1,2,3-triazole derivatives are easily rearranged with involvement of one (the Dimroth rearrangement),[1—3] two (the Cornforth rearrangement),[4,5] three (the L′abbé rearrangement),[6,7] or four side-chain atoms.[8] The neighboring heterocycles[9] can also be involved in such rearrangements, which proceed through highly reactive diazo compounds. This is probably due to the fact that these heterocycles are in equilibrium with α-diazothiones and α-diazoimines, respectively. In the former case, the equilibrium is completely shifted toward thiadiazole,[10] while in the latter case either the cyclic or linear form can dominate depending on the substituents.[11] It was also shown that diazoacetimidolate derivatives undergo irreversible cyclization into the corresponding 1,2,3-triazol-5-olates.[12] A broad spectrum of biological activities and chemical properties of 1,2,3-thiadiazoles and 1,2,3-triazoles may be attributed to the possibility of easy rearrangements of these heterocyclic compounds.[13]

Despite a large number of publications concerned with the synthesis of 1,2,3-thiadiazoles and 1,2,3-triazoles, compounds containing both of these heterocycles are virtually unknown. Probably, this is associated with their high labilities due to possible easy involvement in several consecutive rearrangements.

Results and Discussion

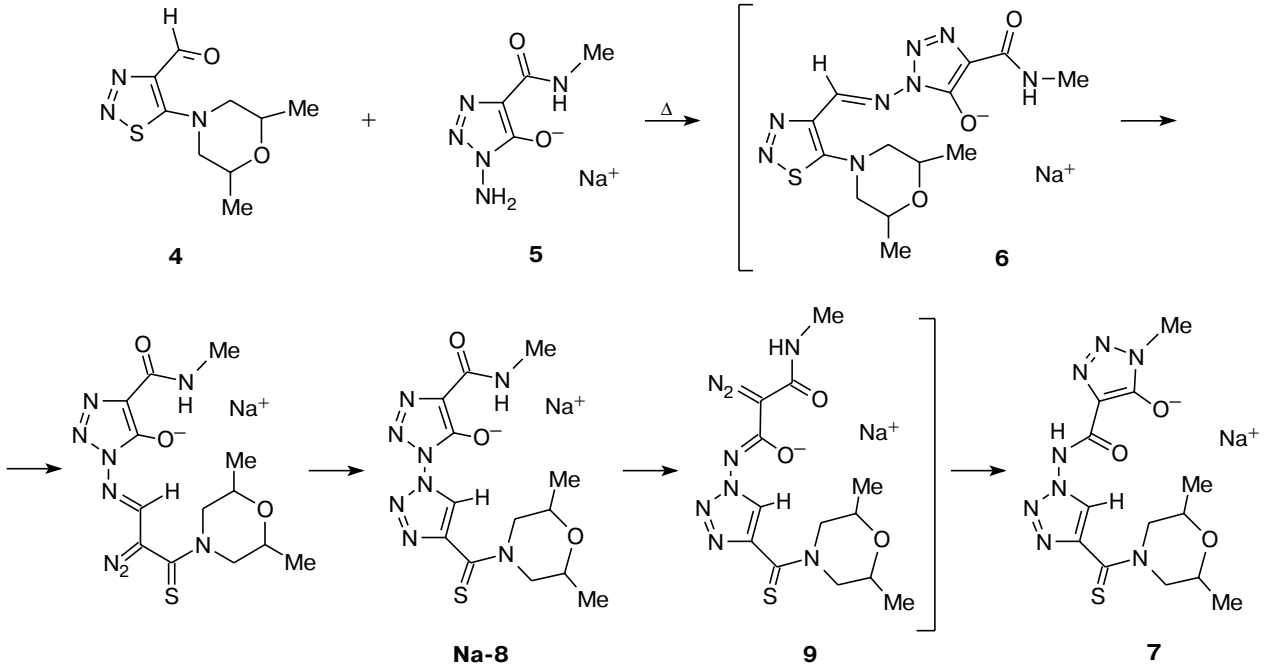
It is known[14] that ethyl 5-chloro-1,2,3-thiadiazole-4-carboxylate (**1**) is readily involved in reactions of nucleophilic substitution of the Cl atom. This allowed us to prepare 5-dimethylmorpholino-1,2,3-thiadiazole derivatives (**2**) in good yield. Smooth reduction of the ester group to hydroxymethyl group by $NaBH_4$, which did not affect the thiadiazole ring, made it possible to

Scheme 1



Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 258—261, February, 2001.

Scheme 2



synthesize 4-hydroxymethyl-5-dimethylmorpholino-1,2,3-thiadiazole (**3**), which is oxidized by active MnO_2 under mild conditions to the corresponding 4-carbaldehyde **4** (Scheme 1).

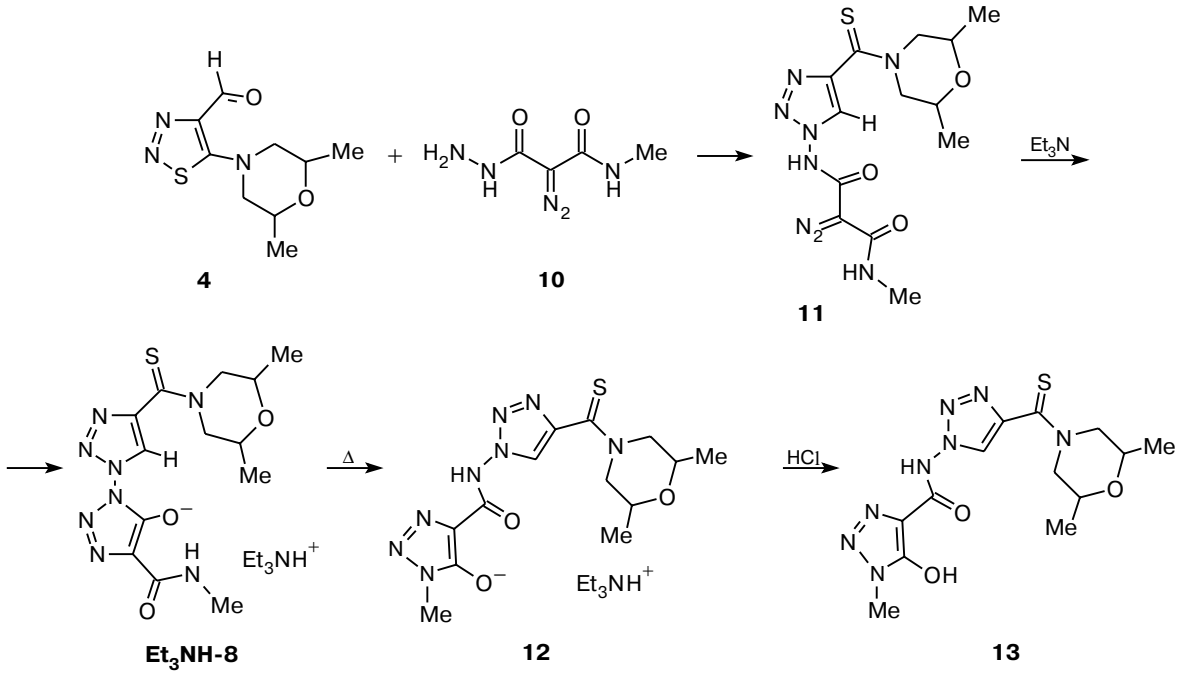
A compound containing both the 1,2,3-thiadiazole and 1,2,3-triazole rings was synthesized by the reaction of aldehyde **4** with 1-amino-4-(*N*-methylcarbamoyl)-1,2,3-triazol-5-olate (**5**), which had been prepared earlier.[15] However, instead of the expected imine (**6**), 4-*N*-(4-thiocarbamoyl-1,2,3-triazole-1-yl)carbamoyl-1-methyl-1,2,3-triazol-5-olate (**7**) was isolated. The structure of the reaction product was proved by data from elemental analysis, ^{1}H NMR and IR spectroscopy, and mass spectrometry, especially by the chemical shift and multiplicity of the signals for the *N*-methyl group (δ 3.79, s) and the methine proton (δ 8.56) in the ^{1}H NMR spectrum.

A plausible mechanism for the formation of compound **7** (Scheme 2) involves the Cornforth rearrangement of imine **6** formed at the first stage to give bitriazole **8**. Then, another Cornforth rearrangement occurs *via* diazo compound **9**. The first rearrangement is similar to that described in Ref. 5, whereas the second is new for 1,2,3-triazol-5-olates.

To confirm the suggested scheme for the formation of compound **7**, we carried out a reaction of compound **4** with diazomalonamohydrazide **10**. The reaction yielded diazo compound **11**, in which the 1,2,3-thiadiazole fragment underwent the Cornforth rearrangement into the 1,2,3-triazole (Scheme 3). The structure of diazo compound **11** was proved by data from IR spectroscopy (the presence of a band for the stretching vibrations of the diazo group at 2120 cm^{-1}) and from the chemical shifts of signals for the *N*-methyl group (δ_H 2.88, d) and for the methine proton (δ_H 9.36) and the thiocarbamoyl (δ_C 186.1) and diazo groups (CN_2) (δ_C 66.4).

Treatment of a solution of compound **11** with a base (triethylamine) gave a compound whose IR spectrum did not contain an absorption band at 2100 cm^{-1} characteristic of diazo compounds, while its ^{13}C NMR spectrum did not show signals for the C atoms of the $>C=N_2$ group at δ 66.4 and of the carbohydrazide group at δ 162.6, but contained signals assigned to the C(5) (δ 157.6) and C(4) atoms (δ 116.7). At the same time, a signal for the methyl group appeared as a doublet at δ_H 2.77. These data allowed us to identify the compound obtained as triethylammonium bitriazololate **8**. It should be noted that recording at ~25 °C gave ^{1}H NMR and ^{13}C NMR spectra containing a double set of signals (with a signal intensity ratio of ~2 : 1 for each pair). The pairs of signals coalesce at 50 °C and reappear upon cooling. Apparently, compound **8** exists as two stereoisomers owing to slow rotation around the N—N bond between two triazole rings. When a solution of compound **8** in Py-d_5 is kept at 50 °C for 15—20 min, another product is formed, whose spectrum does not contain signals for the diazo group; structure **12** was assigned to the product. 1,2,3-Triazol-5-olate is completely rearranged upon refluxing compound **8** in ethanol for 3 days to give product **12**, whose characteristics were identical with those of the previously obtained compound. Acidification of an ethanolic solution of compound **12** gave the corresponding 5-hydroxy-1,2,3-triazole (**13**).

Scheme 3



Thus, it was shown that the reaction of 5-dimethylmorpholino-1,2,3-thiadiazole-4-carbaldehyde **4** with 1-amino-4-(*N*-methyl)carbamoyl-1,2,3-triazol-5-olate **5** follows a tandem of the Cornforth rearrangements to give 4-*N*-(4-dimethylmorpholinothiocarbonyl-1,2,3-triazol-1-yl)carbamoyl-1-methyl-1,2,3-triazol-5-olate **7**.

Experimental

^{1}H NMR spectra were recorded on Bruker DRX-500 (500 MHz) and Bruker 250 (250 MHz) instruments, and ^{13}C NMR spectra were recorded on a Bruker DRX-500 instrument (125 MHz) with Me_4Si as the internal standard. IR spectra were recorded on a UR-25 spectrometer (in pellets with KBr). Mass spectra were obtained with an MAT11 instrument (EI, 70 eV). The course of the reactions was monitored and the purity of the compounds was checked by TLC on Silufol UV-254 plates in chloroform and a chloroform—ethanol mixture (15 : 1). Melting points were not corrected.

Ethyl 5-(2,6-dimethylmorpholino)-1,2,3-thiadiazole-4-carboxylate (2). 2,6-Dimethylmorpholine (2.4 mL, 20 mmol) was added to a solution of chlorothiadiazole **1** (1.97 g, 10 mmol) in 10 mL of ethanol. The reaction mixture was stirred at ~20 °C for 30 min and cooled. The precipitate that formed was filtered off and recrystallized from ethanol. Yield 2.3 g (85%), m.p. 82—84 °C. IR, ν/cm^{-1}: 1710 (C=O). ^{1}H NMR (DMSO-d_6), δ: 1.11 (d, 6 H, 2 Me (morpholine), J = 6.4 Hz); 1.32 (t, 3 H, Me, J = 7.0 Hz); 2.86 (dd, 2 H, 2 NCH, J = 10.4 and 11.3 Hz); 3.66 (dd, 2 H, 2 NCH, J = 10.4 and 3.3 Hz); 3.69—3.84 (m, 2 H, 2 OCH); 4.34 (quintet, 2 H, OCH_2, J = 7.0 Hz). MS, m/z (I_{rel} (%)): 271 $[M]^+$ (75); 243 $[M - N_2]^+$ (100). Found (%): N, 15.9; S, 12.4. $C_{11}H_{17}N_3O_3S$. Calculated (%): N, 15.49; S, 11.82.

4-Hydroxymethyl-5-(2,6-dimethylmorpholino)-1,2,3-thiadiazole (3). $NaBH_4$ (1.0 g, 27 mmol) was added to a solution of thiadiazole **2** (1.0 g, 3.67 mmol) in 50 mL of anhydrous ethanol. The reaction mixture was refluxed for 3 h and cooled. Water (100 mL) was added, and the product was extracted with $CHCl_3$ (3×50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The product was recrystallized from ethanol. Yield 0.47 g (55%), m.p. 88—90 °C. IR, ν/cm^{-1}: 3250 (OH), 1610 (N=N, C=N). ^{1}H NMR ($CDCl_3$), δ: 1.23 (d, 6 H, 2 Me (morpholine), J = 6.1 Hz); 2.34 (t, 1 H, OH, J = 6.1 Hz); 2.76 (dd, 2 H, 2 NCH, J = 11.9 and 10.7 Hz); 3.50 (dd, 2 H, 2 NCH, J = 10.7 and 3.3 Hz); 3.75—3.94 (m, 2 H, 2 OCH); 5.00 (d, 2 H, OCH_2, J = 6.1 Hz). MS, m/z (I_{rel} (%)): 229 $[M]^+$ (36); 201 $[M - N_2]^+$ (100). Found (%): N, 18.3; S, 13.9. $C_9H_{15}N_3O_2S$. Calculated (%): N, 18.33; S, 13.89.

5-(2,6-Dimethylmorpholino)-1,2,3-thiadiazole-4-carbaldehyde (4). Freshly prepared active MnO_2 (11.5 g, 0.12 mol) was added to a solution of compound **3** (1.15 g, 5 mmol) in 50 mL of $CHCl_3$. The reaction mixture was stirred at ~20 °C for 2 h. The inorganic compounds were filtered off, and the solvent was removed *in vacuo*. The residue was triturated with hexane. Yield 0.61 g (53%), m.p. 58 °C. IR, ν/cm^{-1}: 1730 (C=O). ^{1}H NMR (DMSO-d_6), δ: 1.15 (d, 6 H, 2 Me (morpholine), J = 6.4 Hz); 2.87 (dd, 2 H, 2 NCH, J = 10.4 and 11.3 Hz); 3.68 (dd, 2 H, 2 NCH, J = 10.4 and 3.3 Hz); 3.69—3.94 (m, 2 H, 2 OCH); 10.34 (s, 1 H, HC=O). MS, m/z (I_{rel} (%)): 227 $[M]^+$ (11); 199 $[M - N_2]^+$ (25). Found (%): N, 18.9; S, 14.4. $C_9H_{17}N_3O_2S$. Calculated (%): N, 18.49; S, 14.11.

Sodium 4-{*N*-[4-(2,6-dimethylmorpholinothiocarbonyl)-1,2,3-triazol-1-yl]carbamoyl}-1-methyl-1,2,3-triazol-5-olate (7). 1-Amino-1,2,3-triazol-5-olate **5** (0.18 g, 1 mmol) was added to a solution of compound **4** (0.23 g, 1 mmol) in 50 mL of ethanol. The reaction mixture was refluxed for 3 days and concentrated *in vacuo*. The residue was triturated with hexane. Yield 0.17 g (45%), m.p. 124 °C (from hexane). IR, ν/cm^{-1}: 1680 (C=O). ^{1}H NMR (pyridine-d_5), δ: 1.19 (d, 3 H, Me, J = 6.0 Hz); 1.35 (d, 3 H, Me, J = 6.0 Hz); 2.87 (dd, 1 H, NCH, J = 11.3 and 12.1 Hz); 3.00 (dd, 1 H, NCH, J = 10.4 and

12.1 Hz); 3.60—3.90 (m, 2 H, 2 OCH); 3.79 (s, 3 H, NMe); 4.71 (dd, 1 H, NCH, J = 10.4 Hz, 2.1 Hz); 5.36 (dd, 1 H, NCH, J = 12.1 Hz, 2.1 Hz); 8.56 (s, 1 H, C_5H); 9.4 (br.s, 1 H, NH).

{*N*-[4-(2,6-Dimethylmorpholino)thiocarbonyl-1,2,3-triazol-1-yl]carbamoyl}-*N*-methyldiazoacetamide (11). Diazo compound **10** (0.18 g, 1 mmol) was added to a solution of compound **4** (0.23 g, 1 mmol) in 10 mL of ethanol. The reaction mixture was stirred at ~20 °C for 1 h and concentrated *in vacuo*. The residue was triturated with water. Yield 0.28 g (72%), m.p. 192 °C (from water). IR, ν/cm^{-1}: 2980 (NH), 2120 (CN_2), 1685, 1680 (C=O). ^{1}H NMR (pyridine-d_5), δ: 0.97 (d, 3 H, Me, J = 6.2 Hz); 1.10 (d, 3 H, Me, J = 6.2 Hz); 2.80 (dd, 1 H, NCH_{ax}, J = 13.1 and 10.8 Hz); 2.88 (d, 3 H, NH<u>Me</u>, J = 4.7 Hz); 2.97 (dd, 1 H, NCH_{ax}, J = 12.9 and 10.9 Hz); 3.62—3.71 (m, 2 H, 2 OCH); 5.14 (ddd, 1 H, NCH_{eq}, J = 13.1, 2.2, and 2.2 Hz); 5.68 (ddd, 1 H, NCH_{eq}, J = 12.9, 2.2, and 2.2 Hz); 8.93 (br.q, 1 H, NH, J = 4.7 Hz); 9.25 (s, 1 H, C_5H); 10.9 (br.s, 1 H, NH). ^{13}C NMR (pyridine-d_5), δ: 186.1 (s, C=S); 164.2 (s, C=O); 162.6 (s, C=O); 148.4 (s, C(4)); 131.6 (d, C(5), J = 204.3 Hz); 72.3 (d, OCH); 71.6 (d, OCH); 66.4 (s, CN_2); 57.9 (t, NCH); 55.7 (t, NCH); 26.5 (quintet, NCH_3); 18.8 (quintet, CH_3); 18.4 (quintet, CH_3). MS, m/z (I_{rel} (%)): 310 $[M - 2N_2]^+$ (4.2). Found (%): N, 30.2; S, 8.4. $C_{13}H_{18}N_8O_3S$. Calculated (%): N, 30.58; S, 8.26.

Triethylammonium 4′-(2,6-dimethylmorpholino)thiocarbonyl-4-*N*-methylcarbamoyl-1,1′-bi-1,2,3-triazolyl-5-olate (Et_3NH-8). Triethylamine (72 μL, 0.5 mmol) was added to a solution of compound **11** (0.19 g, 0.5 mmol) in 50 mL of ethanol. The reaction mixture was stirred for 10 min and concentrated *in vacuo*. The residue was triturated with hexane. Yield 0.11 g (60%), m.p. > 250 °C (decomp., from hexane). IR, ν/cm^{-1}: 2980 (NH), 1680 (C=O). ^{1}H NMR (pyridine-d_5), δ: two conformers, 1.10 (t, 9 H, $N(CH_2\underline{CH_3})_3$); 0.7—1.2 (m, 6 H, 2 Me); 2.63 (quintet, 6 H, $N(\underline{CH_2}CH_3)_3$); 2.86—2.90 (m, 1 H, NCH); 2.91 (d, 3 H, NHMe); 2.90—3.02 (m, 1 H, NCH); 3.60—3.80 (m, 2 H, 2 OCH); 4.90—5.10, 5.40—5.50 (both m, 1 H, NCH); 5.55—5.70 (m, 1 H, NCH); 7.66 and 8.15 (both br.s, 1 H, NH); 8.86, 9.05 (both s, 1 H, C_5H). ^{13}C NMR (pyridine-d_5), δ: two conformers, 187.5 and 185.3 (s, C=S); 165.1, 165.0 (both s, C=O); 165.7, 157.6 (both s, C(5)); 149.2, 147.1 (both s, C(4′)); 132.1 (d, C(5′), J = 206.7 Hz); 128.4 (d, C(5′), J = 202.6 Hz); 116.7 (s, C(4)); 72.4, 72.3 (both d, OCH); 71.7, 71.6 (both d, OCH); 58.0, 57.9 (both t, NCH); 55.7 (t, NCH); 26.2, 25.3 (both q, NCH_3); 18.8 (q, CH_3); 18.3 (q, CH_3). Found (%): S, 8.8. $C_{13}H_{17}N_8NaO_3S$. Calculated (%): S, 8.26.

Triethylammonium 4-{*N*-[4-(2,6-dimethylmorpholinothiocarbonyl)-1,2,3-triazol-1-yl]carbamoyl}-1-methyl-1,2,3-triazol-5-olate (12). A solution of compound **8** (100 mg, 0.22 mmol) in 10 mL of ethanol was refluxed for 4—6 h. The course of the reaction was monitored by TLC. The solvent was removed *in vacuo*. Salt **12** was triturated with hexane. Yield 75 mg (75%), m.p. 67 °C (from hexane). IR, ν/cm^{-1}: 3020, 2985 (NH), 1690 (C=O).

5-Hydroxy-4-{*N*-[4-(2,6-dimethylmorpholinothiocarbonyl-1,2,3-triazol-1-yl]carbamoyl}-1-methyl-1,2,3-triazole (13). A solution of compound **7** or **12** (0.5 mmol) in 3 mL of ethanol was acidified with conc. HCl to pH 3—4. The precipitate that formed was filtered off. Yield 0.17 g (90%), m.p. 226 °C (from ethanol). IR, ν/cm^{-1}: 3020 (NH), 1680 (C=O). ^{1}H NMR (DMSO-d_6), δ: 1.14 (d, 3 H, Me, J = 6.1 Hz); 1.24 (d, 3 H, Me, J = 6.1 Hz); 2.85 (dd, 1 H, NCH_{ax}, J = 13.4 and 11.3 Hz); 3.09 (dd, 1 H, NCH_{ax}, J = 13.1 and 10.1 Hz); 3.60—3.80 (m, 2 H, 2 OCH); 3.77 (s, 3 H, NMe); 4.70 (ddd, 1 H, NCH_{eq}, J = 13.1, 2.2, and 2.2 Hz); 5.36 (ddd, 1 H, NCH_{eq}, J = 13.1, 2.2, and 2.2 Hz); 8.48 (s, 1 H, C_5H); 12.5 (br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 366 $[M]^+$ (4.1); 338 $[M - N_2]^+$ (1.1); 310 $[M - 2N_2]^+$ (4.1). Found (%): S, 8.4. $C_{13}H_{18}N_8O_3S$. Calculated (%): S, 8.26.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 98-03-33045a) and INTAS (Grant 97-0217).

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Received June 8, 2000
in revised form September 4, 2000