Elimination of a Thiomethyl Substituent from an Anionic 5-Methylenebarbituric Acid Derivative by Oxidation and Substitution

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Dedicated to Professor Helmut Quast on the occasion of his 75th birthday

Triethylammonium 5-[(1,3-dimethyl-2,4,6-trioxo-tetrahydropyrimidin-5(6*H*)-ylidene)-(methylthio)methyl]-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (**5**), obtained from 5-[bis(methylthio)methylene]-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**2**) and 1,3-dimethylbarbituric acid in the presence of triethylamine, is protonated by methanesulfonic acid to give 5,5′-(methylthiomethanediylidene)bis(1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) (**6**) in good yield. Compound **6** is oxidized in two steps by *m*-chloroperbenzoic acid to give 5,5′-(methylsulfinylmethanediylidene)bis(1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) (**7**) and 5-[(1,3-dimethyl-2,4,6-trioxo-tetrahydropyrimidin-5(6*H*)-ylidene)(methylsulfinyl)methyl]-5-hydroxy-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**8**), respectively. Excess pyridine eliminates methanesulfinic acid from **8** to give the zwitterionic 5-[(1,3-dimethyl-2,4,6-trioxo-tetrahydropyrimidin-5(6*H*)-ylidene(pyridinium-1-yl)methyl]-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (**9**). The crystal structures of compounds **6**, **8**, and **9** are reported.

Key words: Heterocycles, Barbituric Acid, Sulfur, Olefin, Crystal Structure

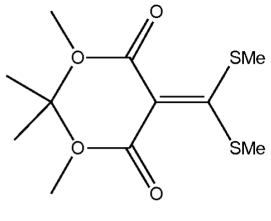
Introduction

Electrophilic methylene compounds are useful precursors in organic synthesis [1]. Bis(thiomethyl)methylene derivatives of Meldrum's acid (**1**) ([2 – 5] and references cited therein) and 1,3-dimethylbarbituric acid (**2**) [6] act as electrophiles owing to the pronounced tendency of their heterocyclic rings to accept negative charges by π electron delocalization.

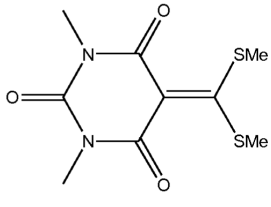
Recently, we reported on the synthesis of the salts **3** and **4** reacting **1** with Meldrum's acid or 1,3-dimethylbarbituric acid in the presence of triethylamine [7, 8] which are of interest as precursors for electron-deficient allenes [9]. Owing to the low stability of Meldrum's acid derivatives towards acids, we have been interested in the preparation and chemistry of the corresponding barbituric acid derivative **5**, and in the substitution of its second thiomethyl substituent.

Results

Similar to **3** and **4**, the salt **5** is obtained from **2** and 1,3-dimethylbarbituric acid in the presence of triethylamine as a stable compound in good yield. The NMR spectra exhibit the corresponding nuclei of the heterocyclic rings to be chemically equivalent at r. t. owing to resonance or dynamic effects as observed for solutions of **3**, for which the enolate function was found to be localized at one ring unit in the solid state [8].



1



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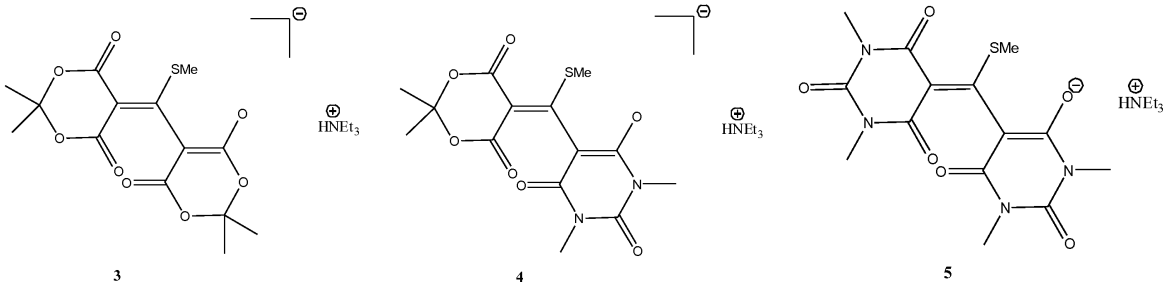

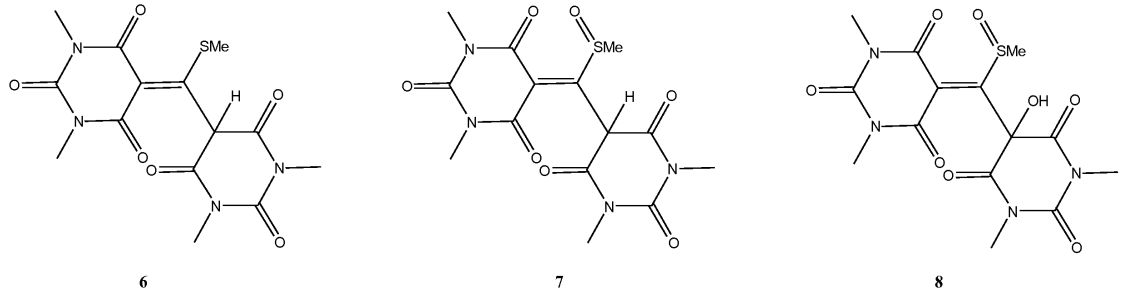

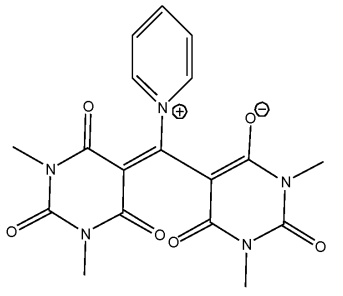

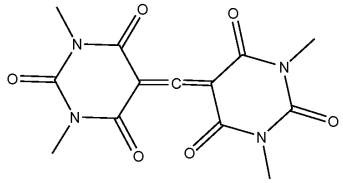

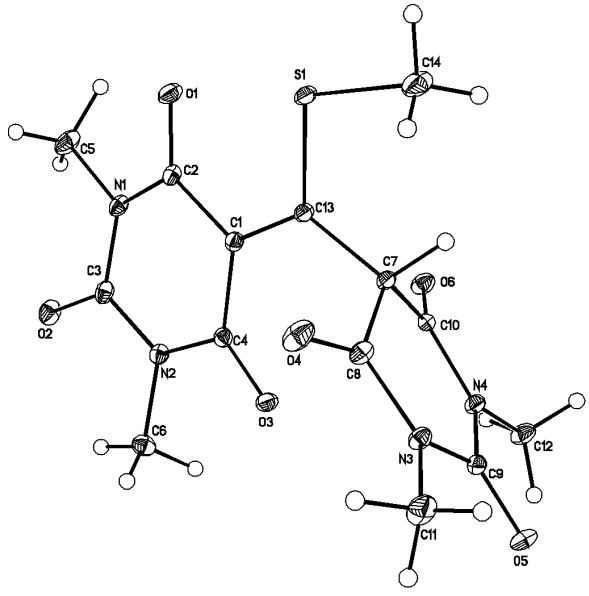

Fig. 1. View of the molecular structure of $C_{14}H_{16}N_4O_6S$ (**6**) in the crystal.

We did not succeed in eliminating thiomethanol and triethylamine on heating **5** *in vacuo* even in the presence of bases. Methanesulfonic acid protonates **5** at the carbon atom C5 of the enolate ring instead of the adjacent oxygen atom to give compound **6** which is also resistant towards thiomethanol elimination.

The reaction of **6** with *m*-chloroperbenzoic acid affords the sulfoxide **7** in good yield. Surprisingly, with two equivalents of *m*-chloroberbenzoic acid compound **8** is formed instead of the expected sulfone. Further oxidation does not occur even under forcing conditions. The carbinol **8** reacts with excess pyridine to give the zwitterionic pyridinium compound **9** under elimination of pyridinium sulfinate.

To get more insight into their bonding, we determined the crystal structures of compounds **6**, **8**,

	6	2 **8**·C_6H_6	**9**·CH_2Cl_2
Empirical formula	$C_{14}H_{16}N_4O_6S$	$C_{34}H_{38}N_8O_{16}S_2$	$C_{19}H_{19}Cl_2N_5O_6$
Formula weight	368.37	878.83	484.29
Temperature, K		173(2)	
Wavelength		0.71073	
Crystal system		monoclinic	
Space group		$P2_1/c$	
a, Å	8.525(2)	17.784(1)	10.647(1)
b, Å	16.977(3)	8.623(1)	22.663(2)
c, Å	11.2182)	26.938(2)	9.067(1)
β, deg	95.99(3)	105.06(1)	97.99(1)
Volume, Å^3	1614.7(6)	3988.8(5)	2166.7(3)
Z	4	4	4
Density, calculated, g/cm^3	1.515	1.460	1.485
Absorption coefficient, mm^{-1}	0.242	0.216	0.347
F(000)	768	1824	1000
θ range for data collection, deg	3.10 – 26.37	3.05 – 22.5	6.83 – 26.37
Reflections collected	21855	31065	28559
Independent reflections	3298	5199	4355
Refinement method		full-matrix least-squares on F^2	
Data / restraints / parameters	3298 / 0 / 291	5199 / 0 / 543	4355 / 0 / 294
Goodness-of-fit on F^2	1.249	1.042	1.104
Final $R1$ / $wR2$ indices [$I \geq 2\,\sigma(I)$]	0.0504 / 0.0998	0.0737 / 0.1684	0.0769 / 0.1768
Final $R1$ / $wR2$ indices (all data)	0.0623 / 0.1041	0.1028 / 0.1818	0.0964 / 0.1885
Extinction coefficient	0.007(1)	0.0015(4)	0.004(4)
Largest diff. peak / hole, e Å^{-3}	+0.28 / −0.29	+0.93 / −0.63	+0.58 / −0.70

Table 1. Crystal data and structure refinement details for $C_{14}H_{16}N_4O_6S$ (**6**), $C_{34}H_{38}N_8O_{16}S_2$ (2 **8**·C_6H_6) and $C_{19}H_{19}Cl_2N_5O_6$ (**9**·CH_2Cl_2).

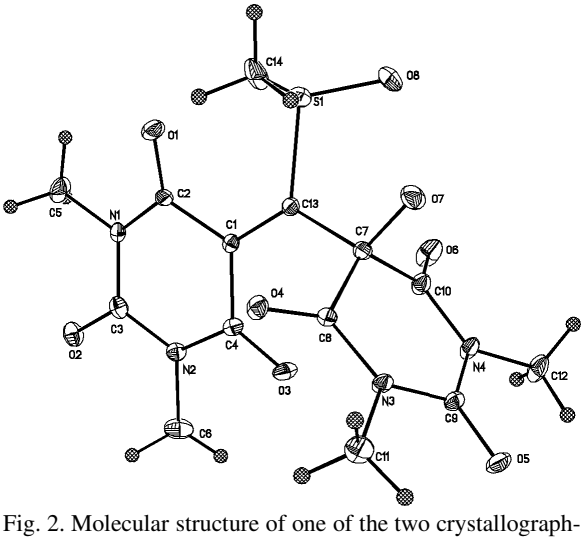

Fig. 2. Molecular structure of one of the two crystallographically independent molecules of $C_{14}H_{16}N_4O_8S$ (**8**) in the crystal.

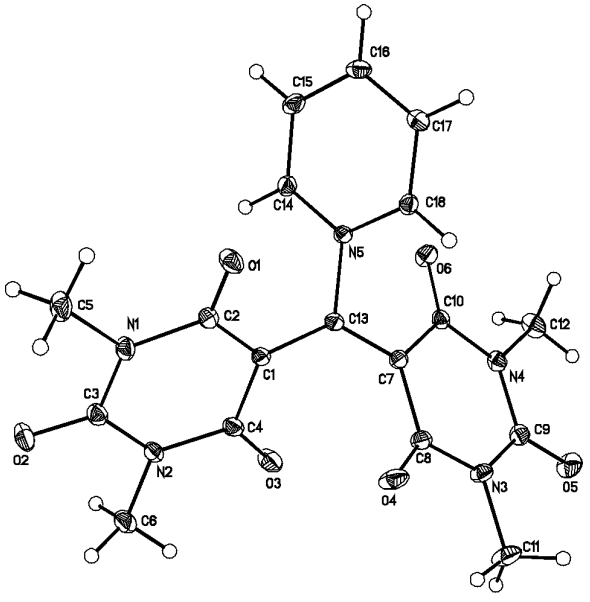

Fig. 3. View of the molecular structure of $C_{18}H_{17}N_5O_6$ (**9**) in the crystal.

and **9** (Tables 1 and 2, Figs. 1 – 3). In the sulfur-containing compounds **6** and **8** we observe similar bond lengths and angles for the heterocycles including their connection to the bridging carbon atom (for individual values see Table 2). As expected, the geometry around the sulfur atoms is determined by the change of their oxidation state which influences their degree of hybridization [**6**/**8**: C(13)–S(1) 1.724(2)/1.812(5), S(1)–C(14) 1.795(3)/1.741(7) Å; C(13)–S(1)–C(14) 105.2(1), 94.7(3)°]. These structural details merit attention because of the lengthening of the C–S bond on going from the sulfide to the sulfoxide thus reflecting the weakening of this bond, possibly by decrease of π bonding.

Table 2. Bond lengths (Å) and angles (deg) for $C_{14}H_{16}N_4O_6S$ (**6**), $C_{34}H_{38}N_8O_{16}S_2$ (2 **8**·C_6H_6) and $C_{19}H_{19}Cl_2N_5O_6$ (**9**·CH_2Cl_2).

	6	2 **8**·C_6H_6	**9**·CH_2Cl_2
S(1)–C(13)	1.724(2)	1.812(5)	–
S(1)–C(14)	1.795(3)	1.741(7)	–
S(1)–O(8)	–	1.517(4)	–
N(1)–C(3)	1.383(3)	1.368(7)	1.376(4)
N(1)–C(2)	1.385(3)	1.385(7)	1.401(4)
N(2)–C(3)	1.389(3)	1.390(7)	1.376(4)
N(2)–C(4)	1.390(3)	1.396(7)	1.404(4)
N(3)–C(8)	1.383(3)	1.345(7)	1.392(4)
N(3)–C(9)	1.388(3)	1.415(7)	1.379(4)
N(4)–C(10)	1.379(3)	1.363(7)	1.394(4)
N(4)–C(9)	1.390(3)	1.376(7)	1.384(4)
O(1)–C(2)	1.223(3)	1.219(6)	1.219(4)
O(2)–C(3)	1.214(3)	1.228(7)	1.216(4)
O(3)–C(4)	1.224(3)	1.211(6)	1.216(4)
O(4)–C(8)	1.205(3)	1.220(6)	1.220(4)
O(5)–C(9)	1.210(3)	1.185(6)	1.215(4)
O(6)–C(10)	1.206(3)	1.209(7)	1.224(4)
O(7)–C(7)	–	1.435(7)	–
C(1)–C(13)	1.379(3)	1.358(7)	1.395(4)
C(1)–C(2)	1.458(3)	1.471(7)	1.463(4)
C(1)–C(4)	1.465(3)	1.467(7)	1.459(4)
C(7)–C(8)	1.506(3)	1.528(7)	1.456(4)
C(7)–C(10)	1.513(3)	1.535(8)	1.454(4)
C(7)–C(13)	1.525(3)	1.534(7)	1.396(4)
N(5)–C(13)	–	–	1.468(4)
N(5)–C(14)	–	–	1.354(4)
N(5)–C(18)	–	–	1.343(4)
C(14)–C(15)	–	–	1.372(5)
C(15)–C(16)	–	–	1.380(5)
C(16)–C(17)	–	–	1.383(5)
C(17)–C(18)	–	–	1.367(4)
C(13)–S(1)–C(14)	105.2(1)	94.7(3)	–
O(8)–S(1)–C(13)	–	105.5(2)	–
O(8)–S(1)–C(14)	–	106.7(3)	–
C(3)–N(1)–C(2)	124.0(2)	124.0(5)	125.0(3)
C(3)–N(2)–C(4)	124.7(2)	125.0(5)	125.4(3)
C(8)–N(3)–C(9)	124.7(2)	125.9(4)	125.1(3)
C(10)–N(4)–C(9)	124.8(2)	122.8(5)	125.2(3)
C(13)–C(1)–C(2)	120.0(2)	120.3(5)	120.6(3)
C(13)–C(1)–C(4)	121.2(2)	122.5(5)	119.1(3)
C(2)–C(1)–C(4)	118.8(2)	117.2(5)	120.2(3)
N(1)–C(2)–C(1)	117.2(2)	118.4(5)	116.0(3)
N(1)–C(3)–N(2)	116.7(2)	117.0(5)	117.0(3)
N(2)–C(4)–C(1)	117.0(2)	117.2(5)	115.6(3)
C(8)–C(7)–C(10)	115.5(2)	115.4(4)	120.5(3)
C(8)–C(7)–C(13)	112.2(2)	108.4(4)	119.2(3)
C(10)–C(7)–C(13)	112.8(2)	111.6(4)	120.3(3)
N(3)–C(8)–C(7)	115.3(2)	113.1(5)	116.3(3)
N(3)–C(9)–N(4)	117.7(2)	119.1(4)	116.8(3)
N(4)–C(10)–C(7)	115.5(2)	115.4(5)	116.0(3)
C(1)–C(13)–C(7)	121.0(2)	125.3(5)	128.0(3)
C(1)–C(13)–S(1)	120.7(2)	119.8(4)	–
C(7)–C(13)–S(1)	118.3(2)	114.6(4)	–
C(1)–C(13)–N(5)	–	–	116.5(3)
C(7)–C(13)–N(5)	–	–	115.5(2)

In **6**, the distance O(1)···S(1) is clearly inside the van der Waals range (2.608 Å). Going from **6** to **8**, a change in the relative orientation of the SMe substituent is observed apparently caused by the formation of a hydrogen bond connecting the SO and OH fragments [O(101)···O(111) 2.515 Å]. This bonding may also be responsible for the lack of sulfone formation. Over all, bond lengths and angles in the surroundings of the sulfur atom in **6** are very similar to those in **2** [6], while **8** resembles closely the structure of $Ph_2S(O)$ [10].

For the pyridine adduct **9**, the X-ray structure reveals an almost symmetrical π electron distribution inside the barbituric acid moieties and their connection [C(1)–C(13) 1.395(4), C(13)–C(7) 1.396(4) Å] which is in contrast to the structure of the anion in the salt **3** [8]. Nevertheless, we observe an interplanar angle between the planes C(1)C(2)O(1) and C(7)C(10)O(6) of 63.9 °.

Concluding Remarks

As expected, the barbituric acid derivative **5** is obtained by the synthetic route formerly outlined for similar salts. Fission of the C–S bond to obtain the electron deficient allene **10** did not occur under thermal conditions. This finding may be interpreted as a result of the π-acceptor properties of the heterocyclic ring which causes strengthening of the C–S bond.

Oxidation of the thiolate sulfur atom lowers this π interaction and enhances its leaving group quality. Thus, nucleophilic substitution of the sulfinyl substituent in **8** occurs with excess pyridine. We will report on our experiments to remove the pyridine substituent from **9** and the properties of the resulting allene **10** in due course.

Experimental Section

All experiments were performed in purified solvents under argon. 1,3-Dimethyl-5-bis(thioethyl)methylenebarbituric acid (**2**) was obtained according to a published procedure [6].

*$C_{20}H_{31}N_5O_6S$ (**5**)*

To a solution of **3** (2.60 g, 10 mmol) and **4** (1.56 g, 10 mmol) in THF (30 mL) triethylamine (1.4 mL, 10 mmol) was added. The mixture was stirred at r. t. for 2 h, then the volatile components were removed *in vacuo*. The residue was stirred in diethyl ether (30 mL) for further 3 h, and the resulting precipitate was filtered to give after recrystallization from DMSO/diethyl ether 3.5 g (75 %) of **5** as stable red crystals. –

^{1}H NMR ([D$_6$]DMSO): δ = 1.13 (t, 9 H, CH_2CH_3, ^3J = 7.0 Hz), 2.18 (s, 3 H, SCH_3), 3.06 (q, 6 H, CH_2CH_3), 3.46 (s, 12 H, NCH_3), 9.00 (s, 1 H, NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 8.54 (CH_2CH_3), 16.59 (SCH_3), 27.36 (NCH_3), 45.77 (CH_2CH_3), 151.70 ($CSCH_3$), 159.84, 179.60 (CO), C^5 not observed. – Elemental analysis for $C_{20}H_{31}N_5O_6S$ (469.56): calcd. C 51.16, H 6.65, N 14.91, S 6.83; found C 50.50, H 7.33, N 14.51, S 6.55.

*$C_{14}H_{16}N_4O_6S$ (**6**)*

To a solution of **5** (4.70 g, 10 mmol) in THF (20 mL) methanesulfonic acid (0.65 mL, 10 mmol) was added. The mixture was stirred at r. t. for 1 h, then the volatile components were removed *in vacuo*. The residue was washed with 20 mL of water and recrystallized from dichloromethane/diethyl ether to give 2.11 g (45 %) of **6** as stable colorless crystals. – ^{1}H NMR (CD_2Cl_2): δ = 2.45 (s, 3 H, SCH_3), 3.08, 3.21, 3.23 (3 s, 12 H, NCH_3), 4.90 (s, 1 H, $C(SCH_3)CH$). – ^{13}C NMR (CD_2Cl_2): δ = 15.75 (SCH_3), 27.42 (NCH_3), 55.61 *C*H, 110.3 (C$^{5,5'}$), 150.2 ($CSCH_3$), 159.1, 160.4, 165.5, 178.2 (CO), C^5 not observed. – Elemental analysis for $C_{14}H_{16}N_4O_6S$ (368.37): calcd. C 45.65, H 4.38, N 15.21, S 8.70; found C 46.27, H 5.07, N 13.90, S 7.97.

*$C_{14}H_{16}N_4O_7S$ (**7**)*

To a solution of **6** (3.68 g, 10 mmol) in dichloromethane (20 mL) *m*-chloroperbenzoic acid (77 %, 2.25 g, 10 mmol) was added at −60 °C. The mixture was stirred overnight, and the volatile components were removed *in vacuo*. To the resulting residue 20 mL of diethyl ether was added at r. t., and the mixture was stirred for 5 min. The filtered precipitate was recrystallized from benzene/light petroleum to give 2.25 g (70 %) of **7** as stable yellow crystals. – ^{1}H NMR ($CDCl_3$): δ = 2.88 (s, 3 H, SCH_3), 3.19, 3.23, 3.30, 3.31 (4 s, 12 H, NCH_3), 6.17 (s, 1 H, $C(SCH_3)CH$). – ^{13}C NMR ($CDCl_3$): δ = 29.16 (NCH_3), 40.58 ($S(O)CH_3$), 45.52 *C*H, 119.3 (C^5), 149.78, 151.74, 160.49, 164.58 (CO), 181.06 ($CS(O)CH_3$). – Elemental analysis for $C_{14}H_{16}N_4O_7S$ (384.36): calcd. C 43.75, H 4.20, N 14.58, S 8.34; found C 44.13, H 4.07, N 14.90, S 7.97.

*$C_{14}H_{16}N_4O_8S$ (**8**)*

To a solution of **6** (3.68 g, 10 mmol) in dichloromethane (20 mL) *m*-chloroperbenzoic acid (77 %, 4.50 g, 20 mmol) was added at −60 °C. The mixture was stirred overnight, and the volatile components were removed *in vacuo*. To the resulting residue 20 mL of diethyl ether was added at r. t., and the mixture was stirred for 5 min. The filtered precipitate was recrystallized from benzene/light petroleum to give 2.76 g (69 %) of **8** as stable yellow crystals. – ^{1}H NMR ($CDCl_3$): δ = 3.13 (s, 3 H, SCH_3), 3.24, 3.33, 3 (2 br s, 12 H, NCH_3), 9.85 (s, 1 H, COH). – ^{13}C NMR ($CDCl_3$): δ = 29.23 (NCH_3), 40.05 ($S(O)CH_3$), 85.06 COH, 121.6 (C^5), 149.66, 151.74, 160.18, 165.73, 167.49 (CO), 181.06 ($CS(O)CH_3$). – Elemental analysis for $C_{14}H_{16}N_4O_8S$ (400.37): calcd. C 42.00, H 4.03, N 13.99, S 8.01; found C 43.07, H 4.63, N 13.64, S 7.41.

*$C_{18}H_{17}N_5O_6$ (**9**)*

Compound **8** (1.00 g, 2.5 mmol) was stirred overnight in 10 mL of pyridine. The volatile components were removed *in vacuo*. To the residue, 20 mL of dichloromethane was added, and the solution was stirred for 5 min. at r. t. The filtered solution was extracted with 10 mL of water. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was recrystallized from dichloromethane/diethyl ether to give 0.51 g (51 %) of **9** as stable red crystals. – ^{1}H NMR ([D$_6$]$_D$MSO): δ = 3.08, (s, 12 H, NCH_3), 8.08 – 9.26 (m, 5 H, py). – ^{13}C NMR ([D$_6$]$_D$MSO): δ = 27.71 (NCH_3), 100.85 (C^5), 127.85, 145.90, 147.81 (py), 151.14, 160.61 (CO), 159.01 (*C*-py). – Elemental analysis for $C_{18}H_{17}N_5O_6$ (399.36): calcd. C 54.14, H 4.29, N 17.54; found C 53.81, H 4.63, N 17.11.

CCDC 710064 (**6**), CCDC 710065 (2 **8**·C_6H_6) and CCDC 710066 (**9**·CH_2Cl_2) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgement

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