Synthesis, Structure and Reactions of 1,3-Dimethyl-5-bis(thiomethyl)methylenebarbituric Acid

Kamal Sweidan[a], Ahmed Abu-Rayyan[b], Ahmad Al-Sheikh[c], Cäcilia Maichle-Mößmer[d], Manfred Steimann[d], and Norbert Kuhn[d]

[a] Faculty of Pharmacy, Al-Zaytoonah University of Jordan, P. O. Box (130) 11733, Amman, Jordan
[b] Faculty of Pharmacy, Al Isra Private University, P. O. Box 22 and 23, Al Isra University Post Office, 11622 Jordan
[c] Department of Pharmacy, The University of Petra, P. O. Box 961343, Amman, Jordan
[d] Institut für Anorganische Chemie der Universität Tübingen, Auf der Morgenstelle 18, D-72076 Tübingen, Germany

Reprint requests to Dr. K. Sweidan. E-mail: kamal_sweidan@hotmail.com, or to Prof. Dr. N. Kuhn. E-mail: norbert.kuhn@uni-tuebingen.de

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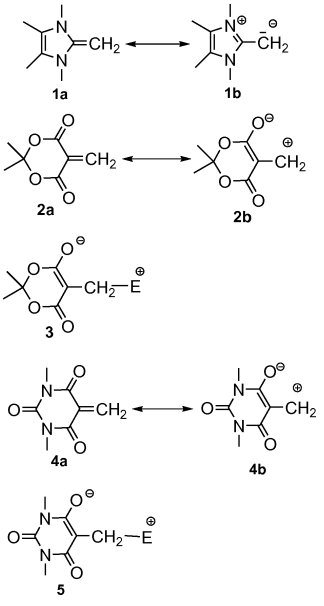
Dedicated to Professor Otto J. Scherer on the occasion of his 75th birthday

1,3-Dimethyl-5-bis(thiomethyl)methylenebarbituric acid (**8**) is obtained from 1,3-dimethylbarbituric acid and CS_2/NEt_3 followed by alkylation with methyl iodide. Compound **8** reacts with aqueous ammonia to give 5-amino(thiomethyl)methylene-1,3-dimethylbarbituric acid (**9**). With benzylamine, the thiomethyl substituent in **9** is replaced to give 5-amino(benzylamino)methylene-1,3-dimethylbarbituric acid (**10**) while with methanesulfonic acid the sulfonate salt **11** is formed. The crystal structures of **8** and **9** are reported.

Key words: Heterocycles, Barbituric Acid, Alkene, Crystal Structure

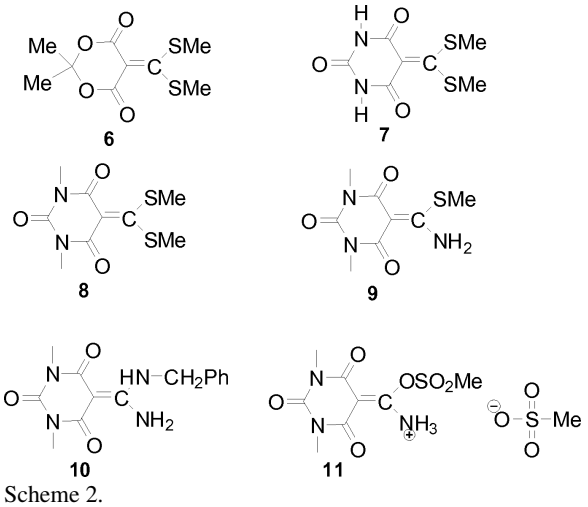
Introduction

In heterocycles, the carbon atoms of exocyclic methylene substituents act as nucleophilic or electrophilic centers depending on the electronic properties of the heterocycle. Thus, 1,3,4,5-tetramethyl-2-methyleneimidazoline (**1**) [1] exhibits ylidic properties and can be coordinated at electron-poor centers [2] while 2,2-dimethyl-5-methylene-4,6-dioxo-1,3-dioxane (**2**) [3], a Meldrum's acid derivative, is attacked by nucleophiles to form zwitterionic compounds (**3**, E = C_5H_5N, PPh_3) [3, 4]. Similarly, 1,3-dimethyl-5-methylene-2,4,6-trioxopyrimidine (**4**), the corresponding barbituric acid derivative, forms stable base adducts (**5**) [5] and dimerizes in the condensed phase [6] (Scheme 1).



Scheme 1.

Though 2,2-dimethyl-5-bis(thiomethyl)methylene-4,6-dioxo-1,3-dioxane (**6**) [7] has been widely used as precursor for Meldrum's acid derivatives [8 – 13], 5-bis(thiomethyl)methylene-2,4,6-trioxopyrimidine (**7**) as the corresponding barbituric acid derivative has been mentioned to a much lesser extent [7, 10, 14]. Owing to their medical relevance, we are interested in 1,3-dimethylbarbituric acid derivatives and report on a new facile synthesis of **8** (Scheme 2), its crystal structure and some reactions.



Scheme 2.

Results and Discussion

*Synthesis and crystal structure of 1,3-dimethyl-5-bis-(thiomethyl)methylenebarbituric acid (**8**)*

Bis(thioalkyl)ylidene derivatives may commonly be prepared from CH-acidic methylene compounds and carbon disulfide in the presence of bases, followed by S-alkylation [8]. We obtained 1,3-dimethyl-5-bis(thiomethyl)methylenebarbituric acid (**8**) from 1,3-dimethylbarbituric acid as yellow crystals in good yield.

A single crystal structure analysis of **8** was performed to get further insight into its structure and bonding (Tables 1 and 2). Compound **8** crystallizes in the monoclinic space group $P2_1/c$ with $Z = 4$.

The structure (Fig. 1) reveals the folded arrangement of the planes adjacent to the exocyclic olefinic

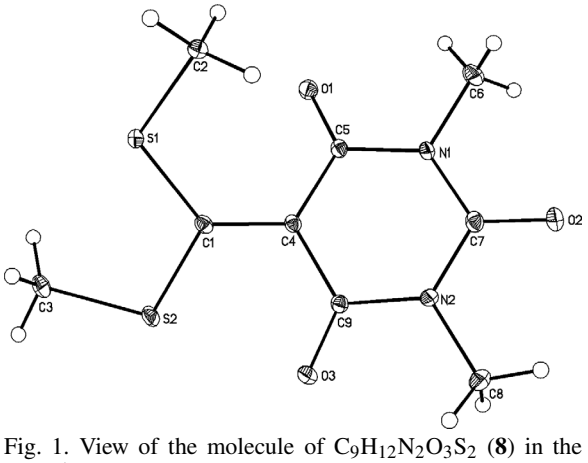


Fig. 1. View of the molecule of $C_9H_{12}N_2O_3S_2$ (**8**) in the crystal.

Table 1. Crystal data and structure refinement for $C_9H_{12}N_2O_3S_2$ (**8**) and $C_8H_{11}N_3O_3S$ (**9**).

	8	**9**
Empirical formula	$C_9H_{12}N_2O_3S_2$	$C_8H_{11}N_3O_3S$
Formula weight	260.33	229.26
Temperature, K	173	
Radiation; λ, Å	MoK_α; 0.71073	
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$C2/c$
a, Å	4.041(1)	9.220(1)
b, Å	13.218(3)	16.329(2)
c, Å	20.592(4)	13.283(2)
β, deg	91.09(3)	103.70(1)
Volume, Å^3	1099.7(4)	1942.8(4)
Z	4	8
Density, calculated, g cm^{-3}	1.572	1.568
Absorption coefficient, mm^{-1}	0.477	0.324
$F(000)$, e	544	960
θ Range data collection, deg	3.24 – 26.37	3.16 – 26.37
Reflections collected / independent	15186 / 2230	13719 / 1994
Refinement method	full-matrix least-squares on F^2	
Data / restraints / parameters	2230 / 0 / 194	1994 / 0 / 181
Goodness-of-fit on F^2	1.200	1.132
Final indices $R1/wR2$ $[I \geq 2\sigma(I)]$	0.0543 / 0.0918	0.0592 / 0.1140
Final indices $R1/wR2$ (all data)	0.0767 / 0.0.978	0.0808 / 0.1218
Extinction coefficient	0.000(1)	0.000(1)
Largest diff. peak / hole, e Å^{-3}	+0.29 / −0.28	+0.34 / −0.22

Table 2. Bond lengths (Å) and angles (deg) for $C_9H_{12}N_2O_3S_2$ (**8**).

S(1)–C(1)	1.727(3)	S(1)–C(2)	1.799(3)
S(2)–C(1)	1.740(3)	S(2)–C(3)	1.801(3)
N(1)–C(7)	1.380(4)	N(1)–C(5)	1.402(4)
N(1)–C(6)	1.468(4)	N(2)–C(7)	1.378(4)
N(2)–C(9)	1.399(4)	N(2)–C(8)	1.471(4)
O(1)–C(5)	1.221(4)	O(2)–C(7)	1.225(4)
O(3)–C(9)	1.222(3)	C(1)–C(4)	1.399(4)
C(4)–C(5)	1.452(4)	C(4)–C(9)	1.456(4)
C(1)–S(1)–C(2)	108.8(2)	C(1)–S(2)–C(3)	104.5(2)
C(7)–N(1)–C(5)	124.7(3)	C(7)–N(1)–C(6)	117.5(3)
C(5)–N(1)–C(6)	117.8(3)	C(7)–N(2)–C(9)	124.5(2)
C(7)–N(2)–C(8)	118.0(3)	C(9)–N(2)–C(8)	117.4(3)
C(4)–C(1)–S(1)	126.5(2)	C(4)–C(1)–S(2)	120.1(2)
S(1)–C(1)–S(2)	113.4(2)	C(1)–C(4)–C(5)	121.8(3)
C(1)–C(4)–C(9)	119.2(3)	C(5)–C(4)–C(9)	118.6(2)
O(1)–C(5)–N(1)	118.8(3)	O(1)–C(5)–C(4)	125.0(3)
N(1)–C(5)–C(4)	116.1(3)	O(2)–C(7)–N(2)	121.8(3)
O(2)–C(7)–N(1)	121.3(3)	N(2)–C(7)–N(1)	116.8(3)
O(3)–C(9)–N(2)	118.6(3)	O(3)–C(9)–C(4)	125.1(3)
N(2)–C(9)–C(4)	116.2(2)		

bond (interplanar angle S(1)C(1)S(2)/C(5)C(4)C(9) 29.8(1)°) which may be a consequence of sterical interaction (S(1)···O(1) 3.142, S(2)···O(3) 2.681 Å). Apparently, the different orientation of the SMe sub-

stituents towards the olefinic bond is influenced by packing effects. The elongation of the central olefinic bond (C(1)–C(4) 1.399(4) Å) is also caused by the push-pull effect of the substituents attached thereon. For further bond lengths and angles see Table 2. Over all, the structure of **8** confirms its zwitterionic nature and parallels that of **6** reported by us recently [15].

*Thiomethylate substitution in 1,3-dimethyl-5-bis(thiomethyl)methylenebarbituric acid (**8**) and subsequent reactions. The crystal structure of 5-amino(thiomethyl)methylene-1,3-dimethylbarbituric acid (**9**)*

Thiomethylate substitution by nucleophiles starting from active electrophilic bis(thiomethyl)methylene compounds is a useful synthetic method [8]. With aqueous ammonia, **8** reacts to give 5-amino(thiomethyl)methylene-1,3-dimethylbarbituric acid (**9**). The results of its crystal structure analysis are shown in Table 1 and Fig. 2. The structure parallels that of **8** concerning the six-membered ring including the exocyclic olefinic bond (C(1)–C(12) 1.425(4) Å). Though the amino substituent preferentially acts as a +M donor, there is only minor lengthening of the olefinic C–S bond (C(12)–S(14) 1.748(3), C(12)–N(13) 1.324(4) Å; N(13)–C(12)–S(14) 119.2(2)°). The interplanar angle between the planes C(2)C(1)C(6) and N(13)C(12)–S(14) is 2.9°; the almost coplanar orientation of these fragments may be influenced by an intramolecular hydrogen bond as a result of the enolate-type charge distribution (O(11)···H(13b) 1.840 Å; C(6)–O(11)···H(13b) 97.6, O(11)···H(13b)–N(13) 143.3°). In addition, the molecules of **9** are linked by intermolecular NHO bonds (H(13a)···O(9a) 2.071 Å; N(13)–H(13a)···O(9a) 147.2°) to form a polymeric chain structure (Fig. 3). For further bond lengths and angles see Table 3.

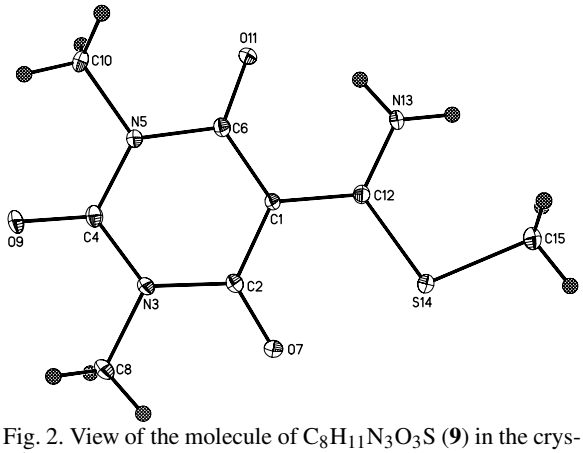


Fig. 2. View of the molecule of $C_8H_{11}N_3O_3S$ (**9**) in the crystal.

Table 3. Bond lengths (Å) and angles (deg) for $C_8H_{11}N_3O_3S$ (**9**).

C(1)–C(12)	1.425(4)	C(1)–C(6)	1.437(4)
C(1)–C(2)	1.436(4)	C(2)–O(7)	1.225(3)
C(2)–N(3)	1.405(4)	N(3)–C(4)	1.374(4)
N(3)–C(8)	1.478(4)	C(4)–O(9)	1.221(3)
C(4)–N(5)	1.381(4)	N(5)–C(6)	1.398(3)
N(5)–C(10)	1.478(4)	C(6)–O(11)	1.228(3)
C(12)–N(13)	1.324(4)	C(12)–S(14)	1.748(3)
S(14)–C(15)	1.808(3)		
C(12)–C(1)–C(6)	119.5(2)	C(12)–C(1)–C(2)	119.5(2)
C(6)–C(1)–C(2)	120.9(2)	O(7)–C(2)–N(3)	119.0(2)
O(7)–C(2)–C(1)	124.6(3)	N(3)–C(2)–C(1)	116.5(2)
C(4)–N(3)–C(2)	124.6(2)	C(4)–N(3)–C(8)	117.2(2)
C(2)–N(3)–C(8)	118.1(2)	O(9)–C(4)–N(3)	122.1(3)
O(9)–C(4)–N(5)	121.3(3)	N(3)–C(4)–N(5)	116.6(2)
C(4)–N(5)–C(6)	125.1(2)	C(4)–N(5)–C(10)	118.0(2)
C(6)–N(5)–C(10)	116.8(2)	O(11)–C(6)–N(5)	118.0(2)
O(11)–C(6)–C(1)	125.9(2)	N(5)–C(6)–C(1)	116.1(2)
N(13)–C(12)–C(1)	120.1(3)	N(13)–C(12)–S(14)	119.2(2)
C(1)–C(12)–S(14)	120.7(2)	C(12)–S(14)–C(15)	102.3(2)

Neither excess ammonia nor more forcing conditions led to the substitution of the second thiomethylate substituent which apparently needs stronger bases or, alternatively, the use of acidic conditions. In fact, the thiomethylate substituent in **9** is replaced by benzylamine in refluxing ethanol to give amino(benzylamino)methylenebarbituric acid (**10**), while with methanesulfonic acid the thiomethylate substituent in **9** is replaced selectively after protonation of the amino group to give the salt **11**.

Concluding Remarks

The synthesis of 1,3-dimethyl-5-bis(thiomethyl)-methylenebarbituric acid (**8**) follows the conception of the analogous Meldrum's acid derivative **6** which plays an important role in organic synthesis. Thus, **9** enables us to parallel the nucleophilic attack at the exocyclic methylene carbon atom of **6** on which we reported recently [16]. In contrast to Meldrum's acid, barbituric acid is stable towards acids. Therefore, we are investigating the oxidation of the thiomethyl substituents to sulfinyl and sulfonyl groups to make the push-pull-type olefinic bond in **9** a less polarized electron-poor one. We will report on our results in the near future.

Experimental Section

All starting materials were purchased from commercial sources and used without further purification. Experiments

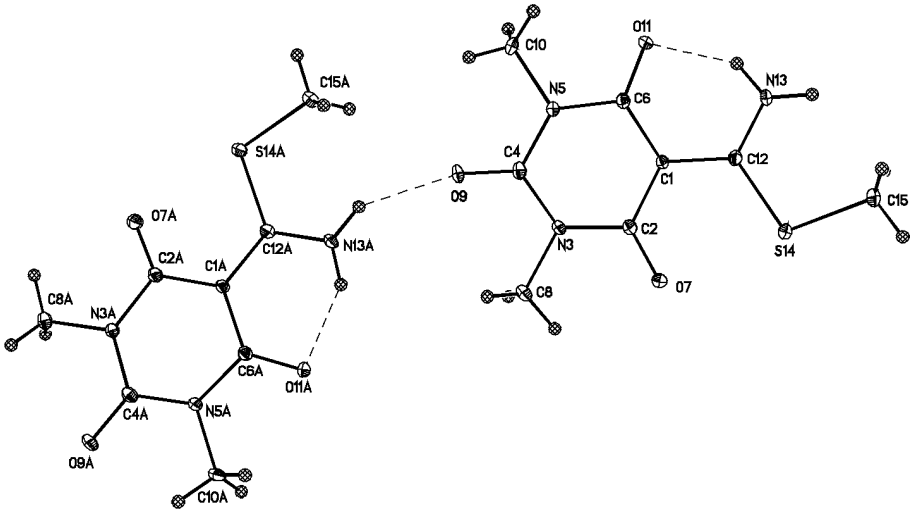


Fig. 3. View of the polymeric hydrogen-bonded chain of $C_8H_{11}N_3O_3S$ (**9**) in the crystal.

were performed in purified solvents under argon. Single crystals of $C_9H_{12}N_2O_3S_2$ (**8**) and $C_8H_{11}N_3O$ (**9**) were obtained by slow evaporation of a diethyl ether solution (**8**) or by slow cooling of a nitromethane solution (**9**).

CCDC 705675 (**8**) and CCDC 705674 (**9**) 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.

*$C_9H_{12}N_2O_3S_2$ (**8**)*

To a solution of 1,3-dimethylbarbituric acid (7.2 g, 46 mmol) in DMSO (20 mL) triethylamine (12.9 mL, 92 mmol) and carbon disulfide (2.8 mL, 46 mmol) were added. The mixture was stirred for 1 h at r. t., and iodomethane (6.0 mL, 92 mmol) was added dropwise at −18 °C. The mixture was stirred for further 5 h at r. t. and then diluted with a small amount of ice. Scratching of the walls of the vessel containing the mixture precipitated the product which was filtered off and washed with water and light petroleum/THF to give 6.5 g (54 %) from diethyl ether as yellow crystals. – ^{1}H NMR (400.13 MHz, [D$_6$]DMSO): δ = 2.52 (s, 6 H, SMe), 3.30 (s, 6 H, NMe). – ^{13}C NMR (100.64 MHz, [D$_6$]DMSO): δ = 21.6 (SMe), 27.4 (NMe), 106.4 (C^5), 150.1 (C^2), 158.5 (C^{4,6}), 194.1 (*C*–SMe). – Elemental analysis for $C_9H_{12}N_2O_3S_2$ (260.33): calcd. C 41.52, H 4.65, N 10.76; found C 41.13, H 4.88, N 10.43.

*$C_8H_{11}N_3O_3S$ (**9**)*

To a solution of **8** (1.2 g, 4.6 mmol) 25 mL of a 25 % aqueous ammonia solution were added. The mixture was stirred at r. t. for 30 min. The resulting precipitate was filtered off and dried *in vacuo* to give 0.86 g (82 %) of the product after recrystallization from DMSO/CH_2Cl_2 as colorless crystals. – ^{1}H NMR (400.13 MHz, [D$_6$]DMSO): δ = 2.41 (s, 3 H, SMe), 3.20 (s, 6 H, NMe), 8.43, 11.63 (2 s, 2 H, NH$_2$). – ^{13}C NMR (100.64 MHz, [D$_6$]DMSO): δ = 13.7 (SMe), 27.2 (NMe), 88.9 (C^5), 150.5 (C^2), 162.7 (C^{4,6}), 177.5 (*C*–SMe). – MS (EI, 70 eV): *m/z* (%) = 229 (16) [M]$^+$, 214 (12) [M – Me]$^+$, 182 (100) [M – SMe]$^+$ and further fragments. – Elemental analysis for $C_8H_{11}N_3O_3S$ (229.26): calcd. C 41.91, H 4.84, N 18.33; found C 41.62, H 5.19, N 17.93.

*$C_{14}H_{16}N_4O_3$ (**10**)*

To a solution of **9** (0.6 g, 2.6 mmol) in ethanol (15 mL), benzylamine (0.37 mL, 3.4 mmol) was added. The mixture was refluxed for 15 h. The precipitate was filtered off and dried *in vacuo* to give 0.55 g (73 %) of the product after recrystallization from $CHCl_3$/diethyl ether. – ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.24 (s, 6 H, NMe), 4.39 (s, 2 H, CH_2), 5.12 (s, 1 H, NH), 7.26 – 7.43 (m, 5 H, Ph), 10.46, 11.20 (2 s, NH$_2$). – ^{13}C NMR (100.64 MHz, $CDCl_3$): δ = 27.6 (NMe), 44.7 (CH_2), 79.8 (C^5), 127.3, 129.2, 130.3, 134.5 (Ph), 151.0 (C^2), 162.7 (C^{4,6}), 163.5 (*C*–NH$_2$). – MS (EI, 70 eV): *m/z* (%) = 288 (100) [M]$^+$, 271 (82) [M – NH$_2$]$^+$, and further fragments. – Elemental analysis for $C_{14}H_{16}N_4O_3$ (288.30): calcd. C 58.32, H 5.59, N 19.43; found C 58.68, H 5.87, N 19.01.

*$C_9H_{15}N_3O_9S_2$ (**11**)*

To a solution of **9** (0.8 g, 3.1 mmol) in CH_2Cl_2 (10 mL), methanesulfonic acid (0.2 mL, 3.1 mmol) was added slowly. The mixture was stirred at r. t. for 6 h. The resulting precipitate was filtered off and dried *in vacuo* to give 0.50 g (45 %) of the product after recrystallization from DMSO/CH_2Cl_2 as colorless crystals. – ^{1}H NMR (400.13 MHz, [D$_6$]DMSO):

δ = 2.68 (s, 6 H, $MeSO_3$), 3.07 (s, 6 H, NMe), 7.20 (t, 3 H, NH_3, ^1J = 52 Hz). – ^{13}C NMR (100.64 MHz, D_2O): δ = 27.8 (NMe), 38.4 ($MeSO_3$), 68.4 (C^5), 153.4 (C^2), 165.8 ($C^{4,6}$), *C*–SMe not observed. – MS (EI, 70 eV, M = cation): *m/z* (%) = 278 (4) $[M]^+$, 276 (37) $[M-2\ H]^+$, 229 (97) $[M-MeOOH]^+$, 200 (100) $[M-SO_2Me]^+$ and further fragments. – Elemental analysis for $C_9H_{15}N_3O_9S_2$ (373.36): calcd. C 28.95, H 4.05, N 11.25; found C 28.53, H 4.48, N 11.43.

Acknowledgement

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