Synthesis and Reactions of 5-[Amino(thiomethyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione

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Z. Naturforsch. **2009**, *64b,* 101 – 105; received October 9, 2008

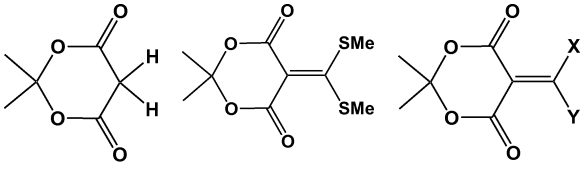
Dedicated to Professor Otto J. Scherer on the occasion of his 75th birthday

5-[Amino(thiomethyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**4**) is obtained from 5-[bis-(thiomethyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1**) and aqueous ammonia in excellent yield. Its reaction with *m*-chloroperbenzoic acid gives the sulfoxide derivative 5-[amino(sulfinylmethyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**5**). With triphenylphosphine, **5** reacts to give triphenyl(thiomethyl)phosphonium 5-cyano-2,2-dimethyl-1,3-dioxane-4,6-dionate (**6**) from which the methyltriphenylphosphonium salt **6a** is obtained with excess triphenylphosphine. The crystal structures of **4**, **5** and **6a** are discussed.

Key words: Meldrum's Acid, Heterocycles, Hydrogen Bonds, Sulfur, Zwitterionic States

Introduction

Meldrum's acid (**1**) derivatives play an important role in organic and pharmaceutical synthesis [1]. 5-[Bis(thiomethyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**2**), first prepared by Huang and Chen [2], may serve as a useful precursor for the preparation of a series of methylene compounds (**3**) [3 – 8]. In the light of our interest in studying intra- and intermolecular hydrogen bonds in Meldrum's acid and barbituric acid derivatives [9 – 11] and in the chemistry of these compounds we report now on the exchange of one thiomethyl substituent by an amino group and subsequent reactions.



Results and Discussion

The well known reaction of compound **2** with amines is restricted to the use of primary and secondary amines to form compounds of the type **3** (X = SMe; Y = NHR, NR^1R^2) [3, 4]. With aqueous ammonia, **2** reacts readily to give 5-[amino(thiomethyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**4**) as a stable solid in excellent yield. Its crystal structure (Tables 1 and 2, Figs. 1 and 2) reveals the presence of an intramolecular N–H···O bond [O(01)···H(8b) 1.86, N(8)–H(8b) 0.856 Å; N(8)–H(8b)···O(01) 142.1°] The bond lengths of the six-membered ring indicate a π electron distribution with a strong enolate contribution [O(01)–C(1) 1.225(2), C(1)–C(6) 1.441(2), C(6)–C(7) 1.425(2), C(7)–N(8) 1.322(2) Å]. Consequently,

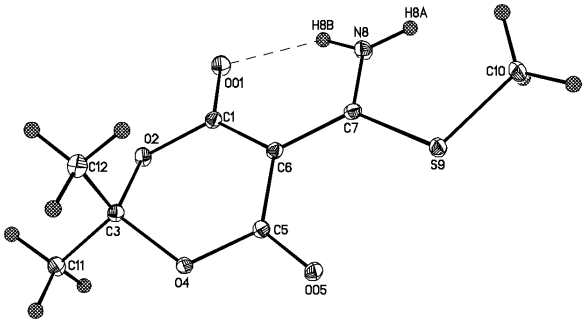


Fig. 1. View of the molecule of $C_8H_{11}NO_4S$ (**4**) in the crystal.

Table 1. Crystal data and structure refinement for $C_8H_{11}NO_4S$ (**4**), $C_8H_{11}NO_5S$ (**5**), and $C_{26}H_{24}NO_4P$ (**6a**).

	4	**5**	**6a**
Empirical formula	$C_8H_{11}NO_4S$	$C_8H_{11}NO_5S$	$C_{26}H_{24}NO_4P$
Formula weight	217.24	233.24	445.43
Temperature, K		173	
λ, Å		0.71073	
Crystal system	triclinic	triclinic	monoclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$
Unit cell dimensions			
a, Å	5.826(1)	7.203(1)	9.209(1)
b, Å	7.172(1)	8.574(2)	16.525(1)
c, Å	11.199(2)	8.799(2)	15.000(2)
α, deg	93.99(1)	106.62(1)	90
β, deg	90.59(1)	103.99(1)	92.08(1)
γ, deg	91.84(1)	98.64(1)	90
Volume, Å^3	466.5(2)	490.89	2281.1(4)
Z	2	2	4
D_{calcd}, g cm^{-3}	1.546	1.578	1.297
$\mu(MoK_\alpha)$, mm^{-1}	0.335	0.331	0.153
$F(000)$, e	228	244	936
θ, deg	3.27 – 26.37	3.29 – 26.37	3.31 – 26.37
Refls. coll.	6699	6988	31701
Refls. indep.	1901	1991	4660
Refinement method		Full-matrix least-squares on F^2	
Param. refined	172	181	386
Goodness-of-fit on F^2	1.137	1.069	1.117
Final $R1/wR2$ [$I \geq 2\sigma(I)$]	0.0309/0.0677	0.0289/0.0740	0.0617/0.1073
Final $R1/wR2$ (all data)	0.0365/0.0700	0.0312/0.0752	0.0786/0.1099
Extinction coeff.	0.026(3)	0.014(4)	0.002(1)
$\Delta\rho_{fin}$ (max/min), e Å^{-3}	+0.28/−0.20	+0.53/−0.25	+0.46/−0.32

Table 2. Bond lengths (Å) and angles (deg) for $C_8H_{11}NO_4S$ (**4**), and $C_8H_{11}NO_5S$ (**5**).

	$C_8H_{11}NO_4S$ (**4**)	$C_8H_{11}NO_5S$ (**5**)		$C_8H_{11}NO_4S$ (**4**)	$C_8H_{11}NO_5S$ (**5**)
C(1)–O(01)	1.225(2)	1.214(2)	O(2)–C(1)–C(6)	118.35(13)	116.75(12)
C(1)–O(2)	1.347(2)	1.357(2)	C(1)–O(2)–C(3)	119.86(12)	117.60(11)
C(1)–C(6)	1.441(2)	1.448(2)	O(2)–C(3)–O(4)	110.22(11)	109.76(11)
O(2)–C(3)	1.436(2)	1.438(2)	C(5)–O(4)–C(3)	119.12(11)	118.56(10)
C(3)–O(4)	1.439(2)	1.448(2)	O(05)–C(5)–O(4)	116.36(13)	117.85(12)
O(4)–C(5)	1.371(2)	1.361(2)	O(05)–C(5)–C(6)	126.99(14)	125.68(13)
C(5)–O(05)	1.216(2)	1.216(2)	O(4)–C(5)–C(6)	116.55(13)	116.42(12)
C(5)–C(6)	1.441(2)	1.446(2)	C(7)–C(6)–C(5)	121.00(13)	120.98(13)
C(6)–C(7)	1.425(2)	1.386(2)	C(7)–C(6)–C(1)	119.25(13)	118.65(13)
C(7)–N(8)	1.322(2)	1.308(2)	C(5)–C(6)–C(1)	119.39(14)	120.13(13)
C(7)–S(9)	1.736(2)	1.837(2)	N(8)–C(7)–C(6)	120.31(14)	126.26(14)
S(9)–C(10)	1.801(2)	1.805(2)	N(8)–C(7)–S(9)	119.05(12)	110.58(11)
S(9)–O(11)		1.494(1)	C(6)–C(7)–S(9)	120.64(11)	123.13(11)
			C(7)–S(9)–C(10)	101.51(8)	94.99(7)
O(01)–C(1)–O(2)	115.78(14)	117.50(13)	C(7)–S(9)–O(11)	–	102.91(7)
O(01)–C(1)–C(6)	125.85(15)	125.64(13)	C(10)–S(9)–O(11)	–	105.11(7)

the orientation of the fragments N(8)H(8a)H(8b) and C(6)C(7)S(9) is almost coplanar (interplanar angle 6.8°). The second NH proton is incorporated into an intermolecular hydrogen bond which links the molecule to the second carbonyl oxygen atom of a neighboring molecule thus forming a polymeric chain structure [O(05B)···H(8a) 2.407, N(8)–H(8a) 0.884 Å; N(8)–H(8a)···O(05B) 135.2°]. For further bond lengths and angles see Table 2.

The oxidation of organic sulfides is a standard method for the synthesis of sulfoxides and sulfones [12]. We obtained 5-[amino(sulfinylmethyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**5**) from **2** and *m*-chloroperbenzoic acid as the final product; apparently, further oxidation of **5** to the corresponding sulfone does not proceed under mild conditions. The crystal structure of **5** (Tables 1 and 2, Fig. 3) parallels that of **4** apart from a slight shorten-

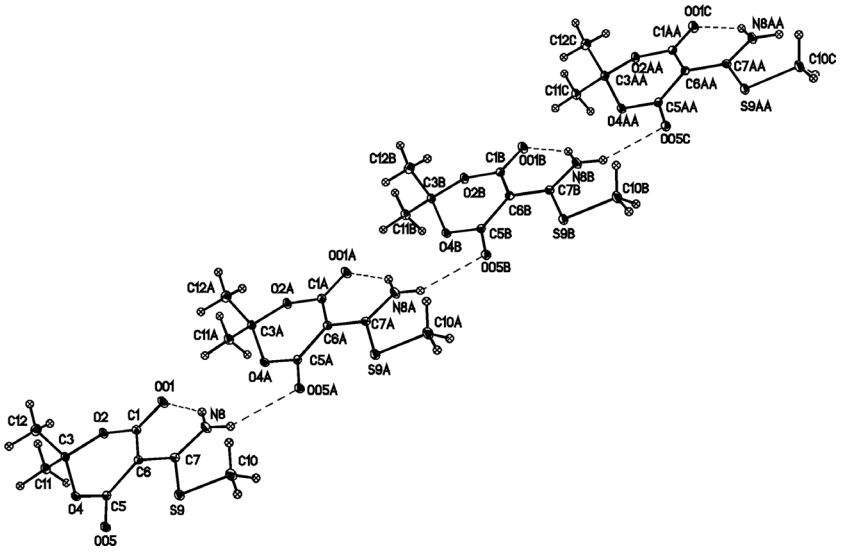


Fig. 2. View of the polymeric chain of $C_8H_{11}NO_4S$ (**4**) in the crystal.

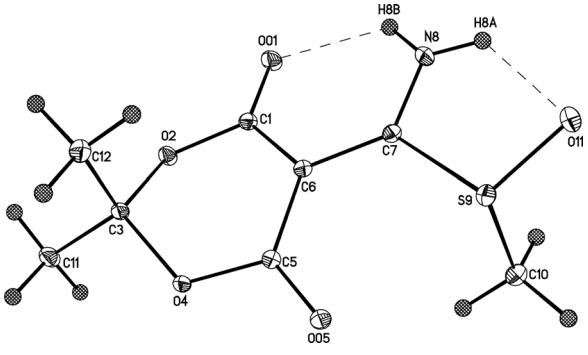


Fig. 3. View of the molecule of $C_8H_{11}NO_5S$ (**5**) in the crystal.

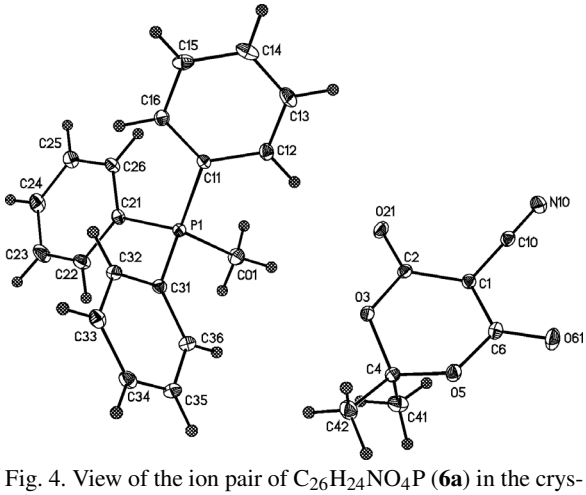


Fig. 4. View of the ion pair of $C_{26}H_{24}NO_4P$ (**6a**) in the crystal.

ing of the central exocyclic olefinic bond [N(8)–C(7) 1.308(2), C(6)–C(7) 1.386(2), C(1)–C(6) 1.448(2), C(1)–O(61) 1.214(2) Å]. Also, the angle between the fragments N(8)H(8a)H(8b) and C(6)C(7)S(9) (1.6°) and the parameters of the intramolecular N–H···O bond [O(01)···H(8b) 2.035, N(8)–H(8b) 0.875 Å; O(01)···H(8b)–N(8) 129.9°] are very similar to those of **4**. Instead of intermolecular contacts, H(8a) forms a second intramolecular O···H–N bridge including the sulfinyl oxygen atom [O(11)···H(8a) 2.083, N(8)–H(8a) 0.869 Å; O(11)···H(8a)–N(8) 121.7°].

We did not succeed in substituting the second thiomethyl group in **2** with excess ammonia. Apparently, the electrophilic nature of **4** is reduced, in comparison with **2**, by the strong +M effect of the amino group. Similarly, **4** does not react with triphenylphosphine under ambient conditions.

The enhanced acidity of the sulfoxide center in **5**, however, allows its nucleophilic attack. Surprisingly, triphenylphosphine attacks the sulfur atom to split the methylene carbon to sulfur bond to give the triphenylthiomethylphosphonium salt **6**, in which the methyleneamino fragment has been transformed to a nitrile function under elimination of water. The mechanism of this fast reaction needs further investigation since no by-products were detected. Excess of triphenylphosphine causes dealkylation of the thiomethylphosphonium ion in **6**, its methyltriphenylphosphonium salt **6a** being formed.

The crystal structure analysis of **6a** (Table 1, Fig. 4) reveals the presence of isolated ions. The structure of

Table 3. Bond lengths (Å) and angles (deg) for $C_{26}H_{24}NO_4P$ (**6a**).

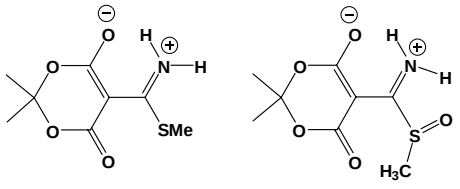
P(1)–C(11)	1.790(2)	P(1)–C(01)	1.790(2)
P(1)–C(31)	1.794(2)	P(1)–C(21)	1.794(2)
O(3)–C(2)	1.371(2)	O(3)–C(4)	1.441(2)
O(5)–C(6)	1.372(3)	O(5)–C(4)	1.437(2)
O(21)–C(2)	1.219(2)	O(61)–C(6)	1.220(2)
N(10)–C(10)	1.148(3)	C(1)–C(10)	1.417(3)
C(1)–C(6)	1.415(3)	C(1)–C(2)	1.424(3)
C(4)–C(42)	1.503(3)	C(4)–C(41)	1.506(3)
C(11)–P(1)–C(01)	108.9(1)	C(11)–P(1)–C(31)	110.2(1)
C(01)–P(1)–C(31)	109.6(1)	C(11)–P(1)–C(21)	110.7(1)
C(01)–P(1)–C(21)	108.0(1)	C(31)–P(1)–C(21)	109.4(1)
C(2)–O(3)–C(4)	117.1(2)	C(6)–O(5)–C(4)	117.6(2)
C(10)–C(1)–C(6)	118.7(2)	C(10)–C(1)–C(2)	118.5(2)
C(6)–C(1)–C(2)	122.4(2)	O(21)–C(2)–O(3)	117.2(2)
O(21)–C(2)–C(1)	126.7(2)	O(3)–C(2)–C(1)	116.1(2)
O(5)–C(4)–O(3)	110.5(2)	O(5)–C(4)–C(42)	106.5(2)
O(3)–C(4)–C(42)	106.3(2)	O(5)–C(4)–C(41)	110.5(2)
O(3)–C(4)–C(41)	110.0(2)	C(42)–C(4)–C(41)	113.0(2)
O(61)–C(6)–O(5)	117.3(2)	O(61)–C(6)–C(1)	126.5(2)
O(5)–C(6)–C(1)	116.1(2)	N(10)–C(10)–C(1)	179.5(2)

the cation agrees with published results [13]. Though being negatively charged, the structure of the anion resembles closely those found in the neutral molecules **4** and **5** indicating similar charge distributions. Bond lengths and angles around the cyano substituent are in the expected range [C(1)–C(10) 1.417(3), C(10)–N(10) 1.148(3) Å; C(1)–C(10)–N(10) 179.5(2)°]. For more details see Table 3.

Concluding Remarks

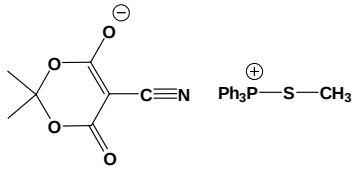
Our results confirm the electrophilic nature of the exocyclic 5-methylene substituent in Meldrum's acid derivatives. In fact, the propensity of the methylene carbon atom to allow an attack by nucleophiles decreases upon the exchange of thiomethyl substituents by amino groups which have stronger π-donating properties as demonstrated by the different reactivity of **2** and **4** towards ammonia. Nevertheless, π donation of the thiomethyl substituent in **4** seems to be present as indicated by its uncommon resistance to oxidation which stops at the sulfoxide derivative **5**.

In **5**, the soft base triphenylphosphine attacks the soft sulfur center under mild conditions according to the HSAB concept [14] while **4**, owing to its lower acidity, does not react. The mechanism of the interesting formation of **6** as well as the reaction of **5** with harder bases are currently under investigation.



4

5



6

Experimental Section

All starting materials were purchased from commercial sources and used without purification. Experiments were performed in purified solvents under argon. Compound **2** was prepared according to a published procedure [2]. Crystals of **4**, **5** and **6a** were obtained by recrystallization from CH_2Cl_2 / diethyl ether.

CCDC 698445 (**4**), CCDC 698444 (**5**), and CCDC 703897 (**6a**) 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.

*$C_8H_{11}NO_4$ (**4**)*

1 g (4 mmol) of **2** was added to 10 mL of aqueous ammonia (25 %). The suspension was stirred for 30 min at r. t. The precipitate was filtered and recrystallized from CH_2Cl_2/diethyl ether to give 0.72 g (82 %) of **4** as pale yellow crystals. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.57 (s, 6 H, 2-Me), 2.41 (s, 3 H, SMe), 8.8, 10.8 (2 s, 2 H, NH_2). – ^{13}C NMR (400 MHz, [D$_6$]DMSO): δ = 17.0 (SMe), 25.88 (2-Me), 82.75 (C^5), 102.2 (C^2), 163.3 (C=O), 177.6 (*C*-SMe). – MS (EI, 70 eV): *m/z* (%) = 217 (75) $[M]^+$, 186 (65) $[M–2\ Me]^+$, 160 (80) $[M–2\ Me, CO]^+$, and further fragments.

*$C_8H_{11}NO_5S$ (**5**)*

To a solution of 0.5 g (2.30 mmol) of **4** in 10 mL of CH_2Cl_2 0.52 g (2.30 mmol) *m*-chloroperbenzoic acid (77 %) was added at −60 °C. The suspension was stirred overnight and CH_2Cl_2 evaporated *in vacuo*. To the resulting precipitate 20 mL of diethyl ether was added at r. t., and the solution was stirred for 5 min. The precipitate was filtered and recrystallized from CH_2Cl_2 / diethyl ether to give 0.48 g (92 %) of **5** as colorless crystals. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (s, 6 H, 2-Me), 2.86 (s, 3 H, SMe), 8.8, 10.8 (2 s, 2 H, NH_2). –

^{13}C NMR (400 MHz, $CDCl_3$): δ = 25.88 (2-Me), 42.30 (S(O)Me), 82.44 (C^5), 105.5 (C^2), 164.31 (C=O), 178.77 (*C* S(O)Me). – MS (EI, 70 eV): *m/z* (%) = 234 (15) $[M]^+$, 192 (55) $[M–2Me, C]^+$, 176 (80) $[M–2 Me, CO]^+$, and further fragments.

*$C_{26}H_{24}NO_4PS$ (**6**)*

To a solution of 0.5 g (2.15 mmol) of **5** in 10 mL of CH_2Cl_2 0.56 g (2.15 mmol) triphenylphosphine was added at r. t. The suspension was stirred overnight, and CH_2Cl_2 was evaporated *in vacuo*. To the resulting precipitate 20 mL of diethyl ether was added at r. t., and the solution was stirred for 5 min. The precipitate was filtered and recrystallized from CH_2Cl_2 / diethyl ether to give 0.91 g (89 %) of **6** as colorless crystals. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (s, 6 H, 2-Me), 2.41 (d, 3 H, SMe), 7.69 – 7.82 (m, 15 H, Ph). – ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.75 (SMe), 26.12 (2-Me), 57.29 (C^5), 102.24 (C^2), 117.66 (CN), 120.00, 130.85, 133.45, 136.12 (Ph), 166.27 (C=O). – MS (FAB neg.): *m/z* (%) = 167.9 (100) $[M]^-$, 152.9 (10) $[M–Me]^-$, 121.9 (5) $[M – 2 Me, CO]^-$. – MS (FAB): *m/z* (%) = 309.1 (100) $[M]^+$, 262.2 (5) $[M–MeS]^+$, 183.0 (5) $[M–MeS, Ph]^+$.

Acknowledgement

Financial support by the Deutsche Forschungsgemeinschaft and the Higher Council for Science and Technology of Jordan is gratefully acknowledged.

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