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NOVEL SYNTHETIC ROUTES TO 1,3,1′,3′-TETRAMETHYLHYDURILIC ACID AND TETRAMETHYLALLOXANTINE (AMALIC ACID) AND THEIR CRYSTAL STRUCTURES

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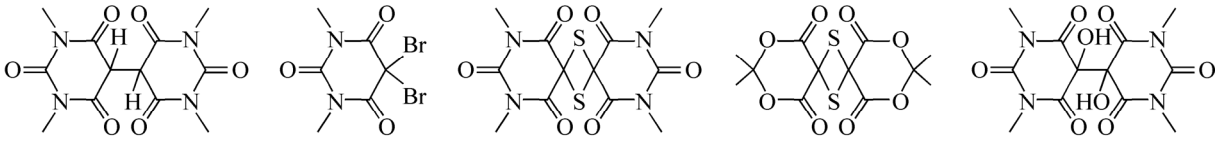
1,3,1′,3′-Tetramethylhydurilic acid (**1**) and tetramethylalloxantine (**5**) were prepared by simple novel methods. The crystal structures of the compounds **1** and **5**·2(DMSO) are reported.

K e y w o r d s: 1,3-dimethylbarbituric acid, 5,5′-bibarbituric acid, hydurilic acid, alloxantine, heterocycles, synthesis, crystal solvate.

Derivatives of barbituric acids are widely known as effective chemotherapeutic agents [1]. Among them, new compounds have been found with analgesic [2] and antibacterial activity [3]. 1,3,1′,3′-Tetramethylhydurilic acid (**1**) and tetramethylalloxantine (**5**) (Scheme 1) are considered as organic derivatives of 1,3-dimethylbarbituric acid (or 5,5′-bibarbituric acid). Although these compounds are known, the suggested synthetic routes have disadvantages. Bredereck [4] prepared 1,3,1′,3′-tetramethylhydurilic acid starting from 4-amino-5-acetamino-1,3-dimethyluracil in five steps followed by isolation from a mixture of products in low yield; elemental analysis was used for its characterization only. Itahara [5] prepared tetramethylalloxantine as a mixture of products by oxidation of nucleic acids in very low yield (2—18 %) followed by using HPLC techniques for separation. The target compound was characterized by nuclear magnetic resonance (NMR) and elemental analysis.



Scheme 1

In this work, the two claimed compounds were prepared in simple practical steps followed by the use of spectroscopic methods and X-ray diffraction analysis to confirm the chemical structures.

Experimental. All experiments were performed in purified solvents under argon. 1,3-Dimethylbarbituric acid, disodium sulfide and triphenylbismuth carbonate were purchased from Aldrich and used without further purification. The elemental analysis was conducted on an elemental analyzer Carlo Erba 1106. The mass spectra (FAB) were acquired on a Finnigan TQS 70 (70 eV in nitrobenzylalcohol matrix at 30 °C) instrument modified by AMD. The high resolution NMR spectra were acquired on a Bruker DRX 250 NMR spectrometer (^{1}H 250,13 MHz; ^{13}C 62,90 MHz, using TMS as external standard).

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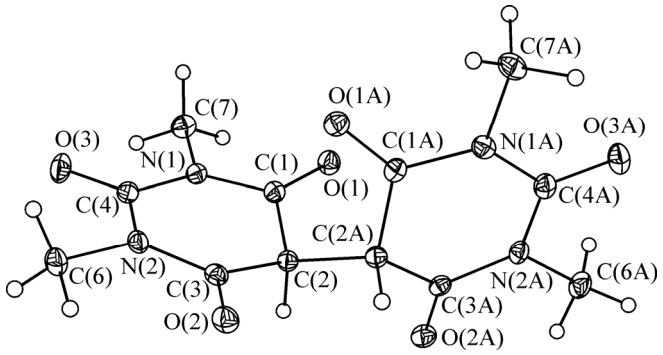

Fig. 1. Molecular structure of **1** as found in the crystal structure studied

Crystal data have been obtained with a STOE IPDS diffractometer and SHELX-97 was used for structure solution and refinement based on F^2. Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre (compound **1**: CCDC No. 695745, compound **5**: CCDC No. 695746). CIF files containing complete information on the studied structures may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, fax +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or from the following web site: www.ccdc.cam.ac.uk/data_request/cif.

1,3,1′,3′-Tetramethyl-[5,5′]bipyrimidinyl-2,4,6,2′,4′,6′-hexaone (**1**). A solution of 0.64 g (1.28 mmol) $BiPh_3CO_3$ and 0.13 g (0.83 mmol) of 1,3-dimethylbarbituric acid in 20 cm^3 CH_2Cl_2 was refluxed for 20 h. After cooling, the solvent was removed under reduced pressure to dryness. The residue was recrystallised from CH_2Cl_2/Et_2O to give 0.07 g (54 %) of **1** as green crystals. M.p. and elemental analysis data were found to be identical to those described in Ref. [4]. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.15 (s, 12 H, 1,3-Me), 3.81 (s, 2 H, CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 28.2 (1,3-Me), 46.9 (C5), 151.2 (C2), 161.5 (C4,6) ppm; MS (EI): *m*/*z* = 310 (M^+), 280 (M^+-2Me) and further fragments.

5,5-Dibromo-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**2**). To a solution of 3.1 g (20 mmol) of 1,3-dimethylbarbituric acid in 40 cm^3 of 1M NaOH, 2 g (40 mmol) of bromine was added dropwise with stirring at 0—5 °C. The resulting solution was stirred for further 4 h. The precipitate was filtered off, washed with 30 cm^3 H_2O and dried under reduced pressure to give 5.5 g (88 %) of **2**. (^{1}H, ^{13}C) NMR spectra, mass spectra were found to be identical to those described in Ref. [7].

5,5′-Dihydroxy-1,3,1′,3′-tetramethyl-[5,5′]bipyrimidinyl-2,4,6,2′,4′,6′-hexaone (**5**). A suspended solution of 1.66 g (5.3 mmol) of **2** in 10 cm^3 THF was added to 0.41 g (5.3 mmol) of Na_2S in 8 cm^3 of H_2O at room temperature. After the reaction mixture was stirred overnight, the precipitate was filtered off and dried under reduced pressure. Recrystallisation of **3** from (DMSO—CH_2Cl_2)/Et_2O afforded 0.38 g (42 %) of colourless crystals. M.p., (^{1}H, ^{13}C) NMR spectra and elemental analysis data were found to be identical to those described in Refs. [5, 12]; MS (FAB): *m*/*z* = 341 (M+), 267 (M^+-4Me, -O) and further fragments.

Results and discussion. With increasing environmental concerns and the need for ″green reagents″, bismuth(V) reagents play an important role in organic synthesis [6]. 1,3,1′,3′-Tetramethylhydurilic acid (**1**) (see Scheme 1) was prepared by refluxing 1,3-dimethylbarbituric acid in CH_2Cl_2 with an excess of Ph_3BiCO_3. The ^{13}C NMR spectrum of **1** shows a slight difference in the chemical shift of the C5 signal (C2 and C2A in the crystal structure, Fig. 1) which appeared at 46.9 ppm relative to its position in 1,3-dimethylbarbituric acid itself (39.8 ppm).

1,3,1′,3′-Tetramethylhydurilic acid (**1**) crystallizes in the tetragonal space group $I4_1/a$ (Figure 1, Tables 1 and 2). The center of the C(2)—C(2A) single bond lies on a twofold crystallographic axis and the central C—C bond [C(2)—C(2A) (1.522(3) Å)] is very close in length to the expected value for a C—C single bond (1.54 Å). The dihedral angle between the planes C(1)C(2)C(3) and C(1A)C(2A)C(3A) is 69.0°.

5,5-Dibromo-1,3-dimethylbarbituric acid (**2**) can be considered as a precursor for the synthesis of new organic derivatives of 1,3-dimethylbarbituric acid due to the ease of its bromine atoms elimination. Many procedures were used in the past for synthesis of **2** including the use of $KBrO_3$/KBr/Dowex® [7] and enzymatic bromination with using haloperoxidases enzymes [8]. We now report a bromination reaction that takes place in an alkaline aqueous medium under mild conditions with cheap reagents and high yield.

Table 1

Crystal Data and Structure Refinement for **1** *and* **5**·2(DMSO)

Parametr	**1**	**5**·2(DMSO)
Empirical formula	$C_{12}H_{14}N_4O_6$	$C_{12}H_{24}N_4O_8$, 2 (C_2H_6OS)
Formula weight	620.54	498.53
Temperature, K	293(2)	208(2)
Radiation wavelength, Å	0.71073	0.71073
Crystal system	Tetragonal	Orthorhombic
Space group	$I4_1/a$	$P2_12_12_1$
Unit cell dimensions, Å	a = 14.112(2), c = 13.642(3)	a = 8.3150(17), b = 15.281(3), c = 17.383(4)
Unit cell volume, Å^3	2717.0(8)	2208.7(8)
Z	8	4
Calculated density, g/cm^3	1.517	1.499
Absorption coefficient, cm^{-1}	1.24	3.02
F(000)	1296	1048
θ range for data collection, deg.	3.56—29.34	3.03—31.00
Index ranges h, k, l (min/max)	–19/19, –18/19, –18/18	–1/5, –1/22, –25/25
Reflections collected	12492	5926
Independent reflections	1857	4163
R(int)	0.0555	0.0379
Completeness to θ, deg.	99.0% to 29.34°	61.0% to 31.00°
Refined parameters	129	391
GOOF on F^2	1.152	0.956
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0612, $wR2$ = 0.1261	$R1$ = 0.0450, $wR2$ = 0.0950
R indices (all data)	$R1$ = 0.0803, $wR2$ = 0.1335	$R1$ = 0.1058, $wR2$ = 0.1058
Largest diff. peak and hole, e/Å^3	0.33 and –0.18	0.62 and –0.35
CCDC deposition No.	695745	695746

As an extension of our earlier investigation of the reaction of 1,3-dimethylbarbituric acid with sulfur-containing reagents, namely thionyl chloride [9], the reaction of **2** with Na_2S surprisingly does not lead to the dithietane **3** analogous to its Meldrum′s acid derivative **4** [10], but rather yields compound **5** instead. The ^{13}C NMR signal of C5 (C1 and C7 in the crystal structure, Fig. 2) in **5** is shifted to a lower field (~85 ppm) compared to that in **1** due to the presence of hydroxyl groups at C5 (Scheme 1).

Table 2

Selected Bond Lengths [Å] *and Angles* [deg.] *for* **1**

N(1)—C(1)	1.375(2)	O(3)—C(4)	1.208(2)	N(2)—C(6)	1.470(3)
N(1)—C(7)	1.475(2)	C(2)—C(3)	1.506(2)	O(2)—C(3)	1.210(2)
N(2)—C(4)	1.394(3)	N(1)—C(4)	1.380(2)	C(1)—C(2)	1.507(3)
O(1)—C(1)	1.208(2)	N(2)—C(3)	1.371(2)	C(2)—C(2A)	1.522(3)
C(1)—N(1)—C(4)	123.74(15)	O(2)—C(3)—N(2)	121.96(17)	O(1)—C(1)—C(2)	121.48(17)
C(4)—N(1)—C(7)	117.41(16)	N(2)—C(3)—C(2)	115.99(16)	C(3)—C(2)—C(1)	115.44(15)
C(3)—N(2)—C(6)	117.99(17)	O(3)—C(4)—N(2)	120.75(18)	C(1)—C(2)—C(2)#1	112.69(12)
O(1)—C(1)—N(1)	122.18(17)	C(1)—N(1)—C(7)	118.43(16)	O(2)—C(3)—C(2)	121.90(17)
N(1)—C(1)—C(2)	116.08(15)	C(3)—N(2)—C(4)	125.10(16)	O(3)—C(4)—N(1)	121.26(18)
C(3)—C(2)—C(2)#1	111.71(18)	C(4)—N(2)—C(6)	116.90(17)	N(1)—C(4)—N(2)	117.97(16)

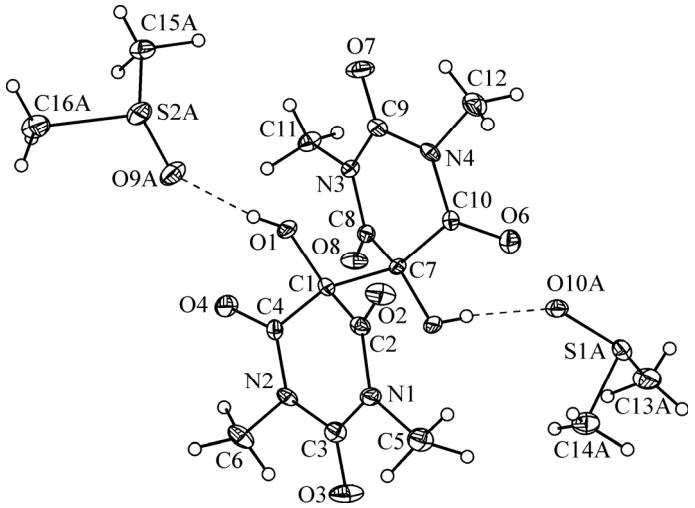

Fig. 2. Molecular structure of the fragment **5**·2(DMSO) in the crystal studied

Tetramethylalloxantine (**5**) crystallizes as a DMSO solvate **5**·2(DMSO) in the orthorhombic space group $P2_12_12_1$ (Fig. 2, Tables 1 and 3). The central C—C single bond [C(1)—C(7) (1.610(4) Å)] is elongated relative to a typical carbon-carbon single bond (1.54 Å) and to the C(2)—C(2A) in **1**. This elongation may be caused by the relative orientation of the two six-membered rings of the molecule which are near coplanar, with the dihedral angle between the planes C(4)C(1)C(2) and C(10)C(7)C(8) of 1.1°. Interestingly, the formation of hydrogen bonds to the DMSO solvent molecules [H(1)…O(9A) (1.860 Å); O(1)—H(1)…O(9A) (162.0°) and H(5)…O(10A) (1.956 Å); O(5)—H(5)…O(10A) (171.8°)] is preferred over the formation of intramolecular ones.

Recently, X-ray powder diffraction was used to investigate crystal structures of products obtained from the reaction of solid 1,3-dimethylbarbituric acid with vapors of NH_3 and volatile amines [11].

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Table 3

Selected Bond Lengths [Å] *and Angles* [deg.] *for* **5**·2(DMSO)

S(1)—O(10)	1.507(3)	O(10)—S(1)—C(14)	104.8(2)	O(9)—S(2)—C(15)	105.9(2)
O(1)—C(1)	1.389(4)	C(2)—N(1)—C(3)	124.1(4)	C(2)—N(1)—C(5)	119.5(5)
O(8)—C(8)	1.207(5)	C(9)—N(3)—C(8)	124.4(4)	C(8)—N(3)—C(11)	116.2(4)
C(1)—C(2)	1.527(6)	O(1)—C(1)—C(4)	110.6(3)	O(1)—C(1)—C(2)	107.6(3)
C(7)—C(10)	1.510(6)	C(4)—C(1)—C(2)	113.1(3)	O(1)—C(1)—C(7)	110.4(2)
S(2)—O(9)	1.487(3)	C(4)—C(1)—C(7)	108.3(3)	C(2)—C(1)—C(7)	106.9(3)
O(5)—C(7)	1.390(4)	O(2)—C(2)—C(1)	121.0(3)	O(5)—C(7)—C(10)	111.8(3)
C(1)—C(4)	1.504(6)	C(10)—C(7)—C(8)	111.2(3)	O(5)—C(7)—C(1)	105.7(2)
C(1)—C(7)	1.610(4)	O(8)—C(8)—C(7)	122.5(3)	O(6)—C(10)—C(7)	122.0(3)
C(7)—C(8)	1.523(6)				

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