Synthesis and structure of 2,5,7,10-tetramethyl-2,4,8,10-tetraazabicyclo[4.4.0]decane-3,9-dione

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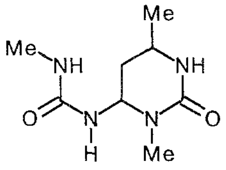
2,5,7,10-Tetramethyl-2,4,8,10-tetraazabicyclo[4.4.0]decane-3,9-dione, a regioisomer of the previously known 2,5,7,8-tetramethyl-2,4,8,10-tetraazabicyclo[4.4.0]decane-3,9-dione, has been synthesized, and its structure has been established by X-ray diffraction analysis. The bicyclic system of this molecule is formed by two heterocycles *cis*-annelated through the C(1)—C(6) bond. The relative configurations of the asymmetric centers are *S* for C(5), and *R* for C(7). In the monohydrate crystal studied, the molecules are linked by O...H—O_w and O...H—N type H-bonds forming a three-dimensional framework.

Key words: methylurea, acetaldehyde, condensation; tetraazabicyclodecanediones, regioisomers; crystal and molecular structure; configuration of asymmetric centers.

2,4,8,10-Tetraazabicyclo[4.4.0]decane-3,9-diones are formed during the condensation of ureas with monoaldehydes.[1] The reaction of *N*-methylurea with acetaldehyde yields two products, *viz.*, 1,4-dimethyl-6-(3′-methylureido)hexahydropyrimidin-2-one (**1**) and 2,5,7,8-tetramethyl-2,4,8,10-tetraazabicyclo[4.4.0]decane-3,9-dione (**2**).



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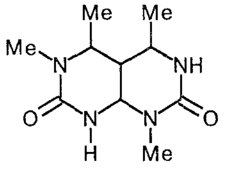

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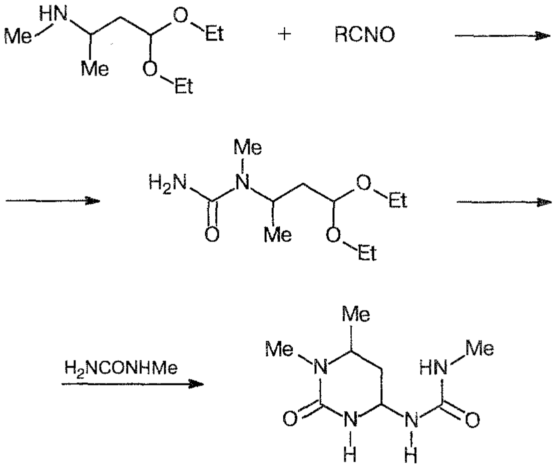
The positions of the *N*-methyl groups in the pyrimidine ring and the ureide residue of molecule **1** can be determined based on the fact that the reactivity of the NH_2 group in methylurea is higher than that of the MeNH fragment in the reaction with formaldehyde.[2] The structure of compound **1** is indirectly confirmed by the fact that the constants of compound **1** differ from those of 3,4-dimethyl-6-(3′-methylureido)hexahydropyrimidin-2-one (**3**), whose structure unequivocally follows from the method of its preparation[3] (Scheme 1).

Scheme 1



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To confirm the structure of compound **2** we prepared it from compound **1** and acetaldehyde.[2] The positions of the *N*-methyl groups in dione **2** are determined by the positions of these groups in monoureide **1**.

In the present work we continued the study of the interaction of methylurea with acetaldehyde (in the 2 : 3 ratio) in an acid medium and showed that, in addition to compound **2**, one of its two possible regioisomers, 4,5,7,8-tetramethyl-2,4,8,10-tetraazabicyclo[4.4.0]decane-3,9-dione (**4**) or 2,5,7,10-tetramethyl-

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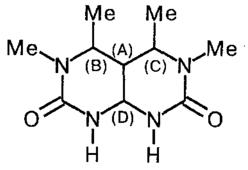
2,4,8,10-tetraazabicyclo[4.4.0]decane-3,9-dione (**5**) is produced.



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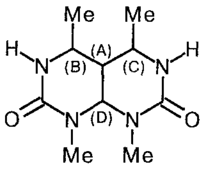

5

This conclusion is consistent with the ^{1}H NMR spectrum of the resulting compound: the chemical shifts, multiplicities, and integral intensities of the signals correspond to those expected for compounds **4** or **5**. However, using only the ^{1}H NMR spectrum it is difficult to decide between compounds **4** and **5**. Therefore, we carried out an X-ray structural study, which unambiguously showed that the structure of the reaction product corresponds to that of **5**. According to the Cambridge Crystallographic Database,[4] tetraazabicyclodecanediones had not been studied by this method previously.

The general view of the monohydrate of compound **5** is presented in Fig. 1. The bond lengths and angles are listed in Tables 1 and 2, respectively. The bicyclic system of molecule **5** is formed by two hexahydropyrimidine rings *cis*-annelated through the C(1)—C(6) bond (the H(1)—C(1)—C(6)—H(6) torsion angle is 66°). These six-membered rings have distorted half-chair conformations: the C(1) and C(6) atoms deviate from the N(2)C(3)N(4)C(5) (plane I) and C(7)N(8)C(9)N(10) (plane II) root-mean-square planes (accurate to ±0.006 and ±0.008 Å, respectively) by 0.157 and −0.528 Å (for plane I) and −0.182 and 0.529 Å (for plane II). The O(11) and O(12) atoms actually lie in planes I and II (the deviations are 0.018 and −0.067 Å), and the C(15) and C(16) atoms of the Me groups are deflected from these planes by −0.172 and −0.255 Å, respectively. The methyl groups at C(5) and C(7) are arranged pseudoequatorially and pseudo-axially. The relative configuration of the C(5) asymmetric center is *R*; that of the C(7) center is *S*.

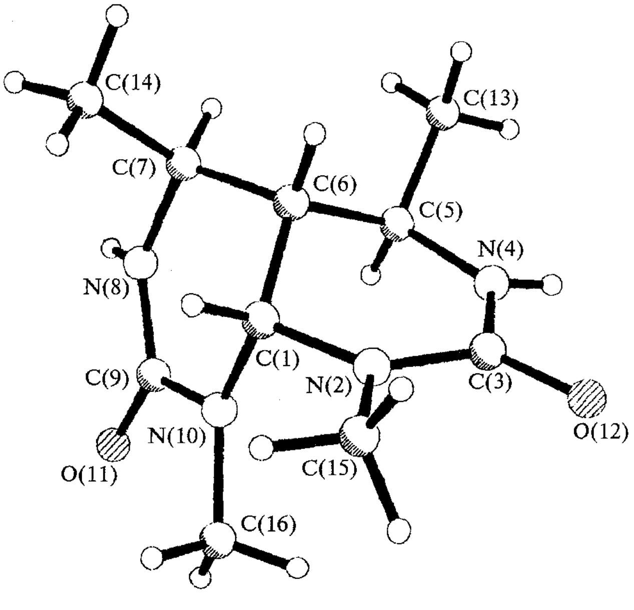

Fig. 1. The general view of molecule **5** (the water molecule is not shown).

The C—N and C=O bond lengths in the C(3)—N(4), C(3)—N(2), C(3)=O(12) and C(9)—N(8), C(9)—N(10), C(9)=O(11) urea moieties differ little from the normal values for C—N (1.347 Å) and C=O (1.241 Å) bonds in acyclic derivatives of ureas.[5]

In the crystal, the molecules are united into a three-dimensional framework by H-bonds like O_w—H...O= and N—H...O= in which the O(11) carbonyl atom forms H-bonds with two H_2O molecules, and the O(12) atom interacts with two H-atoms of the amine fragments of the neighboring molecules: O(11)...H(1)—O_w ($x - 1$, $y + 2$, z) [O...O_w is 2.888(2) Å, O...H(1) is 2.10(5) Å, the O—H—O angle is 159°]; O(11)...H(2)—O_w ($-x$, $-y + 2$, $-z$) [O...O_w is 2.897(2) Å, O...H(2) is 2.10(6) Å, the O—H—O angle is 165°]; O(12)...H—N(4) ($-x$, $-y + 2$, $-z + 1$) [O...N is 2.961(2) Å, O...H is 2.20(3) Å, the O—H—N

Table 1. Bond lengths (*d*) in molecule **5**

Bond	*d*/Å	Bond	*d*/Å
C(1)—N(2)	1.454(2)	C(5)—C(13)	1.524(2)
C(1)—C(6)	1.526(2)	C(6)—C(7)	1.529(2)
C(1)—N(10)	1.478(2)	C(7)—N(8)	1.459(2)
N(2)—C(3)	1.358(2)	C(7)—C(14)	1.526(4)
N(2)—C(15)	1.466(2)	N(8)—C(9)	1.343(2)
C(3)—N(4)	1.349(2)	C(9)—N(10)	1.367(2)
C(3)—O(12)	1.247(2)	C(9)—O(11)	1.245(2)
N(4)—C(5)	1.457(2)	N(10)—C(16)	1.461(2)
C(5)—C(6)	1.522(3)		

Table 2. Bond angles (ω) in molecule **5**

Angle	ω/deg	Angle	ω/deg
N(2)—C(1)—C(6)	110.2(1)	C(1)—C(6)—C(5)	110.2(1)
N(2)—C(1)—N(10)	111.1(1)	C(1)—C(6)—C(7)	109.4(1)
C(6)—C(1)—N(10)	109.4(1)	C(5)—C(6)—C(7)	112.7(1)
C(1)—N(2)—C(3)	22.1(1)	C(6)—C(7)—N(8)	109.0(1)
C(1)—N(2)—C(15)	119.1(1)	C(6)—C(7)—C(14)	112.0(2)
C(3)—N(2)—C(15)	118.8(1)	N(8)—C(7)—C(14)	112.1(1)
N(2)—C(3)—N(4)	117.8(1)	C(7)—N(8)—C(9)	126.6(1)
N(2)—C(3)—O(12)	121.4(1)	N(8)—C(9)—N(10)	118.3(1)
N(4)—C(3)—O(12)	120.8(2)	N(8)—C(9)—O(11)	120.2(1)
C(3)—N(4)—C(5)	126.9(1)	N(10)—C(9)—O(11)	121.5(1)
N(4)—C(5)—C(6)	109.1(1)	C(1)—N(10)—C(9)	121.0(1)
N(4)—C(5)—C(13)	108.1(1)	C(1)—N—(10)—C(16)	117.7(1)
C(6)—C(5)—C(13)	112.7(2)	C(9)—N(10)—C(16)	118.1(1)

angle is 169°]; O(12)...H—N(8) ($x + 1, y - 1, z$) [O...N is 2.963(2) Å, O...H is 2.16(3) Å, the O—H—N angle is 162°].

Table 3. Atomic coordinates (×10^4, or ×10^3 for H atoms) and equivalent isotropic heat parameters(U^{eq}_{iso}/ Å^2, ×10^3, or ×10^2 for H atoms)

Atom	x	y	z	U^{eq}_{iso}
C(1)	−4479(2)	12687(2)	2341(1)	24(1)
N(2)	−2593(2)	11099(2)	2504(1)	25(1)
C(3)	−1591(2)	10494(2)	3520(1)	26(1)
N(4)	−2492(2)	11320(2)	4441(1)	33(1)
C(5)	−4489(2)	12781(2)	4491(1)	25(1)
C(6)	−5758(2)	12824(2)	3588(1)	25(1)
C(7)	−7717(2)	14515(2)	3400(2)	30(1)
N(8)	−7178(2)	16045(2)	2641(1)	35(1)
C(9)	−5477(2)	15985(2)	1848(1)	29(1)
N(10)	−4037(2)	14339(2)	1754(1)	28(1)
O(11)	−5220(2)	17401(2)	1236(1)	44(1)
O(12)	83(2)	9189(2)	3617(1)	37(1)
C(13)	−5494(3)	12483(3)	5822(2)	37(1)
C(14)	−9285(3)	14286(3)	2851(2)	46(1)
C(15)	−1768(3)	10096(2)	1557(2)	36(1)
C(16)	−2374(3)	14277(3)	744(2)	39(1)
O_w	2833(3)	1236(2)	946(2)	62(1)
H(1)	−522(3)	1253(2)	179(2)	3(1)
H(4)	−183(3)	1104(3)	497(2)	4(1)
H(5)	−430(3)	1396(2)	424(2)	3(1)
H(6)	−614(3)	1173(2)	395(2)	3(1)
H(7)	−834(3)	1478(2)	423(2)	3(1)
H(8)	−796(3)	1706(3)	275(2)	4(1)
H(131)	−588(4)	1142(3)	604(2)	7(1)
H(132)	−457(4)	1229(3)	639(2)	6(1)
H(133)	−670(4)	1350(3)	594(2)	6(1)
H(141)	−871(4)	1376(3)	211(2)	7(1)
H(142)	−980(4)	1338(3)	350(2)	7(1)
H(143)	−1051(4)	1539(3)	265(2)	7(1)
H(151)	−33(4)	998(3)	122(2)	7(1)
H(152)	−257(4)	1069(3)	85(2)	6(1)
H(153)	−176(4)	887(4)	184(2)	8(1)
H(161)	−112(3)	1333(3)	101(2)	4(1)
H(162)	−277(4)	1414(3)	3(2)	7(1)
H(163)	−218(4)	1529(4)	54(2)	7(1)
$H(1)_w$	332(5)	14(4)	122(3)	9(1)
$H(2)_w$	352(6)	146(5)	28(4)	14(2)

Experimental

The ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer in D_2O (internal standard).

2,5,7,10-Tetramethyl-2,4,8,10-tetraazabicyclo[4.4.0]decane-3,9-dione (5). *N*-methylurea (14.8 g, 0.2 mol) was dissolved in 50 mL of distilled water and acidified with 7.5 mL of HCl, then acetaldehyde (17 mL, 13.2 g, 0.3 mol) was slowly added with cooling over a period of 15 min. The reaction mixture was heated to 60 °C over a period of 2 h, cooled, neutralized with $NaHCO_3$, and extracted with $CHCl_3$ (7×10 mL). The chloroform extracts and the aqueous phase were worked-up separately. The chloroform extracts were concentrated *in vacuo*, the residue from the third extract was dissolved in AcOEt and boiled with activated coal, and the mixture was filtered. The solvent was evaporated *in vacuo*, and the residue was recrystallized from water. Yield 5—8 %, m.p. 275—277 °C. ^{1}H NMR, δ: 1.20 (d, 6 H, 2 CMe, $J_{H(Me),H(B)} = J_{H(Me),H(C)} = 6.0$ Hz); 1.71—2.09 (m, 1 H, CH(A), $J_{H(A),H(B)} = J_{H(A),H(C)} = 6.0$ Hz, $J_{H(A),H(D)} = 3.0$ Hz); 2.93 (s, 6 H, 2 Me); 3.15—3.66 (m, 2 H, CH(B,C), $J_{H(B),H(A)} = J_{H(C),H(A)} = J_{H(B),H(Me)} = J_{H(C),H(Me)} = 6.0$ Hz); 4.83 (d, H, CH(D), $J_{H(D),H(A)} = 3.0$ Hz).

The X-ray structural study of compound 5. The single crystals of the monohydrate of **5** prepared by crystallization from an aqueous solution are triclinic; at −120 °C a = 7.235(1) Å, b = 8.498(1) Å, c = 11.511(2) Å, α = 70.86(1)°, β = 76.48(1)°, γ = 64.99(1)°, V = 602.2(2) Å^3, Z = 2, d_{calc} = 1.248 g cm^{-3}, space group $P\bar{1}$. $C_{10}H_{18}N_4O_2 \cdot H_2O$, M = 244.29.

Unit cell parameters and intensities of 2720 independent reflections with $I \geq 2\sigma(I)$ were measured on a Siemens P3/PC automatic diffractometer (λ(Mo-Kα), graphite monochromator, θ/2θ scanning, 2θ < 60°). The structure was solved by the direct method and refined by the least-squares method in the full-matrix anisotropic approximation for nonhydrogen atoms. All of the H atoms were revealed from the differential synthesis and refined isotropically at the final cycles. The final residual factors: R = 0.040, R_w = 0.043. The calculations were carried out on an IBM-PC/AT computer using the SHELXTL PLUS programs.[6] The coordinates and heat parameters of the atoms are listed in Table 3.

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