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Synthesis and Structure of 2,4,6,8-Tetramethyl-3,7-dithia-2,4,6,8-tetraazabicyclo[3.3.0]octane 3,3,7,7-Tetraoxide

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Abstract—Condensation of *N*,*N*′-dimethylsulfamide with glyoxal gave 2,4,6,8-tetramethyl-3,7-dithia-2,4,6,8-tetraazabicyclo[3.3.0]octane 3,3,7,7-tetraoxide, a sulfur-containing analog of 2,4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (Mebicar). The product structure was studied by X-ray analysis.

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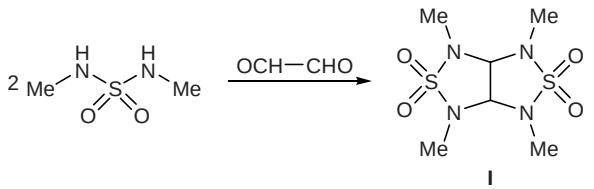
Glycolurils (2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones) exhibit a broad spectrum of biological activity [1–4]; in particular, they constitute a new class of neurotropic agents [1], while 2,4,6,8-tetramethylglycoluril (Mebicar) is used in medical practice as minor (daytime) tranquilizer [2]. In addition, compounds containing a sulfamide moiety show anticonvulsant, hypoglycemic, diuretic, and herbicidal activity [5–8].

The goal of the present work was to synthesize 2,4,6,8-tetramethyl-3,7-dithia-2,4,6,8-tetraazabicyclo-[3.3.0]octane 3,3,7,7-tetraoxide (**I**), a sulfur-containing analog of Mebicar, and to examine its structure. Mebicar is prepared by condensation of *N*,*N*′-dimethylurea with glyoxal in 70% aqueous methanol or water in the presence of hydrochloric acid (pH 1–2) at 90–95°C (yield 61 [9] or 80–85% [10]). We previously showed [11, 12] that the condensation of glyoxal [as 2,2′-bi(4,5-dihydroxy-1,3-dioxolane)] with *N*,*N*′-dialkylsulfamides in concentrated (~36%) hydrochloric acid gives 3,3′-bi(6,8-dialkyl-2,4-dioxa-7-thia-6,8-diazabicyclo[3.3.0]octane 7,7-dioxides) in high yield. Therefore, we examined the effects of pH (1–9), temperature (20–90°C), and reaction time (1–24 h) on the yield of compound **I** in the reaction of *N*,*N*′-dimethylsulfamide with glyoxal in water (Table 1). Under the conditions ensuring formation of glycolurils (pH 1–2, 80–90°C), 3,7-dithia-2,4,6,8-tetraazabicyclo[3.3.0]-octane 3,3,7,7-tetraoxide (**I**) was obtained in 10–13% yield. The yield increased to 23–25% when the reaction was carried out at pH 4–5 (50°C, 4–5 h). Further raising the pH value, temperature, or reaction time did not improve the yield of **I**. Presumably, the reason is steric and electronic effects of the sulfonyl group. In all cases, the reaction mixture contained unreacted *N*,*N*′-dimethylsulfamide.



I

In the ^{1}H NMR spectrum of **I**, protons of the methyl groups resonated at δ 2.90 ppm, and signals from protons in the bridgehead positions appeared at δ 5.09 ppm, i.e. in a weaker field as compared to the corresponding signals of Mebicar (δ 2.81 and 5.05 ppm, respectively).

Table 1. Reaction conditions and yields of compound **I**

pH	Temperature, °C	Reaction time, h	Yield, %
1	90	1	10
1–2	80	3	13
4–5	80	4	14
4–5	50	4	23
4–5	50	5	23–25
4–5	50	7	18
4–5	20	24	0
7	50	5	10
9	50	5	10

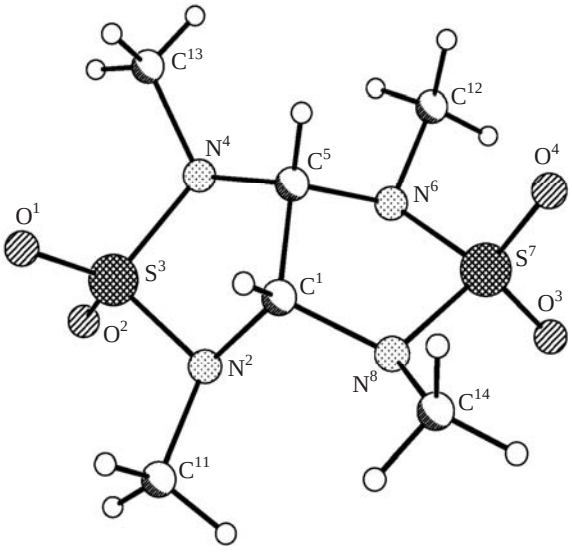
Table 2. Bond lengths *d* in the molecule of 2,4,6,8-tetramethyl-3,7-dithia-2,4,6,8-tetraazabicyclo[3.3.0]octane 3,3,7,7-tetraoxide (**I**)

Bond	*d*, Å	Bond	*d*, Å
C^1–N^8	1.452(4)	O^4–S^7	1.433(2)
C^1–N^2	1.467(4)	N^4–C^5	1.460(4)
C^1–C^5	1.536(4)	N^4–C^{10}	1.467(4)
O^1–S^3	1.427(2)	C^5–N^6	1.465(4)
O^2–S^3	1.429(2)	N^6–C^{11}	1.476(4)
N^2–C^9	1.482(4)	N^6–S^7	1.645(3)
N^2–S^3	1.642(3)	S^7–N^8	1.655(3)
S^3–N^4	1.656(3)	N^8–C^{12}	1.472(4)
O^3–S^7	1.430(2)		

An analogous pattern was observed in the ^{13}C NMR spectrum of **I**: it contained signals at δ_C 32.5 (CH_3) and 75.5 ppm (CH) against δ_C 30.0 and 71.5 ppm, respectively, for Mebicar.

As follows from the mass spectrum, compound **I** is considerably less stable than Mebicar under electron impact. The main ion peaks in the spectrum of **I**, including the molecular ion peak, had low intensity.

Taking into account that the geometric parameters of glycoluril molecules are determined primarily by conjugation between the carbonyl groups and unshared electron pairs on the nitrogen atoms and that sulfamide molecule lacks conjugation between the nitrogen unshared electron pair and sulfonyl group because of steric and electronic factors [13], the structure of compound **I** was studied by X-ray analysis. The results showed (see figure and Tables 2, 3) that, unlike glycolurils, all nitrogen atoms in molecule **I** have pyramidal configuration; they deviate by 0.36–0.42 Å from the plane formed by the substituents. The pyramidal configuration of the nitrogen atom is responsible for considerable deviation of the five-membered rings from planar structure. The tetrahydroimidazole rings in glycolurils usually adopt a flattened *envelope* conformation where the nitrogen atoms or bridgehead carbon atom deviate by 0.05–0.11 Å from the mean-square plane [14, 15]; the corresponding deviations in molecule **I** reach 0.58 Å for N^6 and 0.61 Å for N^2.



Structure of the molecule of 2,4,6,8-tetramethyl-3,7-dithia-2,4,6,8-tetraazabicyclo[3.3.0]octane 3,3,7,7-tetraoxide (**I**) according to the X-ray diffraction data.

Surprisingly, formally equivalent endocyclic S–N and N–C bonds in both five-membered rings of molecule **I** turned out to have different lengths. The S^3–N^4 and S^7–N^8 bonds are longer by 0.01 Å than the S^3–N^2 and S^7–N^6 bonds, whereas the C^5–N^4 and C^1–N^8 bonds are shorter by 0.005–0.015 Å than the C^5–N^6 and C^1–N^2 bonds. Presumably, the observed difference in the bond lengths results from stereoelectronic interactions between the unshared electron pair on the nitrogen atom (*n*) with the antibonding orbital of the S–O bond (*n*-σ* interaction). In fact, shortening of the S–N bond is typical of antiperiplanar orientation of the *n* orbital with respect to the S^3–O^1 and S^7–O^4 bonds with pseudotorsional angles of 171 and 168° for the N^2 and N^6 atoms, respectively. Although such interactions should also lead to change of the S–O bond lengths, no difference between the latter is observed within experimental error. Invariance of the S–O bonds to anomeric interactions is a general characteristic of Period III elements; it can also be determined in part by the crystal lattice effect. In the crystalline structure of compound **I**, all S–O bonds are involved in fairly strong interactions C–H···O, the shortest H···O distance being 2.28 Å for the hydrogen atom on C^5. Thus, apart from steric repulsion, the conformation of molecule **I** is determined by stereoelectronic interactions *n*(N)–σ*(S–O).

It is known that 2,4,6,8-tetraalkylglycolurils are readily soluble in water and organic solvents [16]. The solubility of compound **I** in water at 19°C is 0.13%, i.e., it is lower by a factor of more than 400 than the solubility of Mebicar at the same temperature (54.7%). The solubilities of **I** in chloroform (0.28%) and methylene chloride (0.97%) are also considerably lower than those reported for Mebicar (9.05 and 25.15%, respectively) [16].

Glycolurils are fairly stable to acid hydrolysis. Complete hydrolysis of Mebicar requires heating in

boiling 25% sulfuric acid over a period of 51 h [17]. Under analogous conditions, compound **I** (0.5 M solution) was completely hydrolyzed in 3 h. The rate of hydrolysis and the composition of the hydrolysis products were studied by thin-layer chromatography. The main hydrolysis products of Mebicar are *N*,*N*′-dimethylurea and 1,3-dimethylhydantoin [17]. The hydrolysis of **I** gives *N*,*N*′-dimethylsulfamide as the major product. The observed differences in the properties of compound **I** and Mebicar give no grounds to expect complete analogy in their physiological activity.

EXPERIMENTAL

The NMR spectra were recorded on Bruker AM-250 (^{1}H, 250 MHz) and Bruker AM-300 spectrometers (^{13}C, 75.5 MHz) using acetone-d_6 as solvent; the chemical shifts were measured relative to tetramethylsilane as internal reference. The IR spectra were obtained in KBr on a Specord M82 spectrometer. The mass spectrum (electron impact, 70 eV) was run on a Kratos MS-30 instrument. The melting point was determined using a Sanyo Gallenkamp apparatus. *N*,*N*′-Dimethylsulfamide was synthesized according to the procedure described in [18]. Thin-layer chromatography was performed on Silufol UV-254 plates using chloroform–methanol (9:1) as eluent. The solubilities were determined as described in [19].

2,4,6,8-Tetramethyl-3,7-dithia-2,4,6,8-tetraazabicyclo[3.3.0]octane 3,3,7,7-tetraoxide (I). A solution of 2.48 g (0.02 mol) of *N*,*N*′-dimethylsulfamide in 1.5 ml of water was added to 1.15 ml (0.01 mol) of a 40% aqueous solution of glyoxal (d = 1.2650); if necessary, the mixture was adjusted to pH 4–5 and was heated for 5 h at 45–50°C. The mixture was cooled, and the precipitate was filtered off and recrystallized from dioxane. Yield 0.59–0.68 g (22–25%), mp 221–222°C. IR spectrum, ν, cm^{-1}: 1150, 1310 (SO_2); 2945, 2998 (C–H). ^{1}H NMR spectrum, δ, ppm: 2.90 s (12H, Me), 5.09 s (2H, CH). ^{13}C NMR spectrum, δ_C, ppm: 32.5 (Me), 75.5 (CH). Mass spectrum, m/z (I_{rel}, %): 270 (1.2) $[M]^+$, 178 (1.7), 148 (6.0), 83 (50.3), 72 (100). Found, %: C 26.69; H 5.19; N 20.77; S 23.75. $C_6H_{14}N_4O_4S_2$. Calculated, %: C 26.66; H 5.22; N 20.73; S 23.72.

X-Ray diffraction data for compound I. Colorless crystals (single crystals suitable for X-ray analysis were obtained by crystallization from dioxane at room temperature). Monoclinic crystal system, space group $P2_1/c$; unit cell parameters (120 K): a = 14.893(6), b = 8.560(4), c = 9.097(2) Å; β = 103.94(4)°; V = 1125.5(8) Å^3; Z = 4; d_{calc} = 1.595 g/cm^3; μ(MoK_α) = 4.8 cm^{-1}; F(000) = 568. Intensities of 6575 reflections were measured at 120 K on a Smart 1000-CCD diffractometer, λ(MoK_α) 0.71072 Å, ω scanning, 2θ < 58°; 2951 independent reflections (R_{int} = 0.0496) were used in the structure refinement. The structure was solved by the direct method, followed by successive electron density syntheses. All hydrogen atoms were localized by difference syntheses of electron density. The positions of non-hydrogen atoms were refined with respect to F_{hkl}^2 in anisotropic approximation; the positions of hydrogen atoms were refined in isotropic approximation using the riding model. The final divergence factors were R_1 = 0.0504 [F_{hkl}; from 2951 reflections with $I > 2\sigma(I)$] and wR_2 = 0.1022; number of refined parameters 149, goodness of fit 1.003. All calculations were performed using SHELXTL 5.10 software package.

Table 3. Bond angles ω in the molecule of 2,4,6,8-tetramethyl-3,7-dithia-2,4,6,8-tetraazabicyclo[3.3.0]octane 3,3,7,7-tetraoxide (**I**)

Angle	ω, deg	Angle	ω, deg
$N^8C^1C^5$	108.7(2)	$N^2S^3N^4$	94.07(13)
$N^2C^1C^5$	103.9(2)	$C^5N^4C^{10}$	116.7(3)
$C^1N^2C^9$	115.9(2)	$C^5N^4S^3$	109.9(2)
$C^1N^2S^3$	107.30(19)	$C^{10}N^4S^3$	114.0(2)
$C^9N^2S^3$	114.7(2)	$N^4C^5N^6$	110.9(2)
$O^1S^3O^2$	115.35(13)	$N^4C^5C^1$	108.2(2)
$O^1S^3N^2$	113.59(13)	$N^6C^5C^1$	103.7(2)
$O^2S^3N^2$	109.84(13)	$C^5N^6C^{11}$	115.2(2)
$O^1S^3N^4$	110.65(14)	$C^5N^6S^7$	107.96(19)
$O^2S^3N^4$	111.41(14)	$C^{11}N^6S^7$	113.8(2)
$O^3S^7O^4$	115.93(14)	$N^6S^7N^8$	94.12(13)
$O^3S^7N^6$	110.01(13)	$C^1N^8C^{12}$	118.5(3)
$O^4S^7N^6$	112.36(13)	$C^1N^8S^7$	110.2(2)
$O^3S^7N^8$	111.18(13)	$C^{12}N^8S^7$	114.3(2)
$O^4S^7N^8$	111.18(13)		

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