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PHASE-TRANSFER CATALYTIC SYNTHESIS AND HYPOCHOLESTEROLEMIC ACTIVITY OF THIAZINO[3,2-*a*]BENZIMIDAZOLE AND ITS SILICON ANALOG

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The reaction of 2-mercaptobenzimidazole with 1,3-dichloropropane or bis(chloromethyl)dimethylsilane in the two-phase catalytic system of solid K_2CO_3 – 18-crown-6 – toluene at 111°C leads to a selective formation of tricyclic benzimidazole sulfides in 56 and 92% yields. The synthesized compounds were tested as hypocholesterolemic agents.

Keywords: thiazino[3,2-*a*]benzimidazole, hypocholesterolemic activity, phase-transfer catalysis.

Thiazolobenzimidazoles and similar tricyclic benzimidazole sulfides show high biological effectiveness [1]; in fact showing vasodilator [2], antihypertensive [3-5], anti-inflammatory [6, 7], antiulcer [8-10], and antimicrobial [11-13] activity. The high cholesterol-lowering activity of aromatic silicon-containing sulfides of the types $HetS(CH_2)_nSiR_3$ (n = 1,3) and $HetSCH_2Si(Me_2)CH_2SHet$ has been shown in some patents and articles [14-19].

The synthesis of thiazolobenzimidazoles and related heterocyclic systems has been presented in detail in the review [1]. A first method is based on the synthesis of thiazolo[3,2-*a*]benzimidazoles and thiazino(3,2-*a*]benzimidazoles *via* the reaction of 2-mercaptobenzimidazoles with α-halocarbonyl compounds [20]. A second method is the reaction of 2-mercaptobenzimidazole (or 2,3-dihydrobenzimidazole-2-thione) with α,ω-dihaloalkanes in the systems $NaHCO_3$ – KI – 2-PrOH [21], EtOH – DMF – $NaHCO_3$ [22], Na – ether [23], or NaOH – H_2O – PhH – cetyltributylammonium bromide [24]. However, in many examples the product yields and reaction selectivity were quite low.

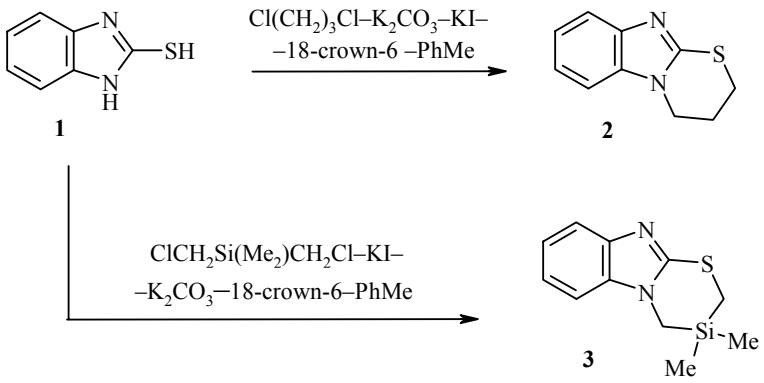

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TABLE 1. Basic Bond Lengths (l) and Valence Angles (ω) in the Structure of Molecule 3

Bond	*l*, (Å)	Valence angle	ω, deg.
S(1)–C(2)	1.804(4)	C(2)–S(1)–C(6)	105.6(2)
S(1)–C(6)	1.740(3)	S(1)–C(2)–Si(3)	112.2(2)
Si(3)–C(2)	1.863(3)	C(2)–Si(3)–C(4)	103.2(2)
Si(3)–C(4)	1.875(3)	Si(3)–C(4)–N(5)	114.3(2)
N(5)–C(4)	1.471(3)	C(4)–N(5)–C(6)	130.0(2)
N(5)–C(6)	1.372(3)	C(4)–N(5)–C(13)	124.2(2)
N(5)–C(13)	1.382(4)	N(5)–C(6)–S(1)	128.0(2)
N(7)–C(6)	1.322(4)	N(5)–C(6)–N(7)	113.2(3)
N(7)–C(8)	1.375(4)	C(6)–N(7)–C(8)	104.8(2)

We have developed a phase-transfer catalytic method for the synthesis of thiazino[3,2-*a*]benzimidazole (**2**) and its sila analog **3** in the system 1,3-dichloropropane or bis(chloromethyl)dimethylsilane – solid K_2CO_3 – solid KI – 18-crown-6 – toluene at high dilution. Under these conditions the products **2** and **3** were separated in 56 and 92% yields respectively.

With the aim of objective establishing the structure of compound **3** we carried out an X-ray crystallographic study of the crystals. Figure 1 shows the spatial model and atomic numbering for the molecule **3**. The basic bond length and valence angle values in the molecule are given in Table 1.

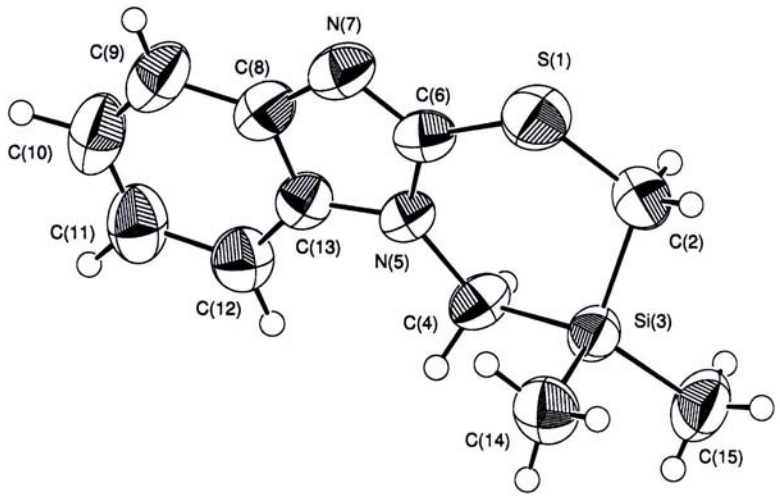

Fig. 1. Structure of the 3,3-dimethyl-3,4-dihydro-2H-1-thia-4a,9-diaza-3-silafluorene (**3**) with atomic numbering and thermal vibrational ellipsoids.

The molecule consists of three condensed rings, of which the benzene and imidazole rings are planar but the 1-thia-5-aza-3-sila-cylcohexane system has a near to *twist* conformation. The values of the torsional angles which characterize this ring conformation are given in Table 2.

The projection of the crystal structure on the crystal plane *yz* is given in Fig. 2. The molecules are associated in the crystal as centrosymmetric dimers *via* weak π-π interaction. The distance between the mean planes of the interacting molecules is 3.815(5) Å. The comparatively loose packing of the **3** molecule is due to relatively low density of the substance (1.217 g/cm^3).

TABLE 2. Some Torsional Angles Values (δ) in the Molecule 3

Torsional angle	δ, deg
S(1)–C(2)–Si(3)–C(4)	56.4(2)
C(2)–Si(3)–C(4)–N(5)	-44.2(2)
Si(3)–C(4)–N(5)–C(6)	21.9(2)
C(4)–N(5)–C(6)–S(1)	-6.8(2)
N(5)–C(6)–S(1)–C(2)	17.5(2)
C(6)–S(1)–C(2)–Si(3)	-43.7(2)

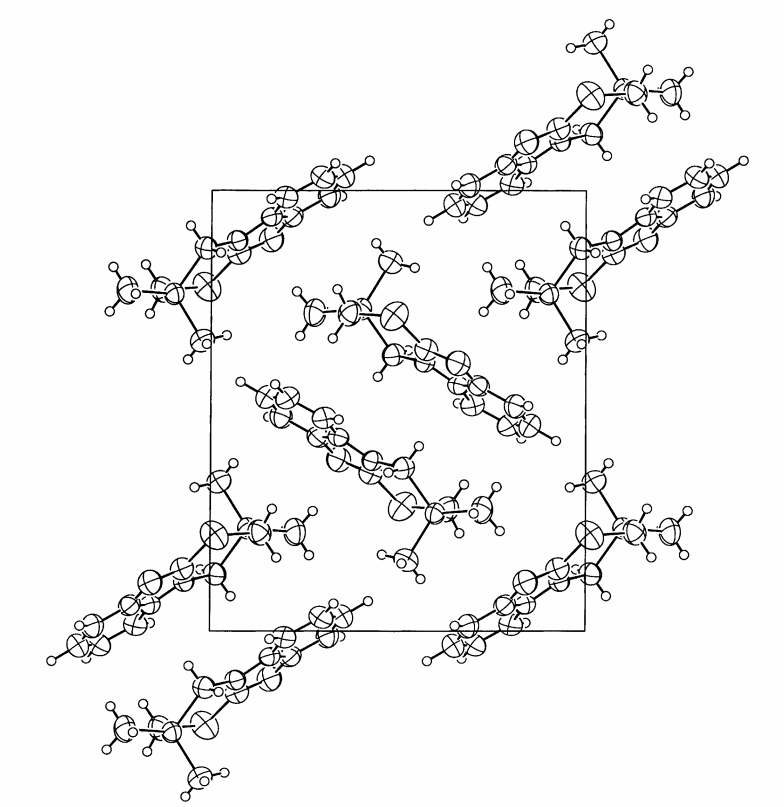

Fig. 2. Projection of the crystal structure of compound **3** along the [1 0 0] direction.

TABLE 3. Cholesterolemic Activity of Compounds **2** and **3** in the Dietary Hypercholsterolemia Model (M±m)

Compound	Cholesterol, mg/dl*			
	Overall	HDL	LDL	K
Cholesterol control	143.2 ± 12.9**	99.8 ± 5.4	43.4 ± 13.4	0.448 ± 0.155***
2	121.2 ± 16.8	106.8 ± 14.2	14.4 ± 4.5	0.135 ± 0.033***
3	124.0 ± 17.9	101.9 ± 13.4	22.1 ± 6.3	0.213 ± 0.051***
Control (standard diet)	98.5 ± 2.3	96.2 ± 2.6	2.3 ± 0.8	0.024 ± 0.007

* HDL is high density lipoprotein, LDL low density lipoprotein, and K the atherosclerosis index (K = HDL/LDL).

** Differences relative to statistical confidence control at $P < 0.05$.

*** Differences relative to statistical confidence control at $P < 0.01$.

TABLE 4. Crystallographic Data for Compound 3

Empirical formula	$C_{10}H_{14}N_2SSi$
M_r	222.386
Crystal symmetry	Monoclinic
Space group	$P\,2_1/c$
Unit cell parameters	
a, Å	6.7001(2)
b, Å	12.4130(4)
c, Å	15.2739(6)
β,deg	107.132(1)
V, Å^3	1213.94(7)
Z	4
Crystal density, d, g/cm^3	1.217
μ, mm^{-1}	0.33
Number of independent reflections	2946
Number of reflections with $I > 3\sigma(I)$	1927
Number of refinement parameters	192
Final difference factor R	0.046
Program used	SIR97 [27], maXus [28]

The compounds synthesized were tested as hypocholesterolemic agents. Compound **2** and its silicon analog **3** were introduced into mice diet orally. It was found that both compounds **2** and **3** have weak activity. The thiazino[3,2-*a*]benzimidazole (**2**) (LD_{50} > 2000 mg/kg) has a better atherosclerosis index (K = 0.135±0.033). The 3,3-dimethyl-3,4-dihydro-2H-1-thia-4a,9-diaza-3-silafluorene (**3**) (LD_{50} = 1055 mg/kg) shows an atherosclerosis index of K = 0.213±0.051.

EXPERIMENTAL

Thiazino[3,2-*a*]benzimidazole (2). 2-Mercaptobenzimidazole (**1**) (2.25 g, 15 mmol), solid K_2CO_3 (8.28 g, 60 mmol), and solid KI (9.96 g, 60 mmol) were added to a solution of 1,3-dichloropropane (1.42 ml , 15 mmol) and 18-crown-6 (0.39 g, 1.5 mmol) in toluene (250 ml). The mixture was refluxed with vigorous stirring for 10 h, filtered through a thin layer of silica gel, and the toluene was evaporated on a rotary evaporator. The product **2** was separated by column chromatography using toluene–ethyl acetate (1 : 1) as eluent. The spectroscopic properties of compound **2** agreed with those given in the study [25]. Yield 1.59 g (56%), mp 137-138°C.

The synthesis and spectroscopic properties of 3,3-dimethyl-3,4-dihydro-2H-1-thia-4a,9-diaza-3-silafluorene (**3**) are given in the study [26].

A monocrystal of compound **3** of size 0.23×0.25×0.32 mm was obtained by crystallization from a mixture of petroleum ether and ethyl acetate. The X-ray analysis was performed on a Nonius KappaCCD automatic diffractometer to $2\theta_{max} = 55°$ ($\lambda_{Mo} = 0.71073$ Å). The basic crystallographic parameters for compound **3** and also the refinement parameters for the structure are given in Table 4.

Cholesterol-lowering activity and toxicity were determined by the methods given in the article [16].

All of the animal experiments were carried out according to the Animal Ethical Committee of BaltLASA (Riga, Latvia).

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