Functionalized 4-methyl-5-phenylthiazole and 1,3-bis(4′-methyl-5′-phenylthiazol-2′-yl)benzene. Approaching thiazole macrocycles

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Dedicated to Professor Alexander Konovalov on his 70th birthday

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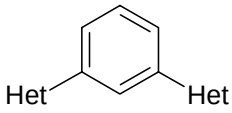
Abstract

The methods of preparation of functionalized 4-methyl-5-phenylthiazoles (**4**), (**5**), (**6**), (**7**), (**8**) and 1,3-bis(4′-methyl-5′-phenylthiazol-2′-yl)benzenes (**10**), (**12**), (**13**), (**14**), (**15**) and 1^5,3^5,8^5,10^5-tetraphenyl-5,6,12,13-tetrathia-1,3,10(2,4),8(4,2)-tetrathiazola-2,9(1,3)-dibenzenacyclotetradecaphane (20) are developed. The homolytic reactions of compounds, containing the fragment CH_2–S (**6**), (**7**), (**8**), (**14**), (**15**) and (**20**) are considered. Under thermolysis of 1,3-bis(4′-mercaptomethyl-5′-phenylthiazol-2′-yl)benzene (**15**) the formation of macrocyle (**32**) take place.

Keywords: Thiazoles, bisthiazoles, functionalization, macrocycles, homolytic reactions, Hantzsch reaction, X-Ray diffraction analysis

Introduction

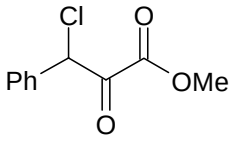
Design and development of methods for synthesis of macrocyclic ligands, containing nitrogen heterocycles, aimed at building the systems of molecular recognition and efficient catalytic systems, attract great attention.[1] Another cause of interest to these structures is the possibility of design on their basis such macrocycles and related 1,3-dihetarylbenzenes **1** of mono- and binuclear metal complexes, related to non-heme metalloproteines.[2] There are several examples of macrocycles, synthesized just for binuclear comlexation.[3] Some of them include biologically active imidazole rings.



1

Het = thienyls,[4] pyrazoles,[5] imidazoles,[6] thiazoles,[7] 1,3,4-oxadiazoles,[8] 1,3,4-thiadiazoles,[9] 1,2,4-triazoles,[10] benzoxazoles,[11] indoles,[12] benzimidazoles,[13] 1,2,4-triazolo[3,2-]isoindoles,[14] 1,2,4-triazolo[3,2-c]quinozaline,[15] 10,10′-arylenebis(7*H*-benzo[*de*]-1,2,4-triazolo-[5,1-*a*]isoquinoline-7-ones.[14]

The presence of rigidly oriented heterocyclic fragments in meta-positions of benzene ring makes 1,3-dihetarylbenzenes 1 rather attractive both as bidentate chelating agents and macrocycle precursors. If heterocyclic nuclei of compounds 1 contain appropriate easily transforming functional groups, they can be used for constructing various types of heteromacrocyclic systems. On the other hand, chloropyruvate 2 is considered to present rather valuable precursor for the synthesis of different functionalized heterocyclic systems including thiazoles.[16]



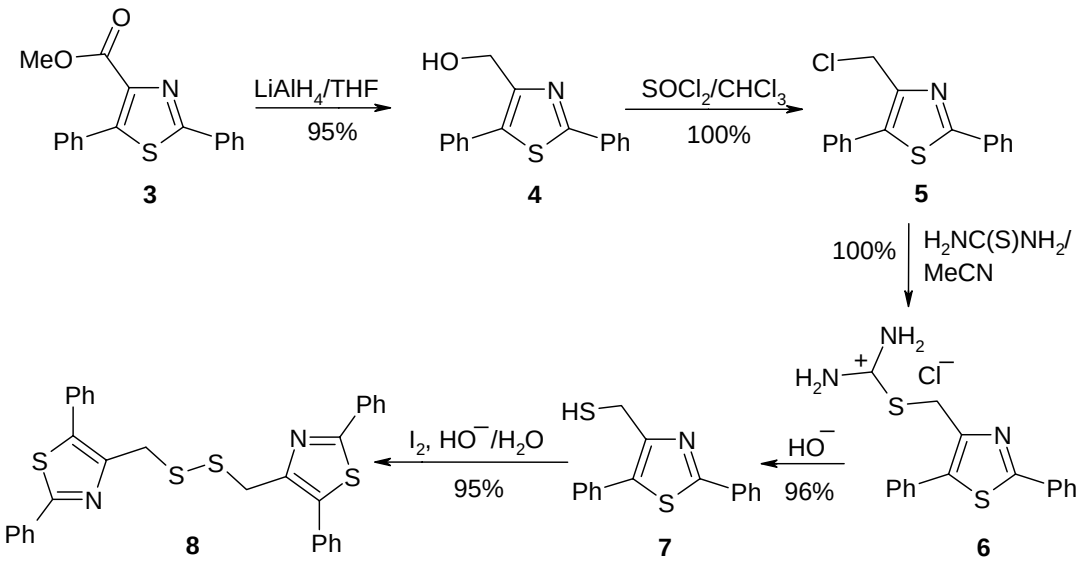
2

Functionalized thiazoles are a good basis for planning the synthesis of thiazole-containing chelating agents, macrocycle precursors like compound **1** and macrocycles from them. Such structures are of interest for organic chemists and biochemists.[17] The use of side-chain functionalized thiazoles, which can be obtained on the basis of the mentioned functionalized thiazoles opens up additional possibilities.

The task of this work is to clear up the possibility of transformation of 2,5-diphenyl-4-methoxycarbonylthiazole into 2,5-diphenylthiazoles, bearing different functional groups in 4-methyl substitute. The expansion of this strategy over bisthiazole – 1,3-bis(4′-methoxycarbonyl-5′-phenylthiazol-2′-yl)benzene **10** gave hope to get bifunctionalized in 4-methyl groups bisthiazoles, presenting potential precursors of thiazole-containing macrocycle precursors and macrocycles. Bis(4-mercaptomethyl)thiazole, the macrocycle precursor with not less than two types of binding sites, being the reduced form of thiol-sulfide redox system with thiazole-containing disulfide macrocycle (or macrocycles) or disulfide oligomers as the oxidized form, would be of special interest in this group.

Results and Discussion

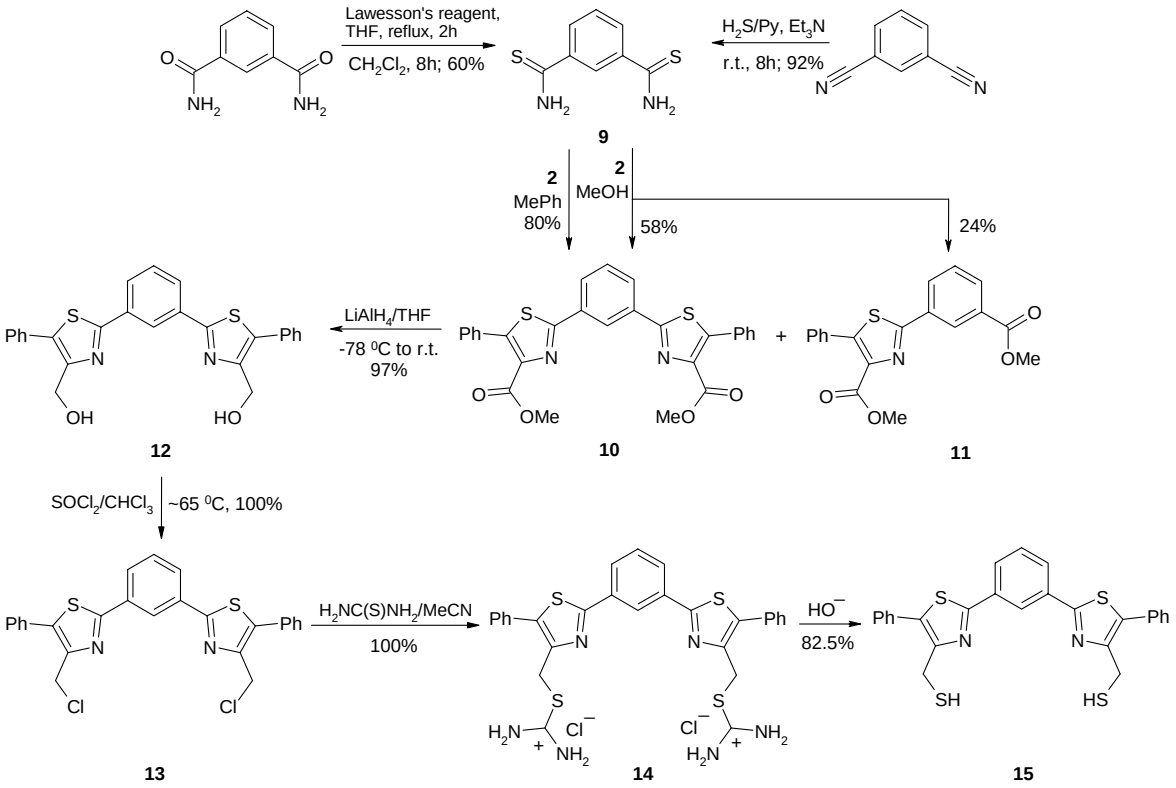
The successive transformation of ester **3** into functionalized at methyl group 4-methyl-2,5-diphenylthiazoles – **4** (alcohol), **5** (chloro), **6** (amidiniummercapto), **7** (thiol) and **8** (disulfide) was realized with almost quantitative yields (Scheme 1), what gives a good opportunity of using thus formed functional groups in the synthesis of various new mono- and polycyclic derivatives of thiazole.



Scheme 1

The transformations presented in scheme 1 are the model ones for the development of the synthesis of bis-thiazoles chelating agents and macrocycle precursors, bearing functional groups 4–CH_2OH, 4–CH_2Cl, 4–$CH_2S(NH_2)_2^+$, 4–CH_2SH in any thiazole cycle, and, since, fit for the construction of several types of macrocycles.

We realized this possibility (scheme 2) starting from thioisophthalamide **9**, which Hantzsch condensation with chloropyruvate **2** results in the formation of 1,3-bis[2-(4-carbmethoxy-5-phenyl)thiazolyl]benzene **10**. If to perform the condensation in MeOH, then under the action of HCl and H_2O, isolated in the Hantzsch reaction, partial methanolysis and dethionation of one thioamide group proceeds, and compound **11** is secondary formed. The reaction similar direction was not observed at the condensation of chloropiruvate **2** with thiobenzamide in EtOH.[16c] Further transformations of diester **10** into diol **12**, dichloride **13**, bisdiamidiniummercapto compound **14**, and dithiol **15** proceed smoothly and with almost quantitative yields.



Scheme 2

To control the structure of the formed products diole **12** was investigated with X-ray diffraction analysis. The compound crystallizes in the space group P-1 with two independent molecules of **12** and solvate THF and H_2O molecules. Figure 1 shows that the molecules are non-planar, the selected bond lengths and angles are presented in Table 1.

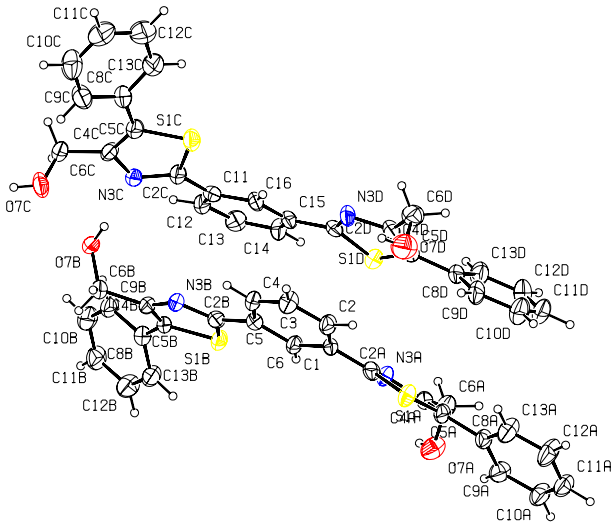


Figure 1. ORTEP plot of two independent molecules in crystal of **12**.
(THF and H_2O solvate molecules are omitted)

Table 1. Selected bond lengths [Å], angles [°] and torsion angles [°] for **12**

S1A-C2A	1.714(7)	S1C-C5C	1.740(8)
S1A-C5A	1.706(7)	S1C-C2C	1.709(7)
S1B-C2B	1.725(7)	S1D-C2D	1.722(7)
S1B-C5B	1.713(7)	S1D-C5D	1.707(8)
C1-C2A	1.466(9)	C2C-C11	1.463(9)
C2B-C5	1.464(10)	C2D-C15	1.473(10)
N3A-C2A	1.337(9)	N3C-C2C	1.328(9)
N3A-C4A	1.370(10)	N3C-C4C	1.406(9)
N3B-C4B	1.361(9)	N3D-C4D	1.384(10)
N3B-C2B	1.329(9)	N3D-C2D	1.293(9)
C4B-C5B	1.369(9)	C4C-C5C	1.353(11)
C4A-C5A	1.378(11)	C4D-C5D	1.371(12)
O7A-C6A	1.434(10)	O7C-C6C	1.433(11)
O7B-C6B	1.427(8)	O7D-C6D	1.436(12)
C2A-S1A-C5A	91.0(3)	C2C-S1C-C5C	90.9(4)
C2B-S1B-C5B	90.0(3)	C2D-S1D-C5D	89.9(4)
C2A-N3A-C4A	110.9(6)	C2C-N3C-C4C	110.7(6)
C2B-N3B-C4B	110.7(6)	C2D-N3D-C4D	111.4(7)
O7A-C6A-C4A	111.1(7)	O7C-C6C-C4C	108.5(7)
O7B-C6B-C4B	113.4(6)	O7D-C6D-C4D	112.2(7)
N3B-C4B-C5B	116.0(6)	N3C-C4C-C5C	115.6(6)
N3A-C4A-C5A	115.5(6)	N3D-C4D-C5D	114.4(7)
S1B-C5B-C4B	109.5(5)	S1D-C5D-C4D	109.8(6)
S1A-C5A-C4A	109.2(5)	S1C-C5C-C4C	109.0(5)
S1A-C2A-N3A	113.4(5)	S1D-C2D-N3D	114.4(5)
S1B-C2B-N3B	113.8(5)	S1C-C2C-N3C	113.8(5)
S1A-C5A-C8A-C13A	-34.4(10)	S1C-C5C-C8C-C13C	23.7(10)
S1B-C5B-C8B-C13B	36.1(10)	S1D-C5D-C8D-C13D	38.1(10)
C2-C1-C2A-S1A	29.4(9)	S1C-C2C-C11-C16	27.1(9)
S1B-C2B-C5-C6	-6.2(10)	S1D-C2D-C15-C14	-10.1(10)
N3A-C4A-C6A-O7A	-94.5(7)	N3D-C4D-C6D-O7D	88.7(9)
N3B-C4B-C6B-O7B	99.7(7)	N3C-C4C-C6C-O7C	96.2(7)
C6-C1-C2A-S1A	-151.5(6)	S1D-C2D-C15-C16	169.4(6)

It should be noted that the molecules of **12** have non-crystallographic two-fold symmetry but loses it in crystal not only owing to deviations of six- and five-membered rings planes from the plane of central rings of molecule, but due to different positions (orientation) of hydroxyl groups from plane of the molecule, as can be seen from the picture of docking two independent molecules in Figure 2.

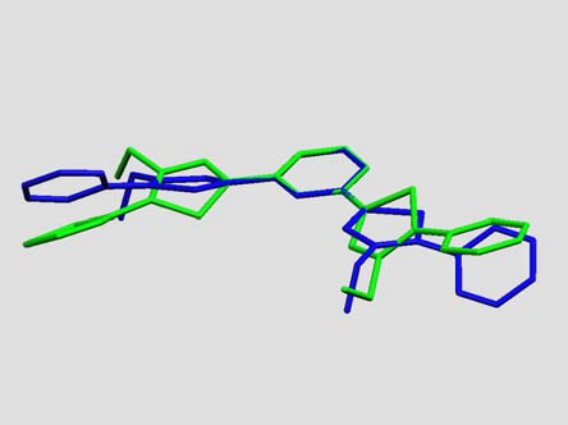


Figure 2. View of docking of two independent molecules of **12;** hydrogen atoms and solvent molecules are omitted; blue – molecule B (central ring numbering C11-C16), green – molecule A (central ring numbering C1-C6 on Figure.1).

Two independent molecules are stacked over each other with a little shift so π - π interactions are observed between phenyl, thiazole, central phenylene rings of first molecule (B) and thiazole, central phenylene and thiazole rings of second molecule (A) respectively, with the shortest distance between interacting planes equal to 3.42(1)Å

Analysis of the crystal packing of **12** showed that from the viewpoint of intermolecular interactions two independent molecules are in a nonequivalent local environment. The corresponding packing diagram, which shows intermolecular interactions, is presented in Figure 3. Hydrogen-bonds parameters are listed in Table 2. The strong O-H…O and O-H…N interactions combine two independent molecules A and B into centrosymmetric tetramers, which are, in turn, combined into continuous layers along [111] crystallographic direction due to another O-H..O contacts between molecules A. The later contacts unite two molecules A into centrosymmetric dimers.

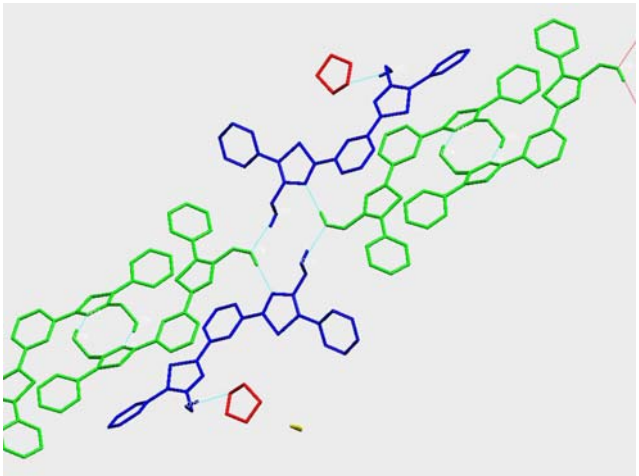


Figure 3. Intermolecular interactions in the crystal of **12**. Color map: green – molecule A, blue – molecule B, red – THF, yellow – H_2O. Hydrogen atoms not participating in hydrogen bonding are omitted.

Table 2. Hydrogen-bonds for **12** [Å and deg.]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O7B-H7B...N3C (0)	0.82	2.02	2.839(8)	176
O7D-H7D...O50 (0)	0.82	2.12	2.919(17)	165
C2-H2...S1A (0)	0.93	2.85	3.186(7)	103
C6-H6...S1B (0)	0.93	2.70	3.116(8)	108
C9A-H9A...O7A (0)	0.93	2.50	3.301(9)	145
C9B-H9B...O7B (0)	0.93	2.50	3.292(9)	143
C13A-H13A...S1A (0)	0.93	2.82	3.175(9)	104
C13B-H13B...S1B (0)	0.93	2.85	3.167(9)	101
C13C-H13C...S1C (0)	0.93	2.64	3.055(9)	108
C13D-H13D...S1D (0)	0.93	2.83	3.155(10)	102
C14-H14...S1D (0)	0.93	2.70	3.110(9)	108
C16-H16...S1C (0)	0.93	2.77	3.133(7)	104
O7C-H7C...O7B (*)	0.82	1.97	2.770(8)	165
O60-H61...N3B (**)	0.86	2.34	3.096(13)	147
O7A-H7A...N3A (***)	0.82	2.05	2.860(8)	170
C54-H54B...O7C (****)	0.97	2.06	2.918(15)	147

Equivalent positions:
(0) X,Y,Z; (*) -X,-Y-Z; (**) 1+X,Y,Z; (***) 1-X,1-Y,1-Z; (****) 1-X,1-Y,-Z

In contrast the independent molecules, B participates in O-H…O contacts with solvate THF molecules. The solvate H_2O molecules form hydrogen bonds with nitrogen atoms of thiazole rings of molecules A. Packing of the molecules in crystal results in formation of colon-like areas, which are filled by the solvate molecules (Figures 4). Such localization of solvate molecules in crystal can be considered as the pseudochannels, and indicates the existence of selected direction and probably the anisotropy of the crystalline properties.

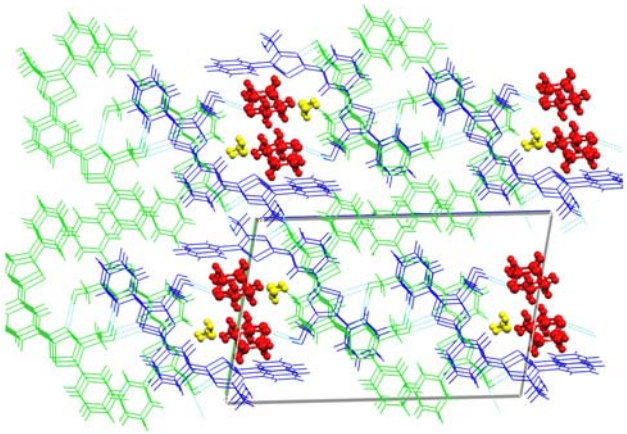
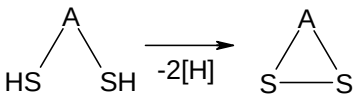


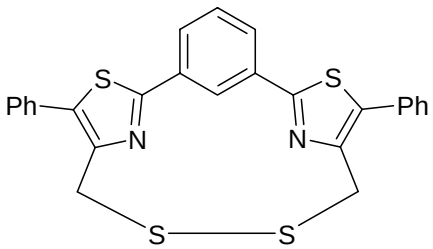
Figure 4. Crystal packing diagram in the crystal of **12**. View along 0a axis. Color map as in Figure 3.

Dithiol **15**, similarly to aliphatic mercaptans, is susceptible to easy oxidation even under the action of the air oxygen, what results in the occurrence of insolvable in chloroform and infusible fraction, evidently presenting the oligomeric disulfide, the product of oxidative polycondensation of thiazolecontaining dithiol **15**. At this dithiol oxidation under the conditions of high dilution one may expect the formation of macrocyclic thiazole-containing disulfides similarly to described for other dithiols HS–A–SH of general formula **16**.[18] However, in contrast to dithiols **16**, used in the above-mentioned works, which interthiol fragment contained rather extensive flexible chains, there are no such chains in our dithiol **15**. Thus, as distinct from the works,[18] the intramolecular oxidative cyclization according to the scheme 3 is problematic for dithiol **15**. Rigidity and rather small value of thizole-containing macrocycle of **17**-type should prevent from free (without geometry distortion) geometrical arrangement of the composing fragments, and, as a consequence, it should be too strained.



16 **17**

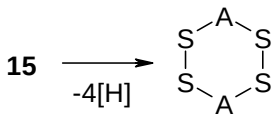
Scheme 3



18

Actually, the quantum-chemical calculations demonstrated that although the geometry of the fragment $–CH_2–S–S–CH_2–$ in macrocycle **18** virtually does not differ from the geometry of dimethyldisulfide, the geometry of dithiazolylphenylene fragment in this macrocycle is distorted substantially compared to the geometry of the same fragment in dithiol **15**. In contrast to absolutely plane aromatic phenylene and two thiazol cycles, in dithiol **15** the mean-root-square deviation from the plane of the same atomic cycles in the macrocyclic thiazole-containing disulfide **18** consists 0.088 and 0.011Å, correspondingly, i.e. the system aromaticity partially decreases. The hydrogen atoms of the macromonodisulfide phenyl fragment deviate noticeably from the planes, formed by the triple of the nearest to them carbon atoms. It is particularly evident for the hydrogen atom at C_2 (the atoms numeration is given here only for the phenylene fragment), displaced inside the macrocycle (11.6° with respect to the plane $C_1–C_2–C_3$). The phenylene fragment bonds with two thiazole cycles deviate notably from the corresponding triples of the carbon atoms (9.2°). All this should result in substantial destabilization of the considered macrocycle.

However, there exists the possibility to realize another direction of dithiols oxidative macrocyclization - with participation of two dithiol molecules according to general scheme 4 with the formation of macrocycles **19** $(AS_2)_2$.



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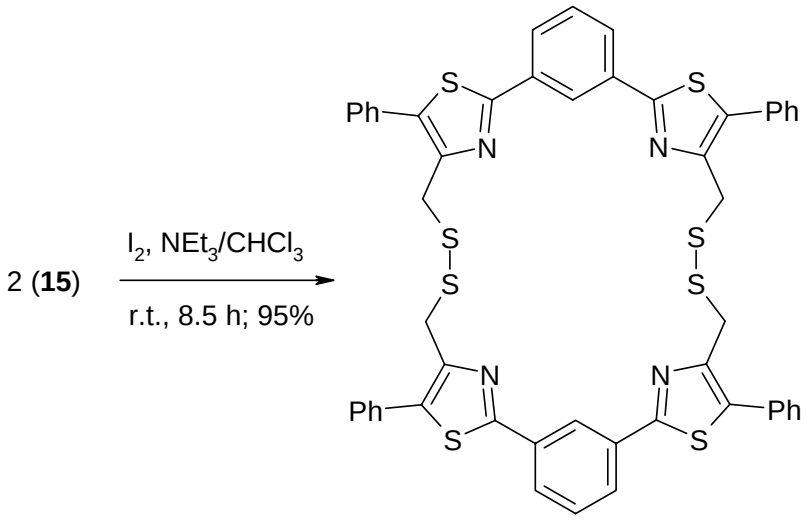
Scheme 4

Quantum-chemical calculations demonstrated, that thiazole-containing macrocycle **20** $(AS_2)_2$, which can be formed according to the general scheme 4 from dithiole **15** (scheme 5), has almost standard geometrical parameters of all its fragments, and so, it is free of strain.

If both macrocycles **18** (AS_2) and **20** $(AS_2)_2$ were not tensioned, the macrocycle **18** formation enthalpy would be half less than that of macrocycle **20**. However, as the calculation demonstrated, the macrocycle **18** formation enthalpy is greater by 12.9 kcal/mol than half of the macrocycle **20** formation enthalpy. This value may serve the measure of compound **18** destabilization. So, at bismercaptane oxidation the macrocycle $(AS_2)_2$ **20** (and, probably, the highest cyclohomologues $(AS_2)_n$, where $n > 2$) formation should be expected, but not macrocycle AS_2 **18.**



20

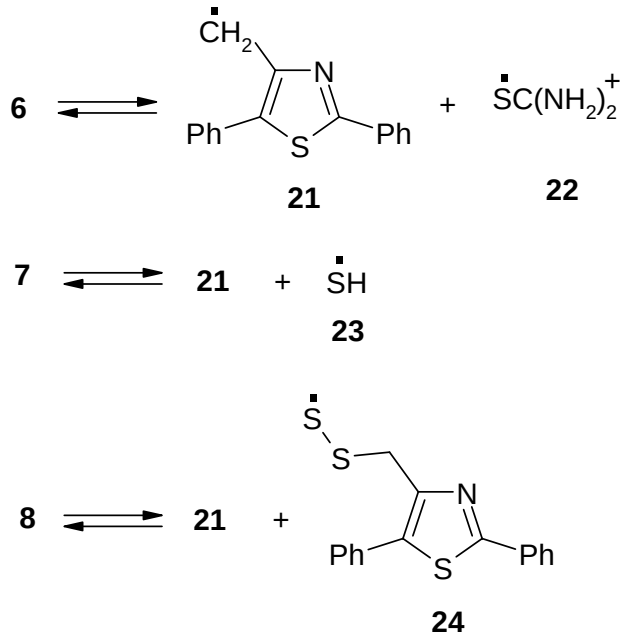
Scheme 5

Actually, at oxidation of thiazole-containing dithiol **15** by iodine under the conditions of high dilution in the presence of the base[18] the dissoluble in organic solvents substance, not containing the group SH in contrast to the initial dithiol **15**, is formed with practically quantitative yield, according to the data of IR and ^{1}H-NMR spectroscopy. Other spectrum parameters of initial and final compounds are practically identical. In MALDI-TOF spectrum of the obtained substance there is a peak corresponding to macrocycle **20** in the value m/z, but the peak, corresponding to macrocycle **18**, is absent.

Interesting results were obtained in the course of mass-spectrometric investigations of the above-described compounds, containing the fragment CH_2–S. In particular, their spectra contain rather intensive peaks with m/z value, substantially exceeding that of molecular peaks of mother compounds.

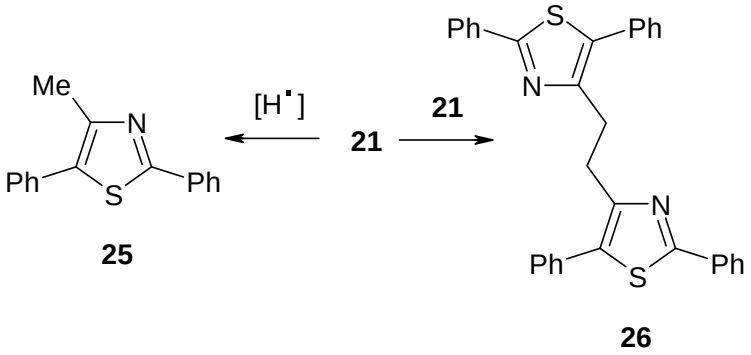
At temperature about 250°C in monothiazoles **6-8** mass-spectra the peaks were fixed, being the evidence of the products of loss by the mother compounds **6-8** the sulfur-containing functional groups in the vapor over these substances; these peaks correspond to the products **25** and **26**. The compound **25** was also detected in the course of chromato-mass-spectrometric experiment.

This phenomenon can be explained by low energy of the bond C_{sp_3}–S(II) cleavage – about 235 kJ/mol.[19] At the temperature 200 – 250°C this bond homolysis occurs. As a consequence of it, the carbon-centralized radical **21** and sulfur-centralized radicals **22-24** are formed from the compounds **6-8** (scheme 6).



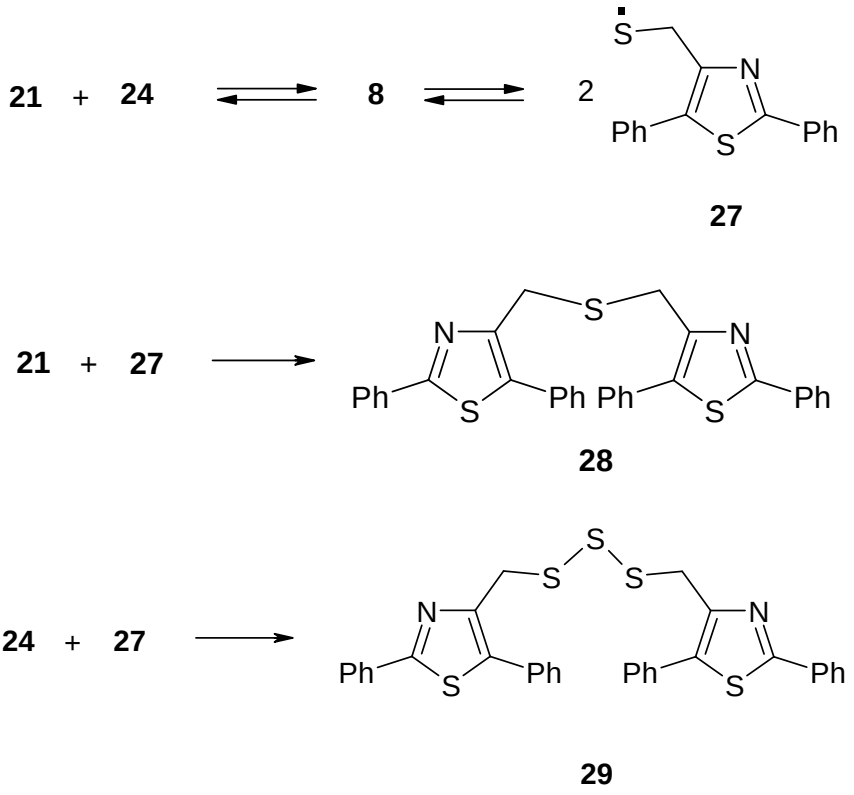
Scheme 6

Radical **21** can be stabilized in two ways – it tears away the hydrogen atom from some molecule of the matrix (S_H2 reaction at hydrogen atom), forming 2,5-diphenyl-4-methylthiazole **25**, or it recombines, forming 1,2-bis(2′,5′-diphenylthiazol-4′-yl)ethane **26** (scheme 7). Chromatographic detection of the product **25** in the vapor of monothiazols **6-8** and fixation of molecular ion of the recombination product **26** in their mass-spectra gives a strong evidence of proceeding the mentioned processes independently on the fortune of molecular ions of the initial monothiazols **6-8**. In particular, the peak, corresponding to the compound **26** by the m/z value, exceeds this value for molecular ions of mother compounds, and thus in the conditions of mass-spectral experiment, where the ion-molecular reactions are practically excluded, the compound **26** can't be formed in the course of fragmentation of the latter in the gas phase.



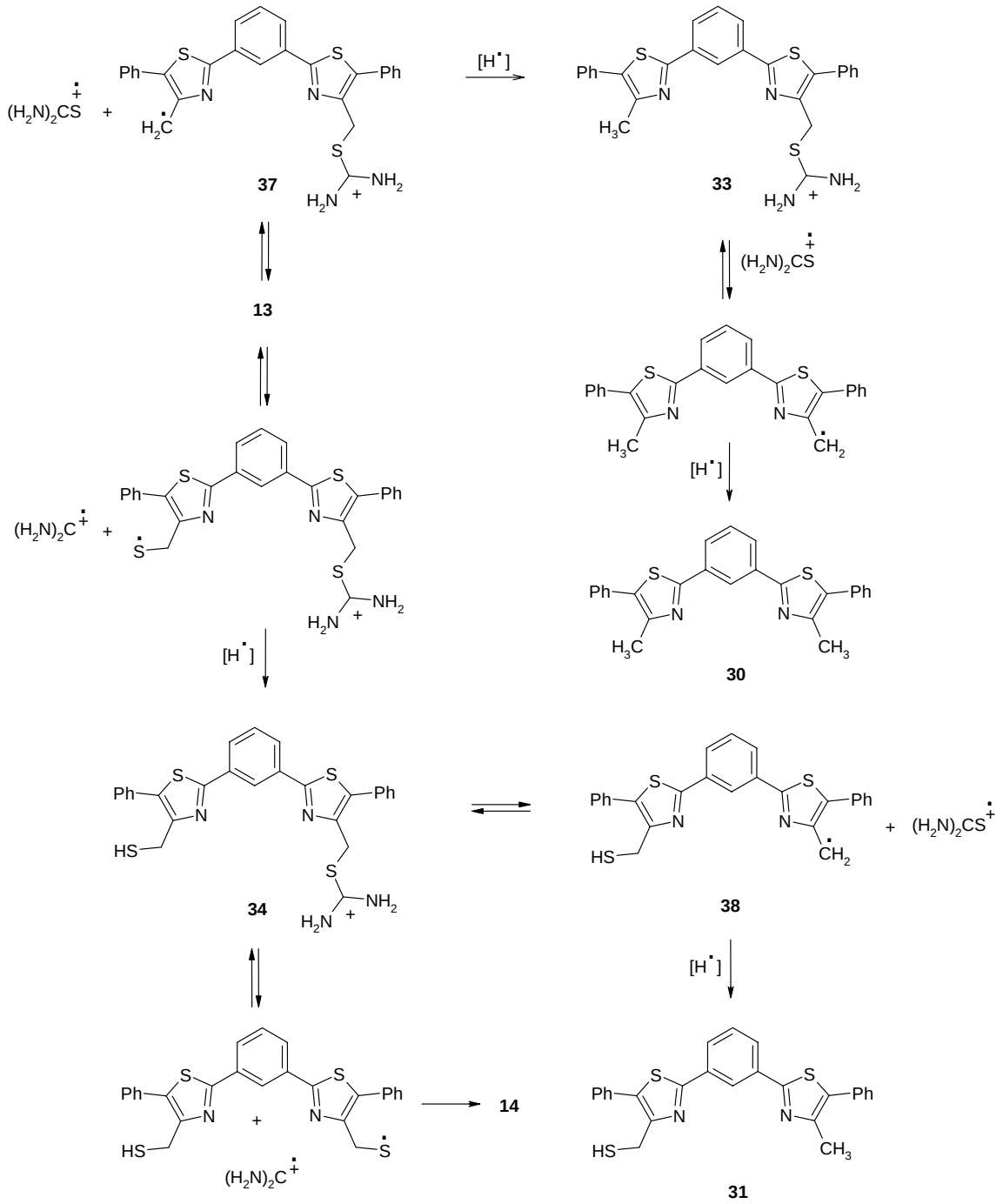
Scheme 7

In addition to the molecular peaks, corresponding to the products **25** and **26,** in MALDI-TOF spectrum of disulfide **8** the peaks of sulfide **28** (the product of the radicals **21** and **27** recombination) and trisulfide **29** (the product of the radicals **24** and **27** recombination) were observed (see scheme 8). Sulfur centralized radical **27** is formed as a consequence of thermal homolysis of S-S bond in disulfide **8,** proceeding in parallel with the CH_2–S bond homolysis: the S-S bond rapture energy is rather low - about 280 kJ/mol.[19]



Scheme 8

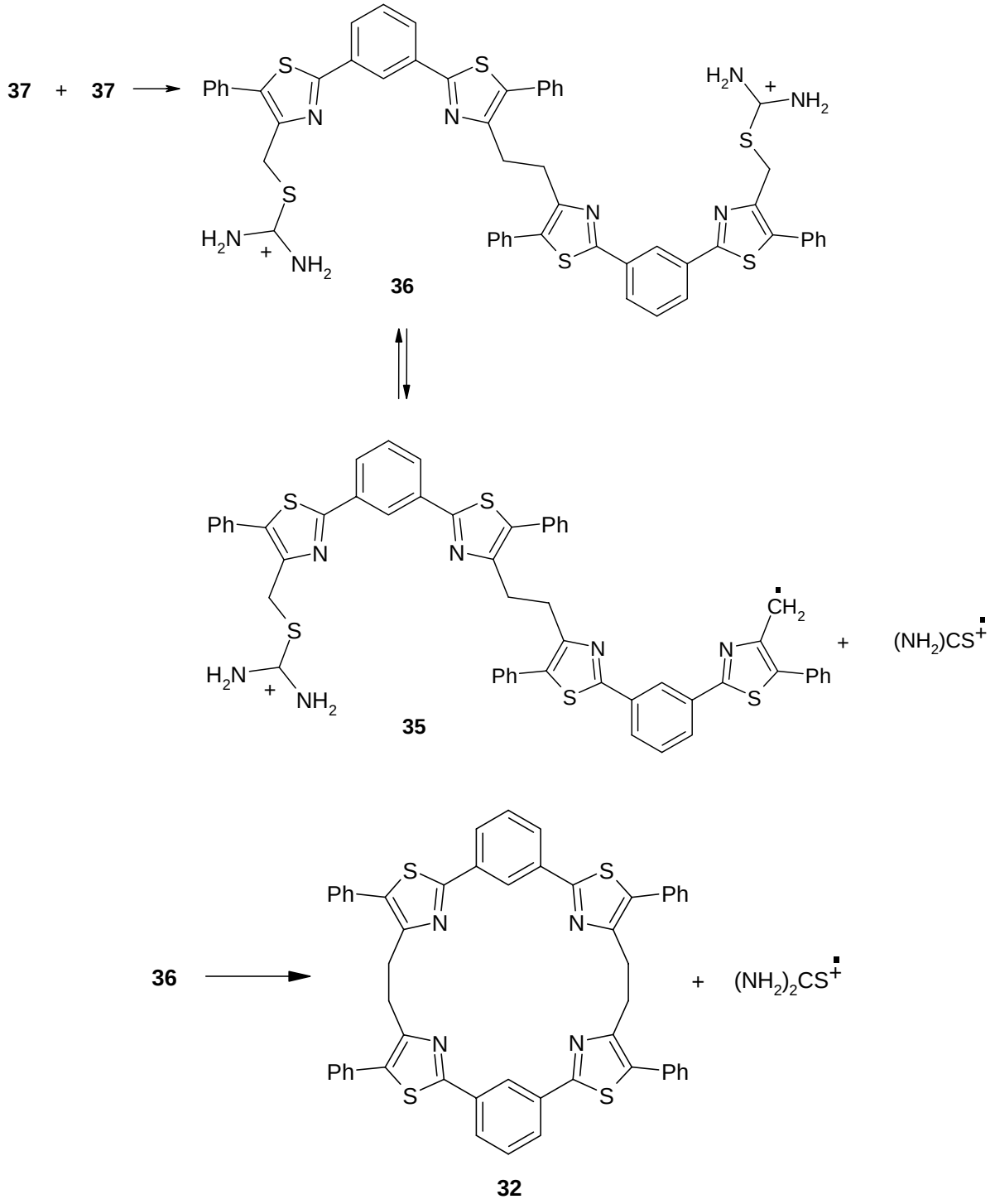
Using the same mechanistic reasons, one can explain the detection of the peaks in bis-isothiouronium salt **14** MS- and MALDI-TOF spectra, corresponding by the m/z values to the molecular ions of the compounds **15**, **30**, **31**, **32**, and (only in MALDI-TOF spectra) the ions **33** and **34** are detected. Their formation (except the macrocycle **32)** is illustrated by scheme 9. All the observed phenomena are based on the parallel homolysis of both the bonds CH_2–S and $^{+}(H_2N)_2C$–S.



Scheme 9

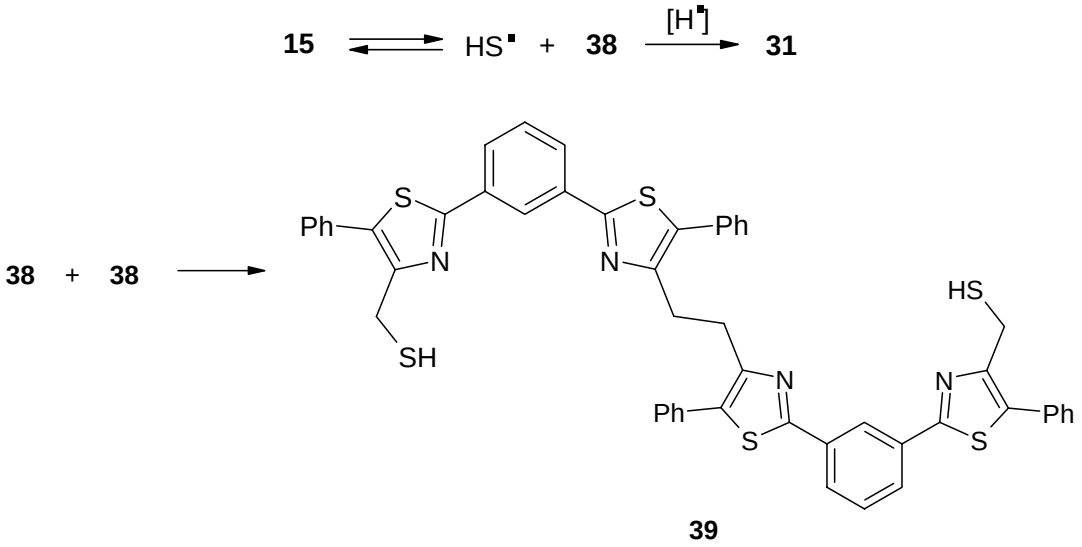
The loss of four sulfur-containing functional groups by the molecules of bis-isothiouronium salt **14** with the formation of cyclophan **32** can be explained by the gas phase monomolecular cyclization by means of S_H2 reaction at carbon atom of the radical **35**, formed in the course of homolysis of compound **36**, formed, in its turn, by means of the radicals **37** recombination (Scheme 10). As well as considered here the homolysis reactions, the S_H2 reaction with CH_2–S bond cleavage is possible due to low energy of this bond. Finally, the detection in the vapor over

the compound **14** of a large molecule **32,** built of the fragments of two molecules of the mother compound, clearly demonstrates that the macrocycle **32** is actually formed not in the course of the fragmentation of the molecular ion of the mother compound in gas phase.



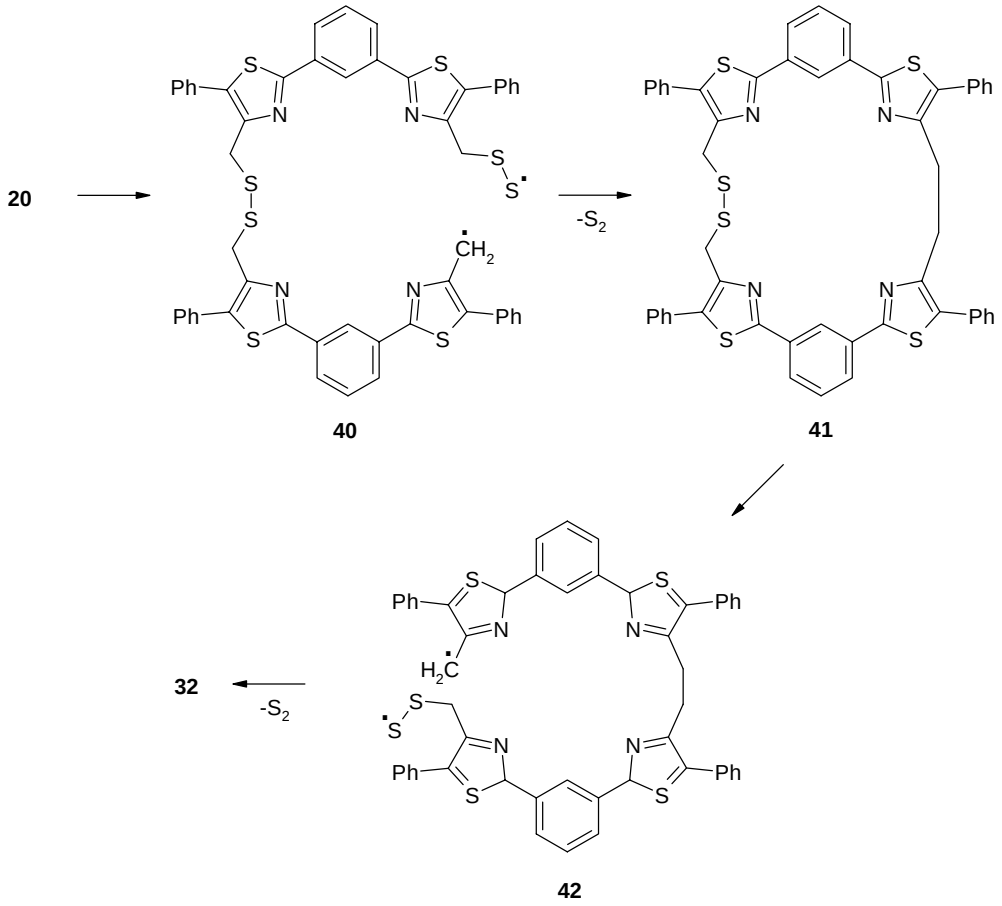
Scheme 10

The dithiol **15** mass-spectrum also bears witness to the homolysis of the CH_2–S – bond – it contains a peak, which could be ascribed by the value m/z to the molecular ion of compound **31,** formed from the radical **38**. In addition to it, in MALDI-TOF spectrum the molecular peak, corresponding to the product of the same radical recombination – the compound **39**, was detected (Scheme 11).



Scheme 11

The characteristic feature of the mass- and MALDI-TOF spectra of cyclophan **20** is the presence of the peak, corresponding by the value m/z to the molecular ion of cyclophan **32**, different from the initial cyclophan by the absence of all the four nonthiazole atoms of sulfur. Its formation is illustrated by the scheme 12. This scheme includes the stages of thermal homolysis of the bonds CH_2–SS (**20** → **40**, **41** → **42**) and cyclization by intramolecular S_H2 reactions of biradicals forming C–C bonds with CH_2–SS bond scission and S_2 loss (**40** → **41**, **42** → **32**).



Scheme 12

Experimental Section

General Procedures. All melting points were determined with Boetius hot-stage apparatus and uncorrected. ^{1}H-NMR spectra were recorded on Bruker MW-250 (250.13 MHz), Bruker MSL-400 (400.13 MHz) and Bruker ASPECT-600 (600 MHz) spectrometers using the corresponding solvent as the internal standard. Electron ionization (EI) mass spectra (60 eV) were obtained on "Finnigan" MAT-212 instrument. GC-MS analysis were performed with Trace MS "Thermo-Quest" instrument (SE-30 capillary column). Matrix-assisted laser desorption ionization (MALDI) mass spectra were obtained on "Finnigan" Dynamo instrument (MALDI-TOF) with 1,8,9-trihydroxyantracene matrix. The IR spectra of compounds were measured on a Bruker FTIR Vector-22. Microanalyses were performed with an elemental analyzer (CHN-3-analyzer, USSR). Quantum-chemical calculations were carried out using the program MOPAC 6 in the PM3 approach. Methyl 3-chloro-2-oxo-3-phenylpropanoate 2 was prepared by the condensation of benzaldehyde with methyl dichloroacetate according to Ref. 16c.

X-ray crystallographic data for **12** were collected at 293(2) K on an Enraf-Nonius CAD-4 diffractometer in the ω/2θ-scan mode, $\theta \leq 74.1°$, using CuK_α radiation with graphite monochromator. The structure was solved by direct method using the SIR[22] program and refined by full-matrix least-squares using SHELXL97[23] program. All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters, and hydrogen atoms bonded to carbon were inserted at calculated positions using a riding model. Hydrogen atoms bonded to oxygens were located from difference maps. All calculations were performed on PC using WinGX[24] suit of programs. Data collection and data reduction were performed on Alpha Station 200 computer using MoLEN[25] program. A summary of the crystal data, data collection, and refinement procedures is given in Table 3.

Table 3. Crystal data and structure refinement for compound **12**

Empirical formula	$2(C_{26}H_{20}N_2O_2S_2)\ C_4H_8O\ H_2O$
Formula weight	1003.28
Temperature	293(2) K
Wavelength	1.54180 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.992(7)Å α = 101.06(5)°. b = 13.988(9)Å β = 90.69(6)°. c = 22.16(2)Å γ = 90.73(6)°.
Volume	2431(3)$Å^3$
Z	2
Density (calculated)	1.371 Mg/m^3
Absorption coefficient	2.26 mm -1
F(000)	1052
Crystal size	0.20 x 0.10 x 0.05 mm^3
Theta range for data collection	2.76 to 25.00°.
Index ranges	-7<=h<=5, -14<=k<=14, -22<=l<=22
Reflections collected	4958
Independent reflections	2378 [R(int) = 0.098]
Refinement method	Full-matrix least-squares on F 2
Data / restraints / parameters	4958 / 433 / 636
Goodness-of-fit on F 2	0.930
Final R indices [I>2sigma(I)]	R1 = 0.0582, wR2 = 0.1312
R indices (all data)	R1 = 0.1783, wR2 = 0.1761
Extinction coefficient	0.0023(4)
Largest diff. Peak and hole	0.378 and -0.381 $e·Å^{-3}$

2,5-Diphenyl-4-hydroxymethylthiazole (4). To suspension of $LiAlH_4$ (0.80 g, 21 mmol) in 35 ml THF at stirring under Ar atmosphere at -60°C the ether **3**[16b] (3.60 g, 12 mmol) was added in portions during 45 min. Then the reaction mixture was stirred for 2 h at the same temperature, and then the temperature was raised up to the room temperature, the reactive mixture was treated with the ice water (50 ml), the formed suspension was acidified by the 5% HCl solution, then it was extracted by AcOEt (3×50 ml) and Et_2O (3×50 ml). The joint extract was washed with the water (2×25ml), with the saturated solution NaCl (25ml) and dried over Na_2SO_4. After the solvent removal *in vacuo* 3.10 g (95%) of product **4** was obtained, mp 104-106°C. IR (nujol, cm^{-1}) 3206, 1600, 1488, 1443, 1354, 1247, 1203, 1081, 1044, 1028, 1005, 990, 764, 750; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 4.62 (2H s), 7.44-7.99 (10H m); *Anal.* Calcd. $C_{16}H_{13}NOS$: C 71.88, H 4.90, N 5.24, S 11.99. Found: C 72.21, H 4.96, N 5.48, S 12.24.

2,5-Diphenyl-4-chloromethylthiazole (5). To the solution of alcohol **4** (3.10 g, 11.6 mmol) in 45 ml of chloroform $SOCl_2$ (3.46g, 29 mmol) was added. Week heating was observed. The reaction mixture was refluxed for 4 h. The solvent and the thionyl chloride excess were removed *in vacuo*. The residuum crystallized at standing. The residuum was treated with 5 % water solution of $NaHCO_3$, washed with water up to neutral reaction, dried in air; 3.30 g (100%) of product **5** was obtained, mp 95-97°C. IR (nujol, cm^{-1}) 3063, 1599, 1257, 1239, 1182, 1015, 954, 916, 764, 740, 719, 693; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.78 (2H s), 7.26-8.00 (10H m); MS m/z: 285 (M^+, 23%), 147 (100%); *Anal.* Calcd. $C_{16}H_{12}ClNS$: C 67.24, H 4.23, Cl 12.41, N 4.90, S 11.25. Found: C 67.33, H 4.26, Cl 12.72, N 4.80, S 11.57.

2,5-Diphenyl-4-amidiniummercaptomethyl-5-thiazole chloride (6). To the solution of thiourea (1.60 g, 21 mmol) in MeCN (100 ml) the solution of chloromethylthiazole **5** (3.00 g, 10.5 mmol) in MeCN (40 ml) was added, at that the residuum immediately precipitated. The reaction mixture was refluxed for 3 h (up to thiourea extinction according to the TLC data), therewith the residuum had totally solved. When cooling the viscous mass formed, the solvent was decanted, the residuum was flooded again with MeCN (50 ml). At grinding the viscous mass turned into powder. It was filtered, washed with water (3×15ml), dried in air, thus isothiouronium salt **6** was obtained (3.80 g, 100%), mp 195–197°C (MeCN). IR (nujol, cm^{-1}) 2738, 1651, 1530, 1311, 1249, 1151, 1083, 1015, 764, 744, 720; NMR (400 MHz, $CDCl_3$) δ 4.67 (2H bs), 7.54-7.96 (10H m), 9.33 (2H bs), 9.38 (2H bs); MALDI-TOF *m*/*z*: 326 (M + H^+ for $C_{17}H_{15}N_3S_2$); *Anal.* Calcd. $C_{17}H_{15}N_3S_2 \cdot HCl$: C 56.42, H 4.46, Cl 9.80, N 11.63, S 17.72. Found: C 56.02, H 4.57, Cl 9.88, N 11.63 S 17.73.

2,5-Diphenyl-4-mercaptomethylthiazole (7). The suspension of isothiouronium salt **6** (0.20 g, 0.55 mmol) in 0.5 N NaOH (2 ml,) was refluxed for 2 h under Ar. In 1 h the suspension completely dissolved. After cooling to the room temperature the reaction mixture was acidified by 2 N HCl solution. The precipitated crystals were dried, water washed (3×15ml), air dried, thiol **7** was obtained (0.15 g, 96%), mp 95-97°C (Me_2CO/H_2O). IR (nujol, cm^{-1}) 2569, 1597, 1530, 1487, 1443, 1330, 1312, 1236, 1182, 1147, 1079, 1014, 915, 762, 724; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.20 (1H t, *J* = 7.64 Hz), 3.93 (2H d, *J* = 7.64 Hz), 7.39-7.97 (10H m); MS m/z: 283

(M^+, 31%), 147 (100%); *Anal.* Calcd. $C_{16}H_{13}NS_2$: C 67.81, H 4.62, N 4.94, S 22.63. Found: C 67.31, H 4.62, N 5.10, S 22.38.

Bis(2,5-diphenyl-thiazol-4-ylmethyl)disulfide (8). The solution of I_2 (0.06 g, 23 mmol) and KI (0.025 g) in 1.35 ml of water was added to the heated up to 45±5 °C suspension of thiol **7** (0.10 g, 0.35 mmol) and K_2CO_3 (0.027 g, 0.20 mmol) in 2 ml of water. The precipitate was water washed off I^-, washed with acetone, and dried; disulfide **8** was obtained (0.10 g, 100%), mp 189–190°C (Me_2CO/H_2O). IR (nujol, cm^{-1}) 1598, 1525, 1484, 1413, 1314, 1221, 1011, 967, 918, 771, 763,722; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.14 (4H s), 7.19-7.98 (10H m); MS m/z: 564 (M^+, 2%), 147 (100%); *Anal.* Calcd. $C_{32}H_{24}N_2S_4$: C 68.05, H 4.28, N 4.96, S 22.71. Found: C 68.25, H 4.28, N 4.91, S 22.50.

Thioisophthalamide (9). (a) From isophthalamide. To a suspension of isophthalamide (2.00 g, 12.2 mmol) in 20 ml of THF Lowesson's reagent (4.95 g, 12.2 mmol) was added at room temperature, and the mixture was refluxed up to the formation of homogeneous solution (for 2 h). After removal of the solvent the residue was solved in 15 ml CH_2Cl_2 and allowed to solidify. The crystals were dried and recrystallized from acetone. The thioisophthalamide **9** (1.43 g, 60 %) was obtained, yellow crystals, mp 203 – 205°C (acetone) (212 C ^{o}, ref.[20], 203^{o}C ref.[23]).

(b) From isophthalodinitrile. The solution (2 g, 15.6 mmol) of isophtalodinitrile in 80 ml of the mixture triethylamine – pyridine (1:1) was bubbled with dry H_2S for 8 h at room temperature. By this time, according to the TLC data, the initial dinitrile is completely spent. The reaction mixture was poured out onto ice, the yellow-lemon precipitate was separated, washed with water (3×20 ml), and 2.82 g (92%) of compound **9** was obtained with mp 211 – 212°C (EtOH). IR (nujol, cm^{-1}) 3157, 1631, 1413, 1291, 889, 798, 653, 592; ^{1}H-NMR (250 MHz, acetone-d_6) δ 7.45 (1H dd, *J* = 7.8, 7.7 Hz), 8.12 (2H d, *J* = 7.8 Hz), 8.44 (1H dd, *J* = 1.8, 1.7 Hz), 9.12 (2H, bs), 9.01 (2H, bs); *Anal.* Calcd. $C_8H_8N_2S_2$: C 48.95, H 4.11, N 14.27, S 32.67. Found: C 49.27, H 3.88, N 14.21, S 32.86.

1,3-Bis(4′-methoxycarbonyl-5′-phenylthiazol-2′-yl)benzene (10) and 4-methoxycarbonyl-2(3′-methoxycarbonylphenyl)-5-phenylthiazole (11). (a) The solution of bisthioamide **8** (2.80 g, 14.3 mmol) and methyl phenylchloropyruvate **2** (4.90 g, 28.6 mmol) in 100 ml of methanol was refluxed for 7 h and left for 2 days at the room temperature (the initial bisthioamide spending was controlled by the TLC method). The precipitated crystals were washed (3×25 ml) with methanol, 5% $NaHCO_3$, water (2×25 ml), 4.23 g (58 %) of compound **10** was obtained, mp 175-176°C (i-PrOH). IR ($CHCl_3$, cm^{-1}) 1717, 1595, 1500, 1335, 1285, 1210, 1180, 1025, 980, 810, 760; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.80 (6H, s), 7.50-7.61 (10H m), 7.74 (1H dd, *J* = 7.83, 7.82 Hz), 8.12 (2H dd, *J* = 7.83, 1.65 Hz), 8.57 (1H, bs); MS m/z: 512 (M^+, 100%); *Anal.* Calcd. $C_{28}H_{20}N_2O_4S_2$: C 65.61, H 3.94, N 5.47, S 12.48. Found: C 65.49, H 3.88, N 5.21, S 12.63.

At the prolonged staying the compound **11** is crystallized from the methanol mother solution (1.20 g, 24%), mp 136°C (i-PrOH). IR ($CHCl_3$, cm^{-1}) 3029, 3009, 2954, 1725, 1438, 1334, 1303, 1174, 694; ^{1}H-NMR (250 MHz, DMSO-d_6) δ 3.87 (3H, s), 3.97 (3H, s), 7.44-7.56 (6H m), 8.13

(1H d, *J* = 7.47 Hz), 8.21 (1H d, *J* = 7.85 Hz), 8.58 (1H, bs); MS m/z: 353 (M^+, 100%); *Anal.* Calcd. $C_{19}H_{15}NO_4S$: C 64.57, H 4.28, N 3.96, S 9.07. Found: C 64.35, H 4.21, N 3.61, S 9.31.

(b) To the solution (1.00 g, 5.1 mmol) of bisthioamide **9** in 130 ml of toluene they added the solution of (2.17 g, 10.2 mmol) methyl phenylchloropyruvate **2** in 10 ml of toluene, and refluxed it for 18 h. About three quarters of the solvent volume were evaporated *in vacuo*. In 10-12 h the precipitate was drained, washed with 5% water solution of $NaHCO_3$ and water (3×50 ml), then air-dried, and 2.1 g (80%) of bisthiazol **10** was obtained, mp 177-179°C (EtOH). IR (vaseline, cm^{-1}) 1720, 1595, 1500, 1335, 1285, 1210, 1180, 1025, 980, 810, 760; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 3.88 (6H, s), 7.44-7.59 (11H m), 8.10 (2H dd, *J* = 7.7.68, 1.28 Hz), 8.51 (1H, bs).

1,3-Bis(4′-hydroxymethyl-5′-phenylthiazol-2′-yl)benzene (12). Under Ar atmosphere to the suspension of $LiAlH_4$ (0.23 g, 6.1 mmol) in 17 ml of absolute THF at stirring at the temperature -78 °C during 25 min bisthiazol **10** (1.33 g, 2.6 mmol) was added in portions. The reaction mixture was stirred at the same temperature for 2 h, then the temperature was increased up to the room temperature, and the mixture was left for a night. Then the solution was poured with the excess of ice water. The formed suspension was acidified with 5% HCl solution, then it was extracted with AcOEt (3×50ml). The organic layer was washed with water (2×25ml), NaCl (25ml) saturated solution and dried over $MgSO_4$. After the solvent evaporation they got 0.90 g of compound **12**. From the water solution 0.25 g of the same product (overall 97%) was isolated, mp 163–165°C (MeOH). For X-ray analysis the monocrystal of **12,** grown from water solution, was employed. IR (nujol, cm^{-1}) 1276, 1206, 1047, 1030, 10005, 802, 752; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 4.63 (4H d, *J* = 5.32 Hz), 5.36 (2H bt, *J* = 5.32 Hz), 7.45-7.71 (11H m), 8.05 (2H d, *J* = 7.64 Hz), 8.63 (1H, bs); *Anal.* Calcd. $C_{26}H_{20}N_2O_2S_2$: C 68.39, H 4.42, N 6.14, S 14.05. Found: C 68.86, H 4.62, N 5.58, S 12.41.

1,3-Bis(4′-chloromethyl-5′-phenylthiazol-2′-yl)benzene (13). To the solution of bis-alcohol **12** (0.30 g, 0.66 mmol) in 30 ml of dry chloroform $SOCl_2$ (0.8 g, 6.6 mmol) was added and refluxed for 4 h. The solvent and the excess of thionylchloride were removed *in vacuo*, the rest light cream-colored residuum was treated with 5% water solution of $NaHCO_3$, washed with water up to the neutral pH, then dried in air, and 0.32 g (100%) of analytically pure product was obtained, mp 214-216°C. IR (nujol, cm^{-1}) 1598, 1573, 1482, 1444, 1426, 1254, 1201, 1145, 1078, 1017, 1001, 966, 947, 907, 866, 799, 759, 735; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.79 (4H s), 7.38-7.48 (2H m), 7.52 (4H dd, *J* = 7.80, 7.32 Hz), 7.57 (1H dd, *J* = 7.86, 7.80 Hz), 7.64 (4H d, *J* = 7.32 Hz), 8.07 (2H dd, *J* = 7.86, 1.29 Hz), 8.55 (1H, s); *Anal.* Calcd. $C_{26}H_{18}Cl_2N_2S_2$: C 63.28, H 3.68, N 5.68, Cl 14.37, S 13.00. Found: C 63.52, H 3.57, N 5.68, Cl 11.04, S 13.20.

1,3-Bis(4′-amidiniummercaptomethyl-5′-phenylthiazol-2′-yl)benzene dichloride (14). To the solution of thiourea (0.31 g, 40 mmol) in 40 ml of acetonitrile the dichloride **13** (0.51 g, 1.00 mmol) solution in 10 ml chloroform was added. The reaction mixture was refluxed, at that the precipitate began to form gradually in 30 – 40 min. The refluxing went on for more 15 h till the reaction completely terminated (the initial reagents exhausted, according to the TLC). The residuum was filtered, acetonitrile washed (3×25ml), air dried; 0.65 g (100%) bis-isothiouronium salt **(14)** was obtained, mp 203 – 205°C (EtOH). IR (KBr, cm^{-1}) 3429, 3193, 3022, 2754, 1650, 1530,

1483, 1442, 1407, 1235, 1207, 1079, 1018, 10001, 882, 797, 761, 697; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 4.76 (4H s), 7.52-7.65 (10H m), 7.74 (1H dd, *J* = 7.88, 7.52 Hz), 8.10 (2H dd, *J* = 7.84, 1.82 Hz), 8.49 (1H bs), 9.43 (8H bs); MALDI-TOF *m*/*z*: 573 (M + H^+ for $C_{28}H_{24}N_6S_4$); *Anal.* Calcd. $C_{28}H_{24}N_6S_4$·2HCl: C 52.08, H 4.06, N 13.02, Cl 10.98, S 19.86. Found: C 51.89, H 3.96, N 12.97, Cl 11.06, S 19.65.

1,3-Bis(4′-mercaptomethyl-5′-phenylthiazol-2′-yl)benzene (15). The 0.40 g (0.62 mmol) bis-isothiouronium salt **13** in the solution of 7.5 ml of 0.5 n NaOH was refluxed for 8 h under Ar atmosphere. After cooling the reaction mixture was neutralized by 5 % HCl water solution. The precipitate was drained, water washed (3×15ml), cold acetone washed (3×15ml), and once more water washed (3×15ml), then air dried, and 0.25 g (82.5%) dithiole **15** was obtained**,** mp 135-140°C (Me_2CO). IR (KBr, cm^{-1}); 3050, 3024, 2969, 2926, 2852, 2503, 1655, 1597, 1528, 1480, 1443, 1419, 1243, 1200, 911. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.42 (2H t, *J* = 7.64 Hz), 3.96 (4H d, *J* = 7.64 Hz), 7.4-8.1 (14H m); MS m/z: 488 (M^+, 74%), 147 (100%); *Anal.* Calcd. $C_{26}H_{20}N_2S_4$: C 63.90, H 4.12, N 5.73, S 26.25. Found: C 63.75, H 3.96, N 5.47, S 26.46.

1^5,3^5,8^5,10^5-Tetraphenyl-5,6,12,13-tetrathia-1,3,10(2,4),8(4,2)-tetrathiazola-2,9(1,3)-dibenzen- acyclotetradecaphane (20). To the stirred solution of Et_3N (0.084 g, 0.83 mmol) in 50 ml $CHCl_3$ the solutions 0.20 g (0.41 mmol) dithiole **15** in 50 ml chloroform and 0.10 g (0.40 mmol) I_2 in 50 ml chloroform were dropped simultaneously from two drop funnels for 8.5 h. After additional stirring for 1 h the reactive mixture was left for a night. Then it was treated with the solution $Na_2S_2O_3$ up to the negative I_2 reaction. After the solvent distillation and drying *in vacuo* they obtained 0.19 g (95%) powder **20**, mp 189-191°C (reprecipitation by the ether from $CHCl_3$). IR (KBr, cm^{-1}); 3052, 2921, 2851, 1597, 1525, 1478, 1442, 1200, 1755, 693. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.13 (8H s), 7.4-8.1 (28H m); MALDI-TOF *m*/*z*: 972 (M^+); *Anal.* Calcd. $C_{52}H_{36}N_4S_8$: C 64.16, H 3.73, N 5.76, S 26.35. Found: C 63.52, H 3.53, N 5.49, S 26.43.

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