Макрогетероциклы
http://macroheterocycles.isuct.ru

Three–unit Products from Condensation of 3–Alkylsubstituted 2,5–Diamino–1,3,4–thiadiazoles with 1,1–Dimethoxy–3–iminoisoindoline

Elena A. Danilova, Tat'yana V. Melenchuk, Ekaterina E. Melekhonova, Maria A. Tyutina, and Mikhail K. Islyaikin[@]

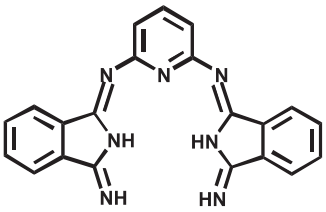
Ivanovo State University of Chemistry and Technology, Ivanovo, 153000, Russia
[@]Corresponding author E-mail: islyaikin@isuct.ru

New representatives of 3-alkyl-5-amino-2-imino-1,3,4-thiadiazolines (alkyl=C_5H_{11}, $C_{10}H_{21}$, $C_{15}H_{31}$) were synthesized by alkylation of 2,5-diamino-1,3,4-thiadiazole with corresponding alkyl bromides. Their condensation with 1,1-dimethoxy-3-iminoisoindoline led to new three-units products of ABA-type – 1,3-bis[(3-alkyl-5-amino-1,3,4-thiadiazol-2(3H)-ylideneamino)]-2H-isoindoles. These compounds were characterised by IR, UV-vis, and NMR spectroscopy, mass-spectromery, data of elemental analysis.

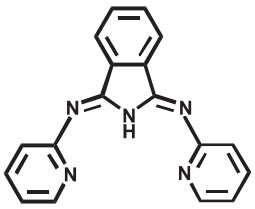
Keywords*:* S,N-Containing heterocycles, porhyrazine precursors, 3-alkyl-5-amino-2-imino-1,3,4-thiadiazolines, 2,5-diamino-1,3,4-thiadiazole, alkylation, condensation.

Introduction

2,6-Bis(1-imino-3-isoindolinylidenamino)pyridine (**1**) as the first representative of the compounds with new conjugated system was synthesized by Linstead and co-workers when they have studied condensation reaction of 1,3-diiminoisoindoline with 2,6-diaminopyridine.[1-3]



1



2

In the middle of the last century a new three-units system of ABA-type (**2**) containing two pyridine fragments (A) and one isoindoline-1,3 ring (B) was synthesized.[2-5] Its inner cavity holds three N-atoms and is able to coordinate a bivalent metal to give the correponding metallocomplexes.[5-6]

Later the method for obtaining of ABA-type compounds was improved by the activation of nitrile groups of phthalonitrile by the salts of alkali-earth metals.[7] The influence of the catalyst, temperature, as well as the nature of amine and solvent on the condensation leading to formation of ABA products was examined.[8] It was shown that a substitution of imino groups in 1,3-diminoisoindoline molecule proceeds stepwise and suggested that using the corresponding molecular ratio of phthalonitrile and arylenamine it is possible to obtain various products. However the used amines were limited by the compounds of aminopyridine and aminothiazole series.[8]

In 1996 the synthesis of unsymmetrically substituted triazoleporphyrazines was reported[9] in which the ABA-type compound derived from 1-dodecyl-3,5-diamino-1,2,4-triazole was used as a precursor. To the best of our knowledge the similar products with 1,3,4-thiadiazole fragments were not yet described.

Experimental

Calculations

Quantum chemical calculations were carried out by means of software package GAMESS (PC)[10] by DFT B3LYP 6-31G(*d,p*) method with full optimization of geometrical parameters. The preparation of the input files and processing of output data of calculations were carried out by Chemcraft program.[11].

Measurements

Electronic absorption spectra in UV- and visible region (UV-vis spectra) were registered on HITACHI U-2001 spectrophotometer in quartz cuvettes having 1-10 mm thickness. MALDI-TOF mass-spectra were measured by Ultraflex Bruker Daltonics mass-spectrometer in a mode of positive ions with the use of reflectomodes with 20 mV target potential. The samples were prepared by dissolving of investigated compounds in chloroform (10^{-4} - 10^{-6} mol·l^{-1}). ^{1}H NMR spectra were registered in $CDCl_3$ on AVANCE 500 MHz spectrometer and Bruker 300 MHz spectrometer. Chemical shifts (ppm) were measured at 295 K using hexamethyldisiloxane (δ=0.037 ppm) or tetramethylsilane (δ=0.0 ppm) as internal standards. IR spectra were registered by AVATAR 360 FT-IR spectrometer for samples pressed in KBr or for solutions in $CHCl_3$.

Synthesis

Previously described procedures were used for synthesis of 2,5-diamino-1,2,4-thiadiazole (**3**)[12] and 1,1-dimethoxy-3-iminoisoindoline (**8**).[13]

General procedure for the synthesis of 5-amino-2-imino-3-alkyl-1,3,4-thiadiazoline. The mixture of 2,5-diamino-1,3,4-thiadiazole (**3**) (2.32 g, 20 mmol), corresponding alkyl bromide (70 mmol) and MeOH (80 ml) was refluxed during 24 hours. Then the solvent was taken away under vacuum. The obtained precipitate was mixed with water and 30% aqueous ammonia solution and stirred two hours at room temperature. The target product was extracted by $CHCl_3$ and solvent was distilled away.

*5-Amino-2-imino-3-pentyl-1,3,4-thiadiazoline, **4***. The product was purified by recrystallization from ethanol to obtain a white powder soluble in the majority of organic solvents, but not in water. Yield 2.64 g (71 %), m.p. = 175-177 °C. Found: C 45.07, H 6.42, N 30.96, S 17.28 %. $C_7H_{14}N_4S$ requires C 45.88, H 6.05, N 30.57, S 17.50 %. M 186.09. *m/z:* 185 $[M+H]^+$. IR (KBr) ν cm^{-1}: 3312 and 3276 (NH_2), 3099 (NH), 2956, 2932 and 2859 (alkyl CH), 2777, 1633, 1607, 1549 (C=N). UV-vis (EtOH, $1.2\cdot10^{-4}$ M) λ_{max} nm (lgε): 210 (3.71). ^{1}H NMR ($CDCl_3$, 200 MHz) δ_H ppm: 3.69 (2H, N-CH_2-), 1.68 (2H, N-CH_2-CH_2-), 1.27 (2H,-CH_2-CH_3), 0.87 (3H,-CH_3).

*5-Amino-3-decyl-2-imino-1,3,4-thiadiazoline, **5***. The product was washed by hexane, recrystallized from ethanol, and then from methanol to give a beige powder soluble in alcohols, dichloromethane, acetone, hexane, benzene and insoluble in water. Yield: 3.23 g (63 %), m.p. =182-184 °C. Found: C 56.13, H 9.77; N 22.45, S 12.63 %. $C_{12}H_{24}N_4S$ requires C 56.21, H 9.43, N 21.85, S 12.50 %. M 256.17. *m/z:* 257 $[M+H]^+$. IR (KBr) ν cm^{-1}: 3425, 3270, 3147, 3054 (NH), 2949, 2920, 2850 (alkyl CH), 1609, 1541 (C=N). UV-vis (EtOH, $1.1\cdot10^{-4}$ M) λ_{max} nm (lgε): 271 (3.69). ^{1}H NMR ($CDCl_3$, 200 MHz) δ_H ppm: 3.39 (2H, N-CH_2-), 1.68 (2H, N-CH_2-CH_2-), 1.25 (14H, -CH_2-), 0.86 (3H,-CH_3).

*5-Amino-3-dodecyl-2-imino-1,3,4-thiadiazoline, **6***, was purified by recrystallization from ethanol and obtained as light-beige wax-like mass, which is soluble in alcohols and CH_2Cl_2, moderately soluble in acetone, hexane and benzene and not soluble in water. Yield 4.66 g (82 %), m.p. 167-169 °C. Found: C 58.22, H 8.47, N 20.14, S 11.89 %. $C_{14}H_{28}N_4S$ requires C 59.11, H 9.93, N 19.44, S 10.95 %. M 284.20. *m/z:* 284 $[M]^+$. IR (KBr) ν cm^{-1}: 3425, 3271, 3059 (NH), 2921, 2851 (alkyl CH), 1609, 1609, 1541 (C=N). UV-vis (EtOH, $1.2\cdot10^{-4}$ M) λ_{max} nm (lgε): 270 (3.72). ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H ppm: 4.28 (s., 2H, -NH_2), 3.74 (t., 2H, N-CH_2-), 1.87 (s., 2H, N-CH_2-CH_2-), 1.30 (m., 18H, -CH_2-), 0.89 (-CH_3).

*5-Amino-3-pentadecyl-2-imino-1,3,4-thiadiazoline, **7***. Gray wax-like product was received after evaporation of solvent and drying in vacuum at 60 - 70 °C. Compound **7** is soluble in acetone, hexane, benzene, moderately soluble in alcohols and dichloroethane. Yield 2.14 g (62.1 %), m.p. = 158-160 °C. Found: C 61.77, H 11.27, N 16.47, S 10.77 %. $C_{17}H_{34}N_4S$ requires C 62.53, H 10.49, N 17.16, S 9.82. M 362. *m/z:* 362 $[M]^+$. IR (KBr) ν cm^{-1}: 3427, 3270, 3056 (NH), 2921, 2852 (alkyl CH), 1610, 1540 (C=N). UV-vis (EtOH, $0.8\cdot10^{-4}$ M) λ_{max} nm (lgε): 271 (3.70). ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H ppm: 4.50 (t., 4H, N-CH_2-), 1.9 (s., 4H, N-CH_2-CH_2-), 1.29 (m., 26H, -CH_2-), 0.91 (t., 6H, -CH_3).

General procedure for the synthesis of 1,3-bis[(3-alkyl-5-amino-1,3,4-thiadiazol-2(3H)-ylideneamino)]-2H-isoindoles. The mixture of 3-alkyl-5-amino-2-imino-1,3,4-thiadiazoline and 1,1-dimethoxy-3-iminoisoindoline (**8**) in MeOH (50 ml) was stirred at 40-45 ºC for 15 hours. After that the reaction mass was poured into 150 ml of water. The obtained precipitate was filtered off and dried at r.t. The product was purified by column chromatography on alumina, (CH_2Cl_2 : methanol : hexane = 10:1:3). The obtained crimson substance was not soluble in water but well soluble in organic solvents, exept hexane.

*1,3-Bis[(5-amino-3-pentyl-1,3,4-thiadiazol-2(3H)-ylideneamino)]-2H-isoindole, **9,*** was synthesized from 5-amino-2-imino-3-penthyl-1,3,4-thiodiazoline (**4**) (1.138 g, 6 mmol) and **8** (0.58 g, 3 mmol). Yield: 166 mg (11.4 %). Found: C 53.86, H 6.57, N 25.05, S 12.34 %. $C_{22}H_{31}N_9S_2$ requires C 54.41, H 6.43, N 25.96, S 13.20 %. M 485.2. *m/z* 484 $[M-H]^+$. IR (KBr) ν cm^{-1}: 3394, 3288, 3120 (NH), 2954, 2924, 2852 (alkyl CH), 1699, 1608, 1548 (C=N). UV-vis (MeOH, $1.66\cdot10^{-5}$ M) λ_{max} nm (lgε): 384 (4.33), 404, 462, 495 (4.48), 527. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H ppm: 7.59 - 7.89 (m., 4H arom.), 5.32 (b.s., 3H, N*H*, NH_2), 4.70, 4.54 (t., 4H, N-CH_2-), 1.58 (s., 4H, N-CH_2-CH_2-), 1.28 (m., 4H, -CH_2-), 0.91 (t., 6H, -CH_3).

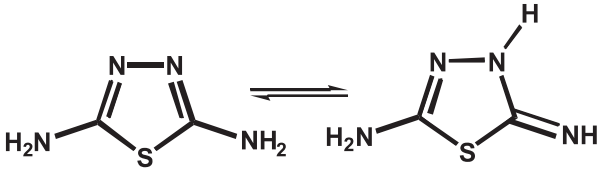
*1,3-Bis[(5-amino-3-decyl-1,3,4-thiadiazol-2(3H)-ylideneamino)]-2H-isoindole, **10,*** was synthesized from 5-amino-2-imino-3-decyl-1,3,4-thiadiazoline (**5**) (0.0574 g, 0.11 mmol) and **8** (0.0106 g, 0.055 mmol). Yield: 172.3 mg (27.6 %). Found: C 60.13, H 8.77, N 20.45, S 9.83 %. $C_{32}H_{51}N_9S_2$ requires C 61.40, H 8.21, N 20.14, S 10.24 %. M 625.4. *m/z* 625 $[M]^+$. IR (KBr) ν cm^{-1}: 3394, 3288, 3120 (NH), 2954, 2924, 2852 (alkyl CH), 1699, 1608, 1548 (C=N). UV-vis (MeOH, $5.50\cdot10^{-4}$ M) nm λ_{max} (lgε): 384 (3.8), 407, 461, 493 (3.96), 528. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H ppm: 7.56 - 7.85 (m., 4H arom.), 7.24 (b.s., 3H, N*H*, NH_2), 3.39 (t., 4H, N-CH_2-), 1.68 (s., 4H, N-CH_2-CH_2-), 1.25 (m., 28H, -CH_2-), 0.86 (t., 3H, -CH_3).

*1,3-Bis[(5-amino-3-dodecyl-1,3,4-thiadiazol-2(3H)-ylideneamino)]-2H-isoindole, **11,*** was synthesized from 5-amino-2-imino-3-dodecyl-1,3,4-thiadiazoline (**6**) (0.0644 g, 0.23 mmol) and **8** (0.022 g, 0.12 mmol). Yield: 25.6 mg (31 %). Found: C 63.03, H 8.22, N 17.47, S 9.18 %. $C_{36}H_{59}N_9S_2$ requires C 63.40, H 8.72, N 18.48, S 9.40 %. M 682.04. *m/z* 682 $[M]^+$. IR (KBr) ν cm^{-1}: 3390, 3285, 3120 (NH), 2955, 2922, 2854 (alkyl CH), 1698, 1610, 1545 (C=N). UV-vis (MeOH, $5.20\cdot10^{-4}$ M) nm λ_{max} (lgε): 384 (3.72), 410, 466, 498 (3.75), 536. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H ppm: 7.58 - 7.90 (m., 4H arom.), 7.24 (b.s., 3H, N*H*, NH_2), 4.28 (s., 2H, -NH_2), 3.74 (t., 4H, N-CH_2-), 1.87 (s., 4H, N-CH_2-CH_2-), 1.30 (m., 36H, -CH_2-), 0.89 (t., 3H, -CH_3).

*1,3-Bis[(5-amino-3-pentadecyl-1,3,4-thiadiazol-2(3H)-ylideneamino)]-2H-isoindole, **12***, was synthesized from 5-amino-2-imino-3-pentadecyl-1,3,4-thiadiazoline (**7**) (1 g, 3 mmol) and 8 (0.27 g, 1.5 mmol). Yield: 0.413 g (36 %). Found C 65.03, H 8.56, N 15.77, S 6.92 %. $C_{42}H_{70}N_9S_2$ requires C 65.93, H 9.22, N 16.47, S 8.38 %. M 764.5. *m/z* 764 $[M]^+$. IR (KBr) ν cm^{-1}: 3394, 3288, 3120 (NH), 2954, 2924, 2852 (alkyl CH), 1699, 1608, 1548 (C=N). UV-vis (MeOH, $1.03\cdot10^{-4}$ M) nm λ_{max} (lgε): 295 (3.95), 301, 385 (3.89), 410, 466, 497 (4.06), 531. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H ppm: 7.58 - 7.90 (m., 4H arom.), 7.24 (b.s., 3H, N*H*, NH_2), 4.50 (t., 4H, N-CH_2-), 1.9 (s., 4H, N-CH_2-CH_2-), 1.29 (m., 48H, -CH_2-), 0.91 (t., 6H, -CH_3). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C ppm: 172.4, 167.8, 164.4, 160.5, 139.5, 134.3, 132.7, 131.7, 123.6, 122.5, 51.1.

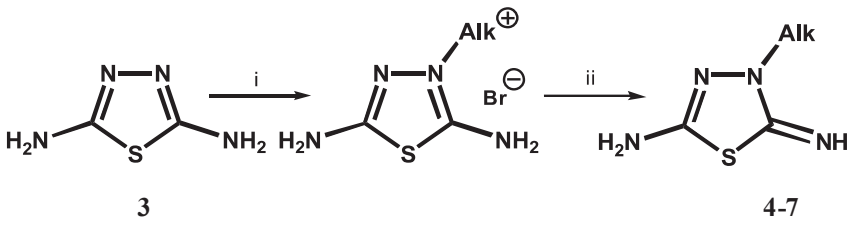
Results and Discussion

2,5-Diamino-1,3,4-thiadiazole (**3**) can exist in two forms, *i.e.* as thiadiazoline (**3a**) and thiadiazolinone (**3b**).[14]



3a **3b**

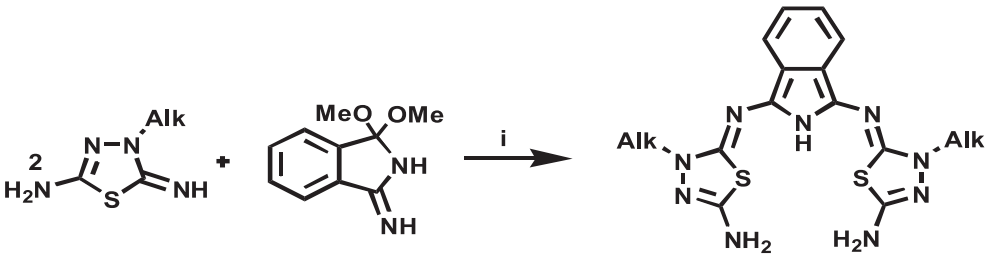
We succeeded in obtaining of thiadiazolinone tautomer by the substitution of the proton located in 1-position of 2,5-diamino-1,3,4-thiadiazole by alkyl group following the alkylation procedure by alkylbromide in boiling MeOH elaborated by us earlier.[15] As a result the compounds **4-7** were obtained following Scheme 1 and characterized by elemental analysis, UV-vis, IR, and ^{1}H NMR spectra and mass-spectrometry.



3 **4-7**

4 – Alk = C_5H_{11}, **5** – Alk = $C_{10}H_{21}$, **6** – Alk = $C_{12}H_{25}$, **7** - Alk = $C_{15}H_{31}$
i – *n*-AlkBr, MeOH, 24 h, boil. **ii** – NH_4OH.

Scheme 1.



4 - 7 **8** **9 - 12**

i: MeOH, 40- 45 ^{0}C, 15 h.
4, 9 – Alk = C_5H_{11}, **5, 10** – Alk = $C_{10}H_{21}$, **6, 11** – Alk = $C_{12}H_{25}$, **7, 12** – Alk = $C_{15}H_{31}$

Scheme 2.

Compounds **9-12** were synthesized for the first time by interaction of **4–7** with 1,1-dimethoxy-3-iminoisoindoline in molar ratio 2:1 in MeOH at 40-45 ºC for 15 hours (Scheme 2).

Compounds **9-12** were separated by pouring the reaction masses into water, a precipitate was filtered and then purified on column with alumina using a mixture of CH_2Cl_2:MeOH:hexane = 10:1:3. The obtained bright-red solids are soluble in the most of organic solvents and contain eventually a mixture of regio-isomeres, which we could not separate in this work. The introduction of dodecyl or pentadecyl fragments into the thiadiazole ring changes the aggregation state. The compounds **11** and **12** are wax-like substances which exhibit a strong fluorescence in organic solvents under UV light.

MALDI-TOF mass-spectrometry was applied to prove the structure of synthesized compounds. The mass-spectrum of **9** is shown in Figure 1. A good correlation of calculated and experimental *m/z* values with characteristic isotopic distribution for molecular ion proves the srtucture of ABA-type product which contains two alkylthiadiazole (A) and one isoindole (B) fragments (Figure 2).

The characteristic bands (2954, 2924, 2852 cm^{-1}) of stretching C-H vibrations of alkyl fragments are seen in the IR spectra of compounds **9-12**. The absorption bands at 3411 and 3296 cm^{-1} can be assigned to the stretching vibrations of N-H bonds in amino- and iminogroups.

A series of signals located at 0.91, 1.29, 1.41, 1.97, 2.21 and 4.5 ppm in the ^{1}H NMR spectra of **9-12** is assigned to protons of the alkyl groups and multiplet at 7.58 – 7.90 ppm to aromatic protons. Integral intensities of these signals confirm this assignment. These results are in agreement with the data reported [9] for the compounds of ABA-type with 1-dodecyl-1,2,4-triazole unit. Most probably the broad signal at 7.24 ppm can be induced by the resonance of protons of amino- and iminogroups. This signal disappears after a small amount of D_2O was dropped into.

^{13}C NMR spectrum of compound **12** is characterized by the presence of three series of signals assigned to carbon

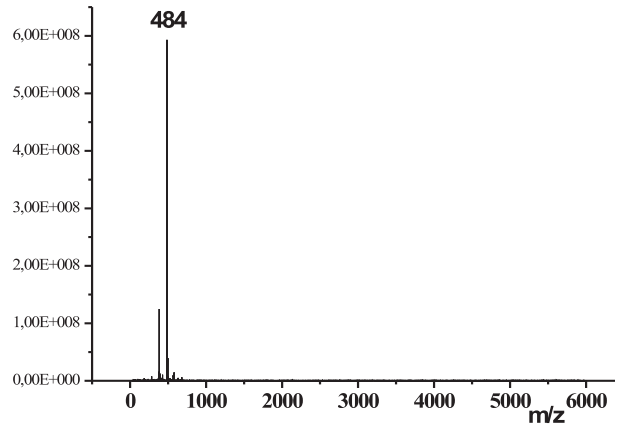


Figure 1. Mass-spectrum of compound **2.**

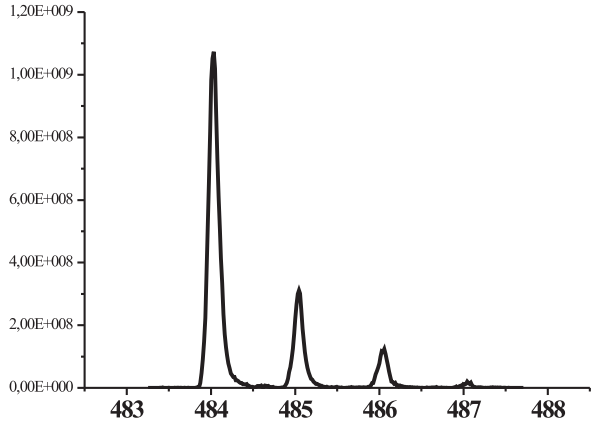


Figure 2. Calculated and experimental *m/z* magnitudes for **2.**

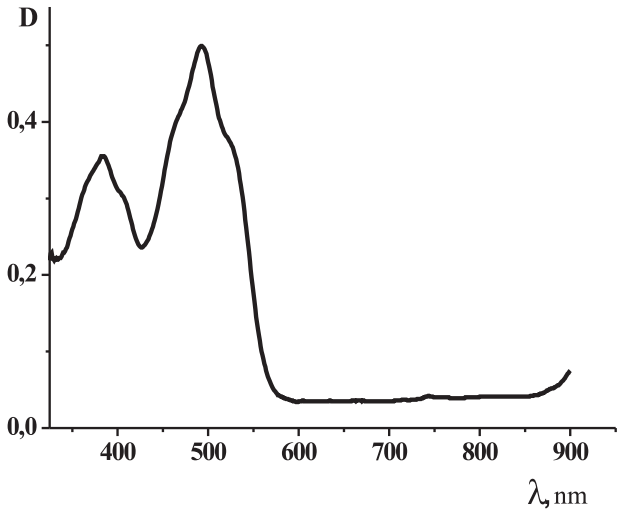


Figure 3. UV-vis spectrum of **9** in MeOH (c = 1.66·10^{-5} M).

atoms of a thiadiazole ring (172.4, 167.8 ppm), isoindole rings (139.5, 134.3, 132.7, 131.7, 123.6, 122.5), and pentadecyl groups (51.1, 31.9, 29.69, 29.65, 29.61, 29.5, 29.4, 29.3, 29.0, 28.6, 26.4, 22.7, 14.1 ppm). There are also two signals of C-atoms of pyrrole fragments located at 164.4, 160.5 ppm and their positions are in good agreement with the data for macroheterocyclic compounds sythesized earlier.[9]

UV-vis spectra of synthesized compounds **9-12** are quite similar. In the spectrum of pentyl substituted three-unit product **9** shown as an example (Figure 3) one can see two main absorption bands with maxima at 384 and 495 nm, and the bands of lower intensity which appear as inflexions at 404, 462 and 527 nm.

Quantum chemistry calculations of 1,3-bis[(5-amino-3-pentyl-1,3,4-thiadiazol-2(*3H*)-ylideneamino)]-2*H*-isoindole **9** having C_{2v} symmetry were carried out with full geometry optimization by DFT B3LYP 6-31G(*d,p*) method implemented in GAMESS (PC) program package.[14] Figure 4

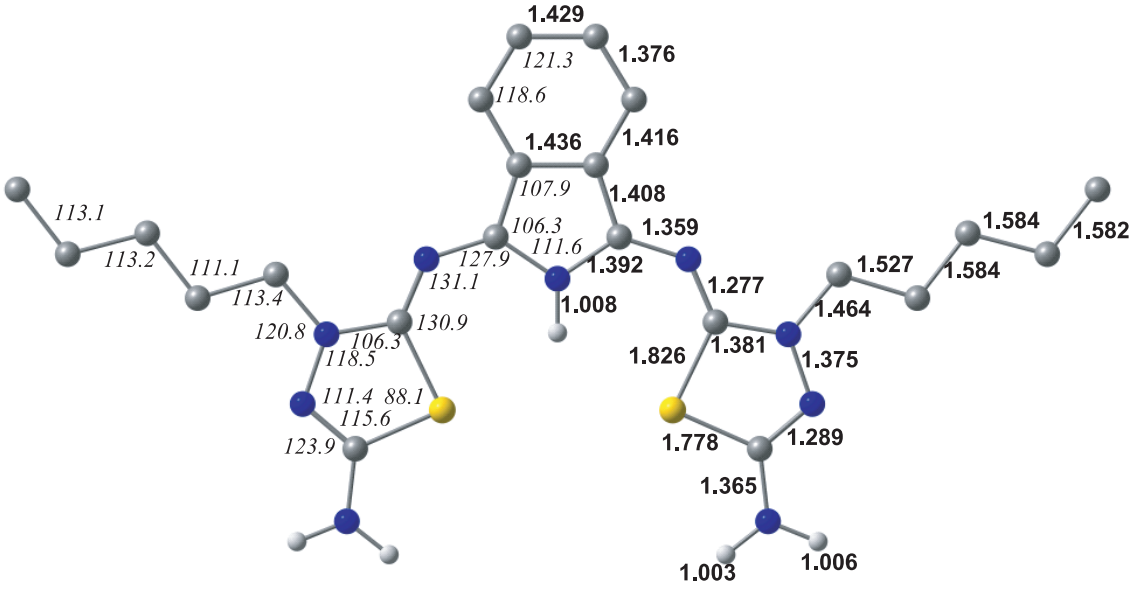


Figure 4. .The model of 1,3-bis[(5-amino-3-pentyl-1,3,4-thiadiazol-2(*3H*)-ylideneamino]-2*H*-isoindole **9**, bond lengths (Å), valence angles (degree). H-Atoms of C-H bonds are eliminated for the sake.

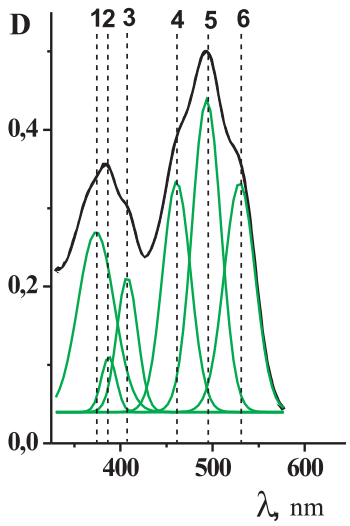


Figure 5. The experimental UV-vis spectrum of **9** in MeOH and spectrum, decomposed into several Gaussian functions.

shows the optimized molecular structure and bond lengths. The framework of the molecule having alkyl groups at N-atoms of the thiadiazole rings adjacent to the isoindole unit is planar. The sulfur atoms are separated by 4.301 Å.

The results of TD DFT calculations of the first ten singlet-singlet electron transfers are given in Table 1.

Table 1. Calculated data of wave-length (nm), strength of oscillator (*f*) and the decomposition of experimental spectrum into several Gaussian functions.

Gaussian constituents of the experimental spectrum		Calculated data (TD DFT)	
λ, nm	Height	*nm*	*f*
374	0.23		
387	0.07	347	0.18
407	0.17		
461	0.29	470	0.53
493	0.40		
529	0.29		

The experimental spectrum of **9** (black line) was decomposed into its Gaussian components (red line) (Figure 5). Hence a good correlation between quantum chemistry calculations and experimental UV-vis spectra of compound **9** can be another proof of structure of three-unit products of ABA-type.

References

1. Evidge J.A., Linstead R.P. *J. Chem. Soc*. **1952**, 5008-5012.
2. Elvidge J.A., Linstead R.P. *J.Chem.Soc*. **1952**, 5000-5007.
3. Elvidge J.A., Golden J.H. *J. Chem. Soc*. **1957**, 700-709.
4. Linstead R.P. *J .Org. Chem*. **1953**, 2873-2884.
5. Clark P.F., Elvidge J.A., Linstead R.P. *J. Chem. Soc*. **1954**, *15*, 2490-2497.
6. Scruggs J.A., Robinson M.A. *Inorg. Chem*. **1967**, *6*, 1006-1010.
7. Siegl W.O. *Inorg. Chem*. **1974**, *10*, 825-832.
8. Siegl W.O. *J .Org. Chem*. **1977**, *42*, 1872-1878.
9. Gema de la Torre, Torres T. *J. Org. Chem*. **1996**, *61*, 6446-6449.
10. Granovsky A.A. *PC GAMESS version 7.1.E (Firefly), build number 5190*, http://classic.chem.msu.su/gran/gamess/index.html
11. Zhurko G.A. http://www.chemcraftprog.com
12. Patent RF № 2313523. Danilova E.A., Islyaikin M.K., Kolesnikov N.A., Melenchuk T.V. B.I. № 36 from 27.12.07 (in Russ.).
13. Baumann F., Binert B., Röch G., Vollmann H., Wolf W. *Angew. Chem*. **1956**, *68*, 133-150.
14. Bambas L. *Five-Membered Heterocyclic Compounds with Nitrogen and Sulfur or Nitrogen, Sulfer, and Oxygen*. New York, London: Interscience publishers LTD, **1952**, 124-142.
15. Danilova E.A., Melenchuk T.V., Stryapan M.G., Islyaikin M.K. *Zh. Obsch. Khim*. **2008**, *78*, 480-481 (in Russ.).

Received 21.04.2009
Accepted 03.07.2009