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Synthesis and Properties of Substituted 3,5-Bis(3-imino-2,3-dihydro-1*H*-isoindol-1-ylideneamino)-1,2,4-thiadiazoles

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Abstract—3,5-Bis(3-imino-2,3-dihydro-1*H*-isoindol-1-ylideneamino)-1,2,4-thiadiazoles have been synthesized by reaction of 3,5-diamino-1,2,4-thiadiazole with methoxy and diimino derivatives of 4-nitro-, 4-bromo-5-nitro-, 4-phenylsulfanyl-, and 4,5-bis(phenylsulfanyl)phthalonitriles.

Keywords: 3,5-diamino-1,2,4-thiadiazole, phthalonitrile, macroheterocyclic compounds

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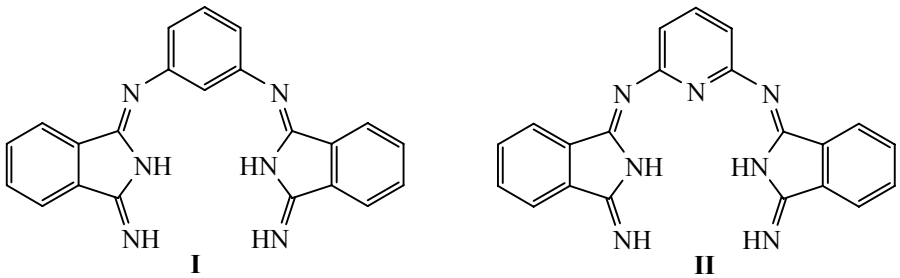
Bis(3-imino-2,3-dihydro-1*H*-isoindol-1-ylideneamino)arenes are intermediate products in the synthesis of symmetrical and unsymmetrical macroheterocyclic compounds. They can be prepared by reaction of 1,3-diimino- or 1,1-dialkoxy-3-imino-2,3-dihydro-1*H*-isoindoles with aromatic diamines at a ratio of 2 : 1 [1]. Reactions of bis(3-imino-2,3-dihydro-1*H*-isoindol-1-ylideneamino)arenes with an equimolar amount of the same diamine or 1,3-diimino-2,3-dihydro-1*H*-isoindole yield ABAB or ABBB macroheterocycles. Despite structural similarity, such compounds exhibit different reactivities. For example, compound **I** having a central benzene fragment reacts with 1,3-diimino-2,3-dihydro-1*H*-isoindole to give macrocycle consisting of three isoindole and one benzene fragment [1], whereas no analogous product could be obtained from pyridine derivative **II** [2]. Nevertheless, bis(3-imino-2,3-dihydro-1*H*-isoindol-1-ylideneamino)arenes and their metal complexes can be used to synthesize ABBB and ABBABB macroheterocycles [1, 2] (Scheme 1).

Numerous bis(3-imino-2,3-dihydro-1*H*-isoindol-1-ylideneamino)arenes with various heteroaromatic fragments have been reported (see, e.g., [3–7]). However, a few data are available on their analogs with a 1,2,4-thiadiazole fragment [8].

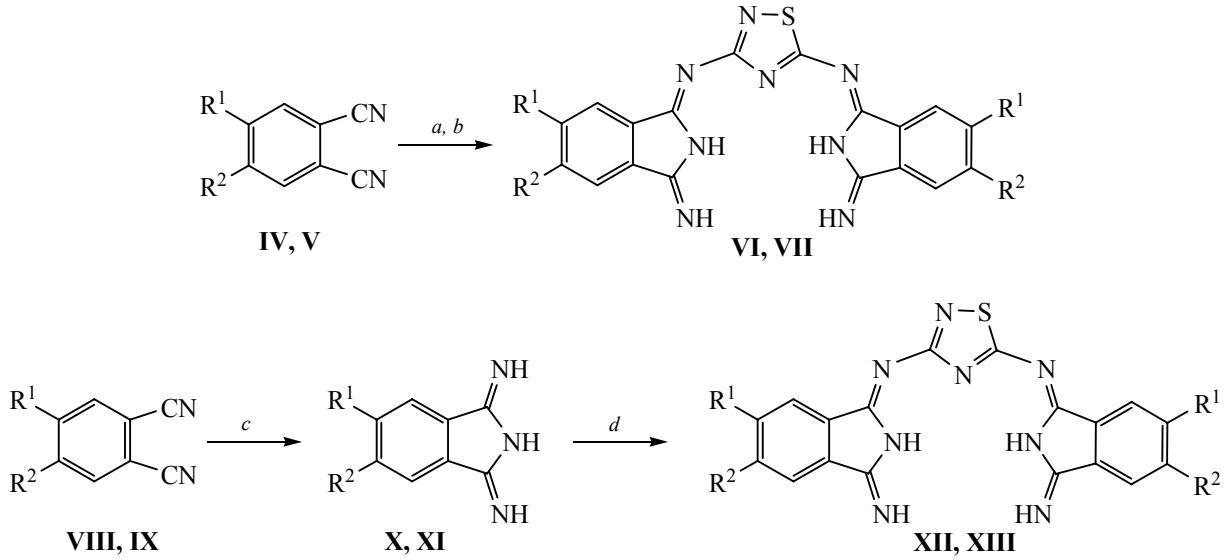
Wide application of 1,2,4-thiadiazoles as pharmacophores in different fields of medicinal chemistry stimulated the synthesis of a large series of their derivatives [9–12]. Taking into account high biological activity of compounds containing a 1,2,4-thiadiazole

Scheme 1.



I **II**

Scheme 2.



(*a*) MeOH, MeONa, 20°C, 2.5 h; (*b*) **III**, NH_4Cl, 40–45°C, 20 h; (*c*) NH_3, MeOH, MeONa, 3.5 h; (*d*) **III**, MeOH, 40–45°C, 6 h. R^1 = SPh, R^2 = H (**IV, VI**), $R^1 = R^2$ = SPh (**V, VII**), $R^1 = NO_2$, R^2 = H (**VIII, X, XII**), $R^1 = NO_2$, R^2 = Br (**IX, XI,**

fragment, we envisioned that substituted 3,5-bis(3-imino-2,3-dihydro-1*H*-isoindol-1-ylideneamino)-1,2,4-thiadiazoles and macroheterocyclic compounds derived therefrom could be biologically active.

The present work was aimed at synthesizing new substituted three-unit compounds containing a 1,2,4-thiadiazole fragment and studying their properties. Compounds **VI**, **VII**, **XII**, and **XIII** were synthesized by condensation of substituted 1,3-diimino2,3-dihydro-1*H*-isoindoles **X** and **XI** or phthalonitriles **IV** and **V** with 1,2,4-thiadiazole-3,5-diamine (**III**) in methanol at 40–45°C. The products were isolated as orange powders readily soluble in DMF. Compounds **VI**, **XII**, and **XIII** were mixtures of regioisomers which we failed to separate (Scheme 2).

The structure of **VI**, **VII**, **XII**, and **XIII** was confirmed by their electronic absorption, NMR, IR, and mass spectra and elemental analyses. Their IR spectra contained absorption bands at 1667 and 1627 cm^{-1} due to bending vibrations of the N–H groups and stretching vibrations of the C=N bonds in the imino groups. Bands in the region 1599–1433 cm^{-1} were assigned to stretching vibrations of aromatic C=C bonds. In the IR spectra of nitro derivatives **XII** and **XIII**, as well as of initial diimines **X** and **XI**, we observed absorption bands at 1353–1341 cm^{-1} due to stretching vibrations of the nitro groups.

Compounds **VI**, **VII**, **XII**, and **XIII** displayed in the ^1H NMR spectra signals from aromatic protons and protons of the imino groups (δ 7.56–7.36 and 3.56/3.77 ppm, respectively, in the spectrum of **VII**). The electronic absorption spectra of all compounds were characterized by a strong absorption maximum in the near-UV region (λ 344–361 nm). The red shift of this maximum in the spectrum of **XIII** (λ 361 nm) is related to the effect of two strong electron-withdrawing substituents.

Ion peaks corresponding to the molecular and fragment ions were present in the mass spectra of **VI**, **VII**, **XII**, and **XIII**. The molecular ion peak in the mass spectrum (MALDI TOF) of **VII** had an *m/z* value of 806.2 $[M + H]^+$, which indicated its BAB structure; the isotope distribution in the molecular ion cluster (see figure) conformed to the calculated ratio. The elemental analyses compositions of **VI**, **VII**, **XII**, and **XIII** were consistent with the assumed structure.

EXPERIMENTAL

The electronic absorption spectra were recorded in the region 250–800 nm on a Hitachi U-2001 spectrophotometer at room temperature. The IR spectra were measured in KBr on a Thermo Nicolet Avatar 360 FT-IR ESP spectrometer. The NMR spectra were taken on a Bruker DRX 500 instrument using tetramethylsilane

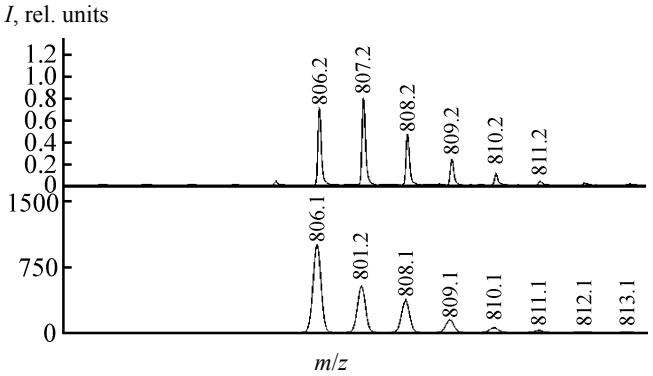
as internal reference. The mass spectra (MALDI TOF, 1,8-dihydroxy-9,10-dihydroanthracen-9-one as matrix) were obtained on VG Autospec and Bruker Reflex III instruments. The elemental compositions were determined on a Flash EA 1112 CHNS-O analyzer.

1,2,4-Thiadiazole-3,5-diamine (**III**) [13], 4-(phenylsulfanyl)phthalonitrile (**IV**) [14], and 4,5-bis(phenylsulfanyl)phthalonitrile (**V**) [15] were prepared according to known procedures.

3,5-Bis[3-imino-5(6)-(phenylsulfanyl)-2,3-dihydro-1*H*-isoindol-1-ylideneamino]-1,2,4-thiadiazole (VI). Phthalonitrile **IV**, 2.7 mmol, was added at 20–25°C to a solution of sodium methoxide prepared from 0.062 g (2.7 mmol) of sodium and 5 mL of anhydrous methanol. The mixture was stirred for 2–3 h at room temperature under argon, 0.145 g (2.7 mmol) of ammonium chloride was added, the mixture was stirred for 10 min, and 0.157 g (1.36 mol) of thiadiazole **III** was added. The mixture was stirred for 20 h at 40–45°C, cooled, and poured into water, and the precipitate was filtered off, washed with water and acetone, and dried in air. Yield 87.3 mg (35.1%). IR spectrum, ν, cm^{-1}: 3417, 3300, 3195 (N–H), 3124, 2956, 2922, 2851 (C–H), 1726, 1627, 1539, 1520, 1470, 1409, 1352, 1301, 1155, 1112, 1068, 1020, 833, 741, 691. ^1H NMR spectrum ($CDCl_3$, 200 MHz), δ, ppm: 8.25 s (2H, N^2H), 7.43–7.71 m (16H, H_{arom}), 3.17–3.79 s (2H, =NH). Electronic absorption spectrum (MeOH), λ_{max}, nm (logε): 254 (4.45), 305 (4.07), 345 (4.03). Mass spectrum (MALDI TOF): *m*/*z* 589 $[M]^+$. Found, %: C 60.83; H 3.02; N 18.83; S 16.04. $C_{30}H_{20}N_8S_3$. Calculated, %: C 61.21; H 3.42; N 19.03; S 16.34. *M* 588.7.

3,5-Bis[3-imino-5,6-bis(phenylsulfanyl)-2,3-dihydro-1*H*-isoindol-1-ylideneamino]-1,2,4-thiadiazole (VII) was synthesized in a similar way from 34.4 mg of 4,5-bis(phenylsulfanyl)phthalonitrile. Yield 15 mg (38%). IR spectrum, ν, cm^{-1}: 3221 (N–H), 3052, 2958, 2920, 2848 (C–H), 1725, 1667, 1599, 1514, 1473, 1443, 1372, 1334, 1158, 1070, 1022, 907, 751, 707, 691, 614, 456. ^1H NMR spectrum ($CDCl_3$, 200 MHz), δ, ppm: 8.25 s (2H, N^2H), 7.56–7.36 m (26H, H_{arom}), 3.56–3.77 s (2H, =NH). Electronic absorption spectrum (CH_2Cl_2): λ_{max} 344 nm. Mass spectrum (MALDI TOF): *m/z* 806 $[M + H]^+$. Found, %: C 61.20; H 3.01; N 18.86; S 16.91. $C_{30}H_{20}N_8S_3$. Calculated, %: C 62.06; H 3.51; N 18.92; S 16.51. *M* 805.03.

5-Nitro-2,3-dihydro-1*H*-isoindole-1,3-diimine (X). Phthalonitrile **VIII**, 15.7 mmol, was added at 20–25°C to a solution of sodium methoxide prepared from 0.15 g (6.5 mmol) of sodium and 11 mL of anhydrous methanol. A weak stream of dry ammonia was passed through the mixture over a period of 30 min at 20–25°C, and the mixture was heated for 3 h under reflux. After cooling, the precipitate was filtered off, washed with water and acetone, and dried under reduced pressure at room temperature. Yield 1.31 g (44%), mp 220–223°C (decomp.). IR spectrum (KBr), ν, cm^{-1}: 3366, 3322, 3251, 3007 (N–H), 1687 (C=O), 1641, 1612, 1522 (NO_2), 1455, 1414, 1347 (NO_2), 1302, 1242, 1174, 1135, 1070, 901, 805.



Experimental (MALDI TOF) and calculated isotope distribution of the molecular ion of compound **VII**.

5-Bromo-6-nitro-2,3-dihydro-1*H*-isoindole-1,3-diimine (XI) was synthesized in a similar way. Yield 2.84 g (67%), mp 217–220°C (decomp.). IR spectrum (acetone), ν, cm^{-1}: 3267, 2926 (NH), 2862, 2732, 1710 (C=O), 1603, 1536 (NO_2), 1476, 1353 (NO_2), 1269, 1172, 934, 664, 540 (C–Br), 475. Found, %: C 38.20; H 2.04; N 19.32. $C_8H_5BrN_4O_2$. Calculated, %: C 35.71; H 1.87; N 20.82.

3,5-Bis[3-imino-5(6)-nitro-2,3-dihydro-1*H*-isoindol-1-ylideneamino]-1,2,4-thiadiazole (XII). A mixture of 0.33 g (2.8 mmol) of thiadiazole **III** and 1 g (5.6 mmol) of diimine **X** in 14 mL of methanol was stirred for 6 h at 40–45°C. The mixture was diluted with 30 mL of water, and the precipitate was filtered off, washed with water, hot methanol, and acetone, and dried. Yield 0.12 g (9%). IR spectrum, ν, cm^{-1}: 3319 (NH), 3099, 2933, 2860, 1719 (C=O), 1636, 1533 (NO_2), 1456, 1416, 1346 (NO_2), 1335, 1172, 1135, 1072, 906, 806, 709. Mass spectrum (MALDI TOF): *m*/*z*: 462 $[M]^+$. Found, %: C 46.88; H 3.29; N 28.26; S 1.60. $C_{18}H_{10}N_{10}O_4S_1$. Calculated, %: C 46.80; H 2.18; N 29.29; S 1.93. *M* 462.02.

3,5-Bis[5(6)-bromo-3-imino-6(5)-nitro-2,3-dihydro-1*H*-isoindol-1-ylideneamino]-1,2,4-thiadiazole (XIII) was synthesized in a similar way from 0.05 g (0.43 mmol) of compound **III** and 0.23 g (0.86 mmol) of diimine **XI** in 10 mL of methanol. Yield 0.18 g (67%). IR spectrum (MeOH), ν, cm^{-1}: 3325, 3208 (NH), 2862, 2924, 2859, 1726 (C=O), 1615, 1539 (NO_2), 1460, 1341 (NO_2), 1276, 1184, 934, 619, 547 (C–Br). Electronic absorption spectrum (MeOH), λ_{max}, nm (log ε): 243 (3.99), 297 (3.91), 361 (3.65), 384 (3.58). Found, %: C 34.90; H 2.90; N 21.65; S 5.4. $C_{18}H_8Br_2N_{10}O_4S_1$. Calculated, %: C 34.86; H 1.30; N 22.58; S 5.17. *M* 620.19.

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