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Synthesis of New Naphthostyryl Derivatives via Nucleophilic Substitution of Methylthio Group with *C*-Nucleophiles. Molecular and Crystal Structure of (*Z*)-2-{Benzo[*cd*]indol-2(1*H*)-ylidene}-2-(4-phenythiazol-2-yl)acetonitrile

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Abstract—Reactions of 2-(methylthio)benzo[*cd*]indol-1-inium iodide with *C*-nucleophiles proceed via substitution of methylthio group to afford new naphthostyryl derivatives. The latter were used in synthesis of the Hantzsch thiazoles. Structure of (*Z*)-2-{benzo[*cd*]indol-2(1*H*)-ylidene}-2-(4-phenylthiazol-2-yl)acetonitrile was studied by XRD.

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Naphthostyryl derivatives (benzo[cd]indoline) are intermediates in the synthesis of dyes and biologically active compounds [1]. In particular, highly effective antineoplastic agents have been found among the specimens of this class of heterocycles [2].

Continuing studies of reactions of nucleophilic substitution in a series of nitrogen-containing heterocycles [3–5], in the present work we investigated the interaction of 2-(methylthio)benzo[cd]indol-1-inium I with CH-acids IIa–IId as C-nucleophiles. The reaction proceeded at reflux of the starting reactants in anhydrous ethanol in the presence of an equimolar amount of triethylamine to give new compounds IIIa– IIId. Reaction of I with malonodinitrile derivative IV occurred possibly via an intermediate A formation to yield new heterocyclic systems, 10-amino-8-imino-8H-benzo[cd]pyrido[1,2-a]indol-9,10-dicarbonitrile V.

Spectral characteristics and chemical transformation confirmed the structure of compounds **IIIa–IIId** and **V**. For instance, in their IR spectra characteristic absorption bands appeared of the stretching vibrations of the conjugated cyano group (2190–2211 cm⁻¹) and amide moiety (1668–1691 cm⁻¹). The ¹H NMR spectra contained the signals of the protons of the naphthalene and amide fragments in their respective regions, as well as the proton signal of $N^{1}H$ as a broadened singlet at 11.92-13.54 ppm.

The Hantzsch reaction of **III** with α -bromoketones **VIa** and **VIb** resulted in the substituted thiazoles **VIIa** and **VIIb** (method *a*). The latter were readily obtained by reacting thiazolylacetonitriles **VIIIa** and **VIIIb** with salt **I** (method *b*) (see Scheme 1).

Characteristic of mass spectra of (Z)-2-{benzo[*cd*]indol-2(1*H*)-ylidene}-2-(4-arythiazol-2-yl)acetonitriles **VIIa** and **VIIb** is the presence of molecular ions peaks of an odd value, confirming an odd number of the nitrogen atoms in their molecules, and of low-intensity peaks $[M + 2]^+$ indicating the sulfur atom presence [10].

An unambiguous assignment to E- or Z-isomer was not possible to be made on the basis of the spectral data only. Therefore the structure of 2-{benzo[cd]indol-2(1H)-ylidene}-N-(2-furan-2-ylmethyl)-2-cyanoacetamide **VIIa** was studied by XRD analysis (see figure, Tables 1, 2).

The phenyl substituent was located in the plane of the thiazole ring [torsion angle $N^3C^{15}C^{17}C^{18}$ 1.8(3)°]. In this position the steric repulsion between the *ortho*hydrogen atoms (short intramolecular contact H^{22} ... H^{16}





II, **III**, X = S(a), O(b-d); R = H(a, b), Ph (c), furan-2-ylmethyl (d); VI–VIII, Ar = Ph (a), 2,4,6-(Me)_3C_6H_2(b).

is 2.23 Å while the sum of the van der Waals radii is 2.32 Å [6]) is compensated by the π -conjugation between the rings, as well as by the attractive contact H¹⁸...N³ 2.54 Å (sum of the van der Waals radii is 2.66 Å).

There was a small turn around the single $C^{12}-C^{14}$ bond [torsion angle $C^{1}C^{12}C^{14}N^{3}$ 6.3(3)°]. Flattened conformation of the molecule was stabilized by weak hydrogen bonding $N^{1}-H^{1}\cdots N^{3}$ (H···N 2.17 Å, N–H···N 125°) [7].



General view of the molecule of VIIa. Thermal ellipsoids of non-hydrogen atoms are shown at the 50% probability.

Table 1. Bond lengths in the structure of VIIa

Bond	<i>d</i> , Å	Bond	<i>d</i> , Å
S^1C^{14}	1.726(2)	C^6C^7	1.373(4)
S^1C^{16}	1.702(2)	C^7C^8	1.408(3)
N^1C^1	1.366(2)	C^8C^9	1.410(3)
N^1C^4	1.399(3)	C ⁹ C ¹⁰	1.373(3)
$N^{2}C^{13}$	1.145(3)	$C^{10}C^{11}$	1.409(3)
$N^{3}C^{14}$	1.316(2)	$C^{12}C^{13}$	1.426(3)
$N^{3}C^{15}$	1.380(3)	$C^{12}C^{14}$	1.451(3)
C^1C^2	1.470(3)	$C^{15}C^{16}$	1.361(3)
$C^{1}C^{12}$	1.371(3)	$C^{15}C^{17}$	1.473(3)
C^2C^3	1.397(3)	$C^{17}C^{18}$	1.380(3)
$C^{2}C^{11}$	1.380(3)	$C^{17}C^{22}$	1.382(3)
$C^{3}C^{4}$	1.399(3)	$C^{18}C^{19}$	1.379(3)
$C^{3}C^{8}$	1.392(3)	$C^{19}C^{20}$	1.362(3)
C^4C^5	1.363(3)	$C^{20}C^{21}$	1.370(3)
C^5C^6	1.418(3)	$C^{21}C^{22}$	1.369(3)

Among the intermolecular interactions in the crystal the shortened contacts $S^{1}...N^{2i}$ [i: -x, 1 - y, -z] 3.28 Å and $S^{1}...S^{1i}$ 3.53 Å should noted (sum of the van der Waals radii are 3.32 and 3.68 Å, respectively), which can be attributed to the σ -hole interactions.

EXPERIMENTAL

¹H NMR spectra were recorded on a Bruker AVANCE DRX-500 (500.07 MHz) in DMSO- d_6 solution, internal reference TMS. Mass spectrum of **IIIa** was registered on a Chrommas GC/MS-Hewlett-Packard 5890/5972 instrument (column HP-5MS, chemical ionization, 70 eV) in CH₂Cl₂ solution. Mass spectra of other compounds were taken on a MKh-1321 instrument (70 eV) with direct admission of the sample into the ion source. IR spectra were recorded on a Perkin-Elmer FIR Spectrum One spectrometer from KBr pellets. Melting points were measured on a Koeffler heating block. The reaction progress and purity of the obtained compounds were monitored by TLC method [Silufol UV-254 plates, eluent acetone–hexane (3 : 5), developing with iodine vapor or UV].

X-ray diffraction analysis. Crystals of **VIIa** are monoclinic, $C_{22}H_{25}N_3S$, at 298 K: *a* 4.8083(3), *b* 19.2612(12), *c* 18.3513(11) Å, β 95.030(5)°, *V* 1693.05(18) Å³, M_r 363.51, *Z* 4, space group $P2_1/c$, d_{calc} 1.426 g cm⁻³, $\mu(MoK_{\alpha})$ 0.203 mm⁻¹, F(000) 776. Parameters of the unit cell and intensities of 12091 reflections (3960 independent, R_{int} 0.047) were measured on an automatic four-circle diffractometer

 Table 2. Bond angles in the structure of VIIa

Angle	ω, deg	Angle	ω, deg
$C^{16}S^1C^{14}$	89.22(10)	C ⁹ C ¹⁰ C ¹¹	123.2(2)
$C^1N^1C^4$	111.57(18)	$C^{2}C^{11}C^{10}$	117.6(2)
$C^{14}N^3C^{15}$	110.64(18)	$C^{1}C^{12}C^{13}$	119.0(2)
$N^1C^1C^2$	106.54(19)	$C^{1}C^{12}C^{14}$	123.58(19)
$N^{1}C^{1}C^{12}$	123.86(19)	$C^{13}C^{12}C^{14}$	117.4(2)
$C^{12}C^1C^2$	129.6(2)	$N^{2}C^{13}C^{12}$	178.4(3)
$C^3C^2C^1$	105.39(19)	$N^3C^{14}S^1$	114.50(16)
$C^{11}C^2C^1$	136.4(2)	$N^{3}C^{14}C^{12}$	123.9(2)
$C^{11}C^2C^3$	118.2(2)	$C^{12}C^{14}S^1$	121.63(16)
$C^2C^3C^4$	110.8(2)	$N^{3}C^{15}C^{17}$	119.45(19)
$C^8C^3C^2$	125.7(2)	$C^{16}C^{15}N^3$	114.46(19)
$C^8C^3C^4$	123.5(2)	$C^{16}C^{15}C^{17}$	126.1(2)
$C^3C^4N^1$	105.7(2)	$C^{15}C^{16}S^1$	111.18(17)
$C^5C^4N^1$	134.0(2)	$C^{18}C^{17}C^{15}$	121.4(2)
$C^5C^4C^3$	120.3(2)	$C^{18}C^{17}C^{22}$	117.2(2)
$C^4C^5C^6$	117.0(2)	$C^{22}C^{17}C^{15}$	121.5(2)
$C^7 C^6 C^5$	122.9(3)	$C^{19}C^{18}C^{17}$	121.2(2)
$C^6C^7C^8$	120.3(3)	$C^{20}C^{19}C^{18}$	120.6(2)
$C^3C^8C^7$	116.0(2)	$C^{19}C^{20}C^{21}$	119.1(2)
$C^3C^8C^9$	114.8(2)	$C^{22}C^{21}C^{20}$	120.5(2)
$C^7 C^8 C^9$	129.2(3)	$C^{21}C^{22}C^{17}$	121.6(2)
$C^{10}C^9C^8$	120.5(3)		

Xcalibur 3 (Mo K_{α} -irradiation, graphite monochromator, CCD detector, ω -scanning, $2\theta_{max}$ 57.8°).

The structure was solved by the direct method using SHELX-97 software [8]. Positions of the hydrogen atoms were geometrically calculated and refined in a *rider* model with $U_{iso} = 1.2U_{eq}$ of the carrier atom. The structure was refined with respect to F^2 using the full-matrix least-square method in anisotropic approximation for non-hydrogen atoms to wR_2 0.115 for 3960 reflections [R_1 0.057 for 2181 reflections with $F > 4\sigma(F)$, S 1.02]. Bond lengths and angles are given in Tables 1 and 2, respectively.

2-(Methylthio)benzo[*cd*]indol-1-inium iodide (I) was prepared by the method of [9].

(Z)-2-{Benzo[cd]indol-2(1H)-ylidene}-2-cyanoethanoamides (IIIa–IIId). A mixture of 3.3 g (10 mmol) of salt I, 10 mmol of CH-acid IIa–IId, and 1.4 mL (10 mmol) of triethylamine in 15 mL of anhydrous ethanol was refluxed for 1 h. After 1 day the formed precipitate was filtered off, washed with ethanol and hexane. (*Z*)-2-{Benzo[*cd*]indol-2(1*H*)-ylidene}-2-cyanoethanethioamide (IIIa). Yield 1.9 g (77%), yellow powder, mp 247–249°C (BuOH). IR spectrum, v, cm⁻¹: 3233–3415 (NH, NH₂), 2211 (C \equiv N). ¹H NMR spectrum, δ , ppm: 7.49–7.61 m (2H, H_{Ar}), 7.73 d (1H, H_{Ar}, *J* 6.8 Hz), 7.91 t (1H, H_{Ar}, *J* 7.3 Hz), 8.26 t (1H, H_{Ar}, *J* 8.0 Hz), 8.44–8.56 m (2H, H_{Ar}, NH₂), 9.34 br.s (1H, NH₂), 13.54 br.s (1H, N¹H). Mass spectrum, *m/z* (*I*_{rel}, %): 250 (100) [*M* – 1]⁺. Found, %: C 66.80; H 3.55; N 16.69. C₁₄H₉N₃S. Calculated, %: C 66.91; H 3.61; N 16.72. *M* 251.312.

(Z)-2-{Benzo[*cd*]indol-2(1*H*)-ylidene}-2-cyanoacetamide (IIIb). Yield 1.4 g (60%), yellow powder, mp 269–270°C (DMF). IR spectrum, v, cm⁻¹: 3290– 3398 (NH, NH₂), 2197 (C=N), 1668 (CONH). ¹H NMR spectrum, δ , ppm: 7.14–7.38 m (3H, 1H_{Ar}, NH₂), 7.44–7.62 m (2H, H_{Ar}), 7.83 t (1H, H_{Ar}, *J* 7.8 Hz), 8.15 d (1H, H_{Ar}, *J* 8.0 Hz), 8.41 d (1H, H_{Ar}, *J* 7.3 Hz), 11.92 br.s (1H, N¹H). Mass spectrum, *m*/*z* (*I*_{rel}, %): 237 (4) [*M* + 2]⁺, 236 (18) [*M* + 1]⁺, 235 (100) [*M*]⁺, 218 (88) [*M* – NH₃]⁺, 190 (86), 164 (41), 49 (9). Found, %: C 71.30; H 3.70; N 17.75. C₁₄H₉N₃O. Calculated, %: C 71.48; H 3.86; N 17.86. *M* 235.248.

(Z)-2-{Benzo[*cd*]indol-2(1*H*)-ylidene}-*N*-phenyl-2-cyanoacetamide (IIIc). Yield 2.4 g (76%), yellow powder, mp 268–269°C (DMF). IR spectrum, v, cm⁻¹: 3240–3398 (NH), 2190 (C=N), 1671 (CONH). ¹H NMR spectrum, δ , ppm: 7.07 t (1H, 1H_{Ar}, *J* 7.6 Hz), 7.21–7.42 m (3H, H_{Ar}), 7.50–7.68 m (4H, H_{Ar}), 7.87 t (1H, H_{Ar}, *J* 7.6 Hz), 8. 19 d (1H, H_{Ar}, *J* 8.0 Hz), 8. 49 d (1H, H_{Ar}, *J* 7.3 Hz), 9.62 br.s (1H, CONH), 12.02 br.s (1H, N¹H). Mass spectrum, *m/z* (*I*_{rel}, %): 313 (5) [*M* + 2]⁺, 312 (20) [*M* + 1]⁺, 311 (100) [*M*]⁺, 219 (88) [*M* – PhNH₂]⁺, 191 (49), 164 (46), 93 (52), 65 (18), 51 (7). Found, %: C 77.10; H 4.13; N 13.35. C₂₀H₁₃N₃O. Calculated, %: C 77.16; H 4.21; N 13.50. *M* 311.347.

(Z)-2-{Benzo[*cd*]indol-2(1*H*)-ylidene-*N*-(furan-2ylmethyl)}-2-cyanoacetamide (IIId). Yield 2.0 g (65%), yellow powder, mp 240–241°C (DMF). IR spectrum, v, cm⁻¹: 3283–3402 (NH), 2195 (C≡N), 1691 (CONH). ¹H NMR spectrum, δ , ppm: 4.40 d (2H, NCH₂, *J* 5.7 Hz), 6.25 d (1H, H³_{furan}, *J* 3.2 Hz), 6.37 d. d (1H, H⁴_{furan}, *J* 3.2, 1.9 Hz), 7.35 d (1H, H_{Ar}, *J* 6.8 Hz), 7.47–7.66 m (3H, H_{Ar}), 7. 85 t (1H, H_{Ar}, *J* 7.3 Hz), 8.17 d (1H, H_{Ar}, *J* 8.2 Hz), 8.35 t (1H, CONH, *J* 5.7 Hz), 11.99 br.s (1H, N¹H). Mass spectrum, *m/z* (*I*_{rel}, %): 316 (20) [*M* + 1]⁺, 315 (100) [*M*]⁺, 314 (6) [*M* – 1]⁺, 219 (31), 220 (10), 192 (43), 164 (30), 154 (15), 96 (11), 81 (72), 53 (19). Found, %: C 72.21; H 4.10; N 13.24. C₁₉H₁₃N₃O₂. Calculated, %: C 72.37; H 4.16; N 13.33. *M* 315.335.

10-Amino-8-imino-8H-benzo[*cd*]**pyrido**[**1,2***-a*]**indole-9,11-dicarbonitrile (V)** was obtained similarly from 3.3 g (10 mmol) of **I** and 1.3 g (10 mmol) of **IV**. Yield 2.5 g (90%), yellow powder, mp 332–333°C (DMF). IR spectrum, v, cm⁻¹: 3290–3415 (NH, NH₂), 2215 (C=N), 1649 [δ (NH₂)]. ¹H NMR spectrum, δ , ppm: 7.15–7.26 m (1H, H_{Ar}), 7.64 br.s (3H, =NH and NH₂), 7.81–8.06 m (2H, H_{Ar}), 8.35 d (1H, H_{Ar}, *J* 7.0 Hz), 8.45 d (1H, H_{Ar}, *J* 7.8 Hz), 8.61 (1H, H_{Ar}, *J* 8.6 Hz). Mass spectrum, *m/z* (*I*_{rel}, %): 284 (20) [*M* + 1]⁺, 283 (100) [*M*]⁺, 282 (5) [*M* – 1]⁺, 218 (75), 191 (21), 164 (17), 127 (11), 49 (25). Found, %: C 71.99; H 3.18; N 24.84. C₁₇H₉N₅. Calculated, %: C 72.08; H 3.20; N 24.72. *M* 283.296.

(Z)-2-{Benzo[cd]indol-2(1H)-ylidene}-2-(4-arythiazol-2-yl)acetonitriles (VIIa, VIIb). a. A mixture of 2.5 g (10 mmol) of amide IIIa and 10 mmol of the corresponding α -bromoketone VIa or VIb in 15 mL of DMF was stirred at 20°C for 1 h and incubated for 1 day. Then the reaction mixture was diluted with equal amount of water and filtered. The precipitate was washed with water, ethanol and hexane.

(*Z*)-2-{Benzo[*cd*]indol-2(1*H*)-ylidene}-2-(4-phenylthiazol-2-yl)acetonitrile (VIIa). Yield 3.2 g (92%), red needles, mp 218–220°C (BuOH). IR spectrum, v, cm⁻¹: 2925 (NH), 2195 (C=N). ¹H NMR spectrum, δ , ppm: 7.32–7.68 m (6H, H_{Ar}), 7.85 t (1H, H_{Ar}, *J* 7.6 Hz), 8.08 s (1H, H⁵_{thiazole}), 8.11–8.22 m (3H, H_{Ar}), 8. 41 d (1H, H_{Ar}, *J* 7.3 Hz), 11.66 br.s (1H, NH). Mass spectrum, *m*/*z* (*I*_{rel}, %): 353 (5) [*M* + 2]⁺, 351 (100) [*M*]⁺, 350 (19) [*M* – 1]⁺, 134 (3). Found, %: C 75.06; H 3.66; N 11.80. C₂₂H₁₃N₃S. Calculated, %: C 75.19; H 3.73; N 11.96. *M* 351.433.

(*Z*)-2-{Benzo[*cd*]indol-2(1*H*)-ylidene}-2-(4-mesitylthiazol-2-yl)acetonitrile (VIIb). Yield 3.2 g (81%), red powder, mp 209–211°C (BuOH). IR spectrum, v, cm^{-1} : 2923 (NH), 2206 (C=N). ¹H NMR spectrum, δ , ppm: 7.32–7.68 m (6H, H_{Ar}), 7.85 t (1H, H_{Ar}, *J* 7.6 Hz), 8.08 s (1H, H⁵_{thiazole}), 8.11–8.22 m (3H, H_{Ar}), 8. 41 d (1H, H_{Ar}, *J* 7.3 Hz), 11.66 br.s (1H, NH). Mass spectrum, *m*/*z* (*I*_{rel}, %): 395 (7) [*M* + 2]⁺, 394 (26) [*M* + 1]⁺, 393 (100) [*M*]⁺, 360 (18), 235 (9), 176 (6), 143 (4). Found, %: C 76.22; H 4.75; N 10.59. C₂₅H₁₉N₃S. Calculated, %: C 76.31; H 4.87; N 10.68. *M* 393.514.

b. Synthesis was performed similarly to the synthesis of III using 3.3 g (10 mmol) of I and 10 mmol

of thiazolylacetonitrile VIIIa or VIIIb. Yield 2.9 g (82%) for VIIa and 3.3 g (85%) for VIIb.

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