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Dedicated to Full Member of the Russian Academy of Sciences N.S. Zefirov on His 70th Anniversary

Synthesis and Structure of 4-Indolyl-5-(thieno[3,2-*b*]pyrrol-6-yl)imidazoles

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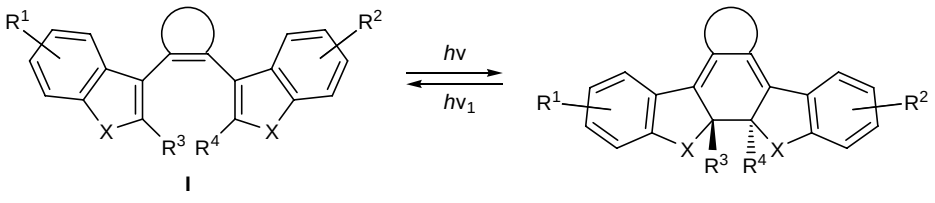
Abstract—A procedure was proposed for regioselective acylation of methyl 2-methyl-4*H*-thieno[3,2-*b*]-pyrrole-5-carboxylate with 2-(3-indolyl)-2-oxoacetyl chloride. Reactions of the resulting methyl 6-[2-(3-indolyl)-1,2-dioxoethyl]-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate with aromatic aldehydes and ammonium acetate in acetic acid afforded the corresponding methyl 6-[2-aryl-4-(3-indolyl)imidazol-5-yl]-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylates. The structure of methyl 6-[2-(4-chlorophenyl)-4-(3-indolyl)imidazol-5-yl]-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate was studied by X-ray analysis.

Bisindolylethenes like **I** exhibit a broad spectrum of biological activity [1, 2] and are potential photochromic compounds [3] (Scheme 1). As a rule, the indole fragments are bridged through maleic anhydride or maleimide moiety. A promising line in the design of new biologically active compounds in the series of indolyl-substituted ethenes involves variation of both the bridging group and heterocyclic fragments [2, 4]. We previously described the synthesis of compounds **II**–**IV** whose molecules contain indole and thiophene fragments bridged through a 1,2,4-triazine moiety [5].

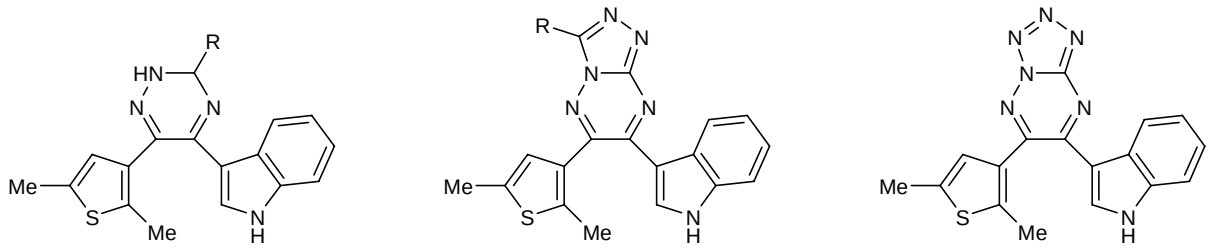
In the present article we report on the synthesis of compounds in which indole and thieno[3,2-*b*]pyrrole fragments are linked through an imidazole bridge. It is known that thienopyrroles as thia analogs of indole exhibit versatile biological activity [6, 7]. The imidazole fragment was built up starting from the corresponding α-dicarbonyl compound, following the ap-

Scheme 1.



I

X = NH, NR.



II **III** **IV**

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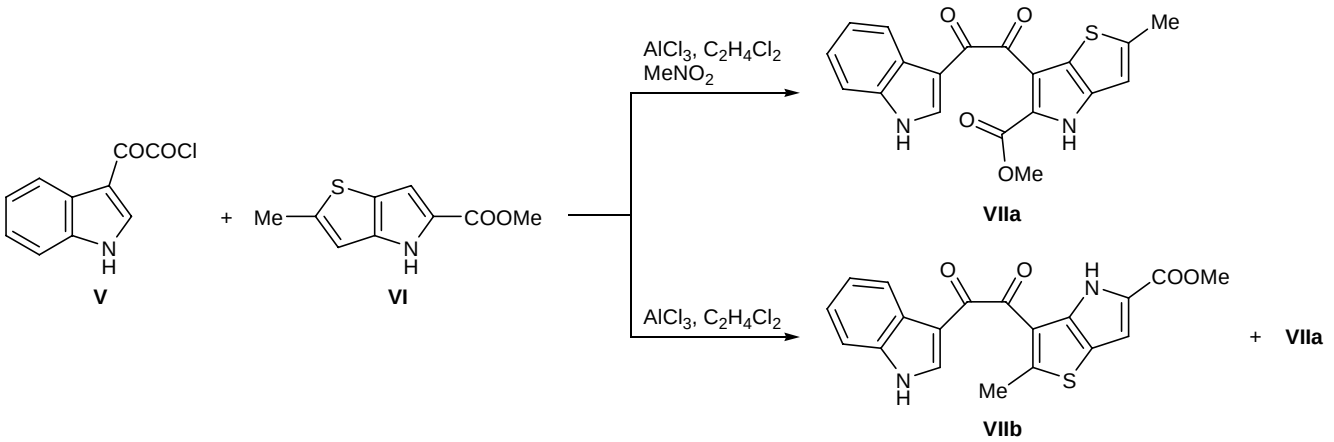
Scheme 2.

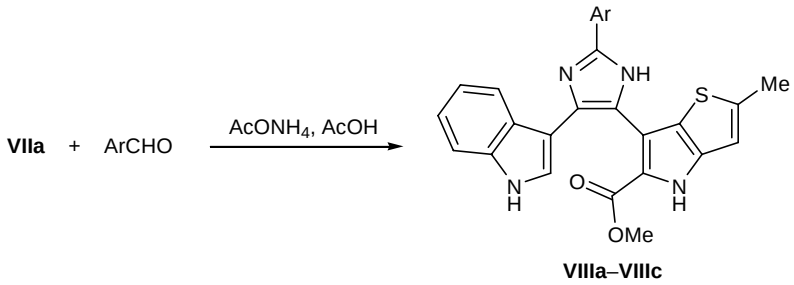


proach developed by us for the synthesis of bis-thienyl derivatives [8]. The required dicarbonyl compound was prepared by reaction of 2-(3-indolyl)-2-oxoacetyl chloride (**V**) with methyl 2-methyl-4*H*-thieno[3,2-*b*]-pyrrole-5-carboxylate (**VI**) (Scheme 2). We previously showed that regioselectivity in the acylation of thienopyrrole **VI** depends on the nature of Lewis acid and solvent [9]. In the present work we found that diketone **VIIa** is formed in a good yield when the reaction is carried out in a mixture of 1,2-dichloroethane and nitromethane in the presence of aluminum chloride. The reaction in dichloroethane leads to a mixture of compound **VIIa** and isomeric product **VIIb**. The addition of nitromethane not only makes the acylation regioselective but also shortens the reaction time. No reaction occurred in the presence of $SnCl_4$.

The ^{1}H NMR spectrum of compound **VIIa** contained singlets from protons in the methyl and methoxy groups and thiophene ring (δ 2.62, 3.35, and 6.80 ppm, respectively), multiplets from the indole protons [δ 7.24 (2H), 7.53 (1H), 8.02 (1H), and 8.25 ppm (1H)], and broadened singlets from the NH protons in the indole and pyrrole fragments (δ 12.10 and 12.75 ppm). Unlike diketone **VIIa**, signals from the methyl protons, proton in the pyrrole fragment, and protons of the ester group in the spectrum of **VIIb** appeared in a weaker field (by 0.1, 0.25, and 0.5 ppm, respectively). It was somewhat surprising that the 2-H signal of **VIIb** was displaced to an appreciable extent (by 0.18 ppm) while signals from the "aromatic" protons almost did not change their positions. The mass spectra of isomeric diketones **VIIa** and **VIIb** were essentially similar, except for considerably greater intensity of the $[IndCO]^+$ ion peak (*m*/*z* 144) in the spectrum of the latter.

By reaction of diketone **VIIa** with aromatic aldehydes and ammonium acetate in acetic acid we obtained the corresponding imidazole derivatives **VIIIa**–**VIIIc** (Scheme 3). Imidazoles in which the 4- and 5-positions are occupied by indolyl and thienopyrrolyl substituents were not reported previously. Therefore, we determined the steric structure and geometric parameters of molecule **VIIIa** by X-ray analysis (Fig. 1). The results unambiguously confirmed that the acylation occurred at position *6* of initial thienopyrrole **VI**. The molecule consists of four almost planar rings: central imidazole (Im), thienopyrrole (TP), indole (In), and benzene (B); in each ring, deviations of atoms

Scheme 3.



Ar = *p*-ClC_6H_4 (**a**), *p*-$MeOC_6H_4$ (**b**), *p*-$O_2NC_6H_4$ (**c**).

from the corresponding mean-square planes do not exceed 0.01 Å. All bond lengths in the imidazole ring are leveled: C^2–C^3 1.395, C^2–N^2 1.376, N^2–C^1 1.347, C^1–N^1 1.325, N^1–C^3 1.384 Å (the bond lengths were determined with an accuracy of no less than ±0.002 Å). The bond lengths in the thienopyrrole and indole rings have their usual values; they coincide within ±0.02 Å with the corresponding bond lengths in structurally related compounds, e.g., derivatives of dithieno-[3,2-*b*:2',3'-*d*]pyrrole [10, 11], indole-3-carvaldehyde, gramine [12], and bisindolylmaleimide [13]. An interesting specificity of the molecular structure is the presence of a planar fragment consisting of the Im, TP, and B rings. The dihedral angles between the rings are as follows: Im/TP 1.41°, Im/B 3.40°, and TP/B 3.11°. The bonds between the Im, TP, and B rings are shorter than the corresponding standard bonds: C^{1A}–C^1 1.458, $C^{6''}$–C^2 1.448 Å. These data suggest formation of a common conjugation system in the above planar fragment. The ester group also lies almost in that plane: the torsion angle $N^4C^{7''}C^{8''}O^1$ is 176.06°, the angle $C^{7''}C^{8''}O^2C^{9''}$ is 167.26°, and the indole ring is turned through an angle of 62.25° with respect to the Im–TP–B plane.

Another specific feature of the molecular structure of **VIIIa** is formation of intramolecular hydrogen bond betweeen the ester carbonyl oxygen atom and hydrogen atom of the NH group in the imidazole fragment (Fig. 2). This hydrogen bond is characterized by the following parameters: $O^1\cdots H(N^2)$ 1.72 Å, $O^1\cdots N^2$ 2.63 Å, $\angle O^1H(N^2)N^2$ 159°. It is quite obvious that the intramolecular hydrogen bond stabilizes planar conformation of the Im–TP–B fragment which is likely to be retained not only in crystal but also in solution. Molecules of **VIIIa** in crystal are coupled via intermolecular hydrogen bonds between the indole N^3 atom and imidazole N^{1A} atom, giving rise to centrosymmetric dimers. The intermolecular hydrogen bond has the following parameters: $H(N^3)\cdots N^{1A}$ 2.22 Å, $N^3\cdots N^{1A}$ 3.021 Å, $\angle N^3H(N^3)N^{1A}$ 148°. Thus the nitrogen atoms in the imidazole ring are involved in two hydrogen bonds (intra- and intermolecular) which determine the steric structure of molecule **VIIIa**.

To conclude, it should be emphasized that we were the first to synthesize 1,2-dihetarylethenes containing both indole and thienopyrrole fragments and to examine specific features of their structure.

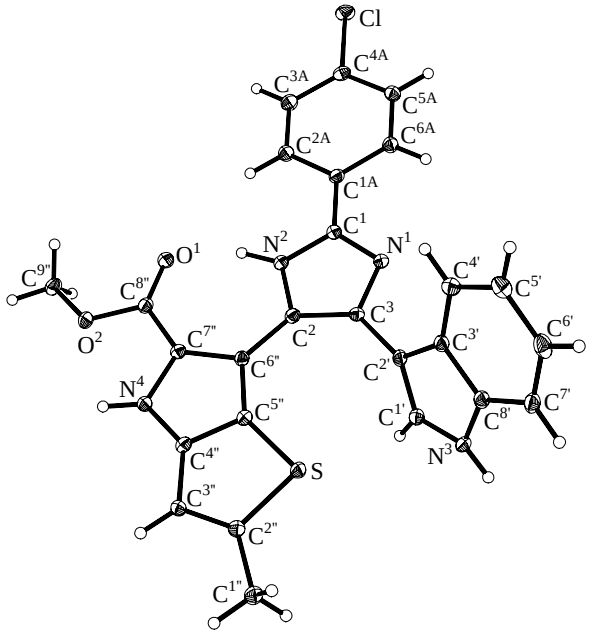


Fig. 1. Structure of the molecule of methyl 6-[2-(4-chlorophenyl)-4-(3-indolyl)imidazol-5-yl]-2-methyl-4*H*-thieno-[3,2-*b*]pyrrole-5-carboxylate (**VIIIa**) according to the X-ray diffraction data.

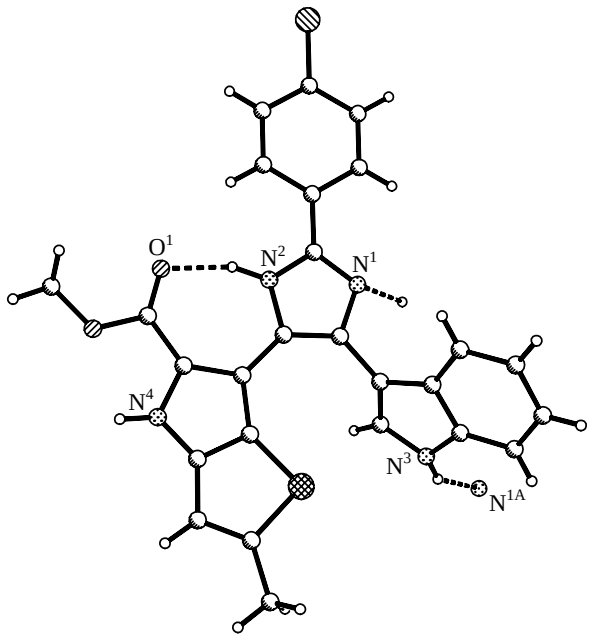


Fig. 2. Intra- and intermolecular hydrogen bonds formed by molecules **VIIIa** in crystal.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer from solutions in DMSO-d_6. The mass spectra (electron impact, 70 eV) were obtained on a Kratos instrument with direct sample admission into the ion source. The melting points were determined on a Boetius microscope apparatus and were not corrected. The progress of reactions was monitored by thin-layer chromatography on Silufol UV-254 plates using petroleum ether–ethyl acetate

(1:2) as eluent. Silica gel from Acros (CAS no. 7631-86-9, 0.060–0.200 mm) was used for column chromatography.

1,2-Dichloroethane was heated for 3 h over P_2O_5 under reflux and distilled. Alcohol was used without additional purification. 2-(3-Indolyl)-2-oxoacetyl chloride (**V**) was synthesized by the procedure described in [14]. The synthesis of methyl 2-methyl-4*H*-thieno-[3,2-*b*]pyrrole-5-carboxylate (**VI**) was reported in [15].

X-Ray diffraction study of methyl 6-[2-(4-chlorophenyl)-4-(3-indolyl)imidazol-5-yl]-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (VIIIa). Yellow rhombic crystals with the composition $C_{26}H_{19}ClN_4O_2S$ were grown from a solution in nitromethane. The unit cell parameters and intensities of 6237 independent reflections were measured at 120 K on a Bruker SMART 1000 diffractometer (MoK_α irradiation, λ 0.711 Å, graphite monochromator, φ–ω scanning in the range $2.05 \le \theta \le 30.22°$). Crystallographic data: *M* 486.96; triclinic system, space group *P*-1; a = 10.584(2), b = 11.054(2), c = 11.085(2) Å; α = 64.463(3), β = 66.968(4), γ = 85.679(4)°; V = 1070.1(3) Å^3; Z = 2; ρ_{calc} = 1.511 g/cm^3. The structure was solved by the direct method. The positions of hydrogen atoms were determined from the difference synthesis of electron density. The structure was refined by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms; the positions of hydrogen atoms were refined in isotropic approximation. The final divergence factors were R_1 = 0.049, wR_2 = 0.113 [for 4640 reflections with $I > 2\sigma(I)$] and R_1 = 0.064, wR_2 = 0.120 (for all independent reflections). The calculations were performed using Bruker SMART [16], SHELXL-97 [17], and Bruker SHELXTL programs [18]. The complete set of crystallographic data was deposited to the Cambridge Crystallographic Data Center (CCDC; entry no. 257961).

Methyl 6-[2-(3-indolyl)-1,2-dioxoethyl]-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (VIIa). To a suspension of 6.0 g (45 mmol) of $AlCl_3$ in a mixture of 20 ml of 1,2-dichloroethane and 5 ml of nitromethane we added in portions 4.16 g (20 mmol) of acyl chloride **V** over a period of 3–5 min under stirring at 18–20°C, and 3.90 g (20 mmol) of thienopyrrole **VI** was then added. The progress of the reaction was monitored by TLC. After 1 h, the mixture was poured into 100 ml of an ice–water mixture, and the product was extracted into ethyl acetate (3×100 ml). The extract was dried over Na_2SO_4 and evaporated under reduced pressure, and the residue was recrystallized from alcohol. Yield 5.49 g (75%), yellowish crystals, mp 239–242°C (from methanol). ^{1}H NMR spectrum, δ, ppm: 2.62 s (3H, CH_3), 3.35 s (3H, OCH_3), 6.80 s (1H, thiophene), 7.24 m (2H, indole), 7.53 m (1H, indole), 8.02 m (1H, indole), 8.25 m (1H, indole), 12.10 br.s (1H, NH), 12.75 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 366 (38) $[M]^+$, 222 (79), 190 (73), 144 (100), 116 (31), 89 (40), 69 (20), 59 (43), 43 (54). Found, %: C 62.14; H 3.83; N 7.72; S 8.68. $C_{19}H_{14}N_2O_4S$. Calculated, %: C 62.28; H 3.85; N 7.65; S 8.75. *M* 366.39.

Methyl 3-[2-(3-indolyl)-1,2-dioxoethyl]-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (VIIb). The reaction was carried out as described above for **VIIa** using 6.0 g (45 mmol) of $AlCl_3$ in 25 ml of 1,2-dichloroethane, 4.16 g (20 mmol) of chloride **V**, and 3.90 g (20 mmol) of thienopyrrole **VI** (reaction time 3 h). According to the ^{1}H NMR data, the product was a mixture of 70% of compound **VIIa** and 30% of **VIIb**. The isomers were separated by chromatography on silica gel using petroleum ether–ethyl acetate as eluent to isolate 1.10 g (15%) of compound **VIIb** as yellowish crystals with mp 229–231°C (from MeOH). ^{1}H NMR spectrum, δ, ppm: 2.72 s (3H, CH_3), 3.85 s (3H, OCH_3), 7.05 s (1H, pyrrole), 7.25 m (2H, indole), 7.52 m (1H, indole), 8.18 m (1H, indole), 8.30 m (2H, indole), 10.80 br.s (1H, NH), 12.00 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 366 (14) $[M]^+$, 222 (8), 190 (23), 144 (100), 116 (25), 89 (18), 59 (18), 43 (27). Found, %: C 62.08; H 3.81; N 7.60; S 8.82. $C_{19}H_{14}N_2O_4S$. Calculated, %: C 62.28; H 3.85; N 7.65; S 8.75. *M* 366.39. In addition, 3.12 g (43%) of **VIIa** was isolated (mp 239–240°C). Overall yield 58%.

General procedure for the synthesis of imidazole derivatives VIIIa–VIIIc. A mixture of 150 mg (0.4 mmol) of diketone **VIIa**, 0.6 mmol of aromatic aldehyde, 200 mg (2.5 mmol) of ammonium acetate, and 5 ml of acetic acid was heated for 6 h under reflux. The mixture was cooled and diluted with 2–5 ml of water, and the precipitate was filtered off and recrystallized from alcohol.

Methyl 6-[2-(4-chlorophenyl)-4-(3-indolyl)imidazol-5-yl]-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (VIIIa). Yield 122 mg (61%), yellowish crystals, mp 252–254°C (from methanol). ^{1}H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 3.76 s (3H, OCH_3), 6.82 s (1H, thiophene), 7.00 m (2H, indole), 7.36 m (1H, indole), 7.50 d (2H, H_{arom}, J = 8.3 Hz), 8.12 d (2H, H_{arom}, J = 8.3 Hz), 8.23 m (1H, indole), 10.86 br.s (1H, NH), 12.05 br.s (1H, NH), 12.43 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 488 (27) $[M]^+$, 486 (100) $[M]^+$, 457 (20), 455 (56), 426 (22), 149 (14), 117 (13), 97 (23), 83 (20), 69 (36), 57 (42), 43 (63).

Found, %: C 63.68; H 4.01; Cl 7.19; N 11.43; S 6.44. $C_{26}H_{19}ClN_4O_2S$. Calculated, %: C 64.13; H 3.93; Cl 7.28; N 11.51; S 6.58. *M* 486.98.

Methyl 6-[4-(3-indolyl)-2-(4-methoxyphenyl)-imidazol-5-yl]-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (VIIIb). Yield 95 mg (48%), yellowish crystals, mp 192–194°C (from MeOH). ^{1}H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 3.65 s (3H, $COOCH_3$), 3.86 s (3H, OCH_3), 6.68 s (1H, thiophene), 7.00 m (5H, indole, H_{arom}), 7.36 m (1H, indole), 7.86 m (1H, indole), 8.12 d (2H, H_{arom}, J = 8.3 Hz), 10.92 br.s (1H, NH), 11.80 br.s (1H, NH), 12.15 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 482 (100) $[M]^+$, 450 (63), 435 (22), 407 (60), 149 (20), 117 (17), 105 (25), 83 (28), 69 (49), 59 (61), 55 (69). Found, %: C 67.02; H 4.52; N 11.63; S 6.57. $C_{27}H_{22}N_4O_3S$. Calculated, %: C 67.20; H 4.59; N 11.61; S 6.64. *M* 482.56.

Methyl 6-[4-(3-indolyl)-2-(4-nitrophenyl)imidazol-5-yl]-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (VIIIc). The product crystallized from the reaction mixture. Yield 141 mg (69%), dark red crystals, mp >350°C (from DMSO). ^{1}H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 3.86 s (3H, OCH_3), 6.90 m (2H, thiophene, indole), 7.36 m (1H, indole), 7.70 m (3H, H_{arom}, indole), 8.38 m (2H, indole), 8.62 d (2H, H_{arom}, J = 8.5 Hz), 10.80 br.s (1H, NH), 11.80 br.s (1H, NH), 12.50 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 497 (31) $[M]^+$, 465 (20), 437 (21), 150 (46), 142 (38), 127 (21), 117 (16), 104 (27), 97 (26), 85 (29), 69 (63), 57 (80), 43 (100). Found, %: C 62.63; H 3.76; N 13.96; S 6.31. $C_{26}H_{19}N_5O_4S$. Calculated, %: C 62.77; H 3.85; N 14.08; S 6.44. *M* 497.53.

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