Russian Journal of Organic Chemistry, Vol. 38, No. 5, 2002, pp. 726–730. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 5, 2002, pp. 763–767.

Synthesis and Properties of 2-(2-Furyl)- and 2-(2-Thienyl)-1-methylphenanthro[9,10-*d*]imidazoles

A. A. Pechkin, M. M. El'chaninov, and V. M. Stoyanov

South-Russian State Technical University, ul. Prosveshcheniya 132, Novocherkassk, 346400 Russia
e-mail: andrey@org.srstu.novoch.ru

Received March 13, 2000

Abstract—Condensation of 9,10-phenanthrenequinone with 2-furaldehyde and 2-thiophenecarbaldehyde in glacial acetic acid in the presence of ammonium acetate gave 2-(2-furyl)- and 2-(2-thienyl)phenanthro[9,10-*d*]-imidazoles which were converted into the corresponding 1-methyl derivatives. The furan and thiophene rings in the products lose their acidophobic properties. Depending on the conditions, electrophilic substitution reactions in 2-(2-furyl)- and 2-(2-thienyl)phenanthro[9,10-*d*]imidazoles occur both at the furan (thiophene) and phenanthrene moieties.

While continuing our search for new biologically active compounds in the series of 2-hetaryl-substituted imidazoles, we formulated the task of developing procedures for preparation of 2-(2-furyl)- and 2-(2-thienyl)-1*H*-phenanthro[9,10-*d*]imidazoles **II**, studying their properties, and elucidating mutual influence of polynuclear phenanthro[9,10-*d*]imidazole aromatic system and classical π-excessive pyrrole-like heterocycles linked together through a single bond.

Oleinikova and Pozharskii showed [1] that, unlike Weidenhagen's [2] and Fillips' [3] procedures, the best results in the synthesis of 2-(2-furyl)-1*H*-phenanthro[9,10-*d*]imidazole are obtained by condensation of 9,10-phenanthrenequinone with 2-furaldehyde in the presence of ammonium acetate in glacial acetic acid [4]. However, methylation of the product in alcoholic alkali was difficult because of the low basicity of the imidazole ring and steric hindrances. Our studies also showed that the procedure described in [4] is quite appropriate for the synthesis of 2-hetarylphenanthro[9,10-*d*]imidazoles. The best results (yield 95%) were obtained for 2-(2-thienyl)-1*H*-phenanthro[9,10-*d*]imidazole, presumably due to lower acidophobicity of 2-thiophenecarbaldehyde as compared to its oxygen-containing analog. We succeeded in effecting methylation of 2-(2-furyl)- and 2-(2-thienyl)-1*H*-phenanthro[9,10-*d*]imidazoles in nearly quantitative yield using the system KOH–DMSO and an equimolar amount of methyl iodide [5]. Unlike alcoholic alkali, the above system ensures much higher rate of the process and completely prevents quaternization. *N*-Methyl derivatives **Ia** and **IIa** were brought into reactions with electrophilic reagents, such as carboxylic acids in polyphosphoric acid (PPA), bromine in dichloroethane and PPA, acetyl nitrate, sulfuric and nitric acids in PPA, etc.

We previously found [6, 7] that various 2-hetarylimidazole systems stabilize five-membered π-excessive heterocycles directly conjugated to imidazole fragments. Loss of acidophobic properties caused by redistribution of extra electron density between the hetaryl and imidazole fragments makes it possible to effect various electrophilic reactions under severe conditions (200°C, polyphosphoric acid, concentrated hydrochloric acid, etc.). As a result, the reactivity range of such compounds is considerably extended. Our studies showed that variation of the aromatic system fused to imidazole ring (benzene, naphthalene, phenanthrene) has no essential effect on the stabilization of molecules in acid medium.

The reaction of compounds **Ia** and **IIa** with carboxylic acids and urotropine in the presence of polyphosphoric acid yields exclusively 5-substituted derivatives **Ib**–**Id** and **IIb**–**IId** (Scheme 1). If position 5 of the furan ring is occupied, as in compounds **Ie** and **Ii**, the site of substitution is ambiguous. For example, benzoylation of **Ie** gives no more than 15% of 2-(5-bromo-2-furyl)-7-benzoyl-1-methylphenanthro-[9,10-*d*]imidazole (**Ih**), whereas by formylation of **Ii** we obtained a mixture of 2-(4-formyl-5-phenyl-2-furyl)- and 2-[5-(2-formylphenyl)-2-furyl]-1-methylphenanthro[9,10-*d*]imidazoles **Ij** and **Ik** at a ratio of 3 : 7 (according to the ^{1}H NMR data; Scheme 2).

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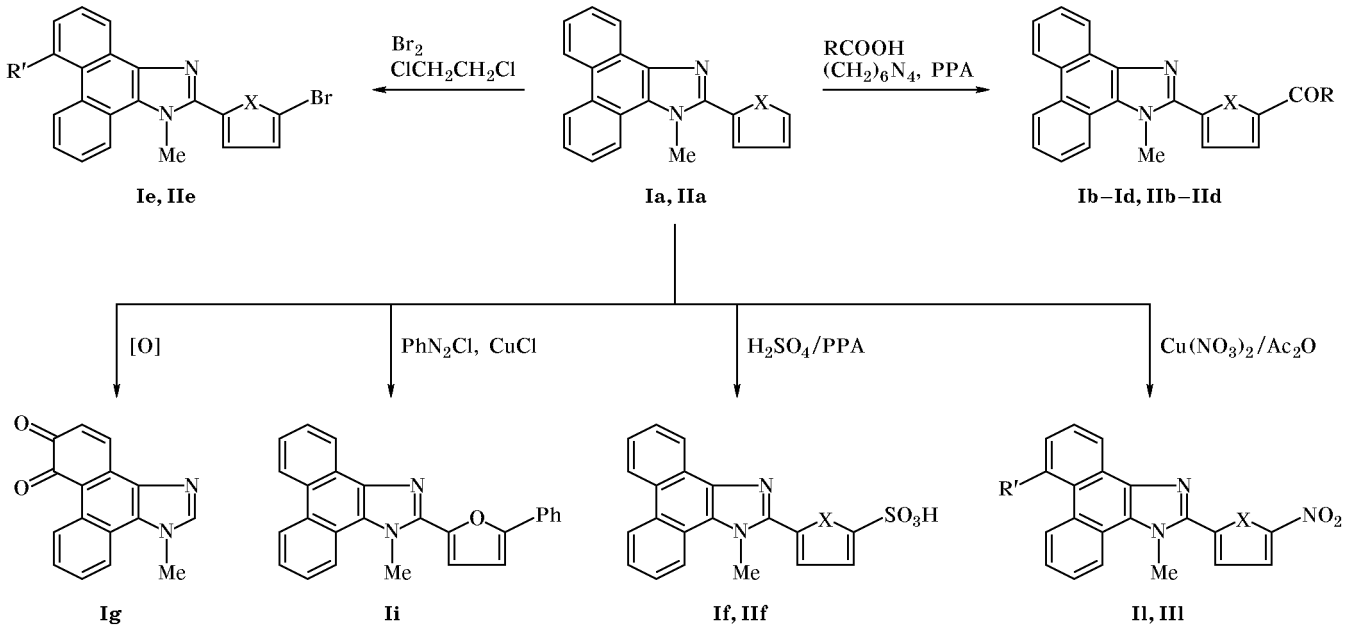
Scheme 1.



I, X = O; **II**, X = S; R = Me (**b**), Ph (**c**), H (**d**); **Ie**, **Il**, R′ = H; **IIe**, R′ = Br; **IIl**, R′ = NO_2; PPA is polyphosphoric acid.

The bromination of **Ia** under mild conditions (Br_2 in dichloroethane at –10°C or in glacial acetic acid at 20°C) afforded 5-bromo-2-furyl derivative **Ie**; the latter was also synthesized from 9,10-phenanthrenequinone and 5-bromo-2-furaldehyde, followed by methylation. However, the bromination of **IIa** under the same conditions resulted in formation of dibromo derivative **IIe**. Here, apart from position *5* of the thiophene ring, the substitution occurred at position *7* of the phenanthro[9,10-*d*]imidazole fragment.

Compound **Ia** was treated with benzenediazonium chloride in acetone at 40–60°C in the presence of a catalytic amount of copper(I) chloride (Meerwein reaction) [8]. As a result, 5-phenyl derivative **Ii** was obtained in 40% yield. Like **Ia**, compound **Ii** was also synthesized from 5-phenyl-2-furaldehyde. As well as the acylation (see above), sulfonation of compounds **Ia** and **IIa** with an equimolar amount of sulfuric acid in polyphosphoric acid at 50–60°C gave 5-sulfofuryl derivatives **If** and **IIf**. When the same reaction was performed at elevated temperature with greater concentration of H_2SO_4, a mixture of sulfonic acids was obtained. The nitration of **Ia** and **IIa** was successful with the use of $Cu(NO_3)_2$–acetic anhydride complex [9]. Compound **Ia** readily reacted at 20°C to form 5-nitro-2-furyl derivative **Il**, whereas with compound

Scheme 2.

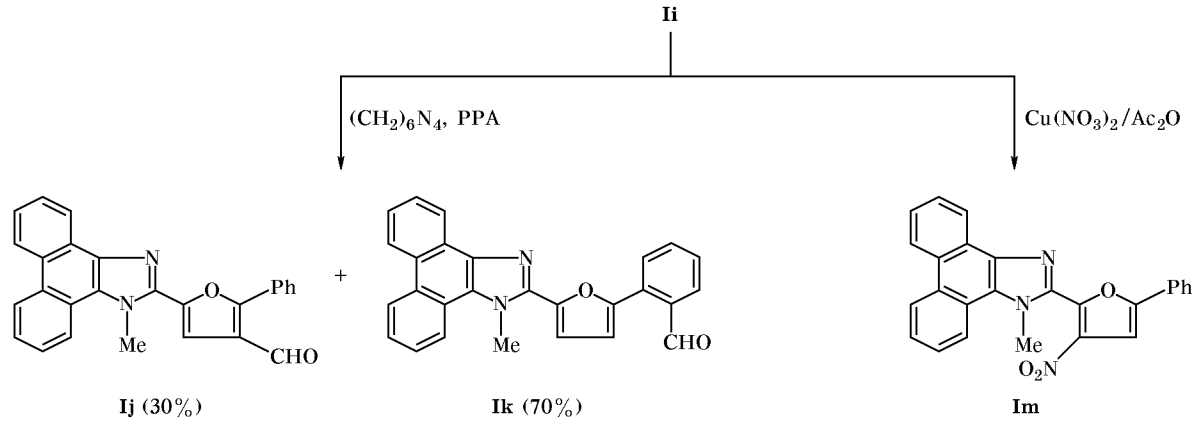


Table 1. Yields, melting points, and elemental analyses of 2-(2-furyl)- and 2-(2-thienyl)-1-methylphenanthro[9,10-*d*]-imidazoles **Ia**–**Im**, **IIa**–**IIf**, and **III**

Comp. no.	Yield, %	mp,[a] °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
Ia	92	182–183	80.94	4.75	9.60	$C_{20}H_{14}N_2O$	80.52	4.73	9.39
Ib	55	194–195	78.01	4.44	8.63	$C_{22}H_{16}N_2O_2$	77.63	4.74	8.23
Ic	35	218–219	80.11	4.43	–	$C_{27}H_{18}N_2O_2$	80.58	4.51	–
Id	52	198–199	76.85	4.27	8.18	$C_{21}H_{14}N_2O_2$	77.29	4.32	8.58
Ie	74	187–188	–	–	7.07	$C_{20}H_{13}BrN_2O$	–	–	7.43
If	42	289–290	68.92	3.87	–	$C_{20}H_{14}O_4S$	68.56	4.03	–
Ig	65	198–199	72.86	3.54	–	$C_{16}H_{10}N_2O_2$	73.27	3.84	–
Ih	15	197–198	66.92	3.91	–	$C_{27}H_{17}BrN_2O_2$	67.37	3.56	–
Ii	40	193–194	–	–	7.22	$C_{26}H_{18}N_2O$	–	–	7.48
Ij	15	209–210	–	–	7.32	$C_{27}H_{18}N_2O_2$	–	–	6.69
Ik	40	214–215	81.01	4.59	–	$C_{27}H_{18}N_2O_2$	80.58	4.51	–
Il	65	267–268	–	–	11.82	$C_{20}H_{13}N_3O_3$	–	–	12.24
Im	70	226–227	–	–	10.17	$C_{26}H_{17}N_3O_3$	–	–	10.02
IIa	95	149–150	76.82	4.19	9.35	$C_{20}H_{14}N_2S$	76.40	4.49	8.91
IIb	62	197–198	73.75	4.22	–	$C_{22}H_{16}N_2OS$	74.13	4.52	–
IIc	40	187–188	77.09	4.68	–	$C_{27}H_{18}N_2OS$	77.49	4.34	–
IId	60	207–208	–	–	8.48	$C_{21}H_{14}N_2OS$	–	–	8.18
IIe	80	200–201	51.22	2.99	–	$C_{20}H_{12}Br_2N_2S$	50.87	2.56	–
IIf	36	>300	65.12	3.77	–	$C_{20}H_{14}O_3S_2$	65.55	3.85	–
III	75	273–274	59.16	3.07	14.27	$C_{20}H_{12}N_4O_4S$	59.40	2.99	13.85

[a] Compounds **Ie**, **If**, **Ih**, **Ii**, **Il**, **Im**, **IIe**, and **IIf** were recrystallized from methanol, and the others, from heptane.

IIa heating for a short time was necessary, and the product was dinitro compound **III**. Unexpected results were obtained in the nitration of **Ii** at 20°C. According to the ^{1}H NMR data for compound **Im**, nitro group enters position *3* of the furan ring rather than *4* as might be expected (Scheme 2). Presumably, the reaction direction is determined by steric effect of the phenyl group in position *5*.

Compounds **Ia** and **IIa** were oxidized with $K_2Cr_2O_7$ in dilute sulfuric acid (10–20%). The process can be stopped at the stage of formation of quinone **Ig**. Under more severe conditions, profound degradation occurs to give mixtures of unidentified products.

It is known that 2-hetarylimidazole derivatives exhibit fungicide activity. The compounds obtained in this work were tested against *Triochophyton rubrum*, and some of them showed moderate fungicide activity.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer in mineral oil. The ^{1}H NMR spectra were obtained on a Varian Unity 300 instrument (300 MHz) in $CDCl_3$ or DMSO-d_6 using HMDS as internal reference. The progress of reactions was monitored by TLC on Al_2O_3 (Brockman activity grade II; eluent $CHCl_3$; development with iodine vapor) and Silufol UV-250 plates (eluent $CHCl_3$). Compounds **Ia** and **IIa** were synthesized by the procedure reported in [4], and **Ii**, by the procedure described in [8]. The nitrating agent was prepared as described in [9]. The yields, melting points, and spectral parameters of the products are given in Tables 1 and 2.

2-(2-Furyl)-1-methylphenanthro[9,10-*d*]imidazole (Ia). A mixture of 2.98 g (10 mmol) of 2-(2-furyl)phenanthro[9,10-*d*]imidazole and 1.12 g (20 mmol) of powdered KOH in 15 ml of DMSO was stirred for 30–40 min at 100–120°C. After cooling, 1.56 g (11 mmol) of methyl iodide was added dropwise at such a rate that the temperature did not exceed 30°C. The mixture was stirred for 1.5 h and diluted with 150 ml of water, and the precipitate of compound **Ia** was filtered off and washed with water.

1-Methyl-2-(2-thienyl)phenanthro[9,10-*d*]imidazole (IIa) was synthesized as described above for compound **Ia**.

Table 2. ^{1}H NMR spectra of 2-(2-furyl)- and 2-(2-thienyl)-1-methylphenanthro[9,10-*d*]imidazoles **Ia**–**Im**, **IIa**–**IIf**, and **III** in $CDCl_3$, δ, ppm (*J*, Hz)

Comp. no.	7-H, d	8-H, d	4-H, d	11-H, d	5-H, 6-H, 9-H, 10-H, m	3′-H, d	4′-H, d	NMe, s	Other protons
Ia	8.80 (8.0)	8.78 (8.2)	8.68 (7.7)	8.47 (7.7)	7.65	7.10 (3.3)	6.63[a]	4.48	7.60 d (1H, 5′-H, 2.2)
Ib	8.80 (8.0)	8.77 (8.1)	8.65 (7.7)	8.45 (7.7)	7.67	7.44 (3.3)	7.38 (3.1)	4.60	2.60 s (3H, CH_3)
Ic	8.83 (8.0)	8.80 (8.1)	8.65 (7.7)	8.48 (7.7)	7.67	7.40 (3.3)	7.52 (3.3)	4.64	7.55 m (3H, H_{arom}), 8.00 d (2H, H_{arom})
Id	8.80 (8.0)	8.78 (8.1)	8.66 (7.7)	8.46 (7.7)	7.70	7.52 (3.3)	7.44 (3.3)	4.60	9.76 s (1H, CHO)
Ie	8.82 (8.0)	8.77 (8.2)	8.65 (7.7)	8.42 (7.7)	7.68	7.38 (3.1)	6.58 (3.3)	4.47	–
If[b]	8.81 (8.0)	8.76 (8.1)	8.68 (7.7)	8.45 (7.7)	7.70	7.15 (3.0)	7.05 (3.3)	4.46	12.05 s (1H, SO_3H)
Ig	–	8.72 (8.0)	8.70 (7.7)	8.65 (7.7)	7.60[c]	–	–	4.56	–
Ih	–	8.80 (8.0)	8.67 (7.7)	8.48 (7.7)	7.68[c]	7.40 (3.1)	7.16 (3.2)	4.66	7.55 m (3H, H_{arom}), 8.00 d (2H, H_{arom}), 8.38 d (1H, 6-H, 8.2)
Ii	8.84 (8.1)	8.74 (8.1)	8.68 (7.7)	8.46 (7.7)	7.68	7.28 (3.0)	7.06 (3.0)	4.60	7.56 m (3H, H_{arom}), 7.94 d (2H, H_{arom})
Ij	8.82 (8.0)	8.74 (8.0)	8.68 (7.7)	8.48 (7.7)	7.68	7.94[d]	–	4.52	7.56 m (3H, H_{arom}), 7.94 d (2H, H_{arom}), 10.20 s (1H, CHO)
Ik	8.84 (8.1)	8.72 (8.0)	8.66 (7.7)	8.47 (7.7)	7.66	7.26 (3.0)	7.05 (3.1)	4.60	7.68 m (2H, H_{arom}), 7.94 m (2H, H_{arom}), 10.04 s (1H, CHO)
Il	8.79 (8.0)	8.70 (8.0)	8.68 (7.7)	8.44 (7.7)	7.67	7.52 (3.3)	7.38 (3.3)	4.60	–
Im	8.84 (8.1)	8.70 (8.1)	8.74 (7.7)	8.50 (7.7)	7.68	–	7.36[d]	4.28	7.48 m (3H, H_{arom}), 7.80 d (2H, H_{arom})
IIa	8.82 (8.0)	8.76 (8.1)	8.68 (7.7)	8.46 (7.7)	7.65	7.50 (3.9)	7.22 (8.7)[e]	4.40	7.55 d (1H, 5-H, 4.0)
IIb	8.81 (8.0)	8.73 (8.0)	8.67 (7.7)	8.43 (7.7)	7.65	7.58 (3.9)	7.77 (3.9)	4.42	2.62 s (3H, CH_3)
IIc	8.80 (8.0)	8.75 (8.0)	8.68 (7.7)	8.44 (7.7)	7.64	7.53 (3.9)	7.77 (3.9)	4.48	7.55 m (3H, H_{arom}), 7.92 d (2H, H_{arom})
IId	8.80 (8.0)	8.75 (8.0)	8.68 (7.7)	8.44 (7.7)	7.68	7.60 (3.9)	7.88 (3.9)	4.45	9.96 s (1H, CHO)
IIe	–	8.72	8.66	8.43	7.66[c]	7.60	7.16	4.40	8.80 d (1H, 6-H)
IIf[b]	8.82 (8.0)	8.73 (8.0)	8.66 (7.7)	8.44 (7.7)	7.67	7.55 (3.9)	7.63 (3.9)	4.40	12.10 s (1H, SO_3H)
III[b]	–	8.82	8.58	8.53	7.70	7.76	8.24	4.44	8.35 (1H, 6-H)

[a] Multiplet.
[b] In DMSO-d_6–CCl_4.
[c] 5-H, 9-H, 10-H.
[d] Singlet.
[e] Triplet.

2-(5-Acyl-2-furyl)-1-methylphenanthro[9,10-*d*]-imidazoles Ib–Id and 2-(5-acyl-2-thienyl)-1-methyl-phenanthro[9,10-*d*]imidazoles IIb–IId (*general procedure***).** A mixture of 2.98 g (10 mmol) of compound **Ia** or 3.14 g (10 mmol) of compound **IIa** and 10–15 mmol of the corresponding acylating agent (benzoic acid, acetic anhydride, or hexamethylenetetraamine) in 20 g of polyphosphoric acid was stirred for 4–6 h at 110–130°C. The mixture was cooled, diluted with 100 ml of cold water, and carefully neutralized with 25% aqueous ammonia. The product was extracted into chloroform (3 × 30 ml), the extract was dried over $CaCl_2$ and evaporated, and the residue was purified by column chromatography on Al_2O_3 (15 × 2.5 cm) using chloroform as eluent.

2-(5-Bromo-2-furyl)-1-methylphenanthro-[9,10-*d*]imidazole (Ie). A cold solution of 2.98 g (10 mmol) of compound **Ia** in 20 ml of dichloroethane was added with stirring over a period of 30 min to a solution of 3.2 g (20 mmol) of bromine in 30 ml of dichloroethane, cooled to –10°C. The mixture was stirred for 1.5 h at 0–5°C, and **Ie** hydrobromide was filtered off, washed 30 ml of dichloroethane, dried, and neutralized with 25% aqueous ammonia.

7-Bromo-2-(5-bromo-2-thienyl)-1-methylphenanthro[9,10-*d*]imidazole (IIe) was synthesized in a similar way.

1-Methyl-2-(5-sulfo-2-furyl)phenanthro[9,10-*d*]-imidazole (If) and 1-methyl-2-(5-sulfo-2-thienyl)-phenanthro[9,10-*d*]imidazole (IIf). A mixture of 2.98 g (10 mmol) of compound **Ia** or 3.14 g (10 mmol) of compound **IIa** and 0.98 g (10 mmol) of sulfuric acid in 20 g of polyphosphoric acid was stirred for 1 h at 60–80°C. The mixture was cooled and diluted with 100 ml of cold water, and the precipitate was filtered off and recrystallized from alcohol.

1-Methyl-6,7-dihydrophenanthro[9,10-*d*]imidazole-6,7-dione (Ig). A mixture of 2.98 g (10 mmol) of compound **Ia** or 3.14 g (10 mmol) of compound **IIa** and 1.8 g of $K_2Cr_2O_7$ in 10% aqueous sulfuric acid was heated for 0.5 h on a water bath. The mixture was cooled, diluted with a small amount of cold water, and neutralized with 25% aqueous ammonia, and the precipitate of quinone **Ig** was filtered off.

1-Methyl-2-(5-nitro-2-furyl)phenanthro[9,10-*d*]-imidazole (Il). Nitrating mixture, 10 ml (20 mmol), was added dropwise with stirring at 20–25°C to a solution of 2.98 g (10 mmol) of compound **Ia** in 20 ml of acetic anhydride. The mixture was then stirred for 30–40 min, the progress of the reaction being monitored by TLC. The product was isolated as described above for compound **Ie**.

1-Methyl-7-nitro-2-(5-nitro-2-thienyl)phenanthro[9,10-*d*]imidazole (IIl) was synthesized in a similar way.

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