ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 7, pp. 1263–1266. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © A.A. Aleksandrov, M.M. El'chaninov, A.S. Dedeneva, 2012, published in Zhurnal Obshchei Khimii, 2012, Vol. 82, No. 7, pp. 1163–1167.

Synthesis and Some Transformations of 2-(2-Thienyl)-1(3)*H*-imidazo[4,5-*f*]quinoline

A. A. Aleksandrov, M. M. El'chaninov, and A. S. Dedeneva

South Russian State Technical University (Novocherkassk Polytechnic Institute), ul. Prosveshcheniya 132, Novocherkassk, 346428 Russia
e-mail: aaanet1@yandex.ru

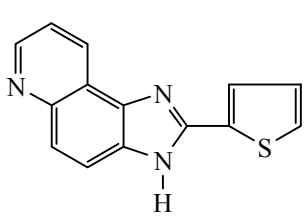
Received May 12, 2011

Abstract—2-(2-Thienyl)-1(3)H-imidazo[4,5-*f*]quinoline was synthesized by the Weidenhagen reaction of quinoline-5,6-diamine with thiophene-2-carbaldehyde. Its methylation in the system KOH–DMSO gave isomeric 1-methyl-2-(2-thienyl)-1*H*- and 3-methyl-2-(2-thienyl)-3*H*-imidazo[4,5-*f*]quinolines, the latter being the major product. The 3-methyl derivative was subjected to electrophilic substitution reactions (bromination, nitration, formylation, acylation, sulfonation). Depending on the conditions, electrophilic attack was directed at the thiophene or quinoline fragment or both these.

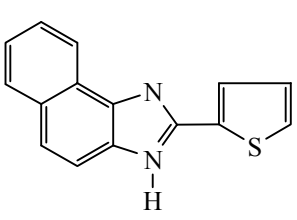
DOI: 10.1134/S1070363212070134

The chemistry of bihetaryls, i.e., compounds whose molecule consist of two heteroaromatic fragments linked through a single bond, attracts increased attention. Bihetaryls containing a thiophene ring are used as pharmaceuticals. For example, 4-(2-thienyl)pyridine derivatives were patented as antiinflammatory agents [1]. Among 2-hetarylimidazoles, 2-(2-thienyl)benzimidazole is known to exhibit antimicro-bial and fungicidal properties [2, 3]. In view of the above stated, we focused on 2-(2-thienyl)-1(3)*H*-imidazo[4,5-*f*]quinoline (**I**) which was not studied previously. Taking into account exceptional pharmacophoric properties of imidazole and thiophene, we anticipated diverse biological activity of compound **I** and its derivatives. Moreover, mutual influence of the imidazoquinoline and thiophene fragments should interestingly affect the reactivity of such compounds.

The present study was aimed at developing a convenient procedure for the synthesis of 2-(2-thienyl)-1(3)*H*-imidazo[4,5-*f*]quinoline (**I**) and examine its reactivity in comparison with naphtho[1,2-*d*]imidazole analog **II**.



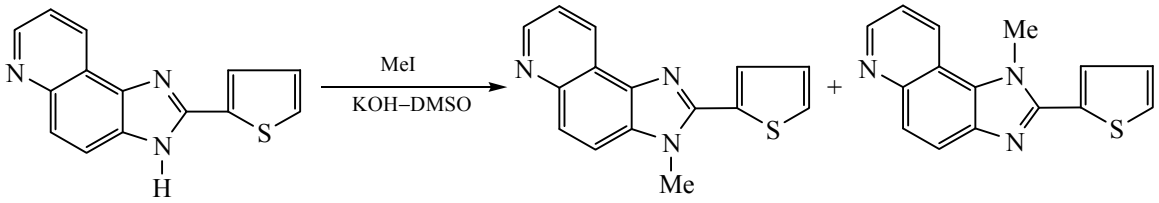
I



II

We initially synthesized 2-(2-thienyl)-1(3)*H*-imidazo-[4,5-*f*]quinoline (**I**) by analogy with compound **II**, i.e., by condensation of quinoline-5,6-diamine with thiophene-2-carbaldehyde in nitrobenzene [4]; however, the yield of the target product was ~52%. We then succeeded in obtaining compound **I** in a higher yield (72%) according to Weidenhagen [5]. Methylation of **I** (as well as of **II** [6]) was successful with the use of an equimolar amount of methyl iodide in the system KOH–DMSO; the yield was nearly quantitative. Due to their intrinsic asymmetry, both compounds **I** and **II** gave rise to mixtures of 1- and 3-methyl derivatives. 1-Methyl isomer **Ib** was formed as minor product, whereas the major product was 3-methyl derivative **Ia**, the ratio **Ia**:**Ib** being 95:5. Signals from methyl protons (δ 4.08 and 4.40 ppm) were assigned to particular isomers on the basis of their chemical shifts. The downfield signal was assigned to 1-methyl-2-(2-thienyl)-1*H*-imidazo[4,5-*f*]quinoline (**Ib**), for the methyl protons in its molecule are additionally deshielded by the quinoline fragment.

N-Methyl derivative **Ia** was subjected to reactions with several electrophiles, namely bromine in dichloroethane, paraformaldehyde in concentrated hydrochloric acid, hexamethylenetetramine in polyphosphoric acid (PPA), acetic anhydride, and benzoic



I **Ia**, 95% **Ib**, 5%

and sulfuric acids in PPA; in addition, compound **Ia** was nitrated with dilute nitric acid (*d* 1.42 g/cm^3).

Electrophilic substitution in 2-thienylimidazoles **Ia** and **IIa** generally requires severe conditions, which indicates considerable deactivation of the thienyl fragment. Obviously, this is the result of electron-withdrawing effect of the imidazol-2-yl substituent fused to quinoline or naphthalene; the effect becomes stronger upon protonation [7]. It is seen that molecule **Ia** is capable of taking up two protons; in this case, electron density on the thiophene ring could be reduced to a greater extent as compared to **IIa**. This assumption was confirmed by the results of B3LYP/6-31G(*d*,*p*) quantum-chemical calculations of the total ($\sigma+\pi$) electron charges on atoms in the thiophene rings of protonated compounds **Ia** and **IIa**. The charge of the thiophene ring in doubly protonated thienylimidazoquinoline **Ia** is –0.388 against –0.485 for singly protonated compound **IIa**. Insofar as all transformations of **Ia** occurred in strongly acidic medium, reduced relative reactivity of thiophene ring in **Ia** might be expected. In fact, our results confirmed this assumption.

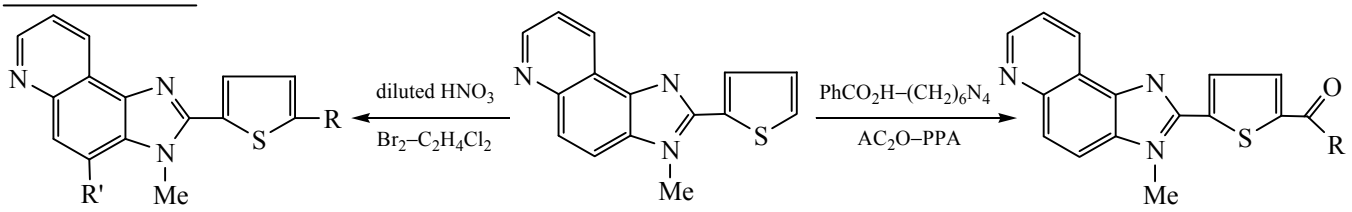
The nitration of **Ia** with the copper nitrate–acetic anhydride complex, i.e., under the conditions corresponding to the nitration of **IIa**, was characterized by a very poor yield. Therefore, we tried to perform radical nitration of **Ia** with dilute nitric acid (*d* = 1.42 g/cm^3). In this case, we obtained 53% of 5-nitro derivative **Ic**. The latter was also synthesized independently by *ipso*-substitution of the bromine atom in 3-methyl-2-(5-bromothiophen-2-yl)-3*H*-imidazo[4,5-*f*]quinoline (**Id**) by nitro group.

The bromination of **Ia** in dichloroethane afforded monobromo derivative **Id** having a bromine atom in position *5* of the thiophene ring. Further bromination at position *4* of the quinoline fragment occurred under prolonged heating of compound **Ia** with 3 equiv of bromine. The yield of dibromide **Ie** was only 28%. For comparison, 3-methyl-2-(2-thienyl)-3*H*-naphtho[1,2-*d*]imidazole (**IIa**) under analogous conditions was directly converted into the corresponding dibromide in 82% yield [6].

Like naphthoimidazole **IIa** studied previously, 3-methyl-2-(2-thienyl)-3*H*-imidazo[4,5-*f*]quinoline (**Ia**) failed to undergo Vilsmeier formylation with DMF–$POCl_3$ even at elevated temperature (80–90°C). On the other hand, heating of **Ia** with hexamethylenetetramine in polyphosphoric acid at 90–100°C produced 31% of 2-(5-formylthiophen-2-yl) derivative **If**; analogous derivative of **IIa** was synthesized in 60% yield [6].

We succeeded in acetylating compound **Ia** in a poor yield (~18%) only by the action of acetic anhydride in PPA at 110–120°C, though its analog **IIa** gave rise to the corresponding acetyl derivative more smoothly (yield 36%). Unlike acetylation, benzoylation of **Ia** was more selective due to the absence of activated methyl group in the acylation product, and the yield of phenyl ketone **Ih** was 49%. Analogous 5-benzoyl derivative of **IIa** was obtained in 55% yield [6].

In contrast to naphthoimidazole analog **IIa**, we failed to isolate sulfonation product of compound **Ia** in the reaction with a mixture of sulfuric and polyphosphoric acids. Presumably, the reason is double



Ic, Id, Ie **Ia** **Ie, Ig, Ih**

I, R = NO_2, R' = H (**c**); R = Br, R' = H (**d**); R = R' = Br (**e**); R = H (**f**), Me (**g**), Ph (**h**).

Table 1. Yields, melting points, and elemental analyses of compounds **I** and **Ia**–**Ih**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
I	72	305–306	67.22	3.47	17.09	$C_{14}H_9N_3S$	66.91	3.61	16.72
Ia	95	154–155	68.23	3.92	16.17	$C_{15}H_{11}N_3S$	67.90	4.18	15.84
Ib	5	145–146	68.17	4.33	15.99	$C_{15}H_{11}N_3S$	67.90	4.18	15.84
Ic	53	265–266	57.73	3.57	17.72	$C_{15}H_{10}N_4O_2S$	58.06	3.25	18.05
Id	66	175–176	52.67	3.17	11.89	$C_{15}H_{10}BrN_3S$	52.34	2.93	12.21
Ie	28	250–251	42.77	1.88	–	$C_{15}H_9Br_2N_3S$	42.58	2.14	–
If	31	247–248	65.27	4.04	14.66	$C_{16}H_{11}N_3OS$	65.51	3.78	14.32
Ig	18	120–121	66.17	4.55	13.88	$C_{17}H_{13}N_3OS$	66.43	4.26	13.67
Ih	49	185–186	70.88	4.07	–	$C_{21}H_{15}N_3OS$	70.57	4.23	–

protonation of the imidazoquinoline fragment, which considerably deactivates the thiophene ring toward electrophilic substitution.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75 IR spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Varian Unity 300 instrument (300 MHz) from solutions in $CDCl_3$ using tetramethylsilane as internal reference. The progress of reactions was monitored by TLC on Al_2O_3 (Brockmann activity grade II) using methylene chloride or chloroform as eluent; spots were developed by treatment with iodine vapor. The elemental compositions were determined on a Perkin–Elmer 2400 analyzer. The melting points were determined in capillaries using a PTP melting point apparatus.

2-(2-Thienyl)-1(3)*H*-imidazo[4,5-*f*]quinoline (I). A mixture of 6.36 g (0.04 mol) of quinoline-5,6-diamine in 75 ml of isopropyl alcohol and, 16 g of copper acetate in 200 ml of water, and 4.48 g (0.04 mol) of thiophene-2-carbaldehyde was heated for 2 h at 80–90°C. The mixture was cooled, the precipitate of copper salt was filtered off and dispersed in 100 ml of isopropyl alcohol, and hydrogen sulfide was passed through the suspension over a period of 1 h. Copper sulfide was filtered off, the filtrate was evaporated by half, and the precipitate was filtered off and recrystallized from ethanol. The yield, melting point, and elemental analysis of compound **I** are given in Table 1.

3-Methyl-2-(2-thienyl)-3*H*-imidazo[4,5-*f*]quinoline (Ia) and 1-methyl-2-(2-thienyl)-1*H*-imidazo[4,5-*f*]-quinoline (Ib). Methyl iodide, 3.12 g (0.022 mol), was added dropwise at 15–20°C under vigorous stirring to a solution of 5.02 g (0.02 mol) of compound **I** in 20 ml of DMSO containing 1.24 g (0.022 mol) of powdered potassium. The mixture was stirred for 2 h, poured into 200 ml of water, and extracted with chloroform (2×50 ml), the extract was evaporated to a volume of 20 ml, dried over sodium sulfate, filtered, and evaporated to obtain 4.13 (78%) of isomer mixture **Ia**/**Ib**. The isomers were separated by column chromatography (70×3.5 cm) on Al_2O_3 using chloroform as eluent. The yields, melting points, elemental analyses, and ^{1}H NMR spectral data of compounds **Ia** and **Ib** are given in Tables 1 and 2.

3-Methyl-2-(5-nitrothiophen-2-yl)-3*H*-imidazo-[4,5-*f*]quinoline (Ic). *a*. A solution of 2.65 g (0.01 mol) of compound **Ia** in 25 ml of nitric acid (d = 1.42 g/cm^3) was stirred for 1 h at 40°C. The mixture was poured into 100 ml of cold water, and the precipitate was filtered off and washed with 2–3 portions of cold water.

b. Sodium nitrite, 0.21 g (0.003 mol), was added in portions to a solution of 0.34 g (0.001 mol) of compound **Id** in 5 ml of acetic acid, and the mixture was heated for 1 h, cooled, poured into 20 ml of water, and then treated as described above in *a*. Samples of **Ic** obtained by the two methods were identical in the melting point (no depression of the melting point was observed on mixing).

3-Methyl-2-(5-bromothiophen-2-yl)-3*H*-imidazo-[4,5-*f*]quinoline (Id). Bromine, 1.06 ml (0.02 mol), was added to a solution of 2.65 g (0.01 mol) of compound **Ia** in 25 ml of dichloroethane. The mixture was heated for 4 h under reflux and evaporated in air, and the residue was recrystallized from alcohol.

4-Bromo-2-(5-bromothiophen-2-yl)-3-methyl-3*H*-imidazo[4,5-*f*]quinoline (Ie). Bromine, 0.80 ml (0.015 mol), was added to a solution of 1.33 g (0.005 mol) of compound **Ia** in 25 ml of dichloroethane. The mixture was heated for 8 h under reflux and evaporated in air, and the residue was dissolved in

Table 2. IR and ^{1}H NMR spectral parameters of compounds **Ia**–**Ih**

Comp. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum ($CDCl_3$), δ, ppm
Ia	–	4.08 s (3H, NCH_3), 7.22 t (1H, H_{Th}, J = 4.0 Hz), 7.48 d (1H, H_{Th}, J = 4.0 Hz), 7.53 d.d (1H, H_{arom}, J = 8.3 Hz), 7.57 d (1H, H_{Th}, J = 4.8 Hz), 7.72 d (1H, H_{arom}, J = 9.0 Hz), 7.97 d (1H, H_{arom}, J = 9.1 Hz), 8.90 d (1H, H_{arom}, J = 4.5 Hz), 8.98 d (1H, H_{arom}, J = 7.4 Hz)
Ib	–	4.40 s (3H, NCH_3), 7.15 t (1H, H_{Th}, J = 3.9 Hz), 7.46 d (1H, H_{Th}, J = 3.9 Hz), 7.47 d.d (1H, H_{arom}, J = 4.4 Hz), 7.65 d (1H, H_{Th}, J = 4.8 Hz), 7.80 d (1H, H_{arom}, J = 9.0 Hz), 8.05 d (1H, H_{arom}, J = 9.1 Hz), 8.69 d (1H, H_{arom}, J = 7.8 Hz), 8.90 d (1H, H_{arom}, J = 4.4 Hz)
Ic	1360 (NO_2, sym.) 1545 (NO_2, asym.)	4.14 s (3H, NCH_3), 7.50 d (1H, H_{Th}, J = 4.2 Hz), 7.53 d.d (1H, H_{arom}, J = 8.3 Hz), 7.58 d (1H, H_{arom}, J = 4.2 Hz), 7.72 d (1H, H_{arom}, J = 9.1 Hz), 7.98 d (1H, H_{arom}, J = 9.1 Hz), 8.90 d (1H, H_{arom}, J 4.5 Hz), 8.99 d (1H, H_{arom}, J = 8.4 Hz)
Id	–	4.05 s (3H, NCH_3), 7.14 d (1H, H_{Th}, J = 3.9 Hz), 7.30 d (1H, H_{Th}, J = 3.9 Hz), 7.50 d.d (1H, H_{arom}, J = 4.2 Hz), 7.70 d (1H, H_{arom}, J = 9.3 Hz), 7.98 d (1H, H_{arom}, J = 9.3 Hz), 8.90 d (1H, H_{arom}, J = 4.4 Hz), 8.95 d (1H, H_{arom}, J = 7.4 Hz)
Ie	–	4.03 s (3H, NCH_3), 7.15 d. (1H, H_{Th}, J = 3.9 Hz), 7.31 d (1H, H_{Th}, J = 3.9 Hz), 7.56 d.d (1H, H_{arom}, J = 4.2 Hz), 8.09 s (1H, H_{arom}), 8.95 d (1H, H_{arom}, J = 6.6 Hz), 9.03 d (1H, H_{arom}, J = 4.4 Hz)
If	1630 (C=O)	4.14 s (3H, NCH_3), 7.54 d (1H, H_{arom}, J = 4.2 Hz), 7.73 d (1H, H_{arom}, J = 9.0 Hz), 7.74 d (1H, H_{Th}, J = 4.0 Hz), 7.84 d (1H, H_{Th}, J = 4.0 Hz), 8.02 d (1H, H_{arom}, J = 9.0 Hz), 8.93 d (1H, H_{arom}, J = 4.5 Hz), 8.97 d (1H, H_{arom}, J = 7.8 Hz), 9.98 s (1H, HO)
Ig	1650 (C=O)	2.58 s (1H, H_3), 4.16 s (3H, NCH_3), 7.56 d.d (1H, H_{arom}, J = 4.2 Hz), 7.71 d (1H, H_{arom}, J = 9.0 Hz), 7.72 d (1H, H_{Th}, J = 3.9 Hz), 7.86 d (1H, H_{Th}, J = 3.9 Hz), 8.00 d (1H, H_{arom}, J = 8.9 Hz), 8.95 d (1H, H_{arom}, J = 4.5 Hz), 8.98 d (1H, H_{arom}, J = 7.8 Hz)
Ih	1670 (C=O)	4.16 s (3H, NCH_3), 7.54 d.d (1H, H_{arom}, J = 4.4 Hz), 7.50–7.53 m (3H, H_{arom}), 7.73 d (1H, H_{Th}, J = 9.0 Hz), 7.73 d (1H, H_{Th}, J = 4.0 Hz), 7.75 d (1H, H_{Th}, J = 4.0 Hz), 7.91 d (2H, H_{arom}, J = 8.4 Hz), 8.03 d (1H, H_{arom}, J = 9.0 Hz), 8.92 d (1H, H_{arom}, J = 4.5 Hz), 9.00 d (1H, H_{arom}, J = 7.8 Hz)

methylene chloride and applied to a column (15 × 2.5 cm) charged with aluminum oxide; the column was eluted with methylene chloride.

5-(3-Methyl-3*H*-imidazo[4,5-*f*]quinolin-2-yl)thiophene-2-carbaldehyde (If). A mixture of 1.33 g (0.005 mol) of compound **Ia**, 2.8 g (0.02 mol) of hexamethylenetetramine, and 20 g of polyphosphoric acid was stirred for 4 h at 90–100°C. The mixture was then diluted with 100 ml of water and carefully neutralized with a solution of ammonia. the precipitate was filtered off and recrystallized from isopropyl alcohol.

1-ethanone (Ig). A mixture of 1.33 g (0.005 mol) of compound **Ia**, 1.53 g (0.015 mol) of acetic anhydride, and 20 g of PPA was stirred for 20 h at 110–120°C. The mixture was diluted with 50 ml of water, carefully neutralized with aqueous ammonia, and extracted with methylene chloride. The product was isolated by column chromatography using methylene chloride as eluent and additionally purified by recrystallization from isopropyl alcohol.

[5-(3-Methyl-3*H*-imidazo[4,5-*f*]quinolin-2-yl)thiophen-2-yl]phenylmethanone (Ih). A mixture of 1.33 g (0.005 mol) of compound **Ia**, 20 g of PPA, and 1.8 g (0.015 mol) of benzoic acid was stirred for 10 h at 150–160°C. The product was isolated as described above for **Ig**.

The yields, melting points, elemental analyses, and IR and ^{1}H NMR spectra of compounds **Ic**–**Ih** are given in Tables 1 and 2.

REFERENCES

1. Akiyoshi, K. and Makoto, K., JPN Patent Appl. no. 60-48880, 1998; *Ref. Zh., Khim*., 1999, no. 19O65P.
2. Simonov, A.M., Rudzit, E.A., El'chaninov, M.M., Kulikova, D.A., Oleinikova, L.Ya., and Ostanchuk, N.V., USSR Inventor's Certificate no. 723853, 1979; *Byull. Izobret*., 1980, no. 11.
3. El'chaninov, M.M., Simonov, A.M., Shcherbakov, V.M., Khosabov, L.M., and Bokaneva, S.A., USSR Inventor's Certificate no. 1032755, 1983; *Byull. Izobret*., 1983, no. 28.
4. Pozharskii, F.T. and Oleinikova, L.Ya., *Khim. Geterotsikl. Soedin*., 1972, no. 11, p. 1555.
5. Weidenhagen, R., Ber., 1936, vol. 69, no. 10, p. 2263.
6. Pechkin, A.A. and El'chaninov, M.M., *Izv. Vyssh. Ucheb. Zaved., Sev.-Kav. Region. Estestv. Nauki*, 2000, vol. 53, no. 4, p. 48.
7. El'chaninov, M.M., *Doctoral (Chem.) Dissertation*, Rostov-on-Don, 2006.