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2-(2-Furyl)-1(3)*H*-imidazo[4,5-*f*]quinoline. Synthesis and Electrophilic Substitution Reactions

A. A. Aleksandrov, A. S. Dedeneva, E. V. Vlasova, and M. M. El'chaninov

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

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Abstract—2-(2-Furyl)-1(3)*H*-imidazo[4,5-*f*]quinoline was synthesized by the Weidenhagen reaction of quinoline-5,6-diamine with furfural. Its alkylation with methyl iodide in the system KOH–DMSO gave two isomeric *N*-methyl derivatives, 2-(2-furyl)-1-methyl-1*H*- and 2-(2-furyl)-3-methyl-3*H*-imidazo[4,5-*f*]quinolines, the latter prevailing. 2-(2-Furyl)-3-methyl-3*H*-imidazo[4,5-*f*]quinoline was brought into electrophilic substitution reactions: bromination, nitration, formylation, acylation, sulfonation. Depending on the reaction conditions, electrophilic attack could be directed at both furan ring and quinoline fragment.

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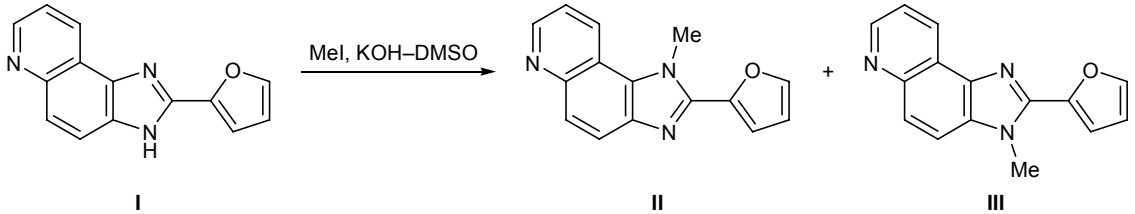
It is known that biheterocycles, i.e., compounds consisting of two heteroaromatic rings linked by a single bond, play an important role in modern theoretical and applied chemistry. They are used for the synthesis of effective metal-complex catalysts, analytical reagents, and pharmaceuticals. This fully applies to fused 2-hetarylimidazole derivatives. The present work was aimed at studying methods of synthesis of 2-(2-furyl)-1(3)*H*-imidazo[4,5-*f*]quinoline (**I**) and its transformations involving the imidazoquinoline and furan fragments by the action of electrophilic and radical reagents.

Compound **I** was synthesized previously in 40% yield by condensation of 5,6-diaminoquinoline with furan-2-carboximidic acid ester hydrochloride in alcohol [1]. However, we succeeded in obtaining better result by reacting 5,6-diaminoquinoline with furfural according to Weidenhagen [2]. In this case, the yield of 2-(2-furyl)-1(3)*H*-imidazo[4,5-*f*]quinoline (**I**) was 72%. Alkylation of compound **I** with an equivalent amount of methyl iodide was successful in the system KOH–DMSO (the yield was nearly quantitative). Insofar as molecule **I** is asymmetric, the alkylation gave a mixture of two N-methyl derivatives: 2-(2-furyl)-1-methyl-1*H*-imidazo[4,5-*f*]quinoline (**II**) and 2-(2-furyl)-3-methyl-3*H*-imidazo[4,5-*f*]quinoline (**III**) (Scheme 1). In keeping with the ^{1}H NMR data, 3-methyl isomer **III** was the major product; its fraction in the reaction mixture was about ~90%, whereas the fraction of 1-methyl isomer **II** did not exceed 7–9%. Protons in the methyl group in compound **III** gave a signal at δ 4.10 ppm in the ^{1}H NMR spectrum, whereas the corresponding signal of 1-methyl isomer **II** was located at δ 4.42 ppm. Obviously, the downfield position of the latter signal is determined by stronger effect of diamagnetic component of the ring current in the quinoline fragment.

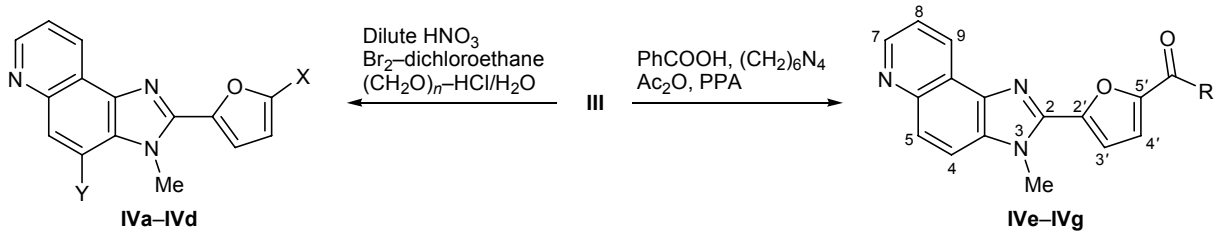
We examined reactions of 2-(2-furyl)-3-methyl-3*H*-imidazo[4,5-*f*]quinoline (**III**) with some electrophilic reagents, in particular with bromine in 1,2-dichloro-

Scheme 1.



I **II** **III**

Scheme 2.



Y = H, X = O_2N (**a**), Br (**b**), $ClCH_2$ (**d**); X = Y = Br (**c**); R = H (**e**), Me (**f**), Ph (**g**).

ethane, with paraformaldehyde in concentrated hydrochloric acid, with urotropine in polyphosphoric acid (PPA), with acetic anhydride, and with benzoic and sulfuric acids in PPA. In addition, compound **III** was nitrated with dilute nitric acid (d = 1.42 g/cm^3).

On the whole, electrophilic replacement in compound **III** occurred smoothly, and the yields were fairly high. Unlike benzimidazole [3], compound **III** failed to undergo nitration with acetyl nitrate at 0°C; therefore, we tried radical nitration of **III** by heating in dilute nitric acid (d = 1.42 g/cm^3). We thus isolated 47% of 5-nitro derivative **IVa**. Compound **IVa** was also synthesized by replacement of the bromine atom in 2-(5-bromofuran-2-yl)-3-methyl-3*H*-imidazo[4,5-*f*]-quinoline (**IVb**) by nitro group. The bromination of **III** with molecular bromine in 1,2-dichloroethane gave compound **IVb** having a bromine atom in position *5* of the furan ring. By prolonged heating of compound **III** with 3 equiv of bromine in boiling dichloroethane we obtained 31% of dibromo derivative **IVc**, the second bromine atom being introduced into position *4* of the imidazoquinoline fragment (Scheme 2).

Chloromethylation of furylimidazoquinoline **III** occurred very difficultly, and the complete conversion was attained only after prolonged heating. The product isolated as hydrochloride was strongly contaminated, so that it was identified via transformation into the free base by treatment with alkali and subsequent purification by column chromatography. The yield of 5-chloromethyl derivative **IVd** was as poor as 27% since the chloromethyl group underwent partial hydrolysis upon alkalization.

Like naphthoimidazole studied previously [4], 2-(2-furyl)-3-methyl-3*H*-imidazo[4,5-*f*]quinoline (**III**) failed to undergo formylation according to Vilsmeier even at elevated temperature (80–90°C). On the other hand, the reaction of **III** with urotropine in PPA at 90–100°C gave 47% of the corresponding 5-formyl derivative **IVe** as the only product.

Taking into account strong deactivating effect of the imidazoquinoline fragment on the furan ring, compound **III** underwent acetylation only by the action of acetic anhydride in PPA at 110–120°C. The reaction was not selective and was accompanied by formation of a number of by-products which were not identified. The contribution of side processes increased as the temperature rose; therefore, the yield of methyl ketone **IVf** did not exceed 33%. The acylation of **III** with benzoic acid was carried out under analogous conditions, but at higher temperature (140–150°C). Unlike acetylation, the benzoylation of **III** occurred smoothly and was not accompanied by formation of by-products (in this case, the product contained no activated methyl group which is capable of being involved in further transformations). The yield of ketone **IVg** was 67%.

In contrast to benzimidazole analogs, we failed to isolate sulfonation product in the reaction of compound **III** with a mixture of sulfuric and polyphosphoric acids. Presumably, the reason is double protonation of the imidazoquinoline fragment and considerable enhancement of its deactivating effect on the furan ring.

EXPERIMENTAL

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

2-(2-Furyl)-1(3)*H*-imidazo[4,5-*f*]quinoline (I). A mixture of 6.36 g (40 mmol) of 5,6-diaminoquinoline in 75 ml of isopropyl alcohol, 16 g of copper

acetate in 200 ml of water, and 3.84 (40 mmol) of furfural 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. The precipitate of copper sulfide was filtered off, the filtrate was evaporated by half, and the precipitate was filtered off and recrystallized from ethanol. Yield 6.77 g (72%), mp 280–281°C. Found, %: C 71.83; H 4.16; N 18.03. $C_{14}H_9N_3O$. Calculated, %: C 71.48; H 3.86; N 17.86.

2-(2-Furyl)-1-methyl-1*H*-imidazo[4,5-*f*]quinoline (II) and 2-(2-furyl)-3-methyl-3*H*-imidazo[4,5-*f*]-quinoline (III). Methyl iodide, 3.12 g (22 mmol), was added dropwise under vigorous stirring at 15–20°C to a solution of 4.70 g (20 mmol) of compound **I** in 20 ml of DMSO containing 1.24 g (22 mmol) of powdered potassium hydroxide. The mixture was stirred for 2 h, poured into 200 ml of water, and extracted with chloroform (2×50 ml). The extracts were combined, evaporated to a volume of 20 ml, dried over sodium sulfate, filtered, and evaporated to obtain 4.08 g (82%) of isomer mixture **II**/**III**. Individual compounds **II** and **III** were isolated by chromatography on a column (70×3.5 cm) charged with aluminum oxide using chloroform as eluent.

Isomer **II**. Yield 0.25 g (7%), mp 66–67°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 4.42 s (3H, NCH_3), 6.68 d.d (1H, 4′-H, J = 3.5 Hz), 7.12 d (1H, 3′-H, J = 3.5 Hz), 7.42 d (1H, 5′-H, J = 1.8 Hz), 7.45 d.d (1H, 8-H, J = 4.4 Hz), 7.73 d (1H, 4-H, J = 9.1 Hz), 8.07 d (1H, 5-H, J = 9.1 Hz), 8.69 d (1H, 9-H, J = 7.8 Hz), 8.09 d (1H, 7-H, J = 4.4 Hz). Found, %: C 72.43; H 4.12; N 17.10. $C_{15}N_{11}N_3O$. Calculated, %: C 72.28; H 4.45; N 16.86.

Isomer **III**. Yield 3.38 g (93%), mp 69–70°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 4.10 (3H, NCH_3), 6.61 d.d (1H, 4′-H, J = 3.5 Hz), 7.15 d (1H, 3′-H, J = 3.5 Hz), 7.49 d.d (1H, 8-H, J = 4.4 Hz), 7.64 d (1H, 5′-H, J = 1.8 Hz), 7.69 d (1H, 4-H, J = 9.1 Hz), 7.96 d (1H, 5-H, J = 9.1 Hz), 8.88 d (1H, 7-H, J = 4.4 Hz), 8.98 d (1H, 9-H, J = 7.4 Hz). Found, %: C 72.28; H 4.57; N 16.77. $C_{15}H_{11}N_3O$. Calculated, %: C 72.28; H 4.45; N 16.86.

3-Methyl-2-(5-nitrofuran-2-yl)-3*H*-imidazo-[4,5-*f*]quinoline (IVa). *a*. A solution of 1.24 g (5 mmol) of compound **III** 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 small portions of cold water. Yield 0.69 g (47%).

b. Sodium nitrite, 0.21 g (3 mmol), was added in small portions to a solution of 0.33 g (1 mmol) of compound **IVb** in 5 ml of acetic acid, and the mixture was heated for 1 h under reflux, cooled, poured into 20 ml of water, and treated as described above in *a*. The products obtained according to methods *a* and *b* were identical in melting point (no depression of the melting point was observed on mixing). Yield 0.19 g (66%), mp 263–264°C (from ethanol). IR spectrum: ν 1370 cm^{-1} (NO_2). ^{1}H NMR spectrum, δ, ppm: 4.21 s (3H, NCH_3), 7.43 d (1H, 3′-H, J = 3.9 Hz), 7.52 d (1H, 4′-H, J = 3.9 Hz), 7.55 d.d (1H, 8-H, J = 4.4 Hz), 7.77 d (1H, 4-H, J = 9.3 Hz), 8.06 d (1H, 5-H, J = 9.0 Hz), 8.93 d (1H, 7-H, J = 4.5 Hz), 8.95 d (1H, 9-H, J = 8.0 Hz). Found, %: C 60.88; H 3.67; N 18.77. $C_{15}H_{10}N_4O_3$. Calculated, %: C 61.22; H 3.43; N 19.04.

2-(5-Bromofuran-2-yl)-3-methyl-3*H*-imidazo-[4,5-*f*]quinoline (IVb). Bromine, 0.53 ml (10 mmol), was added to a solution of 1.24 g (5 mmol) of compound **III** in 25 ml of 1,2-dichloroethane, the mixture was heated for 4 h under reflux and evaporated in air, and the residue was recrystallized from alcohol. Yield 1.26 g (77%), mp 168–169°C. ^{1}H NMR spectrum, δ, ppm: 4.13 s (3H, NCH_3), 6.55 d (1H, 4′-H, J = 3.6 Hz), 7.15 d (1H, 3′-H, J = 3.6 Hz), 7.52 d.d (1H, 8-H, J = 4.2 Hz), 7.73 d (1H, 4-H, J = 9.0 Hz), 8.00 d (1H, 5-H, J = 9.3 Hz), 8.90 d (1H, 7-H, J = 4.4 Hz), 8.97 d (1H, 9-H, J = 8.1 Hz). Found, %: C 55.23; H 3.32; N 13.07. $C_{15}H_{10}BrN_3O$. Calculated, %: C 54.90; H 3.07; N 12.80.

4-Bromo-2-(5-bromofuran-2-yl)-3-methyl-3*H*-imidazo[4,5-*f*]quinoline (IVc). Bromine, 0.80 ml (15 mmol), was added to a solution of 1.24 g (5 mmol) of compound **III** in 25 ml of 1,2-dichloroethane. The mixture was heated for 8 h under reflux and evaporated in air, and the residue was dissolved in methylene chloride and subjected to column chromatography on aluminum oxide (15×2.5 cm) using methylene chloride as eluent. Yield 0.63 g (31%), mp 134–135°C. ^{1}H NMR spectrum, δ, ppm: 4.13 s (3H, NCH_3), 6.57 d (1H, 4′-H, J = 3.6 Hz), 7.30 d (1H, 3′-H, J = 3.6 Hz), 7.59 d.d (1H, 8-H, J = 4.5 Hz), 8.14 s (1H, 5-H), 9.04 d (1H, 7-H, J = 4.5 Hz), 9.05 d (1H, 9-H, J = 8.0 Hz). Found, %: C 43.98; H 2.38; N 10.07. $C_{15}H_9Br_2N_3O$. Calculated, %: C 44.26; H 2.23; N 10.32.

2-(5-Chloromethylfuran-2-yl)-3-methyl-3*H*-imidazo[4,5-*f*]quinoline (IVd). A mixture of 1.24 g (5 mmol) of compound **III**, 1.15 g (13 mmol) of paraformaldehyde, and 10 ml of hydrochloric acid (d = 1.19 g/cm^3) was heated for 8 h at 70–80°C. The mixture was cooled and carefully neutralized with 10% so-

dium hydroxide to pH 7–8. The product was extracted into 50 ml of methylene chloride and purified by chromatography in a column (15×2.5 cm) charged with aluminum oxide using methylene chloride as eluent. Yield 0.40 g (27%), mp 68–69°C. ^{1}H NMR spectrum, δ, ppm: 4.12 s (3H, NCH_3), 4.93 d (2H, CH_2, J = 3.6 Hz), 6.52 d (1H, 4′-H, J = 3.5 Hz), 7.10 d (1H, 3′-H, J = 3.5 Hz) 7.50 d.d (1H, 8-H, J = 4.5 Hz), 7.67 d (1H, 4-H, J = 9.0 Hz), 7.94 d (1H, 5-H, J = 9.0 Hz), 8.86 d (1H, 7-H, J = 4.5 Hz), 8.98 d (1H, 9-H, J = 7.4 Hz). Found, %: C 64.77; H 3.88; N 14.27. $C_{16}H_{12}ClN_3O_2$. Calculated, %: C 64.54; H 4.06; N 14.11.

5-(3-Methyl-3*H*-imidazo[4,5-*f*]quinolin-2-yl)-furan-2-carbaldehyde (IVe). A mixture of 1.24 g (5 mmol) of compound **III** and 2.8 g (20 mmol) of urotropine in 20 g of polyphosphoric acid was stirred for 3 h at 90–100°C. The mixture was diluted with 100 ml of water and carefully neutralized with a solution of ammonia. The precipitate was filtered off and recrystallized. Yield 0.66 g (47%), mp 219–220°C (from isopropyl alcohol). IR spectrum: ν 1680 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 4.28 s (3H, NCH_3), 7.42 d (1H, 3′-H, J = 3.6 Hz), 7.44 d (1H, 4′-H, J = 3.6 Hz), 7.55 d.d (1H, 8-H, J = 4.2 Hz), 7.76 d (1H, 4-H, J = 9.0 Hz), 8.04 d (1H, 5-H, J = 9.3 Hz), 8.93 d (1H, 7-H, J = 4.2 Hz), 8.97 d (1H, 9-H, J = 8.1 Hz), 9.75 s (1H, CHO). Found, %: C 69.66; H 4.17; N 14.87. $C_{15}H_{11}N_3O_2$. Calculated, %: C 69.30; H 4.00; N 15.15.

1-[5-(3-Methyl-3*H*-imidazo[4,5-*f*]quinolin-2-yl)-furan-2-yl]ethanone (IVf). A mixture of 1.24 g (5 mmol) of compound **III** and 1.53 g (15 mmol) of acetic anhydride in 20 g of PPA was stirred for 6 h at 110–120°C. The mixture was then diluted with 50 ml of water and carefully neutralized with a solution of ammonia. The product was extracted into methylene chloride and purified by column chromatography using methylene chloride as eluent. Yield 0.48 g (33%), mp 91–92°C (from isopropyl alcohol). IR spectrum: ν 1660 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 2.57 s (3H, CH_3), 4.27 s (3H, NCH_3), 7.36 d (1H, 3′-H, J = 3.5 Hz), 7.37 d (1H, 4′-H, J = 3.5 Hz), 7.55 d.d (1H, 8-H, J = 4.5 Hz), 7.76 d (1H, 4-H, J = 9.0 Hz), 8.04 d (1H, 5-H, J = 9.0 Hz), 8.93 d (1H, 7-H, J = 4.4 Hz), 8.97 d (1H, 9-H, J = 8.1 Hz). Found, %: C 69.78; H 4.43; N 14.17. $C_{17}H_{13}N_3O_2$. Calculated, %: C 70.09; H 4.50; N 14.42.

[5-(3-Methyl-3*H*-imidazo[4,5-*f*]quinolin-2-yl)-furan-2-yl](phenyl)methanone (IVg). A mixture of 1.24 g (5 mmol) of compound **III**, 20 g of PPA, and 1.8 g (15 mmol) of benzoic acid was stirred for 8 h at 140–150°C. The product was isolated as described above for acetyl derivative **IVf**. Yield 1.18 g (67%), mp 180–181°C (from ethanol). IR spectrum: ν 1640 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 4.21 s (3H, NCH_3), 7.38 d (1H, 3′-H, J = 3.9 Hz), 7.44 d (1H, 4′-H, J = 3.9 Hz), 7.51–7.56 m (3H, 8-H, *m*-H), 7.62 t (1H, *p*-H, J = 7.2 Hz), 7.76 d (1H, 4-H, J = 9.0 Hz), 7.98 d (2H, *o*-H, J = 8.4 Hz), 8.04 d (1H, 5-H, J = 9.0 Hz), 8.93 d (1H, 7-H, J = 4.1 Hz), 8.97 d (1H, 9-H, J = 8.2 Hz). Found, %: C 75.07; H 4.53; N 12.17. $C_{22}H_{15}N_3O_2$. Calculated, %: C 74.78; H 4.28; N 11.89.

REFERENCES

1. Oleinikova, L.Ya., *Cand Sci. (Chem.) Dissertation*, Rostov-on-Don, 1972.
2. Weidenhagen, R., *Ber*., 1936, p. 2263.
3. El'chaninov, M.M., Oleinikova, L.Ya., and Simonov, A.M., *Khim. Geterotsikl. Soedin*., 1979, p. 1047.
4. Pechkin, A.A. and El'chaninov, M.M., *Izv. Vyssh. Uchebn. Zaved. Sev.-Kav. Regiona, Estestv. Nauki*, 2000, p. 48.