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Synthesis of 1-Aryl-3-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinolines

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Abstract—New derivatives of tetrahydrobenzo[*f*]quinoline were synthesized by three-component condensation of benzaldehydes, 2-naphthylamine, and Meldrum's acid. The effect of substituents in the aromatic ring of benzaldehyde on the yield of target products was evaluated.

We described formerly [1] the reaction of *N*-aryl-methylene-2-naphthylamines with 2,2,-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid). It was presumed that the final reaction product, 3-aryl-1,2,3,4-tetra-hydrobenzo[*f*]quinolin-1-one originated from hetero-cyclization of 2-arylaminoketoenol formed by addition of the Meldrum's acid to azomethine followed by decarboxylation of the compound containing a dioxine cycle.

In the present study a three-component condensation was investigated of 2-naphthylamine (**I**),

Table 1. Chemical shifts (δ, ppm) of ^{13}C nuclei in compounds **XVI, XIX, XXIV** (10% solutions in DMSO-d_6)

Atom number	XVI	XIX	XXIV
1 (d)[a]	31.6	31.2	22.1
2 (t)	45.3	45.9	46.1
3 (s)	172.4	172.8	172.6
*4*a (s)	142.1	143.1	143.0
5 (d)	120.4	120.6	120.5
6 (d)	130.2	130.1	130.3
*6*a (s)	129.1	129.0	129.2
7 (d)	126.8	126.4	126.0
8 (d)	120.5	120.5	120.4
9 (d)	124.6	124.7	124.3
10 (d)	120.7	120.9	120.7
*10*a (s)	132.5	132.3	132.4
*10*b (s)	113.7	113.5	113.8
1' (s)	135.4	138.6	129.6
2' (d)	129.8	125.2	147.3
3' (d)	116.3	111.8	148.1
4' (s)	154.8	143.6	112.6
5' (d)	116.6	151.8	122.7
6' (d)	129.7	114.2	121.3

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[a] Multiplicity of signals in spectra registered without decoupling from protons is indicated in parentheses.

Meldrum's acid (**II**), and substituted benzaldehydes **III**–**XV**. The reaction was carried out by boiling a mixture of equimolar amounts of reagents in alcoholic solution. The ^{13}C NMR spectra of compounds obtained (Table 1) show that the reaction products are 1-aryl-3-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinolines since the chemical shift of the carbonyl carbon in compounds **XVI, XIX, XXIV** equal to ~170 ppm indicates that the carbonyl is located in the α-position with respect to NH group. In the spectra of 3-aryl-1,2,3,4-tetrahydrobenzo[*f*]quinolin-1-ones the chemical shift of the carbonyl carbon should be no less than 200 ppm [2].

Besides in the double resonance ^{1}H NMR spectra of compounds **XVI, XIX, XXIV** at irradiation of the broadened singlet of the NH group at 11.35 ppm disappears one of the minor coupling constants ^4J 1.0 Hz in the signals of protons attached to C^2: one signal is a doublet of doublets (^2J 11.0; ^3J 7.5), and the other a doublet (^2J 11.0) with split components of the signal (overall pattern d.d.d at 3.1 ppm). These data also support the assumed structure of compounds **XVI–XXVII**. Basing on these data and those from [3–5] we presume that in the three-component condensation of an appropriate aldehyde, 2-naphthylamine, and Meldrum's acid the cascade heterocyclization occurs not through the addition of Meldrum,s acid to azomethine, but benzaldehydes **III**–**XV** react with enamine A formed from 2-naphthylamine and Meldrum's acid. Simultaneously with formation of the cyclic condensation products occurs the cleavage of the isopropylidene malonate ring providing as a result benzo[*f*]quinoline derivatives **XVI**–**XXVII**.

Experimental results revealed that for the yield of the final product the electronic nature of the substituent in the aldehyde molecule was decisive. In the present research the following aldehydes were studied:
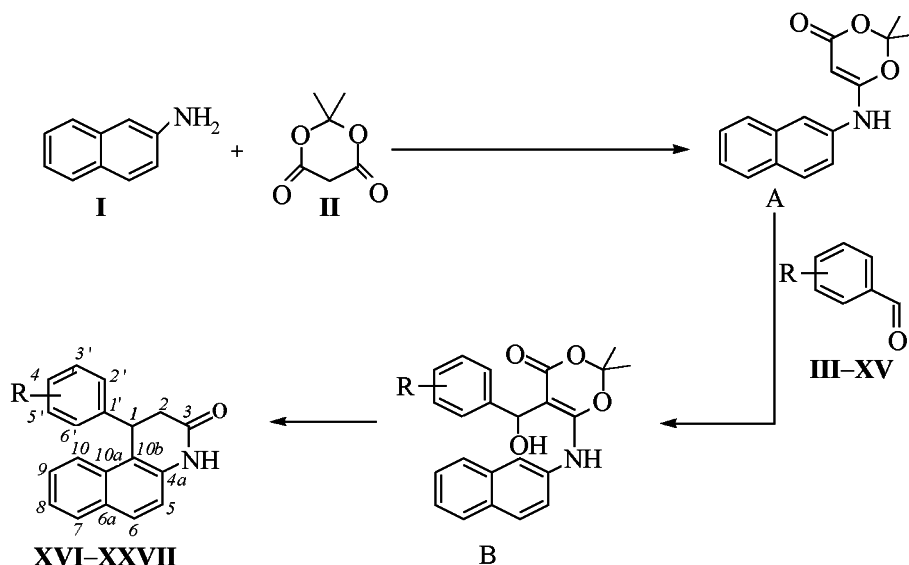
R = 4'-OH (**III**, **XVI**); 3'-OH (**IV**, **XVII**); 3'-OC$_2$H$_5$-4'-OH (**V**, **XVIII**); 3'-Br-4'-OH-5'-OCH$_3$ (**VI**, **XIX**); 4'-OCH$_2$C$_6$H$_5$ (**VII**, **XX**); 3'-OCH$_3$-4'-OCH$_2$C$_6$H$_5$ (**VIII**, **XXI**); 2',3'-di-OCH$_3$ (**IX**, **XXII**); 4'-N(CH$_3$)$_2$ (**X**, **XXIII**); 4'-N(C$_2$H$_5$)$_2$ (**XI**); 4'-C$_6$H$_5$ (**XII**, **XXIV**); 4'-C$_5$H$_4$N (**XIII**, **XXV**); 4'-C$_4$H$_3$S (**XIV**, **XXVI**); 3',4'-OCH$_2$O (**XV**, **XXVII**).

Table 2. Yields, melting points, and elemental analyses of 1-aryl-3-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinolines **XVI**–**XXVII**

Compd. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
XVI	60	318	78.91	5.17	4.82	C$_{19}$H$_{15}$NO$_2$	78.89	5.19	4.84
XVII	75	274	78.88	5.22	4.81	C$_{19}$H$_{15}$NO$_2$	78.89	5.19	4.84
XVIII	70	229	75.70	5.69	4.20	C$_{21}$H$_{19}$NO$_3$	75.68	5.71	4.20
XIX	65	253–254	60.28	4.05	3.54	C$_{20}$H$_{16}$NO$_3$Br	60.30	4.02	3.52
XX	16	212–213	82.31	5.50	3.67	C$_{26}$H$_{21}$NO$_2$	82.32	5.54	3.69
XXI	30	193	79.24	5.65	3.41	C$_{27}$H$_{23}$NO$_3$	79.22	5.62	3.42
XXII	50	275	75.68	5.73	4.19	C$_{21}$H$_{19}$NO$_2$	75.68	5.71	4.20
XXIII	6	287–288	79.77	6.37	8.84	C$_{21}$H$_{20}$N$_2$O	79.75	6.33	8.86
XXIV	38	289–290	85.98	5.43	4.00	C$_{25}$H$_{19}$NO	85.96	5.44	4.01
XXV	58	200–201	78.86	5.09	10.23	C$_{18}$H$_{14}$N$_2$O	78.83	5.11	10.22
XXVI	35	263–264	73.13	4.68	5.02	C$_{17}$H$_{13}$NOS	73.12	4.66	5.02
XXVII	25	260–261	75.73	4.69	4.43	C$_{20}$H$_{15}$NO$_3$	75.71	4.73	4.42

4-hydroxy-(**III**); 3-hydroxy-(**IV**); 4-hydroxy-3-ethoxy-(**V**); 3-bromo-4-hydroxy-5-methoxy- (**VI**); 4-benzyl-oxy- (**VII**); 4-benzyloxy-3-methoxy- (**VIII**); 2,3-di-methoxy- (**IX**); 4-dimethylamino- (**X**); 4-diethyl-amino- (**XI**); 4-phenyl- (**XII**); 4-α-pyridyl- (**XIII**); 4-α-thienyl- (**XIV**), and 3,4-methylenedioxy- (**XV**) benzaldehydes. Since all substituents possess electron-donating properties it was only possible to take into account a various extent in decrease of the

positive charge on the carbon atom of the carbonyl group.

The yields and physico-chemical characteristics of the compounds synthesized are listed in Table 2. As seen from the table, the strongest electron-donors, *N*-dialkylamines, located in the para-position of the aldehyde aromatic ring decrease the electrophilicity of the carbonyl group to such extent that the addition of

Table 3. ^{1}H NMR spectra of 1-aryl-3-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinolines **XVI–XXVII**, δ, ppm (*J*, Hz) (2–5% solutions in DMSO-d_6)

Compd. no.	H^1, d.d. (^4J 1.0, ^3J)	H^2, d.d. (^4J 1.0, ^2J 11.0)	H^2, d.d. (^3J 7.5, ^2J 11.0)	Aromatic protons Ph–R (^3J)	H$^{5-10}$, m
XVI	4.85 (6.0)	2.60	3.00	6.60 d (8.0), 6.88 d (8.0)	7.18–7.45, 7.69–7.90
XVII	4.91 (7.7)	2.65	3.05	6.35–6.68 m	6.91–7.49, 7.19–7.98
XVIII	4.85 (6.4)	2.50	3.00	6.31 d (8.1), 6.6 d (8.1), 6.8 s	7.13–7.48, 7.72–7.92
XIX	5.10 (8.1)	3.18	3.37	6.60–6.70 m	7.40–7.61, 7.90–8.15
XX	4.91 (8.0)	2.61	3.10	6.85 d (8.0), 7.00 d (8.0)	7.10–7.52, 7.79–7.82
XXI	4.92 (6.0)	2.72	3.08	6.35 d (8.0), 6.80 d (8.0)	7.20–7.50, 7.70–7.95
XXII	5.21 (7.6)	2.60	3.10	6.15–7.00 m	6.30–6.80, 7.20–7.80
XXIII	4.90 (7.8)	2.57	3.02	6.65 d (8.0), 6.89 d (8.0)	7.10–7.30, 7.70–7.93
XXIV	5.05 (6.1)	2.60	3.10	7.10–7.68 m	7.80–8.00
XXV	5.10 (6.4)	2.65	3.15	7.10–7.52 m	7.70–8.00
XXVI	I5.29 (6.9)	3.08	3.21	6.70–6.90 m	7.18–7.59, 7.78–8.05
XXVII	4.21 (7.1)	2.70	3.05	6.48–6.80 m	7.20–7.50, 7.73–7.95

enamine A across the carbonyl double bond hardly occurs.

In the case of 4-diethylaminobenzaldehyde (**XI**) also the steric hindrances operate, therefore we failed to isolate from the tar the 1-(4-diethylaminophenyl)-3-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinoline, and the yield of 1-(4-dimethylaminophenyl)-3-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinoline (**XXIII**) attained but 6%. At the same time the electron-donor substituents in the meta-position of the aldehyde benzene ring do not influence the course of reaction so strongly, and therefore the yield of 1-(3-hydroxyphenyl)-3-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinoline (**XVII**) exceeds by 15% the yield of 1-(4-hydroxyphenyl)-3-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinoline (**XVI**).

It should be noted that the yield of the final products from disubstituted aldehydes is favorably affected by the electron-donor substituents in the *meta*-position of the aldehyde benzene ring if the second electron-donor substituent is in the *para*-position. For instance, the yields of 1-(4-hydroxy-3-ethoxyphenyl)-3-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinoline (**XVIII**) and 1-(4-benzyloxy-3-ethoxyphenyl)-3-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinoline (**XXI**) equal respectively to 70 and 30% and are higher than those of 1-(4-hydroxyphenyl)- (**XVI**) and 1-(4-benzyloxyphenyl)-3-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinoline (**XX**) (60 and 16% respectively). This influence may be rationalized by assumption that the presence of the *meta*-substituent impedes the orientation effected by hydroxy or benzyloxy group due to deviation of the aldehyde molecule from coplanarity [6].

The structure of compounds **XVI–XXVII** was confirmed by ^{1}H NMR, IR, UV, and mass spectra. In the IR spectra of these compounds are observed the absorption band of NH group in the region 3500–3220 cm^{-1}), band amide (*I*) at 1750–1600 cm^{-1}, and band amide (*II*) at 1520–1410 cm^{-1}. Among the out-of-plane bending vibrations of aromatic C–H bonds (900–690 cm^{-1}) the bond unaffected by substitution should be mentioned at 845–830 cm^{-1} that is caused by vibrations of two adjacent C–H bonds at the atoms C^5 and C^6 in the benzoquinoline ring. In the IR spectra of compounds **XIX, XXI, XXII** appears a strong absorption band at 2850 cm^{-1} belonging to vibrations of OCH$_3$ group, in the spectrum of compound **XXV** the medium band at 650 cm^{-1} originates from the monosubstituted pyridine, and in the spectrum of compound **XXVI** a band at 580 cm^{-1} corresponds to vibrations of the thiophene ring.

In the mass spectra of compounds **XVI–XXVII** the peak of maximum intensity (100%) *m/z* 196 corresponds to the ion (*M*–R)$^+$. Also the molecular ion M^+ (40–50%) and small number of fragment ions are observed. Peaks of double-charged molecular ions M^{2+} that appear in the spectra are characteristic of fused heterocyclic compounds.

Electron absorption spectra of tetrahydrobenzo[*f*]-quinolines **XVI–XXVII** are observed in the ultra-violet region, and the positions of absorption maxima resembles the spectra of compounds from naphthalene series. The enhanced vibronic structure of absorption bands in the spectra of compounds synthesized is

caused apparently by the influence of a carbonyl group in the α-position with respect to NH group [7].

A specific feature of ^{1}H NMR spectra of tetrahydrobenzo[*f*]quinolines **XVI–XXVII** (Table 3) consists in a downfield shift of the signal from H[1] proton as compared to the usual position of methine proton signals in the cyclic compounds [8].

In the ^{1}H NMR spectra of compounds **XVI–XXVII** appears a group of multiplet signals from the aromatic protons of naphthalene ring in the region 7.10–8.49 ppm in some cases overlapping with the signals of benzene ring that are observed as a multiplet in the 6.31–7.490 ppm range, or as a multiplet and singlet or doublet depending on the substituents position in the benzene ring. All the spectra of compounds synthesized contain a broadened singlet at 10.25–10.45 ppm belonging to the amino group proton. Alongside the above signals the following resonances are observed: in the spectra of compounds **XIX, XXI** a singlet at 3.70–3.87 ppm, in the spectrum of compound **XXII** two singlets at 3.78 and 3.98, and in the spectrum of compound **XVIII** a quartet centered at 3.91 ppm from the protons of methyl group in the substituent. The singlet from the hydroxy group proton appears in the spectra of compounds **XVI–XIX** at 9.25, 9.25, 9.28, and 8.70 ppm respectively. Note that the aryl substituent at C^1 atom is in a pseudoequatorial position. It is evidenced by the value of coupling constant between atoms C^1–$H_{a'}$ (4.21–5.29 ppm) and C^2–H_a (3.00–3.37 ppm) equal to 7.5 Hz. Such decrease in the standard value of the coupling constant $^3J_{a,a}$ (~11 Hz) results from considerable distortion of the bond angles in the cyclohexene ring [9] caused by the presence therein of a lactam group and by conjugation with the naphthalene ring.

In contrast to [10], in reaction of 1-naphthylamine with benzaldehydes and Meldrum's acid we failed to separate products similar to those obtained from 2-naphthylamine, benzaldehydes, and Meldrum's acid, but only tarry substances of unidentified nature. We also did not succeed in alkylating compounds **XVI–XXVII** along procedure from [11]. The latter fact as we believe confirms that the compounds synthesized have amide structure.

EXPERIMENTAL

IR spectra were registered on spectrometer Protege-460 (Nicolet). ^{1}H NMR spectra were recorded on spectrometers Tesla BS-567 A (100 MHz) and Bruker AC-300 (300 MHz) from 2–

5% solutions in deuterated dimethyl sulfoxide, internal reference TMS. ^{13}C NMR spectra were taken on Tesla BS-587 A at operating frequency 20 MHz. Mass spectra were measured on Chromass GC/MS Hewlett Packard 5890/5972 instrument, column HP-5MS (70 eV), solvent dichloromethane. UV spectra of compounds in ethanol solution (*c* 1×10^{-4} mol^{-1}) were recorded on spectrophotometer Specord UV-Vis.

2,2-Dimethyl-1,3-dioxane-4,6-dione (II) (Meldrum's acid). The condensation of malonic acid and acetone in the presence of acetic anhydride was performed by procedure [12]. mp 99–100°C (from alcohol).

1-Aryl-3-oxo-1,2,3,4-tetrahydrobenzo[*f*]quinolines XVI–XXVII. A mixture of 0.01 mol of an appropriate benzaldehyde **III–XV**, 0.01 mol of 2-naphthylamine, and 0,01 mol of Meldrum's acid was boiled in 20–30 ml of ethanol for 0.5–2 h. The separated precipitate was filtered off, washed with ether to remove the unreacted initial compounds, and crystallized from a mixture ethanol–benzene, 2:1 (compounds **XVI, XVI** were crystallized from acetic acid) to obtain the reaction product of a purity no less than 95%.

In preparation of compound **XXV** the reaction mixture after boiling for 1 h was evaporated to 2/3 of its volume, and on cooling the reaction product was precipitated with dioxane. The crystals were filtered off and recrystallized from dioxane.

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