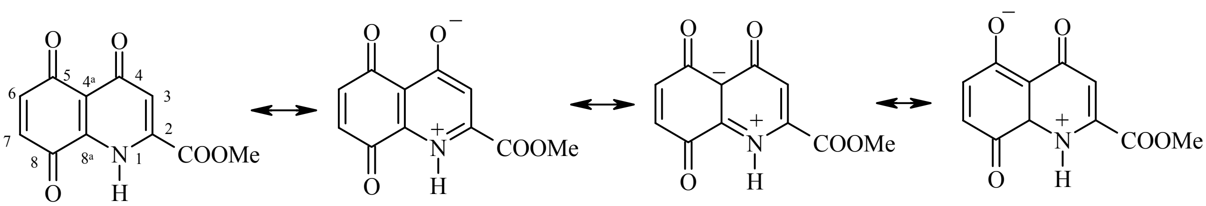
HETEROCYCLIC QUINONES IN THE NENITZESCU REACTION. SYNTHESIS OF FURO- AND PYRROLOQUINOLINES FROM 2-METHOXY-CARBONYL-4-OXO-5,8-QUINOLINEQUINONE

T. I. Mukhanova[1], L. M. Alekseeva[1], A. S. Shashkov[2], and V. G. Granik[1]

Derivatives of furo[2,3-f]quinoline were synthesized by the reaction of the enamines of acetylacetone and benzoylacetone with 2-methoxycarbonyl-4-oxo-5,8-quinolinequinone. A derivative of pyrrolo-[2,3-h]quinoline was obtained from N-benzyl-β-aminocrotonic ester.

Keywords: 3-acyl-5-hydroxy-7-methoxycarbonyl-9-oxofuro[2,3-*f*]quinolines, 1-benzyl-3-ethoxy-carbonyl-8-hydroxy-5-methoxycarbonyl-2-methyl-7-oxopyrrolo[2,3-*h*]quinoline, 2-methoxycarbonyl-4-oxo-5,8-quinone, enamine, Nenitzescu reaction.

The new path that we developed for the synthesis of tricyclic systems containing indole or benzofuran rings as fragments is based on the use of heterocyclic quinones in the Nenitzescu reaction and the use of derivatives of indazolequinone [1], benzofuranquinone [2], and isoquinolinequinone [3] for this purpose. The present work was devoted to the use of an arbitrary quinone 2-methoxycarbonyl-4-oxo-5,8-quinolinedione (**1**), synthesized by the method in [4]. It is known [5] that the electron density at the β-positions of 4-pyridones is substantially increased and it is at these positions that the reactions with electrophilic reagents are directed. From this it can be concluded that the carbonyl at the position 5 of the quinone **1** (added to the β-position of the pyridine ring) is a weaker electron acceptor than the quinone carbonyl at position 8 (structure **A**), while the reactions with nucleophilic reagents, which the enamines (the second component of the Nenitzescu reaction) are, will take place preferentially at position 6.



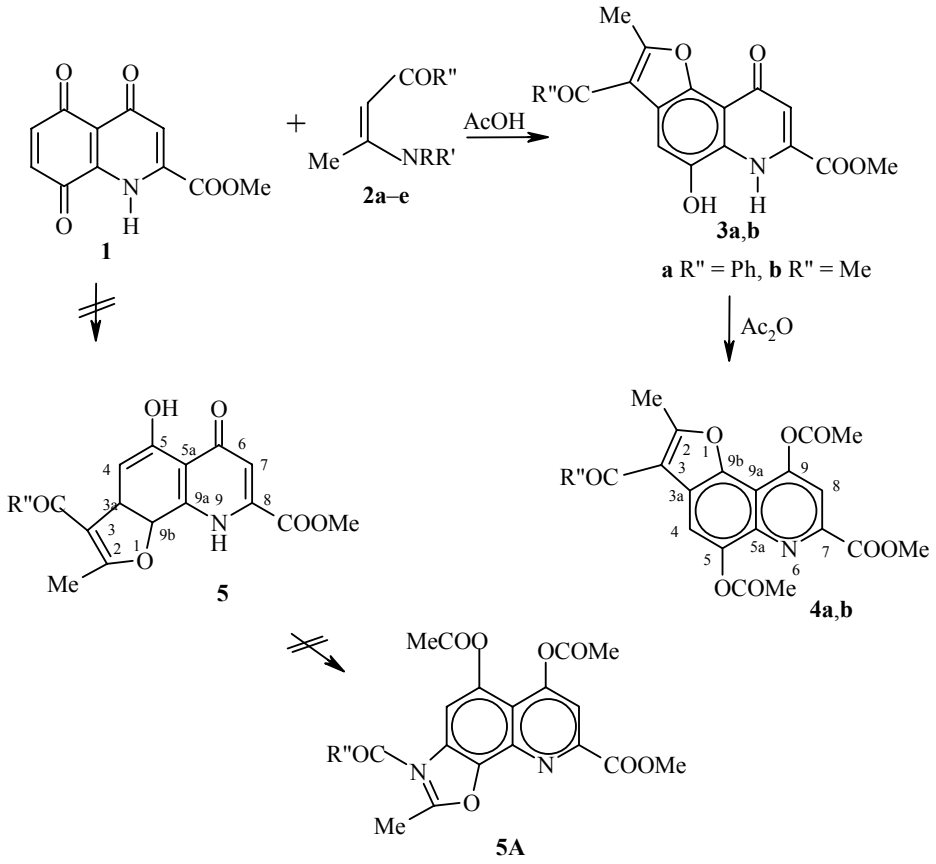
1 **A**

[1] Federal State Unitary Enterprise "The State Scientific Center NIOPIK" (Scientific-Research Institute of Organic Intermediates and Dyes), Moscow 103787; e-mail: makar-cl@ropnet.ru. [2] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 20-26, January, 2004. Original article submitted July 19, 2001.

In addition it can be supposed that, as for isoquinolines, the presence of the electron-withdrawing pyridone ring will lead to difficulty in the oxidation of the intermediate hydroquinone adducts [3], and this must give rise to the preferential formation of the furo- and not the pyrrolotricyclic systems.

The reaction of the quinone **1** with the enamino ketones **2a-e** leads exclusively to 3-acyl-5-hydroxy-7-methoxycarbonyl-2-methyl-9-oxofuro[2,3-*f*]quinolines **3a**,**b**. Compounds **3a**,**b** were subjected to O-acetylation in order to increase the solubility, and their NMR spectra were investigated in this form **4a**,**b**.

In spite of the theoretical treatment, which determines the probability of the formation of compounds **3a**,**b**, it is still necessary to consider the possible production of the isomeric structures **5**.



a R = H, R' = R" = Me; **b** R = H, R' = *p*-MeC$_6$H$_4$, R" = Me; **c** R = R' = Me, R" = Ph;
d R = H, R' = CH$_2$Ph, R" = Ph; **e** R = H, R' = *p*-MeOC$_6$H$_4$, R" = Ph

The ^{1}H NMR spectra of the obtained compounds correspond well to both structures **4** and **5** (see Experimental), and it is impossible on their basis to provide an unambiguous answer to the question as to whether annelation of the furan ring is in fact realized at the 5,6 bond of the quinoline ring.

Examination of the HMBC spectra (^{1}H–^{13}C correlations through two and three bonds, see Table 1) of the obtained acetyl derivatives shows that the derivatives **3** are in fact formed as a result of condensation of the quinone **1** and the enamines **2**. Thus, in the HMBC spectrum of compound **4a** the signal of the 8-H proton (8.11 ppm) has two correlation peaks with the signals of $C_{(9a)}$ and $C_{(9)}$ (112.2 and 152.6 ppm respectively), while the signal of the 4-H proton (7.72 ppm) has three correlation peaks with signals at 139.5, 142.2, and 144.6 ppm, belonging to $C_{(9b)}$, $C_{(5a)}$, and $C_{(5)}$. (It is not possible to assign these signals specifically, which incidentally is not important for solution of the main task, i.e., determination of the structure of the synthesized compounds.) The presence of three correlation peaks for the 4-H signal with the signals of the carbon atoms, observed in the

TABLE 1. The ^{13}C NMR Chemical Shifts of Compounds **4a,b**, and **8** and the Proton-Carbon Correlations in the HMBC spectrum (^{1}H–^{13}C Correlation through Bonds 2 and 3)*

Carbon atoms	^{13}C, δ, ppm		Carbon atoms	^{13}C, δ, ppm
	4a	**4b**		**8**
2	163.1 (2-CH_3)	164.1 (2-CH_3)	2	145.8 (1-CH_2, 2-CH_3)
3	117.1 (2-CH_3)	117.8 (2-CH_3)	3	105.5 (2-CH_3)
3a	125.1 (nc)	124.4 (nc)	3a	112.1 (9-H)
4	115.9 (nc)	116.5 (nc)	3b	*[5]
5	*[2]	*[3]	5	*[5]
5a	*[2]	*[4]	6	112.2 (NH)
7	146.9 (nc)	*[3]	7	176.3 (nc)
8	115.7 (nc)	115.4 (nc)	7a	114.3 (9-H, NH, 6-H)
9	152.6 (8-H)	152.6 (8-H)	8	145.4 9-H)
9a	112.2 (8-H)	111.9 (8-H)	9	102.3 (nc)
9б	*[2]	*[4]	9a	135.4 (1-CH_2)
			1-$CH_2C_6H_5$	46.3 CH_2
				136.0 (3',5'-H) $C_{1'}$
				125.8 $C_{2'6'}$
				128.6 $C_{3'5'}$
				127.3 $C_{4'}$
2-CH_3	14.5	15.3	2-CH_3	13.8
3-COR	190.4 (H-2'6') CO	193.4(CH_3) CO	3-$COOC_2H_5$	167.1 (CH_2) CO
	138.3 (H-3'5') C_1	30.5 CH_3		61.1 CH_2
	128.7, 128.8 $C_{2'6'3'5'}$			12.9 CH_3
	133.1 (H-2'6') $C_{4'}$			
5(and 9)-OCOCH_3	168.5 (CH_3) CO	168.4 (CH_3) CO	5-$COOCH_3$	162.2 (CH_3, 6-H, NH)
	169.4 (CH_3) CO	169.3 (CH_3) CO		CO
	20.5 CH_3	20.4 CH_3		53.1 CH_3
	20.7 CH_3	20.6 CH_3		
7-$COOCH_3$	164.1 (OCH_3) CO	164.1 (OCH_3,8-H) CO	8-OCOCH_3	169.0(CH_3) CO
	52.9 CH_3	52.8 CH_3		20.8 CH_3

* The numbers of the protons with which correlation peaks are observed in the HMBC spectrum are given in parentheses (nc = no correlation). The signals of the protonated carbon atoms were assigned by means of the HSQC spectrum.

*[2] 139.6 (4-H), 142.2 (4-H), 144.6 (4-H).

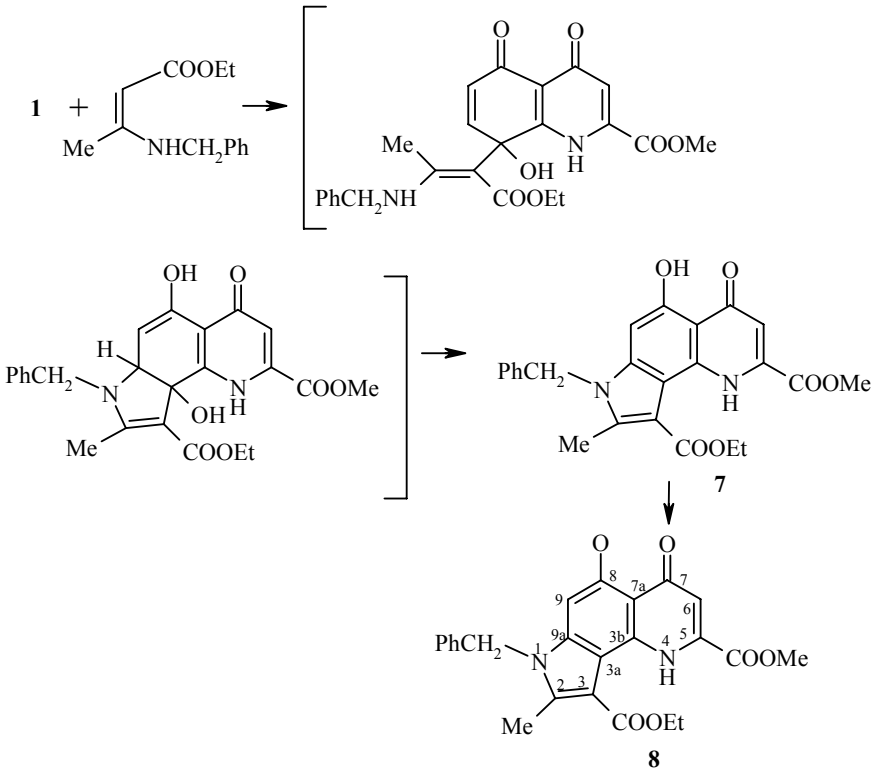
*[3] 144.8 (nc), 147.0 (nc).

*[4] 139.4 (4-H), 141.8 (4-H).

*[5] 135.2 (nc), 136.7 (nc).

downfield region, indicates conclusively in favor of structure **4**. If compounds with structure **5** were obtained, the signal of the proton of the pyrimidine fragment would have correlation peaks similar to those observed in the spectrum, but a correlation peak with an upfield signal for the $C_{(5a)}$ atom (identical with $C_{(9a)}$, δ 112.2 ppm in structure **4**) would be observed for the 4-H signal in addition to the two correlation peaks with the downfield atoms $C_{(9b)}$ and $C_{(5)}$. This is the main argument in favor of the idea that structure **5** is not realized; a general correlation peak for the signals of the two aromatic protons and a signal for a carbon atom with δ 112.2 ppm are not observed in the spectrum. The same logic indicates that compound **4b** has an analogous structure. Consequently, it is possible to state that the reaction of the quinone **1** with the enamines **2** takes place at the position 6 of the quinone with the formation of compounds having structure **3**.

In a continuation of the present research a compound having a weaker electron-withdrawing substituent at the β-position, i.e., N-benzyl-β-aminocrotonic ester **6**, was chosen as enamine component. The reaction of the quinone **1** and the enamine **6** led to the tricyclic compound **7**, which was converted into the O-acetyl derivative **8**. The data from the ^{1}H NMR spectrum, the HMBC spectra (Table 1), and also the ROESY spectrum and the results from the mass spectra make it possible to determine reliably the structure of compound **8**. Its high-resolution mass spectrum contains a molecular-ion peak with *m*/*z* 476.1582 and ion peaks at 434 (M^+– MeCO), 388 (M^+– MeCO–EtOH), 343 (M^+– MeCO–$PhCH_2$), and 297 (M^+– MeCO–EtOH–$PhCH_2$). In the ROESY spectrum there is a strong correlation peak at 5.59/7.27 ppm. This means that the $Ph\underline{CH_2}$ group and the 9-H proton are sterically close. (It is not possible to imagine any other ring closure in which the benzyl substituent would be close to 6-H.) In the HMBC spectrum at 176.3 ppm there is a downfield signal not having a correlation peak with the signals of any protons and assigned to the 7-CO carbon atom. The presence of the pyridone fragment is also favored by the presence of the NH signal in the ^{1}H NMR spectrum in the region of 14 ppm. It can be supposed on the basis of these data that the reaction in this case takes place in the unusual direction:



The HMBC spectrum supports the proposed structure; the signal of the proton at position 9 (7.27 ppm) has two correlation peaks with the upfield carbon atoms – 112.1 ($C_{(3a)}$) and 114.3 ($C_{(7a)}$). Thanks to the presence of a correlation peak in the spectrum at 6.57/114.3 (H-6/$C_{(7a)}$) it is possible to assign these signals having chemical shifts of similar value. The signal of the 9-H proton also has a correlation peak with a downfield signal at 145.4 ppm, assigned to $C_{(8)}$ (correlation with $C_{(8)}$ through two bonds). The signal of the 6-H proton (6.57 ppm) has two correlation peaks – with $C_{(7a)}$ (114.3 ppm) and with 5-CO (162.2 ppm). (In the spectrum there is a correlation peak at 4.00/162.2 (OMe/5-CO)). For the signal of the NH proton (14 ppm) there are three correlation peaks with the following signals: 5-CO (162.2), $C_{(6)}$ (112.2), and $C_{(7a)}$ (143.3 ppm).

The obtained data undoubtedly indicate that the interaction of the quinolinequinone **1** and the enamino ester **6** leads to 1-benzyl-8-hydroxy-2-methoxycarbonyl-3-ethoxycarbonyl-7-oxopyrrolo[2,3-*h*]quinoline (**7**), containing a 6-hydroxyindole fragment. Whereas the retardation of the benzofuran synthesis with decrease in

the electron-withdrawing strength of the substituent at the β-position of the enamine does not seem unusual – the benzofuran cyclization of the intermediate hydroquinone adduct depends directly on the electron deficiency at the α-position of the enamine fragment – the formation of 6-hydroxyindoles has until now only been observed in cases with variation of the structures of the initial enamines (but not quinones), e.g., in the transition from N-alkyl- to N-aryleneamines or to enamines having strong electron acceptors such as cyano and particularly nitro groups at the β-position [6]. In view of the fact that the Nenitzescu reaction very often takes place ambiguously and the yield of the obtained 6-hydroxy derivative is low it is not possible to claim that the use of the heterocyclic quinone **1** in reaction with the enamine **6** changes the direction of this reaction completely and fundamentally and excludes the formation of the normal 5-hydroxyindoles for the Nenitzescu reaction. However, the fact that the structure of the quinone can change this direction so dramatically is a new previously unknown and unexpected phenomenon and requires further detailed investigation.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer (200 MHz). The 2D HMBC NMR spectra (^{1}H and ^{13}C) were obtained on a Bruker DRX-500 spectrometer (at 500 and 125 MHz respectively) using the manufacturer's standard procedures. The high-resolution mass spectra were obtained on a Finnigan MAT TCQ 700 spectrometer (triple quadrupole) with direct injection of the sample into the ion source. The purity of the obtained substances was monitored on Silufol UV-254 and Kieselgel 60 F-254 (Merck) in ethyl acetate.

3-Benzoyl-5-hydroxy-7-methoxycarbonyl-2-methyl-9-oxofuro[2,3-*f*]quinoline (3a). A mixture of the quinone **1** (0.23 g, 10 mmol), 2-*p*-anisidino-3-benzoyl-2-propene (**2e**) (0.27 g, 10 mmol), and glacial acetic acid (4 ml) was heated to 60-70°C, kept at this temperature for 5 min, and then left at room temperature. The next day the crystals that separated were filtered off, washed on the filter with petroleum ether, and dried, and 0.14 g (37.1%) of the furoquinoline **3a** was obtained; mp >300°C (DMF) (decomp.). High-resolution mass spectrum. Found: *m/z* 377.0888 $[M]^{+}$. $C_{21}H_{15}NO_6$. Calculated: M = 377.359.

3-Acetyl-5-hydroxy-7-methoxycarbonyl-2-methyl-9-oxofuro[2,3-*f*]quinoline (3b). The compound was obtained similarly to compound **3a** from the quinone **1** and the enamine **2b** with a yield of 59%; mp >300°C (DMF) (decomp.). High-resolution mass spectrum. Found: *m/z* 315.077 $[M]^{+}$. $C_{16}H_{13}NO_6$. Calculated: M = 315.288.

1-Benzyl-3-ethoxycarbonyl-8-hydroxy-5-methoxycarbonyl-2-methyl-7-oxopyrrolo[2,3-*h*]quinoline (7). The compound was obtained similarly to compound **3a** from the quinone **1** and the enamine **6** with a yield of 32%. After recrystallization from dioxane the pure pyrroloquinoline **7** was isolated with a yield of 13%, calculated on the initial quinone **1**; mp 285-287°C. High-resolution mass spectrum. Found: *m/z* 434.1487 $[M]^{+}$. $C_{24}H_{22}N_2O_6$. Calculated: M = 434.486.

5,9-Diacetoxy-3-benzoyl-7-methoxycarbonyl-2-methylfuro[2,3-*f*]quinoline (4a). To compound **3a** (0.38 g, 10 mmol) acetic anhydride (15 ml) and three drops of sulfuric acid were added. The reaction mixture was heated until the precipitate had dissolved, kept at room temperature for 24 h, and poured into cold water (150 ml). The precipitate was filtered off, washed with water on the filter, and dried. The yield of compound **4a** was 0.38 g (82%). The compound was purified by column chromatography on silica gel. The eluent was ethyl acetate. The solvent was distilled, and compound **4a** was obtained with a yield of 43%; mp 192-194°C (ethanol). High-resolution mass spectrum. Found: *m/z* 419.099 $[M]^{+}$. $C_{23}H_{17}NO_7$. Calculated: M = 357.32. ^{1}H NMR spectrum, δ, ppm: 2.40 (3H, s, 5(9)-$OCOCH_3$); 2.51 (3H, s, 9(5)-$OCOCH_3$); 2.49 (3H, s, 2-CH_3); 3.95 (3H, s, 7-$COOCH_3$); 7.43 (2H, t, 3'-, 5'-H); 7.70 (1H, t, 4'-H); 7.72 (1H, s, 4-H); 7.83 (2H, d, 2'-, 6'-H); 8.11 (1H, s, 8-H).

5,9-Diacetoxy-3-acetyl-7-methoxycarbonyl-2-methylfuro[2,3-*f*]quinoline (4b). The compound was prepared similarly to compound **4a** from the furoquinoline **3b** and acetic anhydride with a yield of 50%. The individual compound was likewise isolated by column chromatography on silica gel. High-resolution mass spectrum. Found: *m/z* 357.084 $[M]^+$. $C_{18}H_{15}NO_7$. Calculated: M = 357.32. ^{1}H NMR spectrum, δ, ppm: 2.47 (3H, s, 5(9)-$OCOCH_3$); 2.58 (3H, s, 9(5)-$OCOCH_3$); 2.67 (3H, s, 3-$COCH_3$); 2.93 (3H, s, 2-CH_3); 3.98 (3H, s, 7-$COOCH_3$); 8.13 (1H, s, 8-H); 8.29 (1H, s, 4-H).

8-Acetoxy-1-benzyl-3-ethoxycarbonyl-5-methoxycarbonyl-2-methyl-7-oxopyrrolo[2,3-*h*]quinoline (8). The compound was prepared similarly to compound **4a** from the pyrroloquinoline **7** and acetic anhydride with a yield of 90%; mp 245-247°C (methanol). High-resolution mass spectrum. Found: *m/z* 476.1582 $[M]^+$. $C_{26}H_{24}N_2O_7$. Calculated: M = 476.49. ^{1}H NMR spectrum: 1.40 (3H, t, 3-$COOCH_2\underline{CH_3}$); 2.27 (3H, s, 8-$OCOCH_3$); 2.69 (3H, s, 2-CH_3); 4.00 (3H, s, 5-$COOCH_3$); 4.44 (2H, t, 3-$COO\underline{CH_2}CH_3$); 5.59 (2H, s, CH_2Ph); 6.57 (1H, s, 6-H); 7.02 (2H, d, 2'-, 6'-H); 7.27 (2H, m, 9-, 4'-H); 7.32 (2H, t, 3'-, 5'-H); 14.00 (1H, NH).

The work was carried out with financial support from the Russian Fund for Fundamental Research (grant No. 99-03-32973).

REFERENCES

1. V. M. Lyubchanskaya, L. M. Alekseeva, S. A. Savina, and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1482 (2000).
2. V. M. Lyubchanskaya, L. M. Alekseeva, S. A. Savina, and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1012 (2003).
3. T. I. Mukhanova, L. M. Alekseeva, and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 670 (2002).
4. J. Baxter and W. R. Phillips, *J. Chem. Soc. Perkin Trans. I*, 2374 (1973).
5. D. Barton and W. D. Ollis, *Comprehensive Organic Chemistry* [Russian translation], Vol. 8, Khimiya, Moscow (1985), p. 30.
6. V. G. Granik, V. M. Lyubchanskaya, and T. N. Mukhanova, *Khim.-Farm. Zh.*, **27**, No. 6, 37 (1993).