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SYNTHESIS OF FURO[3,2-*h*]ISOQUINOLINES BASED ON THE NENITZESCU REACTION

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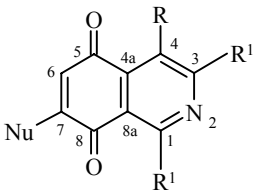
The interaction of derivatives of isoquinolino-5,8-quinone with various enaminocarbonyl compounds occurred regioselectively to give substituted furo[3,2-h]quinolines.

Keywords: enamine, isoquinolinediones, pyrroloisoquinoline, furoisoquinoline.

The synthesis of derivatives of 5-hydroxyindole and 5-hydroxybenzofuran, based on the condensation of quinones with a variety of enamines (the Nenitzescu reaction) has been well studied [1, 2]. The notable synthetic potential of this reaction has been demonstrated with a large number of examples with quinone and enamine starting materials with a wide range of structures. However heterocyclic quinones didn't use in this reaction. In the first time such reaction was carried out by us using as example interaction of indazoloquinolines with different enamines. Syntheses of new furo- and pyrrolo[2,3-*e*]indazoles have been developed [3]. At the same time the use of heterocyclic quinones in the Nenitzescu reaction opens considerable possibilities for the synthesis of new condensed heterocycles with undoubted interest for biological studies. In this connection we have studied in the present work the interaction of various enaminocarbonyl compounds with 4-ethoxycarbonyl-1,3-dimethylisoquinolinedione-5,8 (**1**) [4]. The principal difference between quinone **1** and the indazoloquinone **2** is the different electron density distribution in the quinone part of the molecule.



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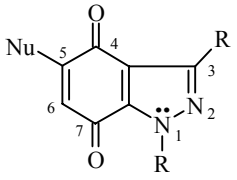

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1 R = COOEt, R^1 = Me; **2** R = Ar

While for compound **2** the electron acceptor effect of the quinone carbonyl at position 4 is decreased by involvement of the electron pair of the cyclic 1-N-atom in conjugation which directs the attack of the nucleophile (an enamine in this case) to position 5, then the reverse situation should occur for quinone **1**. This is a generally accepted and firmly based point of view – in pyridine the electron density is relatively large at position 3 and considerably less at positions 2 and 4 [5]. On the other hand is the effect of the electron accepting ethoxycarbonyl group in position 4, which "withdraws" the electrons from the *o*-position ($C_{(4a)}$) to a greater extent than from the *m*-position ($C_{(8a)}$). Consequently the carbonyl group of the quinone in position 8 which is "saturated" with electrons to a greater extent than the carbonyl at position 4 is the weaker electron acceptor and

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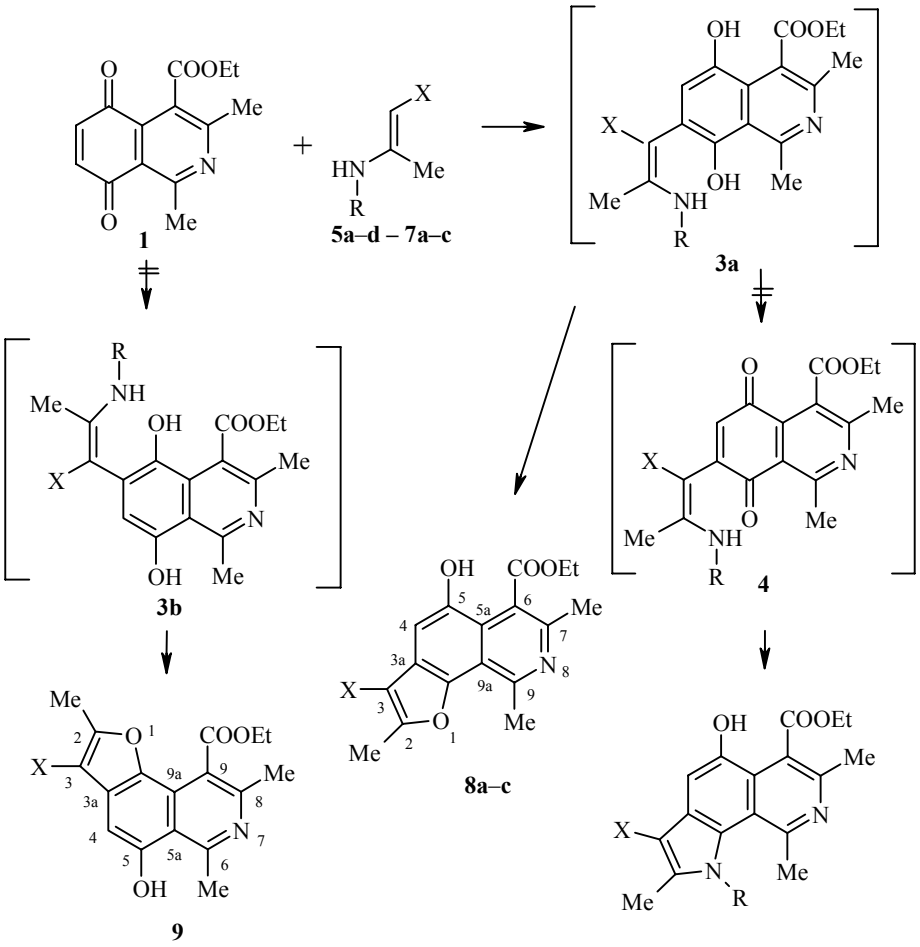
it would be expected that the predominant attack by the nucleophile (an enamine in this case) should be at position 7 rather than at position 6. Thus it is more likely that during the Nenitzescu reaction which occurs *via* the formation of so-called hydroquinone-adducts **3**, it is more likely that the initially formed adduct will be of type **3a** rather than of type **3b**. The most probable transformations of adduct **3a** are nucleophilic attack of the phenol hydroxy group on the α-position of the enamine until to give benzofuran derivatives or oxidation to the quinone-adduct **4** with a subsequent set of reactions which ultimately lead to the synthesis of indoles. As indicated above, both these reaction directions occur in the case of indazoles [3]. However for isoquinoline derivatives of type **3a** oxidation seems less probable because the presence of the electron-accepting ethoxycarbonyl group in the isoquinoline leads to considerable "electron deficiency" in the hydroquinone-adducts **3a** and consequently the rate of oxidation is considerably decreased. Hence the probability of furan cyclization relative to pyrrole cyclization is considerably increased. The experimental results confirm these conclusions. In the first stage of the reaction of quinone **1** the enamino esters **5a-d** were input. It was established that no matter what the substituent at the enamine nitrogen only one compound was formed in the reaction, which corresponded to "furan" cyclization with elimination of an amine fragment.

An analogous result was obtained when the enamino ketones **6a-d** and **7a-c** were used. In each case a single compound was obtained – a furan derivative with a benzoyl group at position 3 of the furan ring from compounds **6a-d** and with an acetyl group at position 3 for compounds **7a-c**. It should be noted that only one furoisoquinoline compound was formed in each case, i.e., the Nenitzescu reaction occurred regioselectively. Even careful investigation (NMR, mass spectra, TLC) of the products remaining in the mother liquors showed the absence of both isomeric furoisoquinolines and pyrroloisoquinolines.

The ^{1}H NMR spectra of the tricyclic compounds obtained (see Experimental) agreed completely with structures **8a-c**, but it was not possible to distinguish them from the isomeric derivatives **9** in this way. An unambiguous indication of the formation of tricyclic structures of type **6** was obtained by analysis of the ^{13}C NMR spectrum of compound **8a** (a complete description of the spectrum is given in the Experimental) with proton coupling and with C-H decoupling of the protons of the methyl groups at positions 2, 7, and 9 from the closest carbon atoms. An examination of the alternative structures **8** and **9** shows that they should differ in the multiplicity of the signals of the carbon atoms found in the stronger field of the aromatic section of the spectrum (108.6-125.9 ppm). The assignment of these signals agrees only with structure **8**: 108.6 (m, $C_{(3)}$, 113.1 (q, $^{3}J_{C9a,9CH_3}$) = 2.8 Hz, $C_{(9a)}$, 122.4 (d, $^{3}J_{C5a,4\text{-}H}$) = 6 Hz, $C_{(5a)}$), 123.9 (q, $^{3}J_{C6,7CH_3}$ = 3 Hz, $C_{(6)}$), 125.9 ppm (s, $C_{(3a)}$). In particular a singlet for $C_{(3a)}$ and two quartets for $C_{(6)}$ and $C_{(9a)}$ are observed in the spectrum, whereas two singlets for $C_{(3a)}$ and $C_{(9a)}$ and one quartet for $C_{(9)}$ should be observed in this region for structure **9**. The following data are in complete agreement with the structure **8a**. Saturating the methyl groups in positions 2 (2.69), 7 (2.57), and 9 (3.09 ppm), apart from conversion of the quartets corresponding to $C_{(2)}$ (164.6), $C_{(7)}$ (139.5), and $C_{(9)}$ (154.7 ppm) into singlets, causes the following changes: the multiplet signal for $C_{(3)}$ (108.6) is converted into a doublet ($^{3}J_{C3,4H}$ = 6Hz), and the quartet signals of $C_{(6)}$ (123.9) and $C_{(9a)}$ (113.1 ppm) are converted into singlets. All of which shows that the Nenitzescu reaction of quinone **1** with enamines occurs regioselectively to give derivatives of furo[3,2-*h*]isoquinoline **8**. The mass spectra confirm this: the most intense ion for all of the furoisoquinolines **8a-c** is [M^{+} - 46] which corresponds to the loss of ethanol and indicates that the OH and COOEt groups are close, which is only characteristic of structures **8** (Scheme 1).

In conclusion two circumstances should be noted. The first is that reaction of quinone **1** with the tertiary enamine, ethyl β-dimethylaminocrotonate, as is general for the Nenitzescu reaction, did not occur at all – according to TLC the starting materials were unchanged. It is possible that this arises from steric hindrance caused by the presence of two substituents on the enamine nitrogen atom. The second is that the effect of the solvent used on the type of cyclization, benzofuranyl or indolyl, in the Nenitzescu reaction has been studied in detail [6]. It was established that when nitromethane was used the indole cyclization prevailed. In the present case, however, replacement of acetic acid by nitromethane did not shift the reaction in the "indole" direction: not even traces of pyrrolo[3,2-*h*]isoquinolines were observed (^{1}H NMR spectrum, mass spectrum).

Scheme 1



5 a R = Me, **b** R = *p*-MeC_6H_4, c R = *p*-$MeOC_6H_4$, d R = CH_2Ph; **6 a–d** X = COPh, **a** R = *p*-MeC_6H_4, **b** R = Ph, **c** R = *p*-$MeOC_6H_4$, **d** R = CH_2Ph; **7 a–c** X = COMe, **a** R = *p*-MeC_6H_4, **b** R = *p*-$MeOC_6H_4$, **c** R = CH_2Ph; **8 a** X = COOEt, **b** X = COPh, **c** X = COMe

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Unity Plus 400 spectrometer (400 MHz) in DMSO-d_6 solution with TMS as internal standard. Mass spectra were recorded with a Finnigan SSQ-710 chromato-mass spectrometer with direct inlet of the sample into the ion source. TLC was carried out on Silufol UV-254 plates with development with UV light.

The enaminocarbonyl starting materials have been described earlier and were made by the known method of interaction of the corresponding carbonyl compounds with aliphatic and aromatic amines [7].

3,6-Diethoxycarbonyl-5-hydroxy-2,7,9-trimethylfuro[3,2-*h*]isoquinoline (8a). Ethyl N-methylamino-crotonate (0.14 g, 1 mmol) was added with stirring to a suspension of 4-ethoxycarbonyl-1,3-dimethyl-isoquinolindione-5,8 (**1**) (0.26 g, 1 mmol) in glacial acetic acid (5 ml). The mixture was stirred and heated at 65-70°C until the solid had dissolved completely and the solution was then kept over night. The crystals which had separated were filtered off, washed on the filter with 50% acetic acid, ethanol, and dried to

give **8a** (0.13 g, 35.1 %); mp 237-239°C (2:1 methanol–dioxane). ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 1.33 (3H, t, 3-COOCH$_2$<u>CH$_3$</u>); 1.40 (3H, t, *J* = 7.2. 6-COOCH$_2$<u>CH$_3$</u>); 2.49 (3H, s, 7-CH$_3$); 2.83 (3H, s, 2-CH$_3$); 3.11 (3H, s, 9-CH$_3$); 4.39 (4H, m, 3-COO<u>CH$_2$</u>CH$_3$, 6-COO<u>CH$_2$</u>CH$_3$); 7.63 (1H, s, 4-H); 10.63 (1H br. s, 5-OH). ^{1}H NMR spectrum (DMSO-d$_6$ + CF$_3$COOD), δ, ppm: 1.34, 1.37 (6H, t, 3- and 6-COOCH$_2$<u>CH$_3$</u>); 2.57 (3H, s, 7-CH$_3$); 2.69 (3H, s, 2-CH$_3$); 3.09 (3H, s, 9-CH$_3$); 4.22, 4.41 (4H, q, 3- and 6-COO<u>CH$_2$</u>CH$_3$); 7.57 (1H, s, 4-H). ^{13}C NMR spectrum, δ, ppm (DMSO-d$_6$ + CF$_3$COOD): 13.9, 14.0, 14.1, 17.4, 21.7 (2-, 7-, 9-CH$_3$, 6-COOCH$_2$<u>CH$_3$</u>, 3-COOCH$_2$<u>CH$_3$</u>), 60.1, 62.1 (6-COO<u>CH$_2$</u>CH$_3$, 3-COO<u>CH$_2$</u>CH$_3$), 108.6 C$_{(3)}$, 110.0 C$_{(4)}$, 113.1 C$_{(9a)}$, 122.4 C$_{(5a)}$, 123.9 C$_{(6)}$, 125.9 C$_{(3a)}$, 139.5 C$_{(7)}$, 141.9 C$_{(9b)}$, 148.7 C$_{(5)}$, 154.7 C$_{(9)}$, 162.7, 166.5 (6-<u>C</u>OOC$_2$H$_5$, 3-<u>C</u>OOC$_2$H$_5$), 164.6 C$_{(2)}$. Found, %: C 64.79; H 5.73; N 3.73. $C_{20}H_{21}NO_6$. Calculated, %: C 64.48; H 5.70; N 3.77.

3-Benzoyl-6-ethoxycarbonyl-5-hydroxy-2,7,9-trimethylfuro[3,2-*h*]isoquinoline (8b) was obtained analogously to **8a** from quinone **1** and 2-*p*-anisidino-3-benzoylpropene-2, yield 52.5%; mp 268-269°C (2:1 dioxane–methanol). ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 1.33 (3H, t, *J* = 7.2, COOCH$_2$<u>CH$_3$</u>); 2.50 (3H, s, 7-CH$_3$); 2.51 (3H, s, 2-CH$_3$); 3.12 (3H, s, 9-CH$_3$); 4.40 (2H, q, COO<u>CH$_2$</u>CH$_3$); 7.18 (1H, s, 4-H); 7.59-7.80 (5H, arom. H); 10.5 (1H, br. s, 5-OH). Found, %: C 70.88; H 5.26; N 3.51. $C_{24}H_{21}NO_5$. Calculated, %: C 71.45; H 5.25; N 3.47.

3-Acetyl-6-ethoxycarbonyl-5-hydroxy-2,7,9-trimethylfuro[3,2-*h*]isoquinoline (8c). The reaction was carried out using quinone **1** and enamines **7a-c** under the conditions described for the synthesis of compound **8a**. The crude product was isolated after the reaction mixture had been kept for 7 days at room temperature. The solvent was evaporated, a minimum amount of isopropanol was added to the residue, the crystals were filtered off, washed on the filter with petroleum ether, and dried to give **8c**, yield ~30%; mp 253-254°C (2:1 methanol–dioxane). ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 1.32 (3H, t, *J* = 7.2, COOCH$_2$<u>CH$_3$</u>); 2.50 (3H, s, 7-CH$_3$); 2.60 (3H, s, CO<u>CH$_3$</u>); 2.89 (3H, s, 2-CH$_3$); 3.09 (3H, s, 9-CH$_3$); 4.32 (2H, q, COO<u>CH$_2$</u>CH$_3$); 7.76 (1H, s, 4-H), 10.6 (1H, br. s, OH). Found, %: C 66.71; H 5.65; N 4.32. $C_{19}H_{19}NO_5$. Calculated, %: C 66.85; H. 5.61; N 4.10.

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