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The Unexpected Formation of a Spiro[benzofuran-3,1′-cyclohexene] Derivative during the Nenitzescu Reaction

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A new synthesis of the spiro[benzofuran-3,1′-cyclohexene] derivative **8**, based on the condensation of *p*-benzoquinone **3** with 3-morpholino-6-ethoxycarbonylcyclohexen-2-one **5**, under Nenitzescu reactions conditions, has been realized.

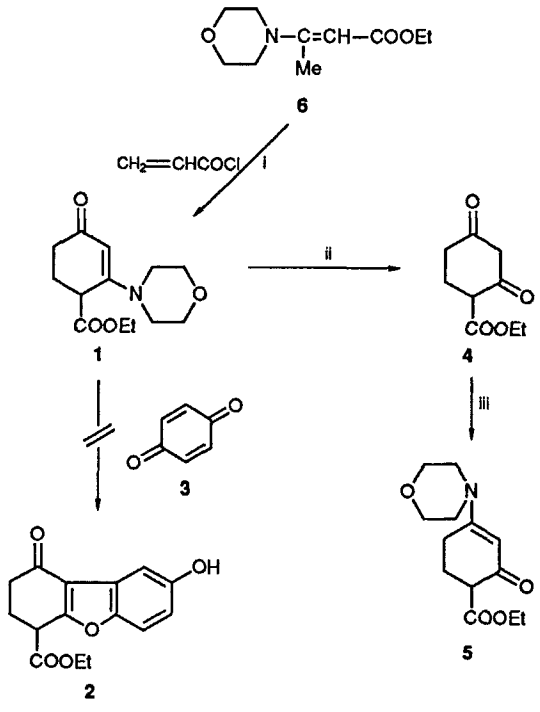
The structures of the starting quinones and enamines are known to have a large influence on the direction of the Nenitzescu reaction.[1–8]

In the present study an attempt is made to employ 3-morpholino-4-ethoxycarbonylcyclohexen-2-one **1** in order to synthesize new dibenzofuran derivatives **2** (Scheme 1). However, compound **1** proved to be unreactive towards *p*-benzoquinone **3** in both aprotic media (dichloroethane, 80 °C) and polar solvents (AcOH, Ac_2O, 20 °C). This is probably due to steric hindrance to conjugation in the enamine fragment, owing to the proximity of the bulky morpholine and ethoxycarbonyl groups. Compound **1** can be hydrolysed to form the diketone **4**, yield 48%, clear oil, mass spectrum M^+ 184. The latter reacted with morpholine to produce the enamine isomer of **1**, 3-morpholino-6-ethoxycarbonylcyclohexen-2-one **5**,† yield 62%, m.p. 78–80 °C (ethyl acetate). ^{1}H NMR spectrum of compound **5** ([$^2H_6$]DMSO), δ (ppm): 2.04–2.62 (m, 4H, 4,5-CH_2), 1.18 (t, 3H, Me), 4.07 (q, 2H, CH_2CH$_3$), 3.31 (m, 4H, NCH_2), 3.62 (m, 4H, OCH_2), 3.25 (q, 1H, J_1 9.3 Hz, J_2 6.3 Hz, 6-CH) and 5.1 (s, 1H, 2-CH).‡ The formation of **5** proceeded selectively and it was impossible to detect enamine **1** in the reaction mixture (TLC).

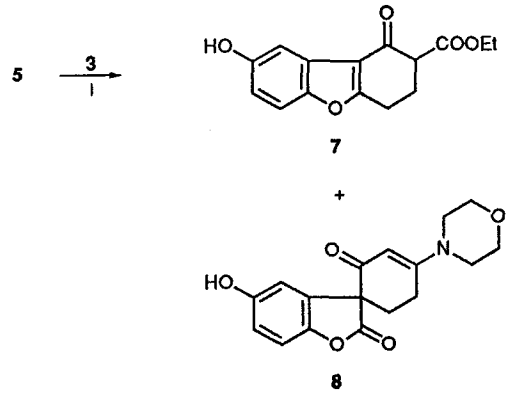
In contrast to enamine **1**, enamine **5** reacted with quinone **3** producing two compounds (Scheme 2). The former was the usual product of the Nenitzescu reaction, 2-ethoxycarbonyl-3,4-dihydro-8-hydroxydibenzofuran-1(2*H*)-one **7**, yield 11%, m.p. 174–175 °C (ethanol), mass spectrum $M^{+\cdot}$ 274, ^{1}H NMR spectrum ([$^2H_6$]DMSO), δ (ppm): 2.2–3.2 (m, 4H, 3,4-CH_2), 3.55 (q, 1H, J_1 8.7 Hz, J_2 4.9 Hz, 2-CH), 1.27 (t, 3H, Me), 4.22 (q, 2H, CH_2CH$_3$), 7.47 (d, 1H, 2.6 Hz, 9-CH), 6.82 (qd, 1H, J_1

† *It is preferable to synthesize compound* **5** *from* β*-morpholinocrotonic ester* **6** *and acryloyl chloride followed by hydrolysis and reaction with morpholine in one stage (without the isolation of intermediates* **1** *and* **4**). The yield of enamine **5** is 32%.

‡ ^{1}H NMR *spectrum of starting enamine* **1**, ([$^2H_6$]DMSO), δ (ppm): 1.20 (t, 3H, Me), 4.15 (q, 2H, CH_2CH$_3$), 2.07–2.27 (m, 4H, 5,6-CH_2), 3.26 (m, 4H, NCH_2), 3.60 (t, 4H, OCH_2), 3.92 (m, 1H, 6-CH), 5.13 (s, 1H, 2-CH).



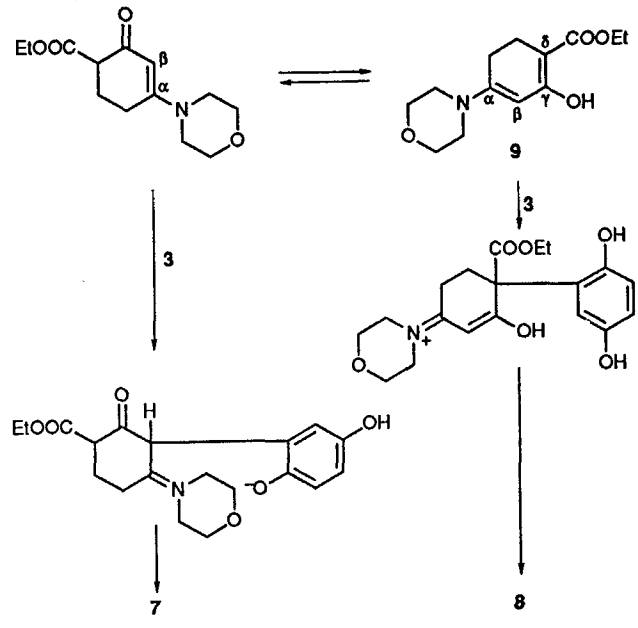
Scheme 1 *Reagents and conditions*: i, after reaction was complete the mixture was filtered and solvent evaporated to yield **1**; ii, AcOH–H_2O (1:1), reflux for 2 h, extraction of **3** (ethyl acetate); iii, benzene, morpholine, *p*-TsOH, reflux



Scheme 2 *Reagents and conditions*: i, addition of **5** to a solution of **3** in AcOH, containing 10% Ac_2O, mixing (20°C, 24 h), filtration of **8**. Compound **7** was isolated from the filtrate.

2.6 Hz, J_2 9 Hz, 7-CH), 7.31 (d, 1H, *J* 9 Hz, 6-CH), 8.64 (s, 1H, OH). The latter compound was 5-hydroxy-4′-morpholinospiro[benzofuran-3,1′-cyclohex-3′-ene]-2(3*H*),2′-dione **8**, yield 7%, m.p. 273–275°C (ethanol). This compound arose as the result of an unexpected reaction with part of the 1,3-diearbonyl fragment of co-compound **5**.

The structure of compound **8** was proved by spectroscopy. IR spectra: 1585 (CO enaminoketone), 1790 (lactone), 3160 (OH) cm^{-1}. ^1H NMR ([$^2H_6$]DMSO), δ (ppm): 2.0–4.0 (m, 4H, 5′,6′-CH_2) 3.46 (m, 4H, NCH_2), 3.67 (t, 4H, O-CH_2), 5.22 (s, 1H, 3′-CH), 6.99 (d, 1H, 4-CH), 7.03 (m, 2H, 6,7-CH), 9.38 (s, 1H, OH); mass spectrum $M^{+\cdot}$ 315. We may suggest that the formation of **7** and **8** is connected with two alternative directions for the addition of quinone **3** (in the Michael reaction):



Scheme 3

either to the β-position of enamine **5** or to the δ-position of tautomeric dienamine **9** followed by cyclization, Scheme 3.

Though the Nenitzescu reaction with dienamines has been described in the literature, the possibility of alternative processes with enamine and β-dicarbonyl fragments is presented here for the first time.

All new compounds gave the expected IR, ^1H NMR and mass spectroscopic data and satisfactory elemental analysis.

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