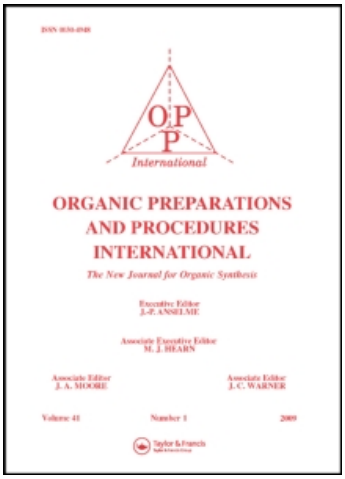

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Hisham A. Abd El-Nabi[a]; A. M. Now El-Din[a]
[a] Department of Chemistry, Faculty of Science, El-Minia University, El-Minia, A. R., EGYPT

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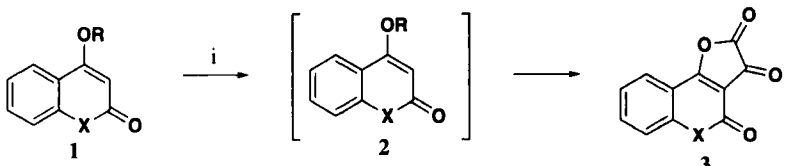
SYNTHESIS AND REACTIONS OF FURO[3,2-c]QUINOLINES AND FURO[3,2-c]COUMARINS.

Hisham A. Abd El-Nabi* and A. M. Nour El-din

Department of Chemistry, Faculty of Science
El-Minia University, El-Minia A. R. EGYPT

As a continuation of our studies on the synthesis[1,2] and reactivity[3-8] of pyrrolo- and furano-2,3-dione, we reported that quinoline-2,4-dione reacted with oxalyl chloride to afford oxazolo[3,2-a]quinolone.[9] Prompted by these results, we investigated the reaction of oxalyl chloride with N-substituted quinolones **1a,b** and 4-hydroxycoumarin **1c**. Since, the fusion of a furan-2,3-dione ring to quinolone or coumarin systems might influence their reactivity, it was thought desirable to synthesize systems having both rings.

Reaction of the sodium salt[10] of N-substituted quinolones **1a,b** with an equimolar ratio of oxalyl chloride in dry toluene at 60°C gave yellow furo[3,2-c]quinolones **3a,b** in 73% and 75% yield respectively (*Scheme 1*). Elemental analyses and spectral data helped characterize the



1 2 3

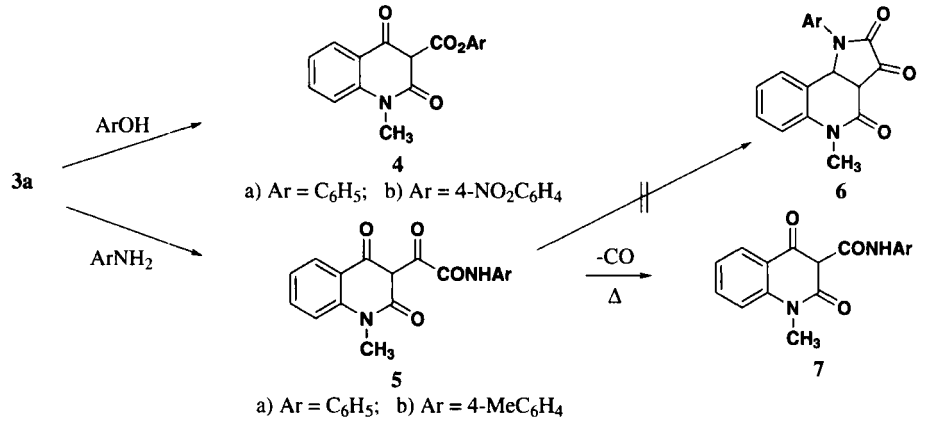
i) ClCOCOCl, Δ, toluene for **3a,b**; DMAP, $AlCl_3$ for **3c**
a) X = NCH_3, R = Na; b) X = NPh, R = Na; c) X = O, R = H

Scheme 1

structure of the products. The IR spectrum of **3a** displayed characteristic absorption bands at 1835, 1780 and 1645 cm^{-1} for three CO groups. Its ^1H NMR showed the absence of a singlet[9] at δ 6.19 (=CH) and the ^{13}C NMR spectrum exhibited signals at 188.1, 161.1 and 157.2 for three C=O groups.

Reaction of 4-hydroxycoumarin **1c** with oxalyl chloride, in the presence of 4-dimethylaminopyridine[11] at reflux in 1,2-dichloroethane for 8 h, gave acid chloride derivative **2c**[1,12] (not isolated), which was then cyclized to 2,3-dioxo-2,3-dihydrofuro[3,2-c]coumarin-2,3,4-trione **3c** with anhydrous aluminum chloride in 1,2-dichloroethane. The elemental analysis and spectral data (*see Experimental Section*) were consistent with the assigned structure. The reactivity of **3a**

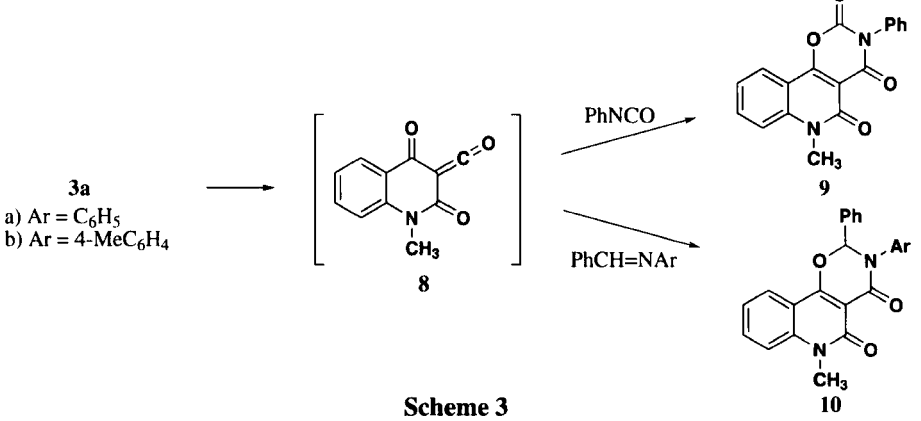
was examined by reactions with phenols and aromatic amines to give ester and amide derivatives[13,14] **4** and **5** respectively. The ester **4a,b** was formed from the reaction of phenols with furo[3,2-c]quinolone **3a** at rather low temperature,[15] namely 70-75°C, as shown in *Scheme 2*. In



Scheme 2

the presence of a CH signal at δ 4.54 and 4.56, the ^{1}H NMR spectra of **5a,b** indicates that the *keto* form is the only one present. The ^{13}C NMR of **5a** shows characteristic signals at 28.52 (NCH_3), 78.58 (CH), 154.00 (CO of amide), 154.87 (C-2), 191.0 (CO) and 194.8 (C-4). Several attempts to cyclize the amide derivative **5** to pyrroledione **6** by using polyphosphoric acid or acetic anhydride as the dehydrating agent were not successful. It is worth noting that heating **5a,b** above its melting point in diphenyl ether gave **7a,b** in 32% and 42% yield respectively by extrusion of carbon monoxide. Elemental analysis and spectral data confirmed the structures of **4**, **5** and **7**.

Thermolysis of **3a** in diphenyl ether at reflux for 20 min gave α–oxoketene intermediate **8** in a way similar to that which we reported recently.[6,13] The formation of **8** was established by trapping with different heterocumulenes, *e. g.* phenyl isocyanate and Schiff's base to give oxazinedione **9** and oxazine derivatives **10a,b** respectively as shown in *Scheme 3*.



Scheme 3

The chemical shift of C-2 in **9** and **10** is in the region usually known from O-C-N system.[6,16] The assignment of all ring carbons of **9** and **10** provided confirmation of the oxazine ring system. Furthermore, the reaction of α-oxoketene intermediate **8** with phenols and amines furnished esters **4a,b** and amides **5a,b** derivatives in 46, 50% and 35, 40% yield respectively.

EXPERIMENTAL SECTION

All mps were determined on a Gallenkamp Melting point apparatus and are uncorrected. Infrared spectra were measured as KBr pellets on a Perkin-Elmer Model 298 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian XL-200 spectrometer in $CDCl_3$ or DMSO-d_6 and TMS as an internal reference; chemical shifts are expressed as δ ppm. Analytical data were obtained on a C,H,N-Elemental Analyzer Carlo Erba 1106. Silica gel 60 (Merck, 230-400 mesh) was used for flash chromatography with chloroform:n-hexane (10:3) as eluent.

Synthesis of Furo[3,2-*c*]quinolones 3a,b.- A suspension of 3 mmol of powdered sodium salt of **1a,b**[10] was heated in dry toluene with 0.257 mL, 3 mmol of oxalyl chloride at 60°C for 2 h. The mixture was centrifuged to separate NaCl. Removal of the solvent under reduced pressure yielded a yellow residue which was recrystallized from dry acetonitrile to afford **3a,b** in 73% and 75% yield respectively.

5-Methyl-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline-2,3,4-trione (3a).- 73% yield, yellow crystals, mp. 138°C (dec.). IR (cm^{-1}): 2980 aliphatic (CH), 1835, 1780 and 1645 cm^{-1} for three (C=O). ^{1}H NMR ($CDCl_3$): δ 3.67 (s, 3H, CH_3) and 7.34-8.02 (m, 4H, aromatic-H). ^{13}C NMR ($CDCl_3$): δ 29.37 (NCH_3), 107.8, 112.32, 116.3, 116.9, 122.3, 122.9, 132.3, 137.8, 157.2, 161.4, 185.6 and 188.1.

Anal. Calcd for $C_{12}H_7NO_4$: C, 62.89; H, 3.08; N, 6.11. Found: C, 62.75; H, 3.12; N, 5.98

5-Phenyl-2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline-2,3,4-trione (3b).- 75% yield, yellow crystals, mp. 157°C (dec.). IR (cm^{-1}): 3050 (aromatic CH), 1830, 1760 and 1635 cm^{-1} for three (C=O). ^{1}H NMR ($CDCl_3$): δ 7.28-8.25 (m, 9H, aromatic-H). ^{13}C NMR ($CDCl_3$): δ 107.8, 112.2, 116.1, 120.9, 123.5, 127.2, 128.2, 128.4, 132.8, 138.3, 138.7, 160.2, 161.1, 186.8 and 187.6.

Anal. Calcd for $C_{17}H_9NO_4$: C, 70.10; H, 3.11; N, 4.81. Found: C, 69.88; H, 3.09; N, 4.59

3,4-Dihydro-2*H*-furo[3,2-*c*]coumarin-2,3,4-trione (3c).- A solution of the 4-hydroxycoumarin (16.2 g, 0.1 mol), oxalyl chloride (27.9 g, 0.22 mol) and 4-dimethylaminopyridine (0.5 g, 0.041 mol)[11] in chloroform (200 mL) was refluxed for 5 h. The solution was concentrated *in vacuo* and the residual oil was dissolved in 1,2-dichloroethane (70 mL), and added dropwise at room temperature into a suspension of aluminum chloride (0.3 mol) in 1,2-dichloroethane (100 mL). After 24 h, the reaction mixture was quenched with ice water (50 mL). The yellow oil was extracted with 1,2-dichloroethane, dried (molecular sieves 4°A) and concentrated *in vacuo*. The yellow residue was purified by flash chromatography using chloroform:*n*-hexane (10:3) as eluent to give 6.9 g. (32% yield) **3c** as pale yellow crystals, mp. 162°C (dec.). IR: 3040 aromatic (CH), 1825, 1750 and 1635 cm^{-1} for three (C=O). ^{1}H NMR ($CDCl_3$): δ 7.30-8.05 (m, 4H, aromatic-H).

^{13}C NMR ($CDCl_3$): δ 103.7, 114.4, 114.8, 122.3, 131.9, 154.4, 158.7, 161.9, 169.6, and 184.9.

Anal. Calcd for $C_{11}H_4O_5$: C, 61.12; H, 1.78. Found: C, 60.87; H, 1.80

Reaction of Furo[3,2-*c*]quinolone 3a with Phenols. General Procedure for 4a,b.- A mixture of 0.299 g. 1 mmol of furo[3,2-*c*]quinolone **3a** and 1 mmol of the corresponding phenols was heated at 70-75°C overnight. Upon cooling and treatment with ether, the product **4a,b** which separated as a white powder was collected and recrystallized from ethanol.

Phenyl 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-quinolinecarboxylate (4a).- 35% yield, white powder, mp. 235°C. IR (cm^{-1}): 2980, 1745, 1675 and 1665 cm^{-1} for aliphatic (CH), ester and two (C=O) groups respectively. ^1H NMR (DMSO): δ 3.35 (s, 3H, NCH_3), 4.85 (s, 1H, CH), 7.10-8.25 (m, 9H, aromatic-H).

Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 68.97; H, 4.23; N, 4.61

4-Nitrophenyl 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-quinolinecarboxylate (4b).- 53% yield, white powder, mp. 257°C. IR (cm^{-1}): 2980, 1740, 1670 and 1660 cm^{-1} for aliphatic (CH), ester and two (C=O) groups respectively. ^1H NMR (DMSO): δ 3.40 (s, 3H, NCH_3), 4.92 (s, 1H, CH), 7.13-8.15 (m, 8H, aromatic-H). ^{13}C NMR (DMSO): δ 27.5 (NCH_3), 73.2 (C-3), 119.5, 119.7, 125.7, 126.3, 127.6, 129.5, 132.3, 142.5, 144.6, 156.5 aromatic carbons, 157.8 (C-2), 162.5 (CO ester) and 190.8 (C-4).

Anal. Calcd for $C_{17}H_{12}N_2O_6$: C, 60.00; H, 3.55; N, 8.23. Found: C, 59.81; H, 3.45; N, 8.06

Reaction of Furo[3,2-*c*]quinolone 3a with Aromatic Amines. General Procedure for 5a,b.- To a solution of **3a** (0.359 g. 1.2 mmol) in 10 mL of dry CH_3CN was added a solution of 1.2 mmol of the corresponding amines in 5 mL of CH_3CN. The product which formed after two hours, was collected and recrystallized from ethanol to give **5a,b** in 78 and 80% yields respectively.

***N*-1-Phenyl-2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-quinolinyl)-2-oxoacetamide (5a)**.- 78% yield, white powder, mp. 184°C (dec.). IR (cm^{-1}): 3400-3250, 2985, 1735, 1715 and 1680 cm^{-1} for (NH), aliphatic (CH) and three (C=O) groups respectively. ^1H NMR (DMSO): δ 3.39 (s, 3H, NCH_3), 4.54 (s, 1H, CH), 7.09-7.85 (m, 9H, aromatic-H) and 12.19 (s, 1H, NH). ^{13}C NMR (DMSO): δ 28.5 (NCH_3), 78.5 (C-H), 154.0 (CO of amide), 154.8 (C-2), 119.4, 122.2, 123.9, 125.5, 126.6, 128.5, 131.5, 132.8, 136.1, 141.4 aromatic carbons, 191.0 (CO), 194.8 (C-4).

Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.83; H, 4.12; N, 8.57

***N*-1-4-Methylphenyl-2-(1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-quinolinyl)-2-oxoacetamide (5b)**.- 80% yield, white powder, mp. 214°C (dec.). IR (cm^{-1}): 3350-3250, 2980, 1740, 1710 and 1675 cm^{-1} for (NH), aliphatic (CH) and three (C=O) groups respectively. ^1H NMR (DMSO): δ 2.15 (s, 3H, p-CH_3), 3.45 (s, 3H, NCH_3), 4.56 (s, 1H, CH), 7.25-7.95 (m, 8H, aromatic-H) and 12.16 (s, 1H, NH).

Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.70; H, 4.68; N, 8.21

Thermolysis of 5a,b.- 1 mmol of **5a,b** was heated at reflux in diphenyl ether (20 mL) for 30 min, the reaction mixture was left to cool, then 10 mL of *n*-hexane was added. The product was

collected, and recrystallized from ethanol to give **7a,b** as white powders in 32 and 42% yield respectively.

***N*-3-Phenyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-quinolinecarboxamide (7a)**.- 32% yield, white powder, mp. 205°C. IR (cm^{-1}): 3350-3250, 2980, 1750, 1690 and 1660 cm^{-1} for (NH), aliphatic (CH) and (C=O) group respectively. ^1H NMR (DMSO): δ 3.43 (s, 3H, NCH_3), 4.97 (s, 1H, CH), 7.38-7.64 (m, 9H, aromatic-H) and 11.38 (s, 1H, NH). ^{13}C NMR (DMSO): δ 27.2 (NCH_3), 76.9 (C-3), 119.4, 119.8, 125.3, 125.6, 127.3, 130.6, 130.8, 132.5, 135.2 and 142.2 aromatic carbons, 159.2 (C-2), 171.6 (CO amide) and 183.4 (C-4).

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.11; H, 4.65; N, 9.34

***N*-3-4-Methylphenyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-quinolinecarboxamide (7b)**.- 42% yield, white powder, mp. 228°C. IR (cm^{-1}): 3350-3250, 2980, 1745, 1680 and 1660 cm^{-1} for (NH), aliphatic (CH) and (C=O) group respectively. ^1H NMR (DMSO): δ 2.15 (s, 1H, CH_3), 3.40 (s, 3H, NCH_3), 4.95 (s, 1H, CH), 7.30-7.70 (m, 8H, aromatic-H) and 11.45 (s, 1H, NH).

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 69.87; H, 4.95; N, 8.89

Reaction of α-Oxoketene 8 with Phenyl Isocyanate, Schiff's bases, Phenols and Amines. General Procedure.- To a solution of compound **3a** (0.358 g. 1.2 mmol) in 15 mL of diphenyl ether which was heated at 165°C, was added dropwise over 15 min a solution of 1.2 mmol phenyl isocyanate, (Schiff's bases, phenols or amines) in 3 mL of diphenyl ether. Heating was continued for 30 min. The reaction mixture was allowed to cool to room temperature, followed by the addition of 30 mL of *n*-hexane. The product was collected by suction to give **10a,b**, **4a,b** or **5a,b** respectively, which were crystallized from ethanol.

6-Methyl-3-phenyl-3,4,5,6-tetrahydro-2*H*-[1,3]oxazino[5,6-*c*]quinoline-2,4,5-trione (9).- 45% yield, white powder, mp. 205°C. IR (cm^{-1}): 2980, 1780, 1680 and 1620 cm^{-1} for aliphatic (CH), (C=O) and (C=C) group respectively. ^1H NMR (DMSO): δ 3.69 (s, 3H, NCH_3), 7.21-8.25 (m, 9H, aromatic-H). ^{13}C NMR (DMSO): δ 28.5 (NCH_3), 107.1 (C-4a), 118.2, 119.4, 125.6, 125.9, 126.6, 129.3, 130.5, 132.8, 134.2 aromatic carbons, 142.5 (C-6a), 150.5 (C-2), 158.1 (C-4), 158.4 (C-5) and 171.3 (C-10b).

Anal. Calcd for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.28; H, 3.68; N, 8.59

6-Methyl-2,3-diphenyl-3,4,5,6-tetrahydro-2*H*-[1,3]oxazino[5,6-*c*]quinoline-4,5-dione (10a).- 63% yield, white powder, mp. 213°C. IR (cm^{-1}): 2980, 1785, 1680 and 1620 cm^{-1} for aliphatic (CH), (C=O) and (C=C) group respectively. ^1H NMR ($CDCl_3$): δ 3.74 (s, 3H, NCH_3), 6.93 (s, 1H, O-CH-N), 6.86-7.94 (m, 14H, aromatic-H). ^{13}C NMR ($CDCl_3$): δ 29.3 (NCH_3), 84.9 (C-2), 102.7 (C-4a), 113.5, 116.40, 124.4, 127.25, 130.54, 132.1, 132.54, 139.57, 139.2 aromatic carbons, 154.4 (C-4), 158.91 (C-5) and 170.54 (C-10b).

Anal. Calcd for $C_{24}H_{18}N_2O_3$: C, 75.38; H, 4.74; N, 7.33. Found: C, 75.21; H, 4.56; N, 7.21

6-Methyl-3-(4-methylphenyl)-2-phenyl-3,4,5,6-tetrahydro-2*H*-[1,3]oxazino[5,6-*c*]quinoline-4,5-dione (10b).- 65% yield, white powder, mp. 234°C. IR (cm^{-1}): 2980, 1780, 1675 and 1610 cm^{-1} for aliphatic (CH), (C=O) and (C=C) group respectively. ^1H NMR (DMSO): δ 2.07 (s, 3H,

p-CH_3), 3.74 (s, 3H, NCH_3), 6.90 (s, 1H, O-CH-N), 7.08-7.98 (m, 13H, aromatic-H). ^{13}C-NMR (DMSO): δ 14.9 (CH_3), 29.2 (NCH_3), 84.8 (C-2), 102.4 (C-4a), 113.5, 116.5, 124.4, 127.3, 130.5, 132.1, 132.5, 132.9, 139.3 aromatic carbons, 152.9 (C-4), 158.5 (C-5) and 170.1 (C-10b). *Anal.* Calcd for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07. Found: C, 75.55; H, 4.89; N, 6.89

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