Reactions of *N*-Hydroxysuccinimide Esters of Anthranilic Acids with Anions of β-Keto Esters. A New Route to 4-Oxo-3-quinolinecarboxylic Acid Derivatives

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Received July 26, 1999; accepted October 12, 1999

A new approach for the synthesis of 4-oxo-3-quinolinecarboxylic acid derivatives is described. This methodology involves the *C*-acylation of the anions of appropriate β-keto esters with novel *N*-hydroxysuccinimide esters of anthranilic acids. The intermediate *C*-acylation products 3 are spontaneously cyclized to afford 3-ethoxycarbonyl-4-oxoquinoline derivatives 4. The introduction of a variety of substituents at positions 1 and 2 of the quinoline ring is feasible with the selection of suitable anthranilic acids and β-keto esters. The structure of the obtained 2-substituted 3-ethoxycarbonyl-4-oxoquinolines was confirmed by IR and NMR spectral data.

Key words quinolones; *N*-hydroxysuccinimide esters; *C*-acylation reaction

4-Oxo-3-quinolinecarboxylic acid derivatives constitute a class of heterocyclic compounds of great importance in pharmaceutical science. The group of antibacterial agents collectivelly known as 'quinolones,' comprises quinoline and 1,8-napthyridine derivatives containing the 4-oxo-3-carboxylic acid moiety. The synthesis and evaluation of antibacterial activity of related compounds is a field of continuing research in medicinal chemistry.[1] Apart from their antimicrobial activity, 4-oxo-3-quinolinecarboxylic acid derivatives have shown anticoccidial[2] and antitumor[3] activity. The inhibition of cell respiration by a series of 4-oxo-3-quinolinecarboxylic acids has been studied as a measure of their membrane-transport properties.[4] Moreover, several reports have appeared concerning the biological properties of 4-oxo-3-quinolinecarboxamides. Recently, the inhibition of human erythrocyte calpain I by quinolinecarboxamides has been reported.[5] The antiherpetic activity of related carboxamides, with or without a substituent at position 2, has also been examined.[6] The antibacterial activity of tricyclic derivatives containing an N-1 to C-2 bridge has been studied in the past few years.[7] 2-Substituted 4-hydroxy-3-quinolinecarboxamides have shown antiarthritic and analgesic activities[8] and it was stated that the nature of the substituent at position 2 specifies the actual activity of these derivatives. A series of 3-quinolinecarboxamides has been designed as serotonin 5-HT_3 receptors antagonists.[9]

Recently, we have established a convenient methodology for the construction of quinoline-2,4-dione derivatives, which involves the *C*-acylation of active methylene compounds with 3,1-benzoxazin-4-ones.[10] A variety of 3-substituted 4-hydroxyquinolin-2-ones, which have found attention lately as *N*-methyl-D-aspartate (NMDA) receptors antagonists,[11] can be prepared according to this method. However, this approach is limited to *N*-unsubstituted analogues and we have failed to extend its applicability to the synthesis of 2-substituted 3-quinolinecarboxylic acid derivatives. In the literature, there have been relatively few investigations concerning the preparation of 2-substituted 3-quinolinecarboxylic acids.[12] The most widely used method involves the reaction of isatoic anhydrides with β-keto esters and the cyclization of the intermediate *C*-acylation compounds.[13] Although, this approach appears to be general, the use of polar solvents with high boiling points and elevated reaction temperatures are required. Nevertheless, the yields reported are low in many cases. Alternative active derivatives of anthranilic acids, capable of reacting with nucleophiles under mild conditions, would be very useful for the preparation of various heterocyclic compounds possessing interesting biological properties.

Results and Discussion

In the course of our studies concerning the synthesis of quinoline derivatives, we elected to prepare the *N*-hydroxysuccinimide (HOSu) esters of anthranilic acids **1a**—**c** as starting materials in reactions with anions of β-keto esters to produce the 2-substituted 3-ethoxycarbonylquinolin-4-ones **4a**—**i**, as outlined in Chart 1.

The HOSu esters of many *N*-protected α-amino acids have been prepared[14] and found wide application in peptide synthesis. Especially, the HOSu ester of anthranilic acid (**2a**) has been found to be an efficient agent for 2-aminobenzoylation of amines.[15] According to the literature preparation, condensation of anthranilic acid with HOSu in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and a catalytic quantity of 4-dimethylaminopyridine resulted the HOSu ester **2a** in 52% yield.[15] Recrystallization from propanol-1 was necessary to obtain the product in acceptable purity. Several attempts made to optimise this procedure gave no satisfactory results. The low yield may be attributed to the formation of

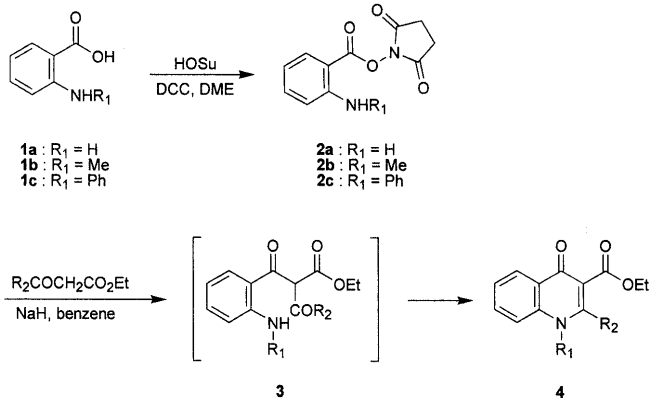

Chart 1

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Table 1. 3-Ethoxycarbonyl-4-oxoquinolines Obtained with the New Methodology

Product	R^1	R^2	Method	Yield (%)	Product	R^1	R^2	Method	Yield (%)
4a	H	Me	A	34	**4g**	Ph	Me	A	65
4b	H	Pr^n	A	28	**4g**	Ph	Me	B	72
4c	H	Ph	A	13	**4h**	Ph	Pr^n	A	55
4d	M	Me	A	26	**4h**	Ph	Pr^n	B	64
4e	Me	Pr^n	A	40	**4i**	Ph	Ph	A	60
4f	Me	Ph	A	51	**4i**	Ph	Ph	B	74

4-Oxoquinoline 4-Hydroxyquinoline

Fig. 1

polyamide products due to partial intermolecular condensation of the active aminoester. In the case of the *N*-substituted anthranilic acids we expected that the secondary amino group would display low nucleophilicity and further protection prior the active ester formation would be unnecessary. Actually, application of a standard protocol involving the condensation of equimolar amounts of **1b** (or **1c**) and HOSu in the presence of 1 eq of DCC afforded the active ester **2b** (or **2c**) in high yield (88 and 76% for **2b** and **2c** respectively). The HOSu esters **2b** and **2c** produced with this procedure were pure solids and could be used without further purification. These products proved to be stable for a long period, even under storage at room temperature.

The reactions of active esters **2a**—**c** with anions of β-keto esters were performed using a three-fold excess of the β-keto ester and sodium hydride (method A). At least one eq excess of the anion is required to react with the highly acidic methine proton of the tricarbonyl compounds **3**. Under these conditions the *C*-acylation products **3** undergo spontaneous cyclization to the desired quinolones **4**. This cyclization clearly involves attack of the amine nucleophile to the ketonic group of the intermediate **3** and subsequent dehydration produces 3-ethoxycarbonyl-4-oxoquinolines **4**. The alternative reaction path involving attack at the ester carbonyl of the intermediate **3** would afford 3-acyl-4-hydroxyquinolin-2-ones. However, formation of quinolin-2-ones was not observed. The *N*-substituted 4-oxoquinolines **4d**—**i** were isolated by evaporation of the solvent *in vacuo* after washing the reaction mixture with water to remove the water-soluble byproduct HOSu and the excess of the β-keto ester. Quinolinones **4a**—**c** possessing an acidic proton were extracted in water and precipitated after acidification of the aqueous extract. Attempts to isolate intermediates **3** were unsuccessful. These compounds may be water-soluble or unstable to the work-up procedure.

Under the conditions mentioned above, reasonable yields of quinolin-4-ones **4** were obtained only after prolonged reaction times. Modification of the reaction conditions in the case of the *N*-phenyl active ester **2c** resulted in the formation of quinolones **4g**—**i** in shorter reaction times (method B). Thus, ester **2c** was stirred with 2.2 eq of the anion of ethyl acetoacetate at room temperature for 2 h, then the temperature was raised slowly to 80 °C and the mixture refluxed for 1 h. Work-up afforded compound **4g** in good yield. The obtained yields are summarized in Table 1.

Although compounds **4d**—**i**, bearing a substituent on N-1, clearly possess a 4-oxoquinoline structure, compounds **4a**—**c** may also adopt the tautomeric 4-hydroxyquinoline structure as shown in Fig. 1.

The structure of compounds **4a**—**i** was established based on IR and NMR spectral data. The IR spectra of compounds **4d**—**i** in Nujol show absorptions at 1710—1730 cm^{-1} for the ester carbonyl and 1620 cm^{-1} for the ring carbonyl, as expected for their 3-ethoxycarbonyl-4-oxoquinoline structure. The presence of similar absortions at 1710—1720 cm^{-1} and 1630—1640 cm^{-1} for compounds **4a**—**c**, indicates a 4-quinolone structure for these derivatives, as well. This assignment is in agreement with previously published[16] structural studies of related *N*-unsubstituted derivatives.

The structure of quinolones **4a**—**i** in solution was studied by ^1H- and ^{13}C-NMR spectroscopy. The proton NMR spectra of compounds **4a**—**c** exhibit a broad signal approximately at 12 ppm which can be assigned either as a NH or an enolic OH proton of the 4-oxo- or 4-hydroxyquinoline form, respectively. Although, proton NMR spectral data do not serve to discriminate the two possible tautomeric forms, ^{13}C-NMR data (see Table 2) indicate the existence of compounds **4a**—**c** in the 4-oxoquinoline form in solution. The ^{13}C chemical shifts of **4a**—**c** have no significant difference from the corresponding *N*-substituted compounds indicating a similar structure for all these compounds. Furthermore, the C-4a signals of compounds **4a**—**c** appear approximately at 125 ppm, a value representative of 4-oxoquinoline derivatives.[17]

Conclusion

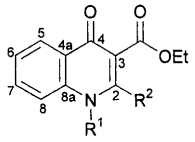
In summary, the synthetically and biologically interesting title compounds can be prepared in one step under mild conditions and in good yields. The proposed methodology provides useful intermediates for the synthesis of more complex substrates in the "quinolone" series.

Experimental

Melting points were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 267 spectrometer. The NMR spectra were recorded on a Gemini-2000 300 MHz spectrometer. Chemical shifts are quoted in ppm (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublets, m=multiplet).

2-Aminobenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester 2a Following the literature procedure[15] the title compound was obtained in 42% yield as a yellow solid, mp 158—162 °C (from 1-propanol) (lit.[15] mp 161.5—163 °C). IR (Nujol) cm^{-1}: 3480 (ν_{as} NH_2), 3430 (ν_s NH_2), 1730 (C=O, ester and imide). ^1H-NMR ($CDCl_3$) δ: 2.89 [4H, s, $(CH_2)_2$], 5.65 (2H, s, NH_2), 6.64—6.70 (2H, m, 5-H, 3-H), 7.35 (1H, pseudotriplet, 4-H), 7.97 (1H, dd, $J_{5,6}$=8.8 Hz, $J_{4,6}$=1.5 Hz, 6-H). ^{13}C-NMR ($CDCl_3$) δ: 25.5 [$(CH_2)_2$], 105.1 (C-1), 116.7, 116.8 (C-3, C-5), 131.2 (C-6), 136.3 (C-4), 151.9 (C-2), 162.8 (ArCO), 169.8 (CON).

Table 2. ^{13}C NMR Spectral Data for 3-Ethoxycarbonyl-4-oxoquinolines **4a**—**i**



	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	CO_2Et	CH_2	CH_3	R^1 and R^2
4a	149.0	114.9	173.6	124.7	125.2	123.8	132.3	118.1	139.3	167.0	60.3	14.0	18.0 (2-CH_3)
4b	154.8	115.3	176.1	125.4	125.8	124.6	132.6	119.4	140.1	167.8	61.2	14.2	35.0—23.0—13.9 (2-Pr^n)
4c	149.6	115.7	173.9	124.8	125.1	124.2	132.6	118.9	139.7	166.4	60.2	13.6	133.9—130.4—128.8—128.4 (2-Ph)
4d	149.3	118.5	174.3	126.4	126.8	123.9	132.6	115.4	141.2	168.0	61.3	14.1	34.5 (N-CH_3), 19.1 (2-CH_3)
4e	152.6	118.7	174.7	126.6	127.1	124.0	132.7	115.5	141.5	168.0	61.4	14.1	34.5 (N-CH_3), 34.1—22.3—14.0 (2-Pr^n)
4f	152.3	119.2	174.1	126.9	127.2	124.3	132.9	116.0	141.2	166.4	60.8	13.6	37.0 (N-CH_3), 133.6—129.9—128.8 (2-Ph)
4g	149.3	118.0	174.6	125.7	126.4	124.0	132.1	117.7	142.2	167.7	61.4	14.1	19.6 (2-CH_3), 138.7—130.7—130.0—129.0 (N-Ph)
4h	153.2	117.8	174.9	125.8	126.4	124.1	132.1	118.1	142.4	167.8	61.4	14.1	33.8—22.9—14.1 (2-Pr^n), 138.4—130.5—130.1—129.5 (N-Ph)
4i	151.8	119.1	124.6	126.2	126.7	124.4	132.4	118.2	142.1	166.3	60.9	13.5	138.7—133.3—130.1—129.7—129.6—129.2—129.0—127.7 (N-, 2-Ph)

2-Methylaminobenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester 2b A solution of DCC (2.5 mmol, 5.16 g) in 1,2-dimethoxyethane (DME) (15 ml) was added dropwise over a period of 20 min to a solution of *N*-methylanthranilic acid (2.5 mmol, 3.78 g) and HOSu (2.5 mmol, 2.88 g) in DME (50 ml) under cooling in an ice-water bath. The mixture was stirred at room temperature for 48 h and the precipitated solid was filtered off and washed with DME. The filtrate was evaporated *in vacuo* and the solid residue treated with diethyl ether, filtered off and washed with diethyl ether to afford compound **2b** as a yellow solid (5.46 g, 88%), mp 142—146 °C. *Anal.* Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.97; H, 4.87; N, 11.29. IR (Nujol) cm^{-1}: 3430 (NH), 1720 (C=O, ester and imide). ^{1}H-NMR ($CDCl_3$) δ: 2.87 [4H, s, $(CH_2)_2$], 2.90 (3H, d, J=4.4 Hz, NCH_3), 6.63 (1H, pseudotriplet, 5-H), 6.69 (1H, d, $J_{3,4}$=8.3 Hz, 3-H), 7.19 (1H, s, NH), 7.46 (1H, pseudotriplet, 4-H), 8.02 (1H, dd, $J_{5,6}$=8.3 Hz, $J_{4,6}$=1.5 Hz, 6-H). ^{13}C-NMR ($CDCl_3$) δ: 25.5 [$(CH_2)_2$], 29.4 (NCH_3), 104.2 (C-1), 111.1 (C-3), 114.9 (C-5), 131.7 (C-6), 136.8 (C-4), 153.1 (C-2), 163.3 (ArCO), 169.9 (CON).

2-Phenylaminobenzoic Acid 2,5-Dioxopyrrolidin-1-yl Ester 2c A solution of DCC (2.5 mmol, 5.16 g) in DME (15 ml) was added dropwise over a period of 20 min to a solution of *N*-phenylanthranilic acid (2.5 mmol, 5.34 g) and HOSu (2.5 mmol, 2.88 g) in DME (80 ml) under cooling in an ice-water bath. The mixture was stirred at room temperature for 24 h and the precipitated solid was filtered off and washed with DME. The filtrate was evaporated *in vacuo*, the oily residue was treated with diethyl ether and the formed solid was filtered off and washed with diethyl ether to afford compound **2c** as a green solid (5.92 g, 76%), mp 126—128 °C (from 2-propanol). *Anal.* Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.59; H, 4.64; N, 9.19. IR (Nujol) cm^{-1}: 3350 (NH), 1720 (C=O, ester and imide). ^{1}H-NMR ($CDCl_3$) δ: 2.91 [4H, s, $(CH_2)_2$], 6.76 (1H, pseudotriplet, 5-H), 7.12—7.42 (7H, m, 3-H, 4-H, NPh), 8.11 (1H, dd, $J_{5,6}$=8.3, $J_{4,6}$=1.5 Hz, 6-H), 8.86 (1H, s, NH). ^{13}C-NMR ($CDCl_3$) δ: 25.6 [$(CH_2)_2$], 106.0 (C-1), 114.0 (C-3), 117.4 (C-5), 123.7 (C-2′), 124.8 (C-4′), 129.6 (C-3′), 131.7 (C-6), 136.8 (C-4), 139.7 (C-1′), 149.7 (C-2), 163.3 (ArCO), 169.7 (CON).

General Procedures for the Preparation of 2-Substituted 4-Oxoquinoline-3-carboxylic Acid Ethyl Esters 4a—i.

Method A: The appropriate β-keto ester (7.5 mmol) was added dropwise to a dispersion of sodium hydride (55—60% sodium hydride in oil; 7.5 mmol) in anhydrous benzene (30 ml) and the thick slurry thus formed was stirred at room temperature for 1 h. The active ester **2** (2.5 mmol) was added and the mixture stirred at room temperature for 3—5 d. a) Compounds **4a**—**c**: The reaction mixture was extracted twice with water and the combined aqueous extracts acidified with 10% hydrochloric acid under cooling in an ice-water bath. The precipitated product was collected by filtration and washed with ice-cold water. b) Compounds **4d**—**i**: The reaction mixture was extracted once with a small amount of water (*ca.* 5 ml), the organic phase was dried over sodium sulfate and evaporated *in vacuo* to afford an oily residue which crystallized after standing at room temperature for 2—3 d.

Method B: The appropriate β-keto ester (2.2 mmol) was added dropwise to a dispersion of sodium hydride (60% sodium hydride in oil; 2.2 mmol) in anhydrous benzene (15 ml) and the thick slurry thus formed was stirred at room temperature for 1 h. The active ester **2c** (1.0 mmol) was added, the mixture was stirred at room temperature for 2 h, then the temperature was raised slowly to 80 °C and the mixture was refluxed for 1 h. After cooling to room temperature the reaction mixture was extracted with a small amount of water (*ca.* 5 ml), the organic phase was dried over sodium sulfate and evaporated *in vacuo* to afford an oily residue which crystallized after standing at room temperature for 2—3 d.

1,4-Dihydro-2-methyl-4-oxoquinoline-3-carboxylic Acid Ethyl Ester 4a The reaction mixture [compound **2a** (0.78 g, 3.3 mmol), ethyl acetoacetate (1.30 g, 10 mmol) and sodium hydride (55—60% sodium hydride in oil; 0.44 g, 10 mmol) in anhydrous benzene (40 ml)] was stirred for 3 d and worked-up according to procedure (a) to afford the title compound as a beige solid (0.26 g, 34%), mp 233—234 °C (from methanol) (lit.[16] mp 231—232 °C). IR (Nujol) cm^{-1}: 3280 (NH), 1710 (C=O, ester), 1640 (C=O, ketone), 1610 (C=C). ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.37 (3H, s, CH_3), 4.21 (2H, q, J=7.0 Hz, $C\underline{H}_2CH_3$), 7.32 (1H, pseudotriplet, 6-H), 7.51 (1H, d, $J_{7,8}$=8.2 Hz, 8-H), 7.65 (1H, pseudotriplet, 7-H), 8.04 (1H, dd, $J_{5,6}$=7.9 Hz, $J_{5,7}$=1.3 Hz, 5-H), 11.85 (1H, s, NH).

1,4-Dihydro-4-oxo-2-propylquinoline-3-carboxylic Acid Ethyl Ester 4b The reaction mixture [compound **2a** (1.18 g, 5.0 mmol), ethyl butyrylacetate (2.38 g, 15 mmol) and sodium hydride (55—60% sodium hydride in oil; 0.65 g, 15 mmol) in anhydrous benzene (45 ml)] was stirred for 2 d and worked-up according to procedure (a) to afford compound **4b** as a white solid (0.36 g, 28%), mp 215—216 °C (from dichloromethane-light petroleum). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.40; H, 6.61; N, 5.36. IR (Nujol) cm^{-1}: 1720 (C=O, ester), 1630 (C=O, ketone), 1610 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.3 Hz, $CH_2CH_2C\underline{H}_3$), 1.23 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 1.78 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.82 (2H, m, $C\underline{H}_2CH_2CH_3$), 4.21 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.34 (1H, pseudotriplet, 6-H), 7.60 (1H, pseudotriplet, 7-H), 7.78 (1H, d, $J_{7,8}$=8.5 Hz, 8-H), 8.34 (1H, dd, $J_{5,6}$=8.2 Hz, $J_{5,7}$=1.3 Hz, 5-H), 12.06 (1H, s, NH).

1,4-Dihydro-4-oxo-2-phenylquinoline-3-carboxylic Acid Ethyl Ester 4c The reaction mixture [compound **2a** (0.94 g, 4.0 mmol), ethyl benzoylacetate (2.31 g, 12 mmol) and sodium hydride (60% sodium hydride in oil; 0.48 g, 12 mmol) in anhydrous benzene (40 ml)] was stirred for 3 d and worked-up according to procedure (a) to afford the title compound as a yellow solid (0.24 g, 20%), mp 265—267 °C (from methanol). *Anal.* Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.64; H, 5.12; N, 4.80. IR (Nujol) cm^{-1}: 3100 (NH), 1710 (C=O, ester), 1610 (C=C, C=O, ketone). ^{1}H-NMR (DMSO-d_6) δ: 0.88 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.94 (2H, q, J=7.0 Hz, $C\underline{H}_2CH_3$), 7.39 (1H, pseudotriplet, 6-H), 7.52—7.78 (7H, m, 7-H, 8-H, Ph), 8.04 (1H, dd, $J_{5,6}$=7.9 Hz, $J_{5,7}$=1.0 Hz, 5-H), 12.06 (1H, s, NH).

1,4-Dihydro-1,2-dimethyl-4-oxoquinoline-3-carboxylic Acid Ethyl Ester 4d The reaction mixture [compound **2b** (0.62 g, 2.5 mmol), ethyl acetoacetate (0.99 g, 7.6 mmol) and sodium hydride (55—60% sodium hydride in oil; 0.33 g, 7.6 mmol) in anhydrous benzene (30 ml)] was stirred for 3 d and worked-up according to procedure (b) to afford the title compound as a white solid (0.16 g, 26%), mp 143—144 °C (from dichloromethane-light petroleum) (lit.[13] mp 142—144 °C). IR (Nujol) cm^{-1}: 1720 (C=O, ester),

1620 (C=O, ketone), 1600 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 2.46 (3H, s, CH_3), 3.69 (3H, s, NCH_3), 4.39 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 7.30 (1H, pseudotriplet, 6-H), 7.41 (1H, d, $J_{7,8}$=8.8 Hz, 8-H), 7.59 (1H, pseudotriplet, 7-H), 8.35 (1H, dd, $J_{5,6}$=7.8 Hz, $J_{5,7}$=1.5 Hz, 5-H).

1,4-Dihydro-1-methyl-4-oxo-2-propylquinoline-3-carboxylic Acid Ethyl Ester 4e The reaction mixture [compound **2b** (0.62 g, 2.5 mmol), ethyl butyrylacetate (1.20 g, 7.6 mmol) and sodium hydride (55—60% sodium hydride in oil; 0.33 g, 7.6 mmol) in anhydrous benzene (30 ml)] was stirred for 3 d and worked-up according to procedure (b) to afford compound **4e** as a white solid (0.27 g, 40%), mp 103—105 °C (from diethyl ether) (lit.[13] mp 102—104 °C). IR (Nujol) cm^{-1}: 1720 (C=O, ester), 1630 (C=O, ketone), 1600 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, t, J=7.3 Hz, $CH_2CH_2C\underline{H}_3$), 1.39 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 1.76 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.75 (2H, m, $C\underline{H}_2CH_2CH_3$), 3.76 (3H, s, NCH_3), 4.42 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 7.38 (1H, pseudotriplet, 6-H), 7.51 (1H, d, $J_{7,8}$=8.8 Hz, 8-H), 7.67 (1H, pseudotriplet, 7-H), 8.45 (1H, dd, $J_{5,6}$=7.8 Hz, $J_{5,7}$=1.5 Hz, 5-H).

1,4-Dihydro-1-methyl-4-oxo-2-phenylquinoline-3-carboxylic Acid Ethyl Ester 4f The reaction mixture [compound **2b** (0.62 g, 2.5 mmol), ethyl benzoylacetate (1.46 g, 7.6 mmol) and sodium hydride (55—60% sodium hydride in oil; 0.33 g, 7.6 mmol) in anhydrous benzene (30 ml)] was stirred for 3.5 d and worked-up according to procedure (b) to afford the title compound as a beige solid (0.39 g, 51%), mp 164—169 °C (from dichloromethane-light petroleum) (lit.[13] mp 167—168 °C). IR (Nujol) cm^{-1}: 1730 (C=O, ester), 1620 (C=O, ketone), 1600 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 3.51 (3H, s, NCH_3), 3.96 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 7.36—7.51 (6H, m, 6-H, Ph), 7.53 (1H, d, $J_{7,8}$=8.3 Hz, 8-H), 7.70 (1H, pseudotriplet, 7-H), 8.50 (1H, dd, $J_{5,6}$=7.8 Hz, $J_{5,7}$=1.5 Hz, 5-H).

1,4-Dihydro-2-methyl-4-oxo-1-phenylquinoline-3-carboxylic Acid Ethyl Ester 4g

(i) Following Method A: The reaction mixture [compound **2c** (0.78 g, 2.5 mmol), ethyl acetoacetate (0.98 g, 7.5 mmol) and sodium hydride (60% sodium hydride in oil; 0.30 g, 7.5 mmol) in anhydrous benzene (30 ml)] was stirred for 5 d and worked-up according to procedure (b) to afford the title compound as a beige solid (0.50 g, 65%).

(ii) Following Method B: The reaction mixture [compound **2c** (0.59 g, 1.9 mmol), ethyl acetoacetate (0.55 g, 4.2 mmol) and sodium hydride (60% sodium hydride in oil; 0.17 g, 4.2 mmol) in anhydrous benzene (20 ml)] was stirred at room temperature for 2 h and under reflux for 1 h. Work-up according to procedure (b) afforded the title compound as a beige solid (0.42 g, 72%), mp 132—137 °C (from diethylether). *Anal.* Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.39; H, 5.65; N, 4.46. IR (Nujol) cm^{-1}: 1710 (C=O, ester), 1620 (C=O, ketone), 1600 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 2.12 (3H, s, CH_3), 4.44 (2H, q, J=7.3 Hz, $C\underline{H}_2CH_3$), 6.62 (1H, d, J=7.8 Hz, 8-H), 7.24—7.46 (4H, m, 6-H, NPh), 7.57—7.69 (3H, m, 7-H, NPh), 8.45 (1H, dd, $J_{5,6}$=7.8 Hz, $J_{5,7}$=1.5 Hz, 5-H).

1,4-Dihydro-4-oxo-1-phenyl-2-propylquinoline-3-carboxylic Acid Ethyl Ester 4h

(i) Following Method A: The reaction mixture [compound **2c** (0.78 g, 2.5 mmol), ethyl butyrylacetate (1.19 g, 7.5 mmol) and sodium hydride (60% sodium hydride in oil; 0.30 g, 7.5 mmol) in anhydrous benzene (30 ml)] was stirred for 7 d and worked-up according to procedure (b) to afford the title compound as a white solid (0.46 g, 55%).

(ii) Following Method B: The reaction mixture [compound **2c** (0.31 g, 1.0 mmol), ethyl butyrylacetate (0.35 g, 2.2 mmol) and sodium hydride (60% sodium hydride in oil; 0.09 g, 2.2 mmol) in anhydrous benzene (15 ml)] was stirred at room temperature for 2 h and under reflux for 1 h. Work-up according to procedure (b) afforded the title compound as a white solid (0.33 g, 64%), mp 157—159 °C (from diethyl ether). *Anal.* Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.26; H, 6.34; N, 4.14. IR (Nujol) cm^{-1}: 1730 (C=O, ester), 1620 (C=O, ketone), 1600 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, t, J=7.3 Hz, $CH_2CH_2C\underline{H}_3$), 1.40 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 1.54 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.40 (2H, m, $C\underline{H}_2CH_2CH_3$), 4.43 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 6.57 (1H, d, J=8.3 Hz, 8-H), 7.27—7.44 (4H, m, 6-H, NPh), 7.58—7.69 (3H, m, 7-H, NPh), 8.44 (1H, dd, $J_{5,6}$=7.8 Hz, $J_{5,7}$=2.0 Hz, 5-H).

1,4-Dihydro-1,2-diphenyl-4-oxoquinoline-3-carboxylic Acid Ethyl Ester 4i

(i) Following Method A: The reaction mixture [compound **2c** (0.78 g, 2.5 mmol), ethyl benzoylacetate (1.45 g, 7.5 mmol) and sodium hydride (60% sodium hydride in oil; 0.30 g, 7.5 mmol) in anhydrous benzene (30 ml)] was stirred for 7 d and worked-up according to procedure (b) to afford compound **4i** as a white solid (0.56 g, 60%).

(ii) Following Method B: The reaction mixture [compound **2c** (0.31 g, 1.0 mmol), ethyl benzoylacetate (0.43 g, 2.2 mmol) and sodium hydride (60% sodium hydride in oil; 0.09 g, 2.2 mmol) in anhydrous benzene (15 ml)] was stirred at room temperature for 2 h and under reflux for 1 h. Work-up according to procedure (b) afforded the title compound as a white solid (0.27 g, 74%), mp 222—223 °C (from diethyl ether). *Anal.* Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 78.16; H, 5.19; N, 3.91. IR (Nujol) cm^{-1}: 1730 (C=O, ester), 1620 (C=O, ketone), 1600 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 4.00 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 6.79 (1H, d, J=8.3 Hz, 8-H), 7.08—7.51 (12H, m, 6-H, 7-H, 2-Ph, NPh), 8.53 (1H, dd, $J_{5,6}$=7.8 Hz, $J_{5,7}$=1.5 Hz, 5-H).

Acknowledgements We wish to thank the Committee of Research of the National Technical University of Athens for a doctoral assistanship (C. M.).

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