Reactions of 2-methyl-3,1-benzoxazin-4-one with active methylene compounds: a new route to 3-substituted 4-hydroxyquinolin-2(1*H*)-ones

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A new route to 3-substituted 4-hydroxyquinolin-2(1*H*)-ones, compounds of great biological importance, is described. The *C*-acylation of active methylene compounds 2 with the 2-methyl-3,1-benzoxazin-4-one 1, under basic conditions, leads to the formation of the new products 3–10, which have been isolated and characterized. Cyclization of the above intermediates furnishes the 3-substituted 4-hydroxyquinolin-2(1*H*)-ones. Spectral data and physical characteristics for all compounds are reported.

Quinoline-2,4-dione derivatives (Fig. 1), substituted at position 3, are important and interesting substances for the synthesis of pharmacologically active compounds.

Recent reports[1] describe a novel class of 4-hydroxyquinolin-2(1*H*)-one derivatives as selective glycine-site NMDA antagonists which possess potent centrally mediated *in vivo* activity after oral administration. Moreover, potential antithyroid agents based on a two-membered ensemble of heterocycles, contain the 4-hydroxyquinolin-2(1*H*)-one system as one of their structural fragments.[2] Some of the quinolinone alkaloids exhibit antimicrobial activity and marked cytotoxicity against animal and plant tumours[3].

A series of 4-hydroxyquinoline-3-carboxylic acid derivatives was recently designed and synthesized as 5-HT_3 receptor antagonists.[4] Recently, Leeson *et al.*[5] reported that 3-alkoxycarbonyl and 3-benzoyl quinolinones (Fig. 1, Y = CO_2R, COPh) with a small electron-withdrawing group at position 7 showed anticonvulsant activity. However, quinolinone derivatives exhibit different activities, depending on their structural class. It is believed that the 'enolic β-dicarbonyl moiety', within the quinoline-2,4-dione framework may act as a brain-penetrating carbonyl bioisostere.[6]

Our current interest in the chemistry of tetramic acids, 3-substituted pyrrolidine-2,4-diones possessing the 'enolic β-dicarbonyl moiety', prompted us to synthesize 4-hydroxyquinolin-2(1*H*)-one derivatives, substituted at position 3.

The unique biological activity and characteristic chemical structure of quinoline-2,4-diones have made their synthesis very attractive over the years. In 1954, Lacey[7] reported a convenient synthesis of 3-acetylpyrroline-2,4-diones from α-amino acid esters and diketene. Similarly, methyl anthranilate was converted into the *N*-acetoacetyl derivative with diketene and the product was cyclized to give 3-acetylquinoline-2,4-dione (Fig. 1, Y = COMe) or **14**. This strategy has been extensively used by other groups in order to construct the quinolinone ring systems with a diversity of substituents.[8]

4-Hydroxyquinolin-2(1*H*)-ones have also been prepared by an alternative route[9] involving the condensation of substituted malonates with anilides.

A significant contribution in the area of quinolinone ring formation has been made by Coppola and co-workers,[10] who investigated the reaction of substituted isatoic anhydrides with a metallated active methylene compound. The acyclic intermediates are relatively unstable and spontaneously cyclize, over varying periods of time. A series of 4-hydroxy-2-oxoquinoline-3-carboxylic acid derivatives was designed and synthesized as 5-HT_3 receptor antagonists by Suzuki and co-workers,[4] using isatoic anhydride derivatives as a starting material.

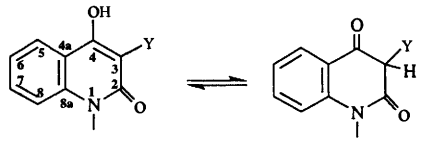


Fig. 1

The acylation of quinoline-2,4-diones, bearing no substituents at the 3-position was regarded as an alternative method of access to complex naturally occurring 3-acylquinoline-2,4-dione derivatives.[11]

In continuing our interest in the synthesis of heterocyclic compounds containing the 'enolic β-dicarbonyl system' through *C*-acylation of active methylene compounds with an activated ester of α-amino acids,[12] we turned our attention to the synthesis of quinolinones by an analogous reaction, using 2-methyl-3,1-benzoxazin-4-one **1** as the acylating agent.

Our new methodology (Scheme 1) involves the *C*-acylation of an active methylene compound **2** with the 2-methyl-3,1-benzoxazin-4-one **1**. The *C*-acylation compounds **3–10** isolated undergo cyclization to 3-substituted 4-hydroxyquinolin-2(1*H*)-ones **11–15** by an intramolecular condensation mechanism.

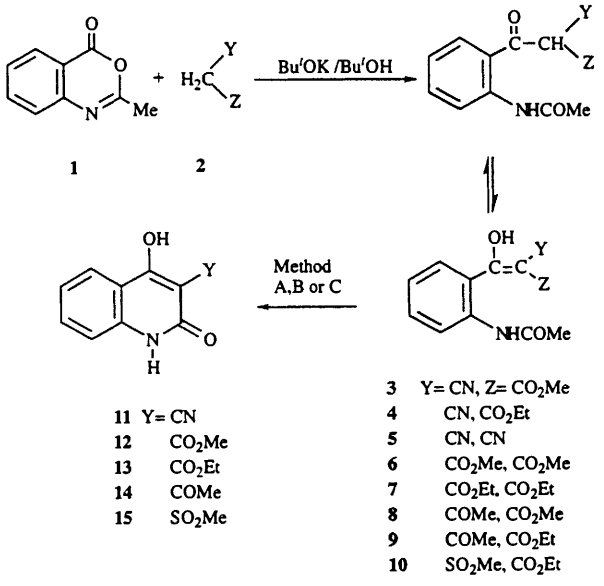
The 2-methyl-3,1-benzoxazin-4-one **1**, which was used as starting material, was prepared from the *N*-acetylanthranilic acid according to a literature procedure.[13]

In a typical *C*-acylation reaction 2 or 3 mol equiv. of the active methylene compound **2** were treated with 2 mol equiv. of potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature. After *ca.* 15 min, 1 mol equiv. of 2-methyl-3,1-benzoxazin-4-one **1** was added to the mixture which was then stirred for 1.5–2 h before treatment with water and diethyl ether; the aqueous layer on acidification gave the *C*-acylation compounds **3–10**, in good yields (Table 1).

The cyclizations were carried out using sodium alkoxide in alcohol–benzene, hydrogen chloride in alcohol or a solution of NaOH–Na_2CO_3. Cyclization was effected by refluxing the *C*-acylation compounds **3** and **4** with 2 mol equiv. of sodium alkoxide in alcohol–benzene or a solution of 8% HCl in alcohol. Work-up of the reaction mixture gave the 3-cyano-4-hydroxyquinolin-2(1*H*)-one **11** as a pure solid which was filtered off.

Table 1 Analytical data of the *C*-acylation compounds, **3–10**

Compound (formula)	Yield (%)	Recrystallization solvent	Mp (°C)	Found (%) (required) C	H	N
3 ($C_{13}H_{12}N_2O_4$)	83	$CHCl_3$–LP	153–154 °C	59.76 (59.99)	4.68 (4.65)	10.49 (10.77)
4 ($C_{14}H_{14}N_2O_4$)	95	$CHCl_3$–LP	144–145 °C	60.90 (61.31)	5.20 (5.15)	10.08 (10.21)
5 ($C_{12}H_9N_3O_2$)	57	MeOH–LP	175–177.5 °C	63.81 (63.43)	4.21 (3.99)	18.37 (18.49)
6 ($C_{14}H_{15}NO_6$)	85	CH_2Cl_2–LP	84–86 °C	57.63 (57.33)	5.19 (5.16)	4.97 (4.78)
7 ($C_{16}H_{19}NO_6$)	85	CH_2Cl_2–LP	93–96 °C	59.53 (59.80)	5.93 (5.96)	4.55 (4.36)
8 ($C_{14}H_{15}NO_5$)	78	CH_2Cl_2–LP	91–93.5 °C	60.80 (60.64)	5.46 (5.45)	5.01 (5.01)
9 ($C_{15}H_{17}NO_5$)	81	CH_2Cl_2–LP	97–99 °C	61.88 (61.85)	5.64 (5.88)	4.82 (4.81)
10 ($C_{14}H_{17}NO_6S$)	70	CH_2Cl_2–LP	105–107 °C	51.53 (51.37)	5.20 (5.24)	4.45 (4.28)



Scheme 1 *Reagents and conditions:* Method A: MeONa–MeOH (for compound **3**) or EtONa–EtOH (for compound **4**), reflux; method B: HCl–MeOH (for compound **3**) or HCl–EtOH (for compound **4**), reflux; method C: Na_2CO_3–NaOH (for compounds **6–10**), room temp.

The attempted ring closure of compounds **6–10** using sodium alkoxide gave only poor yields of the desired products together with *N*-acetylanthranilic acid as a by-product. Cyclization of the above compounds to the corresponding 3-substituted 4-hydroxyquinolin-2(1*H*)-ones **12–15** was successfully performed in aqueous sodium hydroxide combined with sodium carbonate. The compounds **12–15** were obtained as pure solids, in good yields (50–90%).

An important feature of the proposed method has been the use of the benzoxazinone **1** as acylating agent, which represents a unique species of *N*-acetylanthranilic acid derivative where both the carboxylate activation and the amino group protection are achieved simultaneously. It is known that 2-methyl-3,1-benzoxazin-4-one **1** is highly susceptible to acid-catalysed hydrolysis and thus easily converted into *N*-acetylanthranilic acid.[14] Best results were obtained when **1** was worked up with chloroform and aqueous sodium carbonate to give a compound stable for several days.

The two required reactants for the construction of the quinolinone fused ring are the active methylene compound, which provides carbon atoms 2 and 3 of the heterocyclic ring as well as the 3-position substituent, and the benzoxazinone ring that supplies the remainder of the molecule.

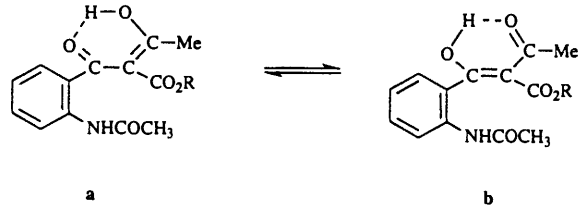
The two-step synthetic sequence described here, constitutes a method for inserting different side chains at the 3-position of the quinolinone ring by using a suitable methylene compound. Moreover, the proposed method provides the nonsubstituted (NH) compounds, which are very useful structures for several drugs.

The structures of the unknown *C*-acylation compounds **3–10** and the 3-substituted 4-hydroxyquinolin-2(1*H*)-ones **11–15** were established on the basis of elemental analyses and spectral data (Tables 1, 2 and 3).

The IR spectra of the *C*-acylation compounds **3–10** (Table 2) show characteristic absorption at 3310–3130 cm^{-1} for the –NH– group, at 1730–1680 cm^{-1} and 1690–1640 cm^{-1} for the –CO– group of the β-dicarbonyl system CO–CH–CO– ⇌ C(OH)=C–CO. For compounds **8** and **9**, where the $-C-COCH_3$ group is present, the intramolecular hydrogen bonded enol carbonyl of the β-diketone system appears at 1650–1630 cm^{-1} (Scheme 2). Moreover, the absorption at 1610–1590 cm^{-1} is attributed to the carbon–carbon double bond, whereas the amide II band appears at 1580–1540 cm^{-1}. The IR spectra of compounds **3** and **4** are also characterized by the presence of a strong absorption band at 2220 cm^{-1} assigned for the CN group.

The IR spectra of 3-substituted 4-hydroxyquinolin-2(1*H*)-ones **11–15** (see Experimental section) showed absorption at 3420–3130 cm^{-1} for the NH group and at 1670–1630 cm^{-1} for the carbonyl and amide carbonyl groups. The spectrum of the product **11** is also characterized by the presence of strong absorption for the CN group at 2224 cm^{-1} (ref. 15).

The ^1H NMR spectra data for the newly obtained *C*-acylation compounds **3–10** are summarized in Table 3. The *N*-acetylanthranyl cyanoacetic esters **3** and **4** were found to exist, in $CDCl_3$ solution, in the enolized form. Their ^1H NMR spectra lacked any resonance characteristic of a methinyl proton, corresponding to the keto form (Fig. 2). On the other hand, compounds **5**, **6**, **7** and **10** were found to exist in the keto form, showing the methinyl proton at δ 4.28–5.90. In $CDCl_3$ solution, compounds **8** and **9** exist as a mixture of two tautomers (Scheme 2). Analysis of the ^1H NMR spectrum of compound **9** shows two sets



Scheme 2

Table 2 IR spectral data [ν_{max}(Nujol)/cm^{-1}] for the *C*-acylation compounds **3–10**

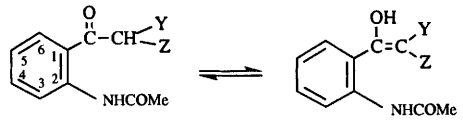


Fig. 2

Compound	NH	CN	CO keto-ester	CO keto	CO enol	Amide I	CO enol (hydrogen bonded)	C=C ring stretching	Amide II
3	3140, m, br	2220, s, sh		1710, w, sh	1660, s, br			1610, s, sh	1570, s, sh
4	3250, m, sh	2210, s, sh		1680, w	1670, s, sh			1610, m, sh	1590, m, sh
5	3310, m, sh	2220, s, sh			1650, m, br			1590, s, sh	1540, s, sh
6	3280, w, br		1730, s, sh	1720, s, sh	1640, m, sh			1600, w, sh	1570, s, sh
7	3300, w, br		1750, s, sh	1730 & 1700, m, sh (doublet)	1650, m, sh			1610, w, sh	1580, m, sh
8	3220, w, br				1675, m, sh	1630, s, br		1590, m, sh	1570, s, sh
9	3130, w, br				1690, s, sh	1650, m, br		1590, m, br	1570, m, br
10	3290, m, br		1740, s, sh	1710, s, sh	1640, s, sh			1610, m, sh	1580, s, sh

Table 3 ^{1}H NMR spectral data for the *C*-acylation compounds **3–10**

Compound	Y	Z	$NCOCH_3$	CH	C_6H_4	NH and/or OH
3[a]		3.93 (3 H, s)	2.18 (3 H, s)		7.02–7.67 (4 H, m, 3–H, 4–H, 5–H and OH) 8.04 (1 H, d, $J_{5,6}$ 7.8, 6–H)	8.27 (1 H, br)
4[a]		1.43 (3 H, t, *J* 7) 4.43 (2 H, q, *J* 7)	2.17 (3 H, s)		7.01–7.77 (4 H, m, 3–H, 4–H, 5–H and OH) 8.06 (1 H, d, $J_{5,6}$ 7.2, 6–H)	8.30 (1 H, br)
5[b]			2.12 (3 H, s)	4.28 (1 H, s)	7–8 (5 H, m)	
6[a]	3.83 (6 H, s)		2.28 (3 H, s)	5.45 (1 H, s)	6.97–7.77 (3 H, m, 3–H, 4–H and 5–H) 8.84 (1 H, d, $J_{5,6}$ 8.5, 6–H)	11.33 (1 H, br, NH)
7[a]	1.28 (6 H, t, *J* 7) 4.30 (4 H, q, *J* 7)		2.27 (3 H, s)	5.37 (1 H, s)	6.97–7.73 (3 H, m, 3–H, 4–H and 5–H) 8.80 (1 H, d, $J_{5,6}$ 8.4, 6–H)	11.23 (1 H, br, NH)
8[a]	1.97 & 2.15 (3 H, s)	3.38 & 3.60 (3 H, s)	2.25 & 2.38 (3 H, s)		6.80–7.67 (3 H, m, 3–H, 4–H and 5–H) 8.62 (1 H, d, $J_{5,6}$ 7.8, 6–H)	11.67 (1 H, br, NH) 13.23 (1 H, s, OH)
9[c]	2.04 & 2.19 (3 H, s)	0.86 & 1.05 (3 H, t, *J* 7) 3.92 & 4.14 (2 H, q, *J* 7)	2.27 & 2.44 (3 H, s)		7.08 (1 H, pseudotriplet, 5–H) 7.56 (1 H, pseudotriplet, 4–H) 7.68 (1 H,, dd, $J_{3,5}$ 1.1, $J_{3,4}$ 7.9, 3–H) 8.73 (1 H, d, $J_{5,6}$ 8.4, 6–H)	11.32 (1 H, s, NH) 13.17 & 16.80 (1 H, s, OH)
10[c]	3.42 (3 H, s)	1.30 (3 H, t, *J* 7) 4.32 (2 H, q, *J* 7)	2.28 (3 H, s)	5.90 (1 H, s)	7.20 (1 H, ddd, $J_{3,5}$ 1, $J_{4,5}$ 7.2, $J_{5,6}$ 8.5, 5–H) 7.67 (1 H, ddd, $J_{4,6}$ 1.3, $J_{4,5}$ 7.2, $J_{3,4}$ 8.5, 4–H) 7.94 (1 H, dd, $J_{3,5}$ 1, $J_{3,4}$ 8.5, 3–H) 8.80 (1 H, d, $J_{5,6}$ 8.5, 6–H)	11.12 (1 H, s, NH)

[a] 60 MHz, $CDCl_3$. [b] 60 MHz, $CDCl_3$–[$^2H_6$]DMSO. [c] 300 MHz, $CDCl_3$.

of signals, in $CDCl_3$ solution, the methyl triplet ($CO_2CH_2CH_3$) at δ 0.86 and 1.05, and the methyl singlet (C–$COCH_3$) at δ 2.04 and 2.19, which correspond to a 6.75 : 1 mixture.

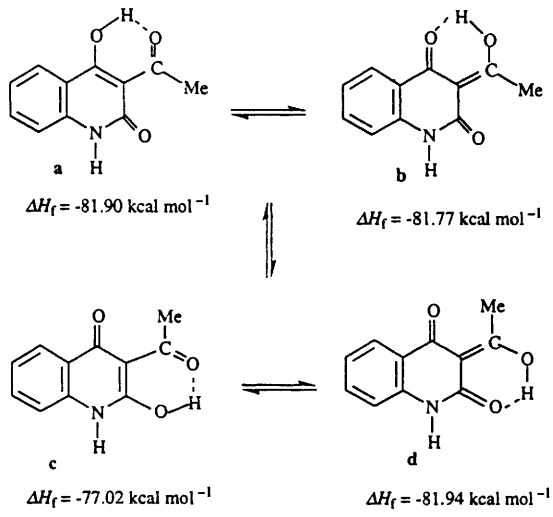
The structural identity of 3-substituted 4-hydroxyquinolin-2(1*H*)-ones, **11–15**, was supported by ^{1}H and ^{13}C NMR spectral results. The chemical shifts are given in the Experimental section. It is possible to assign all protons by comparison with the model system referred to in the literature.[16,17] These compounds were found to exist in the enolized form of the 4-hydroxy-2-quinolone structure, no signal attributable to an sp^3-CH group (methinyl proton) for the quinoline-2,4-dione system being detectable.

One set of signals can be observed in the ^{1}H and ^{13}C NMR spectra of compound **14** (in [$^2H_6$]$DMSO_6$ solution), indicating that the tautomeric equilibrium shown in Scheme 3 is fast on the NMR time scale. Semiempirical quantum mechanics calculations have been used to predict the thermodynamically favourable tautomeric form (Scheme 3). Using the AM1 method[18] the heat of formation values ΔH_f indicated that tautomer **d** was the most stable one.

In conclusion, an efficient route to the preparation of 3-substituted 4-hydroxyquinolin-2(1*H*)-ones, using the 2-methyl-3,1-benzoxazin-4-one as starting material, has been developed. Further investigations are presently being conducted towards the design of biologically active compounds containing the quinolinone moiety and the application of the proposed method to the synthesis of naturally occurring quinolinone derivatives, using functionalized 2-substituted benzoxazinones and the appropriate active methylene compound.

Experimental

Melting points were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. The IR spectra were recorded on Perkin-Elmer 267 spectrometer. The NMR spectra were recorded on either Varian EM-360 60 MHz, Brucker AC-300 300 MHz or Varian Unity Plus 300 MHz spectrometers, using Me_4Si as internal reference. Chemical shifts are quoted in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad); *J* values are given in Hz. Elemental analyses were obtained from the microanalytical laboratory of CNRS (France).



Scheme 3

Preparation of 2-methyl-3,1-benzoxazin-4-one 1

N-acetylanthranilic acid (3.75 g, 0.02 mol) was added to acetic anhydride (20 ml) and the mixture was stirred at 130 °C for *ca.* 1 h, until all the solid had dissolved. The solution, after being cooled to < 80 °C, was evaporated *in vacuo*. Light petroleum (LP) was added to the solid residue to give compound **1** as a yellowish solid (5.8 g, 90%), mp 74–78 °C (lit.,[14b] mp 77–78 °C). The product thus obtained was used for the *C*-acylation reactions without further purification.

General procedure of the *C*-acylation of active methylene compounds with 2-methyl-3,1-benzoxazin-4-one 1

Potassium *tert*-butoxide (6 mmol) was stirred in *tert*-butyl alcohol (30 ml) at room temperature until it dissolved (*ca.* 15 min), after which the active methylene compound **2** (9 mmol if Y = CN and 6 mmol if Y = CO_2R, COMe or SO_2Me) was added dropwise to the mixture. Stirring was continued for 1 h after which compound **1** (3 mmol) was added to the mixture and stirring continued at room temperature for 1.5–2 h. Water and diethyl ether were added to the reaction mixture after which the aqueous layer was separated and acidified with 10% hydrochloric acid, in an ice–water bath. The *C*-acylation compounds **3–10** were isolated as crystalline products, formed directly in the acidified solution, whereas the *C*-acylation compound **5** separated as an oil which was extracted with dichloromethane.

General procedures for the cyclizations of the *C*-acylation compounds 3–10

Method A. The *C*-acylation compound (0.8 mmol) dissolved in a small quantity of ethanol was added to a solution of sodium ethoxide in ethanol [prepared from sodium (0.04 g, 1.7 mmol) in absolute ethanol (4 ml)] containing anhydrous benzene (4 ml). The reaction mixture was refluxed for 5 h, set aside overnight at room temperature and then evaporated *in vacuo*. The solid residue was dissolved in a small quantity of water and the aqueous solution was acidified with 10% hydrochloric acid in an ice–water bath to precipitate the cyclization product as a white solid which was filtered off and washed with cold water.

Method B. The *C*-acylation compound (2 mmol) dissolved in a small quantity of alcohol, was added to a solution of 8% hydrogen chloride in alcohol [prepared from the addition of acetyl chloride (10 ml) in anhydrous alcohol (50 ml)]. The reaction mixture was refluxed overnight, after which it was cooled and evaporated *in vacuo* to give a white precipitate. This was treated with acetone to afford the cyclization product as a white solid after filtration and washing with small amounts of acetone.

Method C. The *C*-acylation compound (1.85 mmol) was dissolved in 7% aqueous sodium carbonate (20 ml) to which 45% aqueous sodium hydroxide (5 ml) was added. The mixture was stirred for 2 h at room temperature after which one of the following work-up procedures was followed, depending on whether a precipitate was formed or the reaction mixture was a thick slurry.

(i) The white precipitate was filtered off and dissolved in a small quantity of water; the aqueous solution was then acidified with 10% hydrochloric acid, in an ice–water bath to give a white solid which was filtered off and washed with small amounts of cold water.

(ii) The reaction mixture was acidified with 10% hydrochloric acid to give a white precipitate which was filtered off and washed with small amounts of cold water.

3-Cyano-4-hydroxyquinolin-2(1*H*)-one 11: from compounds 3 or 4

(a) Following method A. The reaction mixture [the *C*-acylation compound (0.8 mmol) **3** (0.21 g) or **4** (0.22 g) dissolved in the sodium ethoxide in ethanol solution] was refluxed for 5 h and then stored overnight at room temperature. The cyclization product **11** was obtained as a white solid [0.08 g (54%) from **3** and 0.14 g (91%) from **4**], mp 293–296 °C (from MeOH) (lit.,[17] mp 288–290 °C).

(b) Following method B. The reaction mixture [2 mmol of the *C*-acylation compound **3** (0.52 g) or **4** (0.55 g) dissolved in a solution of hydrogen chloride in methanol (for **3**) and hydrogen chloride in ethanol (for **4**)] was refluxed overnight to give the cyclization product **11**, as a white solid [0.13 g, (35%) from **3** and 0.17 g (47%) from **4**], mp 293–296 °C; ν_{max}(Nujol)/cm^{-1} 3420w (NH), 2220s, sh (CN), 1640s, sh (CO, amide 1) and 1600s, sh (C=C ring stretching); δ_H(300 MHz; [$^2H_6$]-DMSO; Me_4Si) 7.28 (1 H, pseudotriplet, 6-H), 7.35 (1 H, d, *J* 8.3, 8-H), 7.68 (1 H, pseudotriplet, 7-H), 8.06 (1 H, d, *J* 8.0, 5-H) and 11.81 (1 H, s, NH).

3-Methoxycarbonyl-4-hydroxyquinolin-2(1*H*)-one 12: from compound 6

Following method C, the reaction mixture was stirred at room temperature for 2 h. Acidification of the reaction mixture with 10% hydrochloric acid gave a white precipitate which was filtered off and washed with cold water to afford **12** (0.3 g, 73%), mp 226–228 °C (from MeOH) (lit.,[11b] mp 210 °C) (Found: C, 60.08; H, 3.95; N, 6.36. $C_{11}H_9NO_4$ requires C, 60.27; H, 4.14; N, 6.39); ν_{max}(Nujol)/cm^{-1} 3130w (NH), 1660s (CO ester, enol form, and amide 1) and 1610m (C=C ring stretching); δ_H(300 MHz; $CDCl_3$–[$^2H_6$]-DMSO; Me_4Si) 3.97 (3 H, s, CO_2CH_3), 7.17 (1 H, ddd, $J_{6,8}$ 0.9, $J_{6,7}$ 7.3 $J_{5,6}$ 8.1, 6-H), 7.31 (1 H, d, $J_{7,8}$ 8.4, 8-H), 7.57 (1 H, ddd, $J_{5,7}$ 1.2, $J_{6,7}$ 7.3, $J_{7,8}$ 8.4, 7-H), 7.98 (1 H, dd, $J_{5,7}$ 1.2, $J_{5,6}$ 8.1, 5-H), 11.51 (1 H, s, NH) and 13.97 (1 H, s, OH); δ_C(75 MHz; $CDCl_3$–[$^2H_6$]-DMSO; Me_4Si) 172.43 (CO ester), 172.16 (C-4), 159.83 (C-2), 140.25 (C-8a), 133.89 (C-7), 124.39 (C-5), 121.60 (C-6), 115.47 (C-8), 113.45 (C-4a), 97.73 (C-3) and 52.54 (CH_3).

3-Ethoxycarbonyl-4-hydroxyquinolin-2(1*H*)-one 13: from compound 7

Following method C, the reaction mixture was stirred at room temperature for 2 h after which it was acidified with 10% hydrochloric acid to give a white precipitate. This was filtered off and washed with cold water to afford the product **13** (0.11 g, 58%), mp 212–215 °C (from EtOH) (lit.,[8b] mp 203–204 °C) (Found: C, 61.98; H, 4.53; N, 6.18. $C_{12}H_{11}NO_4$ requires C, 61.80; H, 4.75; N, 6.01); ν_{max}(Nujol)/cm^{-1} 3130w (NH), 1670m, br (CO ester, enol form and amide 1) and 1630m, br (C=C ring stretching); δ_H(300 MHz; $CDCl_3$–[$^2H_6$]-DMSO; Me_4Si) 1.39 (3 H, t, *J* 7, $-CH_2CH_3$), 4.42 (2 H, q, *J* 7, $-CH_2CH_3$), 7.09 (1 H, pseudotriplet, 6-H), 7.25 (1 H, d, *J* 8.2, 8-H), 7.46 (1 H, pseudotriplet, 7-H), 7.94 (1 H, d, *J* 7.9, 5-H) and 11.41 (1 H, s, NH); δ_C(75 MHz; $CDCl_3$–[$^2H_6$]-DMSO; Me_4Si) 173.22 (CO ester), 172.43 (C-4), 161.12 (C-2), 140.03 (C-8a), 133.95 (C-7), 124.69 (C-5), 121.96 (C-6), 115.66 (C-8), 113.97 (C-4a), 97.73 (C-3), 62.07 (CH_2CH_3) and 14.15 (CH_2CH_3).

3-Acetyl-4-hydroxyquinolin-2(1*H*)-one 14: from compounds 8 or 9

Following method C, the reaction mixture of the *C*-acylation compound (**8** or **9**) was stirred at room temperature for 2 h after which work-up as described above for method C (i) gave compound **14** as a white solid [0.27 g, (72%) from **8** and 0.28 g (75%) from **9**], mp 261–263 °C (from MeOH) (lit.,[7,19] mp 258–259 °C) (Found: C, 65.05; H, 4.53; N, 6.73. $C_{11}H_9NO_3$ requires C, 65.02; H, 4.46; N, 6.89); ν_{max}(KBr)/cm^{-1} 3300w (NH), 3152m (NH sym.), 2880s (OH), 1665s (amide 1), 1649s, sh (CO enol, hydrogen bonded) and 1600s (C=C ring stretching); δ_H(300 MHz; $CDCl_3$–[$^2H_6$]-DMSO; Me_4Si) 2.71 (3 H, s, $COCH_3$), 7.13 (1 H, pseudotriplet, 6-H), 7.25 (1 H, d, $J_{7,8}$ 8.25, 8-H), 7.53 (1 H, pseudotriplet, 7-H), 7.94 (1 H, dd, $J_{5,7}$ 1.2, $J_{5,6}$ 8.0, 5-H), 11.35 (1 H, br, NH) and 17.03 (1 H, br, OH); δ_C(75 MHz; [$^2H_6$]-DMSO; Me_4Si) 205.66 ($COCH_3$), 174.72 (C-4), 161.07 (C-2), 140.51 (C-8a), 134.83 (C-7), 124.75 (C-5), 122.00 (C-6), 115.51 (C-8), 113.32 (C-4a), 105.68 (C-3) and 30.47 (CH_3).

3-Methylsulfonyl-4-hydroxyquinolin-2(1*H*)-one 15: from compound 10

Following method C, the reaction mixture was stirred at room temperature for 1 day, after which work-up as described for method C (ii) gave the compound **15** as a yellowish solid (0.35 g, 80%), mp 290–292 °C (from MeOH) (lit.,[17] mp 324–326 °C) (Found: C, 49.95; H, 3.61; N, 5.97; S, 13.15. $C_{10}H_9NO_4S$ requires C, 50.21; H, 3.79; N, 5.86; S, 13.38); ν_{max}(Nujol)/cm^{-1} 3230w (NH), 1630s, sh (CO, amide 1), 1590s, sh (C=C ring stretching) and 1300s (SO_2 asym. stretching); δ_H(300 MHz; $CDCl_3$–[$^2H_6$]-DMSO; Me_4Si) 3.45 (3 H, s, SO_2CH_3), 7.19 (1 H, ddd, $J_{6,8}$ 1.2, $J_{6,7}$ 6.9, $J_{5,6}$ 8, 6-H), 7.31 (1 H, d, $J_{7,8}$ 8.4, 8-H), 7.59 (1 H, ddd, $J_{5,7}$ 1.5, $J_{6,7}$ 6.9, $J_{7,8}$ 8.4, 7-H), 7.92 (1 H, dd, $J_{5,7}$ 1.5, $J_{5,6}$ 8, 5-H) and 11.89 (1 H, s, NH); δ_C(75 MHz; $CDCl_3$–[$^2H_6$]-DMSO; Me_4Si) 165.47 (C-4), 158.89 (C-2), 140.01 (C-8a), 134.10 (C-7), 124.37 (C-5), 122.19 (C-6), 115.86 (C-8), 113.31 (C-4a), 106.35 (C-3) and 43.25 (CH_3).

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