Novel production of quinol-2(1*H*)-one derivatives from quinol-4(1*H*)-one derivatives

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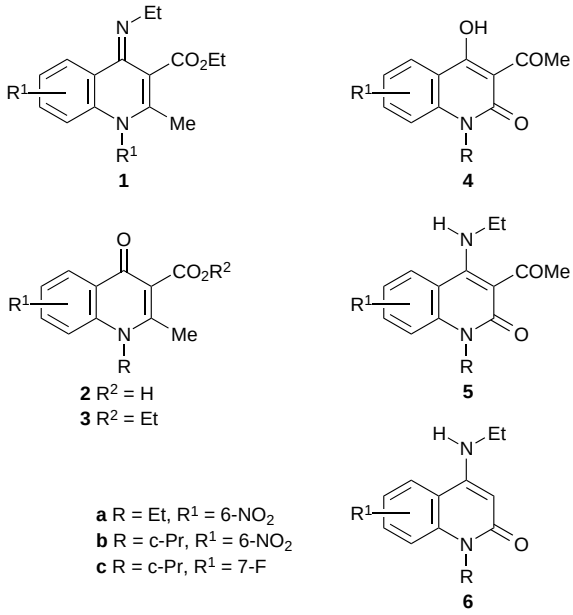
Certain 1-alkyl-4-ethylimino-1,4-dihydro-2-methylquinoline-3-carboxylates transform in alkaline solution to give a variety of 1-alkylquinol-2(1*H*)-one derivatives by competitive C-2 attack by hydroxide followed by rearrangement.

The venerable and extensive field of quinoline chemistry contains numerous and diverse molecular transformations.[1] Here we report the first examples, as far as we are aware, of a quinol-4(1*H*)-one derivative transforming to a quinol-2(1*H*)-one derivative. Alkaline hydrolysis of the recently available ethyl 1-ethyl- or 1-cyclopropyl-4-ethylimino-1,4-dihydro-2-methylquinoline-3-carboxylate **1** in most cases afforded the expected corresponding 4-oxoquinoline-3-carboxylic acid **2** *via* the intermediate ester **3**. However, the saponification of 1-ethyl-6-nitro substituted imine **1a**†‡ was accompanied by a rearrangement which yielded unexpected quinol-2(1*H*)-ones as major products. Thus with very dilute alkali the alkali-soluble 3-acetyl-1-ethyl-4-hydroxy-6-nitroquinol-2(1*H*)-one **4a**‡ (isomeric with the anticipated acid **2a**) and alkali-insoluble 3-acetyl-1-ethyl-4-ethylamino-6-nitroquinol-2(1*H*)-one **5a**‡ were obtained, while with a greater amount of NaOH **4a** and alkali-insoluble 1-ethyl-4-ethylamino-6-nitroquinol-2(1*H*)-one **6a**‡ were obtained (Table 1). The 1-cyclopropyl-6-nitro imine **1b** similarly gave the corresponding compounds **4b**, **5b** and **6b**, respectively. The relative proportions of the aforementioned products varied with the NaOH concentration and the reaction conditions (Table 1). An indication that the rearrangement is not restricted to imine **1** bearing a 6-NO_2 group was shown with the 1-cyclopropyl-7-fluoro substituted **1c** which in aqueous $(Me)_4NOH$–dioxane mixture (to minimise nucleophilic displacement of the fluorine) formed 3-acetyl-1-cyclopropyl-7-fluoro-4-hydroxyquinol-2(1*H*)-one **4c** and the expected quinoline-3-carboxylic acid **2c**.

Of mechanistic significance were the findings that on alkaline hydrolysis (i) even ethyl 1-ethyl-1,4-dihydro-2-methyl-6-nitro-4-oxoquinoline-3-carboxylate **3a** furnished 3-acetyl-4-hydroxyquinol-2(1*H*)-one **4a** (together with the expected 4-oxoquinoline-3-carboxylic acid **2a**) and (ii) 4-ethylaminoquinol-2(1*H*)-one **5a** converted to **4a**, the latter of which was not obtained from acid **2a**.

A tentative rationale based on the available evidence which accounts for the conversion **1** → **4**, **5** and **6** is outlined in Scheme 1 (with imine **1a**): Competitive attachment of OH^- at C-2 of **1a** and at C-2 of 4-oxo ester **3a** (generated from **1a** by conventional hydrolysis of the imine function) gives rise to alcohol intermediates **A** and **B**, respectively. Ring-opening of **B** to a species such as **C** (depicted as a resonance contribution) followed on by an intramolecular *N*-acylation of the ester function in **C** results in **4a**. Similar events stemming from intermediate **A** result in enamine **5a**. The latter substance may subsequently undergo competitive hydrolysis of the 3-acetyl group to yield **6a**, and of the 4-ethylamino function to give **4a**.

It would appear from these preliminary results and the mechanistic analysis that electron-withdrawing group substituted substrates would be especially prone to this rearrange-

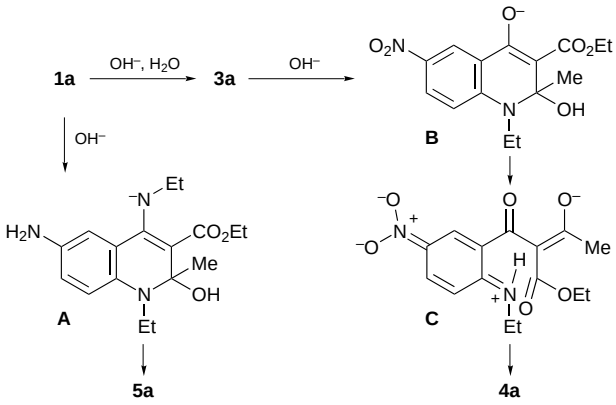


a R = Et, R^1 = 6-NO_2
b R = c-Pr, R^1 = 6-NO_2
c R = c-Pr, R^1 = 7-F

Table 1 Production of quinol-2(1*H*)-one derivatives from quinol-4(1*H*)-one derivatives

Substrate	R	R^1	Amount/ mmol‡	Method§	Product(s)[a] (% yield)[b]
1a	Et	6-NO_2	1	A	**4a**(10), **5a**(63)
			1	B	**4a**(66), **5a**(15)
			10	C	**4a**(54), **6a**(35)
1b	cyclo-C_3H_5	6-NO_2	1	A	**5b** (*ca.* 10)[c]
			10	C	**4b**(61), **6b**(35)
1c	cyclo-C_3H_5	7-F	7.2	D	**4c**(> 6%), **2c**(38%)
3a	Et	6-NO_2	0.28	E	**4a** (*ca.* 18%), **2a** (*ca.* 54%)

[a] The products after purification [silica gel, benzene–acetone (4 : 1), followed by crystallisation] were fully characterised from their ^{1}H NMR ($CDCl_3$) spectra (supplemented on occasion by NOE experiments) and accurate mass measurements (HRMS). [b] Crude. [c] Separated from alkali-insoluble co-product **6b** (silica gel, benzene–acetone, 4 : 1).



Scheme 1

ment, and that the reaction could be extrapolated to include the 2-demethylated analogues of **1** and **3**. Work is currently underway to optimise yields, identify other R^1 substituents in **1** and **3** which favour the rearrangement and to evaluate the synthetic utility of the finding.

In summary, we describe a novel 4-ethyliminoquinoline ⟶ quinol-2(1*H*)-one conversion reaction which leads to products of potential pharmacological interest,[2] and draw attention to the possibility, hitherto unforeseen, of rearrangements having occurred in certain cases during the numerous literature saponifications of 4-oxoquinoline-3-carboxylic esters.

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Footnotes

† *Preparation of imine ester* **1a**. 2-chloro-*N*-ethyl-5-nitrobenzenecarboximidoyl chloride (10 mmol; from the corresponding amide and $SOCl_2$) and ethyl 3-ethylaminobut-2-enoate (11 mmol) were reacted in dry $CHCl_3$ (40 ml) at 0–5 °C for 4–5 d. The solvent was evaporated and the residual mixture of *C*-imidoylated crotonate and cyclised product **1a** was warmed to effect complete conversion to the title compound. Treatment with 2.0 mol dm^{-3} NaOH liberated the acid-soluble substrate **1a** (crude yield, *ca.* 50%).

‡ *Selected spectroscopic data* for **1a**: yellow crystals, mp 111 °C (from EtOAc–hexane); ^{1}H NMR ($CDCl_3$) 1.28–1.45 (m, 9 H), 2.44 (s, 3 H), 3.28 (q, *J* 7 Hz, 2 H), 4.06 (q, *J* 7 Hz, 2 H), 4.28 (q, *J* 7 Hz, 2 H), 7.23 (d, *J* 9.2 Hz, 1 H), 8.21 (dd, *J* 2.7, 9.2 Hz, 1 H), 9.10 (d, *J* 2.7 Hz, 1 H). For **4a**: yellow crystals, mp 172–173 °C (from MeOH); ^{1}H NMR ($CDCl_3$) 1.37 (t, *J* 7.2 Hz, 3 H), 2.85 (s, 3 H), 4.34 (q, *J* 7.2 Hz, 2 H), 7.42 (d, *J* 9.4 Hz, 1 H), 8.50 (dd, *J* 2.7, 9.5 Hz, 1 H), 9.10 (d, *J* 2.7 Hz, 1 H), 17.03 (s, 1 H, removed by D_2O). For **5a**: yellow crystals, mp 160 °C (from MeOH); ^{1}H NMR ($CDCl_3$) 1.35 (t, *J* 7.1 Hz, 3 H), 1.48 (t, *J* 7.1 Hz, 3 H), 2.73 (s, 3 H), 3.82–3.95 (8 line m, converted to quartet by D_2O, 2 H), 4.29 (q, *J* 7.1 Hz, 2 H), 7.37 (d, *J* 9.4 Hz, 1 H), 8.40 (dd, *J* 2.5, 9.4 Hz, 1 H), 9.0 (d, *J* 2.5 Hz, 1 H), 12.0 (br s, 1 H, removed by D_2O). For **6a**: yellow crystals, mp 266–268 °C (from MeOH); ^{1}H NMR ($CDCl_3$) 1.34 (t, *J* 7.2 Hz, 3 H), 1.42 (t, *J* 7.2 Hz, 3 H), 3.25–3.38 (m, converted to quartet by D_2O, 2 H), 4.34 (q, *J* 7.1 Hz, 2 H), 4.92 (br s, 1 H, removed by D_2O), 5.79 (s, 1 H), 7.42 (d, *J* 9.4 Hz, 1 H), 8.38 (dd, *J* 2.4, 9.4 Hz, 1 H), 8.53 (d, *J* 2.4 Hz, 1 H).

§ *Method A*: EtOH (15 ml) containing aqueous 0.50 mol dm^{-3} NaOH (0.50 ml), 55–60 °C, 22 h, evaporate, additional 0.50 mol dm^{-3} NaOH, extract with $CHCl_3$, evaporate $CHCl_3$ phase ⟶ **5**, **6** [separate, silica gel (benzene–acetone, 4 : 1)], acidify (50% HOAc) aqueous phase ⟶ **4**, **2** (separate, *vide supra*), *Method B*: EtOH (15 ml) containing aqueous 0.50 mol dm^{-3} NaOH (2.0 ml), then as in A. *Method C*: MeOH (50 ml) + aqueous 2.0 mol dm^{-3} NaOH (20 ml), reflux, 1.5 h, then as in A (exclude alkali addition). *Method D*: $(Me)_4NOH$ (aqueous 25% solution, 10 ml)—dioxan (20 ml)—H_2O (30 ml), reflux 3 h, evaporate dioxane and approx ½ volume H_2O, extract with $CHCl_3$ ⟶ 0.56 g (alkali-insoluble) complex mixture, acidify (50% HOAc) aqueous phase ⟶ 0.83 g (alkali-soluble) **4c** + **2c**, extract with boiling MeOH ⟶ 120 mg (MeOH-soluble) **4c** + 710 mg (MeOH-sparingly soluble) **2c**. *Method E*: MeOH (15 ml) + aqueous 2.0 mol dm^{-3} NaOH (10 ml), reflux, 1.5 h, evaporate, acidify (50% HOAc), extract with $CHCl_3$ ⟶ **2a** + **4a** (total 56 mg) [molar ratio **2a** : **4a** ≈ 3 : 1, by ^{1}H NMR ($CDCl_3$)].

References

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