

Activation of the 4-oxo function in 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids with thionyl chloride

Theodorus van Es^{*a} and Benjamin Staskun^{*b}

^a Department of Biochemistry and Microbiology, Cook College, Rutgers, The State University of New Jersey, 08903-0231, USA

^b Department of Chemistry, University of the Witwatersrand, Johannesburg, South Africa

Received (in Corvallis, OR) 1st August 1998, Accepted 19th August 1998

Treatment of the title acid successively with SOCl₂ and an aqueous amine mixture or with SOCl₂ and dry amine yielded, *in lieu* of the expected 4-oxo amide, the hitherto unreported 4-imino acid and 4-imino amide *via* a suspected acid chloride-hydrogen chloride complex intermediary.

In the course of on-going quinol-4(1*H*)-one studies¹⁻³ we required certain 1-alkyl-4-oxoquinoline-3-carboxamides **5** (Scheme 1) for comparison with newly synthesised isomeric

alkyl-4-oxoquinoline-3-carboxylic acid **1** is treated successively with SOCl₂ and either an amine or an alcohol. We also demonstrate that the supposed acid chloride **2** is a more complex entity than hitherto envisaged.

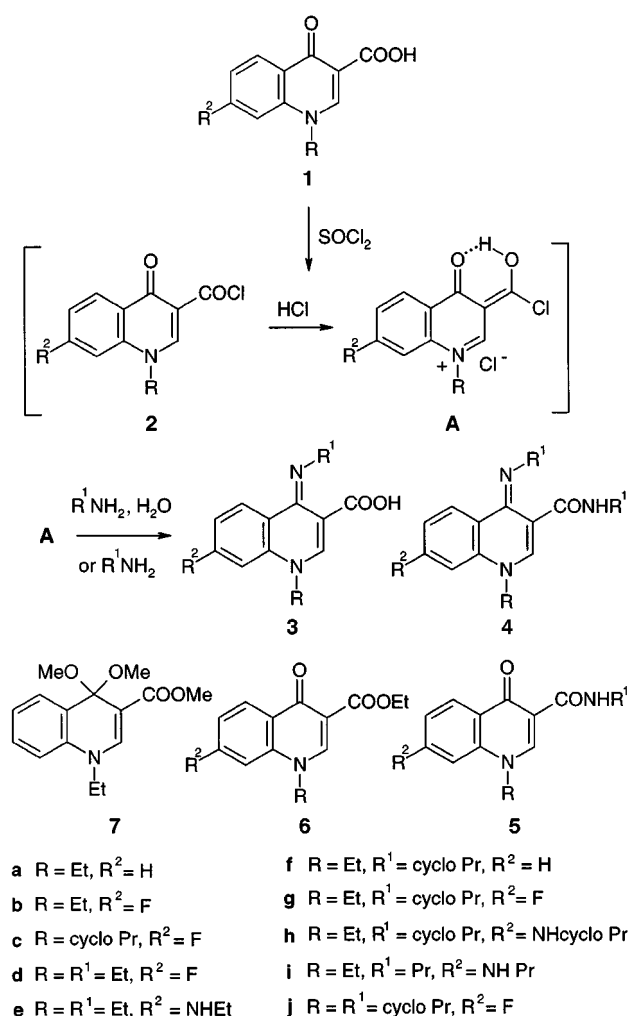
Thus, after refluxing 1-alkyl-4-oxo acid **1** with SOCl₂ for 1 h and removal of solvent, the residue when stirred with an aqueous amine mixture overnight at room temperature yielded mainly 1-alkyl-4-iminoquinoline-3-carboxylic acid **3**; with use of dry (neat) amine the predominant product was the corresponding equally unknown 1-alkyl-4-iminoquinoline-3-carboxamide **4** (Table 1). Structural confirmation of the products was supported by alkaline hydrolysis: imino acid **3** regenerated the appropriate 4-oxo acid **1** while imino amide **4** yielded the desired (*vide supra*) 4-oxo amide **5**.⁶

The relative molar proportions and yields of products **3** and **4** (Table 1) depended on the nature of the 1-alkyl substituent in the 4-oxo acid **1**,⁷ on the nature and type of amine utilised, and on the reaction conditions employed. As shown with the 7-fluoro-4-oxo acid **1b** concomitant nucleophilic substitution of the fluorine occurred in several instances, particularly with use of dry amine, to afford hitherto unreported 7-alkylamino-4-iminoquinoline-3-carboxamides **4** (R² = alkylamino). This observation is notable in view of the relatively more vigorous reaction conditions⁸ normally employed to effect analogous halogen displacements in 1-alkyl-7-halogeno-4-oxo acid **1** derivatives.

In comparison with the above, the representative substrates 1-ethyl-7-fluoro-4-oxo acid **1b**, 4-cyclopropylimino-1-ethyl-7-fluoro acid **3g** and 1-ethyl-7-fluoro-4-oxo amide **5g** when separately stirred with dry cyclopropylamine overnight at room temperature afforded neither 4-imino acid **3** nor 4-imino amide **5** products and each was recovered unchanged.

Exploratory studies with the freshly prepared (somewhat unstable, with slow generation of hydrogen chloride) crystalline product **A** derived from 1-ethyl-4-oxo acid **1a** and SOCl₂ showed the following: (i) elemental (C, H, N, Cl) analysis accorded with a formula C₁₂H₁₁Cl₂NO₂, and with it being a 4-oxo acid chloride **2a**-hydrogen chloride complex;⁹ (ii) product **A** dissolved readily in cold H₂O. Immediate addition of aqueous AgNO₃ gave AgCl (1 equivalent, as determined gravimetrically); the filtrate on standing gradually deposited 4-oxo acid **1a**, or otherwise, following immediate addition of cyclopropylamine, furnished (82%) of 4-imino acid **3f** as was established from comparison with authentic⁶ material; (iii) refluxing product **A** with aqueous NaOH led, after acidification (with 50% HOAc) to the 4-oxo acid **1a** and a filtrate containing two equivalents (as determined volumetrically) of chloride ion, in keeping with the above molecular composition; (iv) utilisation of product **A** for reaction with an aqueous amine mixture or dry amine [as per the usual reaction conditions (*vide supra*)] gave outcomes comparable with those reported in Table 1; (v) product **A** in methanol containing Et₃N likewise underwent substitution at the 4-oxo position, and was converted at room temperature, to the acid-sensitive 4,4-dimethoxy ketal derivative **7**.¹⁰

At this stage the disposition of the hydrogen chloride in complex **A** is uncertain, and a number of possible structures



Scheme 1

1-alkyl-4-iminoquinoline-3-carboxylic acids **3**. Accordingly, recourse was made to a literature method whereby a 1-alkyl-4-oxo acid **1** is treated successively with SOCl₂ and an amine.⁴ The corresponding 1-alkyl-4-oxo acid chloride **2** is the recognised intermediary in this reaction, as it is in the analogous production of 1-alkyl-4-oxo esters **6**.⁵ Here, we report unexpected and, as far as we are aware, unprecedented, outcomes when a 1-

Table 1 4-Imino acids **3** and 4-imino amides **4** from 4-oxo acids **1**/SOCl₂

4-Oxo acid 1	Amine R ¹ NH ₂ R ¹	Reagents	Products ^{a,b} (yield %) ^c	
		Neat R ¹ NH ₂ or R ¹ NH ₂ with H ₂ O (aq.)	Imino acid 3 [mp/°C]	Imino amide 4 [mp/°C]
1b	Et	Aq.	3d (82) [198–200]	±10 ^d
1b	Et	Neat (in dioxane)	3e (78) [208–210]	±20 ^e
1b	cycloPr	Aq.	3g (56) [219–221]	4g (38) [150–151]
1b	cycloPr	Neat	— ^f	4h (>90) [255–256]
1b	Pr	Neat	— ^f	4i (>90) [187–188]
1c	cycloPr	Aq.	3j (82) [235–236]	4j (16) [151–152]
1c	cycloPr	Neat	— ^f	4j (>90)

^a Crystallisations of **3** were usually from EtOH–Et₂O; of **4** usually from EtOAc. ^b All products after purification were characterised from their ¹H NMR spectra supplemented on occasion by an accurate mass (HRMS) determination, an IR spectrum, and/or hydrolysis of **3** to the appropriate 4-oxo acid **1**, and of **4** to the corresponding 4-oxoquinoline-3-carboxamide **5** derivative. ^c Yields refer to vacuum-dried crude material. ^d Suspected oxo amide **5** product. ^e Unresolved complex product mixture. ^f Imino acid **3** was not isolated.

merit consideration including the one shown in Scheme 1. Most of the aforementioned observations are explicable in terms of this structure. The latter possesses an ionic and a covalently bound halogen, as well as a ketonic 4-oxo function potentially susceptible to nucleophilic attack as opposed to the relatively more inert conjugated ketone group as present in either **1** and **2**. The enhanced susceptibility to nucleophilic substitution at the 7-position in substrates **1b** and **1c** may be rationalised by invoking appropriate resonance contributions from structure **A**. Current efforts are being directed towards *inter alia* establishing the structure of **A** ideally from an X-ray study, investigating and extending the complex's synthetic potential, and clarifying the reaction pathways leading from **1** to **3** and **4**.

In summary we show that a hitherto standard literature acylation procedure provides access to novel quinol-4(1*H*)-one derivatives of potential pharmacological interest.

Experimental

General procedure for the synthesis of 4-imino acids **3** and 4-imino amides **4** from 4-oxo acids **1**

This is illustrated with 1-cyclopropyl-7-fluoro-4-oxo acid **1c**: A mixture of **1c** (500 mg) and redistilled SOCl₂ (10 ml) was refluxed for 1 h, then evaporated to dryness. Anhydrous benzene was used to 'chase off' any adhering SOCl₂ and the residue of supposed acid chloride was dried *in vacuo* over KOH pellets. An ice-cold mixture of H₂O (5 ml) containing sodium acetate (1 g) and cyclopropylamine (2 ml) was added and the reaction was stirred overnight at room temperature. The sparingly soluble *N*,1-dicyclopropyl-4-cyclopropylimino-7-fluoro-1,4-dihydroquinoline-3-carboxamide **4j** was collected by filtration (106 mg, 16%); crystals, mp 151–152 °C (from EtOAc); δ_H(CDCl₃) 0.46–1.25 (12H, m), 2.8–3.0 (1H, m), 3.05–3.2 (2H, m), 6.85–6.97 (1H, m), 7.38 (1H, dd, *J* 2.5 and 10.8), † 8.29 (1H, s), 8.4–8.5 (1H, m), 11.1 (1H, br, s, removed by D₂O).

The aqueous filtrate was repeatedly extracted with CHCl₃ and the combined extract was evaporated to yield EtOAc-insoluble material which was mainly 1-cyclopropyl-4-cyclopropylimino-7-fluoro-1,4-dihydroquinoline-3-carboxylic acid **3j** (475 mg, 82%; crystals) mp 235–236 °C (from EtOH–Et₂O); δ_H(CDCl₃) 0.97–1.48 (8H, m), 3.15–3.25 (1H, m), 3.47–3.58 (1H, m), 7.27–7.38 (1H, m), 7.84 (1H, dd, *J* 2.5 and 10.2), 9.11 (1H, s), 9.2–9.3 (1H, m), 14.6 (1H, br, s, removed by D₂O).

In the reactions involving dry (neat) amine, the aforementioned mixture of H₂O, amine and CH₃CO₂Na, was replaced by the chilled amine (4 cm³, large excess).

Preparation of product **A** (R = Et, R² = H)

A mixture of 4-oxo acid **1a** (500 mg) and (redistilled) SOCl₂ (5 ml) was refluxed for 1 h. To the hot solution was added dry benzene to initiate precipitation of **A**. After cooling to room temperature, the colourless crystals were collected by filtration, washed with benzene and dried *in vacuo* over KOH pellets for 3 h (Found: C, 51.02; H, 3.95; N, 4.97; Cl, 29.17. C₁₂H₁₁Cl₂NO₂ requires C, 52.94; H, 4.04; N, 5.15; Cl, 26.10%); ν_{max}(KBr)/cm⁻¹

2300 (br), 1820 (br), 1703, 1620. The crystals when placed on a hot plate at 180 °C initially melted with effervescent evolution of hydrogen chloride, then subsequently resolidified to give 4-oxo acid **1a** (IR spectrum). Product **A** dissolved readily in cold water and was insoluble in CHCl₃.

Preparation of methyl 1-ethyl-1,4-dihydro-4,4-dimethoxyquinoline-3-carboxylate **7**

To a solution of product **A** (117 mg) in MeOH (5 ml) was added Et₃N (200 mg). After 24 h at room temperature, aqueous 1.0 mol dm⁻³ NaOH (10 ml) was added and the mixture was extracted with CHCl₃. Evaporation of the washed organic phase gave the crude title compound (81 mg, 68%). Crystals, mp 162–164 °C (from EtOAc); ν_{max}(KBr)/cm⁻¹ 1680, 1620, 1600; δ_H(CDCl₃) 1.38 (3H, t, *J* 7.1), 2.89 (6H, s), 3.83 (3H, s), 3.91 (2H, q, *J* 7.1), 7.03 (1H, d, *J* 8.3), 7.16–7.26 (1H, m), 7.35–7.44 (1H, m), 7.85 (1H, dd, *J* 1.6 and 7.8), 8.03 (1H, s); *m/z* 277 (M⁺, minor peak), 246 (M⁺ – OMe, base peak), and readily distinguished from its hydrolysis product, namely, the methyl 4-oxo ester, by TLC (alumina, benzene–acetone, 3:1).

Acknowledgements

We are grateful to Professor L. Carlton for helpful NMR discussions, and to Mrs S. Heiss for the acquisition of the NMR spectra. B. S. thanks the University of the Witwatersrand for financial support. We thank Mr J. Moffit for technical assistance.

Notes and references

† *J* Values are given in Hz.

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- Unpublished work, which includes details of the preparation, spectral and chemical properties of the quinoline derivatives **3**, **4** and **5**.
- Certain of the 4-oxo acids **1**, such as **1** (R = benzyl, R² = H or F) eliminated the 1-substituent in refluxing SOCl₂.⁶
- For example, see K. Grohe and H. Heitzer, *Liebigs Ann. Chem.*, 1987, **29**. Such aromatic nucleophilic substitution is facilitated in the complex formed between 4-oxo acid **1** and BF₃; U. Jordis, F. Sauter, M. Burkart, H.-G. Henning and A. Gelbin, *J. Prakt. Chem.*, 1991, **333**, 267.
- In contrast, the 2-methyl derivative of 4-oxo acid **1a** with SOCl₂ gave a drastically different outcome, namely the formation of C₁₁H₄Cl₃NOS, the structure of which is under investigation.⁶
- Ketals of type **7** are also formed from a 4-chloro-3-ethoxycarbonyl-1-ethylquinolinium iodide salt on treatment with an alcohol and base (H. Agui and T. Nakagome, *J. Heterocycl. Chem.*, 1976, **13**, 765).