The Synthesis of 4-Ethyl-2-propyl-3-substituted-pyrrolo[3,4-b]quinoline-1,9-dione Derivatives from 3,3-Dichloro-4-ethyl-thieno[3,4-b]quinoline-1,9-dione and Propylamine

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1. Introduction

It was earlier shown¹ that thionyl chloride acts on 1-ethyl-2-methyl-1,4-dihydro-4-oxo-3-quinolincarboxylic acid 1a (Scheme 1)² to form 3,3-dichloro-4-ethyl-thieno[3,4-b]quinoline-1,9-dione 2a at room temperature, which converts to end-product 3,3,9-trichloro-thieno[3,4-b]quinolin-1-one 3 on heating. It was also shown ¹ that the aminolysis of 3 with an aliphatic primary amine RNH₂ furnishes, inter alia, a 4-chloro-N-alkyl-2-(alkylamino)thioxomethyl-3-quinolinecarboxamide 4, such as 4a, a 2-alkyl-3-alkylamino-9-thio-oxopyrrolo[3,4-b] quinoline derivative 5, such as 5a, and a 9-chloro-2-alkyl-3-alkylamino-9-thio-oxopyrroloquinoline 5b. Compound 5a was envisaged² to arise via hydrosulphide ion, generated in situ, substituting the 9-chlorine atom in 5b in a novel (overall) sulphur rearrangement reaction. Amine salts of 5a, viz. 6, exhibited significant antimicrobial properties³. Here we report: (i) assigning the two D₂O-exchangeable signals in representative amide protons, one near δ 8.07 and the other near δ 8.93. These assignments have now been determined in representative amide 4a R=isoPr (as were also those of 1H- and 13C-NMR peaks in the other currently prepared structures) by means of connectivity information from homo- and heteroatom scalar couplings). Thus in 4a, COSY established coupling between the δ 4.25 (methine, H-3¹) and δ 6.11 (H-2¹) protons, and between the δ 4.75 (methine, H-3¹) and δ 8.93 (H-2¹) protons, while HMBC correlated the δ 4.25 proton with the δ 163.5 carbon (C-1¹) and the δ 4.75 proton with the δ 192 thiocarbonyl carbon (C-1¹), thereby establishing the thiocarbonyl amide proton at δ 8.93.

The like conclusion was reached from a NOE⁴ and a ROESY experiment (in CDCl₃, solvent) and the assumption that in structure 4a only the carbothioamide proton (H-2) could align itself sufficiently close to an aromatic proton (H-8) to elicit a positive response. In the event, exemplified in the ROESY experiment, irradiation of the δ 8.93 (H-2) (carbothioamide) proton led to enhancement of the signals at δ 8.07 (H-8), δ 4.75 (H-3) and δ 4.11 (H-4); in confirmation, irradiation of the δ 8.07 (H-8, aromatic proton) enhanced, inter alia, that of the δ 8.93 (H-2) signal. This outcome was not evident in DMSO-d₆ solvent,
possibly owing to the formation of a bulkier collision complex.

The rate of D₂O-exchange of the amido protons in amide 4 was seemingly influenced by steric and/or electronic factors. Thus, in 4b (R=Pr) (in CDCl₃ at room temperature), both amido protons exchanged completely within minutes, whereas in 4c (R=tert-Bu) each one of the corresponding two required a significantly longer time. This inference was supported with a ¹H NMR (DMSO-d₆, room temperature) monitoring experiment with (currently prepared) amide 7 (vide infra) in which the carbothioamide (δ_H 10.8) proton exchanged significantly faster (within 10 min) than did the carboxamido (δ_H 9.52) proton (>60 min).

Turning now to the application of the aminolysis methodology to title substrate 2a: a mixture of substrate 2a and propylamine (in large excess) was stirred at room temperature with a combination of TLC and HPLC monitoring of the progress of the reaction. Carbothioamide 7 was revealed to be an initial product, its yield reaching an (estimated) optimum value (ca. 70%) in 15-20 min, also formed at an early stage (as evidenced from TLC) was an unexpected reduction product, viz. 4-ethyl-2,3-dihydro-2-propyl-3-(N-propylanino)-pyrrolo[3,4-b] quinoline-1,9-dione 8 (vide infra). The amounts of these and of several other pyrroloquinoline reaction products decreased in the course of reaction owing to subsequent transformation by solvent (propylamine) or reagents generated in situ (PrNH₃⁺Cl⁻, H₂S; vide infra). The formation of 1-ethyl-N-propyl-
2-(N-propylaminocarbonyl)-4-oxo-3-quinolinecarboxamide 13 as a major end-product is currently attributed to the presence of water in the propylamine reactant/solvent.

The following compounds produced in the propylaminolysis reaction(s) were separated and purified, and their structures were determined from spectral and elemental analysis:

The structure of carbothioamide 7 was assigned from its NMR spectral properties (including connectivity information) and elemental analysis (C16H17N3O2). Of the two amido D2O-exchangeable signals (DMSO-d6) at δH 9.52 and δH 10.8, respectively, the latter was shown to be due to the carbothioamide proton (H-2a, Scheme 1). Amide 7 (like its analogue 4b),7 when treated with glacial acetic acid, underwent cyclization—cannellation of propylamine, to give 4-ethyl-2-propyl-3-thioxo-pyrroloquinoline-1,9-dione 9. Modified acid hydrolysis (aqueous HCl, ~90°C) of amide 7 initially yielded 9 and finally, 4-ethyl-2-propyl-pyrrolo[3,4-b]quinoline-1,3,9-trione 10. The 1H NMR spectra of 9 and 10 were noteworthy in that each displayed the α-methylene protons of the 4-ethyl group as a broad and deshielded signal stemming from the anisotropic effect of a proximate hetero atom (vide infra).

Also formed along with amide 7 in the reaction was a novel, i.e. reduction product, 4-ethyl-2,3-dihydro-2-propyl-3-(N-propylamino)-pyrrolo[3,4-b]quinoline-1,9-dione (vide infra). The 1H NMR spectrum of 8 featured, inter alia, four pairs of non-equivalent geminal protons (H-1′, H-1″, H-2′, and H-2″; Scheme 1), respectively. The amino proton (δH 3.52, H-1″) signal, which overlapped one of the H-1′ peaks, was removed by D2O.

Acid hydrolysis converted compound 8 to 4-ethyl-2-propyl-pyrroloquinoline-1,3,9-trione 10. The reaction pathways whereby intermediate A is converted to reduction product 8, and whereby acid hydrolysis transforms 8 to triene 10 remain to be clarified.

The 1H NMR spectrum (CDCl3) of another atypical aminolysis product, viz. 2-propyl-3-imino-pyrroloquinoline product 11, C16H17N3O2, closely resembled those of the 3-thioxo-, and 3-oxo-derivatives, 9 and 10, in exhibiting the α-methylene protons of the 4-ethyl moiety as a deshielded/very broad absorption near δH 5 (vide infra). The signal for the imino proton (near δH 8.5), overlapped that of an aromatic proton, but was well separated (δH 10.13) in DMSO-d6 solvent, and readily removed by D2O. HMBC-coupling correlations (in CDCl3) observed from the proton resonance at δH 3.62 (H-11) located carbon resonances at δC 166.5 (C-1) and δC 188.5 (C-3) and oxo-derivative 10 [δH 164 (C-1 or C-3), δC 165 (C-3 or C-1)]. Structure 11 was chemically substantiated by acid hydrolysis to pyrroloquinoline-1,3,9-trione 10. The formation of imine 11 is considered to arise from propylammonium chloride (generated in situ) acting on 3-(N-propylimino)-pyrroloquinoline derivative 12 (vide infra).

3-Alkylimino-substituted pyrroloquinoline derivatives 5 are normally obtained in good yield from the alkylaminolysis of 3,3,9-trichloro-thienoquinoline-1-one.6 However, the analogous sterically hindered and seemingly more reactive 4-ethyl-2-propyl-3-imino-pyrroloquinoline-1,9-dione 12 was prepared from 4-ethyl-9-oxo-3,3-dichloro-thienoquinoline-1,9-dione 2a and propylamine by conducting the propylaminolysis reaction of substrate 2a in the presence of lead diacetate (to remove interfering H2S generated in situ).

### Table 1

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<th>Atom</th>
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2.1 Mechanistic Aspects

A number of tentative proposals are required to rationalize the formation of several of the aminolysis products, especially of the 3-propylimino-8 and 3-imino-11 derivatives, and are based on the following experimental and literature evidence: (i) As
judged from TLC/HPLC estimations\(^8\) thioamide 7 and 3-propylamino-pyrroloquinoline 8 are among the first products formed in the propylaminolysis reaction; also generated at an early stage are H\(_2\)S and PrNH\(_3\)+Cl\(^–\); (ii) 3-propylimino-pyrroloquinoline 12 appears to be an early, if not the first, non S-containing compound produced in the reaction mixture; (iii) as found experimentally, PrNH\(_3\)+Cl\(^–\) reacts with 12 to give 3-imine 11 and diamide 13; (iv) PrSH, [in the form of its oxidation product, viz. dipropyl disulphide, \((\text{PrS})_2\)] was not formed (in detectable amount) in the course of the propylaminolysis reaction.

Taking cognisance of the above and knowledge of the susceptibility of several of the products to react with propylamine, it is likely that the events/sequences leading to the current pyrroloquinoline derivatives are as follows (Scheme 2):

Thioamide 7 (like its analogue \(5b\) from substrate 3), spontaneously cyclizes to provide the sterically\(^9\) destabilized intermediate A (Scheme 2). Competitive eliminations from A then occur to result in a mixture of some or all of the following products: Elimination (i) of H\(_2\)S provides 3-propylimino-pyrroloquinoline (12); (ii) of propanethiol gives 3-imino-pyrroloquinoline 11; and (iii) of sulphur yields reduction product 3-propylamino-pyrroloquinoline (8); the latter compound can be envisaged to arise from H\(_2\)S acting on the \(\pi\)-bond in 12 as in a Willgerodt-Kindler reaction\(^10\), and involves a sulphur elimination as in (iii).

Experiments in support of, or otherwise to invalidate, the aforementioned suggestions were initiated: (a) It was established that propanethiol in propylamine solution in the presence of air rapidly oxidizes to dipropyl disulphide \((\text{PrS})_2\), and that \((\text{PrS})_2\) in propylamine solution could be detected by TLC (silica gel, benzene, iodine vapour) at a concentration of 0.3-0.4 mg/mL. At no time during the monitoring of the propylaminolysis of 2a (involving stirring and atmospheric exposure) was \((\text{PrS})_2\) detected (although its production would have amounted to well within the limits of detection for the amount of 11 formed). From this observation it is concluded that imine 11 does not arise from intermediate A by elimination of propanethiol. (b) Subsequent investigation indicated that another entity present in the reaction mixture, viz. propylammonium chloride, is most likely the agent responsible for 3-imine 11 production (from 3-propylimino-derivative 12). Experiments showed that 3-propylimino-pyrroloquinoline 12 reacted with propylamine (only) to give diamide 13, and with propylamine containing PrNH\(_3\)+Cl\(^–\) to yield both diamide 13 and 3-imine 11.

2.2. Magnetic Anisotropic Effects

There are many examples in the literature\(^2\)\(^\text{11}\) of the deshielding and line-broadening of 'H NMR signals of protons by the presence in their vicinity of a magnetically anisotropic atom, e.g. halogen, or group, e.g. C=O, C=S and C=N-R. We report the phenomena in the currently prepared 3-thioxo-, 3-oxo-, 3-imino- and 3-propylimino-pyrrolo[3,4-b]quinolines \(9, 10, 11\) and \(12\), respectively, and in their appropriate precursor compounds, viz. the 4-ethyl-, 4-propyl-, and 4-methyl-3,3-dichloro-thieno[3,4-b]quinoline-1,9-diones \(2a, 2b\) and \(2c\), and the intramolecularly\(^12\) H-bonded 1,2-dialkyl-4-oxo-3-quinolinicarboxylic acids \(1a, 1b, 1c, 1d\) and \(1e\).

In all of the aforementioned pyrroloquinoline derivatives the \(\alpha\)-methylene protons (H-111) of the 4-ethyl group lie close to and in the deshielding region of a proximate hetero atom thereby resulting in a broad absorption near \(\delta_{\text{H}}\) 5.0. In the thienoquinolines \(2a\) and \(2b\) the corresponding pair (H-1') are likewise effected by the neighbouring chlorine atoms and resonate as a broad peak (ca. 2H) near \(\delta_{\text{H}}\) 5.0 (2a), and near \(\delta_{\text{H}}\) 4.8 (2b), respectively, while those of the 4-methyl protons in \(2c\) appear as a singlet (3H) at \(\delta_{\text{H}}\) 2.0. Geometrical constraints resulting from the

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**Scheme 2**

Outline of propylaminolysis reaction events/sequences. Exact stereochemistry not specified.
H-bonding in acid 1 place the relevant (H-1) methylenes close to, and in the nodal plane, of the carbonyl oxygen of the carboxyl group as is evidenced from the broad and deshielded absorptions (ca. 2H) near δ\textsubscript{H} 3.5 (1c and 1d), and the singlet (3H) at δ\textsubscript{H} 3.19 for the 2-methyl protons of 1b.

The reality of the anisotropic effects described for the aforementioned current compounds receives support from the following comparative δ\textsubscript{H}-values: (i) As opposed to the very broad and deshielded signal near δ\textsubscript{H} 5.2 (ca. 2H) in 3-propylamino pyrroloquinoline 11, the comparable methylene protons (1\textsuperscript{H}) in 3-propylamino pyrroloquinoline 8 absorb as a doublet [δ\textsubscript{H} 4.81 (1H) and δ\textsubscript{H} 4.43 (1H)]. (ii) In the representative quinoline derivatives (a) 1,2-diethyl-, and (b) 1,2-dimethyl-1(1H)-quinolinoines, the δ\textsubscript{H}-values of the non-deshielded comparable protons (in a) are: 4.25 (2H, q, J 7.2 Hz, H-1\textsuperscript{H}) and 2.75 (2H, q, J 7.4 Hz, H-1\textsuperscript{H}), and in (b)\textsuperscript{11} are: 3.63 (3H, s, H-1\textsuperscript{H}) and 2.37 (3H, s, H-1\textsuperscript{H}), respectively. (iii) The H-bonding geometry requisite for the exhibition of sufficiently fast on the 1H NMR time scale to result in a (deshielded) broadening and deshielding phenomena vary with the temperature, concentration, or presence of lead diacetate (vide supra) (or an appropriate combination) had to be manipulated to afford the desired compound in satisfactory yield.

3.2. Starting Materials

Acids 1a, 1b, 1c, 1d and 1e were prepared by hydrolysis of the respective appropriate 1,2-dialkyl-1,4-dihydro-4-alkylimino-3-quinolinecarboxylates.\textsuperscript{12a} The 3,3-dichloro-thieno[3,4-b]-quinolines 2b and 2c were obtained from the appropriate acid 1 and SOCl\textsubscript{2}, at room temperature as described\textsuperscript{12a} for 2a.

Assignment of D,\textsubscript{O}-exchangeable protons in 4-chloro-N-[1-methylthethyl]-2-[1(1-methylethyl)amino]thioxomethyl]-3-quinolinecarboxamide 4a\textsuperscript{12b}

\[ \delta_{\text{H}} (400 MHz, CDCl\textsubscript{3}) \]

1.29 (3H, d, J 6.6 Hz, H-4\textsuperscript{a}), 1.40 (3H, d, J 6.6 Hz, H-4\textsuperscript{a}), 4.25 (1H, m, H-3\textsuperscript{a}), 4.75 (1H, m, H-3\textsuperscript{b}), 6.1 (1H, m, removed by D,O, H-2\textsuperscript{a}), 7.63 (1H, m, H-2\textsuperscript{b}), 7.78 (1H, m, H-2\textsuperscript{b}), 8.07 (1H, d, J 8.4 Hz, H-8), 8.10 (1H, dd, J 1.4 and 8.4 Hz, H-5), 8.9 (1H, broad signal, removed by D,O, H-2\textsuperscript{b}), δ\textsubscript{H} 100 MHz, CDCl\textsubscript{3}), 21.0 (C-4\textsuperscript{a}), 22.2 (C-4\textsuperscript{b}), 42.5 (C-3\textsuperscript{a}), 47.5 (C-3\textsuperscript{b}), 124.5 (C-5), 129.0 (C-6 or C-7), 129.5 (C-8), 132.0 (C-7 or C-6), 163.5 (C-1\textsuperscript{a}), 192.0 (C-1\textsuperscript{b}). HMBC (CDCl\textsubscript{3}), δ\textsubscript{H} 4.25 (H-3\textsuperscript{a}) correlates with δ\textsubscript{C} 163.5 (C-1\textsuperscript{a}); δ\textsubscript{H} 4.75 (H-3\textsuperscript{b}) with δ\textsubscript{C} 192.0 (C-1\textsuperscript{b}). COSY (CDCl\textsubscript{3}) correlates δ\textsubscript{H} 4.25 (H-3\textsuperscript{a}) with δ\textsubscript{H} 6.1 (H-2\textsuperscript{a}); δ\textsubscript{H} 4.75 (H-3\textsuperscript{b}) with δ\textsubscript{H} 8.9 (H-2\textsuperscript{b}). Gradient ROESY (CDCl\textsubscript{3}): Irradiate: δ\textsubscript{H} 8.93 (H-2\textsuperscript{b}): Observe: δ\textsubscript{H} 4.07 (H-8), 4.75 (H-3), 1.41 (H-4). Irradiate: δ\textsubscript{H} 8.07 (H-8): Observe: δ\textsubscript{H} 8.93 (weak, H-2\textsuperscript{b}). In DMSO-\textit{d}_6 (600 MHz) the two D,O-exchangeable proton signals in 4a are shifted downfield: δ\textsubscript{H} 8.40 (H-2\textsuperscript{a}) and δ\textsubscript{H} 10.45 (H-2\textsuperscript{b}), while some other signals are shifted upfield; e.g. δ\textsubscript{H} 4.01 (H-3\textsuperscript{a}) and δ\textsubscript{H} 4.59 (H-3\textsuperscript{b}). Gradient ROESY (DMSO-\textit{d}_6): Irradiate: δ\textsubscript{H} 4.01 (3\textsuperscript{a}); Observe δ\textsubscript{H} 8.40 (H-2\textsuperscript{a}) and δ\textsubscript{H} 1.13 (H-3\textsuperscript{a}). Irradiate δ\textsubscript{H} 4.59 (H-3\textsuperscript{b}): Observe: δ\textsubscript{H} 10.46 (H-2\textsuperscript{b}), δ\textsubscript{H} 4.01 (weak, H-3\textsuperscript{a}) and δ\textsubscript{H} 1.24 (H-4\textsuperscript{b}). Irradiate δ\textsubscript{H} 8.41 (H-2\textsuperscript{b}): Observe: δ\textsubscript{H} 4.01 (H-3\textsuperscript{b}) and δ\textsubscript{H} 1.13 (H-4\textsuperscript{b}).

1-Ethyl-1,4-dihydro-N-propyl-2-[N-propylamino]thioxomethyl]-3-quinolinecarboxamide 7 and 4-Ethyl-2,3-dihydro-2-propyl-3-(N-propylamino) pyrrolo[3,4-b]quinoline-1,9-dione 8

3,3-Dichloro-4-ethyl-thieno[3,4-b]quinoline-1,9-dione 2a (1.97 g; 6.27 mmol) was added portionwise (over ~5 min) with stirring to ice-cold propylamine (~10 mL, large excess). The reaction mixture was kept overnight at room temperature and stirred with H,O and CHCl\textsubscript{3}. The CHCl\textsubscript{3} extract was dried (anhydrous MgSO\textsubscript{4}) and evaporated under reduced pressure and temperature to a syrup which was taken up in a minimum of warm MeOH\textsubscript{ex}. The syrup was filtered to remove EtOAc and the solution was stored overnight in the freezer. Crystals (775 mg), consisting principally

3. Experimental

3.1. General Methods

Melting points were recorded on a hot-stage microscope apparatus and are uncorrected. TLC was performed on aluminium-backed plates, precoated with 0.25 mm silica gel 60. Column chromatography was carried out on silica gel 60. HPLC solvent generally used to elute: hexane: isoproxy alcohol: 450:50. NMR spectra were recorded on a Bruker AC-200 (200.13 MHz for 1H), a Bruker DPX (399.900 MHz for 1H) or a Bruker DRX (600.18 MHz for 1H) spectrometer. CDCl\textsubscript{3}, was used as solvent unless otherwise noted, and TMS as internal standard. COSY-, HSQC- and HMBC-correlated spectra were routinely used for assignments of signals, supplemented on occasion when warranted by ROESY and NOE experiments. HRMS spectra were recorded at 70 eV on a VG 70 SE mass spectrometer. Propylamine refers to n-propylamine unless otherwise indicated. Several of the compounds formed in the propylaminolysis reaction(s) were very similar by TLC while analytical HPLC showed a number of compounds to have similar retention times. Therefore the compounds were difficult to separate cleanly by column (silica gel) chromatography. Even semi-preparative HPLC (on a 1 cm diameter column) was unsuccessful because of overlap of peaks. Moreover, several of the products such as thioamide 7 and pyrroloquinoline-1,3,9-trione 10 reacted further with propylamine (and at different rates). Therefore, in order to isolate a specific product, reaction conditions such as time, temperature, concentration, or presence of lead diacetate (vide infra) (or an appropriate combination) had to be manipulated to afford the desired compound in satisfactory yield.
of a mixture of products 7 and 8, were filtered off and the mother liquor was evaporated to a syrup (1.26 g). The crystals (775 mg) were applied to a column of silica gel using acetone-benzene (3:7) containing ~5% triethylamine. Based on TLC of the fractions and consolidation, there was obtained slightly impure thioamide 7 (520 mg) and compound 8 (250 mg). The 1.26 g syrup (vide supra) was similarly chromatographed to provide crude thioamide 7 (570 mg; total yield: 1546 mg; ~69%) (vide infra) and compound 8 (69 mg; total yield: 374 mg; ~18%) (vide infra).

1-ethyl-1,4-dihydro-N-propyl-2-(N-(propylamino)thioxomethyl)-3-quinolinecarboxamide 7

Crystals (from ethyl acetate), m.p. 164°C. δN (600 MHz, DMSO-d6) 0.89 (3H, t, 7.4 Hz, H-5″), 0.97 (3H, t, 7.4 Hz, H-5″), 1.35 (3H, t, 7.0 Hz, H-2), 1.45 (2H, sextet, J 7.2 Hz, H-4″″), 1.69 (2H, sextet, J 7.3 Hz, H-4″), 3.13 (2H, m, H-3″), 3.52 (1H, m, H-3″(a)), 3.70 (1H, m, H-1″(a)), 4.47 (1H, m, H-1″(b)), 7.50 (1H, m, H-6), 7.85 (1H, m, H-7), 7.90 (1H, d, 8.7 Hz, H-8), 8.33 (1H, dd, J 1.4 and 8.0 Hz, H-5), 9.52 (1H, bt, H-3″″), removed by D2O, 10.8 (1H, bs, H-2″″), removed by D2O.

δC (150 MHz, DMSO-d4) 7.7 (C-1″), 31.2 (C-2″), 41.5 (C-1″″), 117.8 (C-5″), 126.8 (C-7), 132.9 (C-11″), 154.5 (C-9), 188.5 (C-3). ESI m/z 284 ([M+H]+) (Found: C, 67.77; H, 3.85). In DMSO-d6 solvent showed, inter alia, the D2O-exchangeable proton (1H, H-1″″, s) at δ 10.8 signal (H-2″″) as absent within 10 min and the δ 9.5 (H-3″″″) signal still evident (ca. 20%) after 60 min.

4-Ethyl-2,3-dihydro-2-propyl-3-(N-propylamino)-pyrrolo[3,4-b]quinoline-1,9-dione 8

Needles (from ethyl acetate), mp 208–211°C. Lassaigne sodium fusion test negative for Cl and S. The 1H (600 MHz, CDCl3) 0.95 (3H, t, J 8.7 Hz, H-11(a)), 3.70 (1H, m, 3″11(b)), 4.31 (1H, m, H-11(a)), 4.47 (1H, m, H-11(b)), 7.50 (1H, m, H-6), 7.85 (1H, m, H-7), 7.90 (1H, d, 8.7 Hz, H-8), 8.33 (1H, dd, J 1.4 and 8.0 Hz, H-5), 9.52 (1H, bt, H-3″″), removed by D2O, 10.8 (1H, bs, H-2″″), removed by D2O.

δC (150 MHz, DMSO-d4) 0.95 (3H, t, 8.7 Hz, H-11(a)), 3.70 (1H, m, 3″11(b)), 4.31 (1H, m, H-11(a)), 4.47 (1H, m, H-11(b)), 7.50 (1H, m, H-6), 7.85 (1H, m, H-7), 7.90 (1H, d, 8.7 Hz, H-8), 8.33 (1H, dd, J 1.4 and 8.5 Hz, H-8). δH (600 MHz, CDCl3) 0.97 (3H, t, 8.7 Hz, H-11(a)), 3.70 (1H, m, 3″11(b)), 4.31 (1H, m, H-11(a)), 4.47 (1H, m, H-11(b)), 7.50 (1H, m, H-6), 7.85 (1H, m, H-7), 7.90 (1H, d, 8.7 Hz, H-8), 8.33 (1H, dd, J 1.4 and 8.5 Hz, H-8). δH (600 MHz, CDCl3) 0.97 (3H, t, 8.7 Hz, H-11(a)), 3.70 (1H, m, 3″11(b)), 4.31 (1H, m, H-11(a)), 4.47 (1H, m, H-11(b)), 7.50 (1H, m, H-6), 7.85 (1H, m, H-7), 7.90 (1H, d, 8.7 Hz, H-8), 8.33 (1H, dd, J 1.4 and 8.5 Hz, H-8). δH (600 MHz, CDCl3) 0.97 (3H, t, 8.7 Hz, H-11(a)), 3.70 (1H, m, 3″11(b)), 4.31 (1H, m, H-11(a)), 4.47 (1H, m, H-11(b)), 7.50 (1H, m, H-6), 7.85 (1H, m, H-7), 7.90 (1H, d, 8.7 Hz, H-8), 8.33 (1H, dd, J 1.4 and 8.5 Hz, H-8). δH (600 MHz, CDCl3) 0.97 (3H, t, 8.7 Hz, H-11(a)), 3.70 (1H, m, 3″11(b)), 4.31 (1H, m, H-11(a)), 4.47 (1H, m, H-11(b)), 7.50 (1H, m, H-6), 7.85 (1H, m, H-7), 7.90 (1H, d, 8.7 Hz, H-8), 8.33 (1H, dd, J 1.4 and 8.5 Hz, H-8). δH (600 MHz, CDCl3) 0.97 (3H, t, 8.7 Hz, H-11(a)), 3.70 (1H, m, 3″11(b)), 4.31 (1H, m, H-11(a)), 4.47 (1H, m, H-11(b)), 7.50 (1H, m, H-6), 7.85 (1H, m, H-7), 7.90 (1H, d, 8.7 Hz, H-8), 8.33 (1H, dd, J 1.4 and 8.5 Hz, H-8). δH (600 MHz, CDCl3) 0.97 (3H, t, 8.7 Hz, H-11(a)), 3.70 (1H, m, 3″11(b)), 4.31 (1H, m, H-11(a)), 4.47 (1H, m, H-11(b)), 7.50 (1H, m, H-6), 7.85 (1H, m, H-7), 7.90 (1H, d, 8.7 Hz, H-8), 8.33 (1H, dd, J 1.4 and 8.5 Hz, H-8)
Acid hydrolysis of compounds 8, 11 and 12 to give 4-ethyl-2-propyl-
pyrrrole[3,4-b]quinoline-1,3,9-trione 10

(i) A mixture of 3-propylamino-pyrroloquinoline derivative 8 (22 mg), isopropanol alcohol (1.5 mL) and 2 M HCl (1.0 mL) was refluxed for ~10 h. After cooling and extracting with CHCl3, evaporation of solvent gave a residue of crude title product 10, crystals (from EtOH-H2O), mp 216–221°C.

(ii) A mixture of imine 11 (50 mg), MeOH (10 mL) and 2 M HCl (0.5 mL) was kept at 50°C for 3 h; needles of 10 had started to separate after ~0.5 h. Cooling and filtration gave compound 10 (45 mg), mp 219–220°C.

(iii) Imine 12 (25 mg) treated as in (ii) gave 10 (16 mg), mp 221–2°C.

Each product was identified by mixture mp comparison with authentic compound 10 (vide supra).

1-Ethyl-1,4-dihydro-N-propyl 2-(N-propylaminocarbonyl)-
4-oxo-3-quinolinecarboxamide 13

(i) Pyrorroloquinoline-1,3,9-trione 10 (67 mg) was stirred with propylamine (3 mL) at room temperature. TLC monitoring indicated that substrate 10 had all reacted in 2 h. Evaporation of the reaction and crystallization of the residue (from EtOAc/hexane) gave diamide 13. Crystals, mp 164–165°C. δH (600 MHz, CDCl3) 0.96 (3H, t, J 7.4 Hz, H-5u), 1.06 (3H, t, J 7.4 Hz, H-5u), 1.50 (3H, t, J 7.1 Hz, H-2u), 1.60 (2H, sextet, J 7.3 Hz, H-4i), 1.77 (2H, m, H-4i), 3.45 (4H, overlapping m, H-3i and H-3ii), 4.27 (2H, broad m, H-1u), 6.81 (1H, broad signal, removed by D2O, H-11i1). δC (150 MHz, CDCl3) 11.0 (C-3i), 22.3 (C-2i), 49.5 (C-1i), 117.5 (C-5), 126.3 (C-7), 127.0 (C-5), 134.0 (C-7), 139.0 (C-8a), 178.5 (C-4). The anion of 1c was formed by adding a solution of Na2CO3 in D2O to 1c in CDCl3, δH (600 MHz, CDCl3) 1.19 (6H, two overlapping triplets, H-2i and H-2ii), 2.76 (2H, very broad signal, H-11i), 4.48 (2H, q, J 7.2 Hz, H-5i), ~3.6 (ca. 2H, very broad signal), H-11i1, 4.50 (2H, q, J 7.2 Hz, H-5i), 6.71 (1H, m, H-6), 7.71 (1H, d, J 8.8 Hz, H-8), 8.83 (1H, m, H-7), 8.57 (1H, dd, J 1.4 and 8.1 Hz, H-5i), ~16.5 (1H, broad signal, removed by D2O, H-11i1). δC (150 MHz, CDCl3) 13.3 (C-2i), 14.5 (C-2ii), 24.0 (C-1i), 42.5 (C-1ii), 116.2 (C-8a), 125.6 (C-6), 127.4 (C-5), 134.0 (C-7), 139.0 (C-8a), 160.2 (C-2i), 178.5 (C-4). The anion of 1c was formed by adding a solution of Na2CO3 in D2O to 1c in CDCl3, δH (600 MHz, CDCl3) 1.19 (6H, two overlapping triplets, H-2i and H-2ii), 2.76 (2H, q, J 7.5 Hz, H-5i), 4.42 (2H, q, J 7.2 Hz, H-5i), 7.27 (1H, m, H-6), 7.56 (1H, m, H-7), 6.70 (1H, d, J 8.8 Hz, H-8), 8.04 (1H, d, J 8.1 Hz, H-5i).

3.3. Detection of PrSH as [PrS]+ in Propylamine

It was established that PrSH in PrNH₂ solution is rapidly oxidized in air to dipropyl disulphide (Pr₂S₄). Also, that [PrS]+ in PrNH₂ was detectable by TLC (silica gel, benzene, iodine) at concentrations of 0.3-0.4 mg/mL. A mixture of 3,3-dichloro-thieno[3,4-b]quinolin-1-oxo 2a (38 mg) in PrNH₂ (0.5 mL), exposed to the atmosphere, was stirred and examined by TLC at 17, 23, 48 and 72 h; at no time was [PrS]+ detected. This observation indicated that production of PrSH in the reaction is very unlikely as the amount of [PrS]+, corresponding to the amount of imine 11 formed, would have been detected. It was concluded that imine 11 does not arise from intermediate A (Scheme 2) by elimination of PrSH.

The following experiment showed that the PrNH₂⁺Cl− generated in situ is the probable agent responsible (at least to some extent) for the imine 12→imine 11 reaction (cf. Scheme 2).

3.4. Conversion of Imine 12 into Imine 11 with PrNH₂/PrNH₂⁺Cl−

Imine 12 (10 mg) was added to a stirred solution (0.3 mL) of PrNH₂ containing PrNH₂⁺Cl− (~24 mg). HPLC analysis indicated that the reaction mixture after 1.5 h contained (estimated amounts) imine 12 (67%), diamide 13 (14%) and imine 11 (19%); after 5.5 h: imine 12 (7%), diamide 13 (44%) and imine 11 (49%), and after 24 h: imine 12 (not detected), diamide 13 (45%) and imine 11 (39%).
3,3-Dichloro-4-methyl-thieno[3,4-b]quinoline-1,9-dione 2c

From acid 1e and SOCl₂ at room temp. as described for 2a. Crystals (from EtOAc), mp 166–168°C. δₕ (600 MHz, CDCl₃) 4.35 (3H, s, H-11), 7.57 (1H, t, J 7.6 Hz, H-7), 7.76 (1H, d, J 8.6 Hz, H-5), 7.84 (1H, m, H-6), 8.52 (1H, dd, J 1.5 and 8.0 Hz, H-8). δₜ (150 MHz, CDCl₃) 37.0 (C-1 1), 116.3 (C-5), 126.7 (C-7), 127.3 (C-8), 129.0 (C-8a), 134.2 (C-6), 140.8 (C-4a), 161.5 (C-3a), 172.0 (C-9).

1,2-Diethyl-4(1H)-quinolinone 6

Prepared by decarboxylation of acid 1c. Crystals (from EtOAc-hexane), mp 114°C. δₕ (600 MHz, CDCl₃) 1.35 (3H, t, J 7.4 Hz, H-2₁), 1.43 (3H, t, J 7.1 Hz, H-2), 2.75 (2H, q, J 7.4 Hz, H-1₁), 4.25 (2H, q, J 7.2 Hz, H-1), 6.32 (1H, s, H-3), 7.35 (1H, m, H-6), 7.52 (1H, d, J 8.7 Hz, H-8), 7.64 (1H, m, H-7), 8.45 (1H, dd, J 1.4 and 8.0 Hz, H-5). δₜ (150 MHz, CDCl₃) 13.0 (C-2₁), 14.2 (C-2), 26.5 (C-1₁), 41.0 (C-1), 115.2 (C-8), 123.0 (C-6), 126.8 (C-5), 132 (C-7), 155.0 (C-2), 177.0 (C-4).

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References and notes

2 In the heterocyclic structures, the peripheral substituents are arbitrarily numbered (with primes) for convenient reference in the text.
6 T. van Es and B. Staskun, unpublished work.
8 Whereas product 8 could be eluted from a silica gel column with solvent containing EtNH₃ it failed to emerge in HPLC experiments even with polar solvents. Consequently a combination of TLC and HPLC was routinely utilized to monitor and analyse the product mixtures.
9 π-Bond disruption as a manifestation of steric crowding at position α- to a thiocarbonyl group has been noted. K. Bhattacharyy, V. Ramamurthy and P.K. Das, J. Phys. Chem., 1987, 91, 5626–5631. We thank Dr P. Kahn (Department of Biochemistry and Microbiology, Rutgers University) for the molecular modelling of compound 12, which indicated the conformation of lowest energy as that having the α-methylene protons of the 3-propyl group anti with respect to ones of the 4-ethyl group.