Chlorine- and Sulphur-substituted Pyrrolo[3,4-b]quinolines and Related Derivatives arising from the Aminolysis of 3,3,9-Trichlorothieno[3,4-b]quinolin-1(3H)-one

Theodorus van Es* and Benjamin Staskun*†

* Department of Biochemistry and Microbiology, Cook College, Rutgers, The State University of New Jersey, 08903-0231, USA.
† School of Chemistry, University of the Witwatersrand, P.O. Wits, 2050, South Africa.

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ABSTRACT

The outcome from aminolysis of 3,3,9-trichlorothieno[3,4-b]quinolinone with an alkylamine is dependent on the reaction conditions and extraneous reagents employed. A variety of hitherto unreported products can be obtained and include 4-chloro-2-alkylthiocarbamoyl-quinoline-3-carboxylic acid alkylamides, 9-chloro-2-alkyl-3-alkylimino-pyrrolo[3,4-b]quinolines, 9-chloro-2-alkyl-3-thioxo-pyrrolo[3,4-b]quinolines, 2-alkyl-3-alkylimino-9-thioxo-pyrrolo[3,4-b]quinolines, and 2-alkyl-9-alkylamino-3-alkylimino-pyrrolo[3,4-b]quinolines. The spectral (1H NMR, HRMS) and chemical properties and the structures of the products are described and discussed, and possible mechanistic pathways leading to their formation are presented.

KEYWORDS


1. Introduction

Pyrrolo[3,4-b]quinolines have drawn the attention of chemists for some time. This has been from both a purely synthetic point of view as well as, currently, for the commercially important and naturally occurring compounds such as camptothecin and mappicine that contain this ring system. In general, the existing syntheses rely on multistep methodologies. In the context of our own interest in this area we showed recently that the aminolysis (vide infra) of thienoquinoline substrate 1a with an appropriate amine RNH₂ (R = Et, iso-Pr, sec-Bu, and tert-But, respectively), at 0–5°C for 15 min. With continued reaction (room temperature, 24 h), the more labile alkylamides 2 (those from propylamine and ethylamine) underwent changes, including cyclization, resulting in a product mixture of the appropriate 2-alkyl-9-alkylamino-3-alkylimino-pyrroloquinoline 5 and S-containing product 6 (vide infra). A less labile alkylamide, represented by tert-butylamide 2e, remained largely unaffected even after 24 h reaction, an outcome attributed to steric inhibition to cyclization.

The respective thiocarbamoyl amide structures 2a–2f were confirmed from their spectral (H NMR, HRMS) properties and elemental analysis. The 1H NMR spectrum of each showed, inter alia, two D₂O exchangeable (NH) protons, generally near 6.65 and 6.0 respectively; the exchanges were usually complete within hours, but those in tert-butylamide 2e required several days, again implicating steric factors. Also exhibited, when appropriate, were two sets of α-methylene protons, each set being coupled with one or other of the aforementioned NH protons, and displaying the expected multiplicity on exchange with D₂O. These observations ruled out an isomeric cyclic assignment A (Scheme 2) for alkylthiocarbamoyl alkylamide 2; in A the mercapto proton would be expected to resonate well below 64, while only one set of α-methylene protons would exhibit a complex multiplicity due to coupling.

1H NMR (CDCl₃) monitoring of the spontaneous cyclization in solution at room temperature of 2-propylthiocarbamoyl propylamide 2f (void of a 9-Cl substituent which would otherwise have complicated outcome interpretations) revealed the production of a product mixture of 2-propyl-3-propylimino-pyrroloquinoline 3b (ca. 80%) (arising from elimination of H₂S) and 2-propyl-3-thioxo-pyrroloquinoline 4b (ca. 20%) (arising from elimination of propylamine) as end-products.
In comparison, solid 2f when heated at its m.p. (near 190°C) decomposed with evolution of propylamine and hydrogen sulfide, resulting in a dramatic increase in the production of 3-thioxo-pyrroloquinoline 4b (ca. 60%) at the expense of 3-propylimino-pyrroloquinoline 3b (ca. 40%), as was estimated from an 1H NMR examination of the pyrolysis product.

With respect to the HRMS of the thiocarbamoyl amides 2a–2e, each showed the expected molecular ion, M⁺, and in addition, a substantial (on occasion, a 100% base peak) fragment ion corresponding to (M-RNH₂)+ indicative of 3-thioxo-pyrroloquinoline 4 formation (vide infra); a fragment ion (M-H₂S)⁺, implying 2-alkyl-3-alkylimino-pyrroloquinoline 3 was not evident. Even sterically hindered tert-butylamide 2e cyclized to the corresponding 3-thioxo-pyrroloquinoline 4 on the evidence of a substantial (~65%) fragment ion corresponding to (M-C₄H₉NH₂)+.

Scheme 2 outlines envisaged sequences and pathways (with thiocarbamoyl amide 2a and propylamine as representative reactants) thought to account for the aforementioned spectral observations [and for various chemical outcomes (vide infra)] in terms of the following assumptions: (a) thiocarbamoyl amide 2 when in solution, and on heating, isomerizes to the 3-amino-3-mercapto substituted moiety A. The latter then suffers β-elimination via a four-membered transition state, with competitive loss of both hydrogen sulfide and propylamine, to provide a product mixture of pyrroloquinolines 3a and 4a. (b) With temperature increase, amine elimination proceeds faster than does that of hydrogen sulfide, thereby resulting in a higher amount of 3-thioxo derivative 4 in the product mixture. These suppositions derive from the observations with thiocarbamoyl amide 2f (vide supra). (c) A further surmise is that in the course of a HRMS determination the species resulting from the lowest energy ionization of the entity A has the charge localized on S, as in molecular ion B (Scheme 2) from which preferential loss of propylamine provides the most substantial fragment ion (M-PrNH₂)+.

Thiocarbamoyl alkylamides 2 proved to be useful synthetic precursors for the preparation of a variety of substituted pyrrolo[3,4-b]quinoline derivatives, as is exemplified with the following reactions: (i) stirring together 4-chloro-propylamide 2a and propylamine at room temperature overnight led to a product mixture of the 'simple' (i.e. R=R₁=R₂ in 5, Scheme 1) 2-propyl-9-propylamino-3-propylimino-pyrroloquinoline 5a (ca. 15%) and S-containing complex 6a (ca. 50%); this outcome is in keeping with 2a being an intermediate in the synthesis of these two end-products from trichlorothienoquinoline 1a and propylamine. Reaction in the presence of lead acetate (for removal of liberated H₂S which would otherwise have participated in the synthesis) led to pyrroloquinoline 5a in much improved yield (~83%). (ii) In comparison, stirring 4-chloro-propylamide 2a with
ethylamine furnished a ‘mixed’ (i.e. one or more R substituents in 5, differ) pyrroloquinoline derivative, viz. 9-ethylamino-3-ethylimino-2-propyl-pyrroloquinoline 5c (~50%), and S-containing complex 6b. Likewise, 4-chloro-ethylamide 2b and ‘foreign’ amine, propylamine gave the ‘mixed’ 2-ethyl-propyl-3-propylimino-pyrroloquinoline 5e (~16%) and complex 6a. Product 5e arose in higher yield (56%), and free of S-containing material, on stirring the two reactants in the presence of lead acetate.

(iii) In marked contrast with the effect of amines on thiocarbamoyl amide 2 was that of hydrogen ion. Thus, stirring 4-chloro-propylamide 2a with acid (glacial HOAc or MeOH-aqueous HCl) at room temperature led to the amide cyclizing with preferential loss of propylamine and retention of S, to give exclusively, 9-chloro-3-thioxo-pyrrolo[3,4-b]quinolin-1-one 4a (94%). Propylamide 2f (void of a 9-Cl substituent) likewise yielded (halogen-free) 3-thioxo-pyrroloquinolin-1-one 4b (98%).

(iv) Amide 2 displayed another aspect of its reactivity in the absence of either (extraneous) amine or hydrogen ion. Thus, 2a on stirring with a mixture of lead acetate and lead carbonate in acetonitrile medium at room temperature cyclized with retention of propylamine and loss of H₂S to exclusively afford 9-chloro-pyrroloquinoline 3a (95%). Products 4a and 3a themselves were usefully employed as starting materials in subsequent syntheses (**vide infra**).

The outcomes in (i), (ii) and (iii) are rationalized as follows (Scheme 2): in (i), initial substitution of the mercapto function in intermediary A by propylamine eventuates (**via** C, R = Pr) in the production of 9-chloro-3-propylimino-pyrroloquinoline 3a and hydrogen sulfide. After this, the halogen in 3a suffers competitive substitution by both propylamine and hydrosulfide ion, thereby providing pyrroloquinolines 5a and 6a as end-products. In (ii), where thiocarbamoyl amide 2 is treated with a ‘foreign’ amine (R ≠ Pr), operation of the corresponding aforementioned events and participation of an appropriate amine-imine exchange (**via** C) results in a ‘mixed’ pyrroloquinoline end-product D (Scheme 2). The acid-catalysed reaction in (iii) is conjectured to involve protonation of the amino function in A to form ammonium ion E (Scheme 2) from which product 4a is formed upon elimination.

Also explicable from the foregoing assumptions, and of additional synthetic import were the following reaction outcomes: (v) Treatment of 9-chloro-3-thioxo-pyrroloquinoline 4a with propylamine in the presence of lead acetate at room temperature led exclusively to tripropyl-substituted pyrroloquinoline 5a (73%). Conducting the reaction between 4a and ethylamine in the presence of lead acetate yielded the ‘mixed’ 9-ethylamino-3-ethylimino-2-propyl-pyrroloquinoline 5c (54%). (vi) The feasibility of substituting the 9-halogen in pyrroloquinoline 3a utilizing a nucleophile other than an amine was demonstrated with phenylthiolate ion (PhS⁻); reaction at room temperature gave 9-phenylsulfanyl-2-propyl-3-propylimino-pyrroloquinoline 7a (51%). This result is supportive of the view that sulfhydryl ion
HS: substitutes 3a to provide 9-thioxo derivative 6a. Aminolysis of the reactive analogous 9-propysulfanyl derivative 7b with ethylamine led to cleavage of the thioether bond with production of 9-ethylamino-5-pyrolo[3,4-b]quinolines 5f (74%); substrate 7b was obtained (65%) by alkylating complex 6a with propyl iodide.

It is evident from the above that by judicious selection and application of reagents and conditions set out herein, a variety of ‘simple’ and ‘mixed’ 2-alkyl-9-ethylamino-3-alkylimino-pyrrolo[3,4-b]quinolines can be accessed, and that variations of the substituents can, in principle, be achieved in all positions.

The respective structures of the aforementioned ‘simple’ 2,2-alkyl-9-ethylamino-3-alkylimino-pyrroloquinolines 5a and 5b were supported from their 1H NMR properties which showed, inter alia, the α-methylene protons of the 9-alkylamino group as near δ3.9 and spin-coupled to the amino D₃O-exchangeable proton near δ7.8.

The analysis of the ‘H NMR spectra of the aforementioned ‘mixed’ 2-alkyl-9-ethylamino-3-alkylimino-pyrroloquinolines revealed the following: compounds 5 each dissolved in aqueous acid to form a yellow-green fluorescent solution. The soluble product from 5a was isolated as a mono-hydrogen chloride salt (5a.HCl) in which the acidic proton was bonded to the N of the 3-imino function as was demonstrated from a X-ray crystallographic study; basification of the acid solution regenerated substrate 5a. Warming representative 2-propyl-3-propylimino-pyrroloquinoline 3b in dioxan-aqueous HCl solution led to the ready hydrolysis of its imine function with production of 2-propylpyrroloquinoline-1,3-dione 8 (89%); we had earlier reported an analogous outcome from S-containing complex 2.

Preliminary studies of the chemical properties of the 2-alkyl-9-ethylamino-3-alkylimino-pyrroloquinolines 5 revealed the following: compounds 5 each dissolved in aqueous acid to form a yellow-green fluorescent solution. The soluble product from 5a was isolated as a mono-hydrogen chloride salt (5a.HCl) in which the acidic proton was bonded to the N of the 3-imino function as was demonstrated from a X-ray crystallographic study; basification of the acid solution regenerated substrate 5a. Warming representative 2-propyl-3-propylimino-pyrroloquinoline 3b in dioxan-aqueous HCl solution led to the ready hydrolysis of its imine function with production of 2-propylpyrroloquinoline-1,3-dione 8 (89%); we had earlier reported an analogous outcome from S-containing complex 2.

In summary, the variety of substituted pyrrolo[3,4-b]quinolines 5 that can be accessed under relatively mild conditions promises that further exploration of this area will be rewarding.

2. Experimental

For general experimental details and techniques see ref. 10. High-resolution mass spectra (HRMS) were recorded on a VG 70-SEQ mass spectrometer (by Dr P.R. Boshoff, Cape Technikon Mass Spectrometry Unit).

3,3,9-Trichlorothieno[3,4-b]quinolin-1(3H)-one 1a was prepared by a literature method.

3,3-Dichlorothieno[3,4-b]quinolin-1(3H)-one 1b

2-Methylquinoline-3-carboxylic acid (3.0 g, 16.0 mmol) was heated with a large excess of SOCl₂ (10 cm³) under reflux for 3 h. Evaporation (rotovapor) of the reaction gave a residue of compound 1b which was freed from occluded SOCl₂ by azetropic distillation with benzene. Colourless crystals (2.23 g, 52%), m.p. 174–176°C (lit.¹¹ m.p. 170–171°C (from EtOAc).

Preparation of 4-chloro-2-alkylthiocarbamoyl-quinoline-3-carboxylic acid amylamides 2 (and of a related amide 2f).

General procedure: substrate 1a (500 mg, 1.64 mmol) was added portionwise (over ~5 min) to a large excess (>5 mmol) of stirred ice-cold amine (or in the case of the more volatile ethylamine, a 15–20% solution in dioxan). After 15 min or when the production of compound 2 was maximal (TLC monitoring; silica gel, 2% methanol in benzene containing 5% triethylamine), the reaction mixture was evaporated at low temperature under vacuum (to remove excess amine which would otherwise react further with amide 2 on heating). Water and CHCl₃ were added and the CHCl₃ extract was evaporated at low temperature to yield crude compound 2 together with some pyrroloquinoline 5 as by-product. Trituration with EtOAc dissolved most of the latter, leaving a residue of relatively pure alkylamide 2 which was collected by filtration. Conducting the reaction with ethylamine or with propylamine for 24 h yielded a product mixture of mainly the respective pyrroloquinoline 5 and S-containing complex 6.

4-Chloro-2-propylthiocarbamoyl-quinoline-3-carboxylic acid propylamide 2a

From propylamine; 62% (crude) yield. Together with pyrroloquinoline 5a (ca. 28%). M.p. 166–169°C (decomp., with liberation of H₂S (from EtOAc); ν₃₂₃₀–₂₉₀₀(m), 1630(s), 1530(br, s) cm⁻¹; δH, 0.98–1.11 (6H, m), 1.55–1.90 (4H, m), 3.42 (2H, q → t, J 7.1), 3.75–3.81 (2H, m → t, J 6.8), 6.16 (1H, br t, removed by D₂O), 7.65 (1H, m), 7.77 (1H, m), 8.0 (2H, br m), 9.2 (1H, br peak, removed by D₂O) (Found: C, 57.92; H, 5.77; N, 11.87; S, 8.75; M⁺, 349.1030 (−16%), also 290.0296 (100%). Calc. for C₁₇H₂₀ClN₃OS: C 58.33; H, 5.86; N, 11.98; S, 8.87; M⁺, 349.1039.

4-Chloro-2-ethylthiocarbamoyl-quinoline-3-carboxylic acid ethylamide 2b

From ethylamine (~20% solution in dioxan); 67% (crude) yield. Together with pyrroloquinoline 5b. M.p. 180–182°C (from EtOAc; ν₃₂₃₀–₂₉₀₀(m), 1630(s), 1540(br, s); δH, 1.27 (3H, t, J 7.2), 1.40 (3H, t, J 7.3), 3.46 (2H, m → q, J 7.3), 3.85 (2H, m → q, J 7.3), 7.26 (1H, br peak, removed by D₂O), 7.65 (1H, m), 7.85 (1H, m), 8.08 (1H, dd, J 2.3, 8.2), 8.21 (1H, dd, J 2.1, 8.2), 9.6 (1H, br peak removed by D₂O) (Found: M⁺, 321. Calc. for C₁₇H₁₈ClN₃OS: M, 321).

4-Chloro-2-isopropylthiocarbamoyl-quinoline-3-carboxylic acid isopropylamide 2c

From isopropylamine; 87% (crude) yield, together with (presumably) pyrroloquinoline 5g (ca. 12%). Reaction for 24 h yielded crude product 2c (ca. 44%) and pyrroloquinoline 5g (ca. 28%). M.p. 187–188°C (lit. from EtOAc; δH, 1.30 (3H, d, J 6.5), 1.42 (3H, d, J 6.5), 4.3 (1H, sextet → quintet), 4.8 (1H, sextet → quintet), 9.5 (1H, br d, removed by D₂O), 7.64 (1H, m), 7.78 (1H, m), 8.06 (2H, m), 8.75 (1H, br d, removed by D₂O) (Found: M⁺C₁₇H₁₈ClN₃O₂, 329.0277 (100%). Calc. for C₁₇H₁₈ClN₃OS: M, 329.

4-Chloro-2-sec-butylthiocarbamoyl-quinoline-3-carboxylic acid sec-butylamide 2d

From sec-butylamine; 57% (crude) yield; m.p. 204–205°C (from EtOAc: δH, 0.99–1.11 (6H, m), 1.29 (3H, d, J 6.6), 1.38 (3H, d, J 6.6), 1.55–1.9 (4H, m), 4.13 (1H, m), 4.63 (1H, m), 5.89 (1H, br d, very slowly (within 1 week) removed by D₂O), 7.67 (1H, m), 7.80 (1H, m), 8.05 (1H, d, J 8.0), 8.15 (1H, d, J 8.3), 8.6 (1H, br peak, removed
by D2O) (Found: M+, 377.1328 (9%), and 304.0433 (100%). Calc. for C17H19N3O: M, 377.1329; (M-C,H,NH)3 requires 304.0437).

4-Chloro-2-tert-butylcarbamoylquinoline-3-carboxylic acid tert-butylamide 2e

From tert-butylamine; 57% (crude) yield after 24 h reaction; m.p. 230–232°C (decomp) (from EtOAc-hexane). δH, 1.50 (3H, s), 1.70 (3H, s), 5.89 (1H, br peak, removed by D2O) after several days), 7.6–7.8 (2H, m), 8.05–8.23 (3H, one overlapping peak (1H) removed by D2O after several days) (Found: M+, 377 (100%)); also 304 (65%). Calc. for C17H19N3O (i.e., M-C,H,NH)3 : 304.

2-Propylcarbamoylquinoline-3-carboxylic acid propylamide 2f

This was prepared from dichlorothienoquinoline 2a (422 mg, 1.56 mmol) and propylamine (500 mg, large mmol excess) in dioxan (5 cm3) following the general procedure for 2 (vide supra). Trituration of the crude product with hot hexane removed a small amount of hexane-soluble pyrroloquinoline 3b. The sparingly soluble amide 2f (180 mg [36% crude yield]) was crystallized from hexane-ether; m.p. 187–189°C (decomp., with evolution of H2S); δH, 0.99 (3H, t, J 7.3), 1.09 (3H, t, J 7.4), 1.55–1.73 (2H, sextet), 1.75–1.95 (2H, sextet), 3.36 (2H, q, J 6.8), 3.82 (2H, q, J 6.8), 7.20 (2H, m), 7.4–7.75 (3H, m), 7.97 (1H, m), 8.0 (1H, d, J 8.2), 8.25 (1H, d, J 8.5), 8.62 (1H, s) (Found: C, 72.52; H, 6.80; N, 14.99). A CDCl3 solution of the 1H NMR spectrum revealed the presence of pyrroloquinoline 3b (vide supra) (ca. 90%) and 2-propyl-3-thioxo derivative 4b (ca. 20%).

9-Chloro-2-propyl-3-propylimino-2,3-dihydro-pyrrolo[3,4-b]quinolin-1-one 4a

Propylthiocarbamoyl amide 2a (250 mg, 0.72 mmol) was dissolved in glacial HOAc (10 cm3) and the solution was allowed to remain at room temperature overnight. Ice and water were added upon which the crude product separated and was collected by filtration and dried in vacuo (197 mg, 94%, m.p., 156–162°C) yielding red crystals (from EtOAc-hexane), m.p. 162–163°C; δC (CDCl3, + DMSO-d6), 4.02 (3H, t, J 7.4), 7.50–7.9 (3H, m), 8.0 (1H, m), 8.4–8.5 (2H, m) (Found: C, 57.86; H, 3.56; N, 9.64; S, 10.93; M, 290.0297 (100%)). Calc. for C17H19N3O: C, 57.80; H, 3.81; N, 9.67; S, 11.02; M, 290.0281.

2-Propyl-3-thioxo-2,3-dihydro-pyrrolo[3,4-b]quinolin-1-one 4b

Compound 4b was similarly prepared by treating amide 2f (150 mg, 0.48 mmol) with glacial AcOH (1.5 cm3) at room temperature for 4 h, with TLC monitoring. The crude product (120 mg, 98%) gave red crystals, m.p. 134–135°C (from EtOAc-hexane); δH, 1.01 (3H, t, J 7.3), 1.84 (2H, m), 4.16 (2H, t, J 7.4), 7.75 (1H, m), 7.93 (1H, m), 8.06 (1H, d, J 8.2), 8.47 (1H, d, J 8.6), 8.64 (1H, s) (Found: C, 65.43; H, 4.71; N, 10.80; M+, 256.0672. Calc. for C17H21N3OS: C, 65.57; H, 4.72; N, 10.97; M, 256.0670).

2-Propyl-9-propylamino-3-propylimino-2,3-dihydro-pyrrolo[3,4-b]quinolin-1-one 5a

Compound 5a was originally prepared from propylamine and 3,3,9-trichloro-thienoquinoline 1a. It has now also been obtained in the following ways: (i) addition of 9-chloro-2-propyl-3-thioxo-pyrroloquinoline 4a (100 mg, 0.35 mmol) to a stirred ice-cold mixture of propylamine (2 cm3) and lead acetate (400 mg) in dioxan (10 cm3) resulted in immediate separation of PbS. Stirring was continued at room temperature overnight after which H2O and CHCl3 were added and the precipitated PbS was removed by filtration. The CHCl3 extract of the combined filtrate and washings was evaporated and the residue of crude compound 5a was crystallized from aqueous EtOH (97 mg, 73%; m.p. 73–74°C) and shown to be identical (1H NMR) with the product obtained in the literature. In the absence of lead acetate the reaction afforded a product mixture of compound 5a and S-containing complex 6a.

(ii) Stirring of 9-chloro-2-propyl-3-propylimino-pyrroloquinoline 3a (100 mg, 0.32 mmol) with propylamine (2 cm3) at room temperature for 12 h, followed by evaporation (rotavapor) of excess amine and crystallization (from hexane) gave compound 5a (65 mg, 60%, m.p. 73–74°C), identical (1H NMR) with the product in (i). (iii) 2-Propylthiocarbamoyl propylamine 2a (500 mg, 1.43 mmol) was added with stirring to an ice-cold mixture of lead acetate (3 g) and propylamine (8 cm3, large mmol excess). Stirring was continued at room temperature for 3½ h, after which the crude compound 5a (545 mg, a syrup, which solidified) was collected by filtration and dried in vacuo (197 mg, 94%, m.p., 156–162°C). The 1H NMR spectrum revealed the presence of pyrroloquinoline 3b (vide supra) (ca. 90%) and 2-propyl-3-thioxo derivative 4b (ca. 20%).

9-Propylamino-pyrroloquinoline hydrogen chloride salt 5a·HCl

A mixture of substrate 2,2-dichlorothienoquinoline 1b (422 mg, 1.56 mmol) was added portionwise (over 5–10 min) with stirring to ice-cold propylamine (5 cm3), after which the reaction was kept at room temperature for ~24 h. Excess amine was evaporated at reduced temperature and pressure, and the residue treated with H2O and CHCl3. Evaporation of the CHCl3 extract gave a mixture of compound 3b and propylthiocarbamoyl amide 2f. The mixture was extracted with hot hexane after which the sparingly soluble crude amide 2f was collected by filtration (260 mg, 54%) and identified from its 1H NMR (vide supra). Evaporation of the hexane filtrate and washings gave crude compound 3b (207 mg, 47%). Crystals, m.p. 103–104°C (from EtOH); δH, 0.98 (3H, t, J 7.3), 1.08 (3H, t, J 7.4), 1.70–1.90 (4H, m), 3.86 (2H, t, J 7.4), 4.59 (2H, t, J 7.0), 7.70 (1H, m), 7.85 (1H, m), 8.0 (1H, d, J 8.2), 8.25 (1H, d, J 8.5), 8.62 (1H, s) (Found: C, 72.26; H, 6.21; N, 14.41. Calc. for C17H19N3O: C, 72.52; H, 6.80; N, 14.99).
yellow crystals (m.p., 213–218°C (decomp.)); δ1.05–1.16 (9H, m), 1.75–2.1 (4H, m), 3.99 (2H, q→t, J 12.5), 4.31 (2H, t, J 7.4), 4.63 (2H, t, J 7.3), 7.63 (2H, m→t, J 12.5), 7.8 (1H, m), 8.07 (1H, d, J 8.3), 8.42 (1H, d, J 8.5), 13.8 (1H, br peak removed by D₂O). A portion of the crystallized salt was dissolved in CHCl₃ and the fluorescent yellow-green solution was basified with aqueous NaHCO₃, to provide a colourless CHCl₃ extract. This was dried (Na₂SO₄) and evaporated to give unchanged substrate quinoline 5b.

2-Ethyl-9-ethylamino-3-ethylimino-2,3-dihydro-pyrrolo[3,4-b]quinolin-1-one 5b

Compound 5b was originally prepared from trichlorothienoquinoline 1a and ethylamine.¹

9-Ethylamino-3-ethylimino-2-propyl-3,4-dihydro-pyrrolo[3,4-b]quinolin-1-one 5c

(i) 2-Propylthiocarbamoyl amide 2a (350 mg, 1.0 mmol) was added with stirring to initially ice-cold dioxan [10 cm³] containing ~20% ethylamine (~40 mmol) and the solution was kept overnight at room temperature. Water and CHCl₃ were added after which the organic extract was evaporated to obtain a crude product mixture (438 mg). This was dissolved in hot EtOAc, and on cooling complex 6b separated and was collected by filtration (170 mg, ~30%) and identified (¹H NMR, mixture contained 20% EtNH₂ (i.e. ~80 mmol EtNH₂) which resulted in immediate separation of PbS. After five days at room temperature 5c was isolated (180 mg) as described for pyrroloquinoline 5a (vide supra) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H₂O) and identified from its ¹H NMR. Amide 2b could be replaced by 2-propyl-thioxo-pyrroloquinoline 4a in this particular methodology.

9-Ethylamino-2-propyl-3-propylimino-2,3-dihydro-pyrrolo[3,4-b]quinolin-1-one 5f

A mixture of 9-propylsulfanyl-pyrroloquinolinone 7b (183 mg, 0.50 mmol) and 15 cm³ of dioxan containing 20% EtNH₂ (i.e. ~70 mmol EtNH₂) was stirred at room temperature with HPLC monitoring for 6 h. Evaporation gave a residue (162 mg) which was crystallized (from EtOH-H₂O) to give compound 5f as needles (120 mg, 74%) m.p. 78°C, δ₁.05–1.16 (9H, m), 1.65–1.8 (2H, m), 3.72 (2H, t, J 7.2), 3.85–4.0 (2H, m→q, J 12.5), 4.58 (2H, q, J 7.2), 7.42 (1H, m), 7.6–7.75 (2H, m; from EtOH-H₂O) and identified from its ¹H NMR. Amide 2b was isolated (180 mg) as described for pyrroloquinoline 5a (vide supra) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H₂O) and identified from its ¹H NMR spectrum (Found: M⁺, 324.1930, calculated for C₁₉H₂₄N₄O: M, 324.1939).

3-Ethylimino-2-propyl-9-propylamino-2,3-dihydro-pyrrolo[3,4-b]quinolin-1-one 5d

A solution of pyrroloquinoline 5a (183 mg, 0.54 mmol) in 6 cm³ of dioxan containing 20% EtNH₂ (i.e. ~80 mmol EtNH₂) was stirred at room temperature with HPLC monitoring for 6 h. Evaporation gave a residue (162 mg) which was crystallized (from EtOH-H₂O) to give compound 5d as needles (120 mg, 74%) m.p. 78°C, δ₁.05–1.16 (9H, m), 1.65–1.8 (2H, m), 3.72 (2H, t, J 7.2), 3.85–4.0 (2H, m→q, J 12.5), 4.58 (2H, q, J 7.2), 7.42 (1H, m), 7.6–7.75 (2H, m; from EtOH-H₂O) and identified from its ¹H NMR. Amide 2b was isolated (180 mg) as described for pyrroloquinoline 5a (vide supra) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H₂O) and identified from its ¹H NMR. Amide 2b was isolated (180 mg) as described for pyrroloquinoline 5a (vide supra) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H₂O) and identified from its ¹H NMR. Amide 2b was isolated (180 mg) as described for pyrroloquinoline 5a (vide supra) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H₂O) and identified from its ¹H NMR. Amide 2b was isolated (180 mg) as described for pyrroloquinoline 5a (vide supra) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H₂O) and identified from its ¹H NMR. Amide 2b was isolated (180 mg) as described for pyrroloquinoline 5a (vide supra) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H₂O) and identified from its ¹H NMR. Amide 2b was isolated (180 mg) as described for pyrroloquinoline 5a (vide supra) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H₂O) and identified from its ¹H NMR. Amide 2b was isolated (180 mg) as described for pyrroloquinoline 5a (vide supra) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H₂O) and identified from its ¹H NMR. Amide 2b was isolated (180 mg) as described for pyrroloquinoline 5a (vide supra) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H₂O) and identified from its ¹H NMR. Amide 2b was isolated (180 mg) as described for pyrroloquinoline 5a (vide supra) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H₂O) and identified from its ¹H NMR. Amide 2b was isolated (180 mg) as described for pyrroloquinoline 5a (vide supra) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H₂O) and identified from its ¹H NMR.
(220 mg, 0.78 mmol) and aqueous 2 mol dm$^{-3}$ HCl (1 cm$^3$) in dioxan (3 cm$^3$) was kept at $-50^\circ$C overnight. Cooling and filtering provided crude compound 8 (167 mg, 0.70 mmol; 89%), m.p. 179–182$^\circ$C. Crystals (from EtOH-H$_2$O), m.p. 182–183$^\circ$C, $\delta_{\text{H}}$ 1.00 (3H, t, J 7.4), 1.79 (2H, m), 3.81 (2H, t, J 7.4), 7.7, (1H, m), 7.95 (1H, m), 8.05 (1H, dd, J 1.5, 8.2), 8.44 (1H, dd, J 1.5, 8.2), 8.66 (1H, d, J 0.4) (Found: M+, 240.0910 (100%). Calc. for C$_{14}$H$_{12}$N$_2$O$_2$: M, 240.0899).

Quinoline-2,3-di(carboxylic acid propylamide) 9

A mixture of 2-propyl-pyrroloquinoline-dione 8 (99 mg, 0.41 mmol) and propylamine (2 cm$^3$) was stirred at room temperature for 24 h. Evaporation gave crude compound 9 (130 mg) which was crystallized from EtOH-H$_2$O to give needles (67 mg, 55%), m.p. 146–148$^\circ$C; $\delta_{\text{H}}$ 1.03 (6H, 2 x t, J 7.4), 1.65–1.8 (4H, m), 3.4–3.55 (4H, m), 7.65 (1H, m), 7.7–8.0 (ca. 4H, m; simplifies to 2H (m) with D$_2$O), 8.06 (1H, d, J 8.0), 8.60 (1H, s). (Found: C, 68.20; H, 7.17; N, 13.79; M$^+$, 299.1629 (−6%) and 241.0972 (100%). Calc. for C$_{17}$H$_{21}$N$_3$O$_2$: C, 68.16; H, 7.07; N, 14.09; M, 299.1634 and for (M-C$_3$H$_8$N): 241.0977).

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References and Notes

4 The preparation and analytical characterization of pyrroloquinolines 5a, 5b and of complexes 6a, 6b are reported in a preliminary communication: T. van Es, B. Staskun and M.A. Fernandes, S. Afr. J. Chem., 2003, 56, 30.
8 An account of the chemistry of the S-containing pyrroloquinoline complexes 8 and related compounds, is in preparation.
9 We thank Mr M.A. Fernandes for communicating this information prior to publication.