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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

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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 (^{1}H 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

3,3,9-trichlorothieno[3,4-b]quinolin-1(3H)-one, aminolysis, 2-alkyl-9-chloro-3-thioxo-pyrrolo[3,4-b]quinolines, 2-alkyl-3-alkylimino-9-thioxo-pyrrolo[3,4-b]quinolines, 2-alkyl-9-alkylamino-3-alkylimino-pyrrolo[3,4-b]quinolines.

1. Introduction

Pyrrolo[3,4-b]quinolines have drawn the attention of chemists for some time.[1] 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[2] and mappicine[3] that contain this ring system. In general, the existing syntheses rely on multistep methodologies[1]. In the context of our own interest in this area we showed recently[4] that the aminolysis of 3,3,9-trichlorothieno[3,4-b]quinolinone **1a** (Scheme 1) offers a convenient and brief access to the hitherto undocumented title compounds. Semenov *et. al.*[5] had earlier obtained 2-alkylthiocarbamoyl-quinoline-3-carboxylic acid alkylamides **2** (R^1=H) and S-free 2-alkyl-3-alkylimino-2,3-dihydro-pyrrolo[3,4-b] quinolin-1-one derivatives **3** (R^1=H) as products from the aminolysis of the related 2,2-dichlorothieno[3,4-b]quinolin-1-one **1b**. Here we report on further developments in both of these areas.

TLC monitoring of the reaction between 3,3,9-trichlorothieno[3,4-b]quinolin-1-one **1a**[6] and propylamine at room temperature revealed the production (and in some instances the progressive disappearance) of a number of products, several of which were subsequently preparatively obtained and characterized (*vide infra*). These include 4-chloro-2-propylthiocarbamoyl-quinoline-3-carboxylic acid propylamide **2a** (inter-mediate), 9-chloro-2-propyl-3-propylimino-2,3-dihydropyrrolo[3,4-b]quinolin-1-one **3a** (intermediate), 9-chloro-2-propyl-3-thioxo-2,3-dihydro-pyrrolo[3,4-b]quinolin-1-one **4a** (intermediate), 2-propyl-9-propylamino-3-propylimino-2,3-dihydro-pyrrolo[3,4-b]quinolin-1-one **5a**[4] (end-product), and S-containing complex **6a**[4] (end-product), respectively.

The aforementioned propylamide **2a** and other 9-chloro-2-alkylthiocarbamoyl-quinoline-3-carboxylic acid alkylamides **2** (Scheme 1) were prepared (40–60% yields) in a general procedure which involved stirring trichlorothienoquinoline substrate **1a** with an appropriate amine RNH_2 (R = Et, Pr, *iso*-Pr, *sec*-Bu, and *tert*-Bu, 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 (^{1}H NMR, HRMS) properties and elemental analysis. The ^{1}H NMR spectrum of each showed, *inter alia*, two D_2O exchangeable (NH) protons, generally near δ6.5 and δ9.0 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 D_2O. 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 δ4[7], while only one set of α-methylene protons would exhibit a complex multiplicity due to coupling.

^{1}H NMR ($CDCL_3$) 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 H_2S) and 2-propyl-3-thioxo-pyrroloquinoline **4b** (*ca.* 20%) (arising from elimination of propylamine) as end-products.

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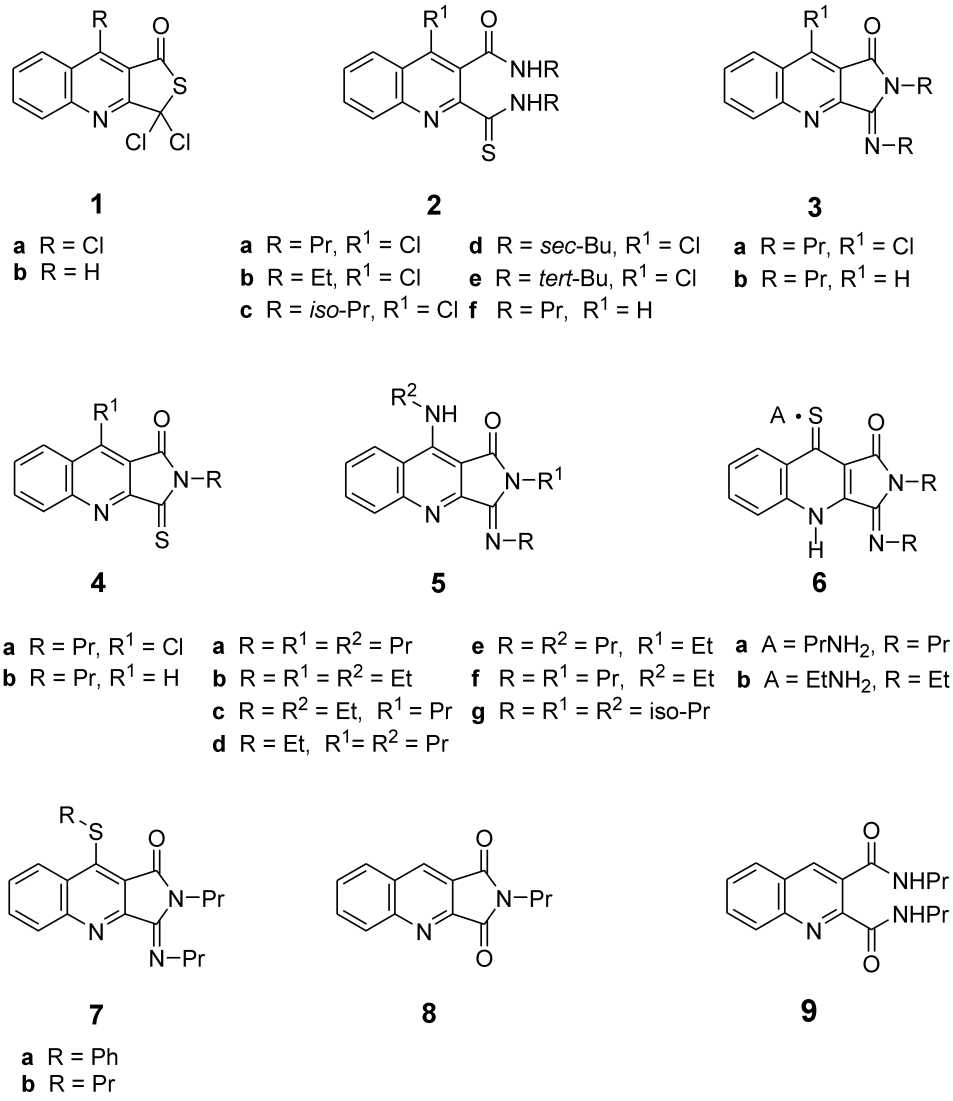


Scheme 1

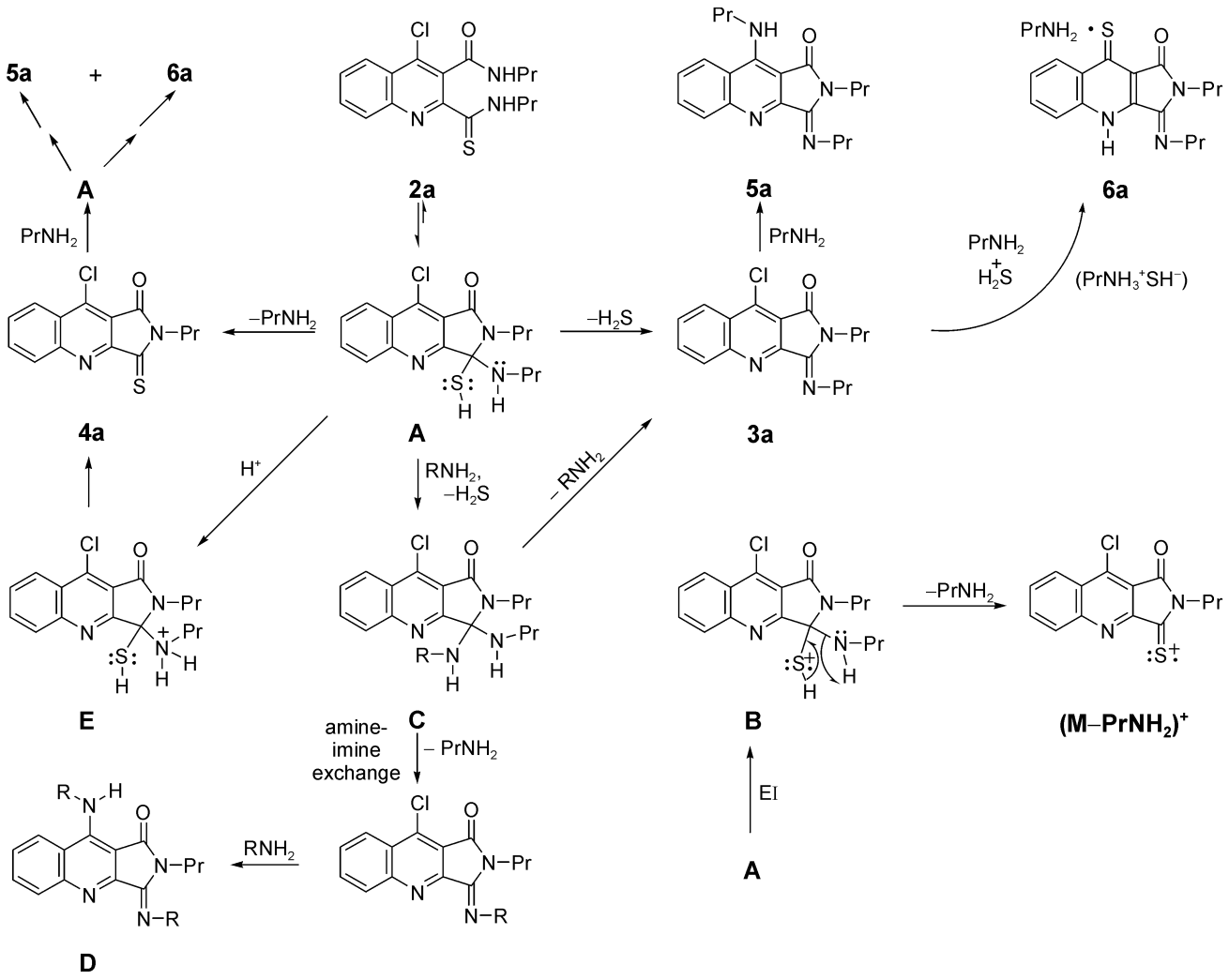
In comparison, solid **2f** when heated at its m.p. (near 190°C) decomposed with evolution of propylamine and hydrogen sulfide, resulting in a dramatic increase in the production of 3-thioxo-pyrroloquinoline **4b** (*ca.* 60%) at the expense of 3-propylimino-pyrroloquinoline **3b** (*ca.* 40%), as was estimated from an ^{1}H 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 $(M\text{-}RNH_2)^+$ indicative of 3-thioxo-pyrroloquinoline **4** formation (*vide infra*); a fragment ion $(M\text{-}H_2S)^+$, 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 $(M\text{-}C_4H_9NH_2)^+$.

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 $(M\text{–}PrNH_2)^+$.

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 = R ^{1} = R^2 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.[4] Reaction in the presence of lead acetate (for removal of liberated H_2S 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



Scheme 2

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-propylamino-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 H_2S 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[8] that sulfhydryl ion

HS^- substitutes **3a** to provide 9-thioxo derivative **6a**. Aminolysis of the reactive analogous 9-propylsulfanyl derivative **7b** with ethylamine led to clearage of the thioether bond with production of 9-ethylamino-pyrroloquinoline **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-alkylamino-3-alkylimino-pyrrolo[3,4-b]quinolines **5** 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-alkyl-9-alkylamino-3-alkylimino-pyrroloquinolines **5a** and **5b** were supported from their ^{1}H 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 D_2O-exchangeable proton near δ7.8.

Analysis of the ^{1}H NMR spectra of the aforementioned 'mixed' pyrroloquinolines **5c** and **5e**, elicited the chemical shifts of the 2-alkyl and 3-alkylimino α-methylene protons as being near δ3.7 and δ4.6, respectively. These shift values taken in conjunction with a weak but significant NOE interaction between the α-methylene protons of the 3-alkylimino group and the 5-H aromatic proton, proved to be diagnostically useful in assigning and substantiating related pyrroloquinoline structures (*vide supra*).

Preliminary studies of the chemical properties of the 2-alkyl-9-alkylamino-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[9]; 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[4] reported an analogous outcome from S-containing complex **6a**. Treatment of dione **8** with propylamine yielded the corresponding quinoline-2,3-(dicarboxylic acid propylamide) **9** (55%).

In summary, the variety of substituted pyrrolo[3,4-b]quinoline derivatives that can be accessed under relatively mild conditions in the aminolysis of 3,3,9-trichlorothienoquinoline **1a** is striking, and 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 V.G. 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[6] method.

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

2-Methylquinoline-3-carboxylic acid (3.00 g, 16.0 mmol) was heated with a large excess of $SOCl_2$ (10 cm^3) under reflux for 3 h. Evaporation (rotavapor) of the reaction gave a residue of compound **1b** which was freed from occluded $SOCl_2$ by azeotropic 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 alkylamides **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 $CHCl_3$ were added and the $CHCl_3$ 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].

*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 H_2S) (from EtOAc); ν_{max} 3200–2900(m), 1630(s), 1530(br, s) cm^{-1}; δ_H 0.98–1.11 (6H, m) 1.55–1.90 (4H, m), 3.42 (2H, q $\xrightarrow{D_2O}$ t, J 7.1), 3.75–3.81 (2H, m $\xrightarrow{D_2O}$ t, J 6.8), 6.16 (1H, br t, removed by D_2O), 7.65 (1H, m), 7.77 (1H, m), 8.0 (2H, m), 9.2 (1H, br peak, removed by D_2O) (Found: C, 57.92; H, 5.77; N, 11.87; S, 8.75; M$^+$, 349.1030 (~16%), also 290.0296 (100%). Calc. for $C_{17}H_{20}ClN_3OS$: C 58.33; H, 5.76; N, 12.06; S, 9.16; M$^+$ 349.1016; $(M\text{-}C_3H_7NH_2)^+$ requires 290.0281).

*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); ν_{max}/cm^{-1} 3200–2900 (m), 1630 (s), 1540 (br, s); δ_H 1.27 (3H, t, J 7.2), 1.40 (3H, t, J 7.3), 3.46 (2H, m $\xrightarrow{D_2O}$ q (J 7.3)], 3.85 [(2H, m $\xrightarrow{D_2O}$ q (J 7.3)], 7.26 (1H, br peak, removed by D_2O), 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 D_2O) (Found: M$^+$, 321. Calc. for $C_{15}H_{16}ClN_3OS$: M, 321).

*4-Chloro-2-iso-propylthiocarbamoyl-quinoline-3-carboxylic acid iso-propylamide **2c***

From *iso*-propylamine; 87% (crude) yield, together with (presumably) pyrrolquinoline **5g** (*ca.* 12%). Reaction for 24 h yielded compound **2c** (*ca.* 44%) and pyrroloquinoline **5g** (*ca.* 28%). M.p. 187–188°C (dec.) (from EtOAc). δ_H 1.30 (3H, d, J 6.5), 1.42 (3H, d, J 6.5), 4.3 (1H, sextet $\xrightarrow{D_2O}$ quintet), 4.8 (1H, sextet $\xrightarrow{D_2O}$ quintet), 5.95 (1H, br d, removed by D_2O), 7.64 (1H, m), 7.78 (1H, m), 8.06 (2H, m), 8.75 (1H, br d, removed by D_2O) (Found: $(M\text{-}C_3H_7NH_2)^+$, 290.0277 (100%). Calc. for $C_{14}H_{11}ClN_2OS$: 290.0281).

*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); δ_H 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 D_2O), 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 D_2O) (Found: M^+, 377.1328 (9%), and 304.0433 (100%). Calc. for $C_{19}H_{24}ClN_3OS$: M, 377.1329; $(M-C_4H_9NH_2)^+$ requires 304.0437).

4-Chloro-2-tert-butylthiocarbamoyl-quinoline-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). δ_H 1.50 (3H, s), 1.70 (3H, s), 5.89 (1H, br peak, removed by D_2O after several days), 7.6–7.8 (2H, m), 8.05–8.23 (3H, one overlapping peak (1H) removed by D_2O after several days) (Found: M^+, 377(100%); also 304 (65%). Calc. for $C_{19}H_{24}ClN_3OS$: M, 377; Calc. for $C_{15}H_{13}ClN_2OS$ (i.e., $M-C_4H_9NH_2$) : 304).

2-Propylthiocarbamoyl-quinoline-3-carboxylic acid propylamide ***2f***

This was prepared from dichlorothienoquinoline **1b** (422 mg, 1.56 mmol) and propylamine (500 mg, large mmol excess) in dioxan (5 cm^3) 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-EtOAc; m.p. 187–189°C (decomp., with evolution of H_2S); δ_H 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 7.2), 6.56 (1H, br t, removed by D_2O), 7.5–7.75 (3H, m), 7.97 (1H, d, J 8.5), 8.04 (1H, s), 9.23 (1H, br peak, removed by D_2O) (Found: C, 64.62; H, 7.19; N, 13.17; S, 9.75. Calc. for $C_{17}H_{21}N_3OS$: C, 64.69; H, 6.71; N, 13.37; S, 10.16). A $CDCl_3$ solution of **2f** was kept at room temperature for two weeks with ^1H NMR monitoring. At the end a redetermination of the ^1H NMR spectrum revealed the presence of pyrroloquinoline **3b** (*vide supra*) (*ca.* 80%) and 2-propyl-3-thioxo derivative **4b** (*ca.* 20%).

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

A mixture of propylthiocarbamoyl amide **2a** (630 mg, 1.81 mmol), $Pb(OAc)_2$ [1.3 g dissolved in H_2O (6 cm^3)], and $PbCO_3$ [0.8 g, suspended in H_2O (6 cm^3)] in CH_3CN (25 cm^3) was stirred at room temperature for ~40 h. Water was added and the mixture was exhaustively extracted with $CHCl_3$ to provide crude compound **3a** as a solid (540 mg, 95%) which was crystallized from hexane; colourless needles, m.p. 110–112°C; δ_H 0.98 (3H, t, J 7.4), 1.06 (3H, t, J 7.4) 1.7–1.9 (4H, m) 3.85 (2H, t, J 7.2), 4.54 (2H, t, J 7.0), 7.75–7.95 (2H, m), 8.24 (1H, dd, J 0.8 and 8.0), 8.45 (1H, dd, J 1.4 and 8.4) (Found: M^+ 315 (100%). Calc. for $C_{17}H_{18}ClN_3O$: M, 315).

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

Substrate 2,2-dichlorothienoquinoline **1b** (422 mg, 1.56 mmol) was added portionwise (over 5–10 min) with stirring to ice-cold propylamine (5 cm^3), 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 H_2O and $CHCl_3$. Evaporation of the $CHCl_3$ 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); δ_H 0.98 (3H, t, J 7.4), 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 $C_{17}H_{19}N_3O$: C, 72.52; H, 6.80; N, 14.99).

9-Chloro-2-propyl-3-thioxo-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 cm^3) 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; δ_H ($CDCl_3$ + DMSO-d_6) 1.02 (3H, t, J 7.4), 1.78–1.90 (2H, m), 4.15 (2H, t, J 7.4), 7.9 (1H, 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 $C_{14}H_{11}ClN_2OS$: 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]quinoline-1-one ***4b***

Compound **4b** was similarly prepared by treating amide **2f** (150 mg, 0.48 mmol) with glacial AcOH (1.5 cm^3) 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); δ_H 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 $C_{14}H_{12}N_2OS$. 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-thienoquinolinone **1a**.[4] It has now also been obtained in the following ways: (i) addition of 9-chloro-2-propyl-3-thioxo-pyrroloquinolinone **4a** (100 mg, 0.35 mmol) to a stirred ice-cold mixture of propylamine (2 cm^3) and lead acetate (400 mg) in dioxan (10 cm^3) resulted in immediate separation of PbS. Stirring was continued at room temperature overnight after which H_2O and $CHCl_3$ were added and the precipitated PbS was removed by filtration. The $CHCl_3$ extract of the combined filtrate and washings was evaporated and the residue of crude compound **5a** was crystallized from aqueous EtOH [87 mg, 73%; m.p. 73–74°C] and shown to be identical (^1H NMR) with the product obtained in the literature.[4] 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 cm^3) 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 propylamide **2a** (500 mg, 1.43 mmol) was added with stirring to an ice-cold mixture of lead acetate (3 g) and propylamine (8 cm^3, 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 isolated as described in procedure (i). Recrystallization (EtOH) gave needles (400 mg, 83%, m.p. 74°C), identified by ^1H NMR. In the absence of lead acetate the reaction provided a product mixture of **5a** and **6a** with the former product present in minor (*ca.* 15%) amount.

9-Propylamino-pyrroloquinoline hydrogen chloride salt ***5a****. HCl*

A mixture of substrate **5a** (88 mg, 0.26 mmol), aqueous 2M HCl (10 cm^3) and $CHCl_3$ (10 cm^3) was stirred at room temperature for several min. The fluorescent $CHCl_3$ extract was dried (Na_2SO_4) and evaporated at low temperature and the residual crude salt (89 mg, 92%) was purified from EtOAc-MeOH to give canary-

yellow crystals (m.p., 213–218°C (decomp.)); δ1.05–1.16 (9H, m), 1.75–2.1 (4H, m), 3.99 (2H, q $\xrightarrow{D_2O}$ t), 4.31 (2H, t, J 7.4), 4.63 (2H, t, J 7.3), 7.63 (2H, m $\xrightarrow{D_2O}$ 1H, m), 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 D_2O). A portion of the crystallized salt was dissolved in $CHCl_3$ and the fluorescent yellow-green solution was basified with aqueous $NaHCO_3$, to provide a colourless $CHCl_3$ extract. This was dried (Na_2SO_4) and evaporated to give unchanged substrate **5a** (^{1}H NMR, mixture m.p.).

*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.[4]

*9-Ethylamino-3-ethylimino-2-propyl-2,3-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 cm^3] containing ~20% ethylamine (~40 mmol) and the solution was kept overnight at room temperature. Water and $CHCl_3$ 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, ~50 %) and identified (^{1}H NMR). Evaporation of the filtrate gave crude compound **5c** (158 mg; ~50%). Crystals, m.p. 95–97°C (from hexane); δ_H 0.95 (3H, t, J 7.4), 1.3–1.5 (6H, m), 1.65–1.8 (2H, m), 3.72 (2H, t, J 7.2), 3.85–4.0 (2H, m $\xrightarrow{D_2O}$ q), 4.58 (2H, q, J 7.2), 7.42 (1H, m), 7.65–7.8 [2H, (1H removed by D_2O], 8.04 (1H, dd J 1.1, 8.3), 8.28 (1H, dd, J 0.8, 8.5) (Found: M$^+$, 310.1805 (100%). Calc. for $C_{18}H_{22}N_4O$: M, 310.1794). The HRMS (of the crystals) also contained a peak (*ca.* 10%) at m/z 324.1930, corresponding to an ethyl-dipropyl-pyrroloquinoline **5** (most likely, **5d**) contaminant (calc. for $C_{19}H_{24}N_4O$: M, 324.1945).

(ii) Compound **5c** was also obtained by adding 9-chloro-2-propyl-3-thioxo-pyrroloquinoline **4a** (150 mg, 0.52 mmol) to a stirred ice-cold mixture of lead acetate (1.5 g) and 20 cm^3 dioxan containing 20% $EtNH_2$ (i.e. ~80 mmol $EtNH_2$) which resulted in immediate separation of PbS. Work-up, as for pyrroloquinoline **5a** (*vide supra*) furnished product **5c**; crystals (from EtOH-H_2O), 87 mg (54%), m.p. 104–105°C, and identical (^{1}H NMR and HRMS, and free of **5d** contaminant) with the product obtained in reaction (i).

*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 cm^3 of dioxan containing 20% ethylamine (~45 mmol) was kept overnight at room temperature and then held at 40–50°C for ~7 days, with HPLC monitoring. After cooling, water and $CHCl_3$ was added and the $CHCl_3$ extract was evaporated to yield a solid (186 mg). This was dissolved in EtOH which on cooling gave crystals of compound **5d** (65 mg, 37%) as needles, m.p. 77–78°C; δ_H 0.95 (3H, t, J 7.4), 1.11 (3H, t, J 7.4), 1.38 (3H, t, J.2), 1.65–1.90 (4H, m), 3.73 (2H, t, J 7.2), 3.85 (2H, q $\xrightarrow{D_2O}$ t, J 7.0), 4.59 (2H, q, J 7.2) 7.43 (1H, m), 7.68 (1H, m), 7.81 (1H, br peak removed by D_2O), 8.03 (1H, d, J 8.4), 8.28 (1H, q, J 8.5) (Found: M$^+$, 324. Calc. for $C_{19}H_{24}N_4O$: M, 324).

*2-Ethyl-9-propylamino-3-propylimino-2,3-dihydro-pyrrolo[3,4-b] quinolin-1-one **5e***

(i) 2-Ethylthiocarbamoyl amide **2b** (300 mg, 0.93 mmol) was added to ice-cold propylamine (5 cm^3; large mmol excess), and the solution was kept at room temperature overnight after which it was worked up as for **5c**. The crude product mixture (320 mg) was dissolved in hot EtOAc from which solution complex **6a** (277 mg, ~80%) (identified from its ^{1}H NMR spectrum) separated on cooling. Evaporation of the mother liquor gave crude product **5e** [48 mg, ~16%), m.p. 107–109°C; from hexane]; δ_H 1.0–1.16 (6H, m), 1.26 (3H, t, J 7.1), 1.71–1.90 (4H, m), 3.77–3.90 (4H, m), 4.51 (2H, t, J 7.0), 7.43 (1H, m), 7.68 (1H, m,), 7.80 (1H, br t, removed by D_2O, 8.04 (1H, dd, J 1.1,8.4), 8.30 (1H, dd, J 0.8, 8.5) (Found: M$^+$ 324.1963 (100%). Calc. for $C_{19}H_{24}N_4O$: M, 324.1945).

(ii) Compound **5e** was obtained in higher yield (and free of S-containing complex **6** side-product) by adding substrate amide **2b** (180 mg, 0.56 mmol) to a stirred chilled suspension of lead acetate (0.70 g) in propylamine (3 cm^3), when there was an immediate separation of PbS. After five days at room temperature **5e** was isolated (180 mg) as described for pyrroloquinoline **5a** (*vide supra*) to obtain crystals (100 mg, 56%), m.p. 121–122°C (from EtOH-H_2O) and identified from its ^{1}H NMR. Amide **2b** could be replaced by 2-propyl-3-thioxo-pyrroloquinoline **4a** in this particular methodology.

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

A mixture of 9-propylsulfanyl-pyrroloquinolinone **7b** (183 mg, 0.50 mmol) and 15 cm^3 of dioxan containing 20% $EtNH_2$ (i.e. ~70 mmol $EtNH_2$) was stirred at room temperature with HPLC monitoring for 6 h. Evaporation gave a residue (162 mg) which was crystallized (from EtOH-H_2O) to give compound **5f** as needles (120 mg, 74%) m.p. 78°C; δ_H 0.95 (3H, t, J 7.4), 1.05 (3H, t, J 7.4), 1.47 (3H, t, 7.2), 1.64–1.84 (4H, m), 3.73 (2H, t, J 7.2), 3.87–3.98 (2H, m $\xrightarrow{D_2O}$ q), 4.51 (2H, t, J 7.0), 7.43 (1H, m), 7.6–7.75 (2H, m; portion (1H) removed by D_2O), 8.04 (1H, dd, J 1.2 and 8.3), 8.29 (1H, dd, J 1.0 and 8.5).

*9-Phenylsulfanyl-2-propyl-3-propylimino-2,3-dihydro-pyrrolo[3,4-b] quinolin-1-one **7a***

Sodium methoxide was prepared from Na (26 mg, 1.1 meq) and methanol (3 cm^3). To this ice-cold solution was added with stirring benzenethiol (130 mg, 1.18 mmol) followed by 9-chloro-pyrroloquinoline **3a** (78 mg, 0.25 mmol). Stirring was continued at 0–5°C for ~ 30 min, and at room temperature for 3 h. Crystals of the title compound which had separated were collected by filtration, washed with ice-cold methanol, and dried (67 mg, 70%). M.p. 115–116°C (from H_2O-EtOH); δ_H ($CDCl_3$) 0.93 (3H, t, J 7.4), 1.08 (3H, t, J .4), 1.6–1.9 (4H), 3.81 (2H, t, J 7.2), 4.56 (2H, t, J 7.0), 7.15–7.30 (~5H, m), 7.6 (1H, m), 7.8 (1H, m), 8.25 (1H, d, J 8.2), 8.52 (1H, d, J 8.5) (Found: C, 70.81; H, 6.30; N, 10.52; S,7.80; M$^+$,389.1569. Calc for $C_{23}H_{23}N_3OS$: C, 70.89, H, 5.95; N, 10.83; S, 8.23, M, 389.1562).

*2-Propyl-3-propylimino-9-propylsulfanyl-2,3-dihydro-pyrrolo[3,4-b] quinolin-1-one **7b***

Complex **6a**[4] (100 mg, 0.27 mmol) was added with stirring to ice-cold propyl iodide (2 cm^3, large mmol excess) followed by anhydrous K_2CO_3 (~100 mg). Stirring was continued until TLC showed the absence of complex **6a** (1–2 h). Water and $CHCl_3$ were added and the organic extract was evaporated to yield the crude compound. Crystals (62 mg, 65%; from hexane); m.p. 60–62°C; δ_H 0.95–1.0 (6H , m), 1.08 (3H, t, J 7.3), 1.55–1.65 (2H, m), 1.7–1.9 (4H, m), 3.35 (2H, t, J 7.2), 3.85 (2H, t, J 7.3), 4.53 (2H, t, J 7.0), 7.71 (1H, m), 7.85 (1H, m), 8.19 (1H, dd, J 1.4, 8.5), 8.80 (1H, dd, J 1.4, 8.5).

*2-Propyl-2,3-dihydro-pyrrolo[3,4-b]quinoline-1,3-dione **8***

A mixture of 2-propyl-3-propylimino-pyrroloquinoline **3b**

(220 mg, 0.78 mmol) and aqueous 2 mol dm^{-3} HCl (1 cm^3) in dioxan (3 cm^3) was kept at ~50°C overnight. Cooling and filtering provided crude compound **8** (167 mg, 0.70 mmol; 89%), m.p. 179–182°C. Crystals (from EtOH-H_2O), m.p. 182–183°C, δ_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 $C_{14}H_{12}N_2O_2$: 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_2O to give needles (67 mg, 55%), m.p. 146–148°C; δ_H 1.03 (6H, 2 xt, 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_2O), 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 $C_{17}H_{21}N_3O_2$: C, 68.16; H, 7.07; N, 14.09; M, 299.1634 and for (M-C_3H_8N): 241.0977).

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