Production of 9-thioxo-2,3,4,9-tetrahydro-pyrrolo[3,4-b]quinolin-1-one derivatives from the aminolysis of 3,3,9-trichloro-3H-thieno[3,4-b]quinolin-1-one

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ABSTRACT

Treatment of the title substrate with propylamine yielded 2-propyl-9-propylamino-3-propylimino-2,3-dihydro-pyrrolo[3,4-b] quinolin-1-one (15%) and a S-containing product (63%). The latter is inferred (from its spectral and chemical properties) to be a (1:1) complex of 2-propyl-3-propylimino-9-thioxo-2,3,4,9-tetrahydro-pyrrolo[3,4-b]quinolin-1-one (derived via an unusual S-rearrangement) with propylamine. The propylamine in the complex is removed by acid or thermally to provide the aforementioned 9-thioxo component which structure was substantiated from a X-ray crystal analysis. Aminolysis of the title substrate with ethylamine afforded the analogous ethyl-substituted products.

KEYWORDS

3,3,9-Trichlorothieno[3,4-b]quinolinone; aminolysis, 9-alkylamino-2,3-dihydro- and 9-thioxo-2,3,4,9-tetrahydro-substituted 2-alkyl-3-alkylimino-pyrrolo[3,4-b]quinolin-1-ones.

In this preliminary account we describe a novel and brief access to hitherto undocumented pyrrolo[3,4-b]quinoline derivatives which latter may find use as synthones for more complicated heterocyclic systems and target molecules. Thus stirring a mixture of title compound **1**[1] with propylamine at room temperature overnight, furnished 2-propyl-9-propylamino-3-propylimino-2,3-dihydro-pyrrolo[3,4-b]quinolin-1-one **2a** (15%) and a S-containing product **A** (63%)[2] (Scheme 1).[3]

Initially the structure of product **A** was elusive owing to its unexpected mode of formation, its relative thermal instability, and the unavailability of a crystal suitable for X-ray crystallography. From ^{1}H NMR spectroscopy the molecule possessed, *inter alia*, three propyl groups, four aromatic protons, and *ca.* 3 D_2O-replaceable protons. An elemental analysis was consistent with a molecular formula $C_{20}H_{28}N_4OS$. In the HRMS, the molecular ion was not discernible; however, the base peak ion accorded with a molecular formula $C_{17}H_{19}N_3OS$, implying loss from product **A** of propylamine.

Treatment of substance **A** with glacial acetic acid at room temperature furnished 1 molar equivalent of propylamine and 1 molar equivalent of a red solid of composition $C_{17}H_{19}N_3OS$ (^{1}H NMR, HRMS, elemental analysis) as found for the aforementioned fragment ion. This red solid was also produced by thermally degrading product **A** in boiling toluene, and its structure as an alternative tautomeric form of the unexpected 2-propyl-3-propylimino-9-thioxo-2,3,4,9-tetrahydro-pyrrolo[3,4-b]quinolin-1-one **3a** was revealed from a X-ray crystallographic analysis (Fig. 1).

Merely mixing together 9-thioxo derivative **3a** and propylamine at room temperature reconstituted product **A**. Taking cognizance of all of the above, the latter structure, in the absence of further details, is tentatively represented as a (1:1) complex **5a**[4] (Scheme 1).

Complex **5a** on acid hydrolysis (aq HCl + MeOH, 50°C) provided 2 molar equivalents of propylamine and 1 molar equivalent of a different red solid ($C_{14}H_{12}N_2O_2S$). This latter was likewise identified (Fig. 2) as 2-propyl-9-thioxo-4,9-dihydro-pyrrolo[3,4-b]quinoline-1,3-dione **4a**, thereby corroborating the structural evidence derived from 9-thioxo derivative **3a**.

From X-ray crystal structures analysis, molecules in **3a** are linked via N-H•••S hydrogen bonds (N(31)-H(31)•••S(9) [x, 1–y, 0.5 + z]: 2.397 Å, 155.45°; N(31•••S(9): 3.200(2) Å) along the *c*-axis (Fig. 3). These are further linked through a weak C-H•••O interaction (C(7)-H(7)•••O(1) [0.5 – x, 0.5 + y, 0.5 – z]: 2.5931 Å, 141.19°; C(7)•••O(1): 3.369(3) Å). In comparison, molecules in **4a** are linked via N-H•••O hydrogen bonds (N(4)-H(4)•••O(1) [0.5 + x, 0.5–y, 0.5 + z]: 1.969 Å, 171.23°; N(4)•••O(1): 2.822(2) Å) along the *c*-axis which are further linked through a weak C-H•••O interaction (C(6)-H(6)•••O(3) [1.5 – x, 0.5 + y, 1.5 – z]: 2.5924 Å, 128.59°; C(6)•••O(3): 3.255(2) Å). The different primary hydrogen bonding type in the two compounds (N-H•••S *vs.* N-H•••O) is due to the zwitterionic nature of **3a**. In this compound, N(31) has positive charge which must be countered by a negative charge on S(9). The hydrogen bond is therefore an electrostatic N^+-H•••S^- interaction, which apparently is energetically more favourable than the alternative N-H•••O hydrogen bond in this compound.

Aminolysis of title substrate **1a** with ethylamine (in dioxan) yielded a mixture of the corresponding ethyl-substituted products, *viz.*, 2-ethyl-9-ethylamino-3-ethylimino-2,3-dihydro-pyrrolo[3,4-b]quinolin-1-one **2b** (~10%) and the (1:1) complex of 2-ethyl-3-ethylimino-9-thioxo-2,3,4,9-tetrahydro-pyrrolo[3,4-b]quinolin-1-one **4b** with ethylamine, *viz.*, **5b** (71%).

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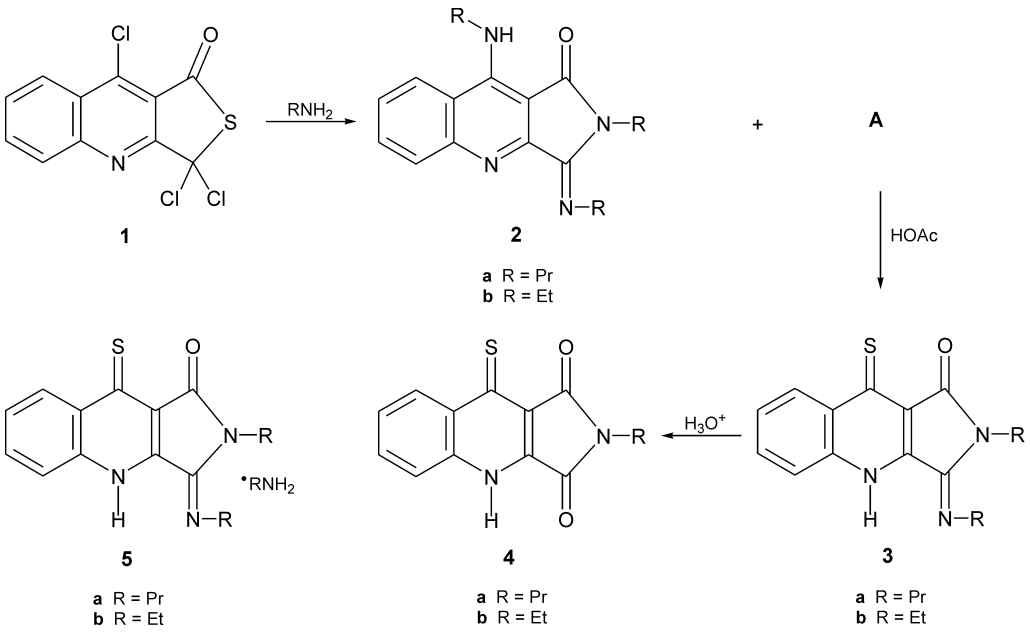

Scheme 1

Formulation **5b** accords with this complex's spectral and analytical properties, and with its chemical behaviour which parallels that of the propylamine-derived product **5a**.

In summary we have shown that aminolysis of title compound **1** provides access to hitherto undocumented trialkyl- and S-substituted pyrrolo[3,4-b]quinoline derivatives. To the best of our knowledge a S-rearrangement similar to this one has not been reported. We are currently defining the scope and mechanistic aspects of this methodology.[5]

Experimental

General experimental details and techniques used are described in reference 6.

*Complex **5a** and 9-propylamino-pyrroloquinoline **2a** from thienoquinoline **1** and propylamine*

Substrate **1** (1.50g, 4.93 mmol) was added in small portions (over a period of 10–15 min) with stirring to ice-cold propylamine (10 ml; large mmol excess). Stirring was continued at room temperature overnight after which the excess of propylamine was evaporated at low temperature and pressure (to prevent further reaction and/or decomposition of title product **5a**). The residue was treated with water and chloroform and the dried (Na_2SO_4) chloroform extract was evaporated (*vide supra*) to give a mixture of complex **5a** and 9-propylamino derivative **2a**. The two products were conveniently separated by dissolving the mixture in hot ethyl acetate and then cooling when the sparingly soluble title product **5a** separated. This was collected by filtration (1.15 g, 63%) and purified by crystallization from ethyl acetate; m.p. 138–142°C (decomp.); ν_{max} (KBr)/cm^{-1} 3050–2880 (br), 1685 (w-m, sh), 1650 (s), 1570 (m), 1550 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (3H, t, J 7.4 Hz), 0.92 (3H, t, J 7.4 Hz), 1.06 (3H, t, J 7.3 Hz), 1.50 (2H, sextet, J 7.3 Hz), 1.68 (2H, sextet, J 7.3 Hz), 1.80 (2H, sextet, J 7.3 Hz), 2.77 (2H, t, J 7.3Hz), 3.72 (2H, t, J 7.2 Hz), 4.53

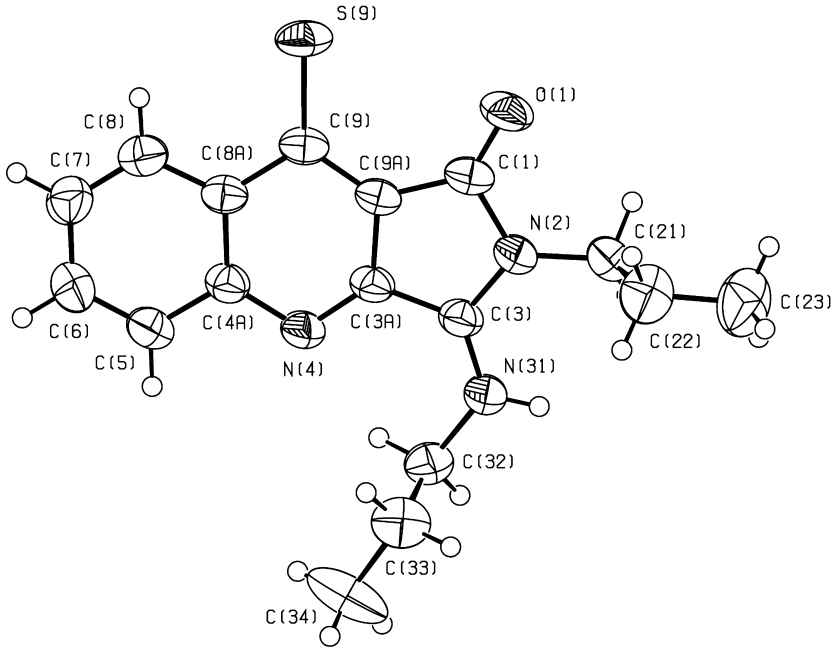

Figure 1 ORTEP drawing (50% ellipsoids) for **3a** showing the labeling of the non-hydrogen atoms.

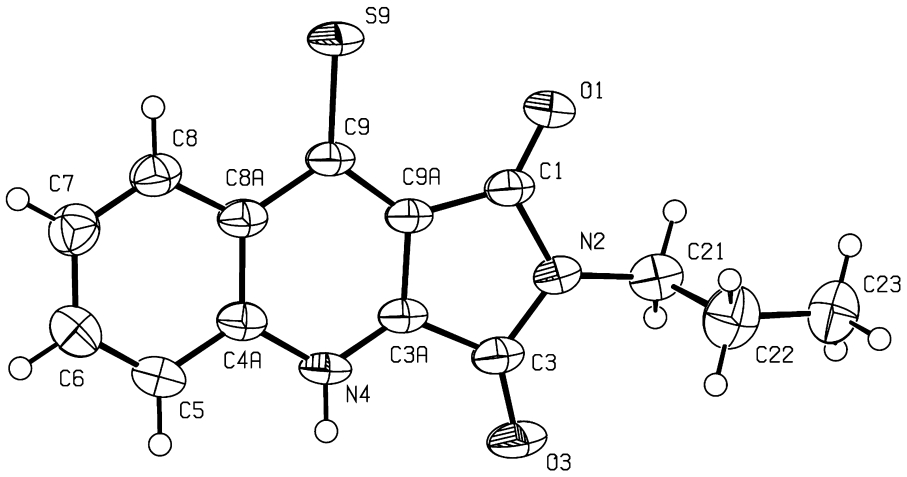

Figure 2 ORTEP drawing (50% ellipsoids) for **4a** showing the labeling of the non-hydrogen atoms.

(2H, t, J 7.1 Hz), 4.5 (*ca.* 3H, broad peak, removed by D_2O), 7.53 (1H, m), 7.71 (1H, m), 8.04 (1H, d, J 8.3 Hz), 8.67 (1H, d, J 8.3 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 11.0, 11.5 and 12.0 (CH_3), 21.6, 22.9 and 25.1 (CH_2), 39.8, 42.4 and 51.6 (CH_2), 119.8, 126.8, 127.2, 130.7, 131.0, 131.6, 147.7, 148.3, 149.9, 162.3 and 169.6. (Found: C, 64.55; H, 7.73; N, 14.8; S, 8.10; EIMS *m/z* (M-$C_3H_7NH_2$)$^+$, 313.1244. Calc. for $C_{20}H_{28}N_4OS$: C, 64.44; H, 7.57; N, 15.10; S, 8.60; (M-$C_3H_7NH_2$), 313.1249). The filtrate and washings were combined and evaporated to provide ethyl acetate-soluble *2-propyl-9-propylamino-3-propylimino-2,3-dihydro-pyrrolo[3,4-b]quinoline-1-one* ***2a***; crystals from hexane (240 mg, 15%), m.p. 73–74°C; ν_{max} (KBr)/cm^{-1} 2900–2800, 1660–1600 (br), 1580 (br); ^1H NMR (200 MHz, $CDCl_3$) δ 0.90–1.15 (9H, m), 1.62–1.90 (6H, m), 3.74 (2H, t, J 7.3 Hz), 3.80–3.90 (2 H, q $\xrightarrow{D_2O}$ t), 4.51 (2H, t, J 7.0 Hz), 7.43 (1H, m), 7.67 (1H, m), 7.82 (1H, br t, removed by D_2O), 8.05 (1H, dd, J 1.2 Hz and 8.4 Hz), 8.28 (1H, dd, J 1.1 Hz and 8.5 Hz). (Found: M$^+$, 338. Calc. for $C_{20}H_{26}N_4O$: M, 338).

Complex ***5b*** *and 9-ethylamino-pyrroloquinoline* ***2b*** *from thienoquinoline* ***1*** *and ethylamine*

Substrate **1** (1.50g, 4.93 mmol) was added in small portions (over a period of 10–15 min) with stirring to an ice-cold solution of ethylamine in dioxan (25% solution, 10 cm^3; large mmol excess). The reaction was continued as for complex **5a** (*vide supra*), taking note that product **5b** is sparingly soluble in $CHCl_3$. Separation of the reaction product mixture with hot EtOAc gave sparingly soluble title compound **5b** (1.15g 71%); m.p. 167–168°C (decomp.) (from EtOAc); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 1.21 (3H, t, J 7.0 Hz), 1.31 (3H, t, J 7.3 Hz), 1.36 (3H, t, J 7.2 Hz), 3.01 (2H, q, J 7.3 Hz), 3.80 (2H, q, J 7.0 Hz), 4.59 (2H, q, J 7.2 Hz), 7.43 (1H, m), 7.58 (1H, m), 7.87 (1H, dd, J 1.0 Hz, 8.1 Hz), 9.07 (1H, dd, J 1.1 Hz, 8.3 Hz). (Found: C, 61.54; H, 6.74; N, 16.83; S, 9.13; M$^+$ (EI) 285.0936. Calc. for $C_{17}H_{22}N_4OS$: C, 61.74; H, 6.71; N, 16.71; S, 9.69; (M-$C_2H_5NH_2$), 285.0936).

From the combined EtOAc filtrate and washings was recovered 2-ethyl-9-ethylamino-3-ethylimino-2,3-dihydro-pyrrolo-[3,4-b]quinolin-1-one **2b** (~10% crude yield) which was purified (from either hexane or EtOH), m.p. 114–115°C; δ_H 1.26 (3H, t, J 7.1 Hz), 1.35–1.50 (6H, m), 3.82 (2H, q, J 7.2 Hz), 3.85–4.0 (2H m $\xrightarrow{D_2O}$ q, J 7.1 Hz), 4.59 (2H, q, J 7.0 Hz), 7.38–7.47 (1H, m), 7.6–7.8 [2H $\xrightarrow{D_2O}$ 1H (aromatic)], 8.05 (1H, dd, J 1.0 Hz and 8.5 Hz), 8.27 (1H, dd, J 1.0 Hz and 8.6 Hz) (Found: M$^+$, 296.1619. Calc. for $C_{17}H_{20}N_4O$: M, 296.1633).

Complex ***5a*** *from 9-thioxo-pyrroloquinoline* ***3a*** *and propylamine*

To substrate **3a** (*vide infra*) (48 mg, 0.15 mmol) was added propylamine (1 cm^3, large excess) and the yellow solution was kept at room temperature overnight. Evaporation of the reaction at low temperature and pressure gave a residue (57 mg, ~100%) of crude title compound **5a**. Crystallization from ethyl acetate

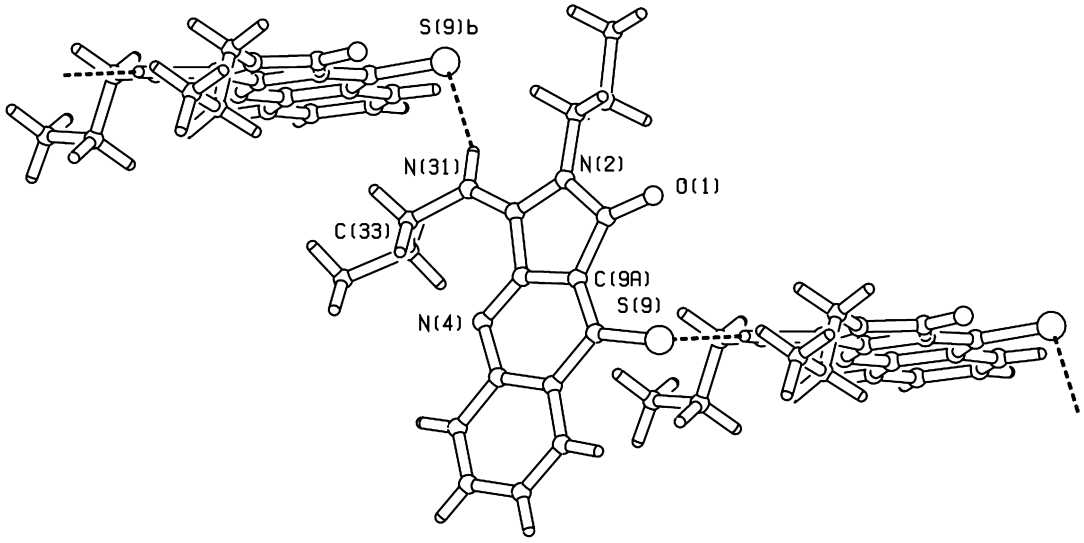

Figure 3 Diagram showing the N$^+$-H•••S$^-$ hydrogen bonding interaction between N(31) and S(9) in the X-ray crystal structure of **3a**.

gave pale-yellow needles [38 mg, m.p. 130–140°C (decomp.)], identical (^{1}H NMR, IR) with crystals of **5a** obtained by the aminolysis of substrate **1**.

Complex **5b** was likewise formed (93 mg, 75%) from 9-thioxo-pyrroloquinoline **3b** (*vide infra*) (110 mg, 0.39 mmol) and ethylamine (25% solution in dioxan; (2 cm^3, large mmol excess) following the analogous procedure for **5a** (*vide supra*).

*2-Propyl-3-propylimino-9-thioxo-2,3,4,9-tetrahydro-pyrrolo[3,4-b] quinolin-1-one **3a***

Title compound **3a** (^{1}H NMR †, IR) resulted from addition of substrate **5a** (500 mg, 1.34 mmol) to stirred glacial acetic acid (4 cm^3) at room temperature; the mixture developed an immediate deep-red colour and product **3a** began to separate. Stirring was continued for 10 min after which product **3a** was collected by filtration, washed successively with acetic acid and hexane, and dried (369 mg, 87%). Red crystals (from MeOH), m.p. 143–144°C; ν_{max} (KBr)/cm^{-1} 1740 (m), 1660 (s), 1465 (s), 955 (s); ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 0.90 (3H, t, J 7.4 Hz), 0.99 (3H t, J 7.4 Hz), 1.59 (2H, sextet, J 7.3 Hz), 1.80 (2H, sextet, J 7.3 Hz), 3.71 (2H, t, J 7.4 Hz), 4.45 (2H, t, J 7.2 Hz), 7.53 (IH, m), 7.68 (IH, m), 7.81 (IH, d, J 7.2 Hz), 8.85 (IH, d. J 8.3 Hz). (Found: C, 64.76; H, 6.40; N, 13.24; S, 9.87; (E1) *m/z* M$^+$, 313.1244. Calc. for $C_{17}H_{19}N_3OS$: C, 65.11; H, 6.11; N, 13.46; S, 10.22; M, 313.1249). The filtrate and washings were combined and acidified with aqueous 2 mol dm^{-3} HCl (~3 cm^3) and evaporated at room temperature. The residue of crude propylamine hydrochloride was treated with benzoyl chloride (1 cm^3) and aqueous 2 mol dm^{-3} NaOH to give crude benzoylpropylamide (205 mg, 1.26 mmol; i.e. 0.94 mmol propylamine from 1 mmol substrate **5a**) identified by comparison [mixture m.p. (83–84°C) and IR] with authentic amide.

*3-Ethyl-3-ethylimino-9-thioxo-2,3,4,9-tetrahydro-pyrrolo[3,4-6] quinolin-1-one **3b***

Similar reaction as for **5a** (*vide supra*) between complex **5b** and glacial acetic acid gave (91%, crude yield) title compound **3b**; red crystals, m.p. 163–164 °C (from EtOH-H_2O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (3H, t, J 7.1 Hz), 1.41 (3H, t, J 7.2 Hz), 3.92 (2H, q, J 7.1 Hz), 4.61 (2H, q, J 7.2 Hz), 7.64–7.72 (1H, m), 7.79–7.87 (1H, m), 8.09–8.18 (2H, m) (Found: C, 62.89; H, 5.67; N, 14.56; S, 11.06; M$^+$, 285.0947. Calc. for $C_{15}H_{15}N_3OS$: C, 63.09; H, 5.30; N, 14.78; S, 11.22; M, 285.0936).

*2-Propyl-9-thioxo-2,3,4,9-tetrahydro-pyrrolo[3,4-b]quinoline-1,3-dione **4a***

To a solution of complex **5a** (170 mg, 0.46 mmol) in MeOH (3 cm^3) was added 1.00 cm^3 of 2.145 mol dm^{-3} aqueous HCl. The wine-coloured solution was kept at 45–50°C for ~4 h and was then cooled to room temperature. Title compound **4a** which had separated was collected by filtration (117 mg, 0.43 mmol; 95%); red crystals, m.p. 218–220°C (from MeOH); (ν_{max} (KBr)/cm^{-1} 3200–3000 (m), 1765 (w, sh), 1700 (s); ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 0.88 (3H, t, J 7.4 Hz), 1.59 (2H, sextet, J 7.3 Hz), 3.60 (2H, t, J 7.2 Hz), 7.58 (1H, m), 7.81 (1H, m), 7.90 (1H, d, J 7.5 Hz), 8.72 (1H, d, J 8.3 Hz). (Found: M$^+$, 272. Calc. for $C_{14}H_{12}N_2O_2S$: M, 272). The filtrate and washings were combined and titrated against 0.695 mol dm^{-3} NaOH using methyl red indicator; this indicated that 1 mmol of complex **5a** had provided 1.97 mmol of propylamine in the course of the hydrolysis.

*2-Ethyl-9-thioxo-2,3,4,9-tetrahydro-pyrrolo[3,4-b]quinoline-1,3-dione **4b***

Similar treatment of 9-thioxo complex **5b** (165 mg, 0.50 mmol) with MeOH + aqueous HCl gave crude compound **4b** (122 mg, 95%), red crystals, m.p. 222–230°C (from MeOH); ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d$_6$) δ 1.29 (3H, t, J 7.2 Hz), 3.73 (2H, q, J 7.2 Hz), 7.5–7.6 (1H, m), 7.65–7.8 (1H, m), 7.94 (1H, d, J 8.2 Hz), 8.8 (1H, d, J 8.0 Hz). The corresponding titration indicated that 1 mmol of complex **5b** had provided 1.92 mmol of ethylamine.

*X-Ray crystallographic analysis for compounds **3a** and **4a***

Intensity data were collected on a Bruker SMART IK CCD area detector difractometer with graphite monochromated Mo K_α radiation (λ = 0.71073 Å). Data reduction was carried out using the program *SAINT+*[7] and absorption corrections were made using the program *SADABS*[8]. The crystal structure was solved by direct methods using *SHELXTL*[9]. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL.* Hydrogen atom positions (specifically H(31) in **3a** and H(4) in **4a**) were located from difference Fourier maps then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using *SHELXTL* and *PLATON.*[10]

Crystal data for **3a**. $C_{17}H_{19}N_3OS$, M = 313.41, monoclinic, space group *C*2/*c* (No. 15), a = 18.581(3), b = 13.760(2), c = 14.272(2) Å, β = 117.518(3)°, V = 3236.1(9) Å^3, Z = 8, D_x = 1.287 Mg m^{-3}, μ = 0.205 mm^{-1}, T = 293(2) K, 10970 reflections collected for 1.93 < θ < 28.33° of which 4018 unique (R_{int} = 0.0406), final R = 0.0475 with $I > 2\sigma(I)$ and 201 parameters, w$R(F^2)$ = 0.1313 for all data.

Crystal data for **4a**. $C_{14}H_{12}N_2O_2S$, M = 272.32, monoclinic, space group $P2_1/n$ (No. 14), a = 10.0845(16), b = 10.5290(15), c = 12.5709(19) Å, β = 107.140(3)°, V = 1275.5(3) Å^3, Z = 4, D_x = 1.418 Mg m^{-3}, μ = 0.252 mm^{-1}, T = 293(2) K, 8811 reflections collected for 2.29 < θ < 28.33° of which 3161 unique (R_{int} = 0.0332), final R = 0.0425 with $I > 2\sigma(I)$ and 173 parameters, w$R(F^2)$ = 0.1171 for all data.

CCDC reference numbers 184005 and 196358 respectively.‡

Acknowledgements

The authors are grateful to Mrs S. Heiss for the acquisition of the ^{1}H NMR spectra. B.S. thanks the University of the Witwatersrand for financial support.

References and Notes

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3 Diagrams in Scheme 1 correspond merely to their nomenclature in the text, and are not meant to detail structural features.

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† The relatively labile proton in each of **3a**, **3b**, **4a** and **4b** was not discerned.

‡ Supplementary crystallographic data for this paper may be obtained from the Cambridge Crystallographic Data Centre (CCDC) via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).