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Thionyl Chloride-induced Conversion of 1-Ethyl-1,4-dihydro-2-methyl-4-oxoquinoline-3-carboxylic Acids to Highly Functionalised Thieno[3,4-*b*]quinoline Derivatives†

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Warming a title acid with $SOCl_2$ gives the corresponding 3,3,9-trichlorothieno[3,4-*b*]quinolin-1(3*H*)-one whereas reaction at room temperature leads to the intermediate 3,3-dichloro-4-ethylthieno[3,4-*b*]quinoline-1(3*H*),9(4*H*)-dione product as established from the respective X-ray crystallographic determinations.

In a recent[1] communication we showed that a 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid **1** is converted by $SOCl_2$ to a product surmised to be an acid chloride–hydrogen chloride complex which on treatment with aqueous amine gave a 4-imino acid while with dry amine the principle outcome was a 4-imino amide.

In a natural extension of the work to the 2-methyl analogues, title acid **2** was refluxed with excess $SOCl_2$ (especially purified,[2] or reagent as received) for 1 h and here we report on the extraordinary outcome in which: (i) the purified product (70–80% crude yield) contained a sulfur atom from the reagent which had somehow become incorporated in reduced form into a new five-membered ring; (ii) the 2-methyl group in **2** was chlorinated; (iii) the 4-oxo function in **2** was replaced by chlorine, and (iv) the ethyl group on N had been eliminated—all in a one-pot reaction. Events as in (i) and (ii) had earlier been observed when 4-methylnicotinic acid[3] and a 2-methylquinoline-3-carboxylic acid[4] were refluxed with $SOCl_2$, while those as in (iii) and (iv) had also been documented,[5] but this is the first instance of all four reactions having collectively occurred in one procedure.

Characterisation of the product as 3,3,9-trichlorothieno[3,4-*b*]quinolin-1(3*H*)-one **4** was made from its spectral (^{1}H NMR, MS) properties and elementary analysis, and was unequivocally established from an X-ray crystallographic determination (Fig. 1). The mirror site symmetry of the molecule in the space group $C2/m$ implies that all the atoms except for Cl(2) are co-planar. The analogous 6-fluorothieno[3,4-*b*]quinolinone **5** was similarly obtained from the 7-fluoro-4-oxo acid **3** and $SOCl_2$. In contrast, the 1-ethyl substituent in 4-oxo acid **1** is retained after similar treatment with $SOCl_2$;[1] it would appear that attachment of a dihydrothiophene-like functionality as in **4** and **5** enhances the tendency to eliminate the 4-alkyl group (*vide infra*).

Another surprise was the relative ease with which the thieno[3,4-*b*]quinoline framework was formed from the reactants. Thus merely keeping a mixture of carboxylic acid **2** and $SOCl_2$ at room temperature for 24 h led to 3,3-dichloro-4-ethylthieno[3,4-*b*]quinoline-1(3*H*),9(4*H*)-dione **6** (80–90%, crude yield). This assignment was unequivocally confirmed in the case of the 6-fluoro analogue **7** (likewise derived from carboxylic acid **3**) from an X-ray crystal analysis (Fig. 2). The molecule deviates significantly from planarity. There are close intramolecular C···Cl and C–H···Cl contacts between C(12) and Cl(1) [3.254(6) Å] and H(121) and Cl(1) [2.59(4) Å], implying hydrogen bonding between the ethyl CH_2 and Cl; this is consistent with the unusually broad ^{1}H NMR peak observed at δ_H 4.9. As far as we are aware, Figs. 1 and 2 show the first X-ray structures of the thieno[3,4-*b*]quinoline ring system. Products **6** and **7** were thermally unstable giving rise to as yet uncharacterised mixtures; however, each was transformed in hot $SOCl_2$ to the corresponding end-product **3** or **4**.

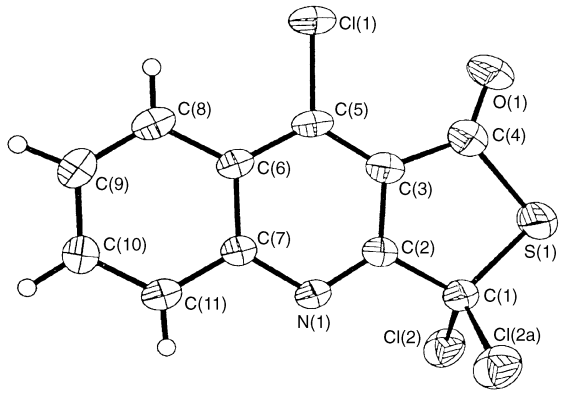

Fig. 1 ORTEX[11] drawing (50% ellipsoids) for **4**, showing the labelling of the non-hydrogen atoms

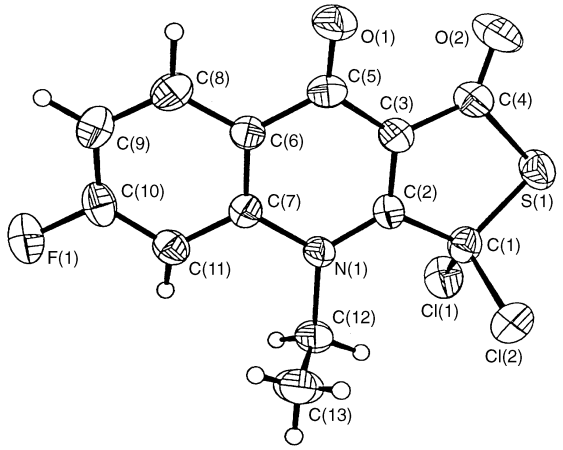

Fig. 2 ORTEX[11] drawing (50% ellipsoids) for **7**, showing the labelling of the non-hydrogen atoms

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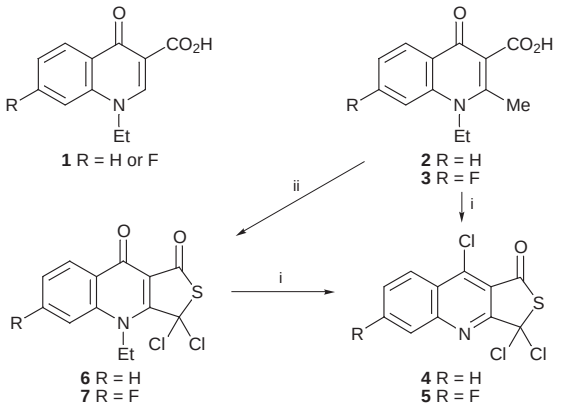
The thieno[3,4-*b*]quinoline system is one of the more than ten classes of product that are obtained from the reaction of $SOCl_2$ with active methylene and related compounds.[6] However, the aforementioned preparations are the first examples of its generation from a quinol-4(1*H*)-one derivative as substrate, being generally accessed by multistep procedures.[7,8]



Scheme 1 *Reagents and conditions*: (i) $SOCl_2$, reflux 1 h; (ii) $SOCl_2$, room temp., 24 h

At present the process whereby, for example, carboxylic acid **2** reacts with $SOCl_2$ to form thienoquinoline **4** remains to be clarified. Nevertheless, two distinct mechanistic schemes may be surmised to operate: (a) a series of reactions such as those postulated[3,9] in related work that brings about the conversion of **2** to intermediate **6**, followed by (b) a sequence whereby **6** gives rise to end-product **4** (Scheme 1).

In summary, we have extended earlier[1,4] findings in the area of quinolinecarboxylic acid chemistry by describing a $SOCl_2$-induced transformation of a 1-ethyl-1,4-dihydro-2-methyl-4-oxoquinoline-3-carboxylic acid into two highly functionalised thieno[3,4-*b*]quinoline derivatives, one being the precursor for the other. Further studies on the mechanistic aspects and applications of this one-pot synthesis and its extension to related substrates are in progress.

Experimental

3,3,9-*Trichlorothieno*[3,4-b]*quinolin*-1(3H)-*one* **4**.—A mixture of carboxylic acid **2**[10] (400 mg) and $SOCl_2$ (5 cm^3) was heated under reflux for 1 h. The excess reagent was evaporated (rotavapor) and the last traces removed azeotropically with benzene. The residue was treated with $CHCl_3$ and saturated aqueous $NaHCO_3$ and the organic phase was washed (H_2O), dried (Na_2SO_4) and evaporated to give crude title compound **4** (70–80%). Crystals, mp 201–203 °C (from EtOAc or EtOAc–hexane) [Found: C, 43.51; H, 1.51; N, 4.55; S, 10.49%; *m/z* 303 (M^+, 3Cl). $C_{11}H_4Cl_3NOS$ requires C, 43.37; H, 1.32; N, 4.60; S, 10.53%; *M*, 303 (Cl = 35)]; δ_H (200 MHz; $CDCl_3$) 7.84–7.89 (1H, m), 8.03–8.07 (1H, m), 8.36–8.38 (1H, m), 8.52–8.55 (1H, m).

The 6-fluoro analogue **5** was likewise obtained (≈90% crude yield) from the 7-fluoro-4-oxo acid **3**.[10] Crystals, mp 178–179 °C (from EtOAc) [Found: C, 41.32; H, 1.18; Cl, 34.22; N, 4.32; S, 10.65%; *m/z* 321 (M^+, 3Cl). $C_{11}H_3Cl_3FNOS$ requires C, 40.95; H, 0.94; C1, 32.98; N, 4.34; S, 9.94%; *M* 321 (Cl = 35)]; δ_H (200 MHz; $CDCl_3$) 7.6–7.7 (1H, m), 8.0–8.05 (1H, m), 8.5–8.6 (1H, m).

3,3-*Dichloro*-4-*ethylthieno*[3,4-b]*quinoline*-1(3H),9(4H)-*dione* **6**.—A mixture of carboxylic acid **2** (394 mg) and $SOCl_2$ (5 cm^3) was allowed to stand at room temp. for ≈24 h. The excess reagent was evaporated (rotavapor) at room temp. and the residue (sparingly soluble in $CHCl_3$ and probably a HCl salt) was treated with $CHCl_3$ and saturated aqueous $NaHCO_3$. The organic phase was washed (H_2O), dried (Na_2SO_4), and evaporated at room temp. to give crude title product **6**. This material was purified by column chromatography on silica using 20% EtOAc in $CHCl_3$ as eluent to furnish dione **6** (487 mg, ≈90%). Crystals, mp 196 °C (from $CHCl_3$, < 40 °C) [Found: C, 50.22; H, 2.67; Cl, 23.32; N, 4.47; S, 10.89%; *m/z* 313 (M^+, 2Cl). $C_{13}H_9Cl_2NO_2S$ requires C, 49.69; H, 2.89; Cl, 22.57; N, 4.46; S, 10.21; *M* 313 (Cl = 35)]; δ_H (200 MHz, $CDCl_3$) 1.66 (3H, t, *J* 7.0 Hz), 5.0 (2H, br peak), 7.53–7.60 (1H, m), 7.7–7.9 (2H, m), 8.55–8.59 (1H, dd, *J* 1.5 and 8.0 Hz).

The 6-fluoro analogue **7** was similarly prepared (≈75%, crude) from 7-fluoro-4-oxo acid **3** (100 mg) and $SOCl_2$ (2 cm^3). Crystals, mp 224–226 °C (with previous sintering) [from EtOAc (< 40 °C)]. δ_H ($CDCl_3$) 1.67 (3H, t, *J* 7.0 Hz), 4.9 (2H, br peak), 7.24–7.33 (1H, m), 7.39–7.45 (1H, dd, *J* 2.0 and 10.9 Hz), 8.54–8.62 (1H, m).

Conversion of Quinolinedione **6** *to Quinolone* **4**.—A solution of carboxylic acid **2** in $SOCl_2$ was kept at room temp. and aliquots were taken at various times for TLC examination. After ≈1½ h the major product was intermediate **6** the amount of which did not change much after 3 h or 21 h reaction. Refluxing the latter mixture or, separately, a sample of **6** in $SOCl_2$, gave end product **4**.

Crystal Data for **4**.— $C_{11}H_4Cl_3NOS$, $M = 304.56$, $\lambda = 0.71069$ Å, monoclinic, space group $C2/m$, $a = 15.0648(19)$ Å, $b = 6.8926(17)$ Å, $c = 11.0546(13)$ Å, $\beta = 91.710(10)°$, $V = 1147.4(3)$ Å^3, $Z = 4$, D_c 1.763 Mg m^{-3}, $\mu = 0.958$ mm^{-1}, $F(000) = 608$, crystal size 0.44 × 0.13 × 0.13 mm. Data were collected at 25 °C on a Nonius CAD4 diffractometer using graphite monochromated Mo-Kα radiation. Unique reflections = 979 [R(int) = 0.0218], observed $I > 2\sigma(I) = 688$. The structure was solved by direct methods (SHELXS-86)[12] and refined by a full matrix least-squares method (SHELXL-97).[12] The final refinement converged to $R_1 = 0.0278$ and $wR_2 = 0.0832$ for observed data and $R_1 = 0.0518$, $wR_2 = 0.1012$ for all data with residuals (maximum peak/hole) of 0.217 and −0.239 e Å^{-3}.

Crystal Data for **7**.—$C_{13}H_8C_{12}FNO_2S$, $M = 332.16$, $\lambda = 0.71073$ Å, monoclinic, space group $C2/c$, $a = 23.149(2)$ Å, $b = 8.0499(7)$ Å, $c = 14.5241(13)$ Å, $\beta = 102.263(2)°$, $V = 2644.8(4)$ Å, $Z = 8$, D_c 1.668 Mg m^{-3}, $\mu = 0.659$ mm^{-1}, $F(000) = 1344$, crystal size 0.56 × 0.06 × 0.05 mm. Data were collected at 25 °C on a SMART CCD area detector diffractometer (by Leanne Cook[a], Centre for Molecular Design) using graphite monochromated Mo-Kα radiation. Unique reflections = 2959 [R(int) = 0.0592], observed $I > 2\sigma(I) = 1513$. The structure was solved by direct methods (SHELXS86)[12] and refined by a full matrix least-squares method (SHELXL-97).[12] The final refinement converged to $R_1 = 0.0696$, $wR_2 = 0.1448$ for observed data and $R_1 = 0.1499$, $wR_2 = 0.1789$ for all data with residuals (max. peak/hole) of 0.270/−0.355 e Å^{-3}. Full crystallographic details, excluding structure factors, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Research (S)*, 1998, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 423/25.

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