Synthesis of Benz[*b*]acridine-6,11,12-triones

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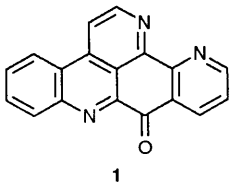
Condensation of 2-lithio-1-methyl-4-quinolone with methyl 2-(chloroformyl)benzoate gives 5-methylbenz[*b*]acridine-6,11-12-trione **3**; addition of the anion of methyl 2-(1,3-dithian-2-yl)-benzoate to 1-methoxycarbonyl-4-quinolone gives 5,5a-dihydro-11-hydroxy-5-methoxycarbonyl-12-oxaspiro{benz[*b*]acridine-6,2′(1′,3′-dithiane)} **7**.

Recently, we have shown how regioselective lithiation of 1-methyl-4-quinolone allows the introduction of substituents at the 2-position of the heterocycle.[1] We have also demonstrated the tandem nucleophilic addition–electrophilic trapping of conjugated enones by reaction with the anion of methyl 2-(1,3-dithian-2-yl)benzoate.[2] We describe here how each of these methodologies can be used in the construction of polycyclic structures similar to those found in sea alkaloids such as ascididemine, **1**.[3]

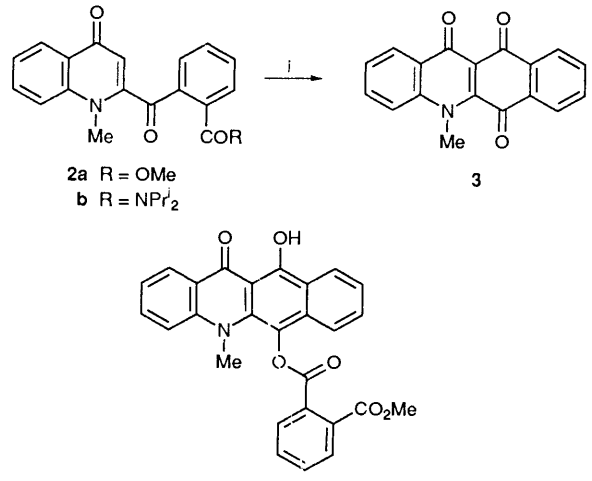


1

Reaction of 2-lithio-1-methyl-4-quinolone, prepared by lithiation using an excess of lithium diisopropylamide (LDA), with methyl 2-(chloroformyl)benzoate gave a mixture of products. An inseparable mixture of the expected keto ester **2a** with keto amide **2b**, formed by reaction of the ester group with excess LDA, was obtained along with tetracyclic quinone **3**, in yields of *ca.* 50 and 10% respectively. When a larger excess of LDA was used, a small amount of phenolic ester **4** was isolated, presumably resulting from a reduction of quinone **3** followed by acylation. Treatment of the mixture of the keto ester and the keto amide with hot concentrated sulfuric acid brought about ring closure and the formation of quinone **3** (Scheme 1), *via* what must be an acid-catalysed intramolecular electrophilic acylation of the quinolone 3-position.

We interpret the production of **3**, directly from reaction of the lithiated quinolone with methyl 2-(chloroformyl)benzoate, as involving a second lithiation, at C-3, probably assisted[4] as shown in Scheme 2, followed by intramolecular acylation.

With the idea that quinones of the type **3**, but with an appropriately placed nitrogen in ring E, could be later intermediates for a synthesis of ascididemine, we went on to examine the reaction of the lithiated quinoline with methyl 3-(chlorformyl)pyridine-2-carboxylate, which produced ketone **5**.



2a R = OMe
b R = NPr^i_2

3

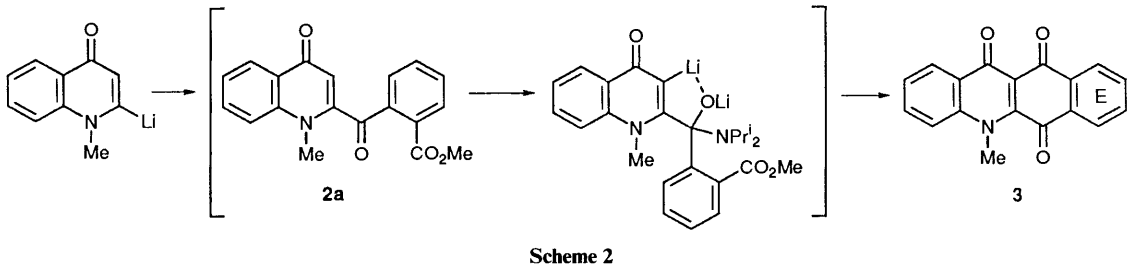
4

Scheme 1 *Reagent:* i, hot conc. H_2SO_4

Unfortunately, conditions such as hot sulfuric, hot polyphosphoric and hot trifluoroacetic acid did not bring about ring closure of this ester: this failure must be associated with the presence, in this substrate, of a basic pyridine nitrogen.

Turning to the prospect that 1-methyl-4-quinolone, in reacting as an enone,[5] might be susceptible to development into a tetracyclic system, *via* a tandem process, we attempted its reaction with the anion of methyl 2-(1,3-dithian-2-yl)benzoate: no product of the desired type could be obtained.[5,6] Arguing that a reduction in the aromatic character of the quinolone heterocyclic ring would make it more enone-like, 4-quinolone was converted into its 1-methoxycarbonyl derivative, **6**, and we were delighted to find that this substrate did indeed undergo a tandem addition with the formation of the tetracyclic substance, **7** (Scheme 3), in which there are two masked carbonyl groups, differentiated for subsequent manipulation.

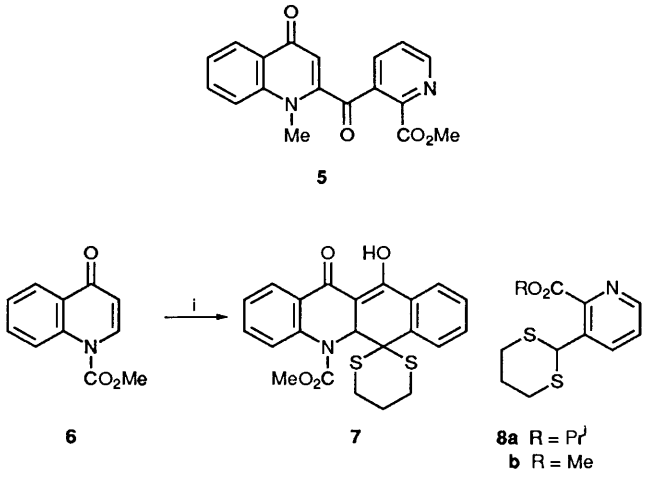
Extrapolation of this idea to a compound suitable for elaboration into the alkaloid required the synthesis of a dithiane, **8** (R = Pr^i), this was achieved using the known[7] isopropyl 3-formylpyridine-2-carboxylate. Unfortunately, no



2a

3

Scheme 2



Scheme 3 *Reagents:* i, methyl 2-(1,3-dithian-2-yl)benzoate, LDA

conditions could be found for the comparable reaction of this dithiane with the quinolone **6**. To ensure that this was not simply a question of steric impediment, the isopropyl ester was transformed into the methyl ester, but again no reaction was observed. The additional anion stabilisation attributable to the pyridine ring, even though the side-chain carbanion is located only at its 3-position, must be sufficient to tip the balance and lower reactivity too much. We found earlier that dithiane carbanions which are too stabilised will not add to 1-methyl-4-quinolone.[5]

Experimental

5-Methylbenz[b]*acridine-6,11,12-trione* **3** *and 11-Hydroxy-5-methyl-6-(2-methoxycarbonylbenzoyloxy)benz*[b]*acridin-12-one* **4**.—A solution 1-methyl-4-quinolone[1] (384 mg, 2.48 mmol) in dry THF (100 cm^3) was added slowly to a cooled (−78 °C) solution of LDA (5 mmol) in dry THF (80 cm^3). The mixture was stirred for 30 min at −78 °C under nitrogen and then a solution of methyl 2-(chloroformyl)benzoate (992 mg, 5 mmol) in dry THF (5 cm^3) was added. The reaction mixture was maintained at −78 °C for 1 h and then at room temperature for 3 h. The organic solvent was removed under reduced pressure, water was added to the residue and then the aqueous solution was extracted with chloroform. The organic solution was washed several times with dilute aqueous sodium hydroxide and after that was dried and evaporated to give a solid residue which was purified by column chromatography over silica. Elution with a gradient of toluene–chloroform (2:8) ⟶ chloroform, gave a mixture of *ester* and *amide*, **2a** and **2b** (371 mg, *ca.* 40%) and with chloroform ⟶ chloroform–methanol (9:1), *trione* **3** (65 mg, 10%) was obtained. Attempts at separation of **2a** and **2b** by further column chromatography or crystallisation were unsuccessful. The mixture of **2a** and **2b** (371 mg) was stirred with conc. sulfuric acid (15 cm^3) at 170 °C for 2 h then cooled to room temperature, poured into crushed ice, basified with potassium carbonate and then extracted with chloroform. The organic solution was dried and evaporated to give an orange solid identified as **3** (230 mg, 41%) (Found: M, 289.0745. $C_{18}H_{11}NO_3$ requires *M*, 289.0739).

Starting from the quinolone (2.0 mmol) in THF (100 cm^3), LDA (7.5 mmol) in THF (80 cm^3) and the acid chloride (2.8 mmol), the above procedure was followed until after the addition of acid chloride when the dark red solution was stirred for 1 h at −78 °C and then for 18 h at room temperature. Comparable work-up and purification by column chromatography, eluting with a gradient of hexane–$CHCl_3$ (3:7) ⟶ $CHCl_3$, gave *benz*[b]*acridin-12-one* **4** (75 mg) (Found: M, 453.1221. $C_{27}H_{19}NO_6$ requires *M*, 453.1213). Elution with a gradient, $CHCl_3$ ⟶ $CHCl_3$–MeOH (8:2), then gave **3** (267 mg, 45%).

2-Methoxycarbonyl-3-pyridyl 1-Methyl-4-oxo-2-quinolyl Ketone **5**.—A solution of 1-methyl-4-quinolone (235 mg, 1.47 mmol) in dry THF (60 cm^3) was added slowly to a cooled (−78 °C) solution of LDA (3.7 mmol) in dry THF (50 cm^3). The mixture was stirred for 30 min at −78 °C under nitrogen and then a solution of methyl 3-(chloroformyl)pyridine-2-carboxylate (575 mg, 2.88 mmol) in dry THF (5 cm^3) was added. The reaction mixture was maintained at −78 °C for 1 h and then at room temperature for 2 h. The organic solvent was removed and the residue was purified by column chromatography over silica. On elution with chloroform, *ketone* **5** (95 mg, 20%) was isolated (Found: M, 322.0946. $C_{18}H_{14}N_2O_4$ requires *M*, 322.0954).

1-Methoxycarbonyl-4-quinolone **6**.—A solution of 4-quinolone (1 g, 6.9 mmol) in dry THF (20 cm^3) was added to a cooled (−78 °C) suspension of NaH (330 mg, 14 mmol) in dry THF (20 cm^3) under nitrogen. The mixture was stirred for 30 min at −78 °C and was then allowed to warm to room temperature, stirred for an additional 30 min and then cooled to −78 °C. Methyl chloroformate (1 cm^3, 13.8 mmol) was added to the reaction mixture which was then stirred 30 min at −78 °C and then 4 h at room temperature. The organic solvent was removed and the residue was purified by flash column chromatography over silica. Elution by CH_2Cl_2–MeOH 9:1 gave *quinolone* **6** (1.2 g, 85%), m.p. 60–61 °C.

5,5a-Dihydro-11-hydroxy-5-methoxycarbonyl-12-oxaspiro-{benz[b]*acridine-5,2′-(1′,3′-dithiane)}* **7**.—A solution of methyl 2-(1,3-dithian-2-yl)benzoate[5] (126 mg, 0.49 mmol) in dry THF (10 cm^3) was added to a cooled (−78 °C) solution of LDA (0.49 mmol) in dry THF (10 cm^3) under nitrogen; the reaction solution became red. The solution was stirred for 30 min at this temperature and after this time a solution of 1-methoxycarbonyl-4-quinolone (100.7 mg, 0.49 mmol) in dry THF (10 cm^3) was added. The reaction mixture was stirred at −78 °C during 3 h and then for 18 h at room temp. The solvent was removed under reduced pressure, aqueous ammonium chloride was added to the residue and the solution was extracted with diethyl ether. The organic layer was washed with brine, dried, and evaporated to give a residue (158 mg) which was purified by flash chromatography on silica using, as eluent, $CHCl_3$–MeOH (9:1). The first fractions gave *dihydrobenz*[b]*acridin-12-one* **7** (104 mg, 64%) (Found: C, 81.2; H, 5.9; N, 4.3. $C_{22}H_{19}NO_4S_2$ requires C, 81.20; H, 5.88; N, 4.30%). Later fractions gave 1-methoxycarbonyl-4-quinolone, **6** (23 mg).

Isopropyl 3-(1,3-Dithian-2-yl)pyridine-2-carboxylate **8a**.—To a mixture of isopropyl 3-formylpyridine-2-carboxylate[6] (0.5 g, 2.6 mmol) and $SOCl_2$–SiO_2[8] (0.5 g) in dry benzene (40 cm^3) was added propane-1,3-dithiol (0.3 cm^3, 3 mmol) and the mixture was stirred and refluxed during 24 h with azeotropic water removal. The silica gel was filtered off and washed with diethyl ether. The combined organic solutions were washed with 5% aqueous sodium hydroxide, dried and evaporated to give *dithiane* **8a** (40 mg, 54%), m.p. 64–66 °C (Found: C, 55.3; H, 6.2; N, 4.9. $C_{13}H_{17}NO_2S_2$ requires C, 55.09; H, 6.04; N, 4.94%).

Methyl 3-(1,3-Dithian-2-yl)pyridine-2-carboxylate **8b**.—A solution of **8a** (85 mg, 0.3 mmol) in dry MeOH (25 cm^3) saturated with HCl was stirred at reflux temperature for 16 h. The solvent was removed at reduced pressure. The residue was basified with 5% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic solution was dried and evaporated to give a residue

which was purified by flash chromatography on silica using, as eluent, $CHCl_3$–MeOH (9:1). The first fractions gave *dithiane* **8b** (35 mg, 45%).

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