PERKIN 1

Synthesis of a thiophene analogue of kuanoniamine A

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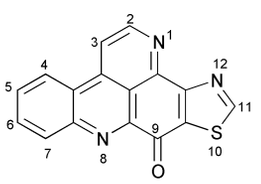
Synthesis of 9-methoxycarbonyl-7*H*-[1]benzothieno[4,5,6-*ij*][2,7]naphthyridin-7-one (**3**)—an analogue of kuanoniamine A (**1**)—*via* hetero Diels–Alder reaction of crotonaldehyde *N,N*-dimethylhydrazone with 2-methoxycarbonylbenzo[*b*]thiophene-4,7-dione and subsequent annelation, is described. The Diels–Alder reaction produced only the adduct with the desired regiochemistry, the structure of which was verified by 2D-NMR experiments.

Introduction

Kuanoniamine A (**1**)[1] is the simplest member of a group of marine alkaloids—pyrido[4,3,2-*mn*]thiazolo[4,5-*b*]acridines—which show strong antitumor activity *in vivo* and *in vitro*. They also exhibit immunosuppressive and antiviral properties.[2] In our efforts to synthesize analogues of kuanoniamine A, we have previously prepared the compound **2**.[3,4] We now report some reactions of the 4,7-dioxobenzo[*b*]thiophene **4b** and synthesis of a thiophene analogue **3** of kuanoniamine A.



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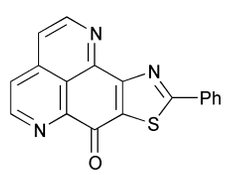

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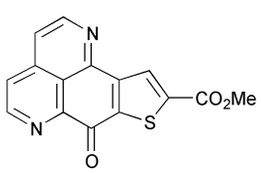

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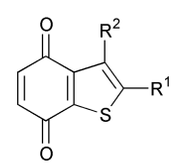
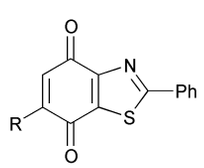
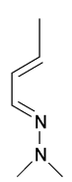


4a $R^1 = R^2 = H$
4b $R^1 = CO_2Me$, $R^2 = H$
4c $R^1 = CO_2Me$, $R^2 = Me$



5a R = H
5b R = Br



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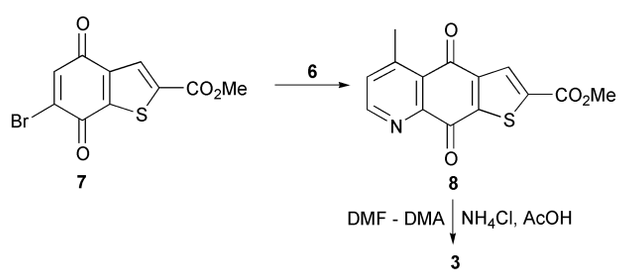
Results and discussion

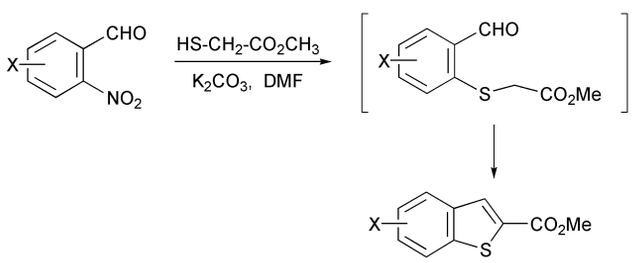
Synthesis of compound **2** involved hetero Diels–Alder reaction of 6-bromo-4,7-dioxo-2-phenylbenzothiazole (**5b**) with crotonaldehyde *N,N*-dimethylhydrazone **6** and subsequent treatment of the resultant oxidised adduct with DMF–DMA followed by ammonium chloride–HOAc.[3] Our synthesis of the thiophene analogue **3**, then, sought to utilize the pathway shown in Scheme 1. The desired dienophile **7** would be prepared by oxidative demethylation of 6-bromo-2-methoxycarbonyl-4,7-dimethoxybenzo[*b*]thiophene.



7 **8** **3**

Scheme 1

Benzo[*b*]thiophenes may be prepared by construction of a benzene ring on to a thiophene system.[5] More often, however, the thiophene ring is constructed on to a benzene ring, and this approach frequently involves thiophenols or their derivatives. The pathway shown in Scheme 2 is a facile, one-step synthesis of methyl benzo[*b*]thiophene-2-carboxylates reported by Beck.[6] Valderrama and Valderrama[7] optimised this method—which is thought to involve displacement of the nitro group by the thiol anion and subsequent aldol condensation—for the synthesis of 4,7-dimethoxybenzo[*b*]thiophenes. The required 2,5-dimethoxy-6-nitrobenzaldehyde is obtainable by nitration (HNO_3) of the readily available 2,5-dimethoxybenzaldehyde.[8] This pathway seemed to be the most straightforward.



Scheme 2

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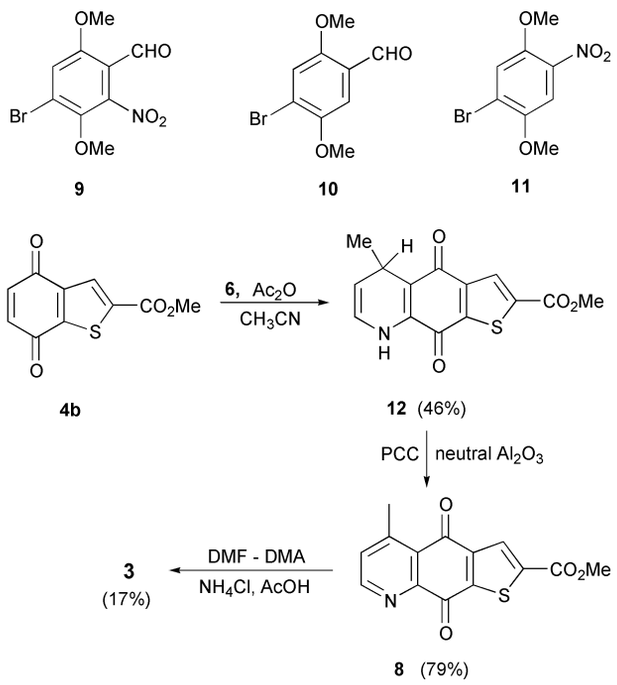
Recognizing that bromination of 2-methoxycarbonyl-4,7-dimethoxybenzo[*b*]thiophene was likely to give a mixture of products, we sought to prepare compound **9** and then attempt thiophene ring formation as shown in Scheme 2. We were, however, unable to prepare **9** by bromination of 2-nitro-3,6-dimethoxybenzaldehyde, and nitration of 4-bromo-2,5-dimethoxybenzaldehyde **10**[9] yielded only 4-bromo-2,5-dimethoxynitrobenzene **11**—the product of *ipso*-nitration. We therefore carried out our sequence as shown in Scheme 3, using the 4,7-dioxo-2-methoxycarbonylbenzo[*b*]thiophene **4b**.[7]

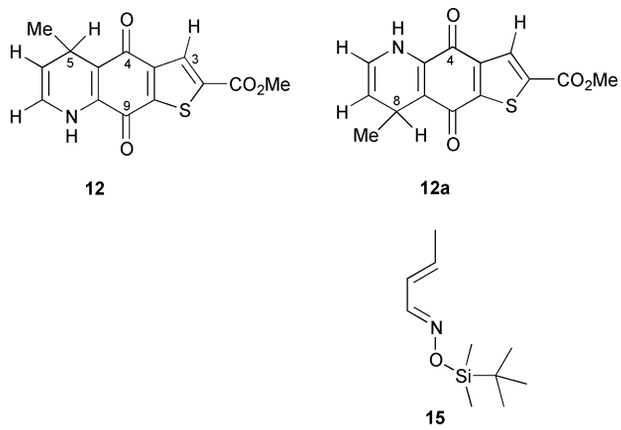


Scheme 3

Interestingly, hetero Diels–Alder reaction of **4b** with crotonaldehyde *N,N*-dimethylhydrazone (**6**) yielded not four products (as in the case of the thiazolo compound **5a**)[3] but two. One of these was a red crystalline compound (23% yield) which we identified as 2-methoxycarbonyl-5-(*N*,*N*-dimethylamino)-4,7-dioxobenzo[*b*]thiophene[10]—the product of addition of dimethylamine to the starting quinone. The other product, a navy blue crystalline compound, was identified as the novel Diels–Alder adduct **12** (19%). Proton magnetic resonance (PMR) data of this compound showed the C-5 methyl group resonating as a doublet at δ 1.17 and the proton at C-5 as a doublet of quartets at δ 3.72. There were also two peaks in the ^{13}C NMR spectrum upfield of δ 27. Together, this confirmed that the adduct was not the fully aromatised product.

Assignment of the regiochemistry of adduct **12** was tentatively based on the report by Valderrama *et al.*[10] They studied hetero Diels–Alder reactions of benzo[*b*]thiophene-4,7-dione **4a** and 2-methoxycarbonyl-3-methylbenzo[*b*]thiophene-4,7-dione **4c** with dienes of type **6** and, based on HOMO–LUMO predictions, reported formation of 5,8-dihydrothieno[3,2-*g*]-quinoline-4,9-diones (analogous to **12**). We confirmed the regiochemical assignment of compound **12** by NMR studies.

The 2D-NMR experiments (HMBC, 500 MHz) with our Diels–Alder adduct showed weak 4-bond coupling between the proton at C-3 (δ 8.09, s) and the carbonyl at δ 175.46, and stronger 3-bond coupling between this proton and the carbonyl at δ 179.48. This marked the carbonyl carbon at position-4 as that resonating at δ 179.48. The proton resonating as a doublet of quartets at δ 3.72 also showed strong 3-bond coupling with this carbonyl carbon, thus ascertaining that this proton was at position-5 as in **12** and not in position-8 as in **12a**. The COSY and HSQC spectra also confirmed the regioisomeric assignment. Diels–Alder reaction had therefore yielded the desired compound **12**, but only in 19% yield.

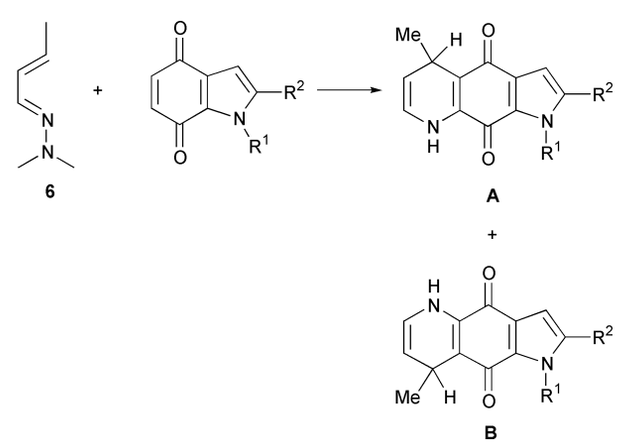


In our efforts to improve the yield of compound **12**, we tried the Diels–Alder reaction using 4-methyl-1-(*tert*-butyldimethylsilyloxy)-1-azabuta-1,3-diene (**15**). This would expel a non-nucleophilic moiety after addition, which would not attack the starting quinone, and thus should result in improved yield. When dienophile **4b** was treated with diene **15**, however, there was no reaction.

Lewis acid catalysis of the Diels–Alder reaction was next attempted. Reaction of **4b** with azadiene **6** in the presence of aluminium chloride, resulted in no increase in product yield. There was, however, marked improvement when aluminium chloride was replaced by acetic anhydride.[11] Adduct yield increased to 46% (*cf.* 19%), and there was no evidence of any 2-methoxycarbonyl-5-(*N*,*N*-dimethylamino)-4,7-dioxobenzo[*b*]-thiophene in the reaction mixture.

With compound **12** in hand, oxidation to the thienoquinoline quinone **8** proceeded very smoothly (79%) using PCC on neutral alumina.[12] Treatment of **8** with DMF–DMA followed by NH_4Cl and acetic acid then produced the desired kuanoniamine analogue **3** in 17% yield.

In a study of hetero Diels–Alder reactions of diene **6** with indoloquinones (Scheme 4),[13] it was reported that the regio-

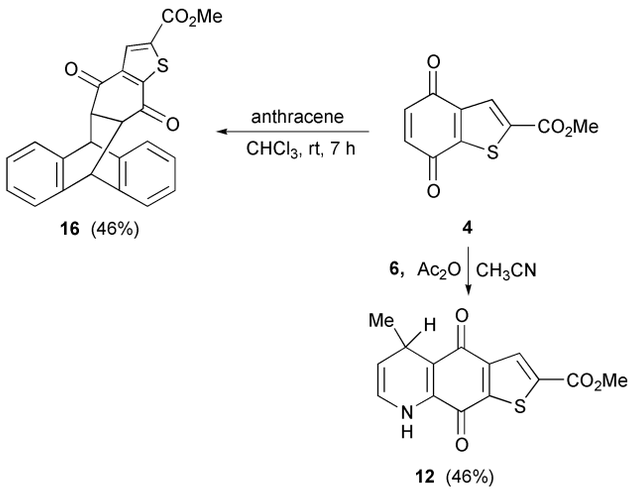


Scheme 4

chemistry of the reaction was governed by the nature of substituents R^1 on the nitrogen atom and R^2 on the carbon atom at position-2. It was found that unsubstituted indoloquinones afforded the 5-methyl-5,8-dihydro-1*H*-pyrrolo[3,2-*g*]-quinoline-4,9-dione **A** as the major product, but when R^1 or R^2 were electron-withdrawing groups, the 8-methyl-5,8-dihydro-1*H*-pyrrolo[2,3-*g*]quinoline-4,9-dione **B** predominated. Our dienophile **4b**, with a methoxycarbonyl group at position-2, behaved differently from its corresponding indoloquinone.

It is also interesting to note that hetero Diels–Alder reactions of dioxobenzothiazole **5a** with anthracene and with diene **6**

produced fully aromatised Diels–Alder adducts[3] whereas similar reactions with 2-methoxycarbonyl-4,7-dioxobenzo-[*b*]thiophene **4b** as dienophile always yielded the incompletely oxidised product (Scheme 5). This seems to indicate that the



Scheme 5

oxidation potential of dioxobenzothiazole **5a** is greater than that of compound **4b**. We will continue in our studies of these compounds.

Experimental

General

All mps are uncorrected. IR spectra were obtained on a Perkin Elmer 735B model or a Perkin Elmer 1600 FT-IR spectrometer and are for KBr discs. Unless otherwise stated, NMR spectra were run on a Bruker 200 MHz spectrometer and were determined in $CDCl_3$ solution. Resonances are reported in δ units downfield from TMS; *J* values are given in Hz. Elemental analyses were carried out by MEDAC Ltd., Egham, Surrey, UK.

5-Methyl-2-methoxycarbonyl-5,8-dihydrothieno[3,2-*g*]quinoline-4,9-dione (12)

To a solution of 2-methoxycarbonylbenzo[*b*]thiophene-4,7-dione **4b**[7] (300 mg, 1.35 mmol) in dry acetonitrile (45 mL), was added acetic anhydride (325 mg, 3.2 mmol) followed by a solution of crotonaldehyde *N,N*-dimethylhydrazone (230 mg, 2 mmol) in dry acetonitrile (5 mL). The resultant yellow solution was stirred for 3 hours at room temperature. (After about 30 minutes the reaction mixture became light blue in colour, and darkened as the reaction progressed.) The solution was concentrated and recrystallised from methanol to give **12** as a navy blue solid (180 mg, 46%), mp 142–145 °C. MS, *m*/*z* (relative intensity) 289 (33), 274 (100), 256 (62). HRMS calcd. for $C_{14}H_{11}NO_4S$: 289.0409; found: 289.0421. ν_{max}/cm^{-1} 1750, 1650; δ_H (500 MHz) 1.17 (3H, d, *J* 6.5, 5-CH_3), 3.72 (1H, dq, *J* 5 and 1.5, 5-H), 3.95 (3H, s, -$COOCH_3$), 4.98 (1H, dq, *J* 5 and 1.5, 6-H), 6.15 (1H, dd, *J* 7.5 and 3, 7-H), 6.76 (1H, br, -NH), 8.09 (1H, s, 3-H); δ_C 24.14, 25.79, 52.99, 109.95, 114.19, 122.47, 131.03, 140.19, 140.83, 141.78, 143.25, 161.55, 175.46, 179.48.

5-Methyl-2-methoxycarbonylthieno[3,2-*g*]quinoline-4,9-dione (8)

To a solution of **12** (100 mg, 34.6 mmol) in dichloromethane (20 mL) was added a mixture of PCC (150 mg, 0.7 mmol) on neutral alumina (1.83 g). This mixture was stirred at room temperature for three hours and then filtered and concentrated. The orange–red crystals were recrystallised from EtOAc to yield **8** (80 mg, 79%), mp 232–235 °C. MS, *m*/*z* (relative intensity) 287 (62), 256 (100), 228 (89). HRMS calcd. for $C_{14}H_9NO_4S$: 287.0252; found: 287.0274. ν_{max}/cm^{-1} 1736, 1718, 1679; δ_H 2.95 (3H, s, 5-CH_3), 4.00 (3H, s, $COOCH_3$), 7.50 (1H, d, *J* 5, 6-H), 8.28 (1H, s, 3-H), 8.90 (1H, d, *J* 5, 7-H); δ_C 22.61, 53.01, 129.51, 131.21, 131.31, 141.26, 142.80, 146.95, 150.31, 151.84, 152.83, 161.11, 176.31, 180.14.

Analogue 3

A solution of **8** (100 mg, 0.35 mmol) in dry DMF (6 mL) was heated at 100 °C for 30 minutes under nitrogen. To this solution DMF–DMA (0.39 mL) was added and the solution was stirred at 120 °C for 1 hour and then overnight at 90 °C. Ammonium chloride (1.9 g) and glacial acetic acid (6 mL) were then added and the solution was heated at 120 °C under nitrogen for 24 hours. The mixture was cooled and poured into water (45 mL) and extracted with dichloromethane (4 × 100 mL). The combined organic layer was then washed with saturated bicarbonate solution (2 × 50 mL), brine (2 × 50 mL), water (2 × 100 mL), then dried (Na_2SO_4) and concentrated. The mixture was purified by column chromatography (ethyl acetate–dichloromethane 1 : 1) to give **3**, (20 mg, 17%), mp 255–258 °C (Found: C, 60.54; H, 2.79; N, 9.19. Calc. for $C_{15}H_8N_2O_3S$: C, 60.80; H, 2.72; N, 9.45%). ν_{max}/cm^{-1} 1715, 1657, 1302; δ_H 4.00 (3H, s, OCH_3), 7.75 (1H, d, *J* 6, 4-H), 7.95 (1H, d, *J* 6, 3-H), 8.68 (1H, s, 10-H), 8.88 (1H, d, *J* 6, 5-H), 9.15 (1H, d, *J* 6, 2-H); δ_C 53.02, 119.33, 119.80, 123.96, 130.44, 138.55, 141.80, 143.67, 144.51, 147.62, 148.49, 148.60, 161.73, 176.60.

The anthracene adduct 16

To a solution of quinone **4b** (200 mg, 110 mmol) in chloroform (5 mL) was added anthracene (197 mg, 110 mmol) with stirring. The solution was stirred at rt for 7 h and then was concentrated *in vacuo* to yield **16** as a brown crystalline solid (180 mg, 46%), mp 190 °C (CH_2Cl_2–EtOH) (Found: C, 72.26; H, 3.91. Calc. for $C_{24}H_{16}O_4S$: C, 71.99; H, 4.03%). ν_{max}/cm^{-1} 1731, 1670, 1526; δ_H 3.38 (2H, m), 3.90 (3H, s), 5.02 (2H, m), 6.95 (2H, m, ArH), 7.28 (4H, m, ArH), 7.48 (2H, m, ArH), 7.92 (1H, s, 3′-H); δ_C 49.10, 49.17, 51.43, 53.0, 76.36, 77.0, 77.63, 123.91, 124.59, 126.69, 130.67, 139.53, 141.40, 141.57, 141.67, 144.11, 150.61, 161.19, 191.34, 191.51.

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