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A novel synthesis of arcyriaflavin-A via an intramolecular sulfur extrusion reaction

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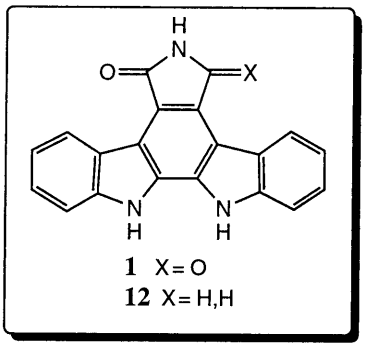
Abstract

2,3-[2′,2″-Biindolyl-3′,3″-dimercapto]maleimide, derived from 2,2′-biindolyl-3,3′-dithiete, dibromomaleimide and n-Bu_3P, undergoes an intramolecular reaction to provide arcyriaflavin-A. © 2000 Elsevier Science Ltd. All rights reserved.

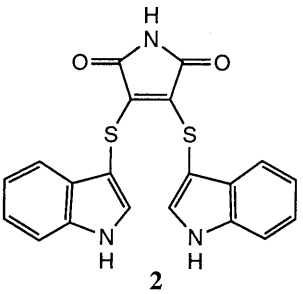
Keywords: alkaloids; Michael reactions; extrusion reactions.

Natural products incorporating the indolo[2,3-*a*]carbazole unit have been, since their isolation, the target of synthesis owing to their diverse and in some instances extraordinary biological properties, such as inhibition of protein kinase C, platelet aggregation and cytotoxic activity.[1,2] We had previously described[3] a synthesis of arcyriaflavin-A (**1**) in 10% yield, which consisted of heating a mixture of the bis-sulfide **2**, Hünig's base and $PdCl_2$ in PhCN at 135°C. It was proposed that the reaction proceeded via **3** to generate the alkaloid **1**.

We report[4] herein an independent preparation of **3**, its characterisation and show that is a useful intermediate for the synthesis of arcyriaflavin-A.



1 X=O
12 X=H,H



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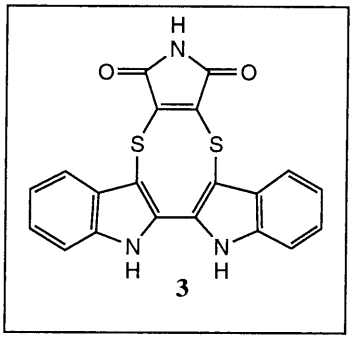

3

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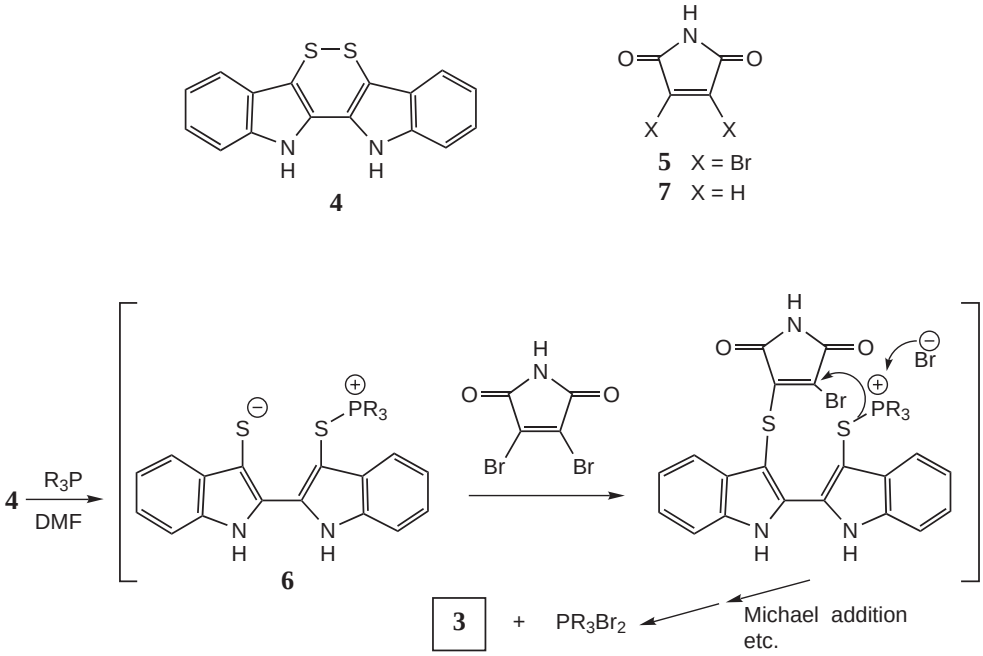
Thus, the known dithiete **4**[5] and n-Bu_3P in DMF, on reaction with dibromomaleimide (**5**), provided the light-sensitive and thermally rather unstable **3**[6] (47%) and 2,2′-bisindole (24%; reconvertible to **4** in 86% yield). It is believed that the transformation occurs via the intermediate **6**, generated by the cleavage of S–S bond in **4**, its subsequent Michael addition to **5** and thence to **3** (Scheme 1).

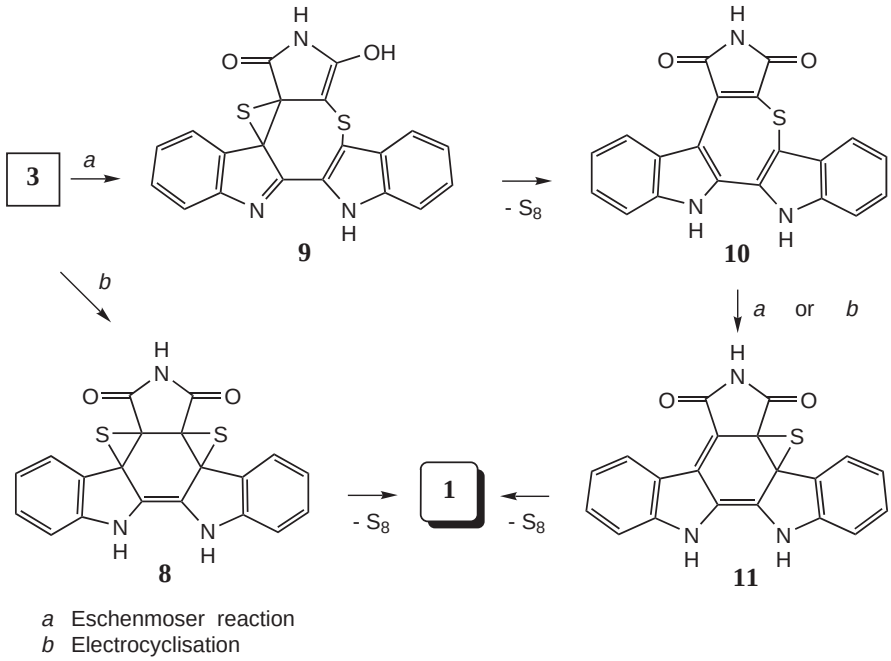


Scheme 1.

Unlike the sluggish intermolecular reaction[7] (sealed tube, 15 days, o-dichlorobenzene, 190°C) between the dithiete **4** and the imide **7**, the bis-sulfide **3** in o-dichlorobenzene required only 24 h (150°C) to provide **1** in 58% yield. Significantly, the same reaction when conducted in the presence of 1,2,2,5,5-pentamethylpiperidine (PMP) proceeded with an appreciable rate enhancement (3 h) and improved yield (68%; see Method A).[8] A similar reaction performed in toluene, under gentle reflux, permitted the isolation of pure **1** in 72% yield (a further 18% in a virtually pure state could be obtained from the toluene solution) (see Method B).[8] The substance thus secured was found to be identical in all respects (TLC, IR, ^{1}H NMR) to a sample of arcyriaflavin-A.

Whilst it is plausible that **1** is formed from **3** in a Diels–Alder process via **8** and subsequent loss of sulfur therefrom, the base-assisted transformation is very likely to involve an iterative Eschenmoser sulfur contraction reaction[9,10] through **9** (Scheme 2). An electrocyclisation of **10** to **11** is also a viable alternative. Facile extrusion of sulfur from near-aromatic bis-episulfide[11] or sulfide[12] has been reported.

Since **1** had been reduced[13,14] to staurosporinone **12**, the aglycone of the protein kinase C inhibitor staurosporine, this work constitutes, in a formal sense, a synthesis of **12**.[15]



Scheme 2.

Acknowledgements

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6. The dithiete **4** (200 mg) in dry DMF (4 ml), under an argon atmosphere, was treated with n-Bu_3P (186 μl) at 0°C. On completion of the reaction (ca. 10 min; TLC control), dibromomaleimide (173 mg) in dry DMF (4 ml) was added dropwise and the resulting mixture, protected from light, was kept at 0–6°C (3 days). It was then diluted with EtOAc, washed repeatedly with water, and dried (Na_2SO_4). Evaporation of the solvent furnished a red residue which on purification by column chromatography (SiO_2; n-hexane/ethyl ether, 2:8) afforded biindolyl (38 mg) and the bis-sulfide **3** (124 mg, 47%; 59% based on recovered biindolyl). Selected data for **3**: ^{1}H NMR (acetone-d_6) δ 7.27 (2H, t, J 7.3 Hz), 7.34 (2H, t, J 7.6 Hz), 7.59 (2H, d, J 8 Hz), 7.76 (2H, d, J 8 Hz), 10.08 (1H, s, exchangeable in D_2O), 11.49 (2H, exchangeable in D_2O); IR (KBr) ν_{max} 3337 (br), 1775, 1720 cm^{-1}. HRMS, M^+ (found) 389.0305. $C_{20}H_{11}N_3O_2S_2$ requires 389.0293.
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8. **Method A**—Compound **3** (38.3 mg) and 1,2,2,6,6-pentamethylpiperidine (17 μl) in *o*-dichlorobenzene (15 ml) was heated under an argon blanket, in an oil bath (2.5 h, 150°C). The solution at room temperature was diluted with ethyl acetate washed with dil. HCl (1N), then with water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure furnished a red residue which was crystallised from EtOAc–*n*-hexane to afford arcyriaflavin-A (19 mg). Purification of the residue from the mother-liquor by ptlc provided an additional quantity of **1** (2.8 mg). **Method B**—A toluene solution (14 ml) of **3** (50 mg) and 1,2,2,6,6-pentamethylpiperidine (46 μl) was refluxed under argon (13 h). The precipitate that formed on cooling the reaction mixture to 0°C was collected by decantion, suspended in EtOAc and stirred with dil. HCl (1N). The organic phase was washed with water and dried (Na_2SO_4). Evaporation of the solvent furnished a red solid (30 mg, 72% yield) which was found to be identical in all respects (TLC, ^{1}H NMR, IR) with a sample of arcyriaflavin-A.[3] A further quantity of virtually pure **1** (7.8 mg, 18%) could be secured by concentrating the original toluene solution to half its bulk and processing the precipitate obtained as above. The reaction in the absence of the base was found to take more than 2 days for completion.
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15. **NOTE ADDED IN PROOF:** In a very recent paper Schröth's group (cf. Schröth, W.; Spitzner, R.; Felicetti, M.; Wagner, C.; Bruhn, C. *Eur. J. Org. Chem.* **2000**, 3093, Ref. 26 cited therein) questioned structure **4**, assigned[5] to the material derived from 2,2′-bisindole and elemental sulfur. Instead it was suggested that it is dimer 5,6,17,18-tetrahydro[1,2,7,8]tetrathiacyclodecino[4,3-*b*:5,6-*b*′:10,9-*b*″:11,12-*b*‴]tetraindole. If it were to be true, then it is assumed that this substance can generate **6** and **4** in situ on reaction with *n*-Bu_3P in DMF.