Thionation of bisindole derivatives with P_4S_{10} or elemental sulfur

Tomasz Janosik,[a,b] Jan Bergman,*[a,b] Birgitta Stensland[c] and Claes Stålhandske[d]

[a] *Unit for Organic Chemistry, CNT, Department of Biosciences at Novum, Karolinska Institute, Novum Research Park, SE-141 57 Huddinge, Sweden*
[b] *Södertörn University College, SE-141 04 Huddinge, Sweden*
[c] *Preformulation and Biopharmaceutics, Solid State Analysis /SBBG B341:3, AstraZeneca PAR & D, SE-151 85 Södertälje, Sweden*
[d] *Department of Inorganic Chemistry 2, Chemical Center, Box 124, SE-221 00 Lund, Sweden*

Received (in Cambridge, UK) 29th October 2001, Accepted 27th November 2001
First published as an Advance Article on the web 4th January 2002

Thionation reactions of several bisindole derivatives using elemental sulfur or P_4S_{10} in pyridine have been studied, leading to formation of several novel structures. The reaction of indigo or isatin with P_4S_{10} gave the structurally new salt **10**, which could be transformed into the ethyl derivative **11**. The first example of a thionated indigo derivative, monothioindigo (**6**), was isolated in low yield from the thionation of isatin. Treatment of 3,3′-biindolyl with sulfur in hot DMF produced the previously known tetrasulfide **1**, which was studied by X-ray crystallography, thus also establishing that **1** is chiral in the crystalline state. The structure of an additional thionation product, the thienoindole derivative **34** was also solved using X-ray crystallography.

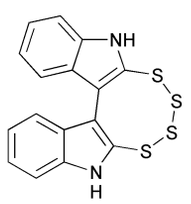
Introduction

Despite the recent interest in bisindoles and indolocarbazoles,[1] only a limited number of sulfur-containing analogues of compounds belonging to this class have been reported. One of the earliest examples is the tetrasulfide **1** with a direct 3,3′-linkage between the indole units, and **1** is preferably prepared *via* the reaction of indole with elemental sulfur in hot DMF.[2] Compound **1** has probably already been obtained in 1938 by Szperl, however, it was not assigned a definite structure.[3] Later studies have demonstrated that **1** is a potent antifungal agent with particularly strong activity against *Botrytis cinerea*.[4] More recently, **1** has been identified as a minor product during the preparation of pentathiepino[6,7-*b*]indole[5] (*vide infra*). All recent studies towards preparation of sulfur containing 2,2′-bisindoles such as the elusive **2**, or their indigoid valence tautomers have led to the formation of 12-membered ring compounds, *e.g.* **3**.[6]

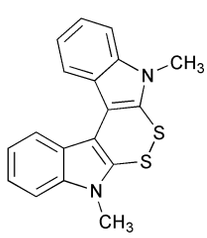
Results and discussion

Previously, we have reported the isolation of pentathiepino-[6,7-*b*]indole (**4**) from the treatment of isatin† (**5**) with P_4S_{10} in refluxing pyridine.[7] This reaction also gives rise to two other isolable products which can be separated using chromatography on silica gel. A deep blue compound assigned the structure **6** (*i.e.* monothioindigo)‡ has now been isolated in small amounts from the above mentioned reaction mixture. The structure was assigned on the basis of NMR, IR and MS data, and was further supported by elemental analysis as well as UV–VIS measurements. Monothioindigo (**6**) displayed a visible light absorption maximum in ethanol at λ_{max} = 582 nm, comparable with indigo (**7**), which exhibits a λ_{max} at 610 nm.[8] The isolation of **6** constitutes the first example of a thionated indigo derivative with an established structure.

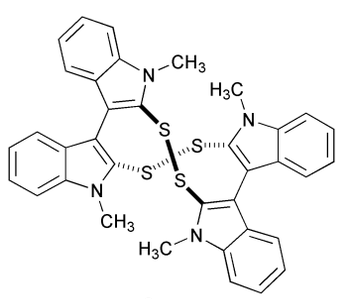
It has been argued[9] that the isomeric structure **9** might be produced *via* electrocyclization of its valence tautomer, dithio-



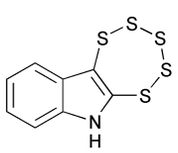
1



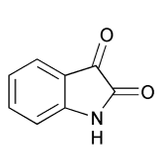
2



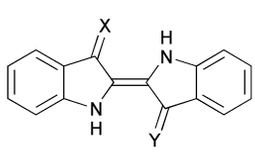
3



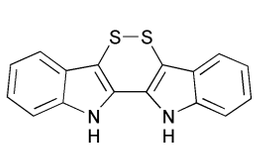
4



5



6 X = S, Y = O
7 X = Y = O
8 X = Y = S

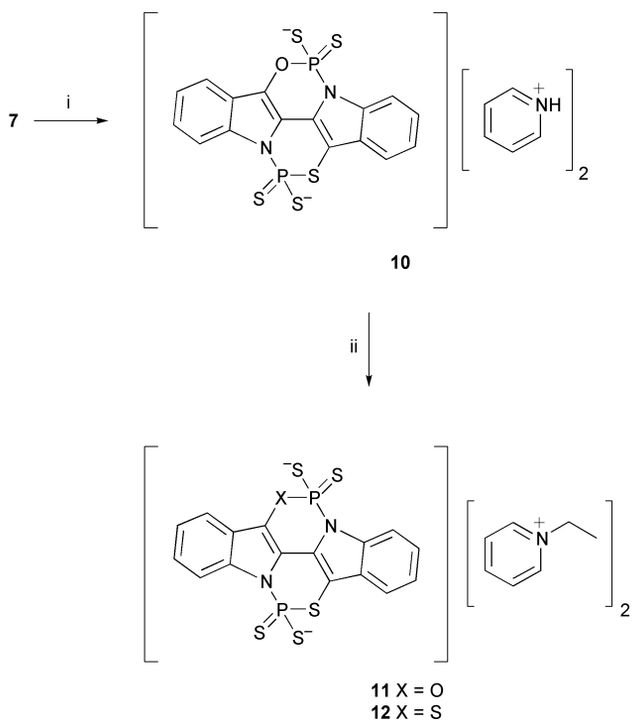


9

† The IUPAC name for isatin is indole-2,3-dione.
‡ The IUPAC name for indigo is $\Delta^{2,2'}$-biindoline-3,3′-dione.

 DOI: 10.1039/b109840c

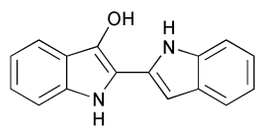
indigo (**8**). Therefore, indigo (**7**) was treated with P_4S_{10} in hot pyridine[10] and a dramatic change took place within 2 h (dark blue solid to yellow solid) which was unexpected, as it has been reported that indigo was unreactive under these very conditions.[11] The yellow solid **10** obtained could be purified by dissolution in weak aqueous sodium hydroxide solution and subsequent reprecipitation with acetic acid. The salt **10** could not be dissolved in any solvent suitable for NMR analysis except DMSO-d_6, which quickly caused extensive degradation. Therefore **10** was dissolved in the system D_2O–NaOD (obtained by dissolution of sodium metal in D_2O), which enabled recording of useful ^1H and ^{31}P NMR data. In the ^{31}P NMR spectrum two different signals at 85.5 and 96.3 ppm clearly indicate a non-symmetrical structure. A small impurity consisting of a fully thionated symmetrical product (*vide infra*) could also be distinguished in the ^{31}P NMR as a very weak single signal at 100.6 ppm. The sparingly soluble crude product **10** was also ethylated as indicated in Scheme 1 which provided a

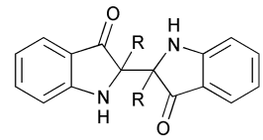


Scheme 1 *Reagents and conditions*: (i) P_4S_{10}, pyridine, reflux 3 h, 57%; (ii) Et_2SO_4, NaOH (aq), rt, 40%.

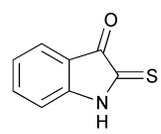
product more suitable for NMR analysis. The salt **11** displayed a COSY spectrum featuring three independent sets of aromatic signals originating from the two indole nuclei and the pyridine ring respectively. Long range ^1H–^{13}C correlations were detected between the pyridine ring and the signals of the ethyl group protons, showing that the ethylation had taken place on the pyridine nitrogen. The structure of **11** was also confirmed by X-ray crystallography albeit the quality of the crystals was poor due to a minor impurity consisting of the fully thionated product **12**, and the X-ray data supported the results obtained from the ^{31}P NMR data.

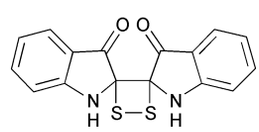
As discussed above, the readily prepared salt **10** can be dissolved in cold dilute aqueous sodium hydroxide. Prolonged interaction or heating of such solutions resulted in hydrolysis yielding indigo (**7**). Treatment of **10** with Raney nickel in hot dioxane produced **13**, which in air readily underwent oxidation leading to **14**.[12] To explain the formation of the unsymmetrical *O,S*-derivative rather than the symmetrical *S,S*-product when indigo (**5**) is treated with P_4S_{10} in pyridine, we suggest that monothioindigo (**6**) is initially formed and is quickly phosphorylated on the sulfur atom, thereby changing the character of the remaining carbonyl group and rendering it susceptible to the second phosphorylation reaction, possibly *via* an enol intermediate.

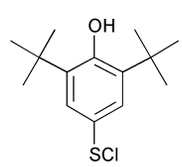

13

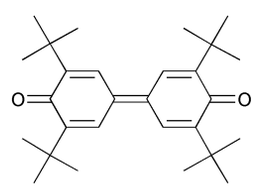

14 R = indol-2-yl

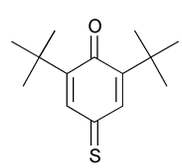
At this stage the main product from the reaction of isatin (**5**) and P_4S_{10} in pyridine was identified as **10**. Here initial formation of **15**, which is known to readily couple to yield indigo (**7**) and sulfur followed by thionation to **6**, accounts for this outcome.[13] It is likely that **15** will form indigo *via* the non-isolable intermediate **16**, which is expected to quickly extrude sulfur and thereby generate indigo. A closely related mechanism has been reported in the quinone series.[14] Thus **17** readily gave the diphenylquinone **18**, *via* the presumed intermediates **19** and **20**. An isomer of **19**, namely **21**, has recently been isolated and characterized.[15] Although we speculate that the pentathiepin

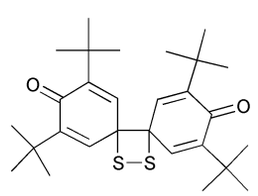

15

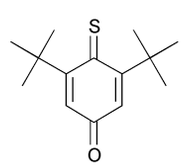

16

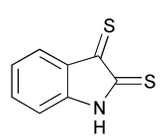

17

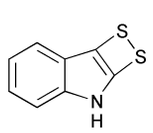

18

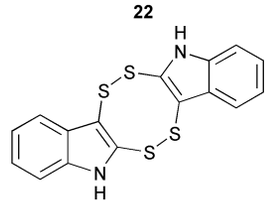

19

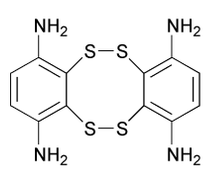

20

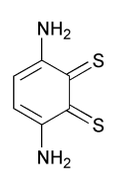

21


22


23

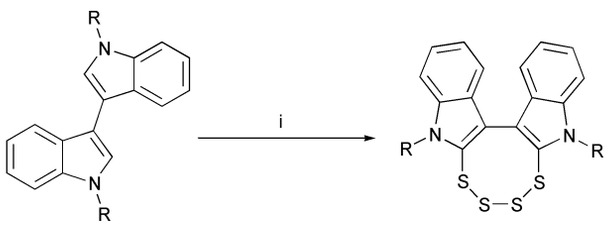

24


25


26

4[5,7] is formed *via* reaction of dithioisatin (**22**) or its ring tautomer **23** (*cf.* ref. 16) with sulfur, compounds of type **24** were never observed. This could be comparable with the reaction wherein **25** was a product and the dithione **26**, or rather a tautomer thereof, was an assumed intermediate.[17]

We now turned our attention towards 3,3′-biindolyl derivatives. Thionation of 3,3′-biindolyl[18] (**27**) with elemental sulfur in refluxing DMF produced a moderate yield of the tetrasulfide **1**, in contrast with an earlier observation.[2] In a similar transformation, *N,N′*-dimethyl-3,3′-biindolyl[19] (**28**) also reacted with sulfur in refluxing DMF to give the known dialkylated tetrasulfide **29**[2,5] in a modest yield (Scheme 2).

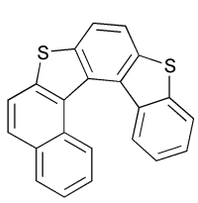


27 R = H
28 R = CH_3

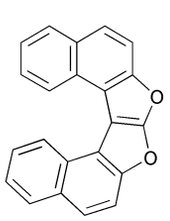
1 R = H (59%)
29 R = CH_3 (19%)

Scheme 2 *Reagents and conditions*: (i) S_8, DMF, reflux.

Many complications are usually encountered in structure determination of polysulfides, thus we have finally unambiguously confirmed the structure of **1** by X-ray crystallography (Fig. 1). Compound **1** is chiral in the crystalline state due to steric repulsion of the indole H-4 atoms. The tetrasulfide **1** crystallizes from DMF as a 1 : 1 solvate in the triclinic non-centrosymmetric space group *P*1 with two independent chiral molecules in the unit-cell. There are examples of closely related chiral heterohelicenes, *e.g.* **30**, which was obtained in optically active form by slow evaporation of a benzene solution of the racemic compound, whereas in solution, fairly quick racemization took place.[20] Recent examples of related studies include an annelated heptathiophene,[21] and several 7,8-dioxa[6]-helicenes of type **31**, which were demonstrated to have low inversion barriers, but nevertheless, chiral conformations could be observed in the solid state.[22]



30



31

In the past a number of workers have studied the thionation of benzil, whereby the dithione has never been isolated,[23] but rather the dimeric product **32** was observed. For this reason the readily available indole analogue **33**[24] of benzil was included in the study. However, treatment of **33** with P_4S_{10} in pyridine gave a complicated mixture from which a small yield of a crystalline compound could be isolated. The structure of the crystalline compound was determined by X-ray crystallography as the thienoindole derivative **34** (Fig. 2). Obviously the growing sulfur chains will eventually attack the adjoining indole ring.

Experimental

NMR spectra were recorded on a Bruker DPX 300 (300 MHz), a Varian Unity Plus (400 MHz) instrument, or a JEOL Eclipse 500 (500 MHz) spectrometer. The ^{31}P NMR spectra were measured with 85% H_3PO_4 as external standard. *J* values are given in Hz. IR spectra were recorded on a Perkin Elmer 1600

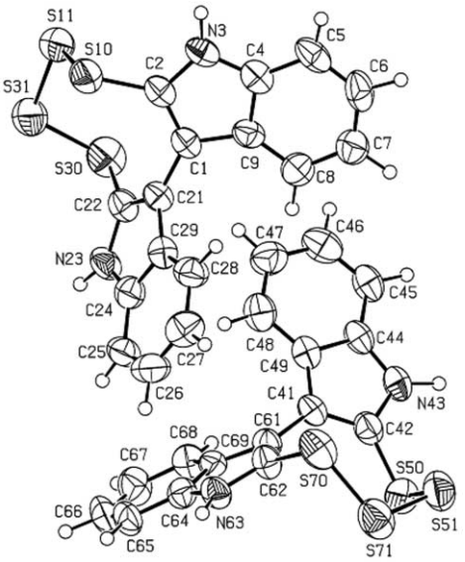


Fig. 1 The two independent molecules of **1** with adopted labelling scheme. The displacement ellipsoids of non-H atoms are drawn at 50% probability level and the H-atoms as spheres with arbitrary radius. The two DMF solvate molecules are excluded for clarity.

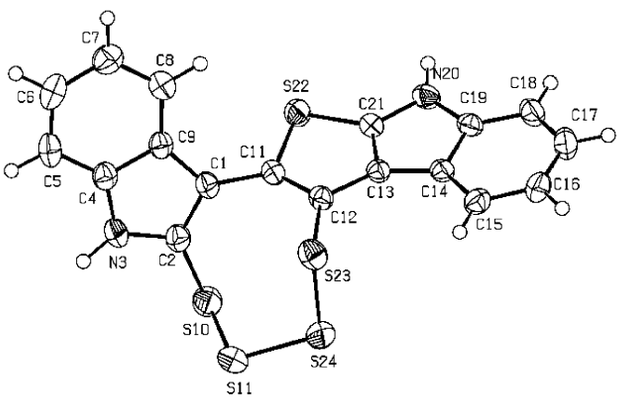
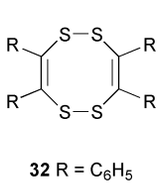
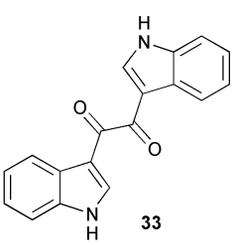


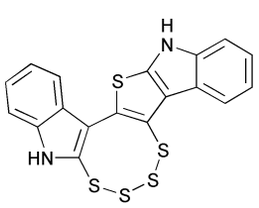
Fig. 2 Molecular structure of **34**, showing the atom labelling used in the crystal structure refinement. Displacement ellipsoids of non-H atoms are drawn at 50% probability level and H-atoms as spheres with arbitrary radius.



32 R = C_6H_5



33



34

FT-IR instrument. MS (ESI) spectra were obtained using a Perkin Elmer API 150 EX spectrometer. The elemental analysis was performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. High resolution mass spectra were performed by Sveriges Lantbruksuniversitet (SLU), Uppsala, Sweden, or E. Nilsson, University of Lund, Sweden. The UV–VIS spectrum was measured using a Pharmacia

Biotech Ultrospec 3000 spectrophotometer. Melting points were taken on a Reichert Kofler hot stage or a Büchi B-545 apparatus and are uncorrected. Chromatography was performed on Merck Silica Gel 60. Solvents were of analytical grade and were used as received.

5*H*,10*H*-[1,2,3,4]Tetrathiocino[5,6-*b*: 8,7-*b*′]diindole 1

3,3′-Biindolyl[18] **27** (320 mg, 1.38 mmol) was heated at reflux with sulfur (375 mg, 11.7 mmol) in DMF (5 mL) for 48 h. The mixture was allowed to cool and was poured into water containing 10–20% ethanol. The precipitate was collected, dried and subjected to chromatography using initially hexane, followed by 10–40% dichloromethane in hexane to yield **1** as a pale yellow solid (290 mg, 59%), mp (dichloromethane–hexane) 301–302 °C (lit.,[2] 305 °C); ν_{max} (KBr)/cm^{-1} 3375, 1396, 1339, 1290, 1222, 1168, 1144, 1128, 1005, 938, 751, 740; δ_H (300 MHz, DMSO-d_6) 7.06 (2H, ddd, *J* 8.0, 6.9, 1.0, ArH), 7.28 (2H, d, *J* 8.0, ArH), 7.31 (2H, ddd, *J* 8.3, 6.9, 1.1, ArH), 7.49 (2H, d, *J* 8.3, ArH), 12.13 (2H, s, NH); δ_C (100.6 MHz, DMSO-d_6) 112.1 (d), 119.3 (s), 120.1 (d), 120.2 (d), 124.5 (d), 124.9 (s), 126.9 (s), 136.2 (s); MS (EI) *m*/*z* 358 (M^+, 10%), 295 (22), 294 (M − S_2, 100), 262 (M − S_3, 30), 261 (30), 147 (24), 130 (23) [Found: HRMS (EI) *m*/*z* 357.9727. $C_{16}H_{10}N_2S_4$ requires *M*, 357.9727].

5,10-Dimethyl-5*H*,10*H*-[1,2,3,4]tetrathiocino[5,6-*b*:8,7-*b*′]-diindole 29

A mixture of *N*,*N*′-dimethyl-3,3′-biindolyl[19] **28** (260 mg, 1 mmol) and sulfur (188 mg, 5.9 mmol) in DMF (4 mL) was heated at reflux for 48 h. After cooling, the mixture was poured into water (25 mL). The precipitate formed was collected by filtration, dried, and subjected to chromatography, initially using hexane, followed by 10% dichloromethane in hexane, to yield 5,10-dimethyl-5*H*,10*H*-[1,2,3,4]tetrathiocino[5,6-*b*:8,7-*b*′]diindole **29** (73 mg, 19%) as a pale yellow solid. All data obtained were in agreement with those published previously.[2,5]

Reaction of isatin 5 with P_4S_{10} in pyridine

Isatin **5** (7.35 g, 0.05 mol) was added to a solution of P_4S_{10} (15 g, 0.033 mol) in pyridine (150 mL). After a period of reflux (2 h) the mixture was concentrated and water added. The obtained solid was washed with water and dried. Extraction of the solid with hot acetonitrile, followed by filtration and evaporation gave a residue that was purified by flash chromatography (dichloromethane) which gave pentathiepino[6,7-*b*]indole **4** (585 mg, 4%). Spectral data of this material were identical with those published previously.[5,7]

Further elution of a blue band with dichloromethane containing methanol (1%) gave monothioindigo **6** (160 mg, 1%) as a deep blue solid; mp (dichloromethane–methanol) 286–288 °C (Found: C, 69.15; H, 3.57; N, 9.86. $C_{16}H_{10}N_2OS$ requires C, 69.04; H, 3.62; N, 10.06%); ν_{max} (KBr)/cm^{-1} 3443, 3198, 1698, 1616, 1579, 1476, 1466, 1390, 1336, 1108, 1092, 993, 920, 747; δ_H (300 MHz, DMSO-d_6) 7.10–7.20 (3H, m, ArH), 7.32 (1H, ddd, *J* 7.6, 7.6, 1.2, ArH), 7.47 (1H, d, *J* 8.0, ArH), 7.63 (1H, ddd, *J* 7.6, 6.8, 1.2, ArH), 7.73 (1H, d, *J* 7.5, ArH), 8.96 (1H, d, *J* 8.0, ArH), 12.79 (1H, s, NH), 13.37 (1H, s, NH); δ_C (75.4 MHz, DMSO-d_6) 109.8 (d), 111.8 (s), 113.7 (d), 119.5 (s), 122.5 (d), 122.9 (d), 123.9 (s), 124.6 (d), 125.1 (d), 128.5 (d), 137.1 (d), 141.6 (s), 141.7 (s), 151.7 (s), 186.7 (s), 189.7 (s); UV–VIS λ_{max} 270, 375, 582 nm; MS (EI) *m*/*z* 279 (M^+ + 1, 20%), 278 (M^+, 100), 250 (58), 218 (33) [Found: HRMS (EI) *m*/*z* 278.0501. $C_{16}H_{10}N_2OS$ requires *M*, 278.0514].

The solid residue (not soluble in acetonitrile) was stirred with sodium hydroxide (aq. 4%, 300 mL) at 15 °C for 2 h. After filtration and acidification with acetic acid, the salt **10** (*vide infra*) was obtained (8.55 g, 58%).

Reaction of indigo 7 with P_4S_{10} in pyridine

Indigo **7** (5.24 g, 0.02 mol) was added to a solution of P_4S_{10} (8.88 g, 0.02 mol) in pyridine (75 mL) at reflux. After further reflux (3 h) the mixture was allowed to cool. The yellow solid was collected by filtration, washed with acetonitrile, then ethanol, and finally dried. Dissolution in sodium hydroxide solution (4%, 250 mL), stirring for 30 min, and finally acidification with acetic acid (to pH ≈ 4) afforded **10** (7.10 g, 57%) as a yellow solid; mp > 260 °C; ν_{max} (KBr)/cm^{-1} 3212 (w), 3147 (w), 3060 (w), 3006 (w), 2943 (w), 2785, 1632, 1606, 1536, 1478, 1432, 1327, 1217, 1188, 1056, 748, 734, 719, 681, 669, 576, 556. Due to exceedingly poor solubility in organic solvents, as well as rapid decomposition in DMSO-d_6, NMR data were recorded in a D_2O solution containing NaOD. The salt **10** (20 mg) was dissolved in a mixture prepared by dissolving sodium (6 mg) in D_2O (0.7 ml) containing DMSO-d_6 (25 mg). δ_H (500 MHz) 7.23–7.35 (9H, m, ArH), 7.47 (1H, d, *J* 7.8, ArH), 7.61 (1H, d, *J* 7.4, ArH), 7.75 (2H, dt, *J* 7.8, 1.4, ArH), 8.35 (1H, d, *J* 8.3, ArH), 8.39–8.41 (2H, m, ArH), 8.63 (1H, d, *J* 7.8, ArH); δ_P (202.5 MHz) 85.5, 96.3.

Ethylation of 10

Compound **10** (2.50 g, 4 mmol) was dissolved in aq. sodium hydroxide (4%, 100 mL), the resulting mixture was stirred at rt for 30 min, followed by addition of diethyl sulfate (3.0 mL, 23 mmol) which quickly gave a yellow precipitate. Stirring was continued for 2.5 h, the yellow salt **11** was collected, washed with water and dried. Further purification could be accomplished by recrystallization from DMF. Yield 1.10 g (40%); mp > 260 °C; ν_{max} (KBr)/cm^{-1} 3050 (w), 1632, 1480, 1423, 1228, 1215, 1157, 1053, 763, 754, 710, 694, 672, 573, 553; δ_H (300 MHz, DMSO-d_6) 1.52 (6H, t, *J* 7.3, 2 × CH_3), 4.60 (4H, q, *J* 7.3, 2 × CH_2), 7.12–7.18 (4H, m, ArH), 7.29–7.32 (1H, m, ArH), 7.46–7.49 (1H, m, ArH), 8.10–8.14 (4H, m, ArH), 8.38–8.41 (1H, m, ArH), 8.56 (2H, app. t, *J* 7.8, ArH), 8.71–8.76 (1H, m, ArH), 9.02 (2H, br d, *J* 5.5, ArH); δ_C (75.4 MHz, DMSO-d_6) 16.2, 56.3, 100.4 (d, J_{C-P} 4.2), 114.4, 115.4, 116.0, 117.3, 118.3 (d, J_{C-P} 9.0), 120.9, 121.2, 121.3 (d, J_{C-P} 5.0), 121.8, 122.4, 127.5 (d, J_{C-P} 9.8), 127.8 (dd, J_{C-P} 6.1, 2.7), 128.0, 132.0 (dd, J_{C-P} 12.6, 2.5), 136.3, 137.0 (d, J_{C-P} 4.4), 144.4, 145.2; δ_P (121.5 MHz, DMSO-d_6) 81.9, 93.9.

Reaction of 33 with P_4S_{10} in pyridine

The dione **33**[24] (2.88 g, 0.01 mol) was added to a solution of P_4S_{10} (8.0 g, 0.018 mol) in pyridine (100 mL). After a period of reflux (3 h) the mixture was concentrated and water added. The mixture of solids obtained was extracted with hot acetonitrile, followed by concentration of the extract, which gave yellow crystals of the thienoindole **34** (430 mg, 9.5%); mp (acetonitrile) > 260 °C (darkens > 235 °C); ν_{max} (KBr)/cm^{-1} 3393, 3374, 1478, 1434, 1381, 1242, 1131, 1010, 929, 871, 754, 742; δ_H (400 MHz, DMSO-d_6) 7.14–7.20 (2H, m, ArH), 7.28 (1H, ddd, *J* 8.0, 6.8, 1.2, ArH), 7.33 (1H, ddd, *J* 8.4, 7.2, 1.2, ArH), 7.48 (1H, d, *J* 8.4, ArH), 7.57 (1H, d, *J* 8.0, ArH), 7.61 (1H, d, *J* 8.0, ArH), 8.08 (1H, d, *J* 7.6, ArH), 11.85 (1H, br s, NH), 12.41 (1H, br s, NH); δ_C (100.6 MHz, DMSO-d_6) 112.1 (d), 112.2 (d), 118.0 (d), 118.1 (s), 119.5 (d), 119.6 (d), 120.1 (s), 121.1 (d), 121.2 (s), 122.6 (d), 123.4 (s), 124.8 (d), 127.3 (s), 127.5 (s), 135.4 (s), 135.7 (s), 140.0 (s), 141.0 (s); MS (ESI) *m*/*z* 413 [M − H]$^-$ [Found: HRMS (EI) *m*/*z* 413.9394. $C_{18}H_{10}N_2S_5$ requires *M*, 413.9447].

The mother liquor contained more of **34** as well as several other, presumably related compounds. However, this mixture has not been further studied.

X-Ray crystallography §

The X-ray data of the two structures **1** and **34** were collected at room temperature with an Enraf-Nonius k-CCD diffract-

§ CCDC reference numbers 173493 and 173494. See http://www.rsc.org/suppdata/p1/b1/b109840c/ for crystallographic files in .cif or other electronic format.

ometer[25] equipped with graphite monochromator and Mo-Kα radiation. The Denzo-SMN Software Package[26] was used for the unit-cell determinations and reduction of the data sets. Both structures were solved by direct methods and refined with full-matrix least squares based on F, taking advantage of the MaXus software package.[27,28] The non-H atoms were refined anisotropically whereas the H-atom positions were verified from Fourier electron density calculations and supplied with isotropic thermal displacement factors, U(iso) = 0.05 Å^2. No absorption corrections were applied.

Crystal data for 5*H*,10*H*-[1,2,3,4]tetrathiocino[5,6-*b*:8,7-*b*′]-diindole 1. $C_{16}H_{10}S_4N_2 \cdot C_3H_7NO$, M_r = 431.62, space group: triclinic, $P\bar{1}$ (No. 1). The unit-cell contains two independent molecules. Unit-cell parameters: a = 8.597(1), b = 10.120(1), c = 13.311(1) Å, α = 92.15(1), β = 101.98(1), γ = 114.11(1)°, V = 1024.3(2) Å^3, Z = 2. D_x = 1.400(1) g cm^{-3}, F(000) = 448. μ (Mo-Kα) = 4.78 cm^{-1}. Crystal dimensions 0.02 × 0.14 × 0.14 mm. A total of 3950 independent reflections [$F^2 > 4\sigma(F^2)$] was refined to give R = 0.038, R_w = 0.053 for 485 parameters ($w = 1/(\sigma^2 F_o^2 + (0.0300)F_o^2)$). $(\Delta/\sigma)_{max}$ = 0.0005, $\Delta\rho_{max}$ = 0.28 eÅ^{-3}, $\Delta\rho_{min}$ = −0.20 eÅ^{-3}, $\Delta\rho_{mean}$ = 0.04 eÅ^{-3}. GOF = 0.979. Absolute configuration: Flack's chirality parameter[29–31], x = −0.15(6) where x is close to zero for the correct chirality of the atom co-ordinate set, and close to one for the incorrect inverted chirality.

Crystal data for compound 34. $C_{18}H_{10}S_5N_2$, M_r = 414.62, space group: monoclinic, $P2_1/n$ (No. 14). Unit-cell parameters: a = 8.909(1), b = 15.535(1), c = 12.651(1) Å, β = 101.26(1)°, V = 1717.2(3) Å^3, Z = 4. D_x = 1.604(1) g cm^{-3}, F(000) = 848. μ(Mo-Kα) = 6.79 cm^{-1}. Crystal dimensions: 0.05 × 0.07 × 0.17 mm. 2214 independent reflections [$F^2 > 3\sigma(F^2)$] were refined to give R = 0.036, R_w = 0.036 for 226 parameters ($w = 1/(\sigma^2 F_o^2 + (0.0300)F_o^2)$). $(\Delta/\sigma)_{max}$ = 0.0004, $\Delta\rho_{max}$ = 0.25 eÅ^{-3}, $\Delta\rho_{min}$ = −0.25 eÅ^{-3}, $\Delta\rho_{mean}$ = 0.06 eÅ^{-3}. GOF = 1.409.

References

1 For reviews, see (*a*) G. W. Gribble and S. J. Berthel, in *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1993, vol. 12 p. 365; (*b*) M. Prudhomme, *Curr. Pharm. Des.*, 1997, **3**, 265; (*c*) U. Pindur, Y.-S. Kim and F. Mehrabani, *Curr. Med. Chem.*, 1999, **6**, 29; (*d*) J. Bergman, T. Janosik and N. Wahlström, *Adv. Heterocycl. Chem.*, 2001, **80**, 1.

2 W. Carpenter, M. S. Grant and H. R. Snyder, *J. Am. Chem. Soc.*, 1960, **82**, 2739.

3 L. Szperl, *Rocz. Chem.*, 1938, **18**, 804.

4 L. Montanari, F. Pavanetto and M. Mazza, *Farmaco, Ed. Sci.*, 1981, **36**, 856.

5 G. W. Rewcastle, T. Janosik and J. Bergman, *Tetrahedron*, 2001, **57**, 7185.

6 (*a*) R. Gompper, K. Hartmann and K. Polborn, *Tetrahedron Lett.*, 1994, **35**, 9195; (*b*) W. Schroth, E. Hintzsche, H. Viola, R. Winkler, H. Klose, R. Boese, R. Kempe and J. Sieler, *Chem. Ber.*, 1994, **127**, 401; (*c*) W. Schroth, M. Felicetti, E. Hintzsche, R. Spitzner and M. Pink, *Tetrahedron Lett.*, 1994, **35**, 1977; (*d*) W. Schroth, E. Hintzsche, M. Felicetti, R. Spitzner, J. Sieler and R. Kempe, *Angew. Chem.*, 1994, **106**, 808; (*e*) W. Schroth, R. Spitzner, M. Felicetti, C. Wagner and C. Bruhn, *Eur. J. Org. Chem.*, 2000, 3093 and references cited therein.

7 J. Bergman and C. Stålhandske, *Tetrahedron Lett.*, 1994, **35**, 5279.

8 W. Lüttke and M. Klessinger, *Chem. Ber.*, 1964, **97**, 2342.

9 (*a*) H. Sieghold, PhD thesis, Göttingen, 1973; (*b*) H. Sieghold and W. Lüttke, *Angew. Chem.*, 1975, **87**, 63.

10 (*a*) E. Fluck and H. Binder, *Z. Anorg. Allg. Chem.*, 1967, **354**, 113; (*b*) M. Meisel and H. Grunze, *Z. Anorg. Allg. Chem.*, 1968, **360**, 277.

11 H. Sieghold, PhD thesis, Göttingen, 1973, pp. 147–148.

12 J. Bergman and N. Eklund, *Chem. Scr.*, 1982, **19**, 193.

13 (*a*) T. Sandmeyer, *Z. Farben Text. Chem.*, 1903, **2**, 129; (*b*) L. Sander, *Chem. Ber.*, 1925, **58**, 820; (*c*) Geigy, *Ger. Pat.,* 1901, 131.934.

14 S. D. Pastor, *J. Org. Chem.*, 1984, **49**, 5260.

15 R. Suzuki, K. Matsumoto, H. Kurata and M. Oda, *Chem. Commun.*, 2000, 1357.

16 M. Breitenstein, R. Schulz and A. Schweig, *J. Org. Chem.*, 1982, **47**, 1979.

17 M. V. Lakshmikantham, M. S. Raasch, M. P. Cava, S. G. Bott and J. L. Atwood, *J. Org. Chem.*, 1987, **52**, 1874.

18 (*a*) J. Bergman, *Acta Chem. Scand.*, 1975, **25**, 1277; (*b*) U. Berens, J. M. Brown, J. Long and R. Selke, *Tetrahedron: Asymmetry*, 1996, **7**, 285.

19 E. Desarbre and J. Bergman, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2009.

20 (*a*) H. Wynberg and M. B. Groen, *J. Am. Chem. Soc.*, 1968, **90**, 5339; (*b*) M. B. Groen, H. Schadenberg and H. Wynberg, *J. Org. Chem.*, 1971, **36**, 2797.

21 A. Rajca, H. Wang, M. Pink and S. Rajca, *Angew. Chem., Int. Ed.*, 2000, **39**, 4481.

22 J. Eskildsen, F. C. Krebs, A. Faldt, P. Sommer-Larsen and K. Bechgaard, *J. Org. Chem.*, 2001, **66**, 200.

23 (*a*) G. N. Schrauzer and H. W. Finck, *Angew. Chem.*, 1964, **76**, 143; (*b*) W. Kusters and P. de Mayo, *J. Am. Chem. Soc.*, 1974, **96**, 3502.

24 J. Bergman and L. Venemalm, *Tetrahedron*, 1990, **46**, 6061.

25 B. V. Nonius, Kappa CCD Server Software., B. V. Nonius, Delft, The Netherlands, 2000.

26 Z. Otwinowski and W. Minor, *Denzo-SMN program Package. Processing of X-ray Diffraction Data Collected in Oscillation Mode. Methods in Enzymology*, 1998, **276**, 302; Z. Otwinowski and W. Minor, *Macromolecular Crystallography*, eds. C. W. Carter Jr and R. M. Sweet, Academic Press, Inc.

27 S. Mackay, C. Edwards, A. Henderson, C. Gilmore, N. Stewart, K. Shanklands, A. Donalds, MaXus program package, 1999. A state-of-the art computer program for solving, refining and publishing crystal structures from X-ray diffraction data, Chemistry Department, The University of Glasgow.

28 A. L. Speck, PLATON97, University of Utrecht, The Netherlands, 1997.

29 G. M. Sheldrick, SHELXL97, University of Göttingen, Germany.

30 H. D. Flack, *Acta Crystallogr., Sect. A Found Crystallogr.*, 1983, **39**, 876.

31 H. D. Flack, *J. Appl. Crystallogr.*, 2000, **33**, 1143.