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OXIDATIVE COUPLING OF INDOLINE-2-THIONE OR OXINDOLE: FORMATION OF CYCLIC AND ACYCLIC INDOLE TRIMERS

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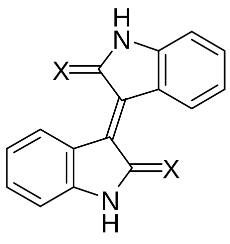
Abstract – Oxidation of indoline-2-thione using *p*-toluenesulfonyl azide produced a modest yield of the structurally novel cyclic sulfur containing indole trimer (**12**). In contrast, the oxidation of oxindole with iodine instead produced an acyclic trimeric indole derivative.

The questionable existence of dithioisoindigo (**1**) has been discussed over the years, and the conclusions reported in these investigations are often contradictory.[1–4] Thus, **1** has been reported by Bailey[1] as a minor yellow product originating from the reaction of indoline-2-thione (**2**) and *p*-toluenesulfonyl azide (in these experiments the interesting molecule (**3**) was claimed as an isolable intermediate), whereas Egyptian workers claimed its isolation as a grey powder from the reaction of isoindigo (**4**) or diazoisatin (**5**) with Lawesson´s reagent.[2] More recent investigations have questioned these results, and it appears that the cyclic valence tautomer (**6**), or rather a "dimer" thereof containing four indole units is formed instead.[3] The preparation of compound (**6**) had previously been claimed by Carpenter and co-workers *via* reduction of the tetrasulfide (**7**) with sodium borohydride in THF, followed by aerial oxidation.[4]



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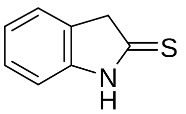
4 X = O



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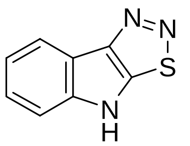

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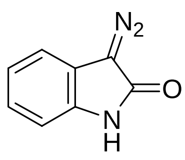

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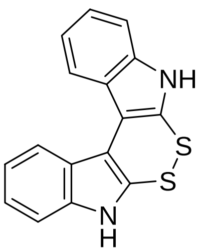

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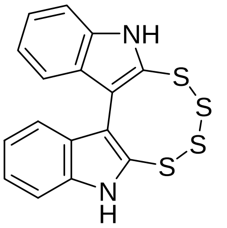

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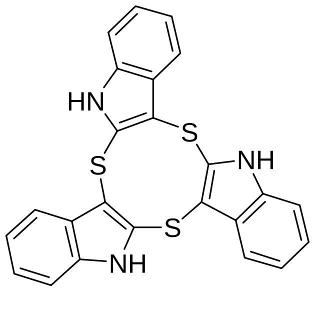
In order to shed some light on these divergent findings, we have reinvestigated the reactions mentioned above, with some very interesting results. The reaction of **4** with Lawesson´s reagent[5] produced in our hands a grey powder giving IR spectral data in reasonable agreement with those reported,[2] however NMR and LC-MS spectral data indicated a complex mixture of products which were difficult to separate and identify. Regrettably, the Egyptian workers did not supply any data other than microanalysis and an IR spectrum.[2] Furthermore, treatment of **2** with *p*-toluenesufonyl azide[6] did not give **1** as reported previously,[1] all attempts lead instead to the isolation of low yields of a novel compound, $C_{24}H_{15}N_3S_3$, which was at first given structure (**8**), as it displayed a molecular ion at *m/z* 441, as well as three different sets of indolic signals in both ^1H and ^{13}C NMR spectra. The appearance of the NMR spectra did not change with temperature. In other words, if the assigned structure (**8**) was correct, one had to assume that **8** was occurring in a non-interconvertible saddle conformer. Such a behavior would be at variance with related CH_2-analogues[7] ($S \rightarrow CH_2$) as well as related thiacalix[3]arenes such as **9**.[8]



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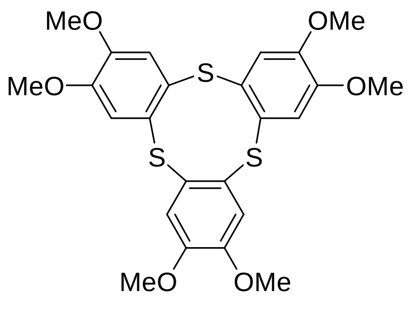

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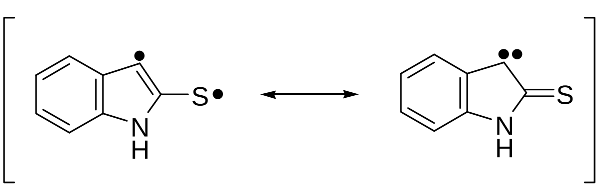
Mechanistically, the formation of **8** seemed to be plausible, as a trimerization of a carbene-like species like **10**, formed by elimination of nitrogen from **3**. In this context, interestingly enough, neither of the conceivable dimers (**6**) or (**11**) was observed. Instead, we suggest, that the species (**10**) initially undergoes 3,3′-coupling followed by reaction with another equivalent of **10** to give the final 9-

membered product (**12**), which is the true structure of the trimeric oxidative coupling product. The finally assigned structure (**12**) was further supported by a control experiment, wherein reduction of **12** with Raney nickel in dioxane gave the expected product mixture of indole and 3,3′-biindolyl (**13**),[9] which gave spectral data identical with those obtained for a reference sample.



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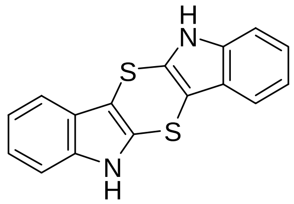

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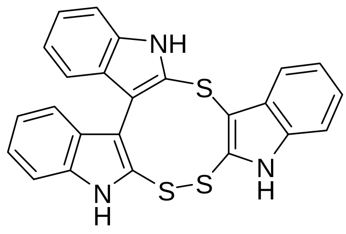

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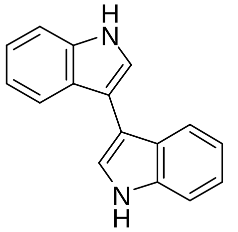

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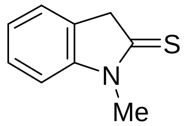
A related oxidation experiment, where *N*-methylindoline-2-thione (**14**) was reacted with iodine, has been reported by Hino to give the dimer (**15**) in 71% yield, without co-formation of any trimeric structures.[10b] The structure of **15** has also been proven recently by X-Ray crystallography.[11] Interestingly, attempts were also performed by the above mentioned workers to couple *N*-methyloxindole under the same conditions, leading only to complex mixtures from which small amounts of *N*,*N*′-dimethylisoindigo (**16**) could be isolated.[10b]



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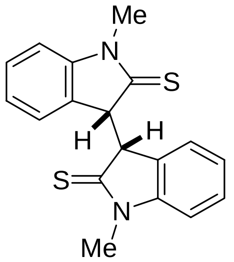

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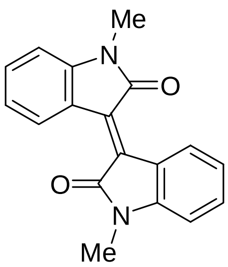

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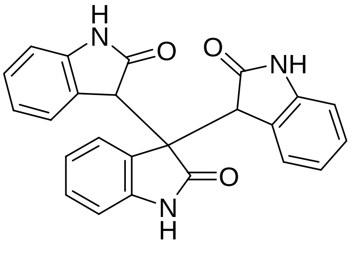
With these findings in mind, we turned our attention towards the reaction of oxindole with iodine in refluxing methanol, which not unexpectedly gave the trimeric product (**17**) in 77% yield. Formation of products containing a nine-membered ring could not be detected, demonstrating the higher propensity of the sulfur atom to stabilize radicals. Several *N*-substituted derivatives of **17** have been obtained previously from the reaction of isatins with oxindoles,[12] or the action of sodium naphthalenide on oxindoles.[13]



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EXPERIMENTAL

NMR spectra were recorded on a Bruker DPX 300 (300 MHz) or a JEOL Eclipse 500 (500 MHz) spectrometers. IR spectra were recorded on a Perkin Elmer 1600 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. HRMS was performed by Sveriges Lantbruksuniversitet (SLU), Uppsala, Sweden. Melting points were taken on 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.

Reaction of 2 with *p*-toluenesulfonyl azide. Compound (**2**)[10] (0.20 g, 1.34 mmol) was dissolved in pyridine (1 mL) followed by addition of a solution of *p*-toluenesulfonyl azide[6] (0.32 g, 1.62 mmol) in pyridine (1 mL). After stirring at rt for 1 h, the solvent was evaporated. The residue was subjected to chromatography (dichloromethane) to afford the fast moving trimer (**12**) (20 mg, 10%). Yellow solid, mp 257–258 °C (decomp);. ν_{max} (KBr)/cm^{-1} 3438, 3392, 3372, 3050 (w), 1392, 1336, 1226, 1146, 1130, 1008, 756, 746; δ_H (500 MHz, DMSO-d_6) 6.94 (ddd, J = 7.8, 7.4, 0.9 Hz, 1H, ArH), 7.01–7.05 (m, 2H, ArH), 7.12 (d, J = 7.8 Hz, 1H, ArH), 7.16 (ddd, J = 8.2, 7.8, 0.9 Hz, 1H, ArH), 7.28–7.33 (m, 3H, ArH), 7.41–7.44 (m, 2H, ArH), 7.50 (d, J = 8.2 Hz, 1H, ArH), 8.44 (m, 1H, ArH), 11.48 (s, 1H, NH), 12.03 (s, 1H, NH), 12.23 (s, 1H, NH); δ_C (125.7 MHz, DMSO-d_6) 107.2 (s), 111.8 (d), 111.8 (d), 111.9 (d), 113.7 (s), 118.5 (s), 119.5 (d), 119.6 (d), 119.8 (d), 120.3 (d), 120.3 (d), 120.9 (d), 122.8 (d), 123.9 (d), 124.1 (d), 126.8 (s), 127.2 (s), 127.6 (s), 128.3 (s), 130.1 (s), 136.1 (s), 136.7 (s), 136.8 (s), 136.9 (s). MS (ESI) *m/z* 440 [M–H] $^-$. Anal. Calcd for $C_{24}H_{15}N_3S_3$: C, 65.28; H, 3.42; N, 9.52. Found: C, 65.18; H, 3.33; N, 9.38.

The reaction mixture contained several other unidentified products, no attempts were however made to isolate further material.

Reduction of 12 with Raney nickel. To a suspension of an excess Raney nickel in dioxane (3 mL) was added compound (**12**) (90 mg, 0.2 mmol) at rt. The mixture was stirred for 19 h, diluted with dioxane (10 mL), and filtered. The filter pad was washed with several portions of dioxane, and the combined filtrate and washing were evaporated to dryness. The residue was purified by column chromatography, initially using hexane–dichloromethane (1:1), followed by increasing amounts of dichloromethane to give indole (10 mg, 42% of theoretical) and 3,3′-biindolyl (**13**) (24 mg, 51% of theoretical). These two products were identical with reference samples according to TLC, ^{1}H NMR and IR spectroscopy.

Compound (17). A mixture of oxindole (1.33 g, 10 mmol) and iodine (2.54 g, 10 mmol) in methanol (20 mL) was heated at reflux for 20 h. After cooling, **17** (0.63 g) was collected as an off-white solid. Additional material (0.38 g) was collected from the mother liquor after standing for 72 h. Total yield: 1.01 g (77%). An analytical sample was obtained after recrystallization from *N*,*N*-dimethylacetamide–acetonitrile, mp 287–289 °C (decomp); ν_{max} (KBr)/cm^{-1} 3307 (br), 3184 (br), 3088 (w), 3028 (w), 2928 (w), 2883 (w), 2821 (w), 1717, 1711, 1686, 1472, 1332, 1241, 768, 751; δ_H (300 Mz, DMSO-d_6) 4.98 (s, 1H, CH), 5.37 (br, 2H, CH and ArH), 6.47 (ddd, J = 7.5, 7.5, 0.8 Hz, 1H, ArH), 6.59 (d, J = 7.5 Hz, 1H, ArH), 6.65 (d, J = 7.8 Hz, 1H, ArH), 6.75-6.80 (m, 2H, ArH), 6.97–7.08 (m, 4H, ArH), 7.17 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H, ArH), 7.36 (d, J = 7.2 Hz, 1H, ArH), 10.41 (s, 1H, NH), 10.57 (s, 1H, NH), 10.71 (s, 1H, NH); δ_C (75.4 MHz, DMSO-d_6) 43.6 (d), 44.4 (d), 54.6 (s), 109.1 (d), 109.2 (d), 109.6 (d), 120.5 (d), 121.2 (d), 121.9 (d), 123.4 (d), 123.6 (d), 123.8 (d), 125.3 (s), 125.4 (s), 128.1 (d), 128.2 (d), 128.2 (s), 129.3 (d), 142.6 (s), 142.7 (s), 143.2 (s), 175.6 (s), 176.1 (s), 176.9 (s). MS (ESI) *m/z* 396 [M+H]$^+$. HRMS (EI) Found *m/z* 395.1249, calcd. for $C_{24}H_{17}N_3S_3$ 395.1270.

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