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Reactions of 2-lithiated indoles with elemental sulfur. Formation of pentathiepino[6,7-*b*]indoles and indoline-2-thiones

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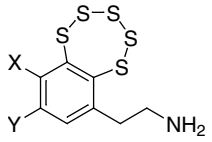
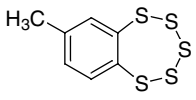
Abstract—The reactions of 2-lithiated indole and 1-methylindole with elemental sulfur have been studied, leading e.g. to a rational approach to pentathiepino[6,7-*b*]indoles **5** and **10**. Notable amounts of the previously known tetrathiocino[5,6-*b*:8,7-*b'*]diindole **11** could be observed as a side reaction in the preparation of **10**. Treatment of the anions of indoline-2-thiones **6** or **7** with sulfur also gave the pentathiepins **5** or **10**, respectively. In addition, a convenient and clean lithiation route to indoline-2-thione (**6**) has been developed.

1. Introduction

Several dopamine derived pentathiepins have been isolated from *Lissoclinum* tunicates, such as varacin (**1**), which was demonstrated to possess cytotoxic activity against the human colon cancer HCT 116.[1] Likewise, the related marine compound lissoclinotoxin A (**2**), isolated from *Lissoclinum perforatum* in 1991, was ascribed antifungal and antimicrobial activities,[2] but was not assigned a correct structure until several years later.[3] Additional biologically active metabolites belonging to this class have been isolated from the Palauan ascidian *Lissoclinum japonicum*, other unidentified *Lissoclinum* species, and also from a *Polycitor* or a *Eudistoma* species.[4] These natural products have attracted considerable interest, in particular varacin (**1**) for which several total syntheses have been developed.[5]



1 X = Y = OCH_3
2 X = OH, Y = OCH_3



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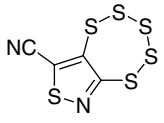

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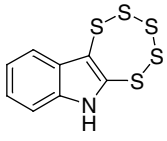

5

Interestingly, numerous synthetic pentathiepins have been known for some time, e.g. **3** which was shown to induce DNA cleavage,[6] and **4** which displays a wide range of antifungal activity.[7] A considerable number of synthetic efforts aiming at non natural pentathiepins[7,8] as well as acyclic pentasulfides[9] have been reported. In our laboratory, work in this area has previously resulted in isolation of 6*H*-pentathiepino[6,7-*b*]indole (**5**) in a low yield from the reaction of isatin with P_4S_{10} in refluxing pyridine, as well as a rigorous determination of the structure by X-ray crystallography.[10]

2-Thioindole derivatives[11] have, for example, been demonstrated as useful intermediates in the synthesis of 2,2′-dithiobisindole tyrosine kinase inhibitors.[12] Indoline-2-thiones **6** and **7** are available via the reaction of the corresponding oxindoles with P_4S_{10} in refluxing benzene or xylene,[13] a procedure which works well for the preparation of **7**, however in the case of the parent indoline-2-thione **6**, the yield is considerably lower and the product obtained requires time-consuming purification. Compound **8** has recently been used as the starting material for the preparation of the cruciferous phytoalexin sinalexin.[14] Thionation of amides has also been effected using in situ reagents prepared from P_4S_{10} and sodium carbonate in THF,[15] however at that time the method was not applied for the preparation of indoline-2-thiones.

Keywords: lithiated indole; indole-2-thiones; pentathiepins.

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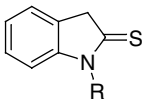
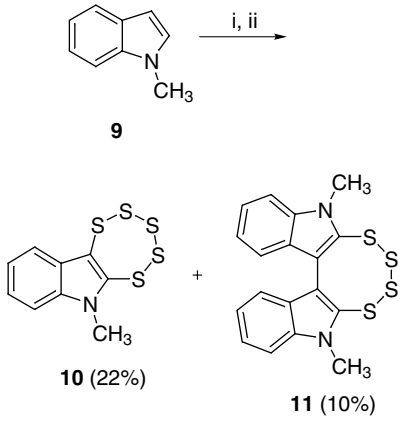


6 R = H
7 R = CH_3
8 R = OCH_3

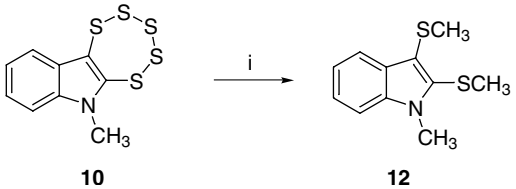
2. Results and discussion

In connection with attempts to develop a more rational methodology for preparation of indolo fused pentathiepins and a milder and cleaner procedure for the synthesis of indoline-2-thiones, thionations of 2-lithio derivatives of indoles have now been studied. The lithiation and thionation of 1-methylindole (**9**) using 20 equiv. elemental sulfur gave 6-methylpentathiepino[6,7-*b*]indole (**10**) together with the known tetrathiodiindole **11** (Scheme 1). The known compound 1-methylindoline-2-thione (**7**) was not observed in this experiment.

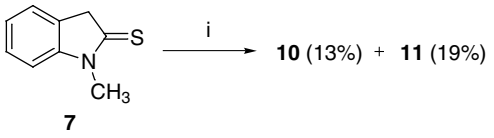
The pentathiepin **10** provided elemental analysis and high resolution mass spectral data which were consistent with the formula $C_9H_7NS_5$, and both ^1H- and ^{13}C NMR spectra supported the assigned structure. The presence of sulfur at both the 2- and 3-positions was confirmed when reduction with sodium borohydride in the presence of iodomethane (Scheme 2) gave the known 1-methyl-2,3-bis-(methylthio)indole (**12**).[16] The second product, compound **11**, similarly gave data supporting the assigned structure, and this was confirmed by direct comparison with an authentic sample previously prepared by the literature route.[17]



Scheme 1. *Reagents and conditions*: (i) *n*-BuLi, THF, −78 to −10°C; (ii) S_8 (20 equiv.), −10°C, 30 min, then AcOH.



Scheme 2. *Reagents and conditions*: (i) $NaBH_4$, CH_3I, THF, 40°C, 30 min, 44%.



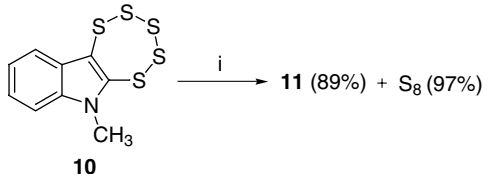
Scheme 3. *Reagents and conditions*: (i) NaH, THF, rt; then S_8, 0°C.

Although 1-methylindoline-2-thione (**7**) was not isolated from the lithiation and the reaction of 1-methylindole with sulfur, it probably was still involved in its anionic thienol form as an intermediate in the formation of the pentathiepin **10**. To test this hypothesis, a sample of the thione **7** was converted into its anion with sodium hydride in THF, and reacted with sulfur (Scheme 3). Compounds **10** and **11** were obtained as previously as the only major products, thereby confirming the intermediacy of the thio anion in their formation. In both of the above reactions, the proportions of the two products were found to change with increased time prior to workup, with the diindole tetrasulfide **11** increasing at the expense of the pentathiepin **10**.

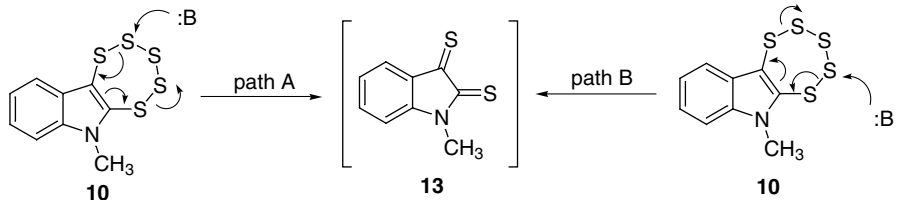
Purified samples of **10** appeared to be relatively stable with respect to conversion to **11**, so to test whether this transformation was a result of the basic medium in the above reactions, an isolated sample of **10** was heated at reflux in ethanol containing triethylamine. A relatively rapid reaction was observed and, apart from elemental sulfur, compound **11** was the only major product observed (Scheme 4).

Although the mechanism of the base induced transformation of **10** into **11** is uncertain, it possibly involves the intermediacy of dithioisatin (**13**), since it is known that 1,2-dithiones are prone to dimerizations and other secondary reactions.[18] Two possible routes to **13** can be proposed, differing only in whether nucleophilic attack by the base occurs on the 2- (path A) or 4- (path B) sulfur atom (Scheme 5).

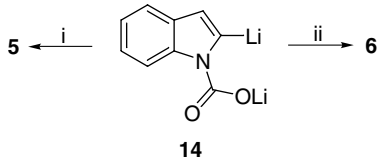
In a further development, we have devised a similar synthesis of the parent 6*H*-pentathiepino[6,7-*b*]indole (**5**) in fair yield via the reaction of the dianion **14** (prepared according to the Katritzky protocol[19] via lithiation of indole, followed by *N*-protection and activation of the 2-position using carbon dioxide, and subsequent lithiation in the 2-position) with 8 equiv. elemental sulfur as the electrophile (Scheme 6). The best yields of **5** were obtained using conditions where the temperature after the addition of sulfur was allowed to rise slowly during 10–12 h from −70 to 10°C. When only one equivalent of sulfur was used to effect the thionation of **14**, indoline-2-thione (**6**) was isolated as the major product. The highest yield of **6** (54%) was obtained when the temperature was kept at −70°C for 30 min, and then allowed to rise to room temperature during 1 h.



Scheme 4. *Reagents and conditions*: (i) Et_3N, EtOH, reflux 30 min.



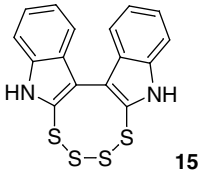
Scheme 5.



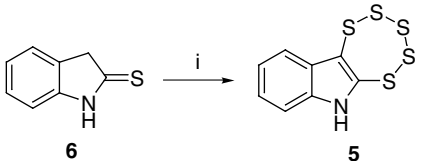
Scheme 6. *Reagents and conditions*: (i) S_8 (8 equiv.), THF, −70 to 10°C (10 h), then AcOH, 29%; (ii) S_8 (1 equiv.), THF, −70 to 20°C (1.5 h), then aq. sat. NH_4Cl, 54%.

However, useful amounts of **6** were also produced when the reaction mixture was allowed to warm slowly to room temperature over 12–18 h. Purification of the thione **6** thus obtained proved to be particularly easy, as trituration of the crude product mixture with diethyl ether gave material of good quality.

Some further observations made during the above mentioned reactions merit some attention. The reaction of **14** with 8 equiv. of sulfur may under some conditions give small amounts of the expected (vide supra) known side product **15**.[17] Thus prolonged reaction times at room temperature lead to increasing amounts of **15**, which is in analogy with the behaviour of 6-methylpentathiepino[6,7-*b*]indole (**10**).



Quenching of the reaction mixture of **14** and sulfur with dilute aqueous sulfuric acid after allowing the temperature to quickly (~30 min) attain room temperature lead to the isolation of the expected intermediate indoline-2-thione (**6**).[13] Longer reaction times at −70°C (~18 h) followed by quenching at −70°C produced only low yields of the previously observed compounds, indicating that the reaction is slow at low temperatures. The indoline-2-thione **6** could also be converted into the pentathiepin **5** in 42% yield via treatment with sodium hydride in THF, followed by addition of sulfur (Scheme 7), thus also in this case suggesting



Scheme 7. *Reagents and conditions*: (i) NaH, THF, −10°C, then S_8, −10 to 20°C, 4 h, 42%.

that the thienol anion of **6** is an intermediate in the formation of **5**. As anticipated, treatment of the pentathiepin **5** with bases (e.g. Et_3N, DBU) in ethanol gave complex mixtures according to TLC. Here the possibility of deprotonation at the indole nitrogen leads to a wide array of reactions.

In conclusion, useful routes to pentathiepino[6,7-*b*]indoles **5** and **10** starting from readily available materials have been developed, providing the first rational syntheses of compounds belonging to this class. In addition, alternative procedures for the synthesis of indoline-2-thiones have been studied, leading to a useful synthesis of the parent indoline-2-thione (**6**).

3. Experimental

3.1. General

NMR spectra were recorded on Bruker DPX 300 (300 MHz) or AMX 400 (400 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. MS (EI) data were recorded on a Varian VG 70SE spectrometer. High resolution mass spectra were performed by Sveriges Lantbruksuniversitet (SLU), Uppsala, Sweden. The elemental analysis was performed by the Microchemical Laboratory at the University of Otago in Dunedin, New Zealand. Melting points were taken on a Reichert Kofler hot stage and are uncorrected. Chromatography was performed on Merck Silica Gel 60. Solvents were of analytical grade and were used as received. THF was distilled from sodium and benzophenone.

3.1.1. Lithiation and reaction of 1-methylindole with sulfur. To a solution of 1-methylindole (3.28 g, 25 mmol) in THF (50 mL) at −78°C under an atmosphere of dry nitrogen, was added *n*-BuLi in hexanes (2.5 M, 13.0 mL, 33 mmol) and the resulting mixture was allowed to warm to −10°C (ice–salt bath) to give a white precipitate. After a further 30 min at −10°C the slurry was added, via a double ended needle, to a stirred suspension of sulfur (16 g, 0.5 mol) in THF (100 mL) at −10°C, to give a deep red colour. The reaction mixture was stirred for a further 30 min at −10°C and acetic acid (2.5 mL) was added. After filtering to remove excess sulfur, the solvent was removed under reduced pressure and the residue was extracted into ethyl acetate (200 mL) and washed with sat. aq. $NaHCO_3$ (50 mL). After drying (Na_2SO_4), the solvent was evaporated and the residue was purified by chromatography. Residual sulfur was removed by elution with hexane, followed by subsequent elution with hexane–dichloromethane (95:5) to give, as a yellow solid, 6-methyl-

pentathiepino[6,7-*b*]indole (**10**) (1.61 g, 22%); mp (dichloromethane–hexane) 124–125°C; IR (KBr) ν_{max} 3044 (w), 2932 (w), 1459, 1442, 1349, 1330, 1233, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 7.22–7.29 (m, 3H), 7.63–7.68 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 31.5 (q), 110.5 (d), 119.1 (s), 120.5 (d), 122.1 (d), 124.6 (d), 128.9 (s), 136.5 (s), 141.3 (s); MS (EI) *m/z* 289 (M^+, 20%), 225 ($M-S_2$, 100); HRMS (EI) Found *m/z* 288.9174, calcd for $C_9H_7NS_5$ 288.9182. Anal. calcd for $C_9H_7NS_5$ C, 37.3; H, 2.4; N, 4.8; S, 55.4%. Found C, 37.6; H, 2.3; N, 4.8; S, 55.4.

Further elution with hexane–dichloromethane (9:1) gave 5,10-dihydro-5,10-dimethyl[1,2,3,4]-tetrathiocino[5,6-*b*:8,7-*b'*]diindole (**11**) (0.48 g, 10%); mp (ethyl acetate) 250–255°C (dec) (lit.[17], 252–254°C); IR (KBr) ν_{max} 3049 (w), 2934 (w), 1449, 1328, 1306, 1226, 1155, 1006, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 6H), 7.10 (ddd, *J*=8.0, 6.9, 1.0 Hz, 2H), 7.37 (ddd, *J*=8.2, 6.9, 1.2 Hz, 2H), 7.43 (d, *J*=8.2 Hz, 2H), 7.46 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) 30.7 (q), 110.3 (d), 120.4 (d), 120.9 (s), 121.3 (d), 124.8 (d), 126.7 (s), 128.0 (s), 137.5 (s). MS (ESI) *m/z* 387 $[M+H]^+$.

3.1.2. Reduction and methylation of 6-methylpentathiepino[6,7-*b*]indole (10). To a mixture of 6-methylpentathiepino[6,7-*b*]indole (**10**) (217 mg, 0.75 mmol) and iodomethane (1 mL) in ethanol (30 mL) was added sodium borohydride (0.28 g, 7.5 mmol) in portions. The resulting solution was stirred at 40°C for 30 min and the solvent was removed under vacuum. After workup in ethyl acetate as before, the product was purified by preparative layer chromatography on silica gel eluting with hexane–dichloromethane (9:1), to give 1-methyl-2,3-bis(methylthio)indole (**12**) (73 mg, 44%) as an oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.40 (s, 3H), 3.86 (s, 3H), 7.17–7.33 (m, 3H), 7.76 (br d, *J*=8.0 Hz, 1H). The spectral data were in agreement with those already reported.[16]

3.2. Reaction of 1-methyl-2-indolinethione (7) with sulfur

A solution of 1-methylindoline-2-thione (**7**) (1.0 g, 6.1 mmol) in dry THF (10 mL) was treated with sodium hydride (0.3 g of a 60% dispersion in mineral oil, 7.4 mmol) at room temperature under nitrogen, and the resulting mixture was added to a stirred suspension of sulfur (2 g, 62 mmol), in THF (20 mL) at 0°C. The mixture was allowed to warm to room temperature with stirring overnight. Standard workup and chromatography as before gave **10** (0.23 g, 13%) and **11** (0.22 g, 19%).

3.3. Reaction of 10 with triethylamine

A suspension of **10** (0.29 g, 1 mmol) and triethylamine (1 mL) in ethanol (20 mL) was heated under reflux for 30 min, cooled and diluted with water. The solid was collected by filtration, dried, and finally purified by chromatography as above, to give sulfur (93 mg, 97% of theoretical) and **11** (172 mg, 89%).

3.3.1. 6*H*-Pentathiepino[6,7-*b*]indole (5). A solution of indole (1.40 g, 12 mmol) in THF (30 mL) was cooled to −70°C under nitrogen atmosphere. *n*-BuLi in hexanes (1.6 M, 7.6 mL, 12.2 mmol) was added at −70°C and the mixture was stirred for 30 min, followed by introduction of carbon dioxide during 10 min. The solvent was removed at reduced pressure (during that time the temperature was allowed to rise to 20°C). Nitrogen was introduced into the reaction vessel, and the residue was dissolved in THF (30 mL), thereafter *t*-BuLi in pentane (1.7 M, 7.1 mL, 12.1 mmol) was added at −70°C, and the mixture was stirred for 30 min. Sulfur (3.08 g, 96 mmol) was thereafter added at −70°C, producing a dark red mixture. The temperature was allowed to rise to 10°C over 10 h. Acetic acid (2 mL) was added and stirring was continued for 15 min, followed by addition of sat. aq. NH_4Cl (50 mL). The mixture was filtered and diluted with ethyl acetate (50 mL). The organic phase was washed with brine (50 mL), dried (Na_2SO_4) and the solvent was thereafter evaporated. The residue was subjected to column chromatography initially using hexane, followed by 5–20% dichloromethane in hexane which afforded 6*H*-pentathiepino[6,7-*b*]indole (**5**) as a yellow crystalline material (960 mg, 29%). An analytical sample was obtained after recrystallization from acetonitrile, mp (acetonitrile) 169–170°C (lit.[10] 170–171°C); IR (KBr) ν_{max} 3355, 1466, 1417, 1388, 1343, 1224, 846, 815, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.33 (m, 3H), 7.67–7.70 (m, 1H), 8.53 (br s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 111.8 (d), 120.6 (s), 120.8 (d), 122.6 (d), 125.3 (d), 130.1 (s), 135.2 (s), 138.0 (s). MS (ESI) *m/z* 274 ($[M-H]^-$, 100%), 210 ($[M-S_2-H]^-$, 48), 178 ($[M-S_3-H]^-$, 53). HRMS (EI) Found *m/z* 274.9025, calcd for $C_8H_5NS_5$ 274.9025.

3.3.2. Indoline-2-thione (6). Indole (5.86 g, 50 mmol) in THF (45 mL) was treated with *n*-BuLi in hexanes (2.5 M, 21 mL, 52.5 mmol) at −70°C under N_2 during 15–20 min. The mixture was kept at −70°C for 30 min, followed by introduction of carbon dioxide during 15 min at −70°C. The solvent was removed at reduced pressure (during that time the temperature was allowed to rise to 20°C). Nitrogen was introduced into the system, and the white residue was dissolved in THF (60 mL), and after cooling to −70°C, *t*-BuLi in pentane (1.7 M, 31 mL, 52.7 mmol) was added during 15–20 min. After stirring at −70°C for 30 min, sulfur (1.6 g, 51.3 mmol) was quickly added in one portion and the resulting yellow mixture was stirred at −70°C for 30 min, and was thereafter allowed to warm to 20°C during 1 h, followed by quenching with sat. aq. NH_4Cl (100 mL). Stirring was continued for 5 min, the mixture was thereafter diluted with water (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (50 mL) and dried over Na_2SO_4. Evaporation of the solvent gave a greenish-beige residue, which was treated with diethyl ether (~20 mL), producing a pale beige precipitate, which was collected by filtration, washed with diethyl ether and dried to give **6** (4.00 g, 54%) as a pale beige solid; mp (diethyl ether) 146–148°C (lit.[13], 147–149°C); IR (KBr) ν_{max} 3092, 2987 (w), 2920 (w), 2877 (w), 1618, 1505, 1467, 1447, 1341, 1296, 1178, 1116, 750 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.01 (s, 2H), 6.96 (d, *J*=7.7 Hz, 1H), 7.04 (ddd, *J*=8.4, 7.6, 1.0 Hz, 1H), 7.19–7.26 (m, 2H), 12.59 (br s, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 49.1 (t), 109.9 (d), 123.2 (d), 124.0 (d), 127.7 (d), 130.8 (s), 145.2 (s), 203.1 (s). MS (ESI) *m/z* 148 $[M-H]^-$.

3.4. Transformation of indoline-2-thione (6) into 6*H*-pentathiepino[6,7-*b*]indole (5)

A solution of indoline-2-thione (**6**) (745 mg, 5 mmol) in THF (20 mL) was added during 15 min to a suspension of sodium hydride (0.44 g of a 60% dispersion in mineral oil, 11 mmol) in THF (20 mL) at −10°C under N_2. After stirring at −10°C for 15 min, sulfur (0.8 g, 25 mmol) was quickly added in one portion at −10°C. The mixture was thereafter allowed to slowly warm to room temperature during 4 h. After quenching with acetic acid (1 mL), sat. aq. NH_4Cl (50 mL) was added, and the resulting mixture was filtered and diluted with ethyl acetate (50 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4) and the solvents were evaporated to give a yellow residue, which was subjected to column chromatography initially using hexane, followed by 10–40% dichloromethane in hexane, to give 6*H*-pentathiepino[6,7-*b*]indole (**5**) as a yellow crystalline solid (580 mg, 42%).

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