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Synthesis of Indolocarbazoles, Bisindoles and Related Sulfur Containing Systems

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ABSTRACT

This thesis is focussed mainly on the synthesis and reactions of various indolocarbazoles, bisindoles and related sulfur containing systems, all possessing structural features present in many biologically active, natural or synthetic compounds.

In the first part, synthetic routes towards the planar, pentacyclic ring systems of indolo[2,3-*c*]carbazole and indolo[3,2-*a*]carbazole are described. The synthesis of the parent indolo[2,3-*c*]carbazole was accomplished *via* a palladium acetate mediated cyclization of 1,2-bis(1*H*-indol-2-yl)ethane, which was also demonstrated to serve as an excellent precursor for the preparation of a variety of cyclohept[1,2-*b*:5,4-*b*′]bisindoles. A variety of indolo[3,2-*a*]carbazoles were obtained conveniently starting from 2,3′-biindolyl *via* electrocyclic reactions, or the interaction of 2,3′-biindolyl with a masked *N,N*-dimethylaminoacetaldehyde. In an extension, it was shown that access to indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazoles and analogues thereof can also be easily gained.

The second part of this thesis deals with the synthesis of the marine alkaloid hyrtiosin B, which was achieved utilizing an efficient and concise route involving acylation of indolozinc reagents derived from 5-methoxyindole, or even better, 5-benzyloxyindole, as the key step.

In the final and major section, the chemistry and reactions of various sulfur containing indoles and bisindoles are discussed. Thionation reactions using elemental sulfur or P_4S_{10} performed on *e.g.,* indigo, isatin, or 3,3′-biindolyl were shown to give bisindoles featuring polysulfur bridges, or having unusual rings incorporating both sulfur and phosphorus. The first example of a thionated indigo derivative with an established structure, *i.e.* monothioindigo was isolated from the reaction of indigo with P_4S_{10} in pyridine. The interaction of sulfur with 2,2′-biindolyl was found to produce a system with four indole moieties having a 12-membered central ring incorporating two *S,S*-linkages. This molecule was also demonstrated to undergo transformation into two different conformers on dissolution in warm strongly polar solvents. In addition, the elusive [1,2]dithiino[4,3-*b*:5,6-*b*′]diindole was isolated as a *N,N*-dimethylacetamide solvate, the structure of which was rigorously confirmed by X-ray crystallography. Moreover, the synthesis and reactions of pentathiepino[6,7-*b*]indoles were studied. Pentathiepino[6,7-*b*]indoles proved to be readily accessible *via* the reaction of 2-lithiated indoles with elemental sulfur. A modification of the conditions, *i.e.* the use of one equivalent of sulfur, permitted a simple route to indoline-2-thiones from indoles. In addition, trimerization reactions of indoline-2-thione or oxindole were investigated, demonstrating that treatment of indoline-2-thione with *p*-toluenesulfonyl azide gives a cyclic trimeric product, while the reaction of oxindole with iodine produces an acyclic trimer.

Keywords: alkaloids, bisindoles, dithiins, indoles, indolocarbazoles, metallation, pentathiepins, polysulfides, tetrathiocins, thionation, X-ray crystallography.

ISBN 91-7349-110-1

LIST OF PUBLICATIONS

This thesis is based on the following articles, which will be referred to in the text by their Roman numerals:

I. "Reactions of 1,2-bis(1*H*-indol-2-yl)ethane: formation of indolo[2,3-*c*]carbazole and cyclohept[1,2-*b*:5,4-*b*′]bisindole derivatives"
Bergman, J.; Janosik, T.; Yudina, L.; Desarbre, E.; Lidgren, G.; Venemalm, L.
Tetrahedron **2000**, *56*, 1911.

II. "Reactions of 2,3′-biindolyl: synthesis of indolo[3,2-*a*]carbazoles"
Janosik, T.; Bergman, J.
Tetrahedron **1999**, *55*, 2371.

III. "Synthesis of hyrtiosin B, a bisindole alkaloid from the Okinawan marine sponge *Hyrtios erecta*"
Bergman, J.; Janosik, T.; Johnsson, A.-L.
Synthesis **1999**, 580.

IV. "Thionation of bisindole derivatives with P_4S_{10} or elemental sulfur"
Janosik, T.; Bergman, J.; Stensland, B.; Stålhandske, C.
J. Chem. Soc., Perkin Trans. 1, in press.

V. "Synthetic, spectroscopic, and X-ray crystallographic studies of [1,2,7,8]tetrathiacyclododecino[4,3-*b*:5,6-*b*′:10,9-*b*″:11,12-*b*‴]tetraindoles"
Janosik, T.; Bergman, J.; Romero, I.; Stensland, B.; Stålhandske, C.; Marques, M. M. B.; Santos, M. M. M.; Lobo, A. M.; Prabhakar, S.; Duarte, M. F.; Florêncio, M. H.
Submitted.

VI. "Reactions of 2-lithiated indoles with elemental sulfur. Formation of pentathiepino[6,7-*b*]indoles and indoline-2-thiones"
Rewcastle, G. W.; Janosik, T.; Bergman, J.
Tetrahedron **2001**, *57*, 7185.

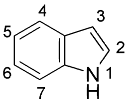
VII. "Oxidative coupling of indoline-2-thione or oxindole: formation of cyclic and acyclic indole trimers"
Janosik, T.; Bergman, J.
Manuscript.

CONTENTS

1 BACKGROUND

1.1 Indoles and bisindoles

Indole[1] (**1**) is one of the most profoundly studied basic heterocyclic systems, the well-known and accepted formula of which was proposed by Baeyer in 1869.[2] The interest in the chemistry of indole (**1**) began in the mid-nineteenth century, and went through a vivid expansion phase during the last decades of the nineteenth century, when much effort was put into studies on probably the oldest and best known colouring matter, the ancient dye indigo (**2**), originally derived from various species of *Indigofera*. Indigo (**2**), which is an example of a simple bisindole, was at an early stage found to produce isatin (**3**) on oxidation,[3] while several years later oxindole (**4**) was obtained from a reduction experiment performed on indigo (**2**).[4] The two simple molecules **3** and **4** constitute excellent examples of highly useful, commercially available, cheap and versatile indole derivatives. The first routes towards synthetic indigo (**2**) were described by Baeyer,[5] and somewhat later by Heumann.[6] Such achievements, together with numerous other pioneering efforts made during these early times, still provide useful procedures for workers involved in indole chemistry.



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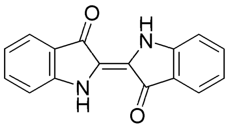

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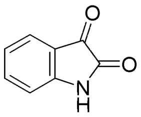

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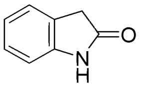

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Indole itself was prepared for the first time by reduction of oxindole (**4**) with zinc dust,[7] a synthesis that was later followed by several alternative preparations of limited synthetic utility, but it was not until the discovery of the Fischer indole synthesis[8] that a wider spectrum of indole derivatives became available, and opened new possibilities for subsequent important

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[1] Sundberg, R. J. *The Chemistry of Indoles,* Academic Press, New York, 1970.

[2] Baeyer, A; Emmerling, A. *Chem. Ber.* **1869**, *2*, 679.

[3] Erdmann, O. L. *J. Prakt. Chem.* **1841**, *24*, 1.

[4] Baeyer, A.; Knop, C. A. *Ann. Chem. Pharm.* **1866**, *140*, 1.

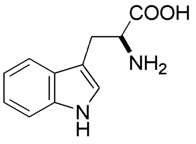
[5] (a) Baeyer, A. *Chem. Ber.* **1878**, *11*, 1296 (b) Baeyer, A. *Chem. Ber.* **1879**, *12*, 456.

[6] (a) Heumann, K. *Chem. Ber.* **1890**, *23*, 3043 (b) Heumann, K. *Chem. Ber.* **1890**, *23*, 3431.

[7] Baeyer, A. *Ann. Chem. Pharm.* **1866**, *140*, 295.

[8] (a) Fischer, E.; Jourdan, F. *Chem. Ber.* **1883**, *16*, 2241 (b) Fischer, E.; Hess, O. *Chem. Ber.* **1884**, *17*, 559. For an excellent monograph, see: (c) Robinson, B. *The Fischer Indole Synthesis,* John Wiley & Sons, Chichester, 1982.

developments. The expansion of this field was enhanced even more when the ring system of indole was recognized as a framework present in many naturally occurring substances possessing powerful biological activities and having important functions in living matter. Thus for instance, the amino acid L-tryptophan (**5**) is an essential nutritional component in the human diet, while the simple compound indole-3-acetic acid (**6**) is known as the principal plant growth regulator. These small molecules, together with closely related substances such as the tryptamine derivative serotonin, a metabolite of importance in brain biochemistry, or the hallucinogenic fungal metabolites psilocin and psilocybin, neatly illustrate the importance and potent activities of naturally occurring indole derivatives.



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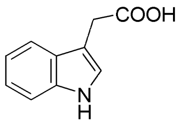

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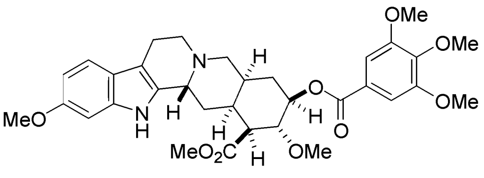
Nature is also a rich source of more complex biologically active natural products containing the indole moiety. Numerous well-known examples belonging to this class, *e.g.* reserpine[9] (**7**), an antihypertensive constituent of the Indian snakeroot *Rauwolfia serpentia*, or the antitumor antibiotic (+)-staurosporine[10] (**8**), which contains the skeleton of indolo[2,3-*a*]carbazole, have together with numerous other indole alkaloids attracted considerable interest, not only as targets for total synthesis, but also as lead compounds in drug development due to their diverse, and sometimes unique, structural features and broad biological activity profiles.



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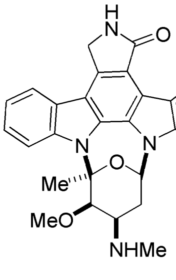

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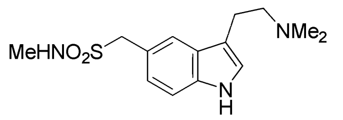
[9] For leading references, see the excellent chapter on the Woodward synthesis of reserpine: Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, VCH, Weinheim, 1996.

[10] Isolation: (a) Ōmura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275 (b) Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun.* **1986,** *135*, 397. For a synthesis, see *e.g.* (c) Wood, J. L.; Stoltz, B. M.; Goodman, S. N.; Onwueme, K. *J. Am. Chem. Soc.* **1997**, *119*, 9652.

Although numerous indole alkaloids have previously been used in medicine, they have in most cases been supplanted by more selective and potent synthetic alternatives. Representative and important examples of such pharmaceuticals are the anti-migraine drug Sumatriptan (**9**), and Indomethacin (**10**), which displays anti-inflammatory and analgesic effects. There is no doubt that a multitude of new indole derivatives will be studied and evaluated in the future as potentially biologically active agents for pharmaceutical applications.



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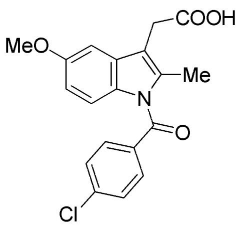

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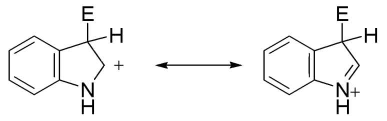
1.2 Fundamental reactivity of indoles towards electrophiles[11]

One of the most dominant features of the chemistry of indoles is the facile electrophilic substitution at C-3, which is feasible even with relatively weak electrophiles. This might be rationalized in terms of stabilization effects in the resulting Wheland intermediate **11**, which can retain the aromaticity of the six-membered ring, in contrast to the intermediate **12** resulting from attack at C-2, where the aromaticity of the benzene ring has to be disrupted if further resonance forms are supposed to exist. Although 3-substituted indoles can undergo direct electrophilic attack at C-2, it appears that in many cases, a pathway involving initial attack at C-3, followed by a migration of the electrophile to C-2 is in operation. These highly predictable reactivity patterns provide an excellent tool for introduction of substituents at C-3, which after subsequent manipulation offer access to a multitude of useful indole derivatives.



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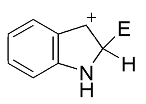

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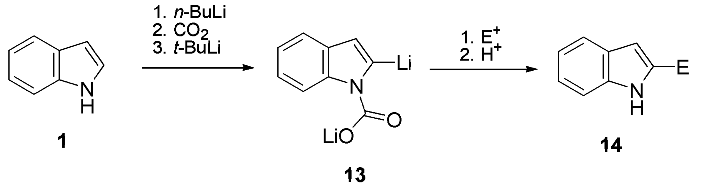
[11] For an excellent introduction to the chemistry and reactivity of indoles, see: Joule, J. A.; Mills, K. *Heterocyclic Chemistry,* 4th ed. Blackwell Science, Oxford, 2000.

Electrophilic substitution at C-2 of a C-3 unsubstituted indole is possible *via* blocking of the nitrogen with a suitable substituent, followed by directed metallation at C-2 and subsequent introduction of the electrophile. The most commonly used *N*-protecting groups include benzenesulfonyl, *p*-toluenesulfonyl (tosyl), *t*-butoxycarbonyl (Boc), or 2-(trimethylsilyl)-ethoxymethyl (SEM), although 2-metallation is also possible employing non-removable groups such as methyl. A very practical one-pot protocol for the preparation of 2-substituted indoles has been developed by Katritzky and co-workers,[12] and involves deprotonation of indole, followed by *N*-protection and activation of the 2-position by formation of the carbamate **13** using CO_2, and subsequent 2-metallation. After a final introduction of the electrophile, the temporary protecting group is removed during acidic workup (Scheme 1), and the 2-substituted indole **14** so obtained can be manipulated further.



Scheme 1.

2 INDOLOCARBAZOLES

2.1 General introduction

The indolocarbazoles[13] constitute a class of pentacyclic aromatic systems based on the carbazole nucleus, to which an additional indole moiety is fused *via* its five membered ring. Thus, there are five possible isomeric indolocarbazoles. The most extensively studied isomer, indolo[2,3-*a*]carbazole (**15**) is a substructure found in several natural products, such as staurosporine (**8**) (Section 1.1), and has therefore attracted considerable attention. The chemistry of **15** is a well explored topic, both regarding the formation of the basic ring system, as well as the preparation and reactivity of its numerous derivatives, in particular the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles.[14] Since the discovery that indolo[3,2-*b*]carbazole (**16**)

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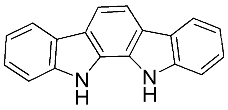
[12] Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935.

[13] For a comprehensive review on indolocarbazoles, see: Bergman, J.; Janosik, T.; Wahlström, N. *Adv. Heterocycl. Chem.* **2001**, *80*, 1.

[14] For reviews covering indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles, see: (a) Gribble, G. W.; Berthel, S. J., in *Studies in Natural Product Chemistry*, Atta-ur-Rahman, Ed., Vol. 12, p. 365, Elsevier, Amsterdam, 1993 (b) Prudhomme, M. *Curr. Pharm. Des.* **1997**, *3*, 265 (c) Pindur, U.; Kim, Y.-S.; Mehrabani, F. *Curr. Med. Chem.* **1999**, *6*, 29.

and numerous derivatives thereof are potent aryl hydrocarbon receptor ligands, considerable activity in the development of synthetic procedures towards this ring system has emerged as well. In contrast, the related isomer indolo[2,3-*b*]carbazole (**17**) has been studied only scantily, and only a few reports dealing with its synthesis are available. Likewise, the angular isomer indolo[2,3-*c*]carbazole (**18**) has been only rarely described, and it was not until recently that the parent compound was prepared. The remaining system indolo[3,2-*a*]carbazole (**19**) has also attracted some interest, as it has been reported that several substituted aza-analogues are potent benzodiazepine receptor ligands.[15] Parts of the work described in this thesis (Papers I and II) will focus on new synthetic approaches towards the indolocarbazole systems **18** and **19**, intermediates in their syntheses, and reactions giving rise to new related structures. Short reviews on these systems will also be provided, for a more comprehensive coverage, c.f. ref 13.



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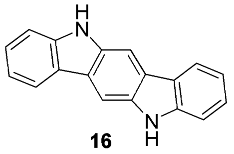

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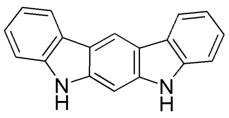

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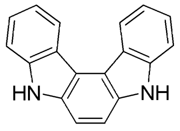

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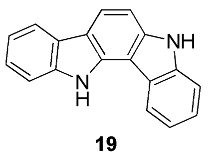

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2.2 Indolo[2,3-*c*]carbazoles and related systems

2.2.1 Previous synthetic efforts

The parent indolo[2,3-*c*]carbazole (**18**) has proven to be the most elusive of all five isomers. Although various substituted examples of **18** have appeared in the literature a long time ago,[16] the assignments of these structures need however to be verified, as the data supporting the results were scarce. The first example of an indolo[2,3-*c*]carbazole with a fully

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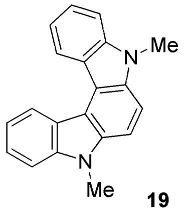
[15] (a) Allen, M. S.; Hagen, T. J.; Trudell, M. L.; Codding, P. W.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1988**, *31*, 1854 (b) Allen, M. S.; Tan, Y.-C.; Trudell, M. L.; Narayanan, K.; Schindler, L. R.; Martin, M. J.; Schultz, C.; Hagen, T. J.; Koehler, K. F.; Codding, P. W.; Skolnick, P.; Cook J. M. *J. Med. Chem.* **1990**, *33*, 2343 (c) Martin, M. J.; Trudell, M. L.; Diaz Araúzo, H.; Allen, M. S.; LaLoggia, A. J.; Deng, L.; Schultz, C. A.; Tan, Y.-C.; Bi, Y.; Narayanan, K.; Dorn, L. J.; Koehler, K. F.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1992**, *35*, 4105.

[16] (a) Madelung, W.; Siegert, P. *Chem. Ber.* **1924**, *57*, 222 (b) Siedel, P. *Chem. Ber.* **1944**, *77*, 788 (c) Clifton P. V.; Plant, S. G. P. *J. Chem. Soc.* **1951**, 461.

established structure was the dimethyl derivative **19**, which was isolated from the irradiation of *N,N′*-dimethyl-*N,N′*-diphenyl-*p*-phenylenediamine (**20**) in the presence of oxygen.[17] Interestingly, this reaction has for some time incorrectly been claimed to produce the isomeric indolo[3,2-*b*]carbazole[18] **21**, it was however later[19] shown to give an outcome which was identical to that reported in the excellent work by Weller and Grellmann.[17]



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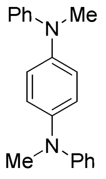

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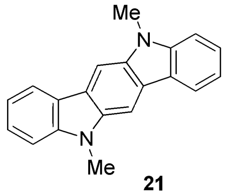

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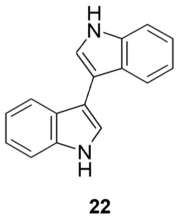
Recently, more high-yielding and rational approaches have been developed, such as a procedure starting from the readily available precursor 3,3′-biindolyl[20] (**22**) or substituted derivatives thereof, which underwent electrocyclization reactions with for example dimethyl acetylenedicarboxylate to provide the disubstituted indolo[2,3-*c*]carbazole **23**; or with various maleimides to afford hexacyclic systems of the general structure **24**.[21] A stepwise procedure involving a Vilsmeier-Arnold-Haack formylation of **22** at the 2-position, followed by a Henry-aldolization of the formyl derivative to the corresponding nitrovinyl substituted 3,3-biindolyl, and a subsequent thermal cyclization in refluxing diphenyl ether to finally give the parent system **18** was also described.[21a–b]



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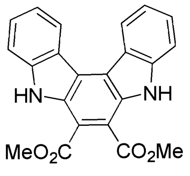

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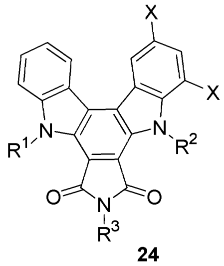

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[17] Weller, H.; Grellmann, K.-H. *J. Am. Chem. Soc.* **1983**, *105*, 6268.

[18] (a) Lamm, W.; Jugelt, W.; Pragst, F. *J. Prakt. Chem.* **1975**, *317*, 284 (b) Lamm, W.; Pragst, F.; Jugelt, W. *J. Prakt. Chem.* **1975**, *317*, 995 (c) Chakrabarty, M.; Batabyal, A. *Synth. Commun.* **1996**, *26*, 3015.

[19] Chakrabarty, M.; Batabyal, A.; Khasnobis, S. *Synth. Commun.* **2000**, *30*, 3651.

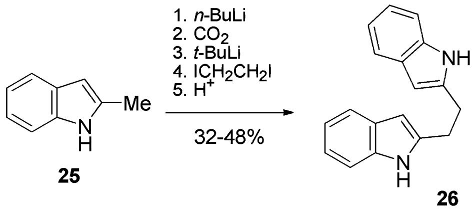
[20] (a) Bergman, J. *Acta Chem. Scand.* **1975**, *25*, 1277 (b) Berens, U.; Brown, J. M.; Long, J.; Selke, R. *Tetrahedron: Asymmetry* **1996**, *7*, 285.

[21] (a) Bergman, J.; Desarbre, E. *Synlett* **1997**, 603 (b) Desarbre, E.; Bergman, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2009. For pyranosylated indolo[2,3-*c*]carbazoles, see also: (c) Voldoire, A.; Sancelme, M.; Prudhomme, M.; Colson, P.; Houssier, C.; Bailly, C.; Léonce, S.; Lambel, S. *Bioorg. Med. Chem.* **2001**, *9*, 357.

Other noteworthy routes leading to indolo[2,3-*c*]carbazole derivatives include a thallium acetate induced oxidation of 2,3-dimethylindole,[22] and various modifications of the double Fischer indolization procedure to produce for example a dihydro derivative of 2,11-dimethoxyindolo[2,3-*c*]carbazole,[23] or heterohelicenes containing the framework of **18**.[24]

2.2.2 New approaches towards indolo[2,3-*c*]carbazoles: formation of cycloheptbisindole derivatives (Paper I)

The indolo[2,3-*c*]carbazole ring system might theoretically be constructed *via* an intramolecular 3,3′-coupling of the precursor 1,2-bis(1*H*-indol-2-yl)ethane (**26**), for which a multi-gram scale synthesis first had to be developed. The bisindole **26** had previously been reported as a minor product from the treatment of 2-methylindole-*N*-carboxylic acid with *N*-methylpyridinium salts.[25] In an application of the Katritzky protocol for sequential *N*-protection and activation of indoles in the 2-position,[12] 2-methylindole (**25**) was thus subjected to homo-coupling using 1,2-diiodoethane as the coupling agent (Scheme 2) to provide the desired precursor **26**.[26] In a later report, compound **26** has also been obtained by German workers utilizing a complex procedure starting from a *N*-protected *o*-toluidine, albeit in an inferior yield.[27]



Scheme 2.

With sufficient amounts of **26** available, coupling experiments were undertaken. The use of equimolar amounts of $Pd(OAc)_2$ in hot acetic acid proved to give the expected indolo[2,3-

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[22] Tholander, J.; Bergman, J. *Tetrahedron* **1999**, *55*, 12595.

[23] Yudina, L. N. *Ph.D. Thesis*, Institute of New Antibiotics, Russian Academy of Medical Sciences, Moscow, 2000.

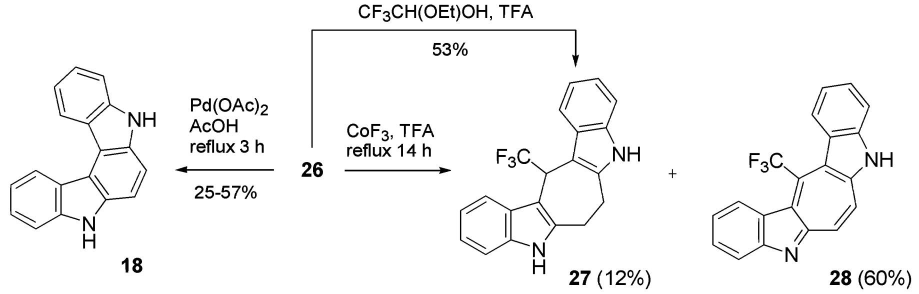
[24] Teuber, H.-J.; Vogel, L. *Chem. Ber.* **1970**, *103*, 3319.

[25] Lavilla, R.; Gotsens, T.; Rodriguez, S.; Bosch, J. *Tetrahedron* **1992**, *48*, 6445.

[26] For a preliminary communication, see: Bergman, J.; Desarbre, E.; Janosik, T.; Lidgren, G.; Venemalm, L. *Heterocycl. Commun.* **1997**, *3*, 397.

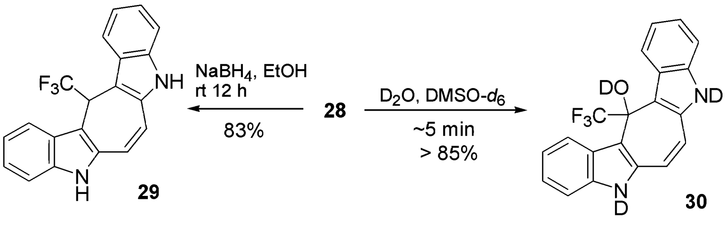
[27] Mahboobi, S.; Burgemeister, T.; Dove, S.; Kuhr, S.; Popp, A. *J. Org. Chem.* **1999**, *64*, 8130.

c]carbazole (**18**) in modest yields (Scheme 3), while catalytic amounts of the palladium source in the presence of an oxidant did not lead to any isolable cyclized species. The low yields observed in this transformation may be the result of degradation of the fairly sensitive product **18**[21a–b] due to the harsh and acidic reaction conditions. When **26** was reacted in hot trifluoroacetic acid (TFA) with CoF$_3$, a reagent previously used for coupling of electron-rich aromatics,[28] a strikingly different outcome was observed, as the cyclohept[1,2-*b*:5,4-*b*′]bisindoles **27** and **28** were isolated from the product mixture using chromatography. The interesting red compound **28** featured only one set of indolic signals in the ^{1}H NMR spectra, indicating a rapid prototropy.



Scheme 3.

An alternative preparation of the rather sensitive bisindole **27** was accomplished in 53% yield by reaction of **26** with trifluoroacetaldehyde ethyl hemiacetal in TFA at room temperature without co-formation of **28** (Scheme 3). When **28** was exposed to sodium borohydride in ethanol, a clean reaction took place, leading to **29**. The leuco-compound **30** was the only product observed when a DMSO-d_6 solution of the red **28** was treated with D$_2$O (Scheme 4), a phenomenon which has been observed already by Emil Fischer in connection with studies on the related rosindoles.[29]



Scheme 4.

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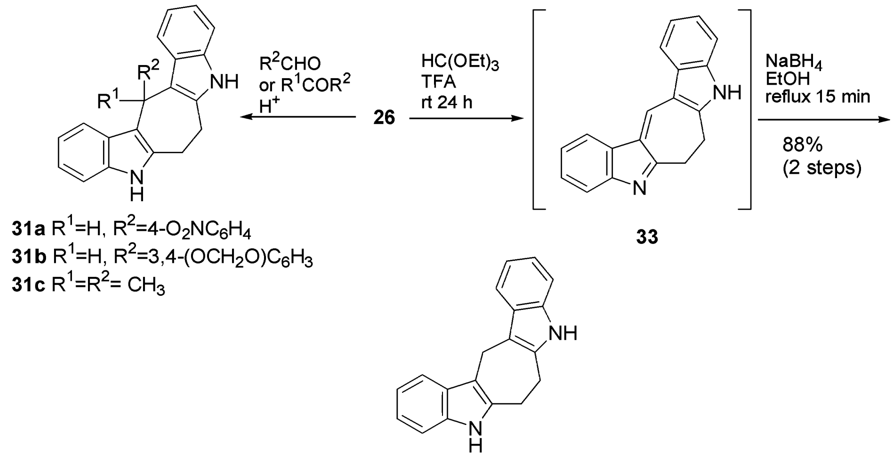
[28] McKillop, A.; Turrell, A. G.; Young, D. W.; Taylor, E. C. *J. Am. Chem. Soc.* **1980**, *102*, 6504.

[29] Fischer, E. *Chem. Ber.* **1886**, *19*, 2988.

Additional bisindoles **31a–c** containing a seven-membered ring were obtained from the common precursor **26** by reaction with aldehydes or acetone under acidic conditions (TFA or *p*-toluenesulfonic acid). The parent cyclohept[1,2-*b*:5,4-*b′*]bisindole **32** was also prepared in high yield using a two-step sequence from **26**, *via* the deep-red intermediate **33** as outlined in Scheme 5. Compounds **31a–b** displayed a quite complex splitting pattern for the methylene protons in the ^{1}H-NMR, which can be attributed to restricted inversion of the central seven-membered ring due to the interference of the bulky substituents with the outer aromatic rings. A similar observation has been reported previously during NMR studies on a series of 9,10-dihydrophenanthrenes.[30]



Scheme 5.

In conclusion, bisindolylethane **26** proved to be a useful precursor both for palladium acetate mediated cyclization to indolo[2,3-*c*]carbazole (**18**), and for the synthesis of cyclohept[1,2-*b*:5,4-*b′*]bisindoles when reacted with carbonyl compounds or their equivalents.

2.3 Indolo[3,2-*a*]carbazoles

2.3.1 Review of previous syntheses

The parent indolo[3,2-*a*]carbazole (**19**) was obtained for the first time in the early 1950s, employing a route involving a Fischer indolization of the bishydrazone **34**, followed by

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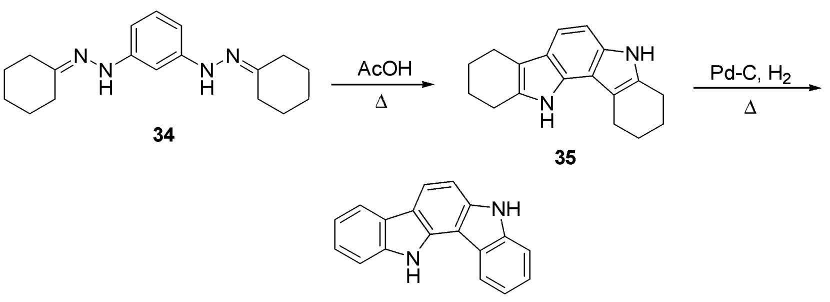
[30] Cosmo, R.; Sternhell, S. *Aust. J. Chem.* **1987**, *40*, 35.

dehydrogenation of the resulting octahydro derivative **35** (Scheme 6).[31] A somewhat later effort involving thermal cyclization of a phenylhydrazone provided an alternative route, which was however marred by the use of harsh reaction conditions and complex starting materials.[32] Some other early examples of related syntheses producing **19**, or simple methylated or hydrogenated derivatives thereof were reported during that time,[33] suffering from poor yields due to the conditions used, or incompatibility with more sensitive substituents. In a recent report, **19** was obtained in low yields *via* cyclization of *N,N′*-diphenyl-1,3-phenylenediamine with palladium acetate in hot acetic acid, or alternatively by irradiation of the same precursor in the presence of iodine.[19] A dimethylated derivative of **19** has also been isolated during yet another recent study employing a Fischer indolization.[34]



19

Scheme 6.

There are several other reports describing the isolation of more complex indolo[3,2-*a*]carbazoles, such as **36**, which was obtained after reaction of the oxindole **37** with *N*-methylindol-3-ylacetonitrile (**38**), followed by cyclization with phosphoric acid (Scheme 7).[35] In addition, two diaryl-substituted indolo[3,2-*a*]carbazoles have been isolated during mechanistic studies on the interaction of indoles with 3-bromoindole under acidic conditions, a procedure which normally produces 2,3′-biindolyls if the acid concentration is kept at levels low enough to avoid further reactions.[36]

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[31] Tomlinson, M. L. *J. Chem. Soc.* **1951**, 809.

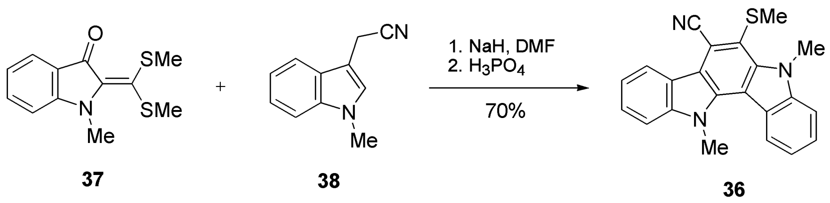
[32] Mann, F. G.; Willcox, T. J. *J. Chem. Soc.* **1958**, 1525.

[33] (a) Hall, J. A.; Plant, S. G. P. *J. Chem. Soc.* **1953**, 116 (b) Jones, N. A.; Tomlinson, M. L. *J. Chem. Soc.* **1953**, 4114.

[34] Royer, H.; Joseph, D.; Prim, D.; Kirsch, G. *Synth. Commun.* **1998**, *28*, 1239.

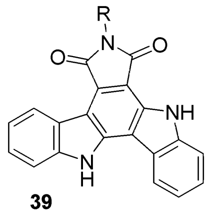
[35] Basaveswara Rao, M. V.; Syam Kumar, U. K.; Ila, H.; Junjappa, H. *Tetrahedron* **1999**, *55*, 11563.

[36] Bocchi, V.; Palla, G. *Tetrahedron* **1986**, *42*, 5019.



Scheme 7.

In our laboratory, a series of indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazoles **39** have been isolated from the reaction of indole with various maleimides in hot acetic acid, or using an alternative route by heating 2,3′-biindolyl (**40**) and the corresponding *N*-substituted maleimides in acetic acid.[37]



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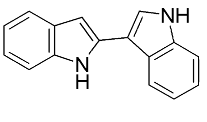

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2.3.2 Indolo[3,2-*a*]carbazoles *via* electrocyclization of 3-ethenyl-2,3′-biindolyl derivatives (Paper II)

A new approach towards the ring system of indolo[3,2-*a*]carbazole (**19**) was devised based on the assumption that an electrocyclization process between the readily available and reactive 2,3′-biindolyl (**40**) and suitable acetylene derivatives or equivalents thereof might produce the desired pentacyclic system. The precursor **40** is most conveniently obtained in multi-gram amounts *via* the acid induced reaction of indole with 3-bromoindole.[38]

The initial attempts were however directed towards developing a simple procedure for the preparation of the parent system **19**. 2,3′-Biindolyl (**40**) was thus reacted with dimethyl-aminoacetaldehyde diethyl acetal in refluxing acetic acid, a clean conversion to indolo[3,2-*a*]carbazole (**19**) was observed (Scheme 8). Similar reaction conditions have been used previously for the synthesis of bisindoles from 2-methylindole.[39]

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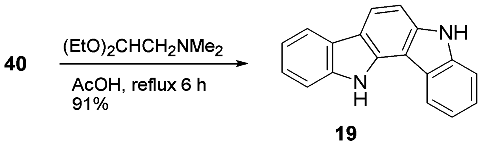
[37] Bergman, J.; Desarbre, E.; Koch, E. *Tetrahedron* **1999**, *55*, 2363.

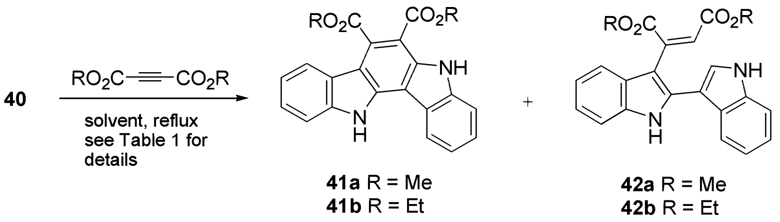
[38] (a) Bocchi, V.; Palla, G. *J. Chem. Soc., Chem. Commun.* **1983**, 1074 (b) Bocchi, V.; Palla, G. *Tetrahedron* **1984**, *40*, 3251.

[39] Yao, A. N. *M. Sc. Thesis*, University of Minnesota, 1963.



Scheme 8.

Heating of dimethyl- or diethyl acetylenedicarboxylate with **40** in benzene, toluene or xylene, lead to the formation of the disubstituted indolo[3,2-*a*]carbazoles **41a–b**, together with compounds **42a–b**, in ratios depending on the solvent used as well as the reaction time (Scheme 9 and Table 1). The reaction seems to proceed *via* initial formation of the adducts **42**, followed by a thermally induced electrocyclization and a final air-induced dehydrogenation. The use of refluxing xylene as the reaction medium provided the best yields of the desired indolocarbazoles **41a–b**, while the reaction in hot benzene gave mixtures with the 3-ethenyl-2,3′-biindolyls **42a–b** as the prevailing components. The reactions were monitored using thin layer chromatography, and the formation of **42a–b** and the subsequent cyclization to the corresponding indolocarbazoles could be observed continuously.

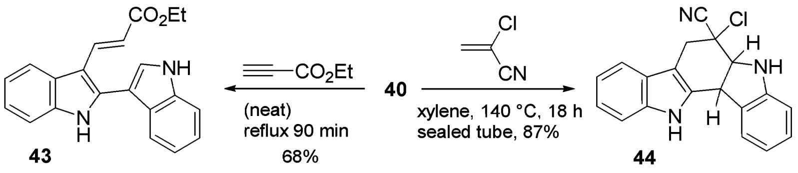


Scheme 9.

R	Solvent	Reaction time (h)	Products and yields
Me	benzene	20	**41a** 17%, **42a** 40%
Me	toluene	24	**41a** 21%, **42a** 40%
Me	xylene	18	**41a** 38%, **42a** 27%
Me	xylene	110	**41a** 51%, **42a** trace
Et	benzene	76	**41b** trace, **42b** 55%
Et	toluene	15	**41b** 16%, **42b** 46%
Et	xylene	48	**41b** 32%, **42b** 55%

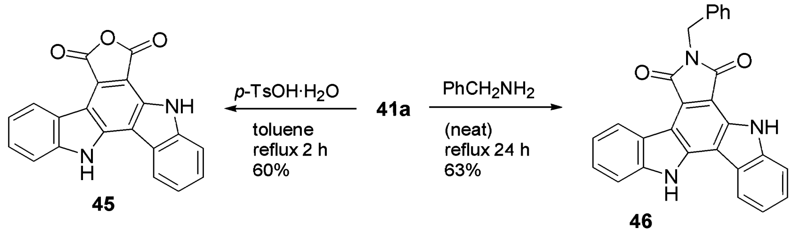
Table 1.

In contrast, the reaction of **40** with neat ethyl propiolate at reflux failed to produce an indolo[3,2-*a*]carbazole, giving instead a respectable yield of the adduct **43** (Scheme 10). The use of xylene as the solvent in this reaction produced only minor amounts of **43** as judged from TLC. Apparently, strongly electron deficient acetylene derivatives are needed to effect a cyclization. Biindolyl **40** was also heated with 2-chloroacrylonitrile in xylene in a sealed tube at 140 °C to furnish the indolo[3,2-*a*]carbazole derivative **44** (Scheme 10).



Scheme 10.

The easy formation of additional fused five-membered rings was demonstrated by the conversion of the diester **41a** into the anhydride **45** using *p*-toluenesulfonic acid monohydrate in refluxing toluene, or the formation of the pyrrolo-fused indolo[3,2-*a*]carbazole **46**[37] upon heating of **41a** in neat benzylamine (Scheme 11).



Scheme 11.

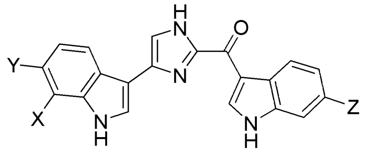
A stepwise synthesis of the parent system **19** involving formylation of **40**, followed by a Henry aldolization and a final thermal cyclization was also accomplished by adapting a protocol previously used for the synthesis of indolo[2,3-*c*]carbazole (**18**).[21a–b]

The results above clearly demonstrate that 2,3′-biindolyl (**40**) can serve as a starting material for a variety of indolo[3,2-*a*]carbazoles and 3-substituted 2,3′-biindolyls thanks to its high reactivity towards electrophiles. Using substituted 2,3′-biindolyls and a wider range of more exclusive dienophiles might further extend the potential of this approach.

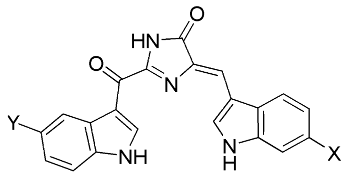
3 BISINDOLES

3.1 Introduction: bisindole alkaloids and synthetic bisindoles

Biologically active indole alkaloids displaying great structural variety are ubiquitous in nature, particularly in marine environments. Several of these compounds have been the subject of extensive synthetic as well as biological studies.[40] The ever growing group of bisindole alkaloids of marine origin is an important class of bioactive compounds isolated from invertebrates such as sponges and tunicates. Representative examples of such natural products are the cytotoxic sponge metabolites topsentins[41] (**47**), and the closely related rhopaladins A–D[42] (**48a–d**) derived from the tunicate *Rhopalaea* sp., which exhibit *e.g.*, antibacterial properties, as well as inhibitory activity against *c-erbB-2* kinase. The search for efficient protein kinase C inhibitors was originally focussed on indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole derivatives such as staurosporine (**8**), but has later expanded into the field of bisindolylmaleimides, thus *e.g.* several macrocyclic compounds with the general structure **49** have proven to display promising effects.[43]



47 X, Y, Z = H, Br, or OH



48a X = OH, Y = Br
48b X = OH, Y = H
48c X = H, Y = Br
48d X = H, Y = H

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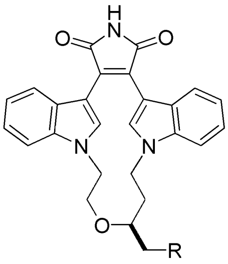
[40] For a recent review on marine natural products, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1, and previous reviews in this series. For an account on marine indole alkaloids, see also (b) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2001**, *18*, 66.

[41] Isolation: (a) Bartik, K.; Breakman, J. C.; Daloze, D.; Stoller, C.; Huysecom, J.; Vandevyer, G.; Ottinger, R. *Can. J. Chem.* **1987**, *65*, 2118 (b) Tsuji, S.; Rhinehart, K. L.; Gunasekera, S. P.; Kashman, Y.; Cross, S. S.; Lui, M. S.; Pomponi, S. A.; Diaz, M. C. *J. Org. Chem.* **1988**, *53*, 5446 (c) Shin, J.; Seo, Y.; Cho, K. W.; Rho, J.-R.; Sim, C. J. *J. Nat. Prod.* **1999**, *62*, 647 (d) Casapullo, A.; Bifulco, G.; Bruno, I.; Riccio, R. *J. Nat. Prod.* **2000**, *63*, 447. For synthetic approaches, see e.g. (e) Breakman, J. C.; Daloze, D.; Stoller, C. *Bull. Soc. Chim. Belg.* **1987**, *96*, 809 (f) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887 (g) Achab, S. *Tetrahedron Lett.* **1996**, *37*, 5503 (h) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 2121.

[42] Isolation: (a) Sato, H.; Tsuda, M.; Watanabe, K.; Kobayashi, J. *Tetrahedron* **1998**, *54*, 8687. Syntheses: (a) Fresnada, P. M.; Molina, P.; Sanz, M. A. *Synlett* **2000**, 1190 [rhopaladin D (**48d**)], (b) Janosik, T.; Johnson, A.-L.; Bergman, J. *Tetrahedron, in press* [rhopaladins A–D (**48a–d**].

[43] (a) Jirousek, M. R.; Gillig, J. R.; Gonzalez, C. M.; Heath, W. F.; McDonald III, J. H.; Neel, D. A.; Rito, C. J.; Singh, U.; Stramm, L. E.; Melikian-Badalian, A.; Baevsky, M.; Ballas, L. M.; Hall, S. E.; Winneroski, L. L.; Faul, M. M. *J. Med. Chem.* **1996**, *39*, 2664 (b) Faul, M. M.; Krumrich, C. A. *J. Org. Chem.* **2001**, *66*, 2024.



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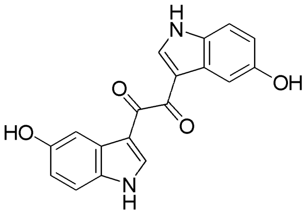
The often unusual structural features and interesting pharmacological effects of bisindoles of marine origin call for further studies in this area, both regarding the isolation and identification of new natural products belonging to this class, and synthesis of the hitherto known structures in order to provide material for biological evaluation.

3.2 Synthesis of hyrtiosin B (Paper III)

Some time ago, the bisindole alkaloid hyrtiosin B (**50**) was isolated from the Okinawan marine sponge *Hyrtios erecta*, and was shown to possess weak cytotoxic activity against human epidermoid carcinoma KB cells *in vitro*.[44] The objective of our study was to devise a concise synthesis of **50** based on a method previously developed in our laboratory for the acylation of indolozinc species generated *in situ* from the interaction of indoles with Grignard reagents followed by transmetallation with zinc chloride,[45] a protocol which has proven to give higher yields and better selectivity than the use of conventional indole magnesium halides.



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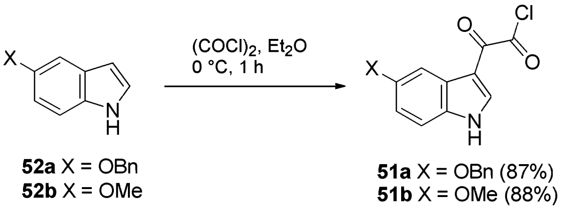
[44] Kobayashi, J.; Murayama, T.; Ishibashi, M.; Kosuge, S.; Takamatsu, M.; Ohizumi, Y.; Kobayashi, H.; Ohta, T.; Nozoe, S.; Sasaki, T. *Tetrahedron* **1990**, *46*, 7699.

[45] Bergman, J.; Venemalm, L. *Tetrahedron* **1990**, *46*, 6061.

The required glyoxylylchlorides **51a–b** were prepared in high yields as described in the literature[46] starting from 5-benzyloxyindole (**52a**) or 5-methoxyindole (**52b**) and oxalyl chloride (Scheme 12).



Scheme 12.

The acylation step was then accomplished by treatment of the indolozinc reagents generated from the indoles **52a** or **52b** with freshly prepared ethylmagnesium bromide, and subsequent transmetallation with anhydrous zinc chloride in ether, followed by addition of the glyoxylylchlorides **51a** or **51b** respectively to provide the symmetrical coupling products **53a–b** as outlined in Scheme 13. After a final *O*-dealkylation of the bisindoles **53a–b** with an excess of BBr_3 in dichloromethane, synthetic hyrtiosin B (**50**) was obtained in good overall yields. The debenzylation occurred readily requiring 4 equivalents of BBr_3, while a larger excess (12 equivalents) was necessary to ensure efficient demethylation. This difference in reactivity is probably due to the higher solubility of **53a**, as cleavage of methyl ethers is generally considered to take place readily with only a slight excess of BBr_3. In this context, it is interesting to note that initial demethylation attempts using the method of Prey (heating with pyridine hydrochloride)[47] failed, as did attempted catalytic debenzylation experiments using palladium on charcoal in the presence of hydrogen.

The same series of transformations were also used to prepare the mono-hydroxy derivative **54** *via* the *O*-benzyloxy precursor **53c**. A closely related derivative possessing a chlorine in the 5-position of one of the indoles instead of a hydroxy group (also prepared using the method of Bergman and Venemalm), has been used as an intermediate in a synthesis of the indolo[2,3-*a*]carbazole alkaloid (–)-tjipanazole F1.[48]

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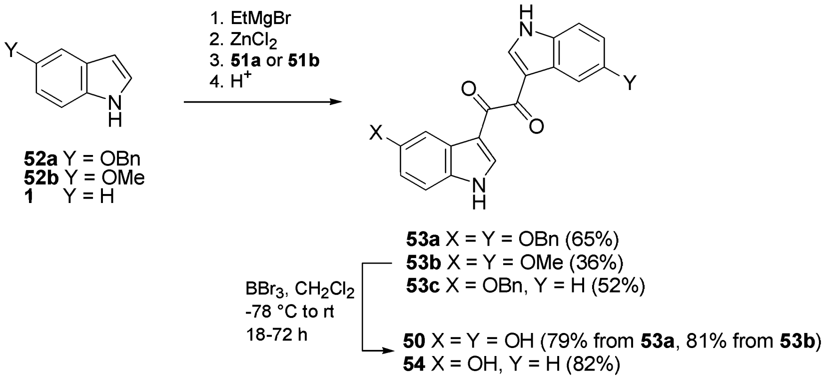
[46] (a) Speeter, M. E.; Anthony, W. C. *J. Am. Chem. Soc.* **1954**, *76*, 6208 (b) Takatori, K.; Takashima, M. *Yakugaku Zasshi* **1963**, *83*, 795 (c) Kralt, T.; Asma, W. J.; Haeck, H. H.; Moed, H. D. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 313 (d) Neumeyer, J. L.; Moyer, U. V.; Leonard, J. E. *J. Med. Chem.* **1969**, *12*, 450.

[47] (a) Prey, V. *Chem. Ber.* **1941**, *74*, 1219 (b) Prey, V. *Chem. Ber.* **1942**, *75*, 350.

[48] Gilbert, E. J.; Ziller, J. W.; van Vranken, D. L. *Tetrahedron* **1997**, *53*, 16553.



Scheme 13.

In conclusion, the marine alkaloid hyrtiosin B (**50**) was prepared efficiently in 38% overall yield from 5-benzyloxyindole (**52a**) using acylation of indolozinc reagents as the key step.

3.3 Synthesis of various related bisindoles

During attempts to prepare pentacyclic bisindole systems containing an eight-membered ring, additional bisindoles were studied. Several previous studies have focussed on the structurally unusual metabolite caulerpin (**55**), originally isolated from the green algae *Caulerpa* sp.[49] The correct structure of **55** was however not assigned unambiguously until several years later, in connection with a low yielding synthesis employing a dimerization of an indole-2-acetic acid derivative.[50] Two closely related red pigments (**56–57**) were later obtained from extracts of *Caulerpa racemosa.*[51] Caulerpin (**55**) itself has also been identified as a plant growth regulator.[52] Recently, the interesting bisindole **58** having a head-to-head arrangement of the two indole nuclei has been prepared *via* an indolo-2,3-quinodimethane intermediate, and was also resolved in the form of its diamide.[53] In addition, the bisindole **59** has been reported as a product from the reaction of 1,2-bis(1*H*-indol-2-yl)ethane (**25**) with ethylmagnesium bromide and *N*-methyl-3,4-dibromomaleimide.[27]

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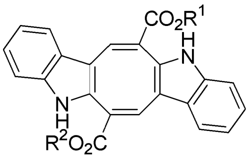
[49] Aguilar-Santos, G. *J. Chem. Soc. C* **1970**, 842.

[50] Maiti, B. C.; Thomson, R. H.; Mahendran, M. *J. Chem. Res. (S)* **1978**, 126.

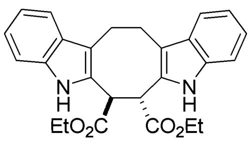
[51] Anjaneyulu, A. S. R.; Prakash, C. V. S.; Mallavadhani, U. V. *Phytochemistry* **1991**, *30*, 3041.

[52] Raub, M. F.; Cardellina II, J. H.; Schwede, J. G. *Phytochemistry* **1987**, *26*, 619.

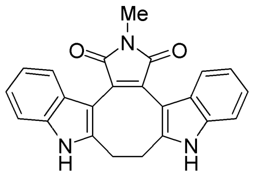
[53] Diker, K.; de Maindreville, M. D.; Lévy, J. *Tetrahedron Lett.* **1999**, *40*, 7459.



55 $R^1 = R^2 = Me$
56 $R^1 = R^2 = H$
57 $R^1 = Me$, $R^2 = H$

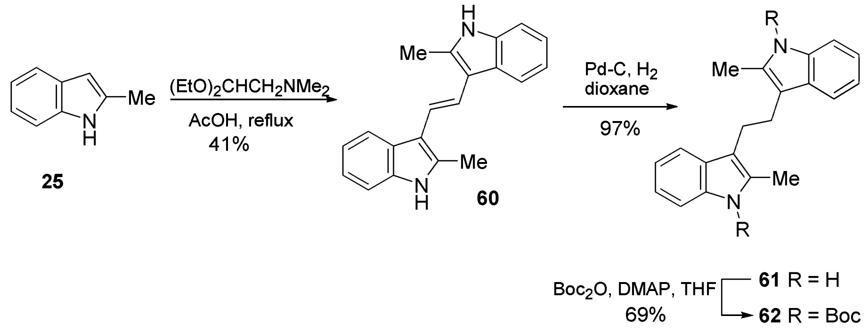


58



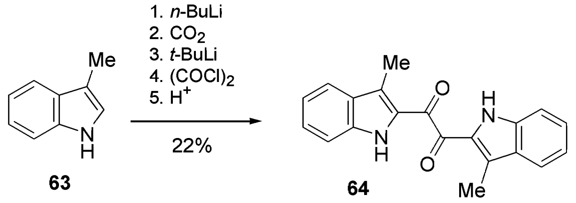
59

Progressing further with our studies on indolocarbazoles, new synthetic efforts towards the rare ring system present in **58** and **59** were considered. The previously known bisindoles **60** and **61**[39] were studied as possible precursors, since they could theoretically be transformed into the desired cyclic system *via* an intramolecular coupling of the indole-2-methyl groups. The alkene **60** was prepared as described previously,[39] from 2-methylindole (**25**) and dimethylaminoacetaldehyde diethyl acetal in refluxing acetic acid, and was then catalytically hydrogenated to afford **61** (Scheme 14). However, all attempted functionalization of **61** (*e.g.* oxidation with CAN or SeO_2) failed, as did treatment with strong bases (*n*-BuLi or *t*-BuLi) followed by addition of potential coupling agents (I_2, CI_4, ICH_2CH_2I). Unsuccessful intramolecular coupling experiments were also performed on the readily available di-Boc derivative **62**. The steric interaction induced by the proximity of the ethylene bridge in the 3-position is perhaps the reason for the low reactivity of **61**, a phenomenon which is even more pronounced in the case of **62**, which has a bulky electron-withdrawing group on both nitrogen atoms. In addition, it has to be noted that construction of eight-membered rings is often a disfavoured reaction when other pathways are available, and the difficulty in formation of the required dianions has also to be considered as a complicating factor.



Scheme 14.

In another application of the Katritzky protocol,[12] 3-methylindole (**63**) was converted in modest yield into the new dione **64** (Scheme 15), which in resemblance to **61** resisted all oxidation attempts of the 3-methyl groups rendering only unchanged starting material. It was thus concluded, that the bisindoles mentioned above are not prone to participate in intramolecular coupling reactions.



Scheme 15.

4 SULFUR CONTAINING INDOLES AND BISINDOLES

4.1 Introduction

Compounds possessing an indole substructure in combination with sulfur containing moieties constitute a large class of molecules displaying diverse structural features, as well as broad biological activity spectra. In this section, the emphasis will be placed on selected indoles which have sulfur atoms attached to positions 2 and/or 3, but even this restriction does not permit giving a comprehensive account, as these systems have been thoroughly studied and exhibit a rich chemistry.

The syntheses and properties of numerous simple mono-thionated indole derivatives such as **65**[54] and **66**[55] have been discussed and studied repeatedly in the literature. For instance, the thione **65** was obtained from the corresponding *gem*-dichloro compound **67** after treatment with potassium ethyl xanthate,[54] while the more sensitive **66** was found to undergo easy coupling under extrusion of sulfur giving indigo (**2**).[55] Previous approaches to indoline-2-thiones like **68–69** have employed the thionation of oxindoles with P_4S_{10} in benzene or toluene,[56] or lithiation routes.[57] The interesting thione **70** has recently been reported as a starting material in

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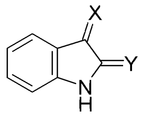
[54] Schönberg, A.; Freese, E. *Chem. Ber.* **1968**, *101*, 701.

[55] (a) Sandmeyer, T. *Z. Farben Text. Chem.* **1903**, *2*, 129 (b) Sander, L. *Chem. Ber.* **1925**, *58*, 820.

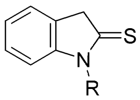
[56] (a) Hino, T.; Yamada, K.; Akaboshi, S. *Chem. Ind. (London)* **1967**, 275 (b) Hino, T.; Tsuneoka, K.; Nakagawa, M.; Akaboshi, S. *Chem. Pharm. Bull.* **1969**, *17*, 550, and references cited therein.

[57] Rewcastle, G. W.; Denny, W. A. *Heterocycles* **1994**, *37*, 701.

the synthesis of the cruciferous phytoalexin sinalexin.[58] The applicability of these compounds in synthesis is further illustrated by the fact that indoline-2-thiones have also served as precursors for the preparation of 2,2′-dithiobisindole tyrosine kinase inhibitors.[59]



65 X = S, Y = O
66 X = O, Y = S
67 X = Cl_2, Y = O



68 R = H
69 R = Me
70 R = OMe

Although numerous thionated indoles related to the dye indigo (**2**) have also been extensively studied and discussed over the years, no thionated indigo derivatives have so far been prepared, all attempts lead instead to the isolation of other products. Thus for example, *N,N′*-dimethyldithioisoindigo (**71**) has been claimed as a product from the reaction of *N*-methylindoline-2-thione (**69**) with *p*-toluenesulfonyl azide in pyridine,[60] or from the thionation of *N,N′*-dimethylisoindigo (**72**) with Lawesson´s reagent.[61] Later studies have demonstrated that one of the isolable products formed in these reactions is the tetraindole **73**, which could be regarded as a "dimer" of the valence tautomer **74** of *N,N′*-dimethyldithioisoindigo (**71**).[62] Another transformation which also needs reconsideration is the claimed reduction of the readily available tetrasulfide **75** into **76**,[63] an outcome which has been questioned recently in the light of studies on systems like **73**.[62] In this context it is also interesting to note that the tetrasulfide **75** was probably obtained already in 1938, but at that time it could not be assigned a definite structure.[64] Compound **75** has also been demonstrated to exhibit powerful antifungal activity, in particular against the fungus *Botrytis cinerea*.[65] All of the examples mentioned above neatly depict the complex and in some cases unexpected reactivity patterns which can be encountered during studies on these systems, and there is no doubt that further studies in this field are necessary to shed light on the sometimes contradictory results.

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[58] Pedras, M. S. C.; Zaharia, I. L. *Org. Lett.* **2001**, *3*, 1213.

[59] (a) Rewcastle, G. W.; Palmer, B. D.; Dobrusin, E. M.; Fry, D. W.; Kraker, A. J.; Denny, W. A. *J. Med. Chem.* **1994**, *37*, 2033 (b) Palmer, B. D.; Rewcastle, G. W.; Thompson, A. M.; Boyd, M.; Showalter, H. D. H.; Sercel, A. D.; Fry, D. W.; Kraker, A. J.; Denny, W. A. *J. Med. Chem.* **1995**, *38*, 58.

[60] Bailey, A. S.; Seager, J. F.; Rashid, Z. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2384.

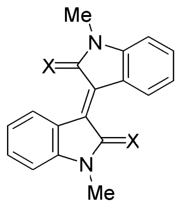
[61] El-Kateb, A. A.; Shabana, R.; Osman, F. H. *Z. Naturforsch.* **1984**, *39b*, 1614.

[62] Schroth, W.; Spitzner, R.; Felicetti, M.; Wagner, C.; Bruhn, C. *Eur. J. Org. Chem.* **2000**, 3093.

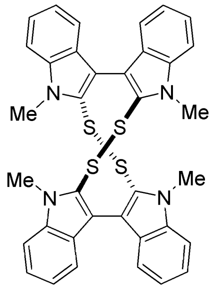
[63] Carpenter, W.; Grant, M. S.; Snyder, H. R. *J. Am. Chem. Soc.* **1960**, *82*, 2739.

[64] Szperl, L. *Rocz. Chem.* **1938**, *18*, 804.

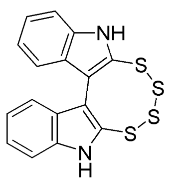
[65] Montinari, L.; Pavanetto, F.; Mazza, M. *Farmaco, Ed. Sci.* **1981**, *36*, 856.



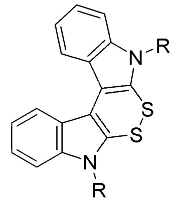
71 X = S
72 X = O



73



75

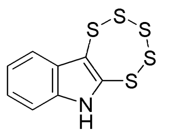


74 R = Me
76 R = H

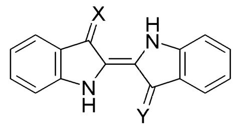
4.2 Synthesis and structure of sulfur containing indoles and bisindoles

4.2.1 Systems with two indole units (Paper IV)

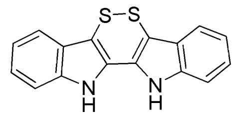
The previously reported formation of pentathiepino[6,7-*b*]indole[66] (**77**) during the reaction of isatin (**3**) with the powerful thionating agent P_4S_{10} in refluxing pyridine,[67] is accompanied by the co-formation of two other, at that time unidentified products. Thus, a deep blue compound which was assigned the structure of monothioindigo (**78**) could now be isolated in low yield from the reaction mixture using chromatography. Monothioindigo (**78**) exhibited a visible light absorption at λ_{max} = 582 nm, to compare with indigo (**2**), which displays a λ_{max} at 610 nm.[68] The characterization of **78** constitutes the first example of a thionated indigo derivative with an established structure.



77



2 X = Y = O
78 X = S, Y = O
79 X = Y = S



80

Theoretically, the interesting molecules thioindigo (**79**), or its valence tautomer, the dithiin **80**, might be prepared by thionation of indigo (**2**).[69,70] For this reason, indigo (**2**) was

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[66] Bergman, J.; Stålhandske, C. *Tetrahedron Lett.* **1994**, *35*, 5279.

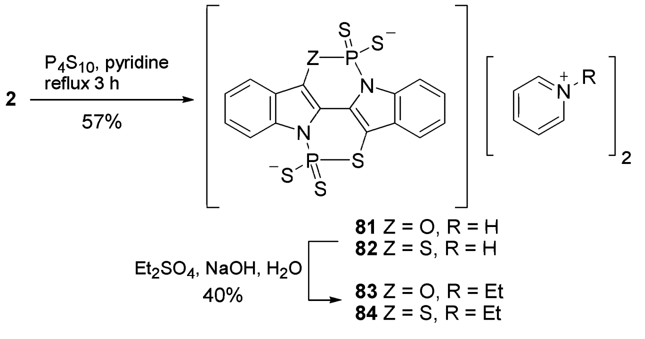
[67] (a) Fluck, E.; Binder, H. *Z. Anorg. Allg. Chem.* **1967**, *354*, 113 (b) Meisel, M.; Grunze, H. *Z. Anorg. Allg. Chem.* **1968**, *360*, 277.

[68] Lüttke, W.; Klessinger, M. *Chem. Ber.* **1964**, *97*, 2342.

[69] Sieghold, H. *Ph.D. Thesis*, Göttingen, 1973.

[70] For a discussion on valence tautomers of indigoids, see also: Sieghold, H.; Lüttke, W. *Angew. Chem.* **1975**, *87*, 63, and the more recent contributions from Schroth and co-workers, e.g. ref. 62.

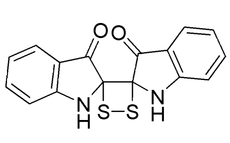
heated with P_4S_{10} in pyridine (Scheme 16), and the initially deep blue solution changed colour into yellow, indicating that a reaction had taken place, which was unexpected, as it has previously been claimed that indigo (**2**) remains unchanged under these very conditions.[69] The sparingly soluble yellow product **81** thus obtained could be purified by dissolution in dilute aqueous sodium hydroxide, and subsequent precipitation with acetic acid. Due to the extremely poor solubility and quick decomposition in *e.g.* DMSO-d_6 of this salt, NMR studies could only be conducted after dissolution of **81** in the system D_2O–NaOD, prepared from D_2O and sodium metal. The ^{1}H NMR data indicated the presence of a pyridine moiety and two different indole systems, thus implying that **81** is non-symmetrical, which was further supported by the presence of two signals at δ 85.5 and 96.3 in the ^{31}P spectrum, where the presence of an additional weak singlet signal at δ 100.6 also suggested the existence of a minor impurity consisting of the symmetrical fully thionated product **82**. In order to prepare a derivative more suitable for spectroscopic studies, **81** was alkylated with diethyl sulfate under basic conditions to afford the salt **83**, the structure of which was elucidated using 1D and 2D NMR experiments, as well as X-ray crystallography,[¶] albeit the quality of the crystals was low due to the presence of an impurity consisting of the symmetrical product **84**. The fact that the non-symmetrical *S,O*-product **81** is formed rather than the *S,S*-product **82** could possibly be rationalized by an initial formation of the isolable intermediate monothioindigo (**78**), which is then easily phosphorylated on the sulfur atom, thus altering the character of the remaining carbonyl, and favouring an *O*-phosphorylation instead of a second thionation. Apparently, a different approach had to be developed to gain access to systems **79** or **80**.



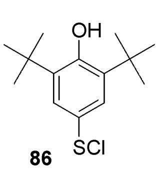
Scheme 16

[¶] The X-ray crystallographic studies were performed by Dr. Birgitta Stensland, Preformulation and Biopharmaceutics, Solid State Analysis /SBBG B341:3, AstraZeneca PAR & D, SE-151 85 Södertälje, Sweden, or by Prof. Claes Stålhandske, Department of Inorganic Chemistry 2, Chemical Center, Box 124, SE-221 00 Lund, Sweden.

Having solved the structures of **81** and **83**, the reaction of isatin (**3**) with P_4S_{10} in pyridine[66] was revisited, leading to the identification of the third and major product as the salt **81** also in that case. A plausible explanation of this outcome involves an initial formation of **66**, which is known to readily couple to give indigo (**2**),[55] possibly *via* sulfur extrusion from the intermediate **85**. A similar mechanism has been proposed in connection with studies involving coupling reactions of **86**, which gave the quinone **87** *via* the intermediates **88** and **89**.[71] In addition, it must be mentioned that the closely related isomeric thione **90** has been isolated recently.[72] The speculation that pentathiepino[6,7-*b*]indole (**77**) is formed by further thionation of dithioisatin (**91**) or the ring tautomer[73] (**92**) could not be verified, as compounds of this type could never be isolated from the reaction mixture.



85



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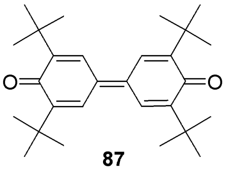
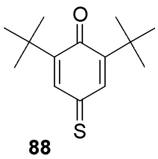
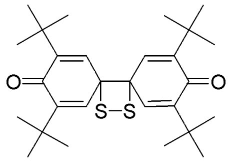


87



88



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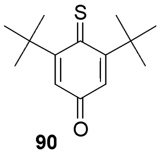
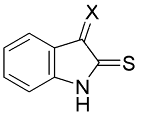
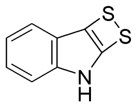


90

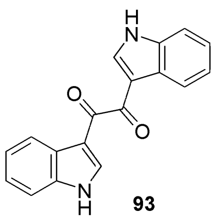


66 X = O
91 X = S

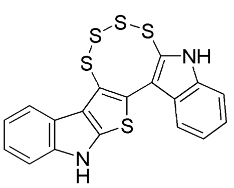


92

In a related thionation experiment, the dione **93**[45] was heated with P_4S_{10} in pyridine, leading to a complex reaction mixture, from which the thienoindole **94** could be isolated in 9.5% yield. The structure of **94** was also rigorously established using X-ray crystallography (Figure 1). Evidently, the growing sulfur chains attack the neighbouring indole ring, thus also demonstrating the propensity of sulfur to participate in the formation of larger rings.



93



94

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[71] Pastor, S. D. *J. Org. Chem.* **1984**, *49*, 5260.
[72] Suzuki, R.; Matsumoto, K.; Kurata, H.; Oda, M. *Chem. Commun.* **2000**, 1357.
[73] Breitenstein, M.; Schultz, R.; Schweig, A. *J. Org. Chem.* **1982**, *47*, 1979.

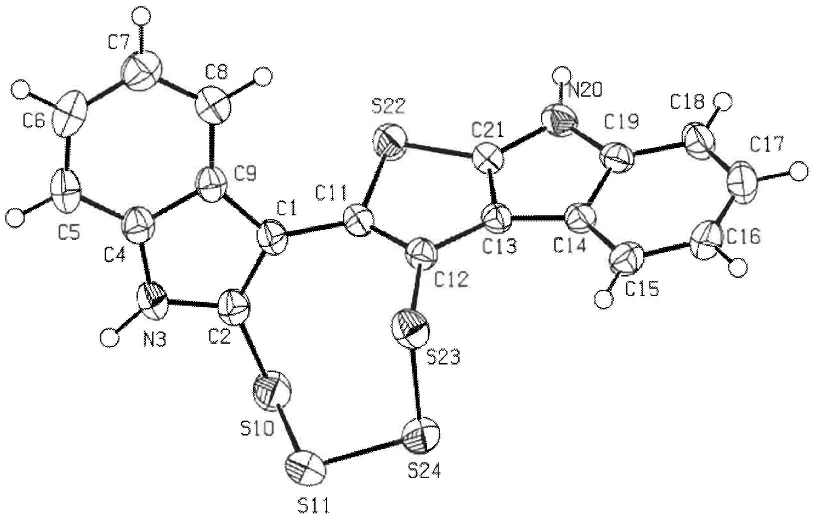
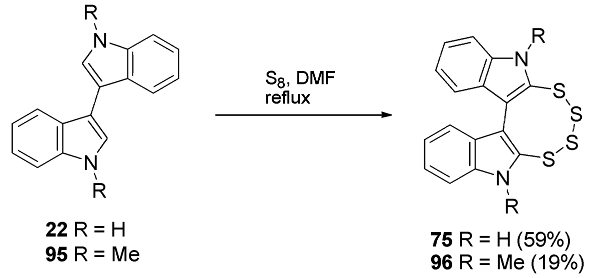


Figure 1. X-ray structure of compound **94.**

Now the attention was turned towards the reactions of 3,3′-biindolyls with elemental sulfur in hot DMF, as it is well established that heating of indole with sulfur in DMF produces the tetrasulfide **75.**[63] When 3,3′-biindolyl[20] (**22**) or *N,N*′-dimethyl-3,3′-biindolyl[21b] (**95**) were treated with sulfur in refluxing DMF (Scheme 17), the formation of the tetrasulfides **75** and **96** were observed, although interestingly enough, the reaction of **22** with S_8 was previously claimed not to give **75** under these conditions.[63]



22 R = H
95 R = Me

75 R = H (59%)
96 R = Me (19%)

Scheme 17.

An X-ray crystallographic study of compound **75** showed that it crystallizes from DMF as a 1:1 solvate in the triclinic non-centrosymmetric space group *P*1 with two independent molecules in the unit cell, thus indicating that **75** is chiral in the crystal, which is caused by steric repulsion of the indole H-4 atoms thus inducing a helical twist in the molecule (Figure 2), and the angles between the 3,3′-connected indolic planes in the two molecules of **75** present in the unit cell are 62.9° and 66.5°, respectively. Previous studies on heterohelicenes have demonstrated that *e.g.*, **97** can be isolated in optically active form by crystallization from benzene, however in chloroform solutions, rather quick racemization could be observed.[74] More recently, several dioxahelicenes such as **98** were shown to display low inversion barriers in solution causing racemization, whereas in the solid state, stable chiral conformations could be observed by X-ray crystallography.[75]

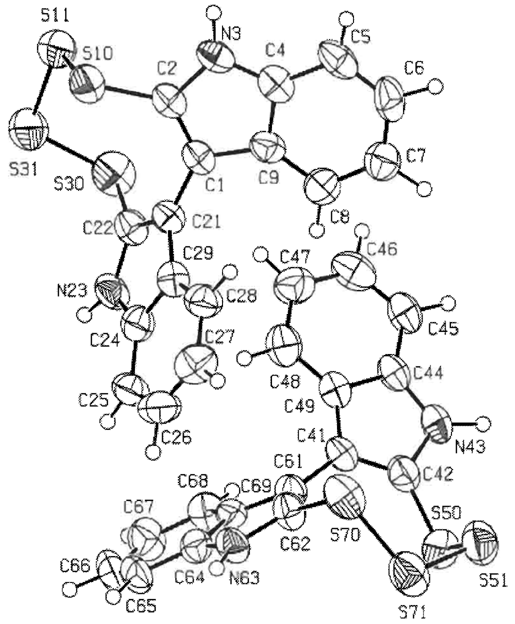


Figure 2. The X-ray crystal structure and conformation of **75**. The two DMF solvate molecules are omitted for clarity.

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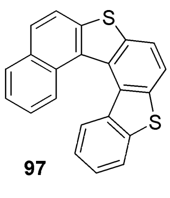
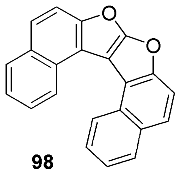
[74] (a) Wynberg, H.; Groen, M. B. *J. Am. Chem. Soc.* **1968**, *90*, 5339 (b) Groen, M. B.; Schadenberg, H.; Wynberg, H. *J. Org. Chem.* **1971**, *36*, 2797.

[75] Eskildsen, J.; Krebs, F. C.; Faldt, A.; Sommer-Larsen, P.; Bechgaard, K. *J. Org. Chem.* **2001**, *66*, 200.



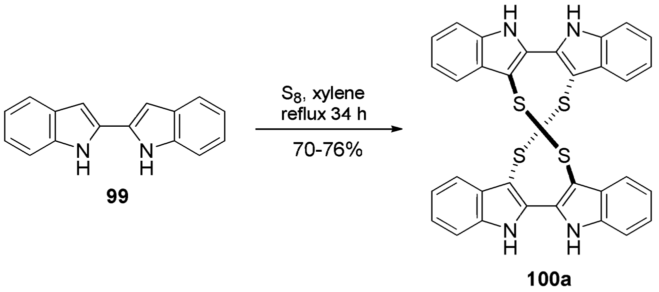
97



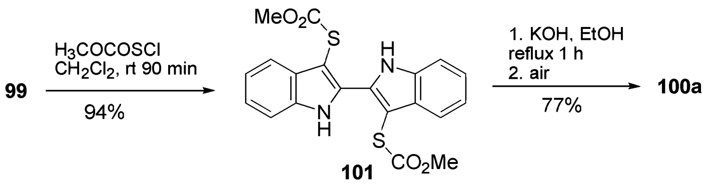
98

4.2.2 Systems with four indole units (Paper V)

During new attempts to prepare the elusive dithiin **80** in a simple fashion from the readily available 2,2′-biindolyl[76] (**99**) and elemental sulfur in refluxing xylene, the previously described yellow tetraindole **100a**[62] was prepared in good yield (Scheme 18). An alternative preparation of **100a** *via* the biindolyl **101** was accomplished using a modified literature procedure[77,78] as outlined in Scheme 19. In similarity with previous attempts,[62,77,78] the still unknown compounds **79** or **80** were never observed in these reactions.



Scheme 18.



Scheme 19.

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[76] Bergman, J.; Koch, E.; Pelcman, B. *Tetrahedron* **1995**, *51*, 5631 and references cited therein.

[77] (a) Schroth, W.; Felicetti, M.; Hintzsche, E.; Spitzner, R.; Pink, M. *Tetrahedron Lett.* **1994**, *35*, 1977 (b) Schroth, W.; Hintzsche, E.; Jordan, H.; Jende, T.; Spitzner, R.; Thondorf, I. *Tetrahedron* **1997**, *53*, 7509.

[78] Schroth, W.; Hintzsche, E.; Felicetti, M.; Spitzner, R.; Sieler, J.; Kempe, R. *Angew. Chem.* **1994**, *106*, 808.

The yellow tetraindole **100a** was found to be extremely insoluble, and when dissolved in hot polar solvents such as DMSO, DMF or *N,N*-dimethylacetamide (DMA), it became evident that transformations into other species took place, as the initially yellow suspensions of **100a** turned increasingly red during heating. For instance, when a preheated solution of **100a** in DMSO-d_6 was analysed, two independent sets of indolic signals were distinguished in the ^{1}H NMR spectrum. Based on this observation, an experiment was performed where **100a** was heated in DMSO for 1 h to produce the red conformer **100b** (Scheme 20), the structure of which was solved by X-ray crystallography after recrystallization of **100b** from a mixture of acetic anhydride and DMA (Figure 3). Several interesting structural features of **100b** could account for its easy formation and isolation. Thus, the indole planes involved in the different 2,2′-biindolyl moieties are almost parallel with an inter-planar distance of approximately 3.7 Å, which facilitates π-stacking. All four indole NH are oriented in different directions, and participate in intramolecular hydrogen-bond-like interactions with the most proximate sulfur atoms, thus probably stabilizing the almost planar arrangement of the 2,2′-biindolyl frameworks.

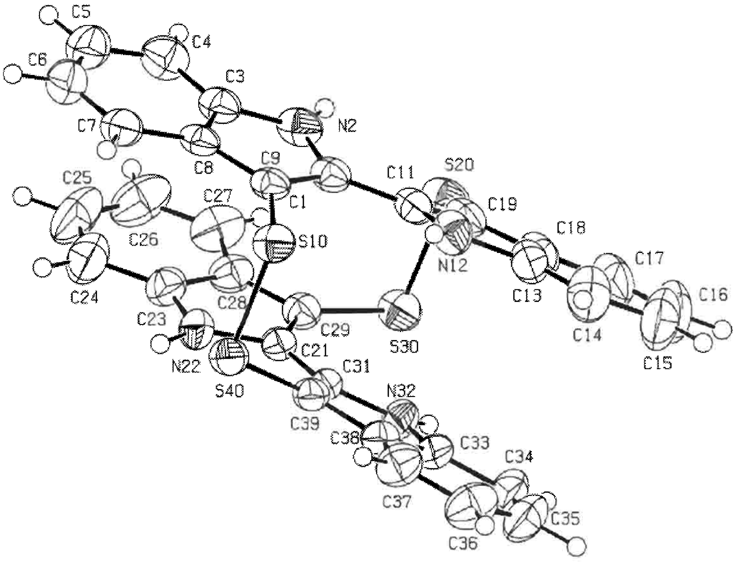
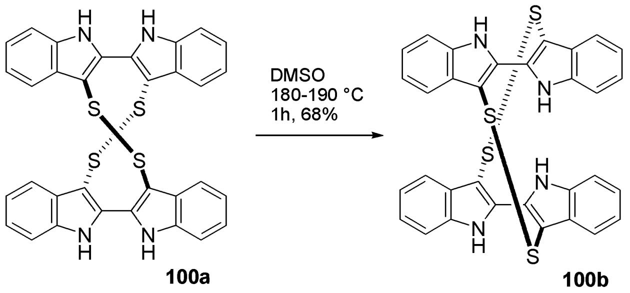
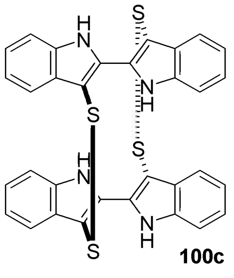


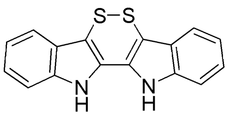
Figure 3. The crystal structure of **100b**.



Scheme 20.

Further NMR studies revealed that a third deep-red conformer with the suggested structure **100c** is formed on heating (145 °C) of **100b** in DMSO-d_6, however it was not possible to isolate this species, as it quickly reverts back to **100b** on cooling. From such solutions, only unchanged **100b** could be isolated. In contrast, compound **100b** underwent an interesting transformation on heating in DMA solely, followed by filtration of the hot solution, as the crystalline material obtained from the filtrate was identified by X-ray crystallography as a DMA solvate of the red dithiin **80** (Figure 4). Obviously, heating of **100b** in DMA alone causes extensive breaking of the *S,S* bridges, while the use of the lower boiling solvent combination consisting of acetic anhydride–DMA ensures that **100b** stays intact throughout the operation. Evidently, the dithiin **80** could only be studied in the solid state, as attempted dissolution of the crystals in $CDCl_3$ caused a rapid dimerization producing a mixture of **100a** and **100b**, while solutions in DMSO-d_6 quickly produced the tetraindole **100c** as the prevailing component of the dimerization mixture.


100c


80

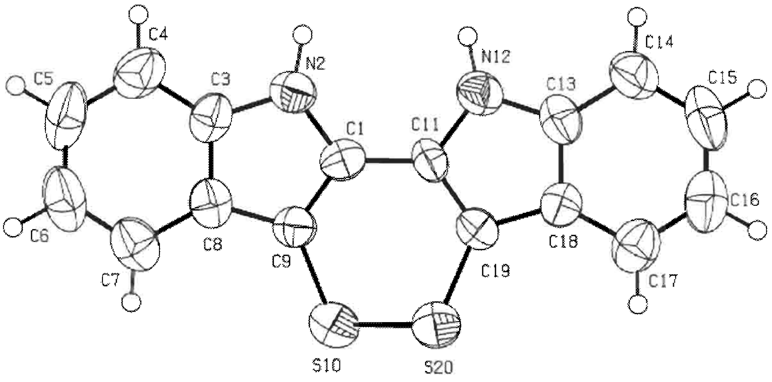


Figure 4. X-ray structure of **80**. The compound crystallizes with a disordered molecule of DMA which is not depicted for clarity.

The assigned structures of the conformers **100a–c** were supported by MS, NMR and UV/Vis data. All compounds **100a–c** displayed molecular ions with *m/z* 588 together with base peaks at *m/z* 294 corresponding to *M*/2 in the EI mode. The ^{1}H NMR data for **100a** featured a shielded aromatic proton signal at δ 5.59 in $CDCl_3$, the only useful solvent for this compound, while both **100b** and **100c** displayed spectra in DMSO-d_6 expected for normal indolic systems, since the indole moieties of **100b–c** are placed more or less directly above each other thus eliminating the possibility of shielding effects. The yellow colour and UV/Vis characteristics (λ_{max} 308 and 385 nm in $CHCl_3$) of **100a** are also consistent with a relatively large angle between the 2,2′-coupled indole planes, while the chromophores present in the red coloured **100b** or **100c** suggest that the 2,2′-connected indoles are roughly co-planar, which is also evident from X-ray data in the case of **100b**. It is also apparent from the X-ray structure of **80** that the arrangement of the two indoles is almost planar as well with an angle of 15.5°, which is also consistent with the deep red colour of the crystals, a feature that can also be attributed to the presence of the central 1,2-dithiin[79] ring. Interestingly, the NMR-data in DMSO-d_6 for the tetraindole **100a** previously obtained by German workers[62] have been erroneously assigned to a mixture of **100a** and "oligomeric material". During our studies on these systems, no larger oligomeric species were ever isolated.

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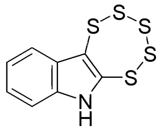
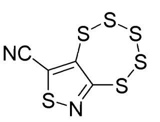
[79] For thorough studies and discussion on various aspects of 1,2-dichalcogenin chemistry, see: Block, E.; Birringer, M.; DeOrazio, R.; Fabian, J.; Glass, R. S.; Guo, C.; He, C.; Lorance, E.; Qian, Q.; Schroeder, T. B.; Shan, Z.; Thiruvazhi, M.; Wilson, G. S.; Zhang, X.; *J. Am. Chem. Soc.* **2000**, *122*, 5052, and references cited therein.

4.2.3 Pentathiepino[6,7-*b*]indoles

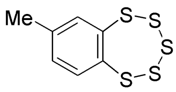
4.2.3.1 A short introduction to pentathiepins. Studies performed in our group on the thionation reactions of isatin[66] leading to the preparation of pentathiepino[6,7-*b*]indole (**77**) (Section 4.2.1) represents an example of the isolation of a pentathiepin fused to a heterocyclic or a carbocyclic ring system, a class of compounds which has attracted considerable interest. Thus *e.g.* compound **102** has been demonstrated to possess a wide range of powerful antifungal activities,[80] while the benzo-fused pentathiepin **103** was recently shown to display DNA cleaving properties.[81] Much effort has also been devoted to developing syntheses[82] of the cytotoxic alkaloid varacin (**104**), isolated from *Lissoclinum* tunicates.[83] The closely related lissoclinotoxin A (**105**) was extracted from *Lissoclinum perforatum* and was also shown to exhibit antimicrobial and antifungal effects,[84] but the correct structure was not elucidated until several years later.[85] A few other metabolites belonging to this class have been isolated from other unidentified *Lissoclinum* species, as well as *Polycitor* or *Eudistoma* species.[86]



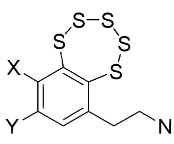
77



102



103



104 X = Y = OMe
105 X = OH, Y = OMe

Numerous other reports dealing with synthetic procedures towards pentathiepins have appeared,[87] and preparative routes aiming at acyclic pentasulfides have also been explored in

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[80] (a) Vladuchick, S. A.; Fukunaga, T.; Simmons, H. E.; Webster, O. W. *J. Org. Chem.* **1980**, *45*, 5122 (b) Vladuchick, S. A. US Patent 4 094 985, June 13, 1978.

[81] Chatterji, T.; Gates, K. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 535.

[82] (a) Behar, V.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 7017 (b) Ford P. W.; Davidson, B. S. *J. Org. Chem.* **1993**, *58*, 4522 (c) Toste, F. D.; Still, I. W. J. *J. Am. Chem. Soc.* **1995**, *117*, 7261 (d) Ford, P. W.; Narbut, M. R.; Belli, J.; Davidson, B. S. *J. Org. Chem.* **1994**, *59*, 5955.

[83] Davidson, B. S.; Molinski, T. F.; Barrows, L. R.; Ireland, C. M. *J. Am. Chem. Soc.* **1991**, *113*, 4709.

[84] Litaudon, M.; Guyot, M. *Tetrahedron Lett.* **1991**, *32*, 911.

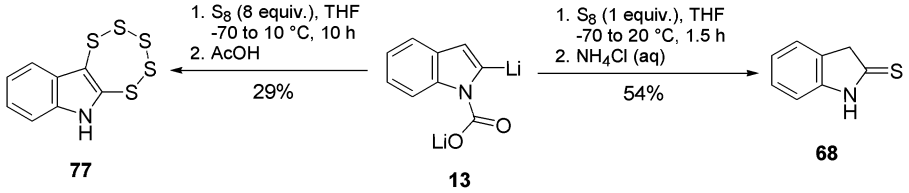
[85] Litaudon, M.; Trigalo, F.; Martin, M.-T.; Frappier, F.; Guyot, M. *Tetrahedron* **1994**, *50*, 5323.

[86] (a) Compagnone, R. S.; Faulkner, D. J.; Carté, B. K.; Chan, G.; Freyer, A.; Hemling, M. E.; Hofmann, G. A.; Mattern, M. R. *Tetrahedron* **1994**, *50*, 12785 (b) Searle, P. A.; Molinski, T. F. *J. Org. Chem.* **1994**, *59*, 6600 (c) Makarieva, T. N.; Stonik, V. A.; Dmitrenok, A. S.; Grebnev, B. B.; Isakov, V. V.; Rebachyk, N. M.; Rashkes, Y. W. *J. Nat. Prod.* **1995**, *58*, 254.

[87] For selected references, see *e.g.* (a) Chenard, B. L.; Harlow, R. L.; Johnson, A. L.; Vladuchick, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 3871 (b) Sato, R.; Ohyama, T.; Ogawa, S. *Heterocycles* **1995**, *41*, 893 (c) Sato, R.; Ohyama, T.; Kawagoe, T.; Baba, M.; Nakayo, S.; Kimura, T.; Ogawa, S. *Heterocycles* **2001**, *55*, 145 (d) Macho, S.; Rees, C. W.; Rodríguez, T.; Torroba, T. *Chem. Commun.* **2001**, 403.

some detail.[88] Most of these efforts have involved reactions of 1,2-dithiols with sulfur in liquid ammonia, or S_2Cl_2 under basic conditions, *i.e.*, readily available and cheap sulfur sources.

*4.2.3.2 Synthesis and reactions of pentathiepino[6,7-*b*]indoles (Paper VI).* It was envisaged that reactions of lithiated indoles with elemental sulfur might provide a feasible method to prepare either pentathiepino[6,7-*b*]indoles, or alternatively indoline-2-thiones,[56] useful intermediates for the synthesis of more complex sulfur containing indoles (See Section 4.1). The standard Katritzky protocol[12] was thus employed on indole, followed by quenching of the resulting dianion **13** with elemental sulfur to produce either a decent yield of pentathiepino[6,7-*b*]indole (**77**) or indoline-2-thione (**68**) depending on the conditions used (Scheme 21). The pentathiepin **77** was the prevailing product when 8 equivalents of sulfur were used as the electrophile and the reaction was allowed to proceed during 10–12 h, whereas the use of only one equivalent of sulfur followed by faster (90 min) warming to room temperature gave acceptable yields of the thione **68**.



Scheme 21.

With prolonged reaction times, the thionation involving 8 equivalents of sulfur gave increasing amounts of the tetrasulfide **75** as the side product. This outcome can perhaps be attributed to the basic reaction conditions, which induce the transformation of pentathiepino[6,7-*b*]indole (**77**) into the highly reactive dithione **91** (Scheme 22), which can in turn undergo 3,3′-coupling (Sections 4.1 and 4.2.1), finally leading to **75**. A similar mechanism, probably involving the intermediate **106**, was supported by the easy, triethylamine-induced formation of the tetrasulfide **96** from *N*-methylpentathiepino[6,7-*b*]indole (**107**), which can be obtained *via* lithiation of *N*-methylindole followed by quenching with sulfur, a reaction where **96** is a side product occurring in considerable amount, even if reaction times are kept relatively short. The attempted transformation of the pentathiepin **77** into **75** proved to produce a complex mixture

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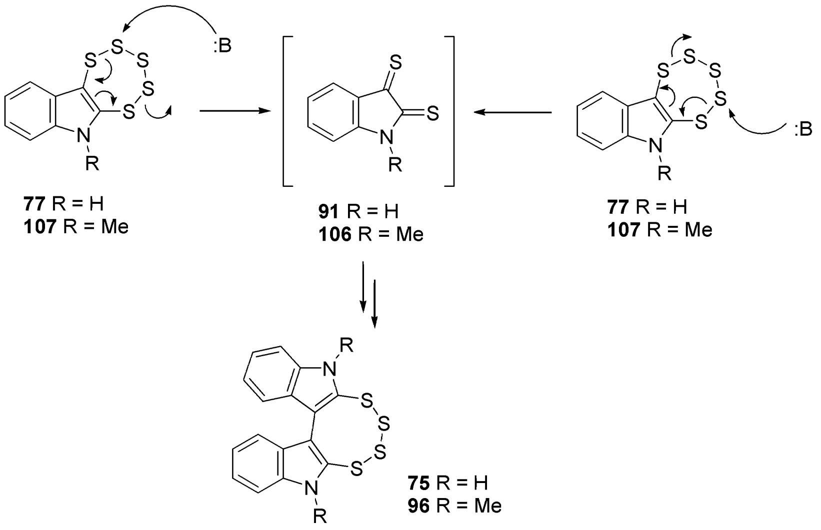
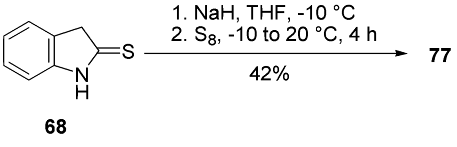
[88] Hou, Y.; Abu-Yousef, I. A.; Harpp, D. N. *Tetrahedron Lett.* **2000**, *41*, 7809, and references cited therein.

containing some **75**, as judged by TLC, which could be expected from the presence of the free indole-NH, which complicates the process.



Scheme 22.

As we suspected that the thione **68** in its thienol form was involved in the process leading to the pentathiepin **77**, a control experiment was performed where **68** was deprotonated with sodium hydride in THF, followed by quenching of the resulting anion with sulfur (Scheme 23), also in this case leading to the pentasulfide **77** in decent yield, thus supporting our hypothesis. A similar experiment leading to **107** was also be performed starting from *N*-methylindoline-2-thione (**69**).

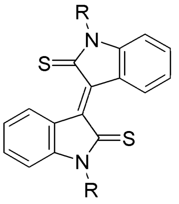


Scheme 23.

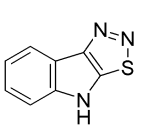
In conclusion, useful routes to pentathiepino[6,7-*b*]indoles and indoline-2-thiones have been developed starting from indoles metallated at C-2, implying that other *N*-protecting/blocking groups than those utilized could also have the potential to be used in similar transformations.

4.2.4 Studies of a sulfur containing indole trimer (Paper VII)

The reaction of *N*-methylindoline-2-thione (**69**) with *p*-toluenesulfonyl azide or *N*,*N*-dimethyl-*p*-nitrosoaniline has previously been erroneously reported to give a product assigned the structure **71**,[60] a result which was later reinvestigated showing that the tetraindole **73** was the actual product (Section 4.1).[62] A somewhat different outcome resulting from a similar transformation involving the parent thione **68** was also claimed, and the purported products **108** and **109** were believed to constitute the major components of the reaction mixture.[60]



71 R = Me
108 R = H



109

All discrepancies concerning these reactions found in the literature triggered us to pursue a reinvestigation, mainly of the reaction of **68** with *p*-toluenesulfonyl azide,[89] as it was not included in the recent study.[62] In our hands, this experiment did not give the products described previously,[60] but led instead to the isolation of a novel compound with the composition $C_{24}H_{15}N_3S_3$, which was at first assigned the structure **110**, since MS data indicated a molecular ion at *m/z* 441, while three independent sets of indolic signals could be discerned in both the ^1H and ^{13}C NMR spectra. Were the initially assigned structure **110** correct, it had to be assumed that a stable saddle conformer was existing, a behaviour which would be at variance with some closely related thiacalix[3]arenes, such as **111**,[90] or the methylene bridged analogue **112**.[91] This could however be ruled out as the NMR spectra of the new compound did not change with temperature.

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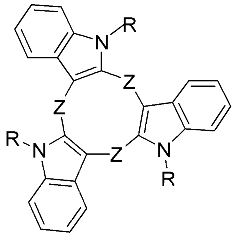
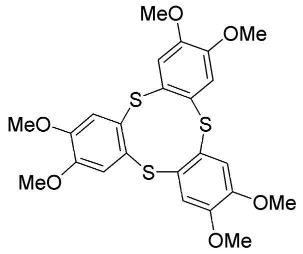
[89] Curphey, T. J. *Org. Prep. Proced. Int.* **1981**, *13*, 112.

[90] (a) Weiss, T. *Ph.D. Thesis*, University of Hamburg, 1976 (b) Haase, H.-W. *Ph.D. Thesis*, University of Hamburg, 1978 (c) von Deuten K.; Klar, G. *Z. Naturforsch.* **1981**, *36b*, 1526 (d) von Deuten, K.; Kopf, J.; Klar, G. *Cryst. Struct. Comm.* **1979**, *8*, 569.

[91] Bergman, J.; Högberg, S.; Lindström, J.-O. *Tetrahedron* **1970**, *26*, 3347.

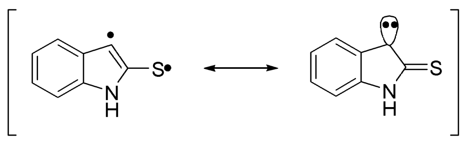


110 R = H, Z = S
112 R = Me, Z = CH_2

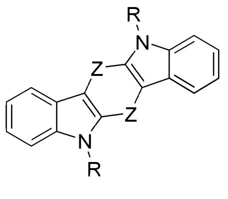


111

A trimerization of a carbene-like species like **113**, formed by elimination of nitrogen from **109**, could theoretically provide a mechanistic rationalization for the formation of species like **110**. However, other conceivable products which could originate from the carbene **113**, such as the dimers **76** or **114** were never observed. The closely related dioxin **115** recently obtained from a base induced coupling of a 2-bromoindoxyl derivative[92] demonstrates however that products of this type can exist. Thus a different mechanistic pathway was considered, wherein the species **113** initially undergoes 3,3′-coupling followed by incorporation of another equivalent of **113** to give the final 9-membered product **116**, which proved to be the true structure of the trimeric oxidative coupling product. Upon reduction of **116** with Raney-nickel in dioxane, the expected product mixture of indole (**1**) and 3,3′-biindolyl (**22**) was obtained, thereby further supporting the signed structure. In this context, it is also interesting to note that an analogue of **112** with R = H, originating from the trimerization of indole-3-carbinol, has been investigated as a strong agonist of the estrogen receptor (ER), and the conformational similarities with the powerful ER ligand tamoxifen imply that this cyclic trimer exhibits an excellent fit into the binding site of the receptor.[93] A study on the ER binding properties of the trimer **116** is currently in progress, and the results will be accounted for in due course.[‡]



113



114 Z = S, R = H
115 Z = O, R = Ac

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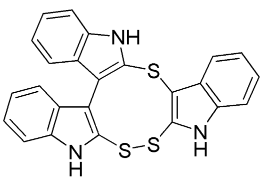
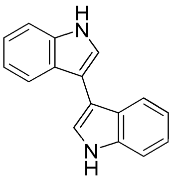
[92] Alphonse, F.-A.; Routier, S.; Coudert G.; Mérour, J.-Y. *Heterocycles* **2001**, *55*, 925.

[93] Riby, J. E.; Feng, C.; Chang, Y.-C.; Schaldach, C. M.; Firestone, G. L.; Bjeldanes, L. F. *Biochemistry* **2000**, *39*, 910.

[‡] This investigation is conducted in collaboration with Prof. Leonard F. Bjeldanes, Division of Nutritional Sciences and Toxicology, 119 Morgan Hall, University of California at Berkeley, Berkeley, CA 94720, USA.

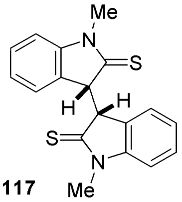


116



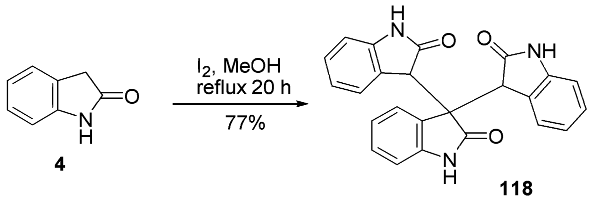
22

The oxidation of 1-methylindoline-2-thione (**69**) using iodine at room temperature has previously been reported to give the dimer **117** in 71% yield.[56b] During these experiments, there was no evidence for formation of trimeric species. In a recent study, the structure of **117** has also been investigated in detail by X-ray crystallography.[94] Interestingly, experiments aiming at oxidation of *N*-methyloxindole under the same conditions produced complex mixtures from which a small amount of *N,N'*-dimethylisoindigo (**72**) was isolated.[56b]



117

When we reacted oxindole (**4**) with iodine in refluxing methanol, the oxidation product **118** was isolated in 77% yield (Scheme 24). The existence of products containing a nine-membered ring were never detected in the reaction mixture, which was not unexpected as it is well established that the sulfur atom has a higher propensity to stabilize radicals than oxygen. Various *N*-substituted derivatives of **118** have been prepared previously *via* the reaction of isatins with oxindoles,[95] or the treatment of oxindoles with sodium naphthalenide.[96]



Scheme 24.

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[94] Baumeister, U.; Hartung, H.; Spitzner, R.; Felicetti, M.; Schroth, W. *Acta Cryst.* **2000**, *C56*, 830.

[95] Stollé, R. *J. Prakt. Chem.* **1922**, *105*, 137.

[96] (a) Banerji, A.; Maiti, S. *Tetrahedron* **1994**, *50*, 9079 (b) Banerji, A.; Maiti, S. *Indian J. Chem. Sect. B* **1994**, *33*, 532.

5 CONCLUDING REMARKS

Studies on systems possessing two indole moieties, such as indolocarbazoles, bisindoles, and closely related sulfur containing ring systems, were undertaken with the aim at developing new preparative methods employing simple and readily available starting materials. During these investigations, many of the target compounds were synthesized, often leading to new interesting related species, and providing new insight for further developments.

Apart from finding an alternative route to the parent system of indolo[2,3-*c*]carbazole, the preparation of a new class of bisindoles with a fused central seven-membered ring was achieved from a common 1,2-bis(indol-3-yl)ethane precursor. New synthetic routes to the previously scantily studied group of indolo[3,2-*a*]carbazoles have also been devised starting from 2,3′-biindolyl, which proved to be an excellent and versatile precursor. This approach possesses further potential to provide additional substituted indolo[3,2-*a*]carbazole derivatives.

A concise and high yielding synthesis of the marine alkaloid hyrtiosin B was accomplished, employing a metallation protocol previously developed in our laboratory. Studies towards related bisindoles having a central eight-membered ring were also undertaken.

Ring systems containing multiple sulfur atoms have often proven to be elusive and difficult to characterize. In the last part of this thesis, rational syntheses of various sulfur containing indoles and bisindoles are described, many of which constitute new and unusual ring systems. It was demonstrated that a variety of new intriguing sulfur containing structures can be obtained from simple bisindoles or indoles by thionation with elemental sulfur or P_4S_{10}, two very cheap and common sulfur sources. Although many of the products could be analysed using standard spectroscopic methods, in some particular cases, X-ray crystallography was recognized as a powerful and indispensable tool for structure determination. Although we have suggested mechanistic explanations for several of the observed transformations, the complex reactivity patterns and sometimes unexpected behaviour of these compounds call for further deeper studies in this field.

6 ACKNOWLEDGEMENTS

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Sist men inte minst vill jag tacka Ann-Louise för all kärlek och omtanke.

7 SUPPLEMENTARY MATERIAL

1,2-Di(2-methylindol-3-yl)ethene (60). (Prepared according to reference 50.) A mixture of 2-methylindole (14.2 g, 0.108 mol) and dimethylaminoacetaldehyde diethyl acetal (8.8 g, 55 mmol) in acetic acid (20 mL) was heated at reflux during 6 h. After cooling, the off-white precipitate was collected, washed with ethanol and dried. Additional material was obtained from the mother liquor on standing. Yield 6.3 g (41%). IR (KBr) 3383, 3045, 1553, 1459, 1310, 1282, 1243, 1017, 940, 737 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.06 (s, 2H), 7.95–7.89 (m, 2H), 7.37–7.32 (m, 2H), 7.16 (s, 2H), 7.12–7.07 (m, 4H), 2.54 (s, 6H); ^{13}C NMR (DMSO-d_6, 75.4 MHz) δ 135.6 (s), 133.5 (s), 126.1 (s), 120.5 (d), 119. 2 (d), 119.0 (d), 117.8 (d), 110.8 (d), 110.6 (s), 12.0 (q).

1,2-Di-(2-methylindol-3-yl)ethane (61). A solution of **60** (5.3 g, 19 mmol) in dioxane (100 mL) containing Pd-C (5%, 0.4 g) was hydrogenated in the presence of hydrogen (35 bar) at room temperature during 9 h. The mixture was filtered through a pad of celite, to afford **61** (5.2 g, 97%) after evaporation of the solvent *in vacuo*. IR (KBr) 3416, 3053, 2936, 2852, 1460, 1428, 1297, 1010, 738 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.60 (s, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 6.8 Hz, 2H), 7.03–6.94 (m, 4H), 2.87 (s, 4H), 2.09 (s, 6H); ^{13}C NMR (DMSO-d_6, 75.4 MHz) δ 135.2 (s), 131.6 (s), 128.3 (s), 119.7 (d), 118.0 (d), 117.1 (d), 110.3 (d), 110.3 (s), 25.3 (t), 10.9 (q).

1,2-Di(1-*tert*-butoxycarbonyl-2-methylindol-3-yl)ethane (62). To a solution of **61** (576 mg, 2.0 mmol) in freshly distilled THF (10 mL) was added Boc$_2$O (1.09 g, 5.8 mmol) in one portion, followed by addition of DMAP (60 mg). The mixture was stirred at room temperature for 48 h, and was thereafter evaporated to dryness *in vacuo*. The residue was passed through a short plug of silica gel eluting with dichloromethane, to afford **62** (630 mg, 69%) as a colourless solid. IR (KBr) 2982, 1717, 1460, 1368, 1329, 1152, 1136, 1112, 998, 758, 738 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.19–8.16 (m, 2H), 7.52–7.49 (m, 2H), 7.31–7.27 (m, 4H), 2.95 (s, 4H), 2.40 (s, 6H), 1.72 (s, 18H); ^{13}C NMR (CDCl$_3$, 75.4 MHz) δ 151.0 (s), 136.0 (s), 133.6 (s), 130.1 (s), 123.5 (d), 122.6 (d), 118.1 (s), 117.7 (d), 115.7 (d), 83.6 (s), 28.5 (q), 24.6 (t), 13.9 (q).

1,2-Di-(3-methylindol-2-yl)-ethane-1,2-dione (64). To a solution of 3-methylindole (2.62 g, 20 mmol) in THF (30 ml) under a nitrogen atmosphere, was added *n*-BuLi in hexanes (2.5 M, 8.5 mL, 21 mmol) at −78 °C. The mixture was stirred for 30 min, followed by introduction of CO_2 during 10 min. The solvent was then removed at reduced pressure, initially at −78 °C, then at room temperature. The white residue was redissolved in THF (40 mL), and the solution was cooled to −78 °C. *t*-BuLi in pentane (1.7 M, 12.5 ml, 21 mmol) was thereafter added, and the resulting yellow solution was stirred at −78 °C for 30 min, followed by addition of oxalyl chloride (0.88 mL, 1 mmol) at −78 °C. The deep red solution was allowed to attain room temperature over night, and was thereafter quenched by addition of sat. aq. NH_4Cl (100 mL). Ether (50 mL) was added, and the organic layer was separated, washed with brine and dried over Na_2SO_4. After evaporation of the solvents *in vacuo*, the residue was triturated with ether to produce a deep-red solid, which was collected, washed with a small amount of ether, followed by hexane, and finally dried to give **64** (550 mg). Additional material (160 mg) was obtained from the mother liquors after treatment with methanol. Total yield 710 mg (22%). IR (KBr) 3398, 1616, 1509, 1436, 1338, 1159, 1051, 846, 749, 741 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 11.92 (s, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.38 (app. t, J = 7.3 Hz, 2H), 7.11 (app. t, J = 7.8 Hz, 2H), 2.33 (s, 6H); ^{13}C NMR (DMSO-d_6, 125.6 MHz) δ 186.3 (s), 138.2 (s), 129.0 (s), 127.7 (s), 127.3 (d), 122.6 (s), 121.5 (d), 120.2 (d), 112.9 (d), 9.9 (q); MS (ESI) *m/z* 315 $[M–H]^-$.