# Facile Dimerisation of 3-Benzylideneindoline-2-thiones

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3-Benzylideneindoline-2-thione, formed by the condensation of indoline-2-thione with benzalde-hyde, undergoes an unexpectedly facile [4 + 2] cycloaddition in solution to yield an unsymmetrical dimer 7. The structure of this dimer, elucidated by NMR spectroscopy and confirmed by X-ray crystallography, is described, and the mechanism and stereospecificity of this reaction is discussed.

In the course of our studies of indoline-2-thiones,[1] we examined the condensation of indoline-2-thione 1 with certain aldehydes and ketones. Both indoline-2-thione 1 and 1-methylindoline-2-thione 2 are known[2,3] to undergo acid- or base-catalysed condensations with acetone at room temperature, to give the expected 3-isopropylidene derivatives 3 and 4, respectively (Scheme 1). Similarly, the condensation of 1 with 4-nitrobenz-aldehyde reportedly[4] gave the 4-nitrobenzylidene adduct 5.

1 R = H
2 R = Me

3 R = H
4 R = Me

8 R = H
11 R = NO₂

7 R = H
10 R = NO₂

5 R = NO₂
6 R = H

9
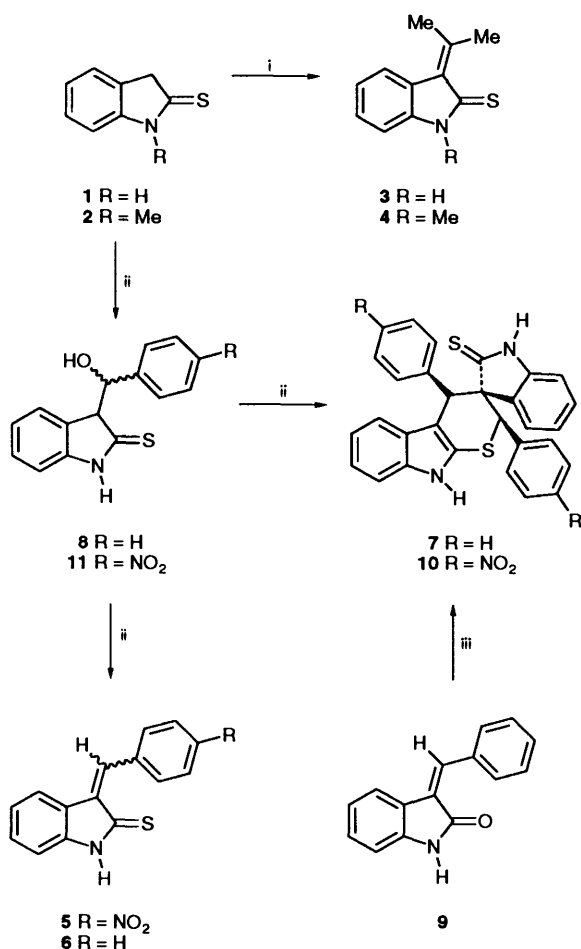
Scheme 1 Synthesis of 3-alkylideneindoline-2-thiones and their dimers. *Reagents and conditions:* i, Me₂CO/H⁺ or Me₂CO/B: (refs. 2 and 3); ii, PhCHO or 4-NO₂C₆H₄CHO/conc. HCl/EtOH or piper-idine/EtOH, 20 °C; iii, P₂S₅/NaHCO₃/dioxane, 100 °C.

Treatment of an ethanolic solution of 1 with an excess of benzaldehyde in the presence of piperidine as catalyst at room temperature (or above) gave immediately a bright orange compound (probably 6) (TLC). However, after a few hours, this compound was converted into a less polar one (TLC), which crystallised from methanol as a cream solid, m.p. 216.5–218 °C (82% yield). The ¹H NMR spectrum of this product indicated the presence of two NH protons and two aliphatic, non-coupled methine (CH) protons, together with twice the number of aromatic protons accounted for by 6. The ¹³C NMR spectrum indicated the presence of only one thiocarbonyl group (δ 205.9 ppm), but two alkyl methines (δ 55.2 and 51.7 ppm) and one quaternary alkyl carbon (δ 66.2). These data, together with high resolution FAB-MS and elemental analysis results suggested the dimeric structure 7. An X-ray crystallographic analysis provided final confirmation of this structure, and determined the relative stereochemistry (see Fig. 1).

The nature of the initial orange condensation product was determined by examining the initial ¹H NMR spectrum of material precipitated with water after reaction for *ca.* 2 min and then recrystallised rapidly from cold CH₂Cl₂–light petroleum. This material appeared from its ¹H NMR spectrum to consist of a mixture of (*E* and *Z*)-3-benzylideneindoline-2-thiones 6 and the precursor hydrate 8, in approximately equal proportions. Signals at δ 4.24 and 5.43 were attributed to the C-3 and benzyl protons respectively of 8, while singlets at δ 7.47 and 8.34 were tentatively assigned to the benzylidene protons of the two 6 isomers. This solid retained its integrity on storage, but in solution both 6 and 8 slowly were converted into the dimer 7, as shown by ¹H NMR spectroscopy.

With HCl as catalyst, the condensation to give 6 was slower, and 7 was formed before 1 had completely reacted. Thiation of 3-benzylideneindolin-2-one 9 with P₂S₅ and NaHCO₃ in dioxane also gave a moderate yield (49%) of 7, although 9 itself did not undergo dimerisation even at 150 °C. Furthermore, 3-isopropyl-ideneindoline-2-thione 3[2] also appeared to be stable in solution.

Acid or base catalysed condensation of 1 with 4-nitrobenz-aldehyde gave the yellow dimer 10, the structure of which was determined by NMR spectroscopy and elemental analysis. The initial condensation product material (precipitated with water as above) gave a deep red solution in EtOH, which faded to yellow over 5 min at ambient temperature. Dimerisation also occurred very quickly on silica gel, preventing a meaningful analysis by TLC. Thus, the dimerisation of 5 appeared to be even more facile than that of 6, and it is unlikely that the compound reported by Oddo *et al.*[4] of m.p. 183 °C is 5.

The results reported here are consistent with an inter-molecular [4 + 2] cycloaddition (a heteroatomic Diels–Alder reaction; see Scheme 2). This is analogous to the well-known dimerisation of certain α,β-unsaturated carbonyl compounds.[5–7] The C-3 benzylidene double bonds in 5 and 6 have adjacent thiocarbonyl and (two) phenyl substituents, which would make them good dienophiles. In oxindoles, the amide oxygen is a relatively poor nucleophile,[8] whereas the thioamide sulphur in indoline-2-thiones is easily alkylated,[3,9] reflecting the ease of thione–thiol tautomerism in these compounds.[9,10] Thus, it is
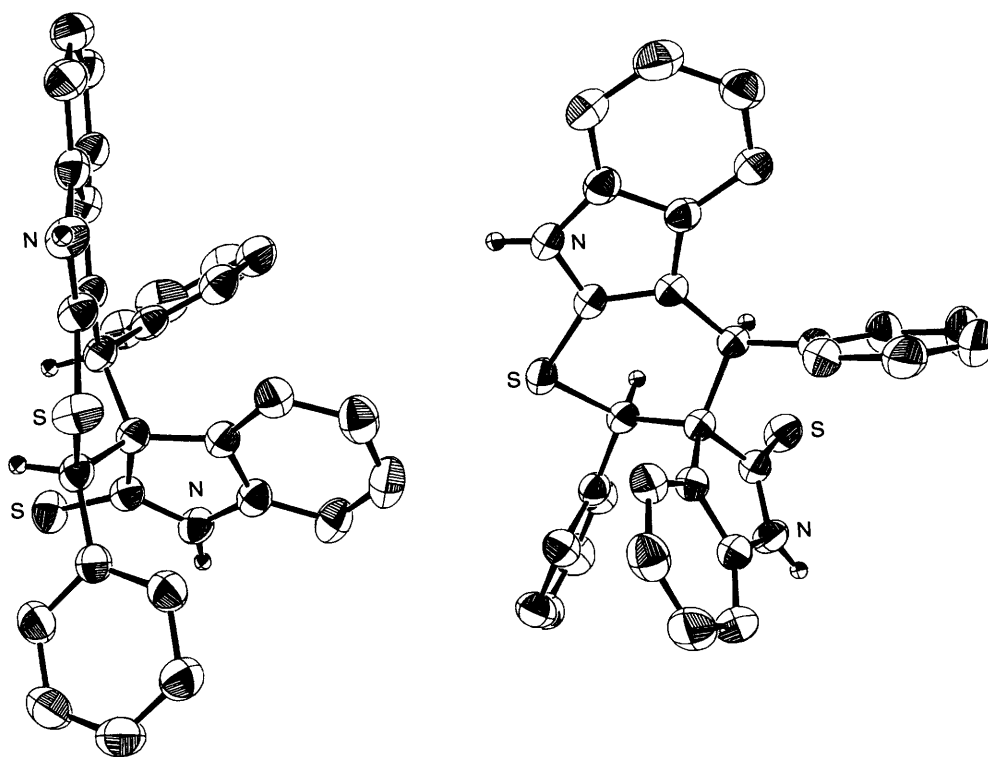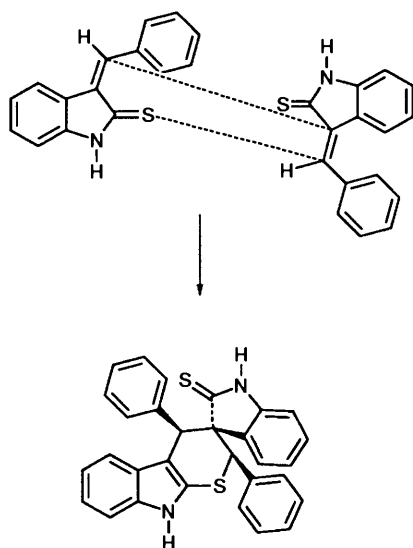
Fig. 1 Two ORTEP views from the X-ray crystal structure determination of 7

Scheme 2 Proposed stereochemistry of the cycloaddition

not too surprising to see a different degree of reactivity for the enone 9 compared with the enethione 6 on cycloaddition. The nucleophilicity of the thioamide sulphur in certain 3-alkyl-ideneindoline-2-thiones has been demonstrated previously, since the condensation of 1 with 1,3-diketones yields thio-pyrano[2,3-b]indoles through intramolecular displacement and cyclisation.[11] The thiocarbonyl of 1 is also known to undergo [2 + 2] photoinduced cycloadditions with electron-deficient alkenes and alkynes.[12-16] Strong heating of crystalline 7 caused a deep orange colour to develop, with the production of some 6, as shown by TLC and ^{1}H NMR spectroscopy. This partial thermal reversibility is also consistent with the proposed mechanism.[6] The dimerisation described here is highly stereo-selective, with only one pair of diastereoisomers (from a possible four pairs) being formed; this is also consistent with the proposed mechanism.[7]

The generality of this unexpected dimerisation has not been demonstrated in this investigation. Nonetheless, the reaction is a further demonstration of the interesting and complex chemistry of indoline-2-thiones.

Experimental

Where analyses are indicated by symbols of the elements, results were within ±0.4% of the theoretical, and were performed by the Microchemical Laboratory, University of Otago, Dunedin. Melting points were determined using an Electrothermal Model 9200 digital melting point apparatus, and are as read. NMR spectra were measured on a Bruker AM-400 spectrometer (Me$_4$Si). Mass spectra were determined on a VG 7070 mass spectrometer at nominal 5000 resolution.

Reaction of Indoline-2-thione 1 with Benzaldehyde.—A stirred solution of indoline-2-thione 1 (0.25 g, 1.68 mmol) in EtOH (2 cm^3) was treated with benzaldehyde (0.20 cm^3, 1.97 mmol) and piperidine (1 drop) at 20 °C. The solution immediately turned dark red, and TLC showed the quantitative formation of a bright orange, less-polar compound. The reaction was quenched with water (2 drops) after 2 min and then cooled in ice to give a precipitate. This was dried and recrystallised rapidly from cold CH$_2$Cl$_2$–light petroleum to give a mixture of (E and Z)-3-benzylideneindoline-2-thione 6 and the precursor hydrate 8; δ_H(CDCl$_3$) 9.69 (br s, 1 H, NH), 9.38 (br s, 1 H, NH), 8.34 (s, 1 H, 3=CH), 8.04 (br s, 1 H, NH), 7.68 (m, 3 H, ArH), 7.47 (s, 1 H, 3=CH), 7.47 (m, 2 H, ArH), 7.33–6.80 (m, 18 H, ArH), 5.43 (s, 1 H, 3-CH) and 4.23 (s, 1 H, 3-H). A 20 mg sample of this material, dissolved in CDCl$_3$ (0.6 cm^3) was monitored by ^{1}H NMR spectroscopy over time. After 4 h, the mixture consisted of ca. 50% of the dimer 7, with about equal amounts of the initially observed components 6 and 8 remaining. After 1 day, the formation of 7 was essentially complete.

When the original reaction mixture was left for 24 h, these products were all converted into the cream-coloured dimer 7 (82% isolated yield), m.p. (MeOH) 216.5–218 °C (Found: C,

74.7; H, 4.9; N, 6.0; S, 13.8. $C_{30}H_{22}N_2S_2$·0.5CH$_3$OH requires C, 74.7; H, 4.9; N, 5.7; S, 13.7%); δ_H(CDCl$_3$) 8.74 (s, 1 H, NH), 8.10 (s, 1 H, NH), 7.87 (d, J 7.4, 1 H, ArH), 7.59 (d, J 7.7, 1 H, ArH), 7.27 (d, J 8.1, 1 H, ArH), 7.13 (m, 4 H, ArH), 7.02 (m, 4 H, ArH), 6.83 (d, J 7.5, 2 H, ArH), 6.70 (m, 2 H, ArH), 6.46 (d, J 7.7, 1 H, ArH), 6.42 (d, J 8.0, 1 H, ArH), 6.08 (d, J 8.0, 1 H, ArH) and 5.33 and 5.25 (2 × s, 2 H, 2 × 3-CH); δ_C(CDCl$_3$) 205.91 (s, CSNH), 142.96, 137.04, 136.35, 134.63 (4 × s, Ar), 131.64 (d, Ar), 131.52 (s, Ar), 130.30 (d, Ar), 129.70 (2 × d, Ar), 128.86, 128.63, 128.56 (3 × d, Ar), 127.75 (2 × d, 1 × s, Ar), 127.69 (s, Ar), 127.42, 126.90, 126.70, 122.96, 121.28 (5 × d, Ar), 119.38 (2 × d, Ar), 110.02 (d, Ar), 109.58 (s, Ar), 109.37 (d, Ar), 66.21 (s, C-3), 55.17, 51.74 (2 × d, 2 × 3-CH) [Found: m/z (HRFABMS) 475.1335. Calc. for $C_{30}H_{23}N_2S_2$: 475.1303 (MH$^+$)].

Thiation of 3-Benzylideneindolin-2-one **9**.—A solution of 3-benzylideneindolin-2-one **9** [17] (0.50 g, 2.26 mmol) in dioxane (10 cm^3) was treated with P$_2$S$_5$ (0.35 g, 1.57 mmol) and NaHCO$_3$ (0.38 g, 4.52 mmol) at 100 °C for 1 h. The solvent was removed under reduced pressure, and the residue was extracted with CH$_2$Cl$_2$. The extract was washed with water and evaporated and the residue was chromatographed on silica gel. Elution with CH$_2$Cl$_2$–light petroleum (2:1) gave **7** (0.26 g, 49%), m.p. and mixed m.p. 216.5–218 °C.

Reaction of Indoline-2-thione **1** *with 4-Nitrobenzaldehyde*.—4-Nitrobenzaldehyde was allowed to react as above with indoline-2-thione. The initial product mixture, isolated after 4 min, was unstable in solution and on TLC, but was assumed to contain the analogous hydroxy compound **11** and the monomer **5**. When the compounds were allowed to react under acidic conditions, as described by Oddo,[4] the only product isolated was **10**. Successive crystallisation from CH$_2$Cl$_2$–light petroleum and EtOH–water gave pure material, m.p. 229–230 °C (Found: C, 62.9; H, 3.6; N, 9.8; S, 11.5. $C_{30}H_{20}N_4O_4S_2$·0.5H$_2$O requires, C, 62.8; H, 3.7; N, 9.8; S, 11.2%); δ_H(CD$_3$OD) 8.02 (dd, J 8.5, 2.5, 1 H, ArH), 7.86 (d, J 8.9, 3 H, ArH), 7.80 (dd, J 8.6, 2.0, 1 H, ArH), 7.51 (dd, J 8.7, 2.5, 1 H, ArH), 7.32 (d, J 8.1, 1 H, ArH), 7.24 (td, J 7.7, 1.3, 1 H, ArH), 7.16 (td, J 7.6, 1.1, 1 H, ArH), 7.04 (d, J 8.7, 2 H, ArH), 6.99 (ddd, J 8.1, 7.2, 1.0, 1 H, ArH), 6.65 (m, 2 H, ArH), 6.60 (d, J 7.7, 1 H, ArH), 6.03 (d, J 8.0, 1 H, ArH) and 5.50 and 5.34 (2 × s, 2 H, 2 × 3-CH); δ_C(CD$_3$OD) 206.36 (s, CSNH), 149.28, 148.20, 146.94, 145.80, 143.54, 138.46 (6 × s, Ar), 133.61, 132.71 (2 × d, Ar), 132.11 (2 × d, Ar), 131.79 (s, Ar), 130.60, 129.98 (2 × d, Ar), 128.90, 128.37 (2 × s, Ar), 124.15 (d, Ar), 123.55 (2 × d, Ar), 123.40, 122.37, 122.31, 120.01, 119.59, 111.63, 111.19 (7 × d, Ar), 108.19 (s, Ar), 67.39 (s, C-3) and 55.34 and 52.35 (2 × d, 2 × 3-CH).

Crystal Structure Determination of **7**.—Crystals of **7** were obtained from MeOH. Crystal data: $C_{30}H_{22}N_2S_2$·2CH$_3$OH;

triclinic, space group $P\bar{2}$; cell constants $a = 10.417(2)$, $b = 11.238(2)$, $c = 13.260(2)$ Å, $\alpha = 110.07(2)$, $\beta = 109.73(2)$, $\gamma = 87.10(2)$°; $Z = 2$; $V = 1368.6(5)$ Å^3, D_c 1.307 g cm^{-3}. Lattice constants and intensity data were measured using Mo-Kα radiation, $\lambda = 0.710\,69$ Å, on a Nonius CAD-4 diffractometer. The data set consisted of 5050 unique reflections in the range $0 < \theta < 25°$, of which 4373 were considered observed [$I > 3\sigma > (I)$]. The structure was solved by direct methods using SHELX-S and refined using SHELX-86. The largest shift/esd values during the final refinement were <0.03. Maximum and minimum peaks in the final difference map were 0.25 and -0.20 eÅ^{-3} respectively. At convergence R and R_w were 0.0351 and 0.0434 respectively. Tables of all positional parameters, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.

Acknowledgements

References

1 A. M. Thompson, G. W. Rewcastle, M. Tercel, E. M. Dobrusin, A. M. Kraker, D. W. Fry and W. A. Denny, J. Med. Chem., submitted.
2 J. Bourdais, Chim. Ther., 1970, 5, 409.
3 T. Hino, K. Tsuneoka, M. Nakagawa and S. Akaboshi, Chem. Pharm. Bull., 1969, 17, 550.
4 B. Oddo and Q. Mingoia, Gazz. Chim. Ital., 1932, 62, 299 (Chem. Abstr., 1932, 26, 4603).
5 G. Desimoni and G. Tacconi, Chem. Rev., 1975, 75, 651.
6 S. B. Needleman and M. C. Chang Kuo, Chem. Rev., 1962, 62, 405.
7 J. Colonge and G. Descotes, in 1,4-Cycloaddition Reactions. The Diels–Alder Reaction in Heterocyclic Syntheses, J. Hamer, ed., Academic Press, New York, 1967, pp. 217–253.
8 E. Wenkert, N. K. Bhattacharyya, T. L. Reid and T. E. Stevens, J. Am. Chem. Soc., 1956, 78, 797.
9 T. Hino, Int. J. Sulfur Chem. B, 1972, 7, 217.
10 T. Hino, T. Suzuki and M. Nakagawa, Chem. Pharm. Bull., 1974, 22, 1053.
11 J. Bordais, Tetrahedron Lett., 1970, 2895.
12 C. Marazano, J. L. Fourrey and B. C. Das, J. Chem. Soc., Chem. Commun., 1977, 742.
13 B. C. Das, J. L. Fourrey, C. Marazano, A. Merrien and J. Polonsky, J. Chem. Res., 1978, (S), 370.
14 T. Nishio, N. Okuda and Y. Omote, J. Chem. Soc., Perkin Trans 1, 1988, 1663.
15 R. M. Acheson and J. D. Wallis, J. Chem. Soc., Perkin Trans. 1, 1981, 415.
16 R. M. Acheson and J. D. Wallis, J. Chem. Soc., Perkin Trans. 1, 1982, 1905.
17 A. Wahl and P. Bagard, C. R. Seances Acad. Sci., 1909, 148, 716.