Unusual Reactions of Magnesium Indolates with Benzenesulfonyl Chloride

Ernest Wenkert,* Peter D. R. Moeller, and Serge R. Piettre

Department of Chemistry (D-006), University of California—San Diego, La Jolla, California 92093

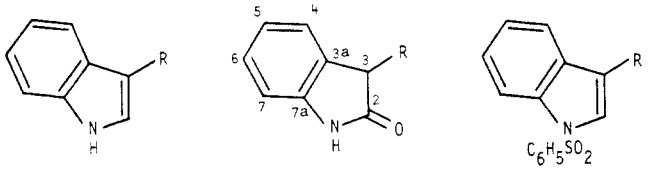
Andrew T. McPhail*

Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received December 17, 1986

Grignard reagents from N-unsubstituted indoles and benzenesulfonyl chloride undergo reaction such as to produce unstable intermediates of β-chlorination and α-sulfonylation, which are transformed into oxindoles or substituted indoles. In the same reaction, yuehchukene (the naturally occurring dehydroprenylindole dimer) is converted into a spirooxindole, containing a strained four-membered ring, which is changed into a spirooxindole isomer with ring expansion on mild acid treatment.

A variety of procedures have been used in the past for the N-arenesulfonylation of indoles.[1,2] When, in continuation of the work on prenylated indoles,[2] it became necessary to prepare 1-(phenylsulfonyl)-3-prenylindole, the Grignard reagent of β-prenylindole (**1a**)[2] was made and



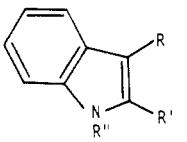
1 **2** **3**

a, R = $CH_2CH{=}CMe_2$; **b**, R = $CHMe_2$; **c**, R = Me

exposed to benzenesulfonyl chloride in tetrahydrofuran solution. Shockingly, the product proved to be 3-prenyloxindole (**2a**, 75% yield). The same reaction sequence with β-isopropylindole (**1b**)[3] led to 3-isopropyloxindole (**2b**,[4] 75%). These extraordinary results were obtained in the face of normal N-benzenesulfonylation of the above two indoles as well as skatole (**1c**) with benzenesulfonyl chloride and aqueous potassium hydroxide in benzene under phase-transfer conditions, i.e., the formation of sulfonamides **3a**[2] (90%), **3b** (86%), and **3c**[1c] (87%), respectively. The unprecedented oxindole formation demanded an inquiry into the causes of the anomalous indole behavior, the results of which are presented herewith.

The reactions of the magnesium indolates, derived from indole (**4a**), skatole (**1c**), and 2,3-dimethylindole (**4b**), with benzenesulfonyl chloride in tetrahydrofuran solution yielded more surprises, affording 1-(phenylsulfonyl)-3-chloroindole [**4c**,[5] 45%; as well as 6% of β-chloroindole (**4d**)[6]], 2-(phenylsulfonyl)skatole (**4e**, 61%), and 2-[(phenylsulfonyl)methyl]skatole (**4f**, 10%), respectively. The formation of the chloro compounds in the reaction of the magnesium salt of indole (**4a**) suggests that benzenesulfonyl chloride acts as a chlorination (rather than benzenesulfonylation) agent and that in all the Grignard reactions the creation of a β-chloroindolenine is the first step.[7] This behavior of the sulfonic acid derivative is in consonance with an earlier example of its β-chlorination of α-arylindoles[8] and its reactions with Grignard reagents derived from alkyl, aryl, and acetylenic halides producing organic chlorides[9] as well as the formation of α-chlorocarbonyl compounds on reaction of other sulfonyl chlorides with enolates.[10] When the Grignard reagents, e.g., from indole (**4a**) and skatole (**1c**), were treated with methanesulfonyl chloride, i.e., a sulfonic acid derivative capable of undergoing acid–base interaction leading to methylenesulfene as an intermediate, a normal N-sulfonylation took place and sulfonamides **4g**[1b] (59%) and **4h** (36%) were obtained. Finally, in an attempt to prepare the α-sulfonylindole derivative **4e** by independent means, sulfonamide **3c** was treated with lithium diisopropylamide and the resultant α-lithio derivative **4i** was exposed to benzenesulfonyl chloride in tetrahydrofuran solution. The product was the α-chloro compound **4j** (69%)—one more example of the formation of an organic chloride on interaction between an organometallic species and an arenesulfonyl chloride.

If it be assumed that in steps subsequent to the initial β-chlorination in the reactions of the indole-based Grignard reagents with benzenesulfonyl chloride, the side



4a: R = R′ = R″ = H
b: R = R′ = Me, R″ = H
c: R = Cl, R′ = H, R″ = $SO_2C_6H_5$
d: R = Cl, R′ = R″ = H
e: R = Me, R′ = $SO_2C_6H_5$, R″ = H
f: R = Me, R′ = $CH_2SO_2C_6H_5$, R″ = H
g: R = R′ = H, R″ = SO_2Me
h: R = Me, R′ = H, R″ = SO_2Me
i: R = Me, R′ = Li, R″ = $SO_2C_6H_5$
j: R = Me, R′ = Cl, R″ = $SO_2C_6H_5$
k: R = *i*-Pr, R′ = $SO_2C_6H_5$, R″ = H
l: R = R′ = H, R″ = $SO_2C_6H_5$

(1) (a) Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *38*, 3324. (b) Illi, V. O. *Synthesis* **1979**, 136. (c) Kano, S.; Sugino, E.; Shibuya, S.; Hibino, S. *J. Org. Chem.* **1981**, *46*, 2979. (d) Saulnier, M. G.; Gribble, G. W. *Ibid.* **1982**, *47*, 757.

(2) Wenkert, E.; Angell, E. C.; Ferreira, V. F.; Michelotti, E. L.; Piettre, S. R.; Sheu, J.-H.; Swindell, C. S. *J. Org. Chem.* **1986**, *51*, 2343.

(3) Trenkler, B. *Justus Liebigs Ann. Chem.* **1888**, *248*, 106.

(4) Schwarz, H. *Monatsh. Chem.* **1903**, *24*, 568. Wenkert, E.; Bhattacharyya, N. K.; Reid, T. L.; Stevens, T. E. *J. Am. Chem. Soc.* **1956**, *78*, 797. Anthony, W. C. *J. Org. Chem.* **1966**, *31*, 77.

(5) For identification purposes, this compound was prepared also by N-benzenesulfonylation of β-chloroindole (**4d**) under phase-transfer conditions as well as chlorination of *N*-(phenylsulfonyl)indole[1b] (see the Experimental Section).

(6) Mazzara, G.; Borgo, A. *Gazz. Chim. Ital.* **1905**, *35*, 320, 563.

(7) The β-chlorination proceeds most likely by way of an initial electron-transfer step, producing the indole radical and benzenesulfonyl chloride radical anion.

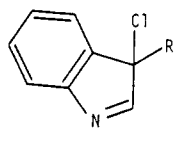
(8) Dalton, L.; Humphrey, G. L.; Cooper, M. M.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2417.

(9) Gilman, H.; Fothergill, R. E. *J. Am. Chem. Soc.* **1929**, *51*, 3501. Truchet, R. *Ann. Chim. (Paris)* **1931**, *16*, 309.

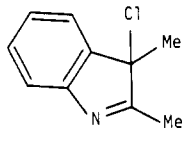
(10) von Meyer, E.; Friessner, A.; von Findeisen, Th. *J. Prakt. Chem.* **1902**, *65*, 528. Hakimelahi, G. H.; Just, G. *Tetrahedron Lett.* **1979**, 3643.

0022-3263/87/1952-3404$01.50/0

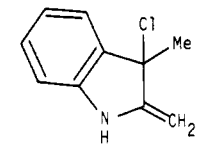
product—magnesium benzenesulfinate—reacts as a nucleophile, simple mechanistic rationales can be offered for the formation of the various products. Whereas mere tautomerization transforms the β-chlorination product **5a** of the reaction of the Grignard reagent from indole (**4a**) into β-chloroindole (**4d**),[11] the reaction of the indolate derived from 2,3-dimethylindole (**4b**) is more complex (albeit following a known path[12]). In the latter reaction, benzenesulfinate anion functions as a carbonium ion trap (chloroindolenine **6** tautomerizing into enamine **7**, chloride solvolysis of the latter, and capture of the indole α-methyl cation **8** by benzenesulfinate).[13]



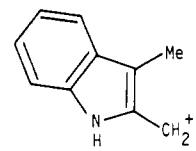
5a, R = H
b, R = Cl
c, R = Me
d, R = *i*-Pr



6

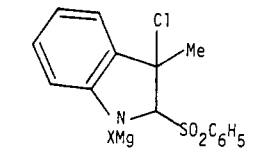


7

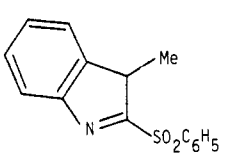


8

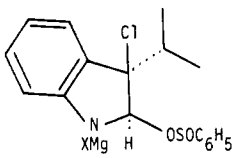
In the reactions of the β-alkylindolates, the involvement of benzenesulfinate occurs at an early stage. Thus, for example, the interaction of the Grignard reagent of skatole (**1c**) with benzenesulfonyl chloride leads most likely to intermediate **5c**, whose combination with magnesium benzenesulfinate yields the indoline **9**. Chloride solvolysis of the latter, 1,2-hydride shift, and tautomerization of the resultant indolenine **10** form the observed product **4e**. Despite the striking difference of the products, the reactions of β-isopropylindole (**1b**) [as well as β-prenylindole (**1a**)] and skatole (**1c**) may follow a related path. In view of the steric bulk of the isopropyl group in the intermediate chloroindolenine **5d**, benzenesulfinate attack occurs probably trans to the alkyl group and via its oxygen site, to avoid proximity of its electron-rich heteroatoms to the chloro substituent. Once again, chloride solvolysis of the resultant indoline **11**, followed by 1,2-hydride shift, affords an indolenine (**12**), whose benzenesulfinyl–oxygen bond cleavage (e.g., by nucleophilic benzenesulfinate attack) and subsequent protonation produce oxindole **2b** (as well as **2a**).



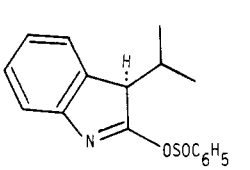
9



10



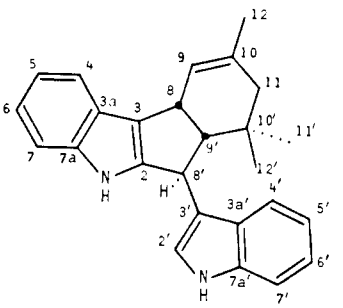
11



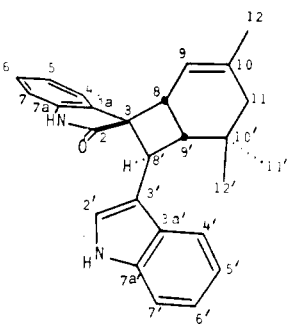
12

All above Grignard reactions were executed in tetrahydrofuran solution, a medium in which they were found to be reproducible. Interestingly, but unfortunately inexplicably at this time, they showed a strong solvent effect. Thus, for example, when the reaction between benzenesulfonyl chloride and the Grignard reagent from β-isopropylindole (**1b**), a reaction which in tetrahydrofuran solution had produced 3-isopropyloxindole (**2b**) in high yield (vide supra), was carried out in ether solution, the products were oxindole **2b** (20%), sulfone **4k** (14%), and a highly fragile, readily decomposing compound of unknown constitution.

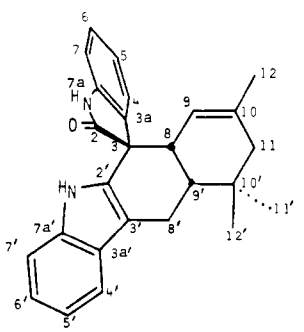
Part of the present study included an attempt to *N*-benzenesulfonylate yuehchukene (**13**), a naturally occurring β-dehydroprenylindole dimer.[2,14] Exposure of the dimagnesio salt of the natural product to 2 equiv of benzenesulfonyl chloride in tetrahydrofuran solution led to a mixture of two oxindoles, **14** (35%) and **15** (11%), and



13



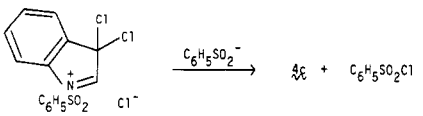
14



15

to recovery of 1 equiv of the sulfonyl chloride. Interaction

(11) The formation of 1-(phenylsulfonyl)-3-chloroindole (**4c**), a product of overreaction and the sole *N*-benzenesulfonyl derivative among all the Grignard reaction products, proceeds probably along the following reaction route: (a) Grignard reagent exchange with production of the indolate of the more acidic β-chloroindole (**4d**), (b) chlorination thereof, (c) N-benzenesulfonylation of the resultant 3,3-dichloroindolenine (**5b**), a sterically unencumbered aldimine (in contrast to imine **6**), and (d) attack of a benzenesulfinate anion by a chlorine of the resultant salt **i**, thereby re-forming benzenesulfonyl chloride and producing **4c**.



i

(12) Inter alia: Wenkert, E.; Hagaman, E. W.; Kunesch, N.; Wang, N.-Y.; Zsadon, B. *Helv. Chim. Acta* **1976**, *59*, 2711.

(13) The reaction of 2,3-dimethylindole (**4b**) is more complicated than intimated. Product **4f** was obtained in poor yield, and two other products were too intractable to be characterized.

(14) Kong, Y.-C.; Cheng, K.-F.; Cambie, R. C.; Waterman, P. G. *J. Chem. Soc., Chem. Commun.* **1985**, 47.

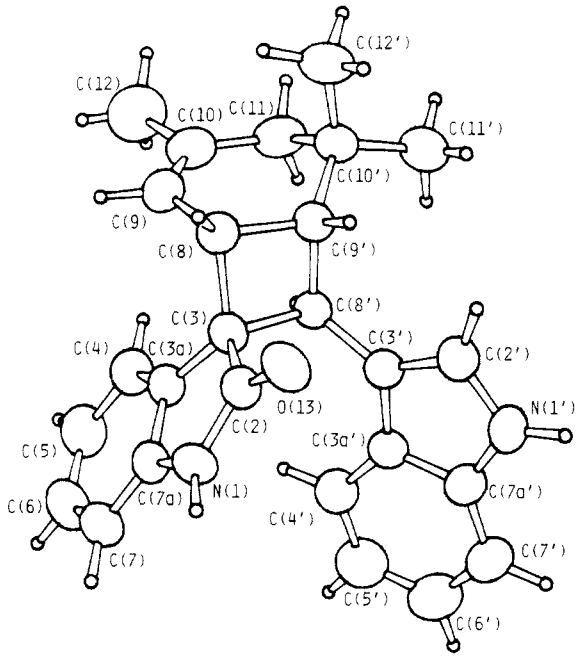


Figure 1. Solid-state conformation of one enantiomer of **14**. Small circles denote hydrogen atoms.

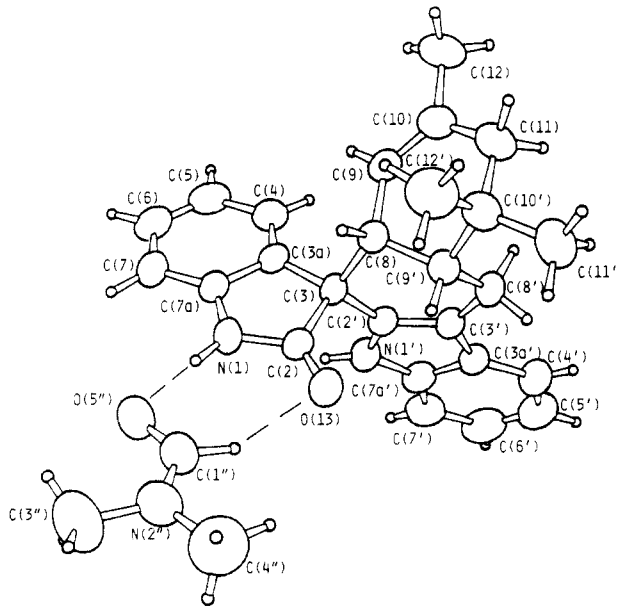
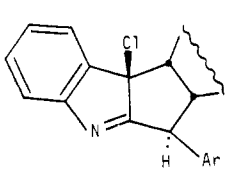


Figure 2. Asymmetric crystal unit in **15**·DMF. Small circles denote hydrogen atoms.

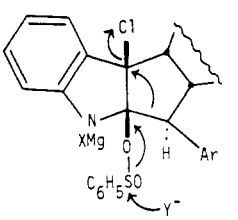
of oxindole **14** with the Lewis acid magnesium sulfate isomerized it into oxindole **15** (82%). When the Grignard reaction was followed by the rearrangement without prior product isolation, oxindole **15** was the sole product (in 39% yield). The structures of the yuehchukene oxidation products were determined by single-crystal X-ray analyses of **14** and the dimethylformamide solvate of **15**, **15**·DMF.

The crystal structures of **14** and **15**·DMF were both solved by direct methods.[15] Full-matrix least-squares refinement of atomic positional and thermal parameters[16] converged at $R = 0.040$ ($R_w = 0.050$, 2652 reflections)[17] for **14** and $R = 0.047$ ($R_w = 0.064$, 2547 reflections) for **15**·DMF. Views of the solid-state conformations of one enantiomer of each product are presented in Figures 1 and 2, respectively. Bond lengths and angles[16] are generally close to normal values save those in the highly strained, nonplanar cyclobutane ring of **14**[18] and around the spiro center, C-3, in **15**·DMF.[18] Molecules of **14** related by centers of symmetry are associated along the *c*-direction by N–H···O hydrogen bonds.[19] In crystals of **15**·DMF, the asymmetric unit comprises a dimethylformamide and **15** molecule associated by N–H···O and weak C–H···O interactions[19] as shown in Figure 2; further N–H···O hydrogen bonds between the other nitrogen atom and the oxygen atom of the reference dimethylformamide molecule link enantiomers in pairs about crystallographic centers of symmetry.

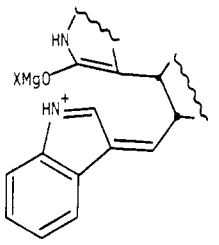
The curious oxidative rearrangement of yuehchukene (**13**) induced by benzenesulfonyl chloride can be explained in the following manner. As an inspection of a yuehchukene model reveals, the β-carbon of the monosubstituted indole unit is hindered sterically, thus barring the formation of an intermediate of type **5** and leading to the recovery of half of the benzenesulfonyl chloride reagent. In the disubstituted indole unit, however, the β face is exposed, permitting the formation of an intermediate of type **6**. In view of the inability of the resultant chloroindolenine **16** to undergo tautomerism (of the **6** → **7** type),



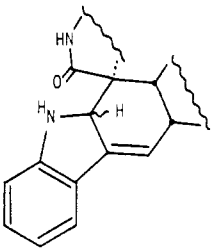
16



17



18



19

the imino α-hydrogen being on the inaccessible face of the compound, it is intercepted by benzenesulfinate anion and produces intermediate **17**. The latter is suited ideally for the rearrangement depicted by the arrows on formula **17**, by analogy with the **11** → **12** → **2b** change, yielding oxindole **14**.[20] The presence of an electron-releasing indole moiety and an electron-withdrawing oxindole unit on vicinal carbons (C-3 and C-8′)[21] of the strained cyclobutane

(15) Crystallographic calculations were performed on a PDP11/44 computer by use of the Enraf-Nonius SDP suite of programs incorporating the direct methods program MULTAN11/82.

(16) Supplementary material, see the paragraph at the end of the paper.

(17) $R = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$.

(18) Significantly elongated distances (Å) follow: C_3–C_8 1.578 (2), C_3–$C_{8'}$ 1.583 (2), C_8–$C_{9'}$ 1.545 (3), $C_{8'}$–$C_{9'}$ 1.548 (2) in **14**; C_2–C_3 1.540 (4), C_3–C_8 1.576 (3) in **15**·DMF.

(19) Hydrogen-bonded distances (Å) follow: N_1···O_{13} (at $-x$, $1-y$, $1-z$) 2.933 (2), $N_{1'}$···O_{13} (at $-x$, $1-y$, $-z$) 2.868 (2) in **14**; $N_{1'}$···$O_{5''}$ 2.868 (3), O_{13}···$C_{1''}$ 3.322 (4), $N_{1'}$···$O_{5''}$ (at $-x$, $-y$, $-z$) 2.890 (3) in **15**·DMF.

(20) For oxidative rearrangements of 2,3-ring-fused indoles into spirooxindoles see, inter alia: Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1953**, *75*, 2572.

ring of oxindole **14** makes the compound vulnerable to ring scission, especially under Lewis acid catalysis. The unraveled intermediate **18** would be expected to re-form a ring (of lowered strain). Subsequent double-bond isomerization of intermediate **19** completes the isomerization of oxindole **14** into **15**.

Experimental Section

Melting points, observed on a Reichert microhotstage, are uncorrected. Infrared spectra of methylene chloride solutions and ultraviolet spectra of methanol solutions were measured on Perkin-Elmer 1330 and IBM 9400 spectrophotometers, respectively. ^{1}H NMR spectra of deuteriochloroform solutions (with Me_4Si as internal standard) were recorded on Varian EM-390 and Nicolet QE-300 spectrometers, and ^{13}C NMR spectra of deuteriochloroform solutions were recorded on the latter instrument operating at 75.5 MHz in the Fourier transform mode. The carbon shifts are in parts per million downfield from Me_4Si: $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. All reactions were carried out under a nitrogen atmosphere, all organic extracts washed with brine and dried over anhydrous $MgSO_4$, and all chromatographic separations executed on silica gel.

Grignard Reactions with Benzenesulfonyl Chloride. General Procedure. A 3.0 M ethereal solution of methylmagnesium bromide (1.70 mL, 5.1 mmol) was added dropwise over a 2-min period to a solution of 5.0 mmol of the indole in 36 mL of anhydrous tetrahydrofuran at room temperature and the mixture then stirred for 1 h. Neat benzenesulfonyl chloride (883 mg, 5.0 mmol) was added over a 1-min period and the stirring continued for 3 h. The mixture then was poured into 100 mL of saturated sodium bicarbonate solution and extracted with 100 mL of methylene chloride. The extract was dried, evaporated, and chromatographed.

3-Prenyloxindole (2a). Elution with 2:1 hexane–ethyl acetate led to the recovery of 75 mg (8%) of starting indole **1a** and to the isolation of 694 mg (75%, based on consumed **1a**) of colorless, crystalline oxindole **2a**: mp 105–106 °C (Et_2O–C_6H_{14}); UV λ_{max} 208 nm (ϵ 22 600), 251 (8400); IR NH 3425 (m), 3190 (br m), C=O 1705 (s), C=C 1619 (m) cm^{-1}; ^{1}H NMR δ 1.58, 1.67 (s, 3 each, methyls), 2.5–2.8 (m, 2, CH_2), 3.4–3.5 (m, 1, CH), 5.1–5.2 (m, 1, olefinic H), 6.9–7.3 (m, 4, aromatic H); ^{13}C NMR δ 17.9 (*Z*-Me), 25.6 (*E*-Me), 29.1 (CH_2), 46.2 (C-3), 109.6 (C-7), 119.5 (CH), 121.9 (C-5), 124.1 (C-4), 127.6 (C-6), 129.6 (C-3a), 134.6 (C), 141.5 (C-7a), 180.5 (C=O); MS, *m/e* 201 (M$^+$, 18%), 133 (base), 69 (49), 41 (31). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.29; H, 7.35; N, 6.96.

3-Isopropyloxindole (2b). Elution with 2:1 hexane–ethyl acetate yielded 52 mg of a compound of unknown structure and 660 mg (75%) of colorless, crystalline oxindole **2b**: mp 107–108 °C (Et_2O–C_6H_{14}) (lit.[4] mp 107–108 °C); UV and IR spectra identical with literature data; ^{1}H NMR δ 0.92, 1.13 (d, 3 each, *J* = 7 Hz, methyls), 2.4–2.6 (m, 1, CH), 3.40 (d, 1, *J* = 4 Hz, α-keto H), 6.90 (d, 1, *J* = 7 Hz, H-7), 7.01 (t, 1, *J* = 7 Hz, H-5), 7.21 (t, 1, *J* = 7 Hz, H-6), 7.25 (d, 1, *J* = 7 Hz, H-4); ^{13}C NMR δ 17.8 (Me), 19.8 (Me), 30.0 (CH), 52.1 (C-3), 109.6 (C-7), 121.8 (C-5), 124.4 (C-4), 127.6 (C-6), 128.2 (C-3a), 142.0 (C-7a), 180.3 (C=O); MS, *m/e* 175 (M$^+$, 67%), 133 (base).

The same reaction in dry ether and elution of the chromatogram as above led to 277 mg of a material that, within minutes of solidification, decomposed with coloration and 210 mg (14%) of 2-(phenylsulfonyl)-3-isopropylindole (**4k**): gum; UV λ_{max} 216 nm (ϵ 39 700), 294 (18 000); IR NH 3427 (m), 3345 (br m), C=C 1615 (w), SO_2 1310 (s), 1160 (s), 1140 (s) cm^{-1}; ^{1}H NMR δ 1.31 (d, 6, *J* = 7 Hz, methyls), 3.81 (septet, 1, *J* = 7 Hz, *i*-Pr CH), 7.1–8.0 (m, 9, aromatic H); ^{13}C NMR δ 22.2 (methyls), 25.5 (CH), 112.6 (C-7), 120.5 (C-6), 122.7 (C-4), 125.5 (C-5), 125.8 (C-3), 126.7 (*o*-C), 127.9 (C-2 or C-3a), 128.5 (C-3a or C-2), 129.1 (*m*-C), 133.1 (*p*-C), 136.4 (C-7a), 142.0 (ipso-C); MS, *m/e* 299 (M$^+$, 75%), 284 (base), 157 (87), 143 (60), 115 (27), 77 (36); exact mass 299.0980, calcd for $C_{17}H_{17}NO_2S$ 299.0979.

Further elution gave 180 mg (20%) of oxindole **2b**.

1-(Phenylsulfonyl)-3-chloroindole (4c) and β-Chloroindole (4d). Elution with 20:1 hexane–ethyl acetate liberated 330 mg (22%) (45%, based on consumed benzenesulfonyl chloride) of colorless, crystalline sulfonamide **4c**: mp 120–121 °C (Et_2O–C_6H_{14}); UV λ_{max} 213 nm (ϵ 23 400), 256 (11 600), 284 (4500), 293 (4300); IR C=C 1585 (w), SO_2 1375 (s), 1175 (s) cm^{-1}; ^{1}H NMR δ 7.3–8.0 (m, 9, aromatic H), 7.56 (s, 1, indole α-H); ^{13}C NMR δ 113.6 (C-7), 113.9 (C-3), 118.9 (C-6), 122.1 (C-5), 123.7 (C-4), 125.7 (C-2), 126.6 (*o*-C), 128.3 (C-3a), 129.2 (*m*-C), 133.9 (*p*-C), 134.2 (C-7a), 137.6 (ipso-C);[22] MS, *m/e* 291 (M$^+$, 73%), 150 (base), 141 (41), 77 (81). Anal. Calcd for $C_{14}H_{10}ClNO_2S$: C, 57.63; H, 3.45; N, 4.80. Found: C, 57.71; H, 3.66; N, 4.78.

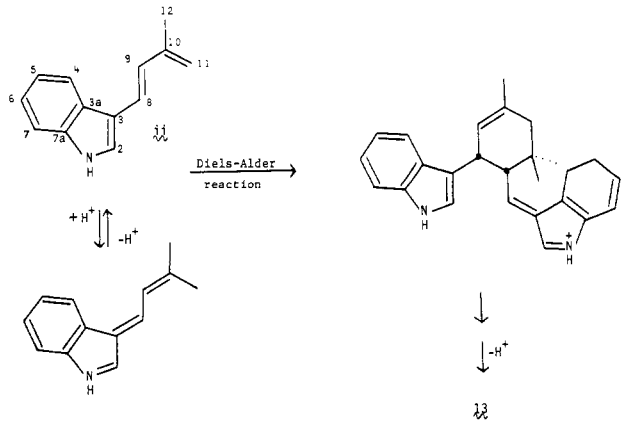
Further elution gave 43 mg (6%) of colorless, crystalline indole **4d**: mp 90–91 °C (hexane) (lit.[6] mp 91.5 °C); UV λ_{max} 220 nm (ϵ 20 400), 274 (5000), 281 (5300), 290 (4200); IR NH 3462 (m) cm^{-1}; ^{1}H NMR δ 7.1–7.7 (m, 4, aromatic H), 7.17 (d, 1, *J* = 3 Hz, α-H); ^{13}C NMR δ 106.3 (C-3), 111.3 (C-7), 118.1 (C-6), 120.3 (C-5), 120.7 (C-4), 122.9 (C-2), 125.2 (C-3a), 134.8 (C-7a); MS, *m/e* 151 (M$^+$, 12%) 117 (base), 90 (40), 89 (27).

2-(Phenylsulfonyl)skatole (4e). Elution with 4:1 hexane–ethyl acetate yielded 825 mg (61%) of colorless, crystalline sulfone **4e**: mp 167–168 °C (Et_2O–C_6H_{14}); UV λ_{max} 216 nm (ϵ 28 400), 234 (15 300), 294 (15 300); IR NH 3435 (m), 3345 (br m), SO_2 1320 (s), 1152 (s) cm^{-1}; ^{1}H NMR δ 2.54 (s, 3, Me), 7.1–8.0 (m, 9, aromatic H); ^{13}C NMR δ 8.8 (Me), 112.2 (C-7), 118.7 (C-3), 120.5 (C-4, C-6), 126.0 (C-5), 126.7 (*o*-C), 128.0 (C-2 or C-3a), 128.8 (C-3a or C-2), 129.1 (*m*-C), 133.1 (*p*-C), 135.9 (C-7a), 141.7 (ipso-C); MS, *m/e* 271 (M$^+$, base), 146 (28%), 130 (22), 129 (27), 107 (22). Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.11; H, 4.76; N, 5.18.

2-[(Phenylsulfonyl)methyl]skatole (4f). Elution with 2:1 hexane–ethyl acetate led to 107 mg of an oil and then to 103 mg of a second oil, both of which decomposed with coloration within a short time. Further elution led to 137 mg (10%) of colorless, crystalline sulfone **4f**: mp 183–185 °C (Et_2O–C_6H_{14}); UV λ_{max} 225 nm (ϵ 38 300), 287 (11 000), 296 (9400); IR NH 3445 (m), SO_2 1312 (s), 1142 (s) cm^{-1}; ^{1}H NMR δ 1.69 (s, 3, Me), 4.48 (s, 2, CH_2), 7.1–7.6 (m, 9, aromatic H); ^{13}C NMR δ (CH_2Cl_2) 7.3 (Me), 54.6 (CH_2), 111.4 (C-7), 113.5 (C-3), 119.2 (C-4 or C-5), 119.7 (C-5 or C-4), 121.5 (C-2, C-6), 128.4 (C-3a), 128.6 (*o*-C), 129.5 (*m*-C), 134.3 (*p*-C), 136.8 (C-7a), 138.0 (ipso-C); MS, *m/e* 285 (M$^+$, 5%), 144 (base), 143 (28). Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91. Found: C, 67.40; H, 5.50; N, 4.83.

Yuehchukene-Based Oxindoles 14 and 15. The reaction was executed with 790 mg (2.2 mmol) of yuehchukene (**13**), 1.44 mL (4.3 mmol) of a 3.0 M ethereal methylmagnesium bromide solution, and 762 mg (4.3 mmol) of benzenesulfonyl chloride according to the general procedure and workup. Elution with 2:1 hexane–ethyl acetate led to the recovery of 310 mg (41%) of unreacted benzenesulfonyl chloride and of 53 mg (7%) of unused yuehchukene (**13**). It then afforded 81 mg (11%) of crystalline, colorless oxindole **15**: mp 190–191 °C (EtOH–hexane); UV λ_{max}

(21) The numbering system of yuehchukene (**13**) and hence of its oxindole conversion products **14** and **15** is based on that of dehydroprenylindole (**ii**), yuehchukene's biogenetic precursor (vide infra).



(22) Related 1-(phenylsulfonyl)-3-bromoindole, reported earlier,[2] possesses a similar spectrum: ^{13}C NMR δ 113.4 (C-7), 119.9 (C-6), 123.8 (C-5), 124.5 (C-4), 125.7 (C-2), 126.7 (*o*-C), 129.2 (*m*-C), 129.5 (C-3 or C-3a), 129.6 (C-3a or C-3), 133.9 (*p*-C), 135.0 (C-7a), 137.6 (ipso-C).

(23) *International Tables for X-ray Crystallography*; Kynoch: Birmingham, England, 1974; Vol. IV.

210 nm (ε 54 200), 226 (50 800), 286 (14 300), 292 (12 500), 262 (13 900, sh); IR NH 3435 (m), C=O 1722 (s), C=C 1622 (m) cm^{-1}; ^1H NMR δ 0.97, 1.15 (s, 3 each, methyls), 1.58 (s, 3, C-10 Me), 1.60, 2.16 (d, 1 each, J = 18 Hz, 2 H-11), 2.49 (dd, 1, J = 16, 10 Hz, eq β-H-8′), 2.79 (m, 2, H-8, H-9′), 2.97 (dd, 1, J = 16, 6 Hz, ax α-H-8′), 5.38 (s, 1, H-9), 6.9–7.6 (m, 8, aromatic H); ^{13}C NMR δ 19.3 (C-8′), 23.8 (C-12), 28.3 (C-11′ or C-12′), 28.4 (C-12′ or C-11′), 32.8 (C-10′), 37.0 (C-8), 39.4 (C-9′), 41.0 (C-11), 53.2 (C-3), 110.1 (C-7 or C-7′), 110.7 (C-7′ or C-7), 110.8 (C-3′), 118.2 (C-4′ or C-5′), 118.5 (C-5′ or C-4′), 119.2 (C-6′), 121.9 (C-4, C-5), 127.6 (C-2′, C-6), 128.6 (C-3a′), 128.9 (C-9), 129.8 (C-3a), 135.7 (C-10), 136.4 (C-7a′), 141.6 (C-7a), 180.2 (C=O); MS, m/e 382 (M^+, 11%), 261 (27), 260 (base), 259 (26), 232 (31), 107 (26); exact mass 382.2056, calcd for $C_{26}H_{26}N_2O$ 382.2044. Recrystallization from dimethylformamide furnished crystals of the dimethylformamide solvate, **15**·DMF, suitable for X-ray analysis.

Further elution gave 270 mg (35%) of colorless, crystalline oxindole **14**: mp 241–242 °C (EtOH–hexane); UV λ_{max} 216 (ε 37 700), 258 (8900), 282 (6700), 290 (6000); IR (Nujol) NH 3380 (m), C=O 1679 (s), C=C 1612 (w) cm^{-1}; ^1H NMR δ 0.83, 0.98 (s, 3 each, methyls), 1.75, 2.26 (d, 1 each, J = 18 Hz, 2 H-11), 1.92 (s, 3, C-10 Me), 3.26 (s, 1, H-8), 3.29 (t, 1, J = 9 Hz, H-9′), 3.91 (d, 1, J = 9 Hz, H-8′), 5.43 (s, 1, H-9), 6.5–7.4 (m, 9, aromatic H); MS, m/e 382 (M^+, 11%), 185 (16), 184 (base); exact mass 382.2040, calcd for $C_{26}H_{26}N_2O$ 382.2044. Anal. Calcd for $C_{26}H_{26}N_2O$: C, 81.63; H, 6.85; N, 7.35. Found: C, 81.53; H, 6.92; N, 7.17. Recrystallization from EtOH afforded crystals suitable for X-ray analysis.

A mixture of 38.2 mg (0.1 mmol) of oxindole **14** and 3.61 g (30.0 mmol) of magnesium sulfate in 10 mL of methylene chloride was stirred at room temperature until all starting oxindole had disappeared (ca. 110 h), as monitored by TLC on silica gel (development with 2:1 hexane–ethyl acetate). It was filtered and the filtrate evaporated. Washing of the residue with ether and crystallization from ethanol–heptane gave 31 mg (82%) of oxindole **15**.

Combining the two reactions in one operation led to a 39% yield of oxindole **15**.

Grignard Reactions with Methanesulfonyl Chloride. The reactions followed the above general procedure except for the replacement of benzensulfonyl chloride by 573 mg (5.0 mmol) of methanesulfonyl chloride.

1-(Methylsulfonyl)indole (4g). Elution with 2:1 hexane–ethyl acetate gave 577 mg (59%) of pale yellow, oily sulfonamide **4g**: UV λ_{max} 218 nm (ε 18 400), 250 (10 300); IR C=C 1605 (w), SO_2 1365 (s), 1170 (s) cm^{-1}; ^1H NMR δ 3.06 (s, 3, Me), 6.69 (d, 1, J = 4 Hz, indole β-H), 7.28, 7.35 (t, 1 each, J = 8 Hz, H-5, H-6), 7.42 (d, 1, J = 4 Hz, indole α-H), 7.61 (d, 1, J = 8 Hz, H-4), 7.90 (d, 1, J = 8 Hz, H-7); ^{13}C NMR δ 40.4 (Me), 108.6 (C-3), 112.7 (C-7), 121.4 (C-6), 123.3 (C-5), 124.6 (C-4), 125.8 (C-2), 130.4 (C-3a), 134.6 (C-7a); MS, m/e 195 (M^+, 75%), 117 (48), 116 (base), 89 (19); exact mass 195.0353, calcd for $C_9H_9O_2NS$ 195.0353.

1-(Methylsulfonyl)skatole (4h). Elution with 2:1 hexane–ethyl acetate yielded 380 mg (36%) of pale yellow, oily sulfonamide **4h**: UV λ_{max} 220 nm (ε 20 500), 256 (7700); IR C=C 1607 (w), SO_2 1359 (s), 1166 (s) cm^{-1}; ^1H NMR δ 2.28 (d, 3, J = 1 Hz, Me), 3.01 (s, 3, SMe), 7.19 (d, 1, J = 1 Hz, indole α-H), 7.31, 7.36 (t, 1 each, J = 8 Hz, H-5, H-6), 7.54 (d, 1, J = 8 Hz, H-4), 7.88 (d, 1, J = 8 Hz, H-7); ^{13}C NMR δ 9.5 (Me), 40.4 (SMe), 112.9 (C-7), 118.4 (C-3), 119.5 (C-6), 122.7 (C-5), 123.0 (C-4), 124.7 (C-2), 129.6 (C-3a), 135.0 (C-7a); MS, m/e 209 (M^+, 35%), 130 (base); exact mass 209.0508, calcd for $C_{10}H_{11}NO_2S$ 209.0509.

Phase-Transfer N-Benzenesulfonylations of Indoles. General Procedure. A 50% potassium hydroxide solution (1.0 mL) was added dropwise to a mixture of 1.0 mmol of the requisite indole and 0.1 mmol of tetra-*n*-butylammonium bisulfate in 3.0 mL of benzene, and the mixture was stirred at room temperature for 5 min. Benzenesulfonyl chloride (264 mg, 1.50 mmol) was added dropwise and the stirring continued for 0.5 h. The mixture was poured into 20 mL of water and extracted with 60 mL of methylene chloride. The extract was dried and evaporated and the residue chromatographed.

1-(Phenylsulfonyl)-3-prenylindole (3a). Elution with 20:1 hexane–ethyl acetate and crystallization of the residue from evaporation of the eluates in hexane–dichloromethane produced 295 mg (90%) of colorless, crystalline sulfonamide **3a**, in all respects identical with an authentic sample.[2]

1-(Phenylsulfonyl)-3-isopropylindole (3b). Elution with 20:1 hexane–ethyl acetate gave a solid, whose crystallization from ether–hexane afforded 256 mg (86%) of colorless, crystalline sulfonamide **3b**: mp 113–114 °C; UV λ_{max} 215 nm (ε 25 700), 254 (12 300), 283 (2900), 292 (3200); IR C=C 1605 (w), SO_2 1368 (s), 1173 (s), cm^{-1}; ^1H NMR δ 1.31 (d, 6, J = 7 Hz, methyls), 3.08 (septet, 1, J = 7 Hz, *i*-Pr CH), 7.2–8.0 (m, 9, aromatic H), 7.30 (s, 1, indole α-H); MS, m/e 299 (M^+, 76%), 284 (base), 158 (65), 141 (25), 77 (17). Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.64; H, 5.88; N, 4.74.

***N*-(Phenylsulfonyl)skatole (3c).** Elution with 20:1 hexane–ethyl acetate led to a solid, whose crystallization with ether–hexane yielded 235 mg (87%) of colorless, crystalline sulfonamide **3c**: mp 120–122 °C (lit.[1c] mp 121–122.5 °C); ^1H NMR data identical with those in the literature;[1c] UV λ_{max} 215 nm (ε 27 400), 254 (13 600), 283 (3900), 293 (3600); ^{13}C NMR δ 9.5 (Me), 113.4 (C-7), 118.6 (C-3), 119.2 (C-6), 122.8 (C-4 or C-5), 122.9 (C-5 or C-4), 124.5 (C-2), 126.5 (*o*-C), 128.9 (*m*-C), 131.6 (C-3a), 133.4 (*p*-C), 135.0 (C-7a), 138.1 (ipso-C).

1-(Phenylsulfonyl)-3-chloroindole (4c). Elution with 2:1 hexane–ethyl acetate yielded 264 mg (91%) of sulfonamide **4c**, in all respects identical with the above sample.

Chlorine gas (709 mg, 10.0 mmol) was passed into a stirring solution of 1.17 g (4.5 mmol) of *N*-(phenylsulfonyl)indole (**4l**)[1b] in 5 mL of methylene chloride at 0 °C and stirring continued at room temperature for 1 h. The mixture was poured into 20 mL of saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was dried and evaporated and the residue chromatographed. Elution with 9:1 hexane–ethyl acetate led to 1.04 g (91%, based on consumed starting sulfonamide **4l**) of crystalline sulfonamide **4c**, in all respects identical with the above sample, and 150 mg (13%) of recovered starting material.

1-(Phenylsulfonyl)-2-chloroskatole (4j). A solution of 273 mg (1.0 mmol) of *N*-(phenylsulfonyl)skatole (**3c**) in 2 mL of anhydrous tetrahydrofuran was added dropwise into a solution of 1.1 mmol of lithium diisopropylamide in 8 mL of anhydrous tetrahydrofuran at 0 °C. The solution was stirred at room temperature for 80 min and then cooled to −78 °C. Benzenesulfonyl chloride (194 mg, 1.1 mmol) was added dropwise and the mixture allowed to reach room temperature. It was poured into 30 mL of water and extracted with methylene chloride. The extract was dried and evaporated. Chromatography of the residue and elution with 20:1 hexane–ethyl acetate gave 161 mg (69%, based on consumed sulfonamide **3c**) of colorless, crystalline sulfonamide **4j**: mp 148–149 °C (Et_2O–hexane); UV λ_{max} 212 nm (ε 27 900), 255 (19 300); IR C=C 1603 (w), SO_2 1378 (s), 1177 (s) cm^{-1}; ^1H NMR δ 2.16 (s, 3, Me), 7.2–8.3 (m, 9, aromatic H); ^{13}C NMR δ 8.8 (Me), 114.8 (C-7), 117.5 (C-3), 118.3 (C-6), 123.7 (C-4 or C-5), 124.8 (C-5 or C-4), 126.7 (*o*-C), 128.9 (*m*-C), 128.9 (C-2 or C-3a), 129.5 (C-3a or C-2), 133.7 (*p*-C), 135.7 (C-7a), 137.9 (ipso-C); MS, m/e 305 (M^+, 30%), 166 (33), 165 (16), 164 (base), 128 (75), 77 (50). Anal. Calcd for $C_{15}H_{12}ClNO_2S$: C, 58.92; H, 3.96; N, 4.58. Found: C, 58.61; H, 4.08; N, 4.43.

Further elution led to the recovery of 63 mg (23%) of starting sulfonamide **3c**.

X-ray Crystal Structure Analyses of 14 and 15·DMF. $C_{26}H_{26}N_2O$ (**14**): M_r 382.51, triclinic, a = 9.992 (2) Å, b = 14.539 (3) Å, c = 8.281 (1) Å, α = 99.83 (1)°, β = 110.68 (1)°, γ = 100.68 (1)°, V = 1067.9 Å^3, Z = 2, D_{calcd} = 1.190 g cm^{-3}, μ(Cu Kα radiation, λ = 1.5418 Å) = 5.3 cm^{-1}; space group $P1$ (C_1^1) or $P\bar{1}$ (C_i^1) from Laue symmetry, shown to be the latter by structure solution and refinement; sample dimensions 0.08 × 0.14 × 0.60 mm.

$C_{26}H_{26}N_2O$·C_3H_7NO (**15·DMF**): M_r 455.61, triclinic, a = 9.633 (2) Å, b = 16.136 (3) Å, c = 8.735 (2) Å, α = 94.32 (2)°, β = 110.41 (2)°, γ = 84.88 (2)°, V = 1266.0 Å^3, Z = 2, D_{calcd} = 1.195 g cm^{-3}, μ(Cu Kα radiation) = 5.6 cm^{-1}; space group $P1$ (C_1^1) or $P\bar{1}$ (C_i^1) as for **14**, shown to be the latter by structure solution and refinement; sample dimensions 0.05 × 0.20 × 0.20 mm.

Preliminary unit cell dimensions and space group information were obtained from oscillation, Weissenberg, and precession photographs. One hemisphere of intensity data from each crystal was recorded on an Enraf-Nonius CAD-4 diffractometer (Cu Kα radiation, incident-beam graphite monochromator; ω–2θ scans, θ_{max} = 67°). From totals of 3803 and 4513 unique forms measured

for 14 and 15·DMF, respectively, those 2652 and 2547 reflections with $I > 3.0\sigma(I)$ were retained for the structure analyses, and the usual Lorentz and polarization corrections were applied. Refined unit cell parameters for each crystal were derived by least-squares treatment of the diffractometer setting angles for 25 reflections ($41° < \theta < 66°$ for 14; $33° < \theta < 43°$ for 15·DMF) widely separated in reciprocal space.

The crystal structures were both solved by direct methods, assuming at the outset that the crystals were centrosymmetric. Approximate coordinates for all non-hydrogen atoms were obtained from *E*-maps and weighted Fourier syntheses. Hydrogen atoms were all located in difference Fourier syntheses evaluated following several rounds of full-matrix least-squares adjustment of non-hydrogen atom positional and anisotropic thermal parameters. With the inclusion of hydrogen atom positional and isotropic thermal parameters as variables in the subsequent least-squares calculations, the refinements converged at $R = 0.040$ ($R_w = 0.050$) for 14 and $R = 0.047$ ($R_w = 0.064$) for 15·DMF.

Neutral atom scattering factors used in the structure factor calculations were taken from ref 23. In the least-squares iterations, $\sum w\Delta^2$ [$w = 1/\sigma^2(|F_o|)$, $\Delta = (|F_o| - |F_c|)$] was minimized.

Acknowledgment. Part of this investigation received financial support from the World Health Organization (Special Programme of Research, Development, and Research Training in Human Reproduction). E.W., P.D.R.M., and S.R.P. are indebted to D. Verdon for the preparation of yuehchukene.

Registry No. **1a**, 17771-42-5; **1b**, 16886-00-3; **1c**, 83-34-1; **2a**, 108665-92-5; **2b**, 108665-93-6; **3a**, 102210-79-7; **3b**, 108666-00-8; **3c**, 58500-84-8; **4a**, 120-72-9; **4b**, 91-55-4; **4c**, 108665-94-7; **4d**, 16863-96-0; **4e**, 108665-95-8; **4f**, 108665-96-9; **4g**, 70390-93-1; **4h**, 108665-97-0; **4j**, 108665-98-1; **4k**, 108665-99-2; **4l**, 40899-71-6; (±)-**13**, 96624-37-2; (±)-**14**, 108675-04-3; (±)-**15**, 108666-01-9; (±)-15·DMF, 108739-47-5.

Supplementary Material Available: Tables of non-hydrogen atom positional and anisotropic thermal parameters, hydrogen atom positional and isotropic thermal parameters, interatomic distances and bond angles, and torsion angles for 14 and 15·DMF (16 pages). Ordering information is given on any current masthead page.

Synthesis and Structural Aspects of (2,5)-1,3,4-Thiadiazolo and (3,5)-1,3,4-Thiadiazolino Thia Crown Ethers[1]

Sebastiano Pappalardo,* Francesco Bottino, and Corrado Tringali

Dipartimento di Scienze Chimiche, Università di Catania, 95125 Catania, Italy

Frank R. Fronczek

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803-1804

Received November 20, 1986

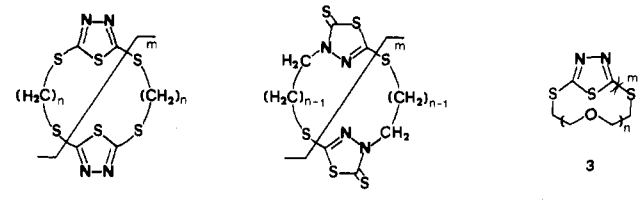
A general route to (2,5)-1,3,4-thiadiazolo thia crown ethers **3**, by the high-dilution reaction of 2,5-dimercapto-1,3,4-thiadiazole dipotassium salt **8** with oligoethylene glycol dihalides **9** in ethanol, is described. The reaction of **8** with bis[2-(2-bromoethoxy)ethyl] ether (**9c**) produced also small amounts of the 15-membered (3,5)-1,3,4-thiadiazolino thione macrocycle **10**, which possesses a ring nitrogen pointing into the complexing cavity. The structures of the macrocycles were firmly established by ^1H and ^{13}C NMR spectroscopy. Macrocycle **10** was further characterized by a single-crystal X-ray diffraction study.

Introduction

Various 1,3,4-thiadiazoles exhibit a penchant for the formation of stable complexes with heavy- and transition-metal ions,[2] some of which have industrial importance[3] or show interesting pharmacological properties.[2d] Besides, some 1,3,4-thiadiazoles have been proposed to act in the presence of appropriate metals as N,N-bridging ligands,[4] giving rise to one-dimensional polynuclear structures,[5] which may be of interest as semiconductors.[6]

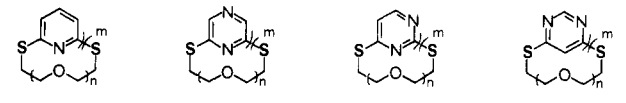
In light of the general interest on the construction of synthetic macrocycles containing heterocyclic subunits,[7] as well as the limited examples of 1,3,4-thiadiazole inclusion in a macrocyclic framework,[8] we became interested

Chart I



1 2 3

Chart II



4 5 6 7

(1) Presented at the 11th International Symposium on Macrocyclic Chemistry, Florence, Italy, Sept 1–4, 1986.

(2) (a) Pnevmaticakis, G. A.; Stakis, E. C.; Fields, E. K. *J. Inorg. Nucl. Chem.* **1966**, *28*, 2059. (b) Gajendragad, M. R.; Agarwala, U. *Aust. J. Chem.* **1975**, *28*, 763. (c) *J. Inorg. Nucl. Chem.* **1975**, *37*, 2429. (d) Zaidi, S. A. A.; Farooqi, A. S.; Varshney, D. K.; Islam, V.; Siddiqi, K. S. *Ibid.* **1977**, *39*, 581; (e) Fabretti, A. C.; Franchini, G. C.; Peyronel, G. *Transition Met. Chem.* **1978**, *3*, 363; (f) *Spectrochim. Acta, Part A* **1980**, *36A*, 517; (g) *Transition Met. Chem.* **1982**, *7*, 105. (h) Osman, M. M.; Makhyoun, M. A.; Tadros, A. B. *Bull. Soc. Chim. Fr.* **1980**, 451. (i) Fabretti, A. C.; Peyronel, G.; Franchini, G. C. *Spectrochim. Acta, Part A* **1979**, *35A*, 229; (j) *J. Coord. Chem.* **1979**, *9*, 111.

(3) Nagasawa, M. U.S. Patent 268 347 (Cl. 106–15), 1966; App. p 3, 1963. Denton, W. M.; Thompson, S. A. M. *Inst. Petrol. Rev.* **1966**, *20* (230), 46. Evva, F. Z. *Wiss. Photogr., Photophys. Photochem.* **1967**, *60*, 145. Miyake, H.; Ogino, Y.; Yokama, A. Jpn. Patent 74-10 986, 1974; *Chem. Abstr.* **1974**, *81*, 107261k.

(4) Fabretti, A. C.; Franchini, G. C.; Peyronel, G. *Spectrochim. Acta, Part A* **1980**, *36A*, 689. Fabretti, A. C.; Franchini, G. C.; Malavasi, W.; Peyronel, G. *Polyhedron* **1985**, *4*, 989.

(5) For a recent review on polymer–metal complexes, see: Kaneko, M.; Tsuchida, E. *J. Polym. Sci., Macromol. Rev.* **1981**, *16*, 397.

(6) Scheider, O.; Hanack, M. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 392.

(7) Newkome, G. R.; Sauer, J. D.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513.

0022-3263/87/1952-3409$01.50/0