Fused Indoles. 1. Synthesis of the 1,9-Dihydrothiazino[3,4-*b*]indole Ring System

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The title compounds were prepared by treating 2-chloroindole-3-carboxaldehydes and 3-acetyl-2-chloroindole with *N*-methylmethanesulfonamide and cyclizing the resulting intermediates with sodium hydride. Spectral data of the products are also discussed.

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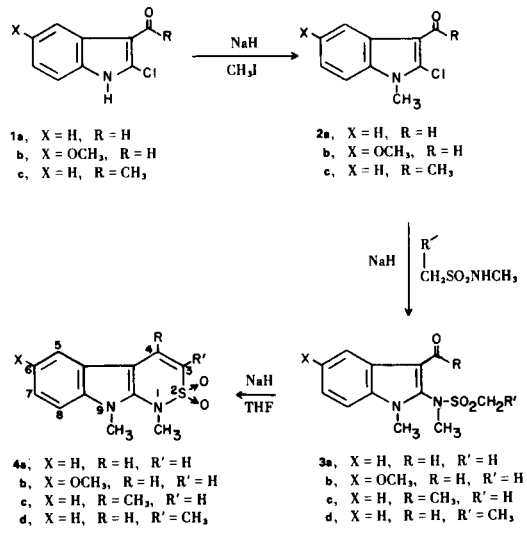
A wide variety of indoles and fused indoles have exhibited interesting biological activities. In our investigations into potentially active pharmaceutical agents we have synthesized the novel fused indole system 1,9-dihydrothiazino[3,4-*b*]indole (**4**).

The intermediate 2-chloroindole-3-carboxaldehydes (**1**, R = H) are readily available by treating the corresponding oxindoles with the Vilsmeier reagent (1,2). The synthesis of 3-acetyl-2-chloroindole (**1c**) was accomplished by treating oxindole with a reagent obtained from dimethylacetamide (DMA) and phosphorus oxychloride ($POCl_3$).

The 2-halo-3-acylindoles (**1**) can be readily alkylated with methyl iodide *via* their *N*-anions preformed with sodium hydride. The resulting *N*-methylindoles (**2**), when treated with *N*-methylmethanesulfonamide (**3**) in the presence of sodium hydride, produced a mixture of **3** and **4** (approximately 50:50). The addition of more sodium hydride to the reaction to affect ring closure only decomposed the mixture. Although **3** was not isolated pure, the crude mixture was purified *via* column chromatography to remove extraneous polar materials, leaving a mixture only containing **3** and **4**. When this mixture was treated at room temperature with sodium hydride in THF, pure **4** was isolated.

The ir spectrum of **4a** contained no carbonyl absorption and exhibited two intense peaks at 1340 and 1150 cm^{-1} which reflects the sulfonamide absorption. In the nmr, two sharp methyl singlets appear at 3.7 and 3.2 δ. The signal appearing at 3.7 δ is assigned to the methyl at position 9 and that at 3.2 δ is assigned to the methyl at the 1 position.



1a, X = H, R = H
b, X = OCH_3, R = H
c, X = H, R = CH_3

2a, X = H, R = H
b, X = OCH_3, R = H
c, X = H, R = CH_3

4a, X = H, R = H, R' = H
b, X = OCH_3, R = H, R' = H
c, X = H, R = CH_3, R' = H
d, X = H, R = H, R' = CH_3

3a, X = H, R = H, R' = H
b, X = OCH_3, R = H, R' = H
c, X = H, R = CH_3, R' = H
d, X = H, R = H, R' = CH_3

In addition, two doublets, with a coupling constant of 9.5 Hz, are observed centered at 7.5 and 6.2 δ. The assignment of these protons, which are located in the 3 and 4 position, was aided by the spectral data from **4c** and **4d**. The doublet at 7.5 δ is assigned to the proton at position 4 due to the fact that in compound **4c**, where this proton is replaced by a methyl group, the doublet disappears and the second doublet at 6.2 δ collapses to one broad peak. In compound **4d**, where the methyl group replaces the proton at position 3, the signal at 6.2 δ disappears, the doublet at 7.5 δ collapses and the resulting signal is observed in the aromatic region.

It is interesting to note that the methyl signals in **4c** and **4d** are split and appear as doublets (J = 2 Hz). This is possibly due to long range coupling to the protons at the 3 or 4 position described above.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover unimelt apparauts and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian A-60 and T-60 spectrophotometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on an LKB 9000 spectrophotometer.

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

3-Acetyl-2-chloroindole (1c).

To a solution of 92.0 g. of phosphorus oxychloride in 200 ml. of chloroform was added 54.0 g. of DMA dropwise (the temperature of the reaction mixture was kept below 20° during the addition). After stirring for 5 minutes, a solution of 27.0 g. of oxindole in 200 ml. of chloroform was slowly added, again keeping the temperature below 20°. After addition, the mixture was refluxed for 5 hours. The reaction mixture was poured onto cold water and the organic phase was separated. The aqueous phase was neutralized with potassium acetate and was allowed to stand at room temperature overnight. The resulting precipitate was

filtered, washed twice with water, then triturated with 500 ml. of hot chloroform yielding 11.2 g. of **1c** (29%), m.p. 240-242°; ir (Nujol): 1610 cm^{-1}; nmr (DMSO): δ 12.3 (very broad, s, 1), 8.3 (m, 1), 7.3 (m, 3), 2.6 (s, 3); ms: (70 eV) m/e 193 (M+).

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.0; H, 4.2; N, 7.2; Cl, 18.3. Found: C, 62.3; H, 4.4 N, 7.4; Cl, 18.7.

2-Chloro-1-methylindole-3-carboxaldehyde (**2a**).

To a cooled solution of 40.0 g. of **1a** (1) in 500 ml. of THF (under a blanket of nitrogen) was added 11.5 g. of sodium hydride (57% in mineral oil, pentane washed) in portions. The mixture was stirred at room temperature for 15 minutes, after which period, 40.0 g. of methyl oidide was added. The resulting mixture was stirred at room temperature for 30 minutes after which it was poured onto cold water. The THF was removed from the mixture under reduced pressure and the resulting precipitate was filtered, washed well with water and crystallized from ether to yield 36.0 g. of **2a** (84%), m.p. = 89-91°; ir (chloroform): 1655 cm^{-1}; nmr (deuteriochloroform): δ 10.1 (s, 1), 8.3 (m, 1), 7.3 (m, 3), 3.8 (s, 3).

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.0; H, 4.2; N, 7.2. Found: C, 62.3; H, 4.2; N, 7.3.

2-Chloro-5-methoxy-1-methylindole-3-carboxaldehyde (**2b**).

The reaction was performed similar to the one described for the preparation of **2a** and the product, **2b**, was isolated in 57% yield, m.p. 112-115°; ir (chloroform): 1650 cm^{-1}; nmr (deuteriochloroform): δ 10.0 (s, 1), 7.7 (m, 1), 7.0 (m, 2), 3.85 (s, 3), 3.65 (s, 3).

3-Acetyl-2-chloro-1-methylindole (**2c**).

The reaction was performed similar to the one described for the preparation of **2a** and the product, **2c**, was isolated in 97% yield, m.p. 109-112°; ir (chloroform): 1645 cm^{-1}; nmr (deuteriochloroform): δ 8.4 (m, 1) 7.3 (m, 3), 3.75 (s, 3), 2.65 (s, 3).

Anal. Calcd. for $C_{11}H_{10}ClNO$: C, 63.6; H, 4.9; N, 6.7; Cl, 17.1. Found: C, 63.7; H, 5.3; N, 6.5; Cl, 17.4.

General Procedure for the Preparation of **3**.

To a solution of 0.09 mole of *N*-methylmethanesulfonamide (3) (or *N*-methylethanesulfonamide in the case of **3d**) in 300 ml. of DMA was added 0.095 mole of sodium hydride (57% in mineral oil, pentane washed) in portions. The solution was stirred at room temperature for 15 minutes, then 0.075 mole of **2** was added and the mixture was stirred at 90° for 3 days. The solvent was removed under reduced pressure and the resulting oil was chromatographed on a column of silica gel. Chloroform was used to elute the products (**3** and **4**). Because **3** and **4** move fairly close together, they were isolated as the mixture free from other contaminations and this mixture was used in the subsequent reactions.

1,9-Dihydro-1,9-dimethylthiazino[3,4-*b*]indole 2,2-Dioxide (**4a**).

To a solution of 11.0 g. of the **3a**/**4a** mixture in 150 ml. of THF (cooled to 5°) was added 3.0 g. of sodium hydride (57% in mineral oil, pentane washed) in portions. After addition, the reaction mixture was allowed to warm to room temperature and was stirred there for 18 hours. The resulting mixture was poured carefully onto 500 ml. of cold water and the oily suspension was extracted into methylene chloride. Evaporation of the solvent under reduced pressure furnished an oil which was crystallized from methylene chloride/ether to yield 3.5 g. of **4a** (30% overall, from **2a**), m.p. 173-174°; ir (chloroform): 1340, 1150 cm^{-1}; nmr (deuteriochloroform): δ 7.6 (m, 1), 7.5 (d, 1, J = 9.5 Hz), 7.3 (m, 3), 6.2 (d, 1, J = 9.5 Hz), 3.7 (s, 3), 3.2 (s, 3).

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.0; H, 4.9; N, 11.3; S, 12.9. Found: C, 57.7; H, 5.2; N, 10.9; S, 12.9.

1,9-Dihydro-1,9-dimethyl-6-methoxythiazino[3,4-*b*]indole 2,2-Dioxide (**4b**).

The reaction of 2.9 g. of the **3b**/**4b** Mixture and 0.5 g. of sodium hydride (50% in mineral oil, pentane washed) was carried out similar to that described for **4a** to yield 0.8 g. of **4b** (17.5% overall, from **2b**), m.p. 200-201°; ir (chloroform): 1340, 1150 cm^{-1}; nmr (deuteriochloroform): δ 7.45 (d, 1, J = 9.5 Hz), 7.0 (m, 3), 6.15 (d, 1, J = 9.5 Hz), 3.8 (s, 3), 3.65 (s, 3), 3.15 (s, 3).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.1; H, 5.1; N, 10.1; S, 11.5. Found: C, 56.1; H, 5.4; N, 10.0; S, 11.1.

1,9-Dihydro-1,4,9-trimethylthiazino[3,4-*b*]indole 2,2-Dioxide (**4c**).

The reaction of 6.5 g. of the **3c**/**4c** mixture and 0.5 g. of sodium hydride (50% in mineral oil, pentane washed) was carried out similar to that described for **4a** to yield 0.7 g. of **4c** (14% overall, from **2c**), m.p. 171-173°; ir (chloroform): 1340, 1160 cm^{-1}; nmr (deuteriochloroform): δ 7.7 (m, 1), 7.3 (m, 3), 6.0 (s, broad, 1) 3.8 (s, 3), 3.2 (s, 3), 2.55 (d, 3).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.5; H, 5.4; N, 10.7; S, 12.3. Found: C, 59.4; H, 5.5; N, 10.7; S, 12.0.

1,9-Dihydro-1,3,9-trimethylthiazino[3,4-*b*]indole 2,2-Dioxide (**4d**).

The reaction of 4.5 g. of the **3d**/**4d** mixture and 1.5 g. of sodium hydride (50% in mineral oil, pentane washed) was carried out similar to that described for **4a** to yield 1.0 g. of **4d** (9% overall, from **2a**), m.p. 172-174°; ir (chloroform): 1340, 1165 cm^{-1}; nmr (deuteriochloroform): δ 7.7-7.1 (m, 5), 3.75 (s, 3), 3.2 (s, 3), 2.3 (d, 3).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.5; H, 5.4; N, 10.7. Found: C, 59.4; H, 5.4; N, 10.5.

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