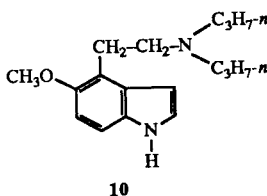




Attempts to oxidize the allyl double bond of **3** (or of its 5-methyl ether) using a variety of oxidizing agents and reaction conditions led only to intractable mixtures, even when the indole ring nitrogen was masked by benzylation. Reduction of the 2,3-double bond of the 5-methyl ether of **3** provided the indoline **5** in 92% yield. The ring nitrogen was protected by benzylation (compound **6**) for the subsequent oxidation step. Attempts to oxidize **6** with acid permanganate as described [2] for conversion of allylbenzene into phenylacetic acid failed; no indoline-4-acetic acid derivative **7** could be detected. However, ozonolysis of **6**, followed by a reductive workup, provided the aldehyde **8** in 77% yield. This aldehyde, when pure, is moderately stable chemically, and it underwent normal reductive amination with di-*n*-propylamine to give **9** in acceptable yields.

Our planned subsequent synthetic strategy involved hydrolytic cleavage of the amide linkage of **9** to provide the free indoline which should be oxidizable to the target indole system **1**. However, literature methods for conversion of indolines into indoles are, with very few exceptions, low yielding, or are of very limited scope [3-5]. For deprotection of the indoline ring nitrogen, potassium *t*-butoxide was utilized; this reagent is reported [6] to be specific for tertiary amides and has been claimed that it is most successful for benzamides. When the hydrolysis was performed under ambient atmosphere, a mixture of two products was obtained, as evidenced by thin layer chromatographic analysis. Mass spectral analysis indicated that these two products were the expected *N*-debenzoylated indoline and the fully aromatized *N*-debenzoylated product **10**.



When the hydrolysis reaction was performed in a nitrogen atmosphere, only a single product (the *N*-debenzoylated indoline) could be visualized by tlc analysis. The hydrolysis reaction was then performed in an open flask exposed to the air, and when all of the amide **9** had been consumed (as evidenced by tlc analysis), air was bubbled through the reaction solution until tlc analysis showed complete conversion to the indole product **10**. Pure **10** was isolated in 41% yield, which compares favorably with most of the literature methods for aromatization of indolines. Air oxidation of an indoline ring to indole in a basic environment appears to be a new, convenient method which may be applicable to a variety of indolines.

Spectral (nmr, ms) data on all compounds were consistent with the proposed structures.

## EXPERIMENTAL

### General.

Melting points were determined in open capillary tubes on a Thomas-Hoover Uni-Melt apparatus, and are uncorrected. Elemental analyses and Karl Fischer quantitative determinations for water were performed by Galbraith Laboratories, Knoxville, TN. Flash column chromatography was performed using a 150 Å pore size, 35-75 μ particle size silica (ANALTECH) and detection was done with a uv light. Chromatographic separations were carried out on a Chromatotron apparatus (Harrison Research) using Kieselgel 60 PF<sub>254</sub> (EM SCIENCE) as the stationary phase. The nmr spectra were recorded on Varian Associates EM 360A spectrometer and Bruker-IBM NR-80 MHz instruments, using tetramethylsilane as the internal standard. Mass spectra were recorded with a Ribermag R10-10C spectrometer. Ozonolyses were performed with a Welsbach T-23 ozonizer.

### 4-Allyl-5-hydroxyindole (**3**).

A solution of 15.7 g (0.091 mole) of 5-allyloxyindole [1] in 40 ml of 1,2,3,4-tetramethylbenzene was heated at 190-195° in an oil bath. The reaction was monitored by tlc (silica, ethyl acetate/hexanes, 15:85). The rearrangement was complete in 2 hours. The cooled reaction solution was chromatographed on silica, and 500 ml of hexanes was passed through the column until all of the 1,2,3,4-tetramethylbenzene was eluted. The column was then eluted with ethyl acetate/methylene chloride/petroleum ether (bp 30-75°)/hexanes (1:1:5:3). Evaporation of solvents from the eluate yielded 14.9 g (95%) of a white solid, which was recrystallized from benzene, mp 50-51°; lit [1] mp 49°.

### 4-Allyl-5-methoxyindole (**11**).

A mixture of 11.1 g (0.064 mole) of **3**, 8.1 g (0.064 mole) of dimethyl sulfate, 1 g of tetrabutylammonium hydrogen sulfate, and 20 ml of 50% sodium hydroxide solution in 80 ml of benzene was vigorously stirred at room temperature for 5 minutes, after which time tlc analysis (silica, ethyl acetate/hexanes 1:7) showed that no starting material remained. Water (100 ml) was then added and the organic layer was washed with water and saturated sodium chloride solution, dried over sodium sulfate, and volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/hexanes 1:7). Removal of volatiles from the eluate gave a yellow oil which was dried under reduced pressure to afford 10.2 g (86%) of pure product which could not be crystallized; ms: *m/e* 188 (*M*<sup>+</sup>); <sup>1</sup>H nmr (DMSO-*d*<sub>6</sub>): δ 3.7 (d, 2H, ArCH<sub>2</sub>), 3.8 (s, 3H, OCH<sub>3</sub>), 4.7-5.1 (dd, 2H, =CH<sub>2</sub>), 5.8-6.3 (m, 1H, allyl CH), 6.4-7.2 (m, 4H, ArH), 9.7 (br s, 1H, N(1) H).

### 4-Allyl-5-methoxy-2,3-dihydroindole (**5**).

Sodium cyanoborohydride (9.3 g, 0.148 mole) was added in one portion to a solution of 9.2 g (0.049 mole) of **11** in 95 ml of acetic acid at 15°, and the resulting suspension was stirred at this temperature for 90 minutes. The reaction flask was then immersed in an ice-water bath, 200 ml of water was added, and the solution was made strongly basic with sodium hydroxide pellets. The aqueous layer was separated and was extracted with four 150 ml portions of diethyl ether. The organic layer was washed with two 100 ml portions of water and one 100 ml portion of saturated

sodium chloride solution. The pooled organic solutions were dried over sodium sulfate and were evaporated under reduced pressure. The white solid residue was chromatographed on a flash column (ethyl acetate/hexanes 1:4). Evaporation of the eluate under reduced pressure afforded 8.5 g (92%) of white crystals, mp 46-47°. The hydrochloride salt was prepared for elemental analysis, mp 171-172° (ethanol/diethyl ether).

*Anal.* Calcd. for  $C_{12}H_{16}ClNO$  (including experimentally determined 0.023% water): C, 63.83; H, 7.14; N, 6.20; Cl, 15.71. Found: C, 63.63; H, 7.10; N, 6.17; Cl, 15.93.

#### 4-Allyl-1-benzoyl-5-methoxy-2,3-dihydroindole (6).

Benzoyl chloride (9 g, 0.063 mole) was added to a suspension of 8.5 g (0.045 mole) of **5** in 50 ml of 10% aqueous sodium hydroxide solution, and the suspension was vigorously shaken on a mechanical shaker until the odor of benzoyl chloride could not be detected. The yellow solid which was suspended in the reaction mixture was collected on a filter and was recrystallized from hot ethanol to afford 11.1 g (84%) of white crystals, mp 109-110°.

*Anal.* Calcd. for  $C_{19}H_{19}NO_2$  (including experimentally determined 0.10% water): C, 77.71; H, 6.52; N, 4.77. Found: C, 77.58; H, 6.47; N, 4.72.

#### 1-Benzoyl-5-methoxy-2,3-dihydroindole-4-acetaldehyde (8).

Compound **6** (2.2 g, 7.5 mmoles) in 100 ml of chloroform was treated with ozone at 10°. When no more ozone was absorbed, the solution was carefully concentrated at room temperature under reduced pressure. The resulting liquid was added slowly at 0° to a suspension of 0.9 g (13.8 mg-atom) of zinc dust in 7 ml of 75% aqueous acetic acid, and this mixture was stirred at 0° for 45 minutes. It was then filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in water, and this mixture was extracted with two 200 ml portions of chloroform. The pooled organic solutions were washed with dilute hydrochloric acid, 5% sodium hydroxide solution, and finally with saturated sodium chloride solution, and then were dried (sodium sulfate). Flash column chromatography (ethyl acetate/hexanes 1:4) gave a white solid which was recrystallized from ethyl acetate to yield 1.7 g (77%) of product, mp 116-117°.

*Anal.* Calcd. for  $C_{18}H_{17}NO_3$  (including experimentally determined 0.055% water): C, 73.16; H, 5.80; N, 4.73. Found: C, 73.10; H, 5.89; N, 4.67.

#### 1-Benzoyl-4-(2'-di-*n*-propylaminoethyl)-5-methoxy-2,3-dihydroindole (9).

A mixture of 1.7 g (5.6 mmoles) of **8**, 3.4 g (0.024 mole) of di-*n*-propylamine hydrochloride, and 30 ml of anhydrous methanol was stirred at room temperature in the presence of 10 g of 3 Å molecular sieves at pH 6-7 (pH paper). After stirring for 3 hours, 0.75 g (0.012 mole) of sodium cyanoborohydride was added and stirring was continued at room temperature overnight. The reaction solution was concentrated under reduced pressure and it was then poured into 100 ml of 5% sodium hydroxide solution and

this mixture was extracted with two 100 ml portions of diethyl ether. The pooled extracts were filtered through *Celite* and washed with saturated sodium chloride solution. Ice was added until two layers formed, and the resulting mixture was extracted with dilute hydrochloric acid. The aqueous extracts were cooled in an ice bath and they were made strongly alkaline with sodium hydroxide pellets. The resulting mixture was extracted with diethyl ether, dried over sodium sulfate, and all volatiles (including excess di-*n*-propylamine) were removed under reduced pressure. The residue was dried under reduced pressure to yield 1.45 g (66%) of well formed white crystals, mp 59-61°. An analytical sample of the oxalate salt was formed in acetone and recrystallized from ethanol/diethyl ether, mp 206-207°.

*Anal.* Calcd. for  $C_{26}H_{31}N_2O_6$  (including experimentally determined 0.079% water): C, 66.30; H, 7.28; N, 5.95. Found: C, 66.50; H, 7.37; N, 5.92.

#### 4-(2'-Di-*n*-Propylaminoethyl)-5-methoxyindole (10).

A solution of 1.53 g (0.004 mole) of **9** in 30 ml of anhydrous diethyl ether was added to a suspension of 2.92 g (0.026 mole) of potassium *t*-butoxide in 30 ml of anhydrous diethyl ether. Water (0.144 g, 0.008 mole) was added and the resulting suspension was stirred at room temperature for 24 hours, during which time a slow stream of air was passed through the mixture. The reaction mixture was cooled in an ice bath and 100 ml of water was added. The organic layer was separated, washed with water and saturated sodium chloride solution, and volatiles were removed under reduced pressure. The residue was separated on a Chromatotron apparatus using a 4 mm silica rotor and eluting with ethyl acetate/petroleum ether (bp 30-75°), 3:5. Evaporation of the eluate and drying of the residue under reduced pressure yielded 0.455 g (41%) of the free base. The bifumarate salt was formed in diethyl ether, mp 173-175°; ms: (free base) 275 ( $M^+$ );  $^1H$  nmr (free base) (deuteriochloroform):  $\delta$  0.8-1.6 (m, 10H, aliphatic *H*), 2.4-2.9 (m, 8H, aliphatic *H*), 3.8 (s, 3H,  $OCH_3$ ), 6.4-7.1 (m, 4H, Ar*H*), 8.4 (br s, 1H, N(*H*)).

*Anal.* Calcd. for  $C_{21}H_{30}N_2O_5$  (including experimentally determined 0.32% water): C, 64.59; H, 7.74; N, 7.17. Found: C, 64.69; H, 7.85; N, 7.06.

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