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A Convenient and Efficient Process to 5-(2-Di-n-Propylaminoethyl)-6-hydroxyindole

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A CONVENIENT AND EFFICIENT PROCESS TO 5-(2-Di-n-PROPYLAMINOETHYL)-6-HYDROXYINDOLE

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Abstract. An intermolecular trapping of the Pummerer intermediate, generated from **9** with TFAA, by **4** at position 5 under mild Lewis acid conditions gave **5**. Sequential treatment of **5** with Ra-Ni, $LiAlH_4$ and again Ra-Ni, afforded **8** in high overall yield.

The continued interest in the indole and indolone derivatives oxygenated at the benzene ring, as well as in the related ergot alkaloids[1] prompted us to attempt the synthesis of 5-(2-di-n-propylaminoethyl)-6-hydroxyindole.

This interest has been because of their novel biological interactions, which this class of compounds exhibit, specifically with the dopamine and/or serotonine receptors,

Thus, as a consequence of these biological properties, they have been the subject of active synthetic investigation, aimed to develop

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derivatives which would possess more potent and selective pharmacological activities.

In our previous paper[1], we have described a novel methodology for introducing an aminoethyl unit directly into the aromatic ring of an indoline derivative, namely the 1-benzenesulfonyl-7-methoxy-indoline. This methodology involves the trapping of a Pummerer intermediate, generated in situ, by a π-electron system in the presence of a Lewis acid under mild reaction conditions[2,3] in an alkylation-homoacylation mode.

Pummerer intermediates have been trapped effectively by aromatic rings and double bonds in the presence of Lewis acid (i.e. $SnCl_4$, $BF_3.OEt_2$, etc) both inter- and intramolecularly[3].

We now wish to report the first synthesis of **8**, in high overall yield by the analogous strategy.

The required 1-benzenesulfonyl-6-benzenesulfonyloxy-indoline **4** was prepared in two steps from 4-benzenesulfonyloxy-2-nitrotoluene **2**, which, in turn, was produced quantitatively from the commercially available 4-methyl-3-nitrophenol **1**. That is, compound **2** was first subjected to Batcho-Leimgruber technology. Reduction of the intermediate enamine to induce cyclization with catalytic hydrogenation under various reaction conditions gave, in our hands, mixture of products. After some experimentation was found that $TiCl_3$ was the reagent of choice for the formation of the indole ring[4].

Treatment of the reagent **9**[1] with $(CF_3CO)_2O$ at 0°C generated the desired Pummerer intermediate which was in turn trapped by the prepared indoline **4** at position 5 in the presence of $SnCl_4$ to produce compound **5** in 92% yield as a syrup. Compound **5** was subsequently desulfurized to **6** with Ra-Ni in 98% yield.

Reduction of the tertiary amide **6** with $LiAlH_4$ produced cheerful results, that is, the concomitant removal of both $PhSO_2$- groups yielding the desired hydroxyindoline **7** in one step. But, to our disappointment, compound **7** was found to undergo aerial oxidation with considerable ease producing decomposition products, hence purification of this intermediate was not attempted. Attempts though to oxidize **7**, as such, to the corresponding indole **8** with MnO_2/CH_2Cl_2 or salcomine/O_2 yielded only complex mixtures. Thus,

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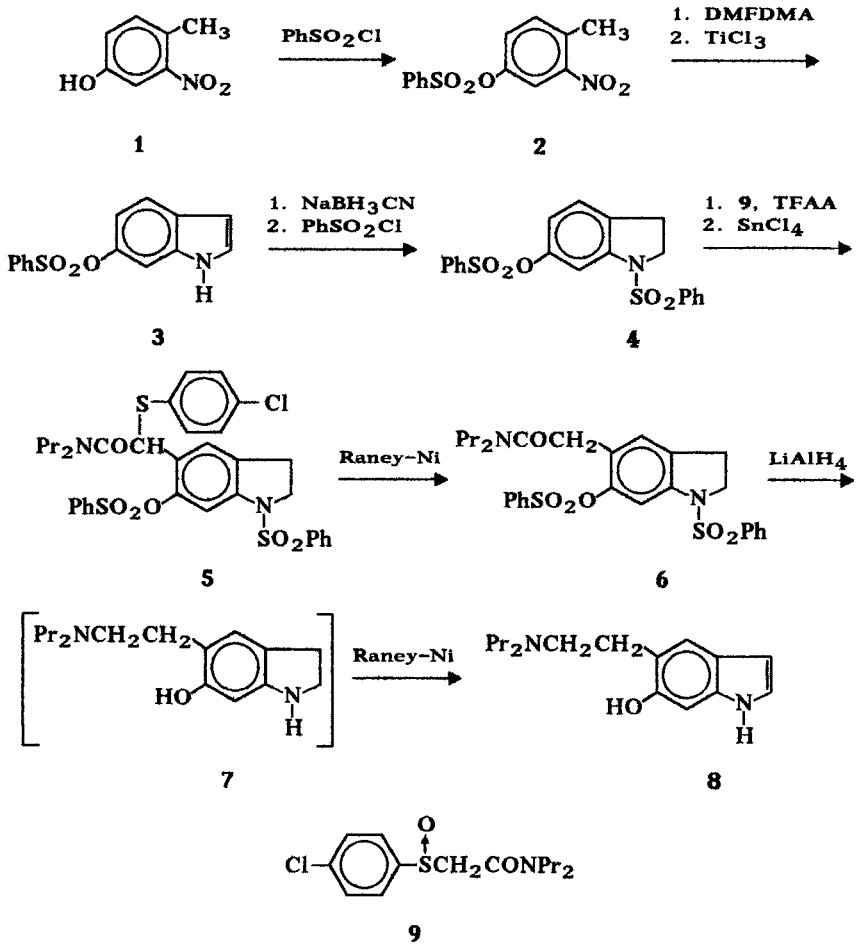

in order to circumvent these frustrations, the compound **7** was protected under argon atmosphere in the form of acetic acid salt and then, as such, the indoline ring was dehydrogenated[5] to the corresponding indole with Ra-Ni, to produce the acetic acid salt of the target compound **8** in 65% yield from **6**.

^{1}H-NMR Analysis. The position of the 2-di-n-propylaminoethyl group in the product **8** could be clearly delineated on the basis of

^{1}H-NMR data. Thus, the signal of H-5 in compound **3** appears as a doublet of doublets at 6.61 ppm with J=8.6 Hz (ortho coupling to H-4) and J=2.1 Hz (meta coupling to H-7). The signal of H-4 appears at 7.44 ppm as a doublet with J=8.5 Hz (ortho coupling to H-5) and the signal of H-7 appears at 7.15 ppm as a doublet with J=2 Hz (meta coupling to H-5). These assignments are also comparable with the signals of the parent compound, 6-hydroxyindole, of **8** reported in the literature[6].

Substitution caused the disappearance of the signal due to H-5 and the colapse of the doublets due to H-4 and H-7 to singlets, whereas the H-4 experiences an upfield shift of 0.3 ppm.

Similarly, further confirmation about the site of substitution is deduced from direct comparison of the NMR data of compounds **4** and **6**. In compound **4** the signal of H-5 appears as a doublet of doublets and the signals of both H-4 and H-7 appear as doublets (see experimental section). In the product **6** the signal of H-5 has disappeared, whereas the H-4 lost its ortho coupling while the H-7 lost its meta coupling. No coupling was observed between them, and both appeared as singlets.

EXPERIMENTAL

4-Benzenesulfonyloxy-2-nitrotoluene 2. To a solution of 4-methyl-3-nitrophenol **1** (15.31 g, 100 mmol) in 250 ml acetone K_2CO_3 was added (27.6 g, 200 mmol) and the mixture was stirred vigorously for 15 min. Then $PhSO_2Cl$ (19.4 g, 110 mmol) dissolved in acetone was added dropwise over a period of 2 h. Most of the solvent was removed and the residue was shaken with CH_2Cl_2 and water. The organic phase was dried over Na_2SO_4 and filtered through silica. Hexane was added to the resulting solution and the product crystallized to afford 29.32 g (100%) of large yellow crystals, m.p. 81-82°C.

CHN: *Calcd:* 53.23, 3.78, 4.78; *Found:* 53.11, 3.88, 4.60.

^{1}H-NMR ($CDCl_3$, BRU KER 300 MHz): 2.56 (s, 3H, CH_3-), 7.20 (dd, 8.4/2.5 Hz, C5-H), 7.30 (d, 8.4 Hz, C6-H), 7.54 (d, 2.2 Hz, C3-H), 7.56-7.86 (m, 5H, $PhSO_2$-).

6-Benzenesulfonyloxy-indole 3. The nitrotoluene **2** (2.93 g, 10 mmol) was dissolved in 20 ml of dry DMF under argon. Dimethylformamide dimethyl acetal (4 ml, 30 mmol) was added through a syringe and the reaction mixture was stirred at 120°C for 5 h. Then it was cooled, diluted with water and extracted with CH_2Cl_2 to give a blood-red solution which was concentrated and redissolved in 50 ml of CH_3OH.

The methanolic solution was transfered to a separatory funnel containing $TiCl_3$ (65ml of commercial 15% solution in 10% HCl, 65 mmol) and ammonium acetate (130 ml of 4M solution). The funnel was shaken well for 10 min, then dilute HCl was added and the product extracted quickly with CH_2Cl_2. The resulting bright yellow solution was dried over Na_2SO_4, filtered through silica and purified on a short silica gel column with hexane-toluene 3:7. The indole was obtained as a yellow syrup which solidified on freezing. Recrystallization from ether afforded 2.13 g (78%) of colorless crystals, m.p. 69-70°C.

^{1}H-NMR ($CDCl_3$): 6.50 (t, 2.1 Hz, C3-H), 6.61 (dd, 8.6/2.1 Hz, C5-H), 7.15 (d, 1.9 Hz, C7-H), 7.21 (t, 2.5 Hz, C2-H), 7.44 (d, 8.6 Hz, C4-H), 7.48-7.83 (m, 5H, $PhSO_2$-), 8.32 (bs, N-H).

1-Benzenesulfonyl-6-benzenesulfonyloxyindoline 4. The indole 3 (2.13 g, 7.8 mmol) was dissolved in a flask containing 15 ml acetic acid, immersed in a water bath. Sodium cyanoborohydride (1.0 g, 16.0 mmol) was added portionwise and the solution was stirred at room temperature for 4 h. One ml of water was added to destroy the excess hydride and most of the acetic acid removed under vacuum. The residue was diluted with water, neutralized with Na_2CO_3, extracted with CH_2Cl_2, dried over Na_2SO_4 and filtered through silica to give a colorless solution.

To the above solution triethylamine (2.4 g, 24 mmol) was added, followed by $PhSO_2Cl$ (1.4 g, 8 mmol). The mixture was stirred for 1 h, then washed with dilute HCl and $NaHCO_3$ solutions, dried over Na_2SO_4 and filtered through silica gel. The product crystallized immediately from CH_2Cl_2-hexane to yield 1.91 g (7.0 mmol, 90%) of white crystals, m.p. 128-9°C.

CHN: *Calcd* 57.82, 4.12, 3.37; *Found* 57.71, 4.21, 3.36.

^{1}H-NMR ($CDCl_3$): 2,87 (t, 2H, C3-H_2), 3.91 (t, 2H, C2-H_2),

6.62 (dd, 8.1/2.2 Hz, C5-H), 6.96 (d, 8.2 Hz, C4-H), 7.32 (d, 2.2 Hz, C7-H), 7.43-7.90 (m, 10H, $PhSO_2$-).

N,N-Di-n-propyl-(p-chlorophenylthio)-(1-benzenesulfonyl-6-benzenesulfonyloxy-5-indolinyl)-acetamide 5. N,N-Di-n-propyl-p-chlorobenzenesulfinyl acetamide **9** (1.65 g, 5.5 mmol) was dissolved in 25 ml of dry CH_2Cl_2 under argon and the solution was cooled in an ice-water bath. TFAA (0.78 ml, 5.5 mmol) was added and the mixture was stirred for 20 min. Then the indoline **4** was added (2.08 g, 5 mmol) followed by dropwise addition of $SnCl_4$ (0.59 ml, 5 mmol). The reaction was left to complete overnight at room temperature. The deep blue reaction mixture was poured into water and extracted with CH_2Cl_2, dried over Na_2SO_4 and filtered through silica gel. The solvent was removed under vacuum to leave a crude orange syrup. Chromatography (SiO_2-toluene) gave the pure product as a pale yellow syrup which resisted crystallization (3.2 g, 4.6 mmol, 92%). After standing for several months in the freezer a sample of the product solidified, m.p. 117-120°C.

^{1}H-NMR ($CDCl_3$): 0.82 (m, 6H, $-N(CH_2CH_2CH_3)_2$), 1.49 (m, 4H, $-N(CH_2CH_2CH_3)_2$), 2.88 (t, 2H, C3-H_2), 3.25 (m, 4H, $-N(CH_2CH_2CH_3)_2$), 3.89 (t, 2H, C2-H_2), 5.51 (s, 1H, C5α-H), 7.1-8.0 (m, 16H, Ar).

N,N-Di-n-propyl-(1-benzenesulfonyl-6-benzenesulfonyloxy-5-indolinyl)-acetamide 6. To a solution of **5** (4.20 g, 6 mmol) in 100 ml ethanol, an adequate quantity of Raney-Ni (~2 teaspoonfuls) was added under argon. The reaction was monitored by TLC until completion (1-2 h). The crude product was filtered through celite. The filter was washed well with ethanol and exhaustively with CH_2Cl_2. The ethanolic washings were concentrated and the combined solution was washed with water to give a colorless solution which was dried (Na_2SO_4), filtered (silica) and concentrated to a pure, colorless syrup which solidified on standing (3.30 g, 100%). This was recrystallized from CH_2Cl_2-hexane to white crystals, m.p. 119-119.5°C.

CHN: *Calcd* 60.41, 5.79, 5.03; *Found* 60.50, 5.83, 5.14.

^{1}H-NMR ($CDCl_3$): 0.83-0.89 (2t, 6H, $-N(CH_2CH_2CH_3)_2$), 1.53

(m, 4H, $-N(CH_2CH_2CH_3)_2$), 2.87 (t, 2H, C3-H_2), 3.19 (m, 4H, $-N(CH_2CH_2CH_3)_2$), 3.47 (s, 2H, C5α-H_2), 3.89 (t, 2H, C2-H_2), 7.07 (s, 1H, C4-H), 7.22 (s, 1H, C7-H), 7.40-7.95 (m, 10H, $PhSO_2$-).

5-(2-Di-n-propylaminoethyl)-6-hydroxyindole 8. Compound **6** (1.11 g, 2 mmol) was added to a suspension of $LiAlH_4$ (2.28 g, 60 mmol) in dry THF (20 ml), under argon. The mixture was stirred for 24 h at 50°. The excess hydride was destroyed with saturated aqueous NaCl. The heavy granular precipitate was washed three times with ether. The washings were decanted under a stream of argon into a flask containing 1 ml of acetic acid.

The ether was evaporated and the crude indoline acetate was taken up in 50 ml of benzene. Raney-Ni (~2 spatulas) was added under argon and the mixture was refluxed under vigorous stirring for 3 h. The colorless solution was decanted and the catalyst washed three times with boiling benzene. The washings were dried with Na_2SO_4 filtered and concentrated at the top of a short silica column. The product was then eluted with ethyl acetate. The indole acetate crystallized immediately from AcOEt-hexane to afford 0.45 g as a white powder (65% from **6**), m.p. 141-142°C).

CHN: *Calcd:* 69.74, 8.19, 8.13; *Found:* 69.90, 8.23, 8.21.

^{1}H-NMR ($CDCl_3$): 0.89 (t, 6H, $-N(CH_2CH_2CH_3)_2$), 1.56 (m, 4H, $-N(CH_2CH_2CH_3)_2$), 2.08 (s, 3H, CH_3COO^-), 2.58-2.68 (m, 4H, $-N(CH_2CH_2CH_3)_2$), 2.82-2.93 (m, 4H, $-CH_2CH_2N=$), 6.37 (bs, C3-H), 6.89 (s, C7-H), 7.02 (t, 3.1 Hz, C2-H), 7.26 (s, C4-H), 7.96 (bs, N-H).

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