Synthesis of 4,9-Dimethoxy-1*H*-benz[*f*]indole

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A three-step synthesis of 4,9-dimethoxy-1*H*-benz[*f*]indole (**4**) starting from 1,4-dimethoxy-2-aminonaphthalene (**1**) is described. Compound **1** was condensed with epichlorohydrin in acidic methanolic solution and the crude reaction product, purified by column chromatography, was cyclized to compound **3** by reflux heating in bromobenzene solution in the presence of excess diethylaniline. Appropriate oxidization with periodate in alkaline solution produced the title compound **4**.

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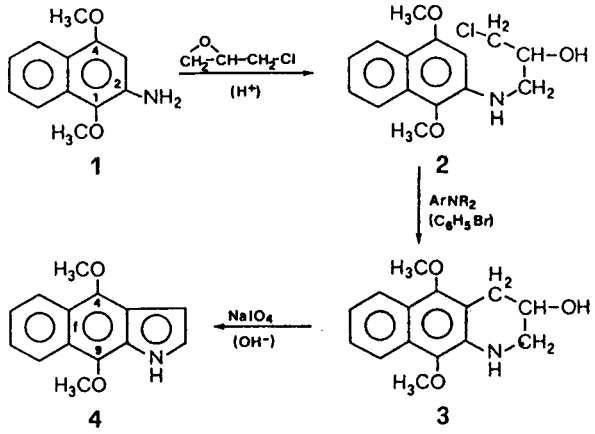
Extending our researches on the synthesis of tricyclic ring systems from substituted naphthalenes, we decided to attempt the synthesis of several new benzindoles with the aim of preparing new potentially chemotherapeutic compounds.

One of our recent reports [1] described the advantageous synthesis of 5,6,7,8-tetrahydro-4,9-dimethoxy-1*H*-benz[*f*]indole, which was then oxidized to a completely planar aromatic compound, although with considerable difficulty and a low yield [2]. For this reason, we were interested in synthesizing alternatively a similar compound, directly fully aromatic.

Several previous attempts at preparing benz[*f*]indole derivatives *via* an *o*-nitration of 1,4-disubstituted-2-(β-nitrovinyl)naphthalene intermediates proved unsuccessful; the difficulties in obtaining the required nitro compounds may have been due to the involvement of the β-position of the activated ring in the naphthalene system, also perhaps accompanied by steric hindrance. The method of synthesis employed followed one of the classical routes devised by Gould and others [3] and subsequently reproposed by Pennington and co-workers [4-6].

Differently from McCaustland *et al.* [7], starting compound **1** was prepared by hydrogenation of 1,4-dimethoxy-2-nitronaphthalene [8], using activated Raney nickel as catalyst. The resulting 1,4-dimethoxy-2-aminonaphthalene (**1**), in methanolic solution, was condensed with epichlorohydrin by shaking the mixture at room temperature for several days in the presence of small amounts of hydrochloric acid. The crude reaction product was purified by silica gel chromatography, yielding the *N*-(γ-chloro-β-hydroxypropyl)-1,4-dimethoxy-2-aminonaphthalene (**2**) which, after addition of diethylaniline excess (1:6), was cyclized in bromobenzene solution by reflux heating for several days. The 1,2,3,4-tetrahydro-3-hydroxy-5,10-dimethoxybenz[*g*]quinoline (**3**), characterized by elemental analysis and conversion to its corresponding picrate, was then oxidized with periodate in alkaline aqueous solution, yielding the expected 4,9-dimethoxy-1*H*-benz[*f*]indole (**4**). This conversion of the tetrahydroquinolinols to indoles had been described in reports enumerated above [5,6]. The synthetic route, although undoubtedly simpler than that previously reported [1], appears laborious because of the copious secondary products from which it must be carefully removed before proceeding to the following synthetic stages.

Further studies directed toward the synthesis of various other hydroxy congeners are currently in progress.



EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli SMP-20 apparatus in open capillaries, and are uncorrected. Proton nmr spectra were recorded in hexadeuterioacetone on a Varian FT-80A instrument; chemical shifts are reported in δ units, downfield from tetramethylsilane. In the case of multiplets, chemical shifts quoted were measured from the approximate center. Integrals correspond satisfactorily to the chemical formula. Elemental analyses were performed by the Microanalytical Laboratory of the Department of Pharmaceutical Chemistry of the University of Padua, using a Perkin-Elmer Elemental Analyzer model 240B. Column chromatography was carried out using Merck silica gel 60 (70-230 mesh ASTM); tlc was performed on silica gel F_{254} plates.

1,4-Dimethoxy-2-nitronaphthalene.

This compound has already been described by Inoue *et al.* [8], mp 97-98°; ^{1}H nmr: δ 4.08 (3H, s, OCH_3 at C-4), 4.11 (3H s, OCH_3 at C-1), 7.30 (1H, s, HC-3), 7.77 (2H, m, HC-6, HC-7), 8.31 (2H, m, HC-5, HC-8).

The starting compound **1** was prepared by hydrogenation (6 hours at 80° and 60 bars) of the corresponding 2-nitro derivative in the presence of Raney-nickel, mp 99-100°; ^{1}H-nmr: δ 3.76 (3H, s, OCH_3 at C-1), 3.90 (3H, s, OCH_3 at C-4), 4.72 (2H, bm, NH_2), 6.58 (1H, s, HC-3), 7.26 (2H, m, HC-6, HC-7), 7.88 (2H, m, HC-5, HC-8).

N-(γ-Chloro-β-hydroxypropyl)-1,4-dimethoxy-2-aminonaphthalene (**2**).

1,4-Dimethoxy-2-naphthylamine (**1**) (6.5 g) was dissolved in 32.5 ml of methanol (1*M*) and epichlorohydrin (2.78 ml in 32.5 ml of methanol, *i.e*, 1*M*) was added slowly under magnetic stirring. To the mixture was then added 0.7 ml of concentrated hydrochloric acid and stirring was continued for seven days at room temperature, during which tlc analysis showed that the starting amine had been satisfactorily condensed. The reaction mixture was poured into water, the acid neutralized with sodium bicarbonate and the product extracted exhaustively with benzene (5 × 800 ml). After drying over sodium sulfate, the benzene was removed in a rotary evaporator. The crude residual oil (7.52 g), dissolved in a small amount of benzene, was placed on a silica gel column and eluted with benzene and a benzene-ether mixture. The desired title compound, after chromatographic purification, appeared as a thick oil (3.9 g) and was used directly in the following synthetic stage. An analytical sample was purified by distillation *in vacuo* at 140° and 0.2 × 10^{-1} torr; ^{1}H nmr: δ 3.35-3.61 (4H, 2m, 2 × CH_2), 3.71 (1H, dd, CH), 3.79 (3H, s, OCH_3 at C-1), 3.98 (3H, s, OCH_3 at C-4), 4.06 (1H, bs, NH), 6.74 (1H, s, HC-3), 7.29 (2H, m, HC-6, HC-7), 7.91 (2H, m, HC-5, HC-8).

Anal. Calcd. for $C_{15}H_{18}ClO_3N$ (mw 295.8): C, 60.92; H, 6.13; N, 4.74; Cl, 11.99. Found: C, 61.28; H, 6.18; N, 4.83; Cl, 12.06.

1,2,3,4-Tetrahydro-3-hydroxy-5,10-dimethoxybenz[*g*]quinoline (**3**).

To a solution of 3.09 g of *N*-(γ-chloro-β-hydroxypropyl)-1,4-dimethoxy-2-aminonaphthalene (**2**) in 500 ml of bromobenzene (0.021 *M*), 6.1 ml of diethylaniline was added, the molar ratio of amine to **2** thus being 6:1. The mixture was heated at reflux for five days. The product was extracted repeatedly with 5% hydrochloric acid (4 × 200 ml) and the extract washed repeatedly with benzene (3 × 250 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* at 40° to give 1.49 g (52%) of crude gummy residue, which was purified by distillation at 125° and 0.3 × 10^{-1} torr, yielding a pale yellow oil.

Anal. Calcd. for $C_{15}H_{17}O_3N$ (mw 259.3): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.64; H, 6.31; N, 5.76.

A small amount of sublimed oil was dissolved in benzene and treated with a benzene solution of picric acid. The picrate was recrystallized repeatedly from toluene, brown needles, mp 206-207°.

Anal. Calcd. for $C_{21}H_{20}O_{10}N_4$ (mw 488.4): C, 51.64; H, 4.13; N, 11.47. Found: C, 51.32; H, 3.97; N, 11.55.

4,9-Dimethoxy-1*H*-benz[*f*]indole (**4**).

A solution of 1,2,3,4-tetrahydro-3-hydroxy-5,10-dimethoxybenz[*g*]quinoline (**3**) (1.15 g, 4.4 mmoles) in 50 ml of ethanol was mixed with an aqueous solution of sodium periodate (4.24 g, 10 mmoles in 50 ml of water) in a two-necked flask equipped with condenser and dropping funnel, through which 100 ml of 8% sodium hydroxide was added slowly. The reaction mixture was refluxed for forty-eight hours, cooled and extracted with ether (3 × 300 ml). The combined extracts were dried over sodium sulfate and concentrated to give 0.49 g (49%) of a resinous product which was distilled at 90° and 0.2 × 10^{-1} torr; ^{1}H nmr: δ 4.07-4.11 (6H, 2s, 2 × OCH_3), 6.65 (1H, d, J = 2.5 Hz, HC-3), 7.25 (1H, d, J = 2.5 Hz, HC-2), 7.78 (2H, m, HC-6, HC-7), 8.13 (2H, m, HC-5, HC-8).

Anal. Calcd. for $C_{14}H_{13}O_2N$ (mw 227.3): C, 73.99; H, 5.77; N, 6.16. Found: C, 73.63; H, 5.68; N, 6.37.

This compound **4**, demethylated by reflux heating with aluminium trichloride in anhydrous benzene solution, furnished the corresponding 4,9-dihydroxy-1*H*-benz[*f*]indole, already described by us [2].

REFERENCES AND NOTES

[1] G. Malesani, M. G. Ferlin and S. Masiero, *J. Heterocyclic Chem.*, **19**, 633 (1982).

[2] G. Malesani, M. G. Ferlin and S. Masiero, *J. Heterocyclic Chem.*, **20**, 459 (1983).

[3] R. G. Gould and W. A. Jacobs, *J. Am. Chem. Soc.*, **61**, 2890 (1939).

[4] F. C. Pennington, M. Jellinek and R. Thurn, *J. Org. Chem.*, **24**, 565 (1959).

[5] F. C. Pennington, L. J. Martin, R. E. Reid and T. W. Lapp, *J. Org. Chem.*, **24**, 2030 (1959).

[6] F. C. Pennington, G. L. Tritle, S. D. Boyd, W. Bowersox and O. Aniline, *J. Org. Chem.*, **30**, 2801 (1965).

[7] D. J. McCaustland, P-L. Chien and C. C. Cheng, *J. Med. Chem.*, **16**, 1311 (1973).

[8] A. Inoue, K. Nakano, N. Kuroki and K. Konishi, *J. Soc. Org. Synth. Chem., Tokyo*, **14**, 513 (1956).