Synthesis and Characterization of 1*H*-Benz[*f*]indole-4,9-dione and the Related Dihydroxy Derivative

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Dehydrogenation and contemporaneous demethylation of the parent 4,9-dimethoxy-5,6,7,8-tetrahydro-1*H*-benz[*f*]indole (**2**) yielded the expected aromatization products **4** and **5** (1*H*-benz[*f*]indole-4,9-dione and 4,9-dihydroxy-1*H*-benz[*f*]indole, respectively).

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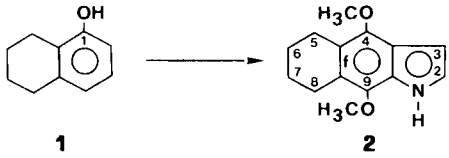
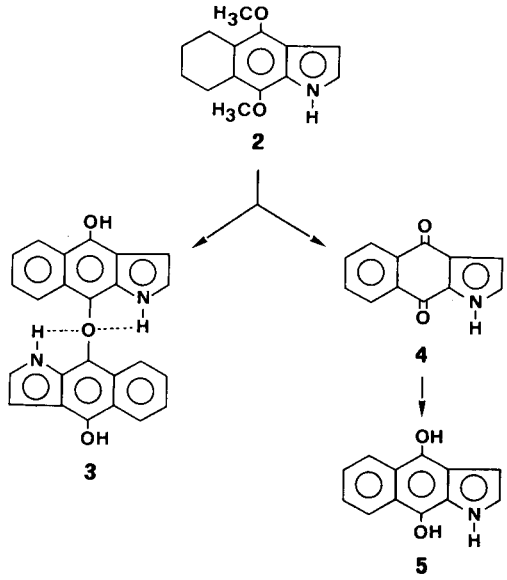
Continuing our investigations on the synthesis and antimicrobial properties of some heterocyclic quinones and corresponding dihydroxy derivatives appertaining to various fused systems (1-7), we have recently reported the chemical preparation of 4,9-dimethoxy-5,6,7,8-tetrahydro-1*H*-benz[*f*]indole (**2**) and related demethylation products (8). The entire synthesis of **2** from simple available 5,6,7,8-tetrahydro-1-naphthol (**1**) required eight advantageous steps.



1 **2**

In this paper we describe the aromatization of this compound **2** achieved after several unsuccessful attempts carried out following the classical methods reported in the literature. In fact, neither a few inorganic oxidizing agents such as the elemental selenium (9-10) or manganese dioxide (11), nor the even more frequently used organic quinonoid compounds (12-13), *i.e.*, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) and chloroanil (2,3,5,6-tetrachloro-1,4-benzoquinone), proved capable of dehydrogenating our synthetic tetrahydro compound **2**, even though the operative procedures were varied.

Otherwise, 4,9-dimethoxy-5,6,7,8-tetrahydro-1*H*-benz[*f*]indole, heated quite a long time at approximately 250° with palladium on activated carbon in benzene solution, furnished a crude residue from which it was possible to separate two different new compounds by fractional sublimation in vacuum. The solid crystalline sublimed first, after recrystallization from benzene, yielded an unexpected elemental analysis poor in oxygen. The constancy of the microanalytical data suggested that this sufficiently stable compound may be a symmetrical ether; this reasonable hypothesis was confirmed by mass and proton magnetic resonance spectrometries, whose spectral measurements were fully consistent with the proposed structure. The mass spectrum of this compound **3** shows no molecular ion. However, a strongly diagnostic peak is present at m/z 363, due to an easy OH· radical loss. Other intense peaks are well related to the proposed structure, as detailed in the Experimental. Therefore, during the aromatization process of benzindole derivative **2**, not only the expected dehydrogenation, but also a whole demethylation, followed by a partial spontaneous dehydration to diaryl ether, takes place. The assigned structure of compound **3** is presumably stabilized and made more compact by the possibility of a double hydrogen bond between the imino groups of the two benzindole units and the ethereal oxygen. When a solution of this compound **3** in acetone is allowed to stand for several days at room temperature, the corresponding dihydroxy monomer **5** is produced; its nmr spectrum in effect agrees with that of a pure authentic sample prepared as described below.



2 **3** **4** **5**

In continuing sublimation in vacuum, a crystalline yellow compound was separated, which turned out to be 1*H*-benz[*f*]indole-4,9-dione (**4**). An easy reduction of this quinone **4** with sodium hydrosulfite in ether produced the

corresponding dihydroxy derivative **5**. Both compounds **4** and **5** were characterized by nmr spectroscopy and elemental analysis.

EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli SPM-20 apparatus in open capillaries and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 457 spectrometer as a potassium bromide pressed discs calibrated against a polystyrene film; absorptions are given in cm^{-1}. Proton nmr spectra were measured in the indicated solvent on a Varian FT-80A instrument; chemical shifts are reported in δ units downfield from tetramethylsilane; the abbreviations s, d, t, m, br, refer respectively to singlet, doublet, triplet, multiplet and broad; in the case of multiplets, chemical shifts quoted were measured from the approximate center. Mass spectrum was run on a YG ZAB 2F instrument, operating at 70 eV (200 μA); the sample was introduced in DEI conditions (14). Elemental analyses were performed by the Microanalytical Laboratory of the Institute of Pharmaceutical Chemistry of the University of Padua.

Aromatization of 4,9-Dimethoxy-5,6,7,8-tetrahydro-1*H*-benz[*f*]indole.

The title compound **2** (0.84 g) was dissolved in 50 ml of dry benzene in a Carius sealed tube and heated with palladium on activated charcoal 10% as catalyst, so that temperature rose slowly over about three hours to 240-250°, this last temperature then being maintained for another eighteen hours. After cooling overnight, the mixture was filtered by suction for removal of the catalyst and the yellowish-green solution concentrated to dryness in a rotary evaporator; 0.63 g of a viscous crude residue was submitted to fractional sublimation in vacuum at 10^{-2} torr.

a) Bis(4-hydroxy-1*H*-benz[*f*]indolyl) Ether (**3**).

After discarding a secondary oily liquid passed at 70-80°, the crystalline greenish product sublimated at 100-110° was collected and crystallized from boiling benzene. This compound, which contains no methoxy groups, decomposed with melting above 275°; ms: m/z 363 $[M - OH]^+$, 271, 232, 210, 198, 182, 168, 154, 141, 127, 115, 100, 88, 77, 63, 53, 39, 28; nmr (deuterioacetone): δ 4.23 (d, OH), 6.74 (d, HC_3), 7.36 (d, HC_2), 7.53 (d, OH), 7.80 (m, HC_6 and HC_7), 8.13 (m, HC_5 and HC_8).

Anal. Calcd. for $C_{24}H_{16}N_2O_3$ (mw 380.4): C, 75.78; H,4.24; N, 7.37. Found: C, 75.95; H, 4.28; N, 7.39.

A solution of this ether **3** in acetone after several days at room temperature spontaneously afforded 4,9-dihydroxy-1*H*-benz[*f*]indole (**5**).

b) 1*H*-Benz[*f*]indole-4,9-dione (**4**).

In continuing sublimation of the above-described crude aromatization residue at 130°, a yellow ochre sublimate was separated which, after removal, was crystallized from boiling toluene, yielding a crystalline compound, mp 282-283°; ir (potassium bromide): 3260 (NH), 1658-1643 (C=O) cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 6.71 (1H, d, HC_3), 7.37 (1H, d, HC_2), 7.81 (2H, m, HC_6 and HC_7), 8.06 (2H, m, HC_5 and HC_8), 12.85 (1H, s br, NH).

Anal. Calcd. for $C_{12}H_7NO_2$: C, 73.09; H, 3.58; N, 7.10. Found: C, 73.19; H, 3.75; N, 7.02.

4,9-Dihydroxy-1*H*-benz[*f*]indole (**5**).

The title compound was prepared by shaking at room temperature an ethereal solution of quinone **4** (200 mg in 10 ml) with an excess of aqueous solution of sodium hydrosulfite for eight hours. After standing, the greenish organic phase was separated, dried over anhydrous sodium sulfate in presence of sodium hydrosulfite and stripped of the solvent in a nitrogen stream to give 127 mg of a crystalline product, which was recrystallized from acetone, green crystals, mp 248-249° dec; nmr (deuterioacetone): δ 4.20 (1H, s, OH, disappeared on addition of deuterium oxide), 6.74 (1H, d, HC_3), 7.11-7.23 (1H, br s, OH, increased on addition of deuterium oxide), 7.37 (1H, d, HC_2), 7.80 (2H, m, HC_6 and HC_7), 8.13 (2H, m, HC_5 and HC_8).

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.27; H, 4.59; N, 7.12.

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