Oxidation Reactions of Indapamide. A Novel Route to the Indole Derivative, *N*-(3-Sulfamyl-4-chlorobenzamido)-2-methylindole

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Indapamide (**1**) is readily oxidized with mild oxidizing agents to the indole derivative **2**. Dehydrogenation of indapamide is a convenient one step synthesis of a complex indole compound.

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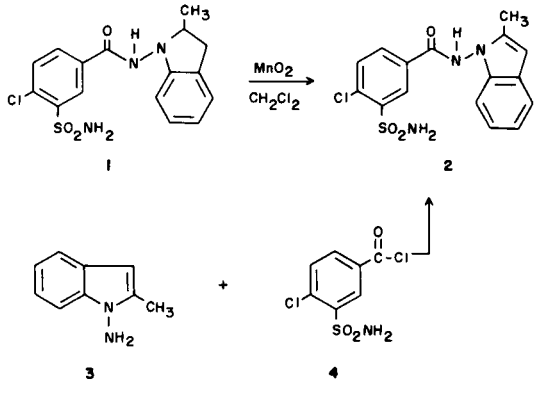
Indapamide **1** is a 2-methylindoline derivative which posesses diuretic and antihypertensive properties (1). The thermal and photolytic decomposition of indapamide was reported to yield a number of products which are formed primarily from cleavage of the [−N−NH−CO−] linkage (2).

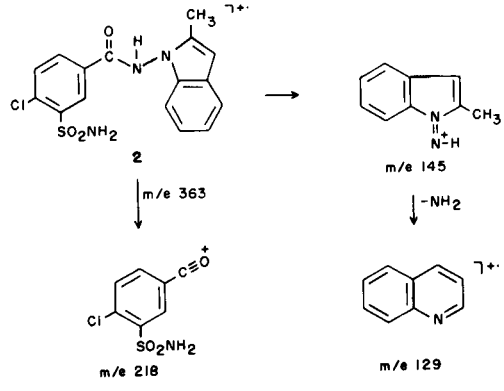
The facile dehydrogenation of indolines to indoles with mild oxidizing agents (3) prompted our investigation of the chemical reactivity of indapamide with manganese dioxide and hydrogen peroxide. Subsequently, a high yield synthesis of the indole derivative **2** by the dehydrogenation of indapamide with manganese dioxide was developed. This process is a simple one step synthesis of a indole compound which is difficult to produce by alternative synthetic procedures.

SCHEME I



Treatment of a solution of indapamide in methylene chloride with an excess of activated manganese dioxide afforded the indole derivative **2** in an overall yield of 45%. This conversion is nearly quantitative as determined by tlc analysis. Since the indole product **2** is practically insoluble in dichloromethane, an extraction procedure with acetone is required to recover the desired product from the inorganic manganese oxides. The pmr spectrum of **2** showed an ABX pattern for the aromatic protons on the benzamide ring and characteristic singlets for the vinyl (δ 6.37) and methyl (δ 2.40) protons. The mass spectrum showed a molecular ion (m/e 363, 30%) and an M +2 peak (m/e 365, 12%) due to the natural abundance of the stable isotopes ^{37}Cl and ^{34}S. Additional peaks at m/e 218 (54%), 145 (100%) and 129 (75%) are attributed to the ions shown in Figure I.

FIGURE I



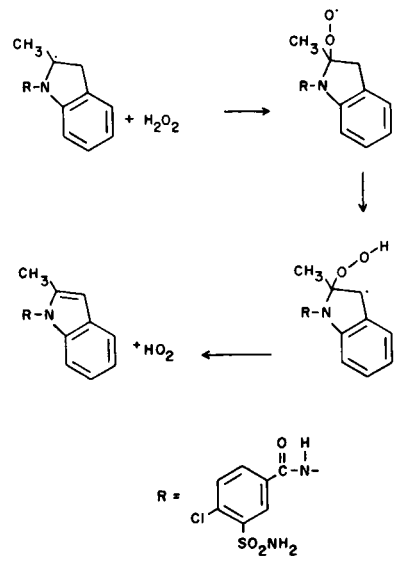
Additional evidence in support of the assigned structure was obtained by synthesis of the indole compound from 1-amino-2-methylindole (**3**) and the acid chloride **4** (4). This compound showed identical spectral and chromatographic properties with **2**.

As a further study on the reactivity of indapamide, the dehydrogenation of this substance was investigated in the presence of the radical initiator, hydrogen peroxide. Thus, by refluxing a sample of indapamide (10 mg, 0.28 mmole) in 100 ml of 0.3% hydrogen peroxide for 1 hour, indole **2** was found to be the major product by tlc. Indapamide was not detected in the reaction mixture.

This reaction is consistent with a free radical oxidation pathway as shown in Figure 2. A hydroperoxide radical is a plausible intermediate in the mechaism of formation of indole **2** which may by produced by isomerization of a peroxy radical (5). In addition, a similar pathway was proposed for auto oxidation of cyclic peptides (6).

In view of the chemical reactivity of indapamide with oxidizing agents manganese dioxide and hydrogen peroxide, analogous metabolic pathways of biological significance can lead to hydroxylated and indole related substances. Reaction of indapamide with manganese dioxide is a convenient synthetic route to an indole derivative.

FIGURE 2



EXPERIMENTAL

General

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 621 spectrometer as potassium bromide discs. Proton magnetic resonance spectra were determined with a Varian EM-360 spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded in the electron ionization mode at 70 eV on a Varian MAT-112 mass spectrometer. Microanalysis was performed on a Perkin-Elmer model 240-A CHN elemental analyzer.

Indapamide (**1**) lot 3B2991/4 was obtained from Servier Laboratories, Gidy 45402, France. Activated manganese dioxide was obtained from Sterling Organics and used without modification.

N-(3-Sulfamyl-4-chlorobenzamido)-2-methylindole (**2**).

A solution of indapamide (1 g, 2.74 mmole) in dichloromethane (200 ml) was shaken overnight at room temperature with excess activated manganese dioxide (2 g, 23 mmole). The heterogeneous reaction mixture was filtered and the brown powder was recovered and extracted with 100 ml of acetone. The acetone extract was then filtered to remove insoluble manganese oxides. The dark filtrate was evaporated to dryness under reduced pressure. A viscous residue was isolated which slowly solidified to a colorless powder. Thin layer chromatographic analysis of a "Sili plate" (250 micron, E. Merck) which was eluted with a mobile phase of toluene-ethyl acetate (60:40) showed a single component at an Rf value of 0.43 (indapamide-Rf 0.31). The powder was recrystallized from 2-propanol/water to give 50% of **2** as pale yellow crystals, mp 255-257°; ir: 3300, 3080, 3025, 1660, 1585, 1510, 1450, 1375, 1340, 1290, 1165, 1035, 920 and 725 cm^{-1}; pmr (deuterioacetone): δ 8.82 (d, 1H), 8.40 (dd, 1H), 7.93 (d, 1H), 7.33 (m, 6H), 6.37 (S, 1H), 2.86 (S, 1H) and 2.40 (S, 3H); ms: m/e (%) 365 (12), 363 (30), 220 (20), 218 (54), 189 (23), 145 (100), 129 (75), 118 (68), 104 (43) and 77 (32).

Anal. Calcd. for $C_{16}H_{14}ClN_3O_3S$: C, 52.82; H, 3.85; N, 11.60. Found: C, 52.72; H, 3.91; N, 11.32.

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