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# OXIDATIONS OF HETEROCYCLIC COMPOUNDS I - HYDROXYLATION OF BENZIMIDAZOLES

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Benzimidazoles, including the drug thiabendazole, are metabolized mainly to 5-hydroxy derivatives.[1] Results of present chemical oxidation leading to the formation of 5-hydroxy derivatives as the sole stable products contrasts with the mixtures of hydroxylated derivatives normally obtained with other heterocyclic systems.

A series of benzimidazoles (I, R=H, R'=H, $CH_3$, $C_2H_5$) were subjected to Udenfriend oxidation at 40°.[2] Column chromatography on alumina of the extract obtained by continuous extraction with ethyl acetate gave the corresponding 5-hydroxy derivatives as crystalline solids[3,4] identified by m.p., elemental analysis and ultraviolet spectral data, all in accordance with reported properties. Notable features included the characteristic adsorption in the ultraviolet (three strong peaks about 215, 250 and 290 nm) coupled with an intense green-yellow fluorescence, clearly distinguishing hydroxylated derivatives and contrasting with the blue fluorescence given by the parent compounds. Infrared and n.m.r. data further supported the assigned structures.

Oxidation of N-methylbenzimidazole (R=$CH_3$, R'=H) in which tautomerism of the heterocyclic ring is removed, gave evidence for two products, the 5- and 6-hydroxy derivatives, characterized as above, indicating the non-selective character of the reaction with respect to these positions.

A rate study of the hydroxylation was made to assess preparative potential. Although the yield of 5-hydroxybenzimidazole at 40° appears low, the direct introduction of the group has advantages of convenience and probably yield. To match

this process very high yields would be required in the preparation of alternate starting materials such as a pre-methoxylated or hydroxylated o-phenylenediamine.

The course of the reaction is illustrated in Figure 1 obtained from spectrophotometric estimations at 280 nm (benzimidazole) and 290 nm (5-hydroxybenzimidazole) following extraction of aliquots and separation of products on t.l.c. plates.[5]

In the early stages the rapid loss of benzimidazole is matched by a rapid formation, on reduced scale, of the 5-hydroxy derivative, reaching a maximum in about 6 hours. After this formation from benzimidazole is apparently outweighed by loss in further oxidation although some remains for long periods.

Maximum yield of the hydroxy derivative was 16%, reduced to 8% in similar oxidation at 70°. Similar results were obtained for 2-alkyl benzimidazoles.

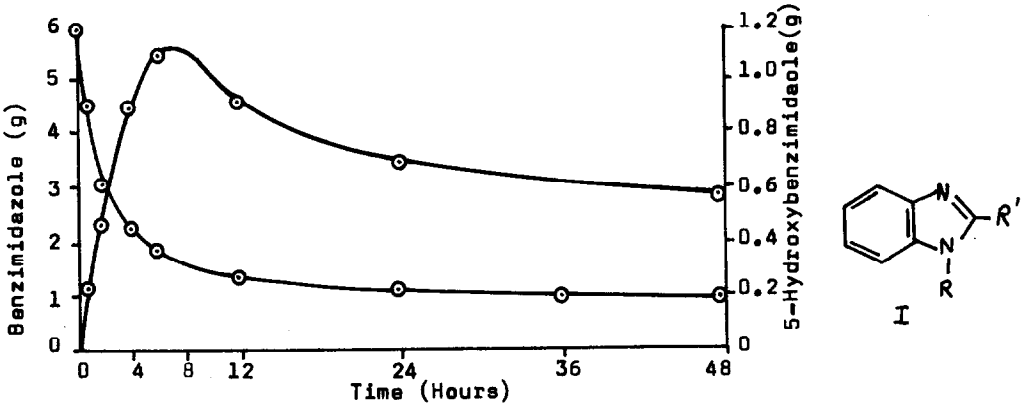


Figure 1 Udenfriend Oxidation of Benzimidazole

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