RESEARCH ON THE CHEMISTRY OF 2-HETARYLBENZIMIDAZOLES.

4.* OXIDATION OF 1-METHYL-2-(5'-METHYL-2'-HETARYL)BENZIMIDAZOLES

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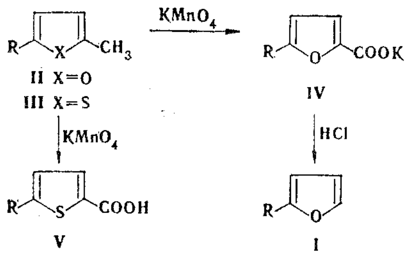
The methyl group in 1-methyl-2-(5'-methyl-2'-hetaryl)benzimidazoles (hetaryl = furyl and thienyl) was oxidized. It was found that a salt of a carboxylic acid, which in an acidic medium loses carbon dioxide to give 1-methyl-2-(2'-furyl)-benzimidazole, is formed when 1-methyl-2-(5'-methyl-2'-furyl)benzimidazole is treated with an aqueous solution of potassium permanganate. The carboxy derivative of thiophene is considerably more stable. Oxidation by means of selenium dioxide leads to the corresponding 5'-formyl derivative. The structures of the compounds obtained were confirmed by data from the IR and PMR spectra.

It has been previously shown [2] that 1-methyl-2-(2'-furyl)benzimidazole (I) is formed instead of the 5'-carboxylic acid when 1-methyl-2-(5'-lithio-2'-furyl)benzimidazole is treated with carbon dioxide. We therefore set out to obtain the 5'-carboxy derivative of 2-hetarylbenzimidazoles by oxidation of the methyl group in the 5' position and to find an explanation for the phenomenon described above.

The oxidation of 5'-methyl-substituted 1-methyl-2-(2'-furyl)- and 1-methyl-2-(2'-thienyl)benzimidazole (II and III) was carried out with potassium permanganate in aqueous media by heating. Owing to the effect of the benzimidazolyl grouping, the hetaryl rings proved to be quite resistant to the action of this oxidizing agent. In II the methyl group is readily oxidized at 30°C, as indicated by the rather rapid conversion of the violet color of the reaction mixture to brown. The oxidation product undergoes rapid decarboxylation during isolation by the action of a 10% solution of hydrochloric acid, and the product is a compound with mp 72-73°C, which was identified as 1-methyl-2-(2'-furyl)benzimidazole (I); this was confirmed by the data from the PMR spectrum, which are identical to the data obtained for standard I. We were able to isolate the carboxylic acid formed in the oxidation of II in low yield and were able to identify it only in the form of salt IV.



I—V R= 1-methyl-2-benzimidazolyl

In contrast to II, 1-methyl-2-(5'-methyl-2'-thienyl)benzimidazole (III) is not oxidized under these conditions. The oxidation was therefore carried out at 80°C. In the isolation of acid V, only a small portion of it underwent decarboxylation; however, it was obtained in only 27% yield because of the difficulty involved in isolating it from the reaction medium.

Since carboxylic acids of the furan [3-4] and thiophene [5, 6] series are stable compounds, the instability of the acids of 2-hetarylbenzimidazoles can evidently be explained by a decrease in the electron density on the carbon atoms in the α position relative to the

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*See [1] for Communication 3.

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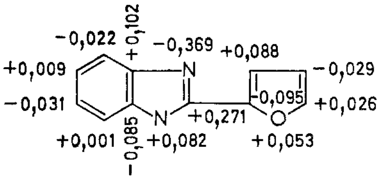
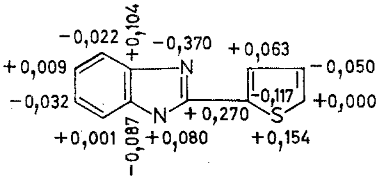
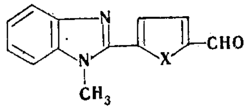
carboxy group; this is due to the effect of the benzimidazolyl grouping. The results of calculations of the π-electron densities by the Pariser—Parr—Pople (PPP) method on the carbon atoms of 2-hetarylbenzimidazoles confirm this assumption.





The higher electron density on the α-carbon atom of 2-(2'-thienyl)benzimidazole is probably the reason for the greater stability of the corresponding acid.

We also carried out the oxidation of 1-methyl-2-(5'-methyl-2'-furyl)benzimidazole (II) and its thiophene analog III with selenium dioxide in anhydrous dioxane. Compounds II and III form aldehydes under these conditions.



VI X=O, VII X=S

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil and solutions in chloroform were recorded with a UR-20 spectrometer. The PMR spectra of solutions in CF_3COOH were recorded with a Tesla BS-467 spectrometer with hexamethyldisiloxane as the internal standard.

1-Methyl-2-(5'-carboxy-2'-furyl)benzimidazole Potassium Salt (IV). A suspension of 2.12 g (10 mmole) of 1-methyl-2-(5'-methyl-2'-furyl)benzimidazole (II) in 100 ml of water was stirred with 4.75 g (30 mmole) of potassium permanganate at 30°C for 1.5 h, after which the manganese dioxide was separated, and the filtrate was evaporated to a volume of 25-35 ml. The concentrated solution was allowed to stand in a refrigerator for 24 h, and the resulting precipitate was removed by filtration to give 0.6 g (21%) of colorless crystals with mp 279-280°C (from water). IR spectrum: 1660 cm^{-1} (C=O). Found: C 56.1; H 3.5; N 10.3%. $C_{13}H_9KN_2O_3$. Calculated: C 55.7; H 3.2; N 9.9%.

1-Methyl-2-(2'-furyl)benzimidazole (I). A 2.12-g (10 mmole) sample of II was oxidized with potassium permanganate as described above. Acidification of the evaporated filtrate with 10% hydrochloric acid solution was accompanied by vigorous carbon dioxide evolution. When CO_2 evolution was complete, I was precipitated from the filtrate with ammonium hydroxide. The yield was 0.9 g (44%). The colorless crystals had mp 72-73°C (from aqueous alcohol) (mp 72-73°C [7]). PMR spectrum: 3.9 (s, 3H, $N-CH_3$), 6.5 (t, 1H, β_4), 7.3 (s, 1H, β_3), 7.4 (s, 4H, aromatic), and 7.6 ppm (s, 1H, α_5).

1-Methyl-2-(5'-carboxy-2'-thienyl)benzimidazole (V). A suspension of 2.28 g (10 mmole) of III in 100 ml of water was stirred with 6.32 g (40 mmole) of potassium permanganate at 80°C for 30 min, after which the mixture was cooled, and the manganese dioxide was separated. The filtrate was evaporated twice, acidified with glacial acetic acid, and allowed to stand in a refrigerator for 72 h, as a result of which 0.7 g (27%) of acid V precipitated from the filtrate. The colorless needles had mp 249-250°C (from alcohol). IR spectrum: 1690 (C=O) and 3480 cm^{-1} (OH). Found: C 60.8; H 4.1; N 10.5%. $C_{13}H_{10}N_2O_2S$. Calculated: C 60.4; H 3.9; N 10.8%.

1-Methyl-2-(5'-formyl-2'-furyl)benzimidazole (VI). A 2.2-g (20 mmole) sample of freshly sublimed selenium dioxide was added gradually to a refluxing solution of 2.12 g (10 mmole) of II in 25 ml of absolute dioxane, and refluxing was continued for 20 h. The mixture was then cooled in a refrigerator for 48 h. The yellow crystals of the reaction product were separated and crystallized from alcohol to give 1.5 g (65%) of a product with mp 148-149°C. IR spectrum: 1680 cm^{-1} (C=O). Found: C 68.7; H 4.1; N 12.5%. $C_{13}H_{10}N_2O_2$. Calculated %: C 69.0; H 4.5; N 12.4%.

1-Methyl-2-(5'-formyl-2'-thienyl)benzimidazole (VII). This compound was obtained by oxidation of 1-methyl-2-(5'-methyl-2'-thienyl)benzimidazole (III) with selenium dioxide for

28 h as in the preparation of VI. The yield was 1.47 g (61%). The yellow crystals had mp 133-134°C (from alcohol). IR spectrum: 1680 cm^{-1} (C=O). Found: C 64.8; H 4.2; N 11.7%. $C_{13}H_{10}N_2OS$. Calculated: C 64.4; H 4.2; N 11.6%.

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BROMINATION OF VINYL DERIVATIVES OF BENZIMIDAZOLE-2-THIONE

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The reaction of vinyl derivatives of benzimidazole-2-thione with bromine was investigated. It is shown that the principal reaction is the addition of the halogen to the double bond of the vinyl group. Depending on the structure of the starting vinyl derivative, elimination of hydrogen bromide or halogenation at the heteroring nitrogen atom, which leads to the formation of hydrohalides, is subsequently possible.

The data available on the reaction of N-vinylazoles with bromine are limited and constitute evidence for the peculiar course of this reaction [1-3]. Thus complexing at the pyridine nitrogen atom and partial addition of the halogen to the vinyl group are primarily observed in the bromination of 1-vinylbenzimidazole.

We have studied the reaction of bromine with 1-vinyl-2-vinylthiobenzimidazole (I), 2-vinylthiobenzimidazole (II), and 1-vinylbenzimidazole-2-thione (III) in CCl_4 at −20 to 20°C.

We found that I readily adds bromine to give a difficult-to-separate mixture of products, the composition of which depends on the ratio of the starting components (Table 1). In the case of small amounts of bromine (1:0.5) poly[1-vinyl-2-(β-bromovinyl)thiobenzimidazole hydrobromide) (IV) is formed in low yield. Its IR spectrum contains the absorption band of a C=C bond attached to a nitrogen atom (1632 cm^{-1}). Under the influence of excess bromine the principal reaction product is poly[1-(α,β-dibromoethyl)-2-(β-bromovinyl)-thiobenzimidazole hydrobromide] (V).

The product of the initial addition of bromine to the vinyl group attached to the sulfur atom (VI) evidently readily splits out hydrogen bromide, which gives rise to instantaneous polymerization of the resulting 1-vinyl-2-(β-bromovinyl)thiobenzimidazole. The liberated HBr coordinates with the aza group to give hydrohalide IV. A second molecule of bromine adds to the N-vinyl group. To prove the structure of tetrabromo derivative V we accom-

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