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RESEARCH ON THE CHEMISTRY OF 2-HETARYLBENZIMIDAZOLE.

3.* REACTION OF 1-METHYL-2-(5'-METHYL-2'-HETARYL)BENZIMIDAZOLES WITH ELECTROPHILIC REAGENTS

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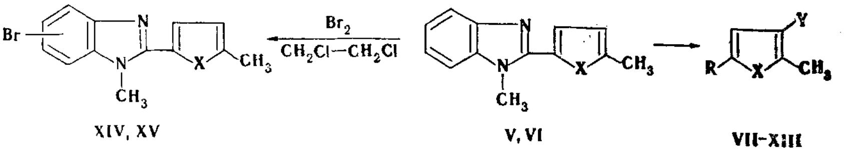
A number of new derivatives of 1-methyl-2-(5'-methyl-2'-hetaryl)benzimidazole were synthesized by electrophilic substitution. The substituent enters the β position of the 4'-hetaryl ring. A furan ring that contains a methyl group in the 5' position undergoes profound destructive oxidation under the influence of acetyl nitrate. Depending on the conditions, bromination leads to the formation of bromo derivatives that are substituted in the benzene or hetaryl ring.

We have previously studied the transformations that occur under the influence of electrophilic reagents on 1-methyl-2-(2'-furyl)- and 1-methyl-2-(2'-thienyl)benzimidazoles (I, II) [1].

We decided to study the effect of a methyl group in the 5 position of the hetaryl ring on the stability of the latter and the orientation of the electrophilic reagent.

2-(5'-Methyl-2'-furyl)- and 2-(5'-methyl-2'-thienyl-benzimidazoles (III, IV) were previously obtained by the reaction of o-phenylenediamine with 5'-methylfurfural and 5-methyl-2-formylthiophene [2]. The products of their methylation (V and VI) were subjected to the action of bromine in dichloroethane and polyphosphoric acid, acetyl nitrate, a mixture of sulfuric and polyphosphoric acids, and paraformaldehyde in the presence of concentrated hydrochloric acid.



V, VII—IX, XIV X=O; VI, X—XIII, XV X=S; VII, X Y=Br; VIII, XI Y=SO_3H; IX, XII Y=CH_2OH; XIII Y=NO_2; R=1-methyl-2-benzimidazolyl

In contrast to I, the furan ring in V is considerably less resistant to the action of acetyl nitrate and undergoes profound destructive oxidation, the products of which undergo subsequent conversion to nitro polymers. Compound VI is nitrated relatively smoothly in the 4' position of the thiophene ring, and the product is obtained in 57% yield.

The chloromethylation of V and VI proceeds with great difficulty. Carrying out the reaction at 70-80°C for 20 h gives the chloromethylation products in low yields, and the products, as a consequence of contamination by the starting compounds, can be isolated only in the form of the hydroxymethyl derivatives.

In contrast to chloromethylation, the action of a mixture of sulfuric and polyphosphoric acids on V and VI leads to the 4'-sulfo derivatives in high yields.

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*See [7] for Communication 2.

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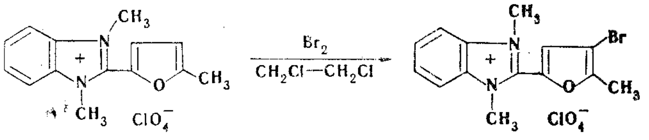
Depending on the conditions, the reaction with bromine proceeds ambiguously: When the reaction is carried out in dichloroethane, the C atoms in the benzene ring, rather than those in the hetaryl ring, as in the bromination of I, undergo attack to give 5(6)-bromo-substituted products. The protons in the benzene ring in the PMR spectra of XIV and XV show up in the form of a singlet (7.40 ppm) and a doublet (7.23 and 7.25 ppm, J = 4 Hz). This result is a consequence of the π-donor effect along the conjugation chain of the hetaryl ring, which bears a methyl group and increases the electron density in the 5(6) position. In an acidic medium protonation of the "pyridine" N atom leads to partial deviation of the hetaryl ring from conjugation with the benzimidazole ring [3, 4], and the C atom in the hetaryl ring undergoes attack. These considerations are confirmed by data on the action of bromine in dichloroethane on the product of quaternization of V.



XVI XVII

Although the β position of the 3 hetaryl ring is the preferred site of attack by the electrophile, since in this case there are greater possibilities for delocalization of the (+) charge in the developing σ complex, substitution occurs in the 4' position; this is evidently associated with the effect of steric factors [5].

EXPERIMENTAL

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

2-(5'-Methyl-2'-furyl)benzimidazole (III). This compound was obtained by the method in [2]. Workup gave 6.3 g (80%) of colorless crystals with mp 267-268°C (from alcohol). Found: C 72.5; H 4.8; N 14.5%. $C_{12}H_{10}N_2O$. Calculated: C 72.7; H 5.1; N 14.1%.

2-(5'-Methyl-2'-thienyl)benzimidazole (IV). This compound was similarly synthesized. Workup gave 6.4 g (75%) of a product with mp 266-267°C (from alcohol). Found: C 67.5; H 4.7; N 13.0%. $C_{12}H_{10}N_2S$. Calculated: C 67.3; H 4.7; N 13.1%.

1-Methyl-2-(5'-methyl-2'-furyl)benzimidazole (V). This compound was obtained by the method in [6]. Workup gave a product with mp 85-86°C (from alcohol) in quantitative yield. Found: C 73.3; H 5.8; N 13.4%. $C_{13}H_{12}N_2O$. Calculated: C 73.6; H 5.7; N 13.2%.

1-Methyl-2-(5'-methyl-2'-thienyl)benzimidazole (VI). This compound was obtained from 2.14 g (10 mmole) of IV by the method used to prepare V. Workup gave a product with mp 75-76°C (from alcohol) in quantitative yield. Found: C 68.1; H 5.2; N 12.2%. $C_{13}H_{12}N_2S$. Calculated: C 68.4; H 5.3; N 12.3%.

1-Methyl-2-(5'-methyl-4'-bromo-2'-furyl)benzimidazole (VII). A mixture of 2.12 g (10 mmole) of V, 3.2 g (20 mmole) of bromine, and 40 g of polyphosphoric acid was stirred at 80-90°C for 8 h, after which it was cooled and diluted with 150 ml of water, and the aqueous mixture was neutralized with ammonium hydroxide. Workup gave 1.6 g (55%) of a product with mp 118-119°C (from alcohol). Found: C 53.2; H 4.0; N 9.3%. $C_{13}H_{11}BrN_2O$. Calculated: C 53.6; H 3.8; N 9.6%.

1-Methyl-2-(5'-methyl-4'-sulfo-2'-furyl)benzimidazole (VIII). A mixture of 2.12 g (10 mmole) of V, 1.96 g (20 mmole) of sulfuric acid (sp. gr. 1.84), and 40 g of polyphosphoric acid was heated with stirring at 120°C for 1 h, after which it was cooled and diluted with 100 ml of water. The precipitated sulfonic acid was removed by filtration to give 2.25 g (77%) of a product with mp >330°C (from water). Found: C 53.8; H 4.5; N 9.8%. $C_{13}H_{12}N_2O_4S$. Calculated: C 53.4; H 4.1; N 9.6%.

1-Methyl-2-(5'-methyl-4'-hydroxymethyl-2'-furyl)benzimidazole (IX). A 2.3-g (26 mmole) sample of paraformaldehyde was added gradually to a solution of 4.24 g (20 mmole) of V in 24 ml of hydrochloric acid (sp. gr. 1.19), and the resulting mixture was heated at 70-80°C for 20 h. It was then cooled and treated with ammonium hydroxide, and the reaction product was extracted with chloroform and chromatographed with a column filled with aluminum

TABLE 1. PMR Spectra of the Hetarylbenzimidazoles

Compound	δ, ppm (CF_3COOH)
VII	2,05 (C, 3H, C—CH_3), 3,75 (C, 3H, N—CH_3), 7,10 (C, 1H, β_3), 7,25 (C, 4H, aromatic)
VIII	2,38 (C, 3H, C—CH_3), 3,90 (C, 3H, N—CH_3), 7,40 (C, 4H, aromatic), 7,70 (C, 1H, β_3), 11,95 (C, 1H, SO_3H)
IX	2,20 (C, 3H, C—CH_3), 3,80 (C, 3H, N—CH_3), 4,43 (C, 2H, CH_2), 5,00 (C, 1H, OH), 7,30 (C, 4H, aromatic)
X	2,13 (C, 3H, C—CH_3), 3,78 (C, 3H, N—CH_3), 7,28 (C, 4H, aromatic)
XI	2,45 (C, 3H, C—CH_3), 3,80 (C, 3H, N—CH_3), 7,33 (C, 4H, aromatic), 7,85 (C, 1H, β_3), 12,05 (C, 1H, SO_3H)
XII	2,30 (C, 3H, C—CH_3), 3,80 (C, 3H, N—CH_3), 5,10 (C, 2H, CH_2), 7,33 (C, 4H, aromatic), 7,63 (C, 1H, β_3)
XIV	2,08 (C, 3H, C—CH_3), 3,73 (C, 3H, N—CH_3), 6,05 (D, 1H, β_4), 7,10 (D, 1H, β_3), 7,23 (Д, 2H, aromatic), 7,40 (C, 1H, aromatic)
XV	2,25 (C, 3H, C—CH_3), 3,80 (C, 3H, N—CH_3), 6,70 (D, 1H, β_4), 7,25 (D, 2H, aromatic), 7,40 (C, 1H, aromatic)
XVII	2,05 (C, 3H, C—CH_3), 3,70 (C, 3H, N—CH_3), 7,00 (C, 1H, β_3), 7,30 (C, 4H, aromatic)

oxide (elution with chloroform) to give 1.3 g (27%) of colorless crystals with mp 187-188°C (from alcohol). IR spectrum: 3170 cm^{-1} (OH). Found: C 69.2; H 6.1; N 11.3%. $C_{14}H_{14}N_2O_2$. Calculated: C 69.4; H 5.8; N 11.6%.

1-Methyl-2-(5'-methyl-4'-bromo-2'-thienyl)benzimidazole (X). This compound was obtained from 2.28 g (10 mmole) of VI by the method used to prepare VII. Workup gave 1.93 g (63%) of colorless crystals with mp 146-147°C (from alcohol). Found: C 51.0; H 4.0; N 9.4%. $C_{13}H_{11}BrN_2S$. Calculated: C 50.8; H 3.6; N 9.1%.

1-Methyl-2-(5'-methyl-4'-sulfo-2'-thienyl)benzimidazole (XI). This compound was obtained from 2.28 g (10 mmole) of 1-methyl-2-(5'-methyl-2'-thienyl)benzimidazole by the method used to prepare VIII. Workup gave 2.4 g (79%) of colorless crystals with mp > 330°C (from water). Found: C 51.0; H 4.2; N 8.8%. $C_{13}H_{12}N_2O_3S_2$. Calculated: C 50.6; H 3.9; N 9.1%.

1-Methyl-2-(5'-methyl-4'-hydroxymethyl-2'-thienyl)benzimidazole (XII). This compound was obtained from 4.56 g (20 mmole) of 1-methyl-2-(5'-methyl-2'-thienyl)benzimidazole by the method used to prepare IX. Workup gave 2.32 g (45%) of snow-white crystals with mp 169-170°C (from alcohol). IR spectrum: 3240 cm^{-1} (OH). Found: C 65.5; H 5.2; N 11.0%. $C_{14}H_{14}N_2OS$. Calculated: C 65.1; H 5.5; N 10.8%.

1-Methyl-2-(5'-methyl-4'-nitro-2'-thienyl)benzimidazole (XIII). A 19-g sample of nitric acid (sp. gr. 1.5) was added at 10°C to 30 g (300 mmole) of freshly distilled acetic anhydride, after which 4.56 g (20 mmole) of VI was added, and the reaction mixture was stirred at 10°C for 2 h. It was then diluted with 100 ml of water, and the precipitated product was removed by distillation to give 2.92 g (57%) of yellow crystals with mp 276-277°C (from DMF). IR spectrum: 1360 cm^{-1} (NO_2). Found: C 60.4; H 4.2; N 16.6%. $C_{13}H_{11}N_3OS$. Calculated: C 60.7; H 4.3; N 16.3%.

1-Methyl-5(6)-bromo-2-(5'-methyl-2'-furyl)benzimidazole (XIV). A solution of 2.4 g (15 mmole) of bromine in 20 ml of dichloroethane was added at 80°C to a solution of 2.12 g (10 mmole) of V in 20 ml of dichloroethane, and the mixture was allowed to stand at 80°C for 3 h. The precipitated hydrobromide of XIV was separated and converted to the base, which was obtained as 2.24 g (77%) of colorless crystals with mp 153-154°C (from alcohol). Found: C 53.8; H 3.9; N 9.4%. $C_{13}H_{11}BrN_2O$. Calculated: C 53.6; H 3.8; N 9.6%.

1-Methyl-5(6)-2-(5'-methyl-2'-thienyl)benzimidazole (XV). This compound was obtained from 2.28 g (10 mmole) of starting VI by the method used to prepare XIV. The compound was heated at 80°C with a solution of bromine in dichloroethane for 8 h. Workup gave 1.93 g (63%) of colorless needles with mp 150-151°C (from alcohol). Found: C 50.5; H 3.2; N 9.3%. $C_{13}H_{11}BrN_2S$. Calculated: C 50.8; H 3.6; N 9.1%.

1,3-Dimethyl-2-(5'-methyl-2'-furyl)benzimidazolium Perchlorate (XVI). A 5-ml sample of a 60% solution of perchloric acid was added to a boiling solution of 3.54 g (10 mmole) of the methiodide of V in 100 ml of water, and the precipitated perchlorate was removed by filtration to give 2.64 g (81%) of colorless crystals with mp 208-209°C (from water). Found: N 8.2%. $C_{14}H_{15}ClN_2O_5$. Calculated: N 8.5%.

1,3-Dimethyl-2-(5'-methyl-4'-bromo-2'-furyl)benzimidazolium Perchlorate (XVII). A 3.26-g (10 mmole) sample of XVI was dissolved in 50 ml of dichloroethane, 3.2 g (20 mmole) of bromine was added, and the mixture was heated at 80°C for 6 h. The solvent was then evaporated, and the reaction product was dissolved by heating in water containing a small amount of propyl alcohol. Cooling of the solution produced yellowish needles with mp 223-224°C. The yield was 2.9 g (72%). Found: C 41.8; H 3.2; N 7.1%. $C_{14}H_{14}BrClN_2O_5$. Calculated: C 41.4; H 3.5; N 6.9%.

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CONFORMATION OF 1,2,3,4-TETRAHYDRO-2-PYRIMIDINONES

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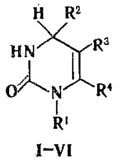
The conformation of a number of 1,2,3,4-tetrahydro-2-pyrimidinones with various substituents in the ring was established on the basis of the vicinal $^3J_{34}$ constants found from the ^1H NMR spectra of these compounds. It is shown that in solution rapid conformational transformations between the two possible "boat" conformations evidently occur.

Compounds I-VI have been examined to establish the conformation of 1,2,3,4-tetrahydro-2-pyrimidinones by NMR spectroscopy [1-4]. The parameters of the spectra of these compounds are presented in Table 1. A vicinal spin—spin coupling constant (SSCC) between the 3-H and 4-H protons, the magnitude of which ranged from 1.5 to 3.2 Hz and depends on the HN_3C_4H dihedral angle, is observed in the spectra.

The NH_3C_4H fragment can be formally regarded as an analog of a cis-peptide bond, for which a dependence of $^3J_{HNCH}$ on the dihedral angle has been found in 5- and 6-membered



I–VI

I $R^1=R^2=R^4=H$, $R^3=COOEt$; II $R^1=H$, $R^2=Ph$, $R^3=COOEt$, $R^4=Me$; III $R^1=R^4=Me$, $R^2=Ph$, $R^3=COOEt$; IV $R^1=R^4=Me$, $R^2=Ph$, $R^3=COOH$; V $R^1=Me$, $R^2=Ph$, $R^3=COOEt$, $R^4=H$; VI $R^1=R^4=Me$, $R^2=Ph$, $R^3=H$

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