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CHEMISTRY OF 2-HETARYLBENIMIDAZOLES.

7.* TRANSFORMATIONS OF TRANS-1-METHYL-2-[β-(2'-FURYL)VINYL] BENZIMIDAZOLE

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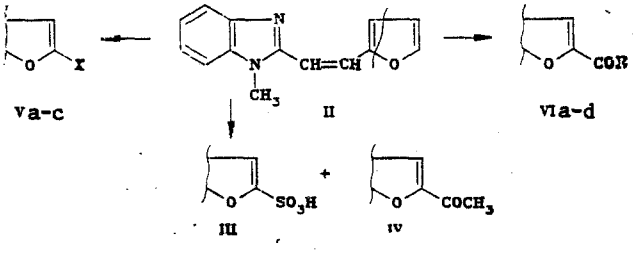
Electrophilic substitution reactions in the furylvinylbenzimidazole series were studied. In nitration, sulfonation, bromination, acylation, formylation, and hydroxymethylation reactions, the substituent enters at the α-position of the furan ring. The presence of a vinylene group reduces the influence of the benzimidazole fragment on the furan ring, and therefore the reactions in the latter proceed considerably more rapidly and under milder conditions than in the case of furylbenzimidazole. Calculated data are given for the π-electronic density on the carbon atoms of furyl-vinylbenzimidazole, obtained by the CNDO method.

The nitration and acetylation of the furan ring in 1-alkyl-2-[β-(2'-furyl)-vinyl] benzimidazole have already been studied in [2].

It was of interest to examine the behavior of 1-methyl-2-[β-(2'-furyl)-vinyl] benzimidazole (II) in other electrophilic substitution reactions, and to compare the reactivity of the furan ring linked directly or through a vinylene group to the benzimidazole radical. For this purpose, we carried out several reactions, as shown in the following scheme:



V a X=Br, b X=CH_2OH, c X=NO_2; VI a R=H, b R=C_2H_5, c R=$CH_2C_6H_5$, d R=C_6H_5

The sulfonation of 1-methyl-2-(2'-furyl)benzimidazole (I) was previously carried out by the action of concentrated sulfuric and polyphosphoric acids at 120°C [3]. Under these conditions, compound II undergoes a complete resinification. We therefore carried out its sulfonation

*For Communication 6, see [1].

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TABLE 1. Characteristics of Synthesized Compounds

Compound	mp, °C (methanol)	IR spectrum, cm^{-1}	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
III	292—293 (from H_2O)	—	55,7	4,1	8,9	$C_{14}H_{12}N_2O_4S$	55,3	4,0	9,2	51
Va	128—129 (125 [6])	—	55,4	4,1	9,5	$C_{14}H_{11}BrN_2O$	55,5	3,7	9,2	58
Vb	192—193	3240	71,2	5,1	11,3	$C_{15}H_{14}N_2O_2$	70,9	5,5	11,0	83
Vc	211—212	1350	62,9	3,8	15,7	$C_{14}H_{11}N_3O_3$	62,5	4,1	15,6	77
VIa	177—178	1680	71,3	5,2	10,9	$C_{16}H_{12}N_2O_2$	71,4	4,8	11,1	64
VIb	190—191	1670	73,1	5,5	9,8	$C_{17}H_{16}N_2O_2$	72,8	5,6	10,0	33
VIc	154—155	1680	76,9	5,0	8,5	$C_{22}H_{18}N_2O_2$	77,2	5,3	8,2	54
VId	163—164	1660	77,1	4,7	8,3	$C_{21}H_{16}N_2O_2$	76,8	4,9	8,5	47

under milder conditions: by the action of sulfuric acid in acetic anhydride at 0°C. Thus, the 5'-sulfo-derivative III was obtained in a yield of 51% with an admixture of an acetylation product IV.

The bromination of benzimidazole II proceeds in acetic acid at room temperature, while compound I is brominated only at 80°C. In both cases, bromine enters at the 5'-position of the furan ring. In the PMR spectrum of the bromine derivative Va, as well as the methyl group signals and the aromatic protons multiplet, there are doublets at 6.1 and 6.4 ppm, belonging to the 4-H' and 3-H' protons of the furan ring, and also doublet signals at 6.6 and 7.15 ppm with J = 16 Hz of the vinylene group protons. The entry of bromine only into the 5'-position of the furan ring has been proved by an alternate synthesis — condensation of 1,2-dimethylbenzimidazole with 5-bromofurfural in acetic anhydride.

The synthesis of 5'-hydroxymethyl- and 5'-nitro-derivatives (Vb,c) proceeds much more rapidly (30 min) than the formation of analogous derivatives of I (6 and 2 h, respectively). Compound Vc was obtained by an alternate synthesis by substituting a nitro group for bromine under the Zincke' conditions.

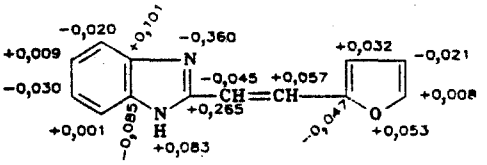
In contrast with the case of furylbenzimidazole I, the formylation of compound II proceeds smoothly, and high yields can be obtained according to Vilsmeier, while the action of urotropin in polyphosphoric acid at 70°C (2 h) leads to the formation of a sparingly soluble polymer, mp > 300°C. Acylation of compound II by the action of carboxylic acids in the presence of polyphosphoric acid also proceeds under mild conditions (50-60°C, 1 h) with the formation of 5'-acyl derivatives VIc-d, while with compound I they were obtained after 6-10 h at 110-150°C.

The steric structure of 1-methyl-2-[β-(2'furyl)vinyl]benzimidazole (II) and its substitution products was established by the PMR spectroscopy method. Thus, in the spectrum of compound II, the signals of the vinyl protons are represented by two doublets with centers at 6.62-6.65 and 7.20 ppm; in the last doublet, one of the components overlaps with aromatic proton signals. The spin—spin coupling constant is J = 16 Hz, which corresponds to the trans-orientation of the substituents at the double bond. The PMR spectra of 5'-bromo-, 5'-nitro-, 5'-hydroxymethyl- and 5'-sulfo-substituted derivatives (Va-c, III) follow a similar pattern.

For the 5'-benzoyl derivative VId, the vinyl proton signals overlap to a large extent with the aromatic proton signals; but it can be assumed that doublets with centers at 7.10 and 7.40 ppm with constant J = 8-10 Hz correspond to the vinyl protons. This indicates a cis-configuration of this compound. At the same time, the presence in the spectrum of this derivative of certain additional signals (for example at 7.50 and 7.15 ppm), appearing in the form of a certain distortion of the form of the lines (a "shoulder" on the signal) leads us to assume the presence of an admixture of a trans isomer. The spectra of other 5'-acyl derivatives (VIa-c) follow a similar pattern.

In the spectra of all the compounds studied there are signals of the $N-CH_3$ group at 3.6-3.8 ppm, the furan ring protons at 6.15 and 6.5 ppm, and the aromatic protons at 7.2-7.3 ppm.

Comparison of the behavior of furylbenzimidazole I and furylvinylbenzimidazole II in the electrophilic substitution reactions shows that they form derivatives 5'-substituted in the furan ring, but the transformations of compound II proceed more rapidly and under milder conditions than those of compound I. The inclusion of the vinylene group between the rings possibly leads to lessening of the influence of the benzimidazole radical on the furan ring. Calculated data on the electron density on the carbon atoms of compound I [4] and II by the CNDO method confirm this supposition.



Thus, the overall π-charge on the furan ring of furylbenzimidazole is equal to +0.043, while on the furan ring in compound II, it is almost half that value (+0.025).

EXPERIMENTAL

The IR spectra were run on a UR-20 spectrophotometer in chloroform, and the PMR spectra – on a Tesla BS-487 spectrometer, using HMDS as internal standard. The MO were calculated by the CNDO method, whose details and parameters are described in [5].

The characteristics of the synthesized compounds are given in Table 1,

1-Methyl-2-[β-(5'-sulfo-2'-furyl)vinyl]benzimidazole (III). A solution of 2.94 g (30 mmoles) of sulfuric acid (d 1.84) in 10 ml of acetic anhydride is added with vigorous stirring at 0°C and in the course of 1 h to a solution of 2.24 g (10 mmoles) of compound II in 10 ml of acetic anhydride. The sulfonic acid precipitate that separates is filtered and washed with a small amount of water.

1-Methyl-2-[β-(5'-acetyl-2'-furyl)vinyl]benzimidazole (IV) is formed as a byproduct in the synthesis of compound III. The mother liquor obtained from the filtration of sulfonic acid III, is cautiously neutralized by a concentrated solution of ammonia to pH 7. The acetylation product is extracted by 50 ml of benzene, chromatographed on a column (h 20 cm, d 3 cm) with 80 g of aluminum oxide, and eluted with benzene. Yield, 0.56 g (21%), mp 167-168°C (from methanol). According to the data in [2], mp 164-165°C. IR spectrum: 1680 cm^{-1} (CO). Found: N 10.7%. $C_{16}H_{14}N_2O_2$. Calculated: N 10.5%.

1-Methyl-2-[β-(5'bromo-2'-bromo-2'-furyl)vinyl]benzimidazole (Va). A. A solution of 3.2 g (20 mmoles) of bromine in 10 ml of acetic acid is gradually added at 20°C, with vigorous stirring, to a solution of 2.24 g (10 mmoles) of compound II in 20 ml of glacial acetic acid. The reaction mixture is left to stand for 1 h, and the precipitate of the hydrobromide of compound Va is filtered. The base is obtained by the action of 100 ml of 10% ammonia solution on the hydrobromide.

B. A mixture of 1.46 g (10 mmoles) of 1,2-dimethylbenzimidazole and 1.75 g (10 mmoles) of 5-bromofurfural in 10 ml of a freshly distilled acetic anhydride is heated for 20 h at 140°C. The reaction mixture is then diluted with 100 ml of water, and the solution is neutralized by concentrated ammonia to pH 7-8. The reaction product that separates is extracted by benzene (2 × 50 ml) and chromatographed on a column (h 20 cm, d 3 cm) with 100 g of aluminum oxide, and eluted with benzene. Yield, 1.7 g (55%). The compounds obtained by methods A and B are identical, as confirmed by a mixed melting point test.

1-Methyl-2-[β-(5'-hydroxymethyl-2'-furyl)vinyl]benzimidazole (Vb). A mixture of 2.24 g (10 mmoles) of compound II, 1.15 g (13 mmoles) of paraform, and 10 ml or hydrochloric acid (d 1.19) is heated for 30 min at 50-60°C, then cooled to 20°C, and cautiously neutralized by a 10% sodium hydroxide solution to pH 7-8. The reaction product is extracted by 50 ml of chloroform, chromatographed on a column (h 20 cm, d 2.5 cm) with 70 g of aluminum oxide, and eluted with chlorform.

1-Methyl-2-[β-(5'-nitro-2'-furyl)vinyl]benzimidazole (Vc). A. A solution of 1.89 g (30 mmoles) of nitric acid (d 1.5) in 10 ml of acetic acid is added dropwise, with vigorous stirring, at 0°C and in the course of 1 h, to a solution of 2.24 g (10 mmoles) of compound

II in 10 ml of a freshly distilled acetic anhydride. The reaction mixture is then poured into 100 ml of ice water, neutralized with a 10% solution of ammonia to pH 7-8, and the product is isolated in a similar way as in the case of compound Va. Yield, 1.3 g (88%), mp 211-212°C.

B. A 1.5 g portion (5 mmoles) of compound Va is dissolved in 15 ml of acetic acid and 1.04 g (15 mmoles) of sodium nitrate are added to this solution. The mixture is boiled for 1 h, then cooled, poured into 50 ml of water, and the product is isolated as described in experiment A. The compounds obtained by methods A and B are identical, as confirmed by a mixed melting point test. Compound Vc has been previously obtained by condensation of 1,2-dimethylbenzimidazole with 5-nitrofurfural [7], mp 210-211°C.

1-Methyl-2-[β-(5'-formyl-2'-furyl)vinyl]benzimidazole (VIa). A 2.24 g portion (10 mmoles) of compound II is dissolved in 4.38 g (60 mmoles) of dimethylformamide. The mixture is cooled to 0°C, and 9.21 g (60 mmoles) of phosphorus oxychloride are added dropwise at a temperature not higher than 10°C. The mixture is then stirred for 10 min at 0°C and then for 2 h at 80°C. The reaction mixture is then poured into 100 ml of water. The mixture is cautiously neutralized by a concentrated solution of ammonia to pH 7-8, and aldehyde VIa is isolated in a similar way as in the case of compound Va.

1-Methyl-2-[β-(5'-acyl-2'-furyl)vinyl]benzimidazoles (VIc, d). A mixture of 2.24 g (10 mmoles) of compound II and 30 mmoles of the corresponding carboxylic acid in 40 g of polyphosphoric acid is stirred for 1 h at 50-60°C. The reaction product is isolated in the same way as in the case of compound Va.

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