SYNTHESIS OF 2-[β-(5'-HALOGENOFUR-2'-YL)VINYL]BENZIMIDAZOLES

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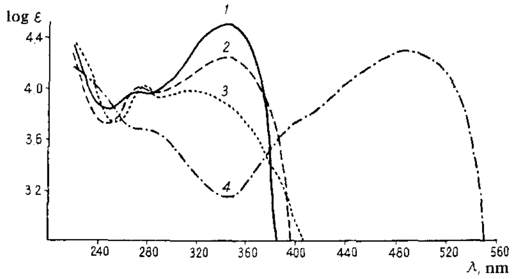
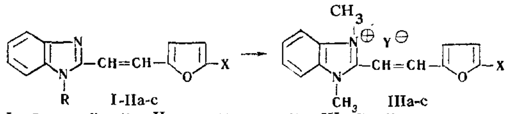
2-[β-(5'-halogenofur-2'-yl)vinyl]benzimidazoles (I) have been synthesized by the condensation of o-phenylenediamine with 5-halogenofur-2-ylacroleins or of 2-methylbenzimidazole with 5-halogenofurfurals. The methiodides of the 1-methyl-substituted derivatives of I readily react with secondary amines (piperidine, dimethylamine) giving methiodides of 2-[β-(5'-dialkylaminofur-2'-yl)vinyl]-1-methylbenzimidazoles.

It has been found previously that the quaternization of the N heteroatom in 1-alkyl-2-(5'-halogenofur-2'-yl)benzimidazoles considerably increases the mobility of the halogen atom in the furan nucleus. Continuing this work, we have synthesized methiodides of 2-[β-(5'-halogenofur-2'-yl)vinyl]-1-methylbenzimidazoles (III) and have studied their reaction with secondary aliphatic and heterocyclic amines.



UV spectra: 1) 2-[β-(5'-bromofur-2'-yl) vinyl] benzimidazole (Ic); 2) 2-[β-(5'-bromofur-2'-yl) vinyl]-1-methylbenzimidazole (IIc); 3) Methiodide of compound IIc; 4) Methiodide of 1-methyl-2--[β-(5'-piperidinofur-2'-yl] vinyl] benzimidazole (IVa).

Compounds I were obtained in good yield by the condensation of o-phenylenediamine with 5-halogenofur-2-ylacroleins under Weidenhagen's conditions [2]. They are readily methylated, forming the 1-methyl-substituted compounds (II) which are smoothly converted into III, which are yellow.



I-IIa-c IIIa-c

Ia R = H, X = H IIa R = CH$_3$, X = H IIIa X = H
Ib R = H, X = Cl IIb R = CH$_3$, X = Cl IIIb X = Cl
Ic R = H, X = Br IIc R = CH$_3$, X = Br IIIc X = Br

Because of the relative complexity of the synthesis of 5-halogenofur-2-yl-acroleins [3] and of the performance of the Weidenhagen reaction, we have attempted to obtain compounds I by condensing 2-methylbenzimidazole with 5-halogenofurfurals by analogy with the synthesis of styrylbenzimidazoles [4]. However, only Ia was obtained in good yield by this method. The lower yields of Ib and Ic can be explained by the presence of a free NH group which undergoes side reactions with the 5-halogenofurfural. In actual fact, the yields of II and III were higher if 1,2-dimethylbenzimidazole or its quaternary salt was condensed with the 5-halogenofurfurals (Tables 1 and 2).

In compounds I and II the halogen atom in the furan nucleus is relatively immobile. On the other hand, in III it possesses a considerable mobility: under the action of secondary amines it is replaced by a secondary amine residue almost as easily as in the methiodides of the 1-alkyl-2-(5'-halogenofur-2'-yl)benz-

Table 1

2-[β-(Fur-2'-yl)vinyl]benzimidazoles

Compound	Mp, °C (solvent)	Empirical formula	N, %		λ$_{max}$, nm	log ε	Yield, %
			found	calculated			
Ia	223 (decomp.) (aqueous ethanol)	$C_{13}H_{10}N_2O$	13.43	13.32	342	4.368	63 (A)*, 81 (B)
Ib	208 (decomp.) (aqueous ethanol)	$C_{13}H_9ClN_2O$	11.47	11.45	344	5.033	67 (A), 59 (B)
Ic	212 (decomp.) (aqueous ethanol)	$C_{13}H_9BrN_2O$	9.48	9.69	348	4.509	71 (A), 51 (B)
IIa	115-116 (ethanol)	$C_{14}H_{12}N_2O$	12.23	12.48	342	4.428	62.5 (A)
IIb	110 (ethanol)	$C_{14}H_{11}ClN_2O$	10.63	10.82	336	4.156	85.7 (A)
IIc	125 (ethanol)	$C_{14}H_{11}BrN_2O$	9.15	9.24	340	4.230	80 (A), 72 (B)

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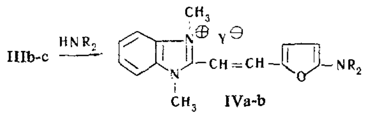
*A and B denote the methods of synthesis of the given compounds, which are described in the experimental part.

Table 2

Methiodides of 2-[β-(Fur-2'-yl)vinyl]-1-methylbenzimidazoles

Compound	Mp, °C (solvent)	Empirical formula	N, %		λ_{max}, nm	log ε	Yield, %
			found	calculated			
IIIa	235 (decomp.) (water)	$C_{15}H_{15}IN_2O$	7.67	7.61	314	4.085	55 (A), 72 (B)
IIIb	224 (decomp.) (water)	$C_{15}H_{14}ClIN_2O$	7.05	6.98	316	3.985	70.6 (A)
IIIc	240 (decomp.) (water)	$C_{15}H_{14}BrIN_2O$	6.40	6.29	310	3.980	54 (A), 90 (B)
IVa	168 (decomp.) (chloroform–petroleum ether)	$C_{20}H_{24}IN_3O$	9.32	9.35	490	4.316	75
IVb	160 (decomp.) (ethanol)	$C_{17}H_{20}IN_3O$	10.80	10.30	—	—	72

imidazoles [1]. In this way the methiodides of 2-[β-(5'-dialkylaminofur-2'-yl)vinyl]-1-methylbenzimidazoles (IV), colored in various bright shades of red, are formed.



IVa NR_2 = N–Piperidino IVb $NR_2 = N(CH_3)_2$

Thus, a lengthening of the chain of conjugation of the double bonds between the halogen atom of the furan nucleus and the onium nitrogen of the imidazole ring on passing from the methiodides of the 1-alkyl-2-(5'-halogenofur-2'-yl)benzimidazoles to IIIb and IIIc does not lower the mobility of the halogen.

The UV spectra of each type of compound that we obtained are extremely similar to one another in the positions of the absorption maxima but differ considerably with respect to the intensity of absorption (tables, figure).

EXPERIMENTAL

2-[β-(Fur-2'-yl)vinyl]benzimidazole (Ia). a) A solution of 16 g (0.08 mole) of copper acetate in 200 ml of water and then 5.5 g (0.045 mole) of furylacrolein [5] in 75 ml of methanol were added to 4.32 g (0.04 mole) of o-phenylenediamine in 100 ml of methanol. The mixture was boiled for 2 hr and left overnight. The precipitate of the copper complex was filtered off and washed with 25 ml of methanol and was suspended in 150 ml of 60% ethanol. A strong current of hydrogen sulfide was passed into the resulting suspension for 2 hr. After the hydrogen sulfide had been driven off by brief boiling, the precipitate of copper sulfide was filtered off and was washed on the filter with 50 ml of hot ethanol. The combined filtrates were evaporated to half bulk and greatly diluted with water. The precipitate of Ia was separated off, recrystallized, and dried in a vacuum desiccator. Compounds Ib and Ic were obtained similarly.

b) A mixture of 1.32 g (0.01 mole) of 2-methylbenzimidazole, 0.96 g (0.1 mole) of furfural, and 0.05 g of boric acid was heated at 140° C for 4–5 hr. The Ia was extracted from the melt with boiling ethanol. Compounds Ib and Ic were obtained similarly.

2-[β-(5'-Bromofur-2'-yl)vinyl]-1-methylbenzimidazole (IIc). a) A solution of 1.45 g (0.005 mole) of Ic, 0.056 g (0.01 mole) of caustic potash, and 1.42 g (0.01 mole) of methyl iodide in 25 ml of ethanol was boiled for 2 hr. After cooling, the potassium iodide was separated off, the filtrate was treated with carbon, and the reaction product was precipitated by the addition of water. Compounds IIa and IIb were obtained similarly.

b) A mixture of 7.3 g (0.05 mole) of 1,2-dimethylbenzimidazole, 7.9 g (0.05 mole) of 5-bromofurfural, and 75 ml of acetic anhydride was heated at 140° C for 16 hr. The acetic anhydride was distilled off, and the residue was treated with 1N hydrochloric acid.

2-[β-(5'-Bromofur-2'-yl)vinyl]-1-methylbenzimidazole methiodide (IIIc). a) A mixture of 1.5 g (0.005 mole) of compound IIc and 0.86 g (0.005 mole) of methyl benzenesulfonate was heated at 130° C for 30 min. The cooled reaction mixture was carefully triturated with an equimolecular amount of 10% potassium iodide solution and then the crystals of IIIc were separated off.

b) A solution of equimolecular amounts of 1,2-dimethylbenzimidazole methiodide and 5-bromofurfural in acetic anhydride was heated at 140° C for 8 hr. The acetic anhydride was distilled off and the residue was recrystallized.

1-Methyl-2-[β-(5'-piperidinofur-2'-yl)vinyl]benzimidazole methiodide (IVa). A solution of 0.4 g (0.001 mole) of IIIb and 0.17 g (0.002 mole) of piperidine in 10 ml of ethanol was boiled for 2 hr. After cooling, the piperidine hydrochloride was filtered off and the solvent was distilled off. The residue consisted of IVa. Compound IVb was obtained similarly.

The UV spectra of the compounds were recorded on an SF-4 spectrophotometer in methanol.

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