SYNTHESIS OF 2-(5'-HALOGENOFURYL-2')BENZIMIDAZOLES

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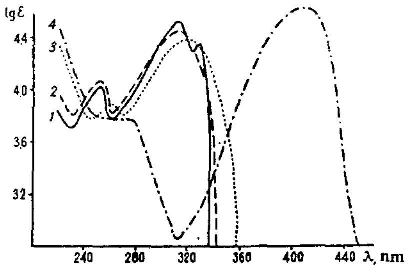
Condensation of o-phenylenediamine with 5-chloro-, 5-bromo-, and 5-iodofurfural under Weidenhagen reaction conditions gives the corresponding 2-(5'-halogenofuryl-2')benzimidazoles. Reaction of the latter with dimethylbenzylphenylammonium chloride gives 1-benzyl derivatives, characterized as the methiodides. In these compounds the halogen is mobile and can be replaced by a N-piperidyl group.

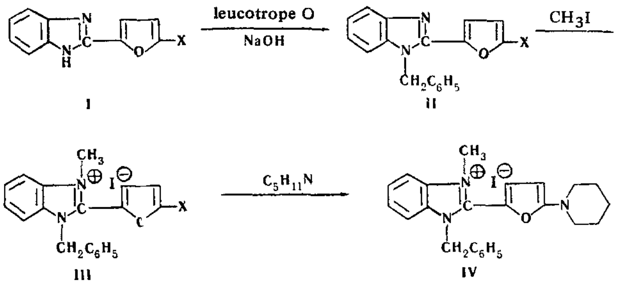
It has been shown [1] that the mobility of α halogen in furfural increases sharply on conversion to azomethines. In this connection it appeared of interest to ascertain the nature of the mobility of halogen in 2-(5'-halogenofuryl-2')benzimidazoles, where the >C=N– bond forming part of the imidazole ring, is formally replaced by an azomethine bond.



Absorption spectra:
1) 2-(5'-bromofuryl-2')benzimidazole; 2) 1-benzyl-2-(5'bromofuryl-2')benzimidazole; 3) 1-benzyl-2-(5'-bromofuryl-2')benzimidazole; 4) 1-benzyl-2-(5'-N-piperidylfuryl-2')benzimidazole.

Compound Ia was previously prepared by condensing o-phenylenediamine with furfural [2, 3], furfurylideneacetophenone [4], or an imino ester of pyromucic acid [5]. The commonest methods of synthesizing benzimidazoles, condensation of carboxylic acids or their derivatives with o-phenylenediamine proved unsuitable for preparing Ia, because under the conditions of the experiment, the furan components resinified.

Since the halogens stabilize the furan ring [6], 5-halogenofurfurals condense more smoothly than furfural, with o-phenylenediamine, to give the corresponding 2-(5'-halogenofuryl-2')benzimidazoles (I). However, an attempt to prepare I by the Phillips method proved unsuccessful [7].



X = a H; b Cl; c Br; d I

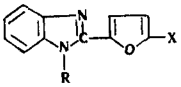
2-(5'-Halogenofuryl-2')benzimidazoles are stable high-melting compounds. Unlike 2-phenylbenzimidazole [8], they are readily benzylated with leucotrope O (dimethylbenzylphenylammonium chloride) to 1-benzyl-2-(5'-halogenofuryl-2')benzimidazoles (II), which can be converted to quaternary salts (III).

Attempts to replace the halogen atom of compounds I and II by a piperidine group at 100° gave a negative result. On the other hand the furan ring halogen in quaternary salts III, is quite mobile. Treatment of III with piperidine leads to replacement of the halogen atom with formation of 1-benzyl-2-(5'-N-piperidylfuryl-2')benzimidazole (IV).

The UV spectra of compounds Ic and IIc are alike. Quaternization of compounds IIc followed by replace-

Table 1

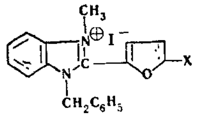
2-(Furyl-2')benzimidazoles

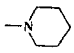


Compound	R	X	Mp, °C	Formula	N, %		Yield, %
					Found	Calculated	
Ib	H	Cl	223–225	$C_{11}H_7ClN_2O$	13.05; 12.95	12.81	80
Ic	H	Br	228–230	$C_{11}H_7BrN_2O$	10.77; 10.82	10.68	72
Id	H	I	189–192 (decomp.)	$C_{11}H_7IN_2O$	8.81; 8.86	9.03	66
IIa	$CH_2C_6H_5$	H	125–127	$C_{18}H_{14}N_2O$	10.35; 10.42	10.18	82
IIb	$CH_2C_6H_5$	Cl	117–118	$C_{18}H_{13}ClN_2O$	9.21; 9.16	9.05	72
IIc	$CH_2C_6H_5$	Br	137–138	$C_{18}H_{13}BrN_2O$	7.94; 7.96	7.93	80
IId	$CH_2C_6H_5$	I	135–136	$C_{18}H_{13}IN_2O$	7.02; 7.12	6.98	70

Table 2

Methiodides of Derivatives of 2-(Furyl-2')benzimidazole



Compound	X	Mp, °C	Formula	N, %		Yield, %	
				Found	Calculated	Method (a)	Method (b)
IIIa	H	206—207	$C_{19}H_{17}IN_2O$	6.36; 6.42	6.72	58	78
IIIb	Cl	188—188,5	$C_{19}H_{16}ClIN_2O$	6.14; 6.18	6.22	69	80
IIIc	Br	204—205	$C_{19}H_{16}BrIN_2O$	5.94; 5.80	5.66	50	83
IIId	I	220—222	$C_{19}H_{16}I_2N_2O$	5.25; 5.32	5.17	56	79
IV		189—190	$C_{24}H_{26}IN_3O$	8.72; 8.60*	8.42	80	87

*Found: I 25.1%, calculated I 25.4%.

ment of the halogen by N-piperidyl causes sharp changes in the positions and intensities of the absorption maxima.

Since 2-(furyl-2')benzimidazole (Ia) has antithelmintic action [9], its 5-halogen substitution products and their derivatives are potentially interesting in this connection.

EXPERIMENTAL

2-(5'-Chlorofuryl-2')benzimidazole (Ib). 8 g (0.04 mole) Cu acetate in 100 ml water was added to 2.16 g (0.02 mole) o-phenylenediamine in 50 ml MeOH, followed by 2.9 g (0.02 mole) 5-chlorofurfural [10,11] in 25 ml MeOH. The mixture was refluxed for 2 hr, then left overnight, the precipitate of copper complex reaction product filtered off, washed with 50 ml MeOH, and suspended in 100 ml 60% EtOH. A vigorous stream of H_2S was passed into the suspension for 2 hr to decompose the complex. Excess H_2S was removed by boiling, and the CuS was filtered off and washed on the filter with 50 ml hot EtOH. The combined filtrate and wash liquid was evaporated to half volume, then highly diluted with water. The precipitate of 2-(5'-chlorofuryl-2')benzimidazole was separated off, as colorless plates.

The bromo and iodo derivatives were prepared similarly. The products are readily soluble in EtOH and acetone, insoluble in water, ether and benzene (Table 1).

1-Benzyl-2-(5'-chlorofuryl-2')benzimidazole (IIb). A mixture of 0.55 g (0.0025 mole) compound **Ib**, 0.1 g NaOH in 2 ml water, and 0.7 g (0.0028 mole) saturated leucotrope O solution was heated for 4 hr on a steam bath, then the dimethylaniline steam distilled off. The residue was rubbed in a mortar with 5% NaOH, separated off, washed with water, and recrystallized from aqueous EtOH. Compounds **IIa**, **IIc**, and **IId** (Table 1) were prepared similarly. They were all soluble in EtOH, acetone, and benzene.

1-Benzyl-2-(5'-chlorofuryl-2')benzimidazole (IIIb). a) A solution of 1.55 g (0.005 mole) compound **IIb** in 15 ml dry benzene and 4 ml MeI was refluxed for 11-12 hr. The solid, which was quaternary salt, was filtered off and washed with benzene.

b) Equimolecular amounts of compound **IIb** and methyl benzenesulfonate were heated together for 30 min at 140°. The melt was dissolved in water and KI added. The methiodide separated out. The compound was identical with that obtained by method (a).

All the methiodides **III** were glistening colorless prisms, soluble in water and EtOH (Table 2).

1-Benzyl-2-(5'-N-pyridylfuryl-2')benzimidazole (IV). A mixture of 0.742 g (0.0015 mole) **IIIa**, 0.25 g (0.003 mole) piperidine, and 2 ml EtOH was heated for 2 hr on a boiling water bath. The **IV** which came down on cooling was filtered off as lemon yellow prisms, soluble in water and EtOH (Table 2).

Compound **IV** was prepared similarly to compounds **IIIb** and **IIId**.

The UV spectra of the compounds were determined with a SF-4 spectrophotometer in MeOH solution.

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