UDC 542.953.4+543.422+547.722+547.78

RESEARCHES IN THE FIELD OF BENZIMIDAZOLE DERIVATIVES XVII*. AZOMETHINES BASED ON 2-AMINOBENZIMIDAZOLES AND FURAN SERIES ALDEHYDES

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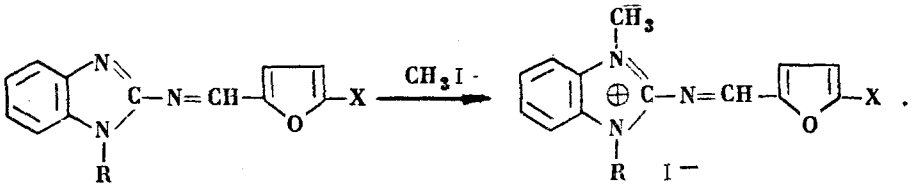
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 1, No. 2, pp. 203-209, 1965

Azomethines containing benzimidazole and furan rings are synthesized from 2-aminobenzimidazoles and 5-substituted furfurals. Some of the resulting azomethines are converted to iodomethylates. The imidazole ring of 2-furfurylideneaminobenzimidazoles has a diminished reactivity to electrophilic reagents because the π-electrons of the imidazole and furan rings are conjugated across an N=CH group.

Products (hydrazones, azomethines, semicarbazones, etc.) of the reaction of furfural derivatives with nitrogen compounds often have a high pharmacological activity [2-4]. In view of this and the biological significance of the benzimidazole system [5], a number of azomethines (I) have been synthesized from certain 2-aminobenzimidazoles and 5-substituted furfurals (cf. also [6]).

Azomethines have been prepared by heating an alcoholic solution of equimolecular amounts of aldehyde and 2-amino derivative (A); addition of a 5-10% aqueous solution of alkali to a solution of the two components in alcohol (B); and grinding aldehyde and 2-aminobenzimidazole with a small amount of 5-10% aqueous alkali (C) [15]. While carrying out the reaction by method A usually requires heating for 1-2 hr, when methods B and C are used the reaction is complete after 15-20 min, even in the cold. Anil yields are 40-75%. Using method A, 5-nitrofurfural readily reacts with 2-aminobenzimidazole, even at room temperature.

The synthetic azomethines are yellow, more rarely red (5-nitro derivatives), soluble in alcohol, and somewhat more difficultly soluble in ether and benzene. All the azomethines are practically insoluble in water, making direct pharmacological investigation impossible. This raises the question of preparing water-soluble derivatives, which must not be hydrochlorides or citrates, since these are readily hydrolyzed in an acid medium. Hence, synthesis of alkyl halide derivatives of azomethines was chosen:



I II

The quaternization of 1-alkyl-2-(furfurylideneamino)benzimidazoles is more difficult than that of 2-aminobenzimidazoles [7, 8]. When alkyl bromides containing two or more carbon atoms (ethyl, propyl) act on azomethines in benzene or xylene, no quaternary compound is formed, even when the solution is boiled for a long time. Only by prolonged heating of the base with excess methyl iodide in xylene was it possible to obtain the corresponding methiodide (II), yield 38-59%. As with 2-aminobenzimidazoles [7, 8], the methyl group adds to the nitrogen hetero-atom of the imidazole ring. This was shown by acid hydrolysis of the methiodides II to 1-ethyl-3-methylbenzimidazoloneimine.

Azomethine methiodides are colorless crystalline substances soluble in water or alcohol on heating.

It did not prove possible to obtain the pharmaceutically more promising 1-ethyl-2-(5'-nitrofurfurylideneamino) benzimidazole methiodide. Heating the base with methyl iodide in a sealed tube or melting it with methyl p-toluenesulfonate results in marked resinification, and most of the starting material is recovered unchanged from the reaction mixture. 1-Ethyl-2-(p-nitrobenzylideneamino)benzimidazole behaves similarly with these reagents**.

The uv absorption spectra of 1-alkyl-2-(furfurylideneamino)benzimidazoles consist of three bands (Fig. 1, Table 2)***. The short-wave band in the region 244-254 mμ usually appears as a shoulder or bend. From its position and the

* For Part XVI see [1].

** It was of interest to investigate alkylation of 1-ethyl-2-benzylidene-aminobenzimidazole. However these compounds could not be synthesized by any of the above methods.

*** The absorption spectra were obtained with a SF-4 spectrophotometer, using methanol solutions containing $1.7-3.9 \cdot 10^{-5}$ mole/*l*.

TABLE 1 N-alkyl-2-furfurylideneaminobenzimidazoles and their methiodides

No.	R*	X*	Compound type	Mp, °C	Crystal form	Crystallizing solvent	Method	Mol. formula	Found, % C	Found, % H	Calculated, % C	Calculated, % H	Yield, %
1	C_2H_5	H	Base	91.5—92	Prisms	Aqueous alcohol	A, C	$C_{14}H_{13}N_3O$	70.43	5.51	70.27	5.48	65—75
2			Methiodide	241—242	Prisms	Acetone	—	$C_{15}H_{16}IN_3O$	47.49	4.22	47.25	4.23	42
3	C_2H_5	Cl	Base	123.5—124	Prisms	Aqueous alcohol	Б	$C_{14}H_{12}ClN_3O$	61.49	4.47	61.43	4.42	69
4			Methiodide	243—244	Prisms	Alcohol + ether	—	$C_{15}H_{15}ClIN_3O$	43.12	3.55	43.34	3.64	38
5	C_2H_5	Br	Base	128—129	Needles	Aqueous alcohol	A, C	$C_{14}H_{12}BrN_3O$	52.66	4.00	52.67	3.80	40—76
6			Methiodide	242—243	Prisms	Alcohol + ether	—	$C_{15}H_{15}BrIN_3O$	38.95	3.31	39.16	3.29	59
7	C_2H_5	I	Base	151.5—152.5	Needles	Alcohol	Б	$C_{14}H_{12}IN_3O$	46.13	3.24	46.04	3.31	69
8			Methiodide	246—247.5	Plates	Alcohol	—	$C_{15}H_{15}I_2N_3O$	35.23	3.08	35.52	2.98	50
9	C_2H_5	NO_2	Base	174—175	Prisms	Benzene	A	$C_{14}H_{12}N_4O_3$	59.37	4.28	59.15	4.25	59
10	$(CH_3)_2CH$	I	Base	179—180	Needles	Alcohol	A	$C_{15}H_{14}IN_3O$	47.48	3.72	47.51	3.72	57
11	C_6H_5	H	Base	164.5—165	Plates	Aqueous alcohol	Б	$C_{18}H_{13}N_3O$	74.56	4.71	74.87	4.54	70

* In formulas I-III.

independence of substituents in the furan ring, it can be related to electron transitions localized in the imidazole ring of the molecule [1, 9]. This band is distinctly suppressed as compared with the same band for 2-aminobenzimidazoles [10, 11] or alkylbenzimidazoles [1]. This is due to conjugation of the imidazole and furan rings across the N=CH group.

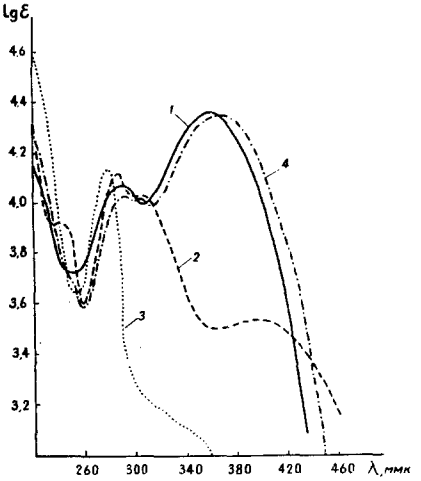


Fig. 1. Absorption spectra of 2-(furfurylideneamino)-1-alkylbenzimidazoles: 1) 2-(furfurylideneamino)-1-ethylbenzimidazole; 2) 2-(5-nitrofurfurylideneamino)-1-ethylbenzimidazole; 3) 2-(furfurylideneamino)-1-ethylbenzimidazole methiodide; 4) 2-(5-chlorofurfurylideneamino)-1-ethylbenzimidazole.

The selective absorption in the 290-330 mμ region is reminiscent of the bathochromic displacement of the B band of N-substituted benzimidazoles [9, 12]. However, the much greater intensity and broadening of the band, accompanied by formation of 2 maxima (289-297 and 305-317 mμ) when substituents (nitro, halogen) are introduced, indicates the superposition of two electronic transitions in this region: the B bands of benzimidazole and electronic transitions embracing the aldehyde component and the azomethine bond. A similar band (usually related to type E_2) is found in the spectra of benzanils [13].

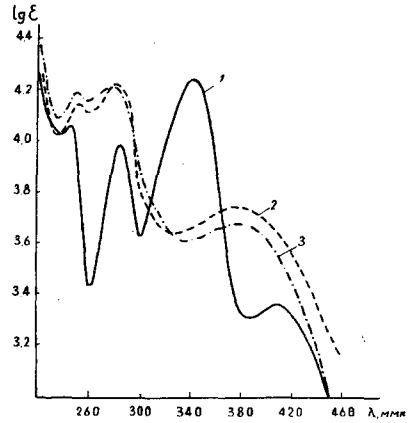


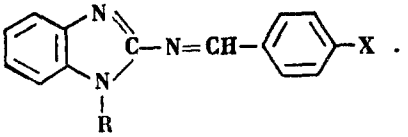
Fig. 2. Absorption spectra of 2-(benzylideneamino)benzimidazoles: 1) 2-(p-dimethylaminobenzylideneamino)-1-benzylideneimidazole; 2) 2-(p-nitrobenzylideneamino)-1-ethylbenzimidazole; 3) 2-(p-nitrobenzylideneamino)-1-benzylideneimidazole.

No doubt the long-wave absorption, a very intense, wide maximum in the 360-400 mμ region, is due to oscillation of π-electrons along the entire system of conjugated bonds (K band). Bands of this type are found with all azomethines [13], aromatic azo compounds, azoxy compounds [14], etc. Halogens in the α position in the furan ring cause a moderate bathochromic shift of the K band (Cl, +8 mμ, Br, +8 mμ, I +15 mμ), while the nitro groups shift it 40 mμ into the red region. Moreover, in 1-ethyl-2-(5'-nitrofurfurylideneamino)benzimidazole the strong bathochromic K band shift is accompanied by a sharp drop in intensity.

The K band is absent from the absorption spectra of 1-ethyl-2-furfurylideneaminobenzimidazoles (Fig. 1), and the absorption curve for them is reminiscent of that of 1, 3-dialkylbenzimidazoloneimines [15]. Evidently the presence of a positive charge in the imidazole ring definitely hinders its π-electrons from participating in conjugation with the π-electrons of the furan ring.

The uv spectra of 1-alkyl-2-benzylideneaminobenzimidazoles (III) also consist of three similar absorption bands (Fig. 2). As usual [16], replacement of a furan by a benzene ring promotes hypsochromic shift of the K and E_2 bands. Replacement of the electron-donating dimethylamino- group in the aldehyde com-

ponent of these compounds by the electron-accepting nitro group gives rise to bathochromic and hypsochromic effects in the K band, which, as seen above, is also observed in azomethines with a furan ring:



III

The uv spectrum of 1-benzyl-2-p-dimethylaminobenzylideneaminobenziminazole[§] is also found to have a less intense (log ε 3.37) absorption band in the 405-410 mμ region, which evidently characterizes the n → π* electronic transition (R band).

Thus, review of the electronic absorption spectra of azomethines I and III shows that in these compounds the π-electrons of the imidazole ring are involved in conjugation with the furan (or benzene) ring across the N=CH group. Because of this the nucleophilicity of the imidazole ring, and consequently its tendency to quaternization as compared with 2-aminobenzimidazoles, is decreased. When a nitro group is present in the aromatic ring of the aldehyde moiety, the basicity of the azomethines is lowered to such an extent that methylation does not occur, even under drastic conditions.

In both 1-alkyl-2-furfurylideneaminobenzimidazoles and 2-aminobenzimidazoles the lone pair of electrons is conjugated with the π-electrons of the imidazole ring (see also [17]). Hence the pyridine nitrogen hetero-atom undergoes alkylation.

TABLE 2

Absorption spectra of azomethines and their methiodides

No.	In formulas, I, II, III		λmax (lgε)		
	R	X	I_m band	B, E_2 bands	K band
1	C_2H_5	H	252 (3.74)	290 (4.07)	360 (4.35)
2	Methiodide		247 (3.68)	277 (4.15)	—
3	C_2H_5	Cl*	—	296 (3.97) 306 (3.96)	369 (4.38)
4	C_2H_5	Br	254 (3.46)	292 (4.04) 308 (4.03)	368 (4.34)
5	Methiodide		—	277 (4.13) 283 (4.11)	—
6	C_2H_5	J	254 (3.46)	297 (3.86) 317 (4.02)	375 (4.39)
7	C_2H_5	NO_2	244 (3.93)	289 (4.13) 306 (4.03)	400 (3.54)
8	C_2H_5	NO_2	252 (4.16)	283 (4.21)	376—377 (3.74)
9	$CH_2C_6H_5$	NO_2	252 (4.19)	282 (4.22)	376—377 (3.67)
10	$CH_2C_6H_5$	$N(CH_3)_2$	245 (4.07)	284 (4.00)	342 (4.25)

* In octane.

The methiodides of 1-ethyl-2-furfurylideneaminobenzimidazole, 1-ethyl-2-(5'-bromofurfurylideneamino)benzimidazole, and 1-ethyl-(5'-iodofurfurylideneamino)benzimidazole have, at concentrations of 500 and 2500 γ/ml, a slight action against Staphylococcus aureus and the hay bacillus. The compounds are inactive against typhoid and enteric bacteria and yeast-like organisms of the genus Candida (G. R. Finn).

EXPERIMENTAL

Below are given typical procedures for preparing 2-furfurylideneaminobenzimidazoles by each of the three methods mentioned above.

A. 2-Ethyl-2-furfurylideneaminobenzimidazole. A solution of 1 g furfural and 1.6 g 2-amino-1-ethylbenzimidazole in 15 ml alcohol is boiled for 3 hr. The alcohol is distilled off, and the oily dark-brown residue is placed over potassium or sodium hydroxide in a desiccator. After 24 hr the semicrystalline mass is crystallized from aqueous alcohol, to give yellow crystals of azomethine melting at 91.5-92°, yield 65%. In preparing the 2-(5'-nitrofurfurylideneamino) derivative, the reaction product separates directly from the reaction mixture.

§ Thanks are due to Yu. M. Yutilov for supplying the 1-benzyl-2-p-dimethylaminobenzylideneaminobenzimidazole.

B. 1-Ethyl-2-(5'-chlorofurfurylideneamino)benzimidazole. A 5% aqueous solution of potassium hydroxide is added dropwise with stirring to a solution of 0.32 g of 2-amino-1-ethylbenzimidazole and 0.26 g 5-chlorofurfural in 3 ml alcohol. A yellow oil comes out at the junction of the solutions of alkali and organic reactants, crystallizing upon further addition of alkali. In all, about 3 ml alkali solution are added. After two hours the material is filtered off with suction, and washed with water and a small amount of alcohol. The compound is dried over potassium hydroxide in a desiccator. Yield 69%, yellow needles (from aqueous alcohol), mp 123.5-124°.

C. 1-Ethyl-2-(5'-bromofurfurylideneamino)benzimidazole. A mixture of 0.32 g 2-amino-1-ethylbenzimidazole, 0.35 ml 5-bromofurfural, and 1-1.5 ml 5-10% aqueous potassium hydroxide solution is triturated for a few minutes. Sometimes the mixture has to be heated slightly to speed up the reaction. There ensues a gradual yellowing of the reaction mass and formation of azomethine crystals. These are separated and washed with water. Yield 76%, yellow needles (from aqueous alcohol), mp 128-129°.

1-Ethyl-2-furfurylideneaminobenzimidazole methiodide. A solution of 0.01 mole of the azomethine and 20-30 ml dry xylene is boiled with 3-5 ml methyl iodide for 4-6 hr. The ppt formed is separated, washed with benzene, and crystallized, using activated carbon.

Hydrolysis of methiodides. A solution of methiodide in dilute hydrochloric acid is boiled for 30 min, the resultant 5-substituted furfural is extracted with ether, and the aqueous layer first neutralized with ammonia and then treated with an alcoholic solution of picric acid. A picrate melting at 163-164° separates and is found to be identical with the picrate of 1-methyl-3-ethylbenzimidazoloneimine [8].

1-Ethyl-2-(p-nitrobenzylideneamino)benzimidazole is prepared in the same way as 1-benzyl-2-(p-nitrobenzylideneamino)benzimidazole [18]. Yield 68%, orange needles (from alcohol) mp 178°. Found: C 65.17; H 4.67%, calculated for $C_{16}H_{14}N_4O_2$: C 65.29; H 4.79%.

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9 December 1963

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