ON BENZIMIDAZOLES. VIII.*

PREPARATION AND PROPERTIES OF 2-PHENYLFURYLBENZIMIDAZOLES

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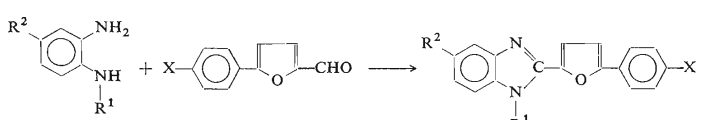
Cyclization of 1,2-phenylenediamine,4-nitro-1,2-phenylenediamine, and 4-nitro-2-amino-N-methylaniline with 5-(4-X-phenyl)-2-furaldehydes was used to synthesize a series of 2-(5-(4-X-phenyl)-2-furyl)-, 2-(5-(4-X-phenyl)-2-furyl)-5(6)-nitro- and 1-methyl-2-(5-(4-X-phenyl)-2-furyl)-5-nitrobenzimidazoles where X is H, CH_3, OCH_3, Cl, Br, and NO_2. Their electronic spectra are discussed.

As a continuation of our previour work[1], which dealt with the preparation of 2-phenyl- and 2-furyl-substituted benzimidazoles, we prepared a series of phenylfuryl-substituted benzimidazoles with the aim to investigate their physico-chemical and biological properties, especially with regard to depigmentation effect towards *Euglene gracilis*[2]. In the synthesis we made use of the cyclization of corresponding 1,2-phenylenediamines with appropriate substituted phenyl-2-furaldehydes in nitrobenzene[3] or aqueous–ethanolic medium in the presence of cupric acetate:



$X = H, CH_3, CH_3O, Cl, Br, NO_2$
$R^1 = H, CH_3, R^2 = H, NO_2$

The 2-(5-(4-X-phenyl)-2-furyl)-, 2-(5-(4-X-phenyl)-2-furyl)-5,6-nitro-, and 1-methyl-2-(5-(4-X-phenyl)-2-furyl)-5-nitrobenzimidazoles prepared, their physical constants and analyses are recorded in Table I. Benzimidazoles of the first series, except compound *VI*, are colourless, nitrobenzimidazoles of the other two series are yellow. They dissolve only in highly polar solvents. 4-Nitro-1,2-phenylenediamine and

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TABLE I

Properties of Prepared Compounds

Number X	Formula (m.w.)	Calculated/Found % C	% H	% N	M.p., °C (yield, %)	Solubility in water M . 10^{-6}
		2-(5-(4-X-phenyl)-2-furyl)benzimidazoles				
I	$C_{17}H_{12}N_2O$	78·53	4·62	10·77	221—223	1·60
H	(260·3)	78·41	4·58	10·77	(76)	
II	$C_{18}H_{14}N_2O$	78·92	5·12	10·21	217—219	0·53
CH_3	(274·3)	79·11	5·08	9·95	(56·5)	
III	$C_{18}H_{14}N_2O_2$	74·55	4·82	9·65	262—263	0·64
CH_3O	(290·3)	74·42	4·76	9·92	(62)	
IV	$C_{17}H_{11}ClN_2O$	69·23	3·73	9·58	225	0·45
Cl	(295·5)	69·32	3·61	9·67	(70·5)	
V	$C_{17}H_{11}BrN_2O$	60·18	3·24	8·26	269	0·23
Br	(340·2)	60·18	3·03	8·11	(68·5)	
VI	$C_{17}H_{11}N_3O_3$	66·88	3·61	13·77	271—273	1·92
NO_2	(305·3)	66·83	3·78	13·61	(78)	
		2-(5-(4-X-phenyl)-2-furyl)-5-nitrobenzimidazoles				
VII	$C_{17}H_{11}N_3O_3$	66·88	3·61	13·77	229—231	4·89
H	(305·3)	66·92	3·48	13·67	(52)	
VIII	$C_{18}H_{13}N_3O_3$	67·71	4·07	13·17	231—233	1·00
CH_3	(319·3)	67·63	3·92	13·17	(65)	
IX	$C_{18}H_{13}N_3O_4$	64·75	3·88	12·53	234—236	1·94
CH_3O	(335·3)	64·51	3·59	12·41	(56·5)	
X	$C_{17}H_{10}ClN_3O_3$	60·09	2·65	10·94	268—270	0·40
Cl	(339·7)	59·91	2·73	11·07	(62)	
XI	$C_{17}H_{10}BrN_3O_3$	53·12	2·60	10·94	281—283	0·50
Br	(384·2)	53·41	2·73	11·07	(60)	
XII	$C_{17}H_{10}N_4O_5$	58·25	2·86	16·05	348—350	0·75
NO_2	(350·3)	57·90	2·85	16·36	(65·5)	
		1-methyl-2-(5-(4-X-phenyl)-2-furyl-5-nitrobenzimidazoles				
XIII	$C_{18}H_{13}N_3O_3$	67·71	4·07	13·17	238—239	0·54
H	(319·3)	67·45	4·18	13·06	(73·5)	
XIV	$C_{19}H_{15}N_3O_3$	68·51	4·51	12·61	225—227	0·61
CH_3	(333·3)	68·67	4·54	12·48	(82)	
XV	$C_{19}H_{15}N_3O_4$	65·48	4·29	12·03	243—244	0·88
CH_3O	(349·3)	65·20	4·09	12·10	(86)	
XVI	$C_{18}H_{12}ClN_3O_3$	61·10	3·39	11·88	207—209	0·39
Cl	(353·3)	61·31	3·31	11·67	(76)	
XVII	$C_{18}H_{12}BrN_3O_3$	54·28	3·01	10·55	248—250	0·74
Br	(398·2)	54·32	3·08	10·53	(78)	
XVIII	$C_{18}H_{12}N_4O_5$	59·35	3·29	15·38	276—277	0·60
NO_2	(363·3)	59·41	3·20	15·50	(65)	

4-nitro-2-amino-N-methylaniline used in cyclisation were prepared by partial reduction of appropriate dinitro compounds by hydrogen sulphide in ammonia-ethanolic medium[4-6]. 5-(4-X-Phenyl)-2-furaldehydes were obtained by Merwein arylation of 2-furaldehydes by appropriate diazonium salts[7,8]. The synthesis of benzimidazoles consisted in preparing corresponding Schiff base in ethanol, its isolation and cyclization in nitrobenzene (derivatives *IV*, *V* and *VII–XVIII*). Compound *V* was prepared by a modified procedure, using pyridine, the Schiff base was not isolated, but directly cyclized by adding nitrobenzene. Derivatives *I–III* were obtained according to Weidenhagen[4], since in the presence of nitrobenzene the cyclization is accompanied by extensive polymerization of the products.

In the previous work we reported that 2-furyl-5-(6)-nitro- and 2-furyl-5(6)-aminobenzimidazoles, due to formation of intramolecular hydrogen bond between the imine hydrogen of benzimidazole and lone electron pair of the furan ring oxygen, have two distinctly different melting points. This indicates that in compounds of this type there are structural conditions for the existence of 5-nitro-2-furyl- and 6-nitro-2-furylbenzimidazoles. With analogous compounds *VII–XII* (Table I), which contain in the 2-benzimidazole position the arylfuran in place of the furan portion, this phenomenon has not been observed. All the compounds have only one melting

TABLE II

UV Spectra of Prepared Compounds

Number	λ_{max}, nm[a]; (log ε)					
I	221 (4·41)	i 238 (3·98)	271 (4·00)	335 (4·58)	345 (4·65)	364 (4·45)
II	i 222 (4·47)	i 238 (4·09)	277 (4·13)	i 343 (4·65)	352 (4·70)	371 (4·51)
III	222 (4·55)	238 (4·22)	274 (4·23)	338 (4·79)	348 (4·85)	367 (4·66)
IV	225 (4·31)	i 239 (4·01)	275 (4·08)	340 (4·61)	350 (4·68)	360 (4·49)
V	i 225 (4·31)	i 241 (3·94)	276 (4·04)	342 (4·54)	352 (4·62)	372 (4·42)
VI	i 217 (4·30)	245 (3·92)	307 (4·19)	—	—	379 (4·45)
VII	219 (4·02)	239 (4·04)	256 (4·05)	317 (4·29)	—	372 (4·39)
VIII	219 (4·25)	241 (4·13)	258 (4·42)	321 (4·35)	—	376 (4·46)
IX	i 218 (4·33)	—	262 (4·03)	327 (4·42)	—	384 (4·55)
X	222 (4·27)	239 (4·17)	259 (4·18)	321 (4·39)	—	372 (4·51)
XI	223 (4·24)	242 (4·15)	262 (4·17)	325 (4·38)	—	379 (4·61)
XII	217 (4·21)	239 (4·19)	287 (4·16)	—	—	392 (4·56)
XIII	220 (4·19)	i 240 (4·07)	260 (4·16)	328 (4·40)	—	366 (4·38)
XIV	219 (4·21)	240 (4·11)	259 (4·21)	329 (4·42)	342 (4·42)	366 (4·43)
XV	i 219 (4·12)	—	263 (4·19)	346 (4·33)	—	373 (4·34)
XVI	224 (4·19)	i 239 (4·12)	261 (4·20)	327 (4·44)	347 (4·44)	364 (4·46)
XVII	223 (4·18)	239 (4·10)	261 (4·20)	329 (4·43)	348 (4·44)	362 (4·55)
XVIII	219 (4·10)	241 (4·14)	288 (4·16)	—	—	373 (4·45)

[a] i = inflex.

point. This fact can be attributed either to increased aromaticity of the furan ring due to the aryl group present, or to unfavourable orientation of the arylfuran portion of the molecule in crystalline state.

The electronic spectra of all the compounds under study are complex and show 6 to 7 absorption bands (Table II). This is not surprising when one compares the structure of these compounds *e.g.* with 2-(5-X-furyl-2-)-5-nitrobenzimidazole[9,10], *i.e.* with the compound not containing the aryl group in the 5 position of the furan ring. The electronic spectra of these compounds show 4 absorption maxima. The presence of phenyl in the 5 position of the furan ring therefore substantially modifies the electronic spectra. The compounds studied all show two absorption maxima in the region around 205 nm and 220 nm; the former corresponds to π–π^* transitions which are similar to the 2nd band of benzene and the latter to electronic transitions in the furan ring (with 5-phenylfural this band occurs at 222 nm). The absorption band in the 238–242 nm region can be assigned to the electronic transitions localized in the imidazole ring which induce polarization of the C=N bond[11]. The position of this band is practically constant, which indicates that the band is little affected by the nature of substituents. Another maximum, occurring in the 256–277 nm region, can be ascribed to electronic transitions for the benzenoid system modified by the amidic chromophor[11]. This band is strongly influenced especially by the nitro group (derivatives *VI*, *XII*, and *XVIII*), in which case it suffers bathochromic shift. From comparison of these bands for individual series of the compounds studied it follows that in the case of 2-(5-(4-X-phenyl)-2-furyl)benzimidazoles it is bathochromically shifted by 10–20 nm. This fact can be explained by the presence of the nitro group in the 5 position of benzimidazole[11]. It is known[1,11] that 2-substituted (phenyl-, furyl-, thienyl- and similar)benzimidazoles show absorption band in the region of 312–355 nm which can be assigned to electronic transitions in an arylideneimidinic system. Similar absorption bands are observed with all the compounds studied, except for the nitro derivatives (*VI*, *XII*, and *XVIII*) where this band overlaps with other bands to give a broad band at 373–392 nm which presumably includes also the arylfurfurylideneimidinic chromophor. Broad absorption bands with maxima above 340 nm correspond to the oscillations of π-electrons over the whole conjugated system. Most compounds of the first (*I*–*VI*) and the third (*XIII*–*XVIII*) series show two maxima in this region, namely at 342–252 nm and 360–389 nm.

EXPERIMENTAL

Synthesis

A) A solution of 5-aryl-2-furaldehyde (0·025 mol) and 1,2-phenylenediamine (0·025 mol) in ethanol (50 ml) was refluxed 1·5–2 h. After cooling the mixture to room temperature, the Schiff base formed was filtered with suction, dried and then introduced to boiling nitrobenzene (20 ml). After 15 min refluxing, the mixture was cooled, the precipitate of benzimidazole was filtered

with suction, washed on filter successively with ethanol and ether, and recrystallized from an appropriate solvent. Compounds *XIII—XVIII* were prepared using pyridine (in place of ethanol) as solvent, in which 4-nitro-2-amino-N-methylaniline is very soluble. In this case the Schiff base formed was not isolated but directly cyclized by adding nitrobenzene and refluxing the mixture.

B) A solution of 1,2-phenylenediamine (0·1 mol) in ethanol (500 ml) was mixed with a solution of cupric acetate (36·3 g, 0·2 mol) in water (400 ml) and then an appropriate 5-aryl-2-furaldehyde was added with stirring. The mixture was refluxed 5 h with stirring, cooled and the cuprous salt formed was filtered with suction, suspended in methanol (500 ml) and decomposed by a strong stream of hydrogen sulphide while hot. The benzimidazole so released was filtered with suction and recrystallized from an appropriate solvent.

Spectral Measurements

Electronic absorption spectra in the near ultraviolet region were recorded with Specord UV VIS spectrophotometer. Ethanolic solutions ($2{\cdot}5-5 \cdot 10^{-5}$ M) of the compounds were measured in 1 cm thick cells. The accuracy of the measurements was ± 1 nm.

For all the compounds studied their solubility in water was determined spectrophotometrically, by saturation according to the method described in ref.[12]. The obtained values in M/l are recorded in Table I.

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