ON BENZIMIDAZOLES. VII.*

PREPARATION AND PROPERTIES OF 2-(5-X-2-FURYL)-5(6)-SUBSTITUTED BENZIMIDAZOLES

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The preparation and the ultraviolet spectra of twelve 5(6)-nitro-, or 5(6)-amino-2-(5-X-2-furyl)-benzimidazoles, where X = H, CH_3, Cl, Br, J, $COOCH_3$, is described. The question of the existence of 5-, or 6-nitro-2-furyl-substituted benzimidazoles was also investigated on the basis of the transformation of their structure and by means of deuteriations and infrared spectroscopy in the 3400–3150 cm^{-1} region.

In papers[1–7] we have described the preparation and the study of the physicochemical and biological properties[8] of series of differently substituted benzimidazole derivatives in which the imino hydrogen of the imidazole cycle was substituted by an aryl or alkyl residue. In view of the fact that benzimidazoles contain an acid hydrogen it interested us to learn whether in the case of 2-furyl-5(6)-X-substituted benzimidazoles an interaction between the imino hydrogen of benzimidazole and the oxygen of the furan nucleus takes place. The justification of this assumption follows from the chemical nature of furan and its derivatives. The proton accepting properties of the furan oxygen are evident from the intramolecular bond of the hydroxyl group hydrogen of furyl alcohol with the oxygen of the furan nucleus[9], and the intramolecular bond with the pyrrole nucleus hydrogen[10]. On the other hand the formation of an intramolecular bond through imino hydrogen was observed in 2-phenylbenzimidazoles which contain in *o*-positions a group with free electron pairs[11,12] (OH, NH_2). Therefore, it could be expected that if such an interaction should be observed also in 2-furyl-5(6)-X-substituted benzimidazoles, it would affect its mobility during the tautomeric shift.

For the synthesis of 5(6)-nitrobenzimidazoles described in this paper, of several possible routes the Weidenhagen method[5,13] was utilised, consisting in the condensation of the appropriately substituted 1,2-diaminobenzene with aldehydes and subsequent oxidation of Schiff's base with copper(II) acetate. The corresponding 5(6)-

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aminobenzimidazoles were obtained on reduction of nitro compounds with stannous chloride in hydrochloric acid.

EXPERIMENTAL

Synthesis of 2-(5-X-2-Furyl)-5(6)-nitrobenzimidazoles

To a suspension of 4-nitro-1,2-diaminobenzene (23 g, 0·15 mol) and 5-substituted furaldehyde (0·17 mol) in methanol (500 ml) cupric acetate (60 g, 0·3 mol) in 500 mol of water was added and the mixture was heated on a water bath under stirring for 3 hours. After cooling the copper benzimidazole salt formed was filtered off under suction, washed with water and suspended in 600 ml of 95% ethanol. Hydrogen sulfide vas introduced into this suspension, gently boiled, for one hour. The hot reaction mixture was filtered, boiling water was added to the filtrate to incipient turbidity and then allowed to crystallise (Table I).

Synthesis of 2-(5-X-2-Furyl)-5(6)-aminobenzimidazoles

5(6)-Nitrobenzimidazole derivative (0·05 mol) and $SnCl_2.2\,H_2O$ (33·8 g, 0·15 mol) were suspended in 75 ml of hydrochloric acid. The temperature of the stirred solution increased spontaneously to 80—90°C and the nitro compound passed into solution. After 15—20 minutes the complex stannic salt began to separate which at the end of the reaction (3—4 h) filled the whole flask. If the temperature does not increase spontaneously, the reaction mixture should be heated at 80—90°C. After cooling the reaction mixture the complex salt was filtered off, washed with conc. hydrochloric acid, and dissolved in a small volume of water. After pH was adjusted to 2, hydrogen sulfide was introduced into the cold solution for 30 minutes. The formed sulfide is filtered off and the amine is precipitated from the filtrate on addition of sodium carbonate solution (pH 6·5). The precipitate formed is filtered off, washed with water, and dried. The dry precipitate is well powdered and extracted with toluene in a Soxhlet apparatus (Table I).

2-Furyl-5(6)-nitrobenzimidazole-[1-D]

To a solution of potassium (0·58 g; 0·015 g-atom) in methanol (50 ml) 3·5 g (0·015 mol) of 2-furyl-5(6)-nitrobenzimidazole (m.p. 212—214 and 222—224°C) were added and the formed potassium salt of benzimidazole was allowed to pass into solution. The red solution was filtered and the filtrate evaporated to dryness. The potassium salt was dried at 100°C and then dissolved in excess D_2O (99·87%). Soon yellow crystals of the deuteriated compound began to precipitate; m.p. 154—156°C.

Spectral Measurements

The infrared absorption spectrum of 2-furyl-5(6)-nitrobenzimidazole was measured on a Unicam SP-100 spectrophotometer in chloroform which was purified from ethanol by double filtration through a column filled with blue silica gel. The calibration of the apparatus was made using a polystyrene foil. The IR spectrum of 2-furyl-5(6)-nitrobenzimidazole-[1-D] was measured on the same apparatus in deuteriochloroform (99·5%). For the weak solubility of the substances their saturated solutions were measured in KBr cells of 1 mm strength. Electronic absorption spectra in the near UV region of both series of the investigated substances were measured on an ultraviolet spectrophotometer ORD/UV — 5, Jasco, Tokyo. The measurements were carried out in 1 cm cells in 95% ethanol. The concentrations of the substances varied in the range 0·029 to 0·062 mg/ml. The accuracy of the measurements was ± 1 nm.

RESULTS AND DISCUSSION

The newly synthetised 2-(5-X-2-furyl)-5(6)-nitro or 5(6)-aminobenzimidazoles, their physical constants and elemental analyses are given in Table I. 5(6)-Nitrobenzimidazoles are yellow to orange, poorly soluble in non-polar solutions.

TABLE I
Properties of the Benzimidazole Derivatives

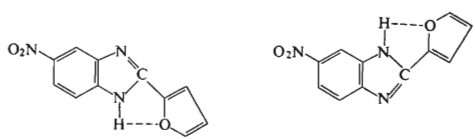
X	Formula (mol. w.)	Calculated/Found % C	% H	% N	M.p., °C	Yield, % (solvent)
		2-(5-X-2-Furyl)-5(6)-nitrobenzimidazoles				
H	$C_{11}H_7N_3O_3$	57·66	3·08	18·34	212—214	65
	(229·1)	57·72	3·15	18·39	222—224	(ethanol)
CH_3	$C_{12}H_9N_3O_3$	59·28	3·78	17·27	231—232	61
	(243·1)	58·97	3·62	17·16	239—240	(ethanol)
Cl	$C_{11}H_6ClN_3O_3$	50·13	2·29	15·95	241—242	65
	(263·5)	49·80	2·43	15·94	252—254	(ethanol)
Br	$C_{11}H_6BrN_3O_3$	42·88	1·96	13·64	258—259	62
	(308·1)	43·49	1·90	13·68	274—276	(ethanol)
J	$C_{11}H_6JN_3O_3$	37·20	1·70	11·83	109—118	66
	(355·1)	37·66	1·82	11·73		(ethanol)
$COOCH_3$	$C_{13}H_9N_3O_5$	54·36	3·15	14·62	241—243	85
	(287·2)	53·92	3·10	14·53	253—254	(ethanol)
H[a]	$C_{11}H_7N_3O_2S$	53·98	2·98	17·05	113—114	67
	(245·2)	54·35	3·19	16·93		(ethanol)
		2-(5-X-2-Furyl)-5(6)-aminobenzimidazoles				
H	$C_{11}H_9N_3O$	66·32	4·55	21·08	227—228	75
	(199·2)	66·74	4·63	21·03	240—242	(toluene)
CH_3	$C_{12}H_{11}N_3O$	67·57	5·20	19·72	250—251	58
	(213·1)	67·45	5·34	19·90	262—263	(toluene)
Cl	$C_{11}H_8ClN_3O$	56·54	3·45	18·00	198—205	53
	(233·7)	56·82	3·61	17·99		(toluene)
Br	$C_{11}H_8BrN_3O$	47·50	2·90	15·11	211—212	64
	(278·1)	48·07	2·76	15·21	224—226	(toluene)
J	$C_{11}H_8JN_3O$	40·63	2·48	12·91	108—109	55
	(325·1)	40·25	2·34	12·81	118—119	(toluene)
$COOCH_3$	$C_{13}H_{11}N_3O_3$	60·69	4·31	16·32	152—153	60
	(257·2)	61·03	4·25	16·27	167—168	(ethanol)

[a] 2-Thienyl-5(6)-nitrobenzimidazole.

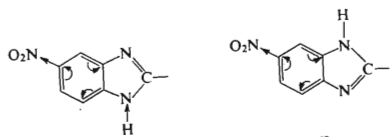
From Table I it is evident that all 2-furyl-5(6)-nitro- and 2-furyl-5(6)-aminobenzimidazoles are characterised by a double melting point. Two melting temperatures are consistently found even after several crystallisations of completely pure substances; it was impossible to prepare samples with a single melting point. The differences between the two melting temperatures are in the range of 8°C to 17°C and they change with the change of the solvent from which they were crystallised. When the melting points were determined on a Kofler block a part of the crystals melted within a narrow temperature range and the remaining part of the crystals melted completely again within a narrow range at a higher temperature. The elemental analysis showed that the substances were pure. The existence of two melting points may be tentatively explained either by the existence of several crystal modifications (polymorphy; improbable, because in spite of the change of the structure of the substances two melting points persisted), or by isomerism. Numerous attempts at the preparation of two isomers of benzimidazoles substituted in benzene nucleus were unsuccessful in consequence of the tautomerism of the amino hydrogen. For example, the reductive cyclisation of 3-nitro-4-acetamidobenzoic acid and 4-nitro-3-acetamidobenzoic acid with tin in hydrochloric acid gave an identical derivative, *i.e.* 2-methylbenzimidazole-5(6)-carboxylic acid[14]. Similar results were obtained also by other authors[15,17] even when cyclisation was carried out in a neutral medium[18].

In benzimidazoles described in this paper the position 2 of the imidazole cycle is connected with the furan nucleus which enables the formation of an intramolecular hydrogen bond between the amino hydrogen of benzimidazole and the free electron pair of the furan oxygen. Thus, the structural requirements are fulfilled for the independent existence of 5-nitro-2-furyl- and 6-nitro-2-furylbenzimidazole in consequence of the fact that hydrogen may be retained either on one or on the other nitrogen atom. In consequence of the formation of the hydrogen bond, free rotation of the furan nuclei around the single C—C- bond in the position 2 of benzimidazole is not possible.

The hydrogen bonds between the imino hydrogen of benzimidazole and the oxygen of furan nucleus cannot be energetically equivalent in both isomers because the effect



SCHEME 1



I *II*

SCHEME 2

of the nitro group on the acidity of the imino hydrogen will be different. In 5-nitro derivative *I* the NO_2 group is in *para*-position with respect to the N—H grouping while in 6-nitro derivative *II* it is in *meta*-position.

However, the five-membered cycle formed in consequence of the intramolecular hydrogen bond is labile, which impairs the isolation of single isomers. Attempts at separation of the supposed isomers were carried out with 5(6)-nitro-2-furylbenzimidazole by chromatography on alumina (activity II, according to Brockmann) in methanol–benzene 1 : 9, as well as by fractional crystallisation from ether and chloroform. Chromatographic separation was not successful, but the reaction course was interesting. For the separation 5(6)-nitro-2-furylbenzimidazole was taken, m.p. 212—214°C and 222—224°C; during column chromatography eluates were analysed by thin-layer chromatography and it was found that the R_F value of the eluates remained unchanged. As a more polar solvent methanol was used. Therefore, it was supposed that one of the isomers remained bound onto the column filling. However, when the filling was eluted with ethanol and the eluate evaporated no benzimidazole was obtained. As the substance in all eluates had identical R_F value the eluates were combined, diluted with water, and the m.p. of the precipitated benzimidazole determined: 226—227°C. Benzimidazole having this melting point was recrystallised from boiling ethanol. The formed crystals again had a double melting point. On prolonged extraction of 5(6)-nitro-2-furylbenzimidazole with cold ether benzimidazole of m.p. 214·5 to 217°C was obtained.

In order to explain the existence of the two forms of 2-furylbenzimidazoles substituted in the benzene nucleus we also prepared 2-furyl-5(6)-nitrobenzimidazole-[1-D]. We were interested to learn whether the deuteriated product would display two melting points and whether this change would be discernible in the IR spectra. For the preparation of 2-furyl-5(6)-nitrobenzimidazole-[1-D] the observed fact has been made use of, that the potassium salt of 2-furyl-5(6)-nitrobenzimidazole, soluble in cold water, very rapidly hydrolyses in H_2O to the corresponding insoluble benzimidazole.

Hydrolysis in water in the cold gave benzimidazole with one melting point 226—228°C. However, when this imidazole was recrystallised from boiling 50% ethanol, the double melting point reappeared. From this it can be concluded that the more labile isomer is formed on addition of a certain amount of thermal energy during crystallisation from the hot solvent. Deuteriated benzimidazole prepared on hydrolysis of the potassium salt of 2-furyl-5(6)-nitrobenzimidazole in D_2O in the cold, had only one melting temperature, 154—156°C.

In the IR spectra of all 5(6)-nitro- and 5(6)-aminobenzimidazoles a broad absorption band of the intramolecular hydrogen bond[19] appears in the 3400—3150 cm^{-1} region in addition to the characteristic bands for the imidazole and furan cycles[6], and the bands of corresponding functional groups. The position and the shape of this band is approximately equal for all benzimidazoles (maximum of 2-furyl-5(6)-nitrobenzimidazole at ~3200 cm^{-1}, in the deuteriated analog maximum at ~2260 cm^{-1}). The study of this question by means of IR spectroscopy meets with grave difficulties, because benzimidazoles are very poorly soluble in unpolar solvents. We therefore investigated the substances with a modified structure: *a*) furan oxygen was substituted by sulfur; *b*) iminohydrogen of benzimidazole was substituted by

deuterium or by a methyl group. The preparation and the isolation of 2-thienyl-5(6)-nitrobenzimidazole is carried out in the same manner as for 2-furyl-5(6)-substituted benzimidazoles. This benzimidazole has a single melting point, 113–114°C. Similar to deuteriated 2-furyl-5(6)-nitrobenzimidazole, all 1-methyl-2-(5-X-furyl)-5(6)-nitro- and 5-aminobenzimidazoles also had a single melting point[6]. From this it can be judged that the cause of double melting points consists in the existence of two isomeric forms in the benzene nucleus of substituted 2-furylbenzimidazoles, due to the intramolecular hydrogen bond of the benzimidazole with furan ring oxygen.

In Table II ultraviolet spectral data of all benzimidazoles mentioned in this paper are given. The UV spectra of benzimidazoles with a double melting point are identical with the spectra of benzimidazoles with a single melting point. Similarly, the UV spectra of hydrochlorides of these substances are also equal. At 10^{-5}M concentration of these substances in ethanol (used for the measurement of the UV spectra) a strong interaction was observed between the molecules of 2-furylbenzimidazoles with the solvent, which abolished the intramolecular hydrogen bonds. It is a phenomenon similar to that observed during the separation of isomers on alumina where both

TABLE II
Ultraviolet Absorption Spectra of Benzimidazole Derivatives

X	λ_{max}, nm[a], (log ε)			
	2-(5-X-2-Furyl)-5(6)-nitrobenzimidazoles			
H	i 216 (3·94)	s 241 (4·04)	280 (4·43)	342 (4·32)
CH_3	i 215 (3·99)	243 (4·03)	288 (4·36)	350 (4·26)
Cl	—	s 244 (4·09)	283 (4·38)	341 (4·31)
Br	—	s 245 (3·98)	287 (4·36)	343 (4·31)
J	i 201 (4·02)	i 252 (3·99)	290 (4·31)	348 (4·33)
$COOCH_3$	213 (4·06)	—	293 (4·00)	342 (4·06)
H[b]	197 (4·38)	s 244 (4·00) s 264 (4·07)	286 (4·10)	342 (4·15)
	2-(5-X-2-Furyl)-5(6)-aminobenzimidazoles			
H	206 (4·41)	s 241 (4·02)	260 (4·06)	330 (4·31)
CH_3	208 (4·45)	s 230 (3·96)	267 (4·07)	337 (4·38)
Cl	207 (4·48)	s 240 (4·04)	263 (4·10)	335 (4·37)
Br	206 (4·49)	235 (4·03)	266 (4·08)	337 (4·37)
J	207 (4·37)	s 235 (3·90)	269 (3·97)	338 (4·29)
$COOCH_3$	207 (4·38)	—	254 (4·00)	358 (4·26)

[a] i Inflexion, s shoulder; [b] 2-thienyl-5(6)-nitrobenzimidazole.

isomers have the same R_F value. The substituents introduced appreciably change the character of the UV spectra. In the spectra of 2-furyl-5(6)-nitrobenzimidazoles three bands appear. The first, appearing as a shoulder at 241 to 251 nm, is due to electron transitions in the benzimidazole cycle, while the second one, at 280 to 293 nm is due to $\pi \rightarrow \pi^*$ transitions of the benzenoid system modified by the amidinic bond of imidazole[20]. The absorption maxima between 341–350 nm probably correspond to furfurylidene-imidine chromophore[6]. The greatest change of the spectra is caused by the $COOCH_3$ group in the position 5 of the furan nucleus, or also the substitution of oxygen in the furan cycle for sulfur. The spectra of 2-(5-X-2-furyl)-5(6)-amino benzimidazoles are similar to one another and a greater change is caused again only by the presence of the $COOCH_3$ group. With the exception of the last derivative four absorption bands in the 206–208 nm, 330–341 nm, 254–269 nm, and 330–350 nm regions appear in all the others. The last three of these bands belong to similar electron transitions as in 2-furyl-5(6)-nitrobenzimidazoles. The band at 206–208 nm may be assigned to the $\pi \rightarrow \pi^*$ electron transition, similar to the second band of benzene. In comparison with benzene this band is shifted to higher wavelengths in consequence of the NH_2 group present on the benzene nucleus.

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