INVESTIGATION OF THE REACTION OF FURFURAL WITH o-PHENYLENEDIAMINES

S. I. Burmistrov and V. M. Sannikova

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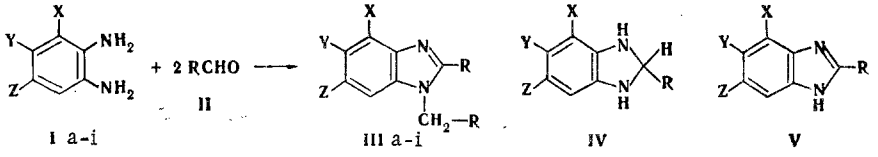
1,2-Disubstituted benzimidazoles were synthesized by the reaction of furfural and 5-methylfurfural with o-phenylenediamines in an alcoholic acidic medium.

Furfural reacts with o-phenylenediamine hydrochloride in aqueous solution in a ratio of 2:1 to give 1-(2-furylmethyl)-2-(2-furyl)benzimidazole [1-5]. We have found that when the well-known method for the synthesis of 1,2-disubstituted benzimidazoles (III) is used, because of resinification, the yield of purified substance is less than 50%. The reaction of aldehydes II with o-diamines I also gives benzimidazolines IV, which can be oxidized to benzimidazoles V. It has been established [6] that only V are formed in high yields when an oxidizing agent (copper acetate) is added to the reaction mixture. 2-Substituted benzimidazoles [7-10] are also therefore always formed under the conditions for the synthesis of III if one does not exclude access to the air [7-10]. 1-(5-Methyl-2-furylmethyl)-2-(5-methyl-2-furyl)-4,6-dichlorobenzimidazole (IIIh) and 2-(5-methyl-2-furyl)-4,6-dichlorobenzimidazole (Vh) were isolated in the reaction of 5-methylfurfural with diamine Ih in methanol solution in the case of access to the air.

Purer benzimidazoles III are obtained in high yields with all of the investigated diamines if the reaction is carried out in methanol in a stream of an inert gas rather than in water.



III a-g R = 2-furyl; a X=Y=Z=H; b X=Y=H, Z=CH_3; c X=Y=H, Z=NO_2; d X=Z=H, Y=Cl; e X=Z=H, Y=Br; f X=Z=Cl, Y=H; g X=Z=Br, Y=H; IIIh, i R = 5-methyl-2-furyl 2; h X=Z=Cl, Y=H; i X=Z=Br, Y=H

o-Diamines Ib, c react with II to give 1,2,6-trisubstituted benzimidazoles, while o-diamines Id, e react with II to give 1,2,5-trisubstituted benzimidazoles (IIIb-e). Only 1,2,4,6-tetrasubstituted benzimidazoles IIIf-i were isolated in the reaction of 3,5-dihalo-1,2-diamines If-i (Table 1).

TABLE 1. Benzimidazoles IIIa-i and Vh

Compound	mp, °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	N	Hal*		C	H	N	Hal*	
IIIa	95—96	72,7	4,5	10,6		$C_{16}H_{12}N_2O_2$	72,7	4,5	10,6		98
IIIb	128—129	73,3	5,0	10,2		$C_{17}H_{14}N_2O_2$	73,4	5,0	10,1		97
IIIc	158—159	62,2	3,5	16,1		$C_{16}H_{11}N_3O_4$	62,1	3,6	13,6		95
IIId	146—147	64,7	3,7	10,0	11,4	$C_{16}H_{11}ClN_2O_2$	64,3	3,7	9,4	11,9	97
IIIe	124—125	56,1	3,1	8,2	23,4	$C_{16}H_{11}BrN_2O_2$	56,0	3,2	8,2	23,3	97
IIIf	173—174	57,0	2,6	7,5	21,7	$C_{16}H_{10}Cl_2N_2O_2$	57,6	3,0	8,4	21,3	98
IIIg	174—175	45,4	2,3	6,7	37,8	$C_{16}H_{10}Br_2N_2O_2$	45,5	2,4	6,6	37,9	95
IIIh	135—136	59,8	3,8	7,7	16,7	$C_{18}H_{14}Cl_2N_2O_2$	59,8	3,9	7,8	16,7	64
IIIi	150—151	48,1	3,0	6,1	35,6	$C_{18}H_{14}Br_2N_2O_2$	48,0	3,1	6,2	35,6	99
Vh	231—232	53,8	3,0	10,3	26,7	$C_{12}H_8Cl_2N_2O$	53,9	3,0	10,5	26,6	31

*For IIId, f, h, Vh, Hal = Cl; for IIIe, g, i, Hal = Br.

F. É. Dzerzhinskii Dnepropetrovsk Institute of Chemical Technology, Dnepropetrovsk 320005. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 816-819, June, 1981. Original article submitted February 6, 1979; revision submitted July 15, 1980.

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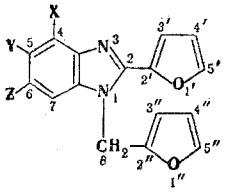
TABLE 2. PMR Spectra of Benzimidazoles

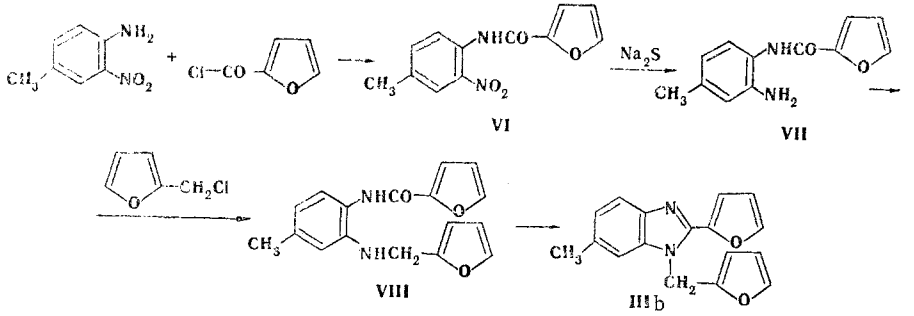


Compound	δ, ppm*									
	4-H	5-H	7-H	8-H	3′-H	4′-H	5′-H	3″-H	4″-H	5″-H
IIIb	7,24	7,06	7,29	5,43	7,33	6,46	7,53	6,21	5,98	6,96
IIIc	7,62	8,14	8,54	5,69	7,63	6,59	7,72	6,39	6,02	7,01
IIIh	—	8,25	8,24	6,02	7,74	7,01	8,07	6,71	6,63	7,60

*The spectra of IIIb, c were obtained in CF_3COOH, while the spectrum of IIIh was obtained in d_6-DMSO; $J_{45} = 9.0$, $J_{57} \approx J_{4'5'} \approx J_{4''5''} = 1.8$-$2.0$; $J_{47} = 0.6$; $J_{3'4'} \approx J_{3''4''} = 3.5$-$3.7$; $J_{3'5'} \approx J_{3''5''} < 1$ Hz.

It follows from the experimental data that the furylmethyl grouping in most cases is attached to the more basic nitrogen atom of the o-diamine. The 6-methyl-2-(2-furyl)-1-(2-furylmethyl)benzimidazole structure (IIIb) of the product of the reaction of furfural with 3,4-diaminotoluene was established on the basis of the PMR spectrum. The singlet at 5.43 ppm with a relative intensity of two protons was assigned to the signal of the methylene group. The signals of the protons of the furan rings are found at weaker field and were assigned with respect to their spin–spin coupling constants (SSCC) as indicated in Table 2. The two signals with close chemical shifts, viz., 7.24 and 7.29 ppm, should be assigned to the protons of the benzene ring. Since the signal at 7.24 ppm is found at stronger field, it is reasonable to assign it to the proton in the vicinity of the protonated atom of the imidazole ring. The splitting of this signal (J = 9.0 and 1.8 Hz) shows that the methyl group is in the 6 position.

The structure of IIIb was also proved by alternative synthesis via the following scheme:



In this case we isolated intermediates VI and VII but were unable to isolate VIII.

The assignment of the signals of the protons of the furan rings was made on the basis of the PMR spectra of furfural and furfuryl alcohol, as well as with allowance for the data in [11, 12]. Splitting of the signals for the 4-H proton with spin–spin coupling constants $J_{34} = 3.5$, $J_{45} = 1.7$, and $J_{35} = 0.8$ Hz is observed in the spectrum of furfural. A similar phenomenon is observed in the spectra of III, and this confirms the presence of furan rings in these substances.

The benzimidazole ring affects the chemical shifts of the protons of the furan rings; it has a stronger effect on the ring bonded directly to it. In the PMR spectrum of IIIb the chemical shifts of the protons of one ring are found at 6.46-7.53 ppm, while the chemical shifts of the protons of the second ring are found at 5.98-6.96 ppm. In the case of the first furan ring they are shifted to weaker field, whereas in the case of the second furan ring they are found at stronger field, and this confirms its bonding with the benzimidazole ring through the CH_2 group.

Substituents in the benzimidazole ring also have an effect on the chemical shifts of the protons of the furan rings. In particular, since the CH_3 and NO_2 groups have opposite effects, the chemical shifts of the protons of the furan rings of IIIb are found at stronger field than in the case of IIIc.

EXPERIMENTAL

The course of the reactions and the purity of the compounds were monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 plates with chloroform as the mobile phase and development with iodine vapors. The TLC data confirm the formation of one reaction product isomer. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard.

2-(2-Furyl)-1-(2-furylmethyl)benzimidazole (IIIa). A 3.84-g (0.04 mole) sample of furfural, 3.6 ml of 10% hydrochloric acid, and 10 ml of water were added to a solution of 2.2 g (0.02 mole) of Ia in 10 ml of methanol, and the reaction was carried out in a stream of helium. The mixture was allowed to stand for 5-6 h, after which it was made alkaline, and the precipitate was removed by filtration and recrystallized with activated charcoal from aqueous alcohol to give colorless crystals with mp 95-96°C.

Compounds IIIb-g were similarly obtained and were crystallized from aqueous alcohol (IIIb was purified with a chromatographic column filled with silica gel to give a single isomer with R_f 0.11).

In the synthesis of 6-nitro-2-(2-furyl)-1-(2-furylmethyl)benzimidazole (IIIc) the mixture was heated in a flask equipped with a reflux condenser on a water bath for 2 h, whereas heating was continued for 2-3 min in the case of IIIf, g.

4,6-Dichloro-2-(5-methyl-2-furyl)-1-(5-methyl-2-furylmethyl)benzimidazone (IIIh). A 1.77-g (0.01 mole) sample of Ih was dissolved in 40 ml of methanol, and the solution was heated and treated rapidly with 3.6 ml of 10% hydrochloric acid and 2.2 g (0.02 mole) of 5-methylfurfural. The solution became intensely red. The mixture was heated in a flask equipped with a reflux condenser on a water bath for 15 min, after which water was added dropwise until the mixture became turbid. The precipitate was removed by filtration and crystallized from aqueous alcohol to give colorless crystals with mp 135-136°C. Compound IIIi was obtained in the same way. Workup of the filtrate give Vh, which was purified similarly.

3-Nitro-4-(2-furoylamino)toluene (VI). A 3.0-g (0.02 mole) sample of 3-nitro-4-aminotoluene was dissolved in 10 ml of pyridine, 2.6 g of furoyl chloride was added dropwise with vigorous stirring, and the mixture was allowed to stand for 3-4 h. The precipitate was removed by filtration to give yellow crystals with mp 138-139°C (from alcohol). Found: C 58.8; H 4.3; N 11.5%. $C_{12}H_{10}N_2O_4$. Calculated: C 58.5; H 4.1; N 11.4%.

3-Amino-4-(2-furoylamino)toluene (VII). A 2.5-g (0.01 mole) sample of VI was suspended by heating in 40 ml of alcohol, a solution of 7.9 g of sodium sulfide in 20 ml of water was added in the course of 1 h with stirring, and the mixture was stirred until the red coloration disappeared. The solution was diluted with water and allowed to stand with cooling to give colorless needles with mp 107-108°C (from alcohol). Found: C 66.5; H 5.8; N 13.2%. $C_{12}H_{12}N_2O_2$. Calculated: C 66.7; H 5.5; N 13.0%.

6-Methyl-2-(2-furyl)-1-(2-furylmethyl)benzimidazole (IIIb). A 1.2-g (0.01 mole) sample of 2-chloromethylfuran was added to a solution of 2.16 g (0.01 mole) of VII in 20 ml of ethanol, and the mixture was heated with stirring in a flask equipped with a reflux condenser on a water bath for 2 h, after which it was diluted with water. The precipitate was removed by filtration to give a substance with mp 128°C (from aqueous alcohol). The reaction product was identified by chromatography and also from the absence of a melting-point depression for a mixture with the previously obtained IIIb.

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RESEARCH ON THE CHEMISTRY OF PYRAZOLIDINE.

25.* ALKYLATION OF 4-CYCLOHEXYLIDENE-1-PHENYL-3,5-DIOXOPYRAZOLIDINE

B. L. Moldaver and M. E. Aronzon

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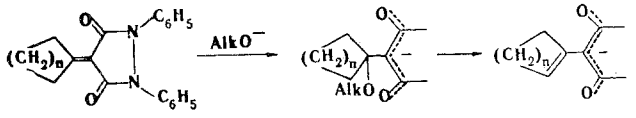
Products of alkylation in the 2 and 4 positions, as well as at the C_3=O group, were obtained by the reaction of 1-phenyl-4-cyclohexylidene-3,5-dioxopyrazolidine with alkyl halides in the presence of sodium methoxide. The reaction of sodium deuteromethoxide with 1-phenyl-4-cyclohexylidene-3,5-dioxopyrazolidine was studied.

It is known that 4-arylidene- and 4-cycloalkylidene-substituted 1,2-diphenyl-3,5-dioxopyrazolidines (I, II) react with sodium alkoxides as organic Lewis acids by adding an alkoxy group to the exocyclic polarized double bond [1, 2]. In the case of II one observed successive splitting out of a molecule of alcohol to give enolate III. The structure of enolates III is confirmed by spectroscopy and the production of the corresponding alkylation products.



II III

n = 2, 3

It seemed of interest to study the behavior in this reaction of a 4-cycloalkylidene-1-phenyl-3,5-dioxopyrazolidine in which, in addition to C—H acidity and the properties of an organic Lewis acid, N—H and O—H acidities are also possible, which permits the formation of a large number of products of reaction with alkoxides.

With this in mind we investigated the PMR spectra of a solution of 1-phenyl-4-cyclohexylidene-3,5-dioxopyrazolidine (IV) in deuteromethanol in the presence of sodium deuteromethoxide. The PMR spectrum of starting IV in $CDCl_3$ is similar to the PMR spectrum of II (n = 3) and contains signals of six aliphatic (1.68 ppm) and four allyl (3.17 ppm) protons, as well as the signal of the proton of an NH group, the position of which (8.5-9.08 ppm) depends on the concentration. These results constitute evidence that IV exists in the dioxo form in $CDCl_3$. Disappearance of the signal of allyl protons and the appearance of the previously absent signals at 2.08, 2.42, and 5.91 ppm are observed in the spectrum of a solution of starting IV in CD_3OD after the addition of one equivalent of CD_3ONa in deuteromethanol. These changes are similar to those observed when a solution of CD_3ONa in deutero-

*See [1] for Communication 24.

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