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HALOGENATION AND NITRATION OF o-METHOXYBENZODIOXAHETEROCYCLES

V. K. Daukshas, É. B. Udrenaite,
V. L. Gineitite, A. Yu. Rukshenas,
G. G. Komovnikova, and A. V. Barauskaite

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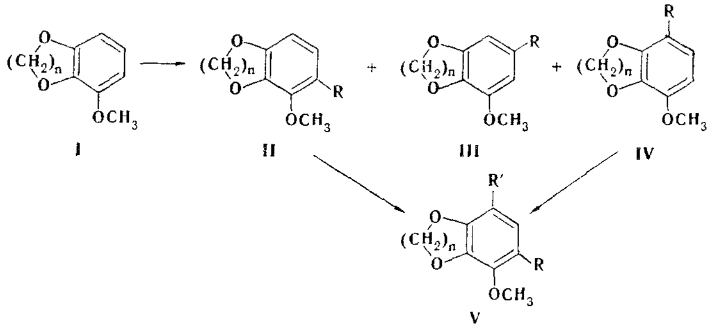
The composition of the products of electrophilic chlorination, bromination, iodination, and nitration of 4-methoxybenzo-1,3-dioxol, 5-methoxybenzo-1,4-dioxane, and 6-methoxybenzo-1,5-dioxepan were established. The reasons for the pathways via which the substitution reactions proceeds are discussed.

Halo and nitro derivatives of 5-methoxybenzo-1,4-dioxane (I, n = 2) are used in the synthesis of physiologically active substances [1]. In a continuation of our search for methods for the preparation of new compounds of this type [2, 3] we studied the compositions of the products of halogenation and nitration of I (n = 1-3).



The ratios of products II-IV are presented in Table 1. The structures of II and IV are confirmed by the presence of two doublets of aromatic protons (J = 8-10 Hz) in the PMR spectra. In the case of III ($R = NO_2$) J = 2-3 Hz. The signals of the methoxy groups of isomers II are shifted to strong field as compared with those of isomers IV (Table 2). The structure of dihalo derivatives V (n = 1, R = R' = Cl, Br, I) proves their formation from the corre-

TABLE 1. Ratios of the Products of Substitution Reactions of I

n	R	II	III	IV
1	Cl	1	0	0
	Br [3]	1,9	0	1
	I	1,3	0	1
	NO_2 [3]	0	1	0
2	Cl	4	0	1
	Br [2]	1	0	5
	I	0	0	1
	NO_2 [2]	1	8	2,7
3	Cl	1	0	1
	Br, I	0	0	1
	NO_2	0	1	0

V. Kapsukas Vilnius State University, Vilnius 232734. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1315-1319, October, 1980. Original article submitted October 17, 1979; revision submitted February 11, 1980.

TABLE 2. Characteristics of the Synthesized Compounds

Type of compound	n	R	R′	mp, °C (solvent)	UV spectrum		PMR spectrum,	
					λ_{max} nm	log ε	OCH_3 (c)	$O(CH_2)_nO$
II	1	Cl	—	48—49,5 (hexane)	212 240 288	4,51 3,63 3,05	3,93	5,85 (s)
II	1	I	—	28—30,5 (hexane)	217 238 285	4,53 3,85 3,09	3,93	5,85 (s)
IV	1	I	—	109—110 (CCl_4)	219 234 274	4,66 4,10 3,13	3,84	5,94 (s)
V	1	Cl	Cl	68—69 (hexane)	217 290	4,62 2,96	3,91	5,96 (s)
V	1	Cl	Br	87—88 (hexane)	217 290	4,59 3,03	3,91	5,96 (s)
V	1	Br	Cl	91,5—92,5 (hexane)	217 290	4,66 2,99	3,91	5,95 (s)
V	1	Br	Br	91—92,5 (hexane)	217 232 283	4,65 4,06 3,09	3,91	5,94 (s)
V	1	Br	I	101—102 (hexane)	223 239 284	4,66 4,15 3,13	3,96	5,99 (s)
V	1	I	I	116—117 (hexane)	226 241 279	4,66 4,06 3,14	3,94	5,95 (s)
II	2	Cl	—	—[a]	210 233 275	4,51 3,90 2,74	3,80	4,19 (s)
IV	2	Cl	—	75—75,5 (pentane)	212 236 285	4,64 4,09 3,54	3,71	4,22 (s)
IV	2	I	—	79—80 (petroleum ether)	218 237 268	4,04 4,08 3,02	3,72	4,21 (s)
V	2	Cl	I	63—64,5 (methanol)	220 237 290	4,30 4,11 3,08	3,75	4,25 (s)
I	3	—	—	45—46[b] (pentane)	207 224 273	4,07 3,65 2,85	3,61	2,1 (m)[c] 4,04 (t)[d]
IV	3	Br	—	59—60 (petroleum ether)	213 234 280	4,20 3,91 2,88	3,65	2,1 (m)[c] 4,07 (t)[d] 4,15 (t)[d]
IV	3	I	—	62—62,5 (petroleum ether)	216 238 278	4,28 4,10 3,03	3,72	2,2 (m)[c] 4,13 (t)[d] 4,20 (t)[d]
III	3	NO_2	—	117—118 (acetone)	206 223 240 330	4,16 4,11 3,77 3,81	3,82	2,2 (m)[c] 4,2 (m)[d]

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[a] This compound had bp 121-123°C (1 mm) and n_D^{20} 1.5621. [b] This
OCH_2 group; J = 6 Hz. [e] This is the percentage of nitrogen.

δ, ppm (CCl_4)	Found, %			Empirical formula	Calculated, %		
H_{Ar}	C	H	Hal		C	H	Hal
6,33 (d, 7-H) 6,73 (d, 6-H)	51,8	4,0	19,3	$C_8H_7ClO_3$	51,5	3,8	19,0
6,21 (d, 7-H) 7,10 (d, 6-H)	34,7	2,7	45,3	$C_8H_7IO_3$	34,6	2,5	45,6
6,23 (d, 5-H) 6,93 (d, 6-H)	34,2	2,7	45,5	$C_8H_7IO_3$	34,6	2,5	45,6
6,78 (s, 6-H)	43,7	2,6	32,0	$C_8H_6Cl_2O_3$	43,5	2,7	32,1
6,91 (s, 6-H)	36,5	2,6	43,1	$C_8H_6BrClO_3$	36,2	2,3	43,4
6,93 (s, 6-H)	36,0	2,3	43,1	$C_8H_6BrClO_3$	36,2	2,3	43,4
7,08 (s, 6-H)	31,0	2,0	52,0	$C_8H_6Br_2O_3$	31,0	1,9	51,6
7,25 (s, 6-H)	27,0	2,0	57,9	$C_8H_6BrIO_3$	26,9	1,7	57,9
7,42 (s, 6-H)	23,8	1,9	62,5	$C_8H_6I_2O_3$	23,8	1,5	62,8
6,50 (d, 8-H) 6,79 (d, 7-H)	53,8	4,7	17,5	$C_9H_9ClO_3$	53,9	4,5	17,7
6,24 (d, 6-H) 6,70 (d, 7-H)	53,7	4,4	17,9	$C_9H_9ClO_3$	53,9	4,5	17,7
6,20 (d, 6-H) 7,11 (d, 7-H)	37,3	3,5	43,2	$C_9H_9IO_3$	37,0	3,1	43,5
7,25 (s, 7-H)	33,1	2,9	50,0	$C_9H_8ClIO_3$	33,1	2,5	49,7
6,2—6,7 (m)	66,2	7,3	—	$C_{10}H_{12}O_3$	66,6	6,7	—
6,25 (d, 7-H) 6,91 (d, 8-H)	46,4	4,2	30,7	$C_{10}H_{11}BrO_3$	46,4	4,3	30,8
6,25 (d, 7-H) 7,20 (d, 8-H)	39,7	4,0	41,0	$C_{10}H_{11}IO_3$	39,2	3,6	41,5
7,32 (d) 7,40 (d)	53,6	4,8	6,1[e]	$C_{10}H_{11}NO_5$	53,3	4,9	6,2[e]

compound had bp 157-158°C (15 mm). [c]The CH_2 group. [d]The sponding monohalo derivatives II and IV. In addition, the signal of the aromatic proton of V is found at stronger field as compared with the signals of II and IV.

Chlorination of bromo compound II (n = 1, R = Br) gave V (n = 1, R = Br, R' = Cl) and a small amount of dichloro compound V (n = 1, R = R' = Cl), while isomer V (n = 1, R = Cl, R' = Br) was synthesized by chlorination of bromo compound IV (n = 1, R = Br) and bromination of chloro compound II (n = 1, R = Cl). Iodination of bromo compound II (n = 1, R = Br) gave V (n = 1, R = Br, R' = I); however, the bromination of iodo compound IV (n = 1, R = I) was complicated because of reduction of the iodo derivative by hydrogen bromide and gave a mixture of V (n = 1, R = Br, R' = I), II (n = 1, R = Br), and V (n = 1, R = R' = Br) in a ratio of 1:2:1. A mixture of bromo compound IV (n = 1, R = Br) with dibromo compound V (n = 1, R = R' = Br) in a ratio of 1:1 was similarly obtained by bromination of iodo compound II (n = 1, R = 1). Chlorination of iodo compound IV (n = 2, R = I) and iodination of chloro compound II (n = 2, R = Cl) gave V (n = 2, R = Cl, R' = I). We were unable to isolate chloro compounds II and IV (n = 3, R = Cl) in individual form, and their structures were determined from the PMR spectrum of the mixture.

The increase in the relative amounts of isomers IV on passing from the chloro derivative through the bromo derivative to the iodo derivative (Table 1) can be explained by the steric effect of the methoxy group. The sensitivity of bromine and iodine as reagents to steric effects is well known [4]. The deformation in I (n = 1) of the aromatic ring by the five-membered heteroring condensed with it (the Mills—Nixon effect) may prevent the formation of chloro compound IV (n = 1, R = Cl), while the formation of chloro compound IV (n = 2, R = Cl) may be prevented by partial deviation of the methoxy group in I (n = 2) from the plane of the ring [2], which promotes substitution in the para position.

The reasons for the different pathways for halogenation (the formation of halo derivatives II and IV) and nitration (the formation of nitro derivative III) of I (n = 1), which has a planar structure, were examined in [3]. In principle, the same regularity is also observed for I (n = 2, 3), in which the conjugation of the unshared electron pairs of oxygen atoms with the aromatic electron system is appreciably disrupted because of rotation of the alkoxy substituents about the C_{Ar}—O bond (Table 1). This is indicated by the drawing together of the λ_{max} (ε) values in hexane of the long-wave UV absorption bands of I as the number of methylene groups (n) increases from one to three [274 (990), 270 (720), and 270 nm (630)] and that of 1,2,3-trimethoxybenzene [268 nm (580)], the 2-methoxy group of which is almost completely deflected from the plane of the ring by rotation [6]. The retention of the para-orienting effect of an alkoxy group that is markedly rotated about the C_{Ar}—O bond is well known [7-10]. In addition, 1,2,3-trimethoxybenzene also forms only a 5-nitro derivative [11], viz., an analog of III (R = NO_2). Consequently, the formation of admixed derivatives II and IV (R = NO_2) in the nitration of I (n = 2) is probably not due to disruption of its coplanarity [2] but rather to other reasons.

EXPERIMENTAL

The spectroscopic study, the chromatographic determination of the ratios of isomers II-IV, and their preparative separation were carried out as in [2]. Chlorination and bromination were carried out with equimolar amounts of halogen at 20°C in CCl_4 containing iron (0.02 mole per mole of halogen).

Iodination. A mixture of 0.01 mole of I, II, or IV, 0.008 mole of yellow mercuric oxide, 0.01 mole of iodine, and 10 ml of ethanol was shaken until the color of iodine vanished, after which the ethanol was removed by vacuum distillation, and the reaction product was extracted with ether.

6-Methoxybenzo-1,5-dioxepan (I, n = 3). A mixture of 10 g (0.07 mole) of pyrogallol 1-methyl ether, 20 ml of ethylene glycol, 0.1 g of copper powder, and 15 g (0.14 mole) of sodium carbonate was stirred at 130°C, and 18 g (0.09 mole) of 1,3-dibromopropane was added in the course of 1 h. The mixture was stirred for another 8 h at 130°C, cooled, and diluted with water. The reaction product was extracted with chloroform to give 5.1 g (40%) of product.

6-Methoxy-8-nitrobenzo-1,5-dioxepan (III, n = 3, R = NO_2). A mixture of 2 g (11 mmole) of I (n = 3), 9 ml of acetic acid, and 1.5 g (13 mmole) of 56% nitric acid was stirred at 10°C for 2 h, after which it was poured into water. The yield of III (n = 3, R = NO_2) was 1.4 g (70%).

The characteristics of the compounds that were synthesized for the first time are presented in Table 2.

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RESEARCH IN THE ISOXAZOLE SERIES.

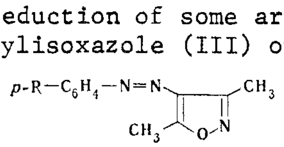
38.* POLAROGRAPHIC REDUCTION OF 4-ARYLAZOISOXAZOLES

I. G. Markova, S. M. Vinogradova,
and S. D. Sokolov

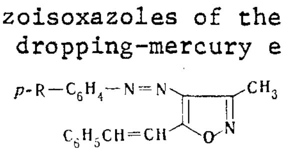
UDC 543.253:547.786

The indicated compounds are reduced on a dropping-mercury electrode in aqueous alcohol solutions at pH > 7 in one two-electron wave to 1,2-disubstituted hydrazines; four-electron reduction with the formation of amines takes place in acidic media. Two one-electron reduction waves are observed in dimethylformamide (DMF). Satisfactory $E_{1/2}-\sigma$ correlation equations were obtained for 4-arylazo-3,5-dimethyloxazoles.

We have previously studied the polarographic behavior of methyl- and phenylisoxazoles [2], as well as their halo derivatives [3], in anhydrous dimethylformamide (DMF). We established that only phenylisoxazoles undergo reduction with cleavage of the N—O bond of the hetero ring in the first step. In a continuation of our systematic studies, in the present research we studied the reduction of some arylazoisoxazoles of the I and II types and 3-phenyl-4-phenylazo-5-methylisoxazole (III) on a dropping-mercury electrode.



I a–e



II a–e

I-II a $R=H$; b $R=CH_3$; c $R=CH_3O$; d $R=Br$; e $R=NO_2$

The polarographic behavior of I was studied in both aqueous alcohol nonbuffer and buffer solutions with pH values from two to 12 and in anhydrous DMF with a saturated solution of tetramethylammonium iodide as the base electrolyte. Because of their low solubility in an

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*See [7] for Communication 37.

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