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STUDY OF HALOGENATION OF 5(6)-HYDROXYBENZIMIDAZOLE AND ITS DERIVATIVES

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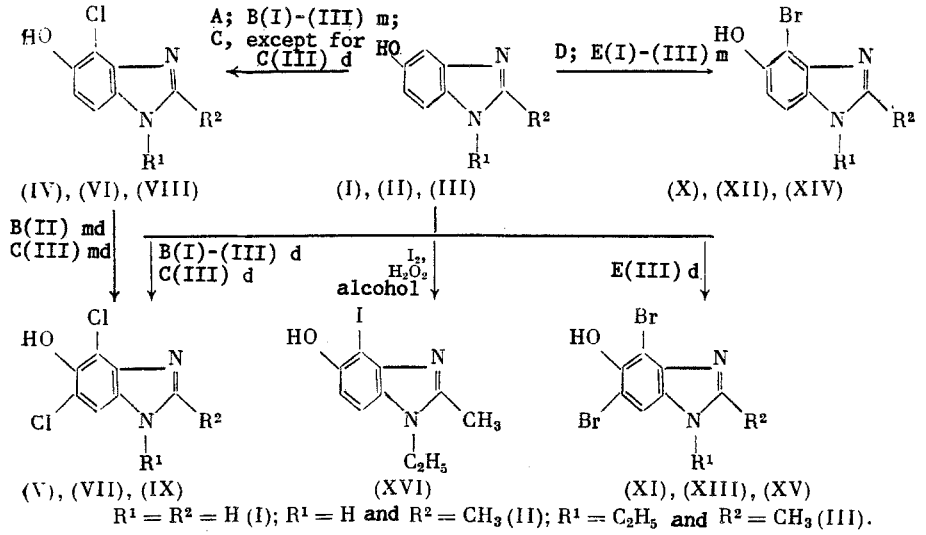
Derivatives of 5(6)-hydroxybenzimidazole have antioxidant properties and the ability to stimulate plant growth [1, 2]. It therefore appeared to be expedient to continue the search for biologically active compounds in this series. For this purpose, we studied the halogenation of 5(6)-hydroxybenzimidazole (I) and some of its derivatives, which also made it possible to investigate the characteristic features of the behavior of the benzimidazole ring in electrophilic substitution reactions.

Comparison of the reactivity of 5-hydroxybenzimidazolone, or its N,N'-dimethyl derivative shows that the 6-position of the benzene ring displays higher activity than the 4-position [3]. We found earlier [4], using the aminomethylation of (I) and its 2-methyl derivative (II) as an example that the benzene ring of benzimidazole is to some extent deactivated with respect to electrophilic substitution by the imidazole ring annelated with it. Thus, in contrast to phenol, the aminomethylation of (I) was successful only when it was carried out with an excess of secondary amine and after prolonged heating, while in an acid medium. Mannich bases were formed in low yield. In view of the results obtained, which indicate nonunequivocality of the occurrence of the electrophilic substitution of (I) and (II), depending on the conditions under which it is being carried out, we carried out the halogenation of (I) and its derivatives using various agents in weakly basic and acidic media. As starting compounds we selected (I), (II), and 1-ethyl-2-methyl-(I) (III).

The first stage in the investigation was the study of the chlorination of (I)-(III) using SO_2Cl_2 or a mixture of H_2O_2 with an aqueous or alcoholic solution of HCl. Chlorination by means of SO_2Cl_2 (method A) proceeds smoothly even at 20°C in a practically quantitative yield. Increase in the amount of SO_2Cl_2 and the reaction time, and also heating to 90°C [method A(I)-(III)d] do not lead to the formation of a dichlorosubstituted product, i.e., SO_2Cl_2 acts selectively only at the 4-position.



$R^1 = R^2 = H$ (I); $R^1 = H$ and $R^2 = CH_3$ (II); $R^1 = C_2H_5$ and $R^2 = CH_3$ (III).

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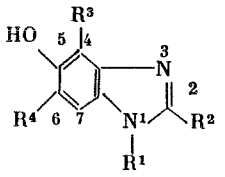
TABLE 1. Products of Halogenation of Derivatives of 5(6)-Hydroxybenzimidazole



Compound	R^1	R^2	R^3	R^4	Method	Yield, %	Mp, °C	Found/Calculated, % C	Found/Calculated, % H	Empirical Formula	δ, ppm 2-CH_3	δ, ppm 1-CH_2—CH_3	δ, ppm H^6	δ, ppm H^7	δ, ppm H^2	$J_{H^6H^7}$, Hz
(IV)	H	H	Cl	H	A (I) m	73,5	184–185	49,27	3,29	$C_7H_5N_2OCl$	–	–	6,85 d (1H)	7,29 d (1H)	9,15 s (1H)	9,2
								49,87	2,99							
(V)	H	H	Cl	Cl	B (I) d	53,6	217–218	36,03	2,40	$C_7H_4N_2OCl_2 \cdot HCl$	–	–	–	7,70 s (1H)	9,30 s (1H)	–
								35,11	2,10							
(VI)	H	Me	Cl	H	A (II) m	57,2	141–142	52,02	3,96	$C_8H_7N_2OCl$	2,87 s (3H)	–	7,30 d (1H)	7,75 d (1H)	–	9,0
					B (II) m	17,6		52,62	3,85							
					C (II) m	53,3										
					A (II) d	76,1										
					C (II) d	70,1										
(VII)	H	Me	Cl	Cl	B (II) d	47,3	263–265	37,23	3,18	$C_8H_6N_2OCl_2 \cdot HCl$	2,84 s (3H)	–	–	7,45 s (1H)	–	–
					B (II) md	27,7	(dec)	37,90	2,78							
(VIII)	Et	Me	Cl	H	A (III) m	90,6	267–269	47,93	5,13	$C_{10}H_{11}N_2OCl \cdot HCl$	2,77 s (3H)	1,38 t (3H) 4,17 q (2H)	6,51 d (1H)	7,07 d (1H)	–	9,0
					B (III) m	40,3		48,60	4,89							
					C (III) m	76,5										
					A (III) d	81,0										
(IX)	Et	Me	Cl	Cl	B (III) d	22,6	197–198	42,08	3,88	$C_{10}H_{10}N_2OCl_2 \cdot HCl$	2,77 s (3H)	1,40 t (3H) 4,50 q (2H)	–	7,37 s (1H)	–	–
					C (III) d	74,7		42,66	3,94							
					C (III) md	71,5										
(X)	H	H	Br	H	D (I) m	90,1	244–246	28,21	2,07	$C_7H_5N_2OBr \cdot HBr$	–	–	6,57 d (1H)	7,10 d (1H)	8,87 s (1H)	9,0
					E (I) m	79,6		28,60	2,06							
					D (I) d	83,3										
(XI)	H	H	Br	Br	E (I) d	75,1	272–274	23,23	1,97	$C_7H_4N_2OBr_2 \cdot HBr$	–	–	–	7,77 s (1H)	9,12 s (1H)	–
								22,55	1,35							
(XII)	H	Me	Br	H	D (II) m	69,3	298–300	30,62	2,65	$C_8H_7N_2OBr \cdot HBr$	2,71 s (3H)	–	6,54 d (1H)	6,99 d (1H)	–	9,0
					E (II) m	79,2	(dec)	31,20	2,62							
					D (II) d	76,8										
(XIII)	H	Me	Br	Br	E (II) d	51,7	310–312 (dec)	25,83	2,27	$C_8H_6N_2OBr_2 \cdot HBr$	2,91 s (3H)	–	–	7,59 s (1H)	–	–
								24,84	1,82							
(XIV)	Et	Me	Br	H	D (III) m	96,8	276–278	36,29	3,87	$C_{10}H_{11}N_2OBr \cdot HBr$	2,82 s (3H)	1,48 t (3H) 4,32 q (2H)	6,87 d (1H)	7,47 d (1H)	–	9,0
					E (III) m	81,4		35,74	3,60							
					D (III) d	89,4										
(XV)	Et	Me	Br	Br	E (III) d	76,5	260–262	28,23	3,20	$C_{10}H_{10}N_2OBr_2 \cdot HBr$	2,87 s (3H)	1,47 t (3H) 4,35 q (2H)	–	7,89 s (1H)	–	–
								28,95	2,67							
(XVI)	Et	Me	I	H	–	62,9	215–216 (dec)	38,94	3,70	$C_{10}H_{11}N_2OI$	2,83 s (3H)	1,47 t (3H) 4,32 q (2H)	6,67 d (1H)	7,32 d (1H)	–	9,0
								39,77	3,67							

Monochlorination by an equivalent amount of 30% H_2O_2 in concentrated HCl [method B(I)-(III)m] is accompanied by the formation of disubstituted product. Thus, it is impossible to eliminate the starting compound: For example, (III) reacts with the formation of a mixture of products in a ratio of the starting compound:mono-:dichloro-(III) = 1:2:1. The use of 60% H_2O_2, and also increase in temperature and reaction time does not entirely eliminate the starting compound, but merely increases the yield of the disubstituted derivative and the colored products of the oxidative splitting of the benzimidazole ring [5].

The use of an alcoholic solution of HCl and H_2O_2 [method C(I)-(III)m], makes it possible to avoid completely the formation of a disubstituted derivative, whereby the reaction proceeds quantitatively, rapidly [in the case of (III), ~5 min] and exothermally (cooling is necessary).

Since method A(I)-(III)d does not lead to the formation of 4,6-dichloro derivatives (I)-(III), the reaction was carried out under more rigorous conditions. Using excess H_2O_2 in aqueous HCl solution by method B(I)-(III)d, 4,6-dichloro derivatives can be obtained without the admixture of monosubstituted products.

However, as expected, an intense oxidative splitting of the ring thus takes place, which increases with increase in the H_2O_2 concentration, temperature and time of reaction (up to 2/3 of the starting compound).

It should be noted that the data of Fries et al. [6] stating that 4,6-dichloro-(I) and 4,6-dichloro-(II) were formed are in the first case erroneous, and in the second are inaccurate.

The disadvantages of methods A(I)-(III)d and B(I)-(III)d could be overcome only in the case of (III), by using an alcoholic solution of HCl and a fivefold excess of H_2O_2 with prolonged heating of the reaction mixture to 90°C [method C(I)-(III)d]. Thus, the starting product practically completely transforms into 4,6-dichloro-(III) in a three times higher yield than by the method C(I)-(III)d. The products of the oxidative splitting are present in negligible amounts only. The theoretical possibility of the chlorination of the mono- into the dichloro derivative (III) is readily realized by means of an alcoholic solution of HCl (20%) and H_2O_2 [method C(I)-(III)md].

Investigation of the bromination of (I)-(III) with bromine [7] and dioxane dibromide [8] was carried out at various equivalent ratios of the reaction components, and at various temperatures and reaction durations. A different course of reaction was also observed in glacial and diluted AcOH media [7].

Compounds (I) and (III) react in glacial AcOH at 20°C with dioxane dibromide [method D(I)-(III)m] with the formation of the corresponding 4-bromo derivatives (I) and (III) in practically quantitative yield, while in the case of (II), 4-bromo-(II) is formed with difficulty, and a threefold excess of dioxane dibromide does not make it possible to eliminate completely the initial (II). It should be noted that with a threefold excess of dioxane dibromide in glacial acetic acid, it is impossible to obtain 4,6-dibromo derivatives of (I)-(III) at 20°C, and even prolonged heating leads to the formation of 4-bromo derivatives of (I)-(III) with traces of 4,6-dibromo derivatives.

It was shown that the bromination reaction of (I)-(III) with bromine at 20°C does not proceed in glacial or dilute AcOH, and only prolonged heating of the reaction mixture to 90°C [method E(I)-(III)m] provides 4-bromo and 4,6-dibromo derivatives of (I)-(III). Increase in the amount of bromine and duration of heating does not lead to the formation of more than disubstituted bromo derivatives.

Iodination by means of a I_2 + KI mixture in sodium carbonate, ammonia and alkali does not lead to the formation of iodine derivatives of (I)-(III) substituted in the benzene ring. The reaction mixture thus darkens, a chestnut-colored precipitate separates, which is insoluble in water and benzene, and partially soluble in alcohol; the precipitate is a difficultly fusible substance, and has a polymeric structure, possibly formed by disproportionation of mono- and diiodoarenes [9].

A competing oxidation process is also not to be excluded during iodination, affecting compounds containing a phenolic hydroxyl in the aromatic ring of the molecule [10].

Iodination of (I)-(III) in glacial acetic acid by means of the I_2 + H_2O_2 mixture at 20°C does not proceed, and heating of the reaction mixture to 90°C for 4 h leads only to

4-iodo-(III), but extensive resinification thus takes place. The use of ethanol as the solvent increases the yield of 4-iodo-(III) by one and half times. The reaction of (III) with an equivalent amount of iodine and also with its two- and threefold excess proceeds to completion even at 20°C with the formation of 4-iodo-(III). Compounds (I) and (II) do not react under these conditions. Carrying out the reaction by heating with excess iodine does not make it possible to obtain 4, 6-diodo-(III), but results in a considerable decrease in the yield of 4-iodo-(III) and in extensive resinification.

Attempts to carry out the iodination of (I)-(III) by the Tronov–Novikov method [11] in a nitration mixture containing iodine, and also by means of $CuCl_2$ as the catalyst [12], did not lead to the formation of iodine derivatives. In the first case, traces of nitro derivatives can be possibly formed [13], and in the last case, the formation of a molecular complex with Cu is not excluded [14].

The structure of the compounds obtained is confirmed by the PMR spectra: In the spectra of the monosubstituted derivatives of (I)-(III), a signal of the H^4 proton in the weak field is absent, while the H^6 and H^7 signals are in the form of doublets with $J_{6,7}$ = 9.0-9.2 Hz. Introduction of the second substituent into the benzene ring leads to the disappearance of the H^6 signal, while the H^7 signal becomes a singlet (Table 1).

Thus, the halogenation experiments of (I)-(III) showed that the first halogen atom enters position 4, and then only does the 6-position of benzimidazole become reactive, which confirms the data of Fries et al. [6].

This confirms the effect of the hydroxy group, which turns out to be stronger than the specific activity of the 6-position of benzimidazole.

EXPERIMENTAL

The PMR spectra were obtained in D_2O on a Varian T-60 spectrometer, using t-BuOH as external standard (1.27 ppm with reference to TMS).

Monochlorination of (I). Method A(I)m. A 0.41-ml portion (0.0055 mole) of SO_2Cl_2 was added dropwise to a solution of 0.67 g (0.005 mole) of (I) in 20 ml of glacial AcOH, and the mixture was stirred for 1 h. The precipitate that separated out was filtered off, dissolved in water, and neutralized with sodium carbonate; yield, 0.62 g of 4-chloro-(I) (IV) (recrystallized from aqueous alcohol).

Dichlorination of (I). Method C(I)d. A 1.69-ml portion (0.015 mole) of 30% H_2O_2 was added dropwise to a solution of 0.67 g (0.005 mole) of (I) in 10 ml of concentrated HCl, and the mixture was stirred at 90°C for 1 h. The crystals that separated out on cooling were filtered off, washed with acetone, dried, and recrystallized from absolute alcohol; yield, 0.64 g of a 4,6-dichloro-(I) (V) hydrochloride. Base (V) was obtained by neutralization of the aqueous solution of the hydrochloride, followed by recrystallization from aqueous alcohol, mp 202-204°C (cf. [6]). Found, %: C 42.03; H 2.31. $C_7H_4N_2OCl_2$. Calculated, %: C 41.41; H 1.99.

Monochlorination of (II). Method A(II)m. A 0.41-ml portion (0.0055 mole) of SO_2Cl_2 was added dropwise to a solution of 0.74 g (0.005 mole) of (II) in 10 ml of glacial AcOH. The crystals that formed were separated, washed with acetone, dissolved in water, and the solution was neutralized with sodium carbonate. The precipitated material was chromatographed on a column with silica gel L-100/160 and by elution with MeOH; after recrystallization from aqueous alcohol, 0.52 g of 4-chloro-(II) (VI) was separated. The hydrochloride of (VI) was obtained by treatment with an alcoholic solution of HCl, followed by recrystallization from absolute alcohol, mp 288-290°C (dec.). Found, %: C 43.16; H 3.75. $C_8H_7N_2OCl \cdot HCl$. Calculated, %: C 43.86; H 3.81.

Method B(II)m. A 0.62-ml portion (0.0055 mole) of 30% H_2O_2 was added dropwise to a solution of 0.74 g (0.005 mole) of (II) in 40 ml of concentrated HCl, and the mixture was stirred at 90°C for 2.5 h. The solvent was distilled off, the residue was neutralized and chromatographed on a column according to method A(II)m; yield, 0.16 g of (VI).

Method C(II)m. A 0.9-ml portion (0.015 mole) of 60% H_2O_2 was added dropwise to a solution of 0.44 g (0.003 mole) of (II) in 40 ml of a 20% alcoholic solution of HCl, and the mixture was stirred for 20 min. The precipitate that separated out was filtered off, washed with acetone, and recrystallized from absolute alcohol; yield, 0.35 g of hydrochloride of (VI).

Dichlorination of (II). Method A(II)d. A 1.11-ml portion (0.015 mole) of SO_2Cl_2 was added dropwise to a solution of 0.74 g (0.005 mole) of (II) in 10 ml of AcOH, and the mixture was stirred at 90°C for 2 h. The precipitate that separated out was filtered off, and treated according to method C(II)m; yield, 0.83 g of hydrochloride of (VI).

Method B(II)d. A 3-ml portion (~0.025 mole) of a 30% H_2O_2 was added dropwise to a solution of 0.74 g (0.005 mole) of (II) in 40 ml of concentrated HCl and the mixture was stirred at 90°C for 1 h. The precipitate that separated out was filtered off and treated according to method C(II)m; yield, 0.60 g of 4,6-dichloro-(II) (VII) hydrochloride (cf. [6]). Base (VII), mp 135-136°C (aqueous alcohol). Found, %: C 45.13; H 3.63. $C_8H_6N_2OCl_2$. Calculated, %: C 44.27; H 3.25.

Method B(II)md. A 1.13-ml portion (0.01 mole) of 30% H_2O_2 was added dropwise to a solution of 0.66 g (0.003 mole) of hydrochloride of (VI) in 30 ml of concentrated HCl, and the mixture was stirred at 90°C for 1.5 h. The solvent was then evaporated to half its volume, and the precipitate that separated out on cooling was filtered off and treated according to method C(II)m; yield, 0.21 g of (VII).

Method C(II)d. A 0.9-ml portion (0.015 mole) of 60% H_2O_2 was added dropwise to a solution of 0.44 g (0.003 mole) of (II) in 30 ml of a 20% alcoholic solution of HCl, and the mixture was stirred at 90°C for 1.5 h. The precipitate that separated out on cooling was filtered off and treated according to method C(II)m; yield, 0.46 g of hydrochloride of (VI).

Monochlorination of (III). Method A(III)m. A 0.27-ml portion (0.0033 mole) of SO_2Cl_2 was added dropwise to a solution of 0.53 g (0.003 mole) of (III) in 10 ml of glacial AcOH. The precipitate that separated out was filtered off and treated by method C(II)m; yield, 0.58 g of 4-chloro-(III) (VIII) hydrochloride. Base (VIII), mp 288-289°C (aqueous alcohol). Found, %: C 57.97; H. 5.73. $C_{10}H_{11}N_2OCl$. Calculated, %: C 57.02; H 5.26.

Method B(III)m. A 0.37-ml portion (0.0033 mole) of 30% H_2O_2 was added dropwise to a solution of 0.53 g (0.003 mole) of (III) in 10 ml of concentrated HCl, and the mixture was stirred at 90°C for 1 h. The solvent was evaporated, the residue was neutralized, and chromatographed on a column according to method A(II)m; yield, 0.22 g of base (VIII).

Method C(III)m. A 0.56-ml portion (0.01 mole) of 60% H_2O_2 was added dropwise at 5°C to a solution of 0.53 g (0.003 mole) of (III) in 10 ml of 20% alcoholic solution HCl, and the mixture was stirred for 5-10 min. The crystals that separated out were filtered off and treated according to method C(II)m; yield, 0.49 g of (VIII).

Dichlorination of (III). Method A(III)d. A 0.75-ml portion (0.01 mole) of SO_2Cl_2 was added dropwise to a solution of 0.18 g (0.001 mole) of (III) in 75 ml of glacial AcOH, and the mixture was stirred at 90°C for 2 h. The solvent was evaporated off and the residue was treated according to method C(II)m; yield, 0.20 g of (VIII).

Method B(III)d. A 1.69-ml portion (0.015 mole) of 30% H_2O_2 was added dropwise to a solution of 0.53 g (0.003 mole) of (III) in 10 ml of concentrated HCl, and the mixture was stirred at 90°C for 1 h. The solvent was evaporated to half its volume, and the crystals that separated out were filtered off and treated according to method C(II)m; yield, 0.19 g of 4,6-dichloro-(III) (IX) hydrochloride. Base (IX), mp 206-207°C (alcohol). Found, %: C 48.53; H 4.51. $C_{10}H_{10}N_2OCl_2$. Calculated, %: C 49.00; H 4.11.

Method C(III)d. A 1.69-ml portion (0.015 mole) of 30% H_2O_2 was added dropwise to a solution of 0.53 g (0.003 mole) of (III) in 10 ml of 20% alcoholic solution of HCl, and the mixture was stirred at 90°C for 1.5 h. The solvent was evaporated to half its volume, and the crystals that separated out were filtered off and treated according to method C(II)m; yield, 0.63 g of (IX).

Method C(III)md. A 1.13-ml portion (0.01 mole) of 30% H_2O_2 was added dropwise to a solution of 0.49 g (0.002 mole) of (VIII) in 20 ml of 20% alcoholic solution of HCl, and the mixture was stirred at 90°C for 1 h. The solvent was evaporated to a quarter of its volume, and the residue was treated according to method C(II)m; yield, 0.40 g of (IX).

Monobromination of (I). Method D(I)m. Dioxane dibromide (DD) (0.545 g, 0.0022 mole) was added in portions to a solution of 0.268 g (0.002 mole) of (I) in 10 ml of glacial AcOH, and the mixture was stirred for 1 h. The material that separated out was filtered off and treated according to method C(II)m; yield, 0.53 g of 4-bromo-(I) (X) hydrobromide. Base (X), mp 114-116°C (aqueous alcohol). Found, %: C 38.81; H 2.42. $C_7H_5N_2OBr$. Calculated, %: C 39.47; H 2.37.

Method E(I)m. A solution of 0.275 ml (0.0055 mole) of Br_2 in 2 ml of AcOH was added in portions to a solution of 0.67 g (0.005 mole) of (I) in 12 ml of 75% AcOH, and the mixture was stirred at 90°C for 2.5 h. The precipitate that separated out on cooling was filtered off and treated according to method C(II)m; yield 1.17 g of (X).

Dibromination of (I). Method D(I)d. Dioxane dibromide (DD) (1.09 g, 0.0044 mole) was added in portions to a solution of 0.268 g (0.002 mole) of (I) in 10 ml of glacial AcOH, and the mixture was stirred at 90°C for 2.5 h. The precipitate that separated out was filtered off and treated according to method C(II)m; yield 0.49 g of (X).

Method E(I)d. A solution of 0.6 ml (0.012 mole) of Br_2 in 3 ml of AcOH was gradually added to a solution of 0.67 g (0.005 mole) of (I) in 20 ml of 75% AcOH, and the mixture was stirred at 90°C for 2 h. The precipitate that separated out on cooling was filtered off, and treated according to method C(II)m; yield 1.40 g of 4,6-dibromo-(I) (XI) hydrobromide. Base (XI), mp 257-259°C (aqueous alcohol). Found, %: C 29.32; H 1.44. $C_7H_4N_2OBr_2$. Calculated, %: C 28.80; H 1.38.

Monobromination of (II). Method D(II)m. Dioxane dibromide (DD) (0.82 g, 0.0033 mole) was added in portions to a solution of 0.444 g (0.003 mole) of (II) in 30 ml of glacial AcOH, and the mixture was stirred at 90°C for 1 h. The precipitate that separated out on cooling was filtered off and treated according to the method C(II)m; yield 0.64 g of 4-bromo-(II) (XII) hydrobromide. Base (XII), mp 145-147°C (aqueous alcohol). Found, %: C 43.07; H 3.22. $C_8H_7N_2OBr$. Calculated, %: C 42.32; H 3.11.

Method E(II)m. A solution of 0.3 ml (0.006 mole) of Br_2 in 3 ml of AcOH was gradually added to a solution of 0.74 g (0.005 mole) of (II) in 20 ml of 75% AcOH, and the mixture was stirred at 90°C for 2.5 h. The precipitate that separated out on cooling after the evaporation of 2/3 of the solvent was filtered off and treated according to method C(II)m; yield 1.22 g of (XII).

Dibromination of (II). Method D(II)d. Dioxane dibromide (DD) (1.64 g, 0.0066 mole) was added in portions to a solution of 0.444 g (0.003 mole) of (II) in 30 ml of glacial AcOH, and the mixture was stirred at 90°C for 1.5 h. The precipitate that separated out on cooling was filtered off and treated according to method C(II)m; yield 0.71 g of (XII).

Method E(II)d. A solution of 0.55 ml (0.011 mole) of Br_2 in 5 ml of AcOH was added dropwise to a solution of 0.74 g (0.005 mole) of (II) in 40 ml of 75% AcOH, and the mixture was stirred at 90°C for 4.5 h. Three quarters of the solvent were distilled off and the material that separated out was filtered off, and treated according to method C(II)m; yield 1.00 g of 4,6-dibromo-(II) (XIII) hydrobromide. Base (XIII), mp 242-244°C (dec.) (aqueous alcohol). Found, %: C 32.11; H 1.77. $C_8H_6N_2OBr_2$. Calculated, %: C 31.41; H 1.98.

Monobromination of (III). Method D(III)m. Dioxane dibromide (DD) (0.545 g, 0.0022 mole) was added in portions to a solution of 0.352 g (0.002 mole) of (III) in 20 ml of glacial AcOH, and the mixture was stirred for 30 min. The material that separated out was filtered off and treated according to method C(II)m; yield 0.65 g of 4-bromo-(III) (XIV) hydrobromide. Base (XIV), mp 259-261°C (aqueous alcohol). Found, %: C 46.52; H 4.15. $C_{10}H_{11}N_2OBr$. Calculated, %: C 47.08; H 4.35.

Method E(III)m. A solution of 0.17 ml (0.0033 mole) of Br_2 in 1 ml of AcOH was added dropwise to a solution of 0.528 g (0.003 mole) of (III) in 12 ml of 75% AcOH, and the mixture was stirred at 90°C for 1.5 h. The crystals that separated out on cooling were filtered off, and treated according to method C(II)m; yield 0.82 g of (XIV).

Dibromination of (III). Method D(III)d. Dioxane dibromide (DD) (1.09 g, 0.0044 mole) was added in portions to a solution of 0.352 g (0.002 mole) of (III) in 20 ml of AcOH, and the mixture was stirred at 90°C for 1.5 h. The precipitate that separated out on cooling was filtered off and treated according to method C(II)m; yield 0.6 g (XIV).

Method E(III)d. A solution of 0.33 ml (0.0066 mole) of Br_2 in 2 ml of AcOH was added dropwise to a solution of 0.528 g (0.003 mole) of (III) in 12 ml of 75% AcOH, and the mixture was stirred at 90°C for 3.5 h. The material that separated out on cooling was filtered off and was treated according to method C(II)m; yield 0.95 g of 4,6-dibromo-(III) (XV) hydrobromide. Base (XV), mp 224-226°C (aqueous alcohol). Found, %: C 35.17; H 2.82. $C_{10}H_{10}N_2OBr_2$. Calculated, %: C 35.96; H 3.02.

Iodination of (III). A 0.9-ml portion (~0.009 mole) of 30% H_2O_2 was added dropwise with stirring to a solution of 0.528 g of (III) and 0.381 g (0.0015 mole) of I_2 in 20 ml of alcohol and the mixture was stirred for 6.5 h. The material that separated out was filtered off and recrystallized from aqueous alcohol; yield 0.57 g of 4-iodo-(III) (XVI). Hydrochloride of (XVI), mp 227-229°C (dec.) (absolute alcohol). Found, %: C 36.28; H 3.80. $C_{10}H_{11}N_2OI \cdot HCl$. Calculated, %: C 35.47; H 3.57.

CONCLUSIONS

1. New halogen derivatives of 1-ethyl-2-methyl-, 2-methyl- and 5-hydroxybenzimidazole were obtained.

2. A method for the chlorination of aromatic compounds by an alcoholic solution of hydrogen chloride in the presence of hydrogen peroxide was proposed, which enables carrying out the reaction with a high yield.

3. The reactivity of the series of 5(6)-hydroxybenzimidazole derivatives during the electrophilic substitution (halogenation) was shown to be as follows: 1-ethyl-2-methyl-5-hydroxybenzimidazole > 5(6)-hydroxybenzimidazole ≥ 2-methyl-5-hydroxybenzimidazole.

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