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Halogenation of 2-Unsubstituted and 2-Methylimidazo[4,5-*b*]pyridine Derivatives

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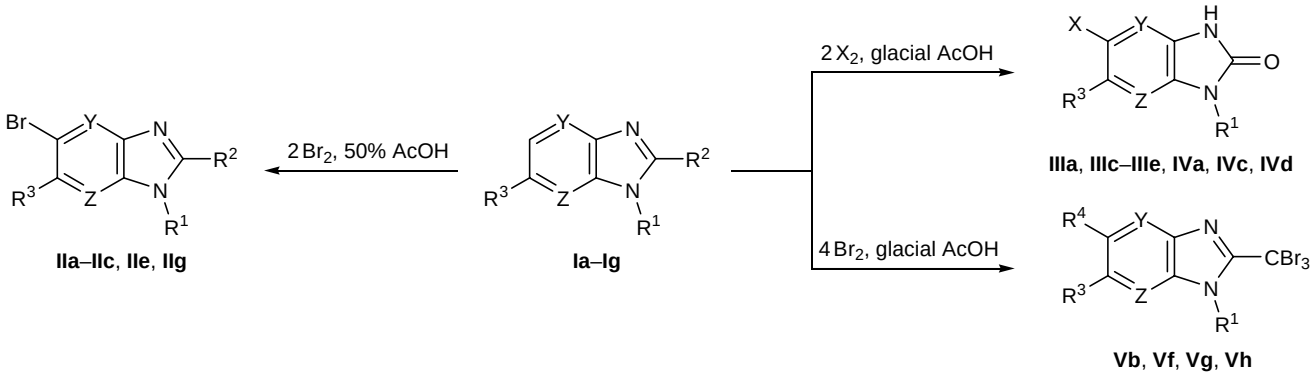
Abstract—Halogenation of 2-unsubstituted and 2-methylimidazo[4,5-*b*]pyridines and their *N*-methyl derivatives with bromine and chlorine in acetic acid takes different pathways, depending on the acetic acid concentration. The bromination in 50% aqueous acetic acid gives only 6-bromoimidazo[4,5-*b*]pyridines; bromination and chlorination of 2-unsubstituted imidazo[4,5-*b*]pyridines in glacial acetic acid leads to 5,6-dibromo(dichloro)imidazo[4,5-*b*]pyridin-2-ones, and bromination of 2-methylimidazo[4,5-*b*]pyridines in glacial acetic acid involves both the pyridine ring and the 2-methyl group to afford the corresponding 6-bromo-2-tribromomethylimidazo[4,5-*b*]pyridines.

Imidazo[4,5-*b*]pyridine is the closest structural analog of purine which plays an important role in biochemical processes occurring in living organisms and plants. In the recent years, interest in halogen derivatives of imidazopyridine has increased considerably due to wide spectrum of their biological activity. For example, 5(6)-halo-1- and -3-alkyl(aryl)imidazo[4,5-*b*]pyridin-2-ones and *N*-oxides derived therefrom exhibited stimulating and antidepressant properties [1], 5-haloimidazo[4,5-*b*]pyridin-2-ones showed pronounced antisecretory and antiulcer activity [2], and 1,3-dialkyl-5(6)-haloimidazo[4,5-*b*]pyridin-2-ones were recommended as effective antiinflammatory, antiphlogistic, and analgetic agents [3]. Some halogen-containing imidazopyridines possess antiviral properties, e.g., 3-alkyl-2-trifluoromethyl-5(6)-mono- and

Scheme 1.



I, $R^1 = R^2 = R^3 = H$, Y = CH, Z = N (**a**); $R^1 = R^3 = H$, R^2 = Me, Y = CH, Z = N (**b**); R^1 = Me, $R^2 = R^3 = H$, Y = CH, Z = N (**c**); R^1 = Me, $R^2 = R^3 = H$, Y = N, Z = CH (**d**); $R^1 = R^2 = H$, R^3 = Me, Y = CH, Z = N (**e**); $R^1 = H$, $R^2 = R^3$ = Me, Y = CH, Z = N (**f**); $R^1 = R^2$ = Me, $R^3 = H$, Y = CH, Z = N (**g**); $R^1 = R^2$ = Me, $R^3 = H$, Y = N, Z = CH (**h**); **II**, $R^1 = R^2 = R^3 = H$, Y = CH, Z = N (**a**); $R^1 = R^3 = H$, R^2 = Me, Y = CH, Z = N (**b**); R^1 = Me, $R^2 = R^3 = H$, Y = CH, Z = N (**c**); $R^1 = R^2 = H$, R^3 = Me, Y = CH, Z = N (**e**); $R^1 = R^2$ = Me, $R^3 = H$, Y = CH, Z = N (**g**); **III**, $R^1 = H$, R^3 = Br, X = Br, Y = CH, Z = N (**a**); R^1 = Me, R^3 = Br, X = Br, Y = CH, Z = N (**c**); R^1 = Me, R^3 = Br, X = Br, Y = N, Z = CH (**d**); $R^1 = H$, R^3 = Me, X = Br, Y = CH, Z = N (**e**); **IV**, $R^1 = H$, R^3 = Cl, X = Cl, Y = CH, Z = N (**a**); R^1 = Me, R^3 = Cl, X = Cl, Y = CH, Z = N (**c**); R^1 = Me, R^3 = Cl, X = Cl, Y = N, Z = CH (**d**); **V**, $R^1 = R^3 = H$, R^4 = Br, Y = CH, Z = N (**b**); $R^1 = H$, R^3 = Me, R^4 = Br, Y = CH, Z = N (**f**); R^1 = Me, $R^3 = H$, R^4 = Br, Y = CH, Z = N (**g**); R^1 = Me, R^3 = Br, $R^4 = H$, Y = N, Z = CH (**h**).

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Table 1. Yields, melting points, and elemental analyses of compounds **IIa**–**IIc**, **IIe**, **IIg**, **IIIa**, **IIIc**–**IIIe**, **IVa**, **IVc**, **IVd**, **Vb**, and **Vf**–**Vh**

Comp. no.	Yield, %	mp, °C (solvent)	Found, %			Formula	Calculated,%		
			C	H	N		C	H	N
IIa	61	225–227[a] (ethanol)	36.12	1.99	40.14	$C_6H_4BrN_3$	36.39	2.04	40.35
IIb	53	297–299[b] (ethanol)	39.43	2.78	19.65	$C_7H_6BrN_3$	39.65	2.85	19.82
IIc	29	117–118[c] (ethanol)	39.40	2.80	19.67	$C_7H_6BrN_3$	39.65	2.85	19.82
IIe	45	206–207[d] (2-propanol–water, 1 : 1)	39.45	2.75	19.63	$C_7H_6BrN_3$	39.65	2.85	19.82
IIg	42	157–159 (benzene–heptane, 1 : 1)	42.30	3.51	18.37	$C_8H_8BrN_3$	42.50	3.57	18.59
IIIa	31	>360 (DMF)	24.41	0.98	14.20	$C_6H_3Br_2N_3O$	24.60	1.03	14.35
IIIc	38	>320 (DMF)	27.16	1.58	13.48	$C_7H_5Br_2N_3O$	27.39	1.64	13.69
IIId	26	>320 (DMF)	27.20	1.57	13.50	$C_7H_5Br_2N_3O$	27.39	1.64	13.69
IIIe	40[e]	>310[f] (DMF)	36.64	2.60	18.25	$C_7H_6Br_2N_3O$	36.87	2.65	18.43
IIIe	56[g]	313–315[f] (DMF)	36.68	2.58	18.21	$C_7H_6Br_2N_3O$	36.87	2.65	18.43
IVa	29	357–360 (DMF)	35.11	1.42	20.43	$C_6H_3Cl_2N_3O$	35.32	1.48	20.60
IVc	31	373–376 (DMF)	38.34	2.26	19.10	$C_7H_5Cl_2N_3O$	38.56	2.31	19.27
IVd	30	317–320 (AcOH)	38.37	2.23	19.08	$C_7H_5Cl_2N_3O$	38.56	2.31	19.27
Vb	60	141–143 (ethanol–water, 4 : 1)	18.50	0.59	9.16	$C_7H_3Br_4N_3$	18.74	0.67	9.36
Vf	28	>300 (DMF)	20.57	1.02	8.89	$C_8H_5Br_4N_3$	20.76	1.09	9.08
Vg	25	130–132 (ethanol)	18.45	1.06	9.13	$C_7H_5Br_4N_3$	18.65	1.12	9.32
Vh	32	200–202 (benzene)	18.42	1.04	9.11	$C_7H_5Br_4N_3$	18.65	1.12	9.32

[a] Published data [11]: mp 227–228°C.
[b] Published data [13]: mp 299°C.
[c] Published data [14]: mp 118–119°C.
[d] Published data [11]: mp 204–205°C.
[e] From **Ie**.
[f] Published data [15]: mp >300°C.
[g] From **IIe**.

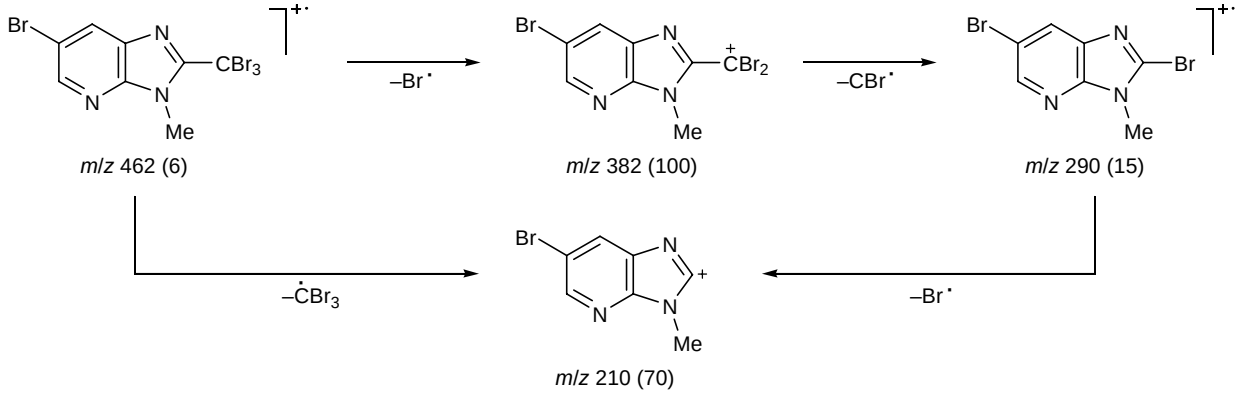
-5,6-dihaloimidazo[4,5-*b*]pyridines are especially effective against herpes cytomegalovirus (HCMV) [4]. Antihelmintic agents, pesticides (including insecticides) [5], defoliants [6], compounds suppressing biosynthesis in plants [7], and growth-regulating agents [8] were also found among halogen derivatives of imidazo[4,5-*b*]pyridines.

Until now, the main procedure for the preparation of halogen derivatives of imidazo[4,5-*b*]pyridines is cyclocondensation of halo-substituted *o*-diaminopyridines with carboxylic acids and their derivatives [9]. The goal of the present work was to synthesize halogen derivatives of imidazo[4,5-*b*]pyridines via direct introduction of a halogen atom into the pyridine ring containing no activating amino and oxo groups. As shown in [10], direct bromination of 1,2-dimethylimidazo[4,5-*b*]pyridine with excess bromine in 50% aqueous acetic acid at 70°C yields 6-bromo-1,2-dimethylimidazo[4,5-*b*]pyridine. The structure of the product was proved by independent synthesis, cyclization of 2-amino-5-bromo-3-methylaminopyridine on heating in boiling acetic anhydride [11].

In continuation of our studies on the halogenation of imidazo[4,5-*b*]pyridine derivatives [12], we performed bromination of imidazo[4,5-*b*]pyridines having no substituent in the 2-position and 2-methyl-substituted analogs **Ia**–**Ic**, **Ie**, and **Ig** with 2 equiv of bromine in 50% aqueous acetic acid at 95–100°C. The products were the corresponding 6-bromoimidazo-[4,5-*b*]pyridines **IIa**–**IIc**, **IIe**, and **IIg**, which were isolated in 29–61% yield (Scheme 1, Table 1). Their structure was confirmed by ^{1}H NMR spectroscopy (Table 2). Compounds **IIa**–**IId** showed in the ^{1}H NMR spectra two doublets from protons in the pyridine fragment with a coupling constant ^3J of 1.94–2.00 Hz (Table 2). Our results are consistent with the data of [10] on the bromination of 1,2-dimethylimidazo-[4,5-*b*]pyridine in 50% acetic acid.

Surprisingly, halogenation of compounds **Ia**, **Ic**–**Ie**, and **IIe** in glacial acetic acid afforded 5,6-dibromo-

Scheme 2.



(dichloro)imidazo[4,5-*b*]pyridin-2-ones **IIIa**, **IIIc**–**IIIe**, **IVa**, **IVc**, and **IVd** (Table 1). The structure of **IIIa**, **IIIc**–**IIIe**, **IVa**, **IVc**, and **IVd** was confirmed by the ^{1}H and IR spectra. In the ^{1}H NMR spectra of these compounds we observed only one signal belonging to 7-H in the pyridine fragment. Their IR spectra contained an absorption band at 1695–1705 cm^{-1} due to stretching vibrations of the C^2=O carbonyl group (Table 2). Thus halogenation in glacial acetic acid of imidazo[4,5-*b*]pyridines having no substituent on C^2 leads to introduction of two halogen atoms into the pyridine ring, and the imidazole fragment is oxidized to 2-oxo derivative. We have found no published data on analogous transformations of heterocyclic compounds. We were the first to propose a plausible mechanism of halogenation of imidazo[4,5-*b*]pyridine (**Ia**) in glacial acetic acid [12].

New results were also obtained in the bromination of 2-methylimidazo[4,5-*b*]pyridines **Ib** and **If**–**Ih** in glacial acetic acid. Unlike the reaction in 50% aqueous acetic acid, the bromination of **Ib** and **If**–**Ih** in glacial acetic acid resulted in replacement of both 6-H and all hydrogen atoms in the 2-methyl group by bromine atoms. The structure of products **Vb** and **Vf**–**Vh** was confirmed by the ^{1}H NMR spectra, and compound **Vg** was also examined by mass spectrometry (Table 2). The molecular weight of **Vg**, determined from the mass spectrum, coincided with the calculated value. The main fragmentation pathways of **Vg** under electron impact [16] include elimination of bromine atoms and CBr and CBr_3 groups (Scheme 2).

It should be noted that the bromination of **Ie** and **IIe** in glacial acetic acid afforded 6-bromo-5-methylimidazo[4,5-*b*]pyridin-2-one (**IIIe**) as the only product. In this case, bromination of the α-methyl group in the pyridine fragment might be expected, as in the bromination of 2-methylquinoline and its 8-methoxy derivative under analogous conditions [17]. However, our results show that only the 2-methyl group in **Ib** and **If**–**Ih** is converted into tribromomethyl in the bromination in glacial acetic acid.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Gemini-200 spectrometer (200 MHz) from solutions in DMSO-d_6 or $CDCl_3$ using HMDS as internal reference. The IR spectra were measured on a Specord 75IR spectrometer from samples prepared as KBr pellets. The mass spectrum of **Vg** was obtained on a Varian 311-A instrument under standard conditions. The purity of the products was checked by TLC on Silufol UV-254 plates using alcohol or chloroform as eluent; spots were detected under UV light or by treatment with iodine vapor. Initial compounds **Ia**, **Ic**, and **Id** were prepared as described in [18]; compounds **Ib**, **Ie**, **Ig**, and **Ih** were synthesized as reported in [10, 11, 19, 20], respectively, and imidazopyridine **If** was prepared by analogy with **Ig** [20].

2,5-Dimethylimidazo[4,5-*b*]pyridine (If). Yield 74%, mp 181–183°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.20 s (3H, 2-CH_3), 2.40 s (3H, 5-CH_3), 6.58 d (1H, 6-H, J = 7.62 Hz), 7.37 d (1H, 7-H, J = 7.62 Hz). Found, %: C 65.02; H 6.05; N 28.74. $C_8H_9N_3$. Calculated, %: C 65.29; H 6.16; N 28.55.

6-Bromoimidazo[4,5-*b*]pyridines IIa–IIc, IIe, and IIg (*general procedure*). Bromine, 11 mmol, was added in portions to a solution of 5 mmol of imidazo-[4,5-*b*]pyridine **Ia**–**Ic**, **Ie**, or **Ig** in 25 ml of 50% aqueous acetic acid under stirring at 20–25°C. The mixture was heated for 5 h on a boiling water bath and evaporated to dryness, the residue was dissolved in 20 ml of water, the solution was neutralized with 25% aqueous ammonia, and the precipitate was filtered off

Table 2. Spectral parameters of compounds **IIa**–**IIc**, **IIe**, **IIg**, **IIIa**, **IIIc**–**IIIe**, **IVa**, **IVc**, **IVd**, **Vb**, and **Vf**–**Vh**

Comp. no.	^{1}H NMR spectrum,[a] δ, ppm	IR spectrum, ν(C=O), cm^{-1}
IIa	8.21 d (1H, 7-H, *J* = 2.0 Hz), 8.37 d (1H, 5-H, *J* = 2.0 Hz), 8.39 s (1H, 2-H)	
IIb	2.59 s (3H, 2-CH_3), 8.02 d (1H, 7-H, *J* = 1.96 Hz), 8.27 d (1H, 5-H, *J* = 1.96 Hz)	
IIc	3.94 s (3H, 3-CH_3), 8.07 s (1H, 2-H), 8.24 d (1H, 7-H, *J* = 2.0 Hz), 8.49 d (1H, 5-H, *J* = 2.0 Hz)	
IIe	2.70 s (3H, 5-CH_3), 8.16 s (1H, 2-H), 8.28 s (1H, 7-H)	
IIg	2.68 s (3H, 2-CH_3), 3.84 s (3H, 3-CH_3), 8.03 d (1H, 7-H, *J* = 1.94 Hz), 8.34 d (1H, 5-H, *J* = 1.94 Hz)	
IIIa	7.50 s (1H, 7-H), 11.19 br.s (1H, 1-H), 11.75 br.s (1H, 3-H)	1695
IIIc	3.30 s (3H, 3-CH_3), 7.67 s (1H, 7-H), 11.57 br.s (1H, 1-H)	1695
IIId	3.36 s (3H, 1-CH_3), 7.80 s (1H, 7-H), 11.70 br.s (1H, 3-H)	1700
IIIe	2.61 s (3H, 5-CH_3), 7.37 s (1H, 7-H), 10.83 br.s (1H, 1-H), 11.32 br.s (1H, 3-H)	1705
IVa	7.48 s (1H, 7-H), 11.21 br.s (1H, 1-H), 11.74 br.s (1H, 3-H)	1700
IVc	3.25 s (3H, 3-CH_3), 7.47 s (1H, 7-H), 11.40 br.s (1H, 1-H)	1695
IVd	3.33 s (3H, 1-CH_3), 7.48 s (1H, 7-H), 11.93 br.s (1H, 3-H)	1700
Vb	8.27 d (1H, 7-H, *J* = 1.98 Hz), 8.56 d (1H, 5-H, *J* = 1.98 Hz)	
Vf	2.63 s (3H, 5-CH_3), 8.22 s (1H, 7-H)	
Vg[b]	4.29 s (3H, 3-CH_3), 8.34 d (1H, 7-H, *J* = 1.96 Hz), 8.59 d (1H, 5-H, *J* = 1.96 Hz)	
Vh	4.25 s (3H, 1-CH_3), 8.29 d (1H, 7-H, *J* = 2.0 Hz), 8.55 d (1H, 5-H, *J* = 2.0 Hz)	

[a] The ^{1}H NMR spectra of **IIa**, **IIb**, **IIe**, **IIIa**, **IIIc**–**IIIe**, **IVa**, **IVc**, **IVd**, **Vb**, **Vf**, and **Vh** were recorded in DMSO-d_6, and of the others, in $CDCl_3$.

[b] Mass spectrum of **Vg**, *m*/*z* (I_{rel}, %): 462 (6) $[M]^+$, 382 (100), 290 (15), 288 (35), 210 (70), 198 (85), 183 (45), 156 (40), 79 (81).

and purified by recrystallization from appropriate solvent (Table 1).

5,6-Dibromo- and 6-bromo-5-methylimidazo[4,5-*b*]pyridin-2-ones IIIa and IIIc–IIIe (*general procedure*). A solution of 11 mmol of bromine in 3 ml of glacial acetic acid was added dropwise under stirring to a solution of 5 mmol of imidazopyridine **Ia**, **Ic**–**Ie**, or **IIe** in 20 ml of glacial acetic acid. An abundant solid precipitated, the suspension was heated for 5 h on a boiling water bath, and the solvent was distilled off under reduced pressure to dryness. The residue was dissolved in 15 ml of water, the solution was neutralized with 25% aqueous ammonia, and the precipitate was filtered off, dried, and recrystallized from appropriate solvent (Table 1).

5,6-Dichloroimidazo[4,5-*b*]pyridin-2-ones IVa, IVc, and IVd (*general procedure*). Dry chlorine was passed over a period of 15 min through a solution of 2.1 mmol of imidazo[4,5-*b*]pyridine **Ia**, **Ic**, or **Id** and 4.2 mmol of sodium acetate in 7 ml of glacial acetic acid. The resulting suspension was heated for 5 h on a boiling water bath until it turned homogeneous. The solvent was distilled off under reduced pressure to dryness, the residue was dissolved in 15 ml of water, and the solution was neutralized with 25% aqueous ammonia. The precipitate was filtered off, washed with water, dried, and recrystallized from appropriate solvent (Table 1).

6-Bromo-2-tribromomethylimidazo[4,5-*b*]pyridines Vb and Vf–Vh (*general procedure*). A solution of 20 mmol of bromine in 5 ml of glacial acetic acid was added in portions under stirring to a solution of 5 mmol of imidazo[4,5-*b*]pyridine **Ib** or **If**–**Ih** and 20 mmol of sodium acetate in 15 ml of glacial acetic acid. An abundant solid precipitated, the suspension was heated for 5 h on a boiling water bath, the solvent was distilled off under reduced pressure to dryness, the residue was dissolved in 15 ml of water, and the solution was neutralized with 25% aqueous ammonia. The precipitate was filtered off, dried, and recrystallized from appropriate solvent (Table 1).

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