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Halogenation of Imidazo[4,5-*b*]pyridin-2-one Derivatives

Yu. M. Yutilov, Kh. Ya. Lopatinskaya, N. N. Smolyar, and S. V. Gres'ko

Litvinenko Institute of Physical Organic and Coal Chemistry, National Academy of Sciences of Ukraine, ul. R. Lyuksemburg 70, Donetsk, 83114 Ukraine
e-mail: yutilov@skif.net

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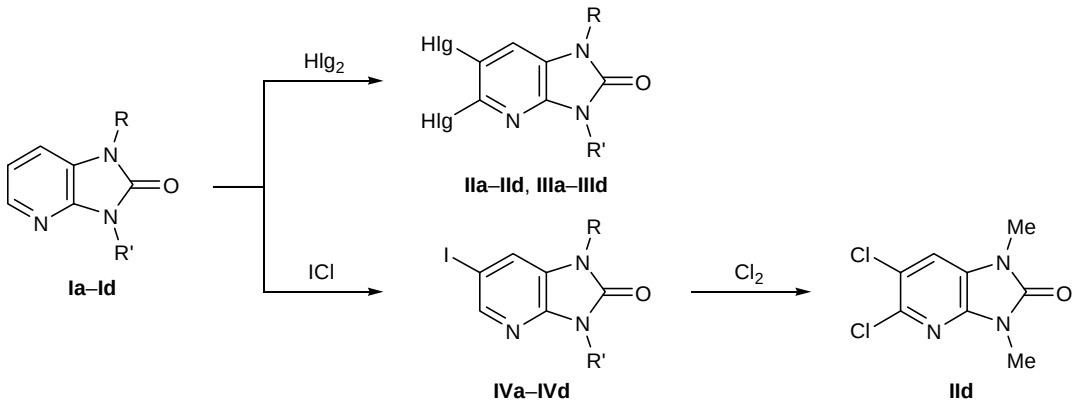
Abstract—Chlorination and bromination of 2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one and its *N*-methyl-substituted derivatives in acetic acid at 90–95°C leads to formation of the corresponding 5,6-dichloro-(dibromo)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones. Iodination of the same substrates with ICl under analogous conditions yields 6-iodo derivatives. Chlorination of 6-iodo-1,3-dimethyl-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one is accompanied by replacement of the iodine atom by chlorine with formation of 5,6-dichloro-1,3-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one. Bromination of 6-bromo- and 6-chloro-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones gives 5,6-dibromo- and 5-bromo-6-chloro-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-ones, respectively.

Some halogen derivatives of imidazo[4,5-*b*]pyridine were found to exhibit a broad spectrum of biological activity, in particular herbicide, bacteriostatic, antiviral, and antitumor [1]. 5(6)-Haloimidazo[4,5-*b*]-pyridin-2-ones were proposed as efficient analgetic, antiphlogistic, and antiinflammatory agents [2]. A new upsurge of the interest in imidazo[4,5-*b*]pyridines has been induced by the discovery of pronounced antihypertensive properties in some halogenated compounds of this heterocyclic series; it has stimulated extensive search for new more efficient and selective blocking agents of angiotensin II receptors, which are useful for the treatment of serious hypertension in humans [3].

The known methods for the synthesis of halogen derivatives of imidazo[4,5-*b*]pyridine are based on cyclization of *o*-diaminopyridines already containing halogen atoms in the pyridine ring [4]. Published data on direct halogenation of imidazo[4,5-*b*]pyridine derivatives are very poor; for example, Kazymov *et al.* [5] briefly reported on the bromination of 1,2-dimethylimidazo[4,5-*b*]pyridine to the corresponding 6-bromo derivative.

In continuation of our studies on halogenation of imidazo[4,5-*b*]pyridines [6], in the present work we made an attempt to synthesize chloro-, bromo-, and iodo-substituted derivatives of imidazo[4,5-*b*]pyridine containing an oxo group in position *2* of the imidazole

Scheme 1.



R = R' = H (**a**), R = Me, R' = H (**b**), R = H, R' = Me (**c**), R = R' = Me (**d**); **II**, Hlg = Cl; **III**, Hlg = Br.

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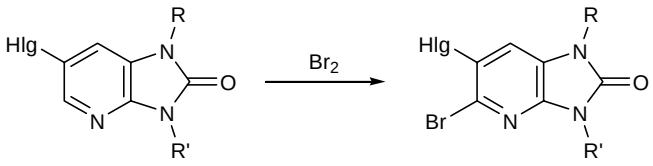
Scheme 2.



Va, **Vd**, **VIa**, **VId** **IIIa**, **IIId**, **VIIa**, **VIId**

R = R' = H (**a**), R = R' = Me (**d**); **V**, **VII**, Hlg = Cl; **III**, **VI**, Hlg = Br.

fragment. For this purpose, 2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (**Ia**) and 1-methyl-, 3-methyl-, and 1,3-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones **Ib**–**Id** were treated with gaseous chlorine in acetic acid at 90–95°C in the presence of sodium acetate. As a result, the corresponding 5,6-dichloro derivatives **IIa**–**IId** were obtained in 43–94% yield (Scheme 1, Table 1). Under analogous conditions, reactions of compounds **Ia**–**Id** with excess bromine gave 5,6-dibromo derivatives **IIIa**–**IIId** in high yields (Table 1).

The structure of compounds **IIa**–**IId** and **IIIa**–**IIId** was confirmed by the IR and ^{1}H NMR spectra (Table 2). Their IR spectra contained an absorption band at 1695–1700 cm^{-1} due to stretching vibrations of the carbonyl group in the imidazole fragment. In the ^{1}H NMR spectra of **IIa**–**IId** and **IIIa**–**IIId** we observed only one signal at δ 7.24–7.80 ppm, which belongs to aromatic proton (7-H) in the pyridine ring (Table 2).

Unlike chlorine and bromine, compounds **Ia**–**Id** failed to react with molecular iodine. On the other hand, heating of imidazopyridines **Ia**–**Id** with iodine(I) chloride under analogous conditions resulted in formation of only monoiodo derivatives **IVa**–**IVd** in 26–55% yield (Scheme 1, Table 1). The ^{1}H NMR spectra of **IVa**–**IVd** contained signals from protons in the pyridine ring (5-H and 7-H) as doublets with a coupling constant ^3J of 1.6 Hz.

The chlorination of 6-iodo-1,3-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one (**IVd**) was accompanied by replacement of the iodine atom by

Table 1. Yields, melting points, and elemental analyses of compounds **IIa**–**IId**, **IIIa**–**IIId**, **IVa**–**IVd**, **VIIa**, and **VIId**

Comp. no.	Yield, %	mp, °C (solvent)	Found, %			Formula	Calculated,%		
			C	H	N		C	H	N
IIa[a]	79	359–360 (DMF)	35.14	1.42	20.36	$C_6H_3Cl_2N_3O$	35.32	1.48	20.59
IIb	58	319–320 (AcOH)	38.35	2.28	19.05	$C_7H_5Cl_2N_3O$	38.56	2.31	19.27
IIc	43	372–375 (*i*-PrOH)	38.39	2.21	19.12	$C_7H_5Cl_2N_3O$	38.56	2.31	19.27
IId[b]	94	195–196 (MeOH)	41.14	3.15	17.93	$C_8H_7Cl_2N_3O$	41.40	3.04	18.11
IIIa[b]	78	>360 (DMF)	24.45	1.00	14.18	$C_6H_3Br_2N_3O$	24.60	1.03	14.35
IIIb	72	>320 (DMF)	27.14	1.60	13.52	$C_7H_5Br_2N_3O$	27.39	1.64	13.69
IIIc	67	>320 (DMF)	27.25	1.59	13.59	$C_7H_5Br_2N_3O$	27.39	1.64	13.69
IIId[b]	90	223–224 (benzene)	30.31	2.24	13.37	$C_8H_7Br_2N_3O$	29.94	2.20	13.09
IVa	51	314–316 (DMF)	27.43	1.56	15.90	$C_6H_4IN_3O$	27.61	1.54	16.10
IVb	28	>250 (DMF–H_2O)	30.41	2.15	15.12	$C_7H_6IN_3O$	30.57	2.20	15.28
IVc	26	>325 (DMF)	27.23	1.58	13.55	$C_7H_5Br_2N_3O$	27.39	1.64	13.69
IVd	55	186–187 (benzene)	33.28	2.75	14.45	$C_8H_8IN_3O$	33.24	2.79	14.53
VIIa	79	>350 (DMF)	28.78	1.15	16.76	$C_6H_3BrClN_3O$	29.00	1.22	16.91
VIId	80	200–202 (benzene)	34.54	2.50	15.05	$C_8H_7BrClN_3O$	34.75	2.55	15.20

[a] Compounds **IIa** and **IId** were also obtained from **VIa** and **VId**, respectively, in 79% yield.
[b] Compounds **IIIa** and **IIId** were also obtained from **VIa** and **VId** in 76 and 87% yield, respectively.

Table 2. ^{1}H NMR and IR spectral data of compounds **IIa**–**IId**, **IIIa**–**IIId**, **IVa**–**IVd**, **VIIa**, and **VIId**

Compound no.	^{1}H NMR spectrum,[a] δ, ppm	IR spectrum, ν(CO), cm^{-1}
IIa	7.49 s (1H, 7-H), 11.20 br.s (1H, 1-H), 11.74 br.s (1H, 3-H)	1700
IIb	3.33 s (3H, 1-CH_3), 7.48 s (1H, 7-H), 11.93 br.s (1H, 3-H)	1700
IIc	3.26 s (3H, 3-CH_3), 7.47 s (1H, 7-H), 11.40 br.s (1H, 1-H)	1695
IId	3.08 s (3H, 1-CH_3), 3.11 s (3H, 3-CH_3), 7.24 s (1H, 7-H)	1700
IIIa	7.51 s (1H, 7-H), 11.18 br.s (1H, 1-H), 11.75 br.s (1H, 3-H)	1695
IIIb	3.36 s (3H, 1-CH_3), 7.80 s (1H, 7-H), 11.70 br.s (1H, 3-H)	1700
IIIc	3.34 s (3H, 3-CH_3), 7.58 s (1H, 7-H), 11.80 br.s (1H, 1-H)	1695
IIId	3.39 s (3H, 1-CH_3), 3.45 s (3H, 3-CH_3), 7.36 s (1H, 7-H)	1700
IVa	7.58 d (1H, 7-H, J = 1.6 Hz), 8.17 d (1H, 5-H, J = 1.6 Hz), 11.04 br.s (1H, 3-H), 11.25 br.s (1H, 1-H)	1700
IVb	3.42 s (3H, 1-CH_3), 7.54 d (1H, 7-H, J = 1.6 Hz), 8.11 d (1H, 5-H, J = 1.6 Hz), 11.01 br.s (1H, 3-H)	1695
IVc	3.33 s (3H, 3-CH_3), 7.82 d (1H, 7-H, J = 1.6 Hz), 8.11 d (1H, 5-H, J = 1.6 Hz), 11.20 br.s (1H, 1-H)	1695
IVd	3.39 s (3H, 1-CH_3), 3.45 s (3H, 3-CH_3), 7.47 d (1H, 7-H, J = 1.6 Hz), 8.22 d (1H, 5-H, J = 1.6 Hz)	1700
VIIa	7.52 s (1H, 7-H), 11.19 br.s (1H, 1-H), 11.78 br.s (1H, 3-H)	1695
VIId	3.39 s (3H, 1-CH_3), 3.45 s (3H, 3-CH_3), 7.21 br.s (1H, 7-H)	1700

[a] The ^{1}H NMR spectra of compounds **IIa**–**IIc**, **IIIa**–**IIIc**, **IVa**–**IVc**, **VIIa**, and **VIIId** were recorded in DMSO-d_6, and of **IId**, **IIId**, and **IVd**, in $CDCl_3$.

chlorine, and the product was 5,6-dichloro-1,3-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one (**IId**). It was identical to a sample obtained from compound **Id** in the IR and ^{1}H NMR spectra and melting point (no depression of the melting point was observed for a mixed sample). The bromination of **IVd** under analogous conditions resulted in formation of a complex mixture of products which we failed to isolate and identify.

By bromination of 6-chloro(bromo)imidazo[4,5-*b*]-pyridin-2-ones **Va**, **Vd**, **VIa**, and **VId** we obtained both mixed dihalo derivatives, 5-bromo-6-chloro-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones **VIIa** and **VIId**, and 5,6-dibromo analogs **IIIa** and **IIId** (Scheme 2). The latter were identical to those obtained by bromination of compounds **Ia** and **Id** (Tables 1, 2).

Thus the chlorination and bromination of imidazo-[4,5-*b*]pyridin-2-one and its *N*-methyl derivatives readily occurs at positions *5* and *6* of the heterocyclic system, leading to the corresponding dihalo-substituted products, while the iodination gives only 6-iodo derivative. The chlorination of 6-iodo-1,3-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one (**IVd**) is accompanied by replacement of the iodine atom to afford 5,6-dichloro-1,3-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one (**IId**).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Gemini-200 spectrometer (200 MHz) from solutions in DMSO-d_6 and $CDCl_3$ using hexamethyldisiloxane as internal reference. The IR spectra were obtained on a UR-20 spectrometer from samples dispersed in mineral oil and on a Specord 75IR instrument in KBr. The purity of the products was checked by TLC on Silufol UV-254 plates using alcohol or chloroform as eluent; spots were visualized by irradiation with UV light or treatment with iodine vapor. Initial compounds **Ia**–**Id**, **Va**, and **VIa** were synthesized as described in [7]. Compound **Vd** was prepared by the procedure given in [8].

5,6-Dichloro-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones IIa–IId (*general procedure*). Dry gaseous

chlorine was passed over a period of 15 min through a solution of 1.5 mmol of imidazo[4,5-*b*]pyridin-2-one **Ia**–**Id** and 3.3 mmol of sodium acetate in 7 ml of glacial acetic acid. The mixture was then heated for 5 h on a boiling water bath, and the precipitate was filtered off and washed with water. When the product did not separate from the mixture, it was evaporated to dryness, the residue was mixed with 5 ml of water, and the mixture was neutralized with 25% aqueous ammonia. The precipitate was filtered off and purified by recrystallization from appropriate solvent (Table 1).

5,6-Dibromo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones IIIa–IIId (*general procedure***).** A solution of 3.3 mmol of bromine in 0.6 ml of glacial acetic acid was added dropwise to a solution of 1.5 mmol of imidazopyridine **Ia**–**Id** and 3 mmol of sodium acetate in 15 ml of glacial acetic acid. The mixture was heated for 5 h on a boiling water bath, and the precipitate was filtered off, washed with water, and recrystallized from appropriate solvent (Table 1).

6-Iodo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones IVa–IVd (*general procedure***).** A solution of 3.3 mmol of iodine(I) chloride in 2 ml of glacial acetic acid was added with stirring to a solution of 1.5 mmol of imidazopyridine **Ia**–**Id** and 3.3 mmol of sodium acetate in 5–7 ml of glacial acetic acid. The mixture was heated for 3 h at 95–100°C and for 1 h at 120°C and was evaporated to dryness. The residue was dissolved in 5 ml of water, and the solution was neutralized with 25% aqueous ammonia and treated with an aqueous solution of sodium sulfite to reduce liberated iodine (until the solution turned colorless). The precipitate was filtered off, dried, and purified by recrystallization from appropriate solvent (Table 1).

6-Bromo-1,3-dimethyl-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (VId). Dimethyl sulfate, 3 ml (30 mmol), was added in portions at 0°C to a solution of 2.3 g (10 mmol) of 6-bromo-3-methyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one [9] in 22 ml of 7% aqueous sodium hydroxide. After 0.5 h, the mixture was allowed to warm up to 20–25°C and was kept for 1 h at that temperature, 20 ml of 50% aqueous sodium hydroxide was added, and the mixture was cooled. The precipitate was filtered off and dried. Yield 1.8 g (75%), mp 163–165°C (from hexane–benzene, 3:1). IR spectrum, ν, cm^{-1}: 1705 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.40 s (3H, 1-CH_3), 3.46 s (3H, 3-CH_3), 7.28 d (1H, 7-H, J = 1.8 Hz), 8.09 d (1H, 5-H, J = 1.8 Hz). Found, %: C 39.47; H 3.25; N 17.19. $C_8H_8BrN_3O$. Calculated, %: C 39.69; H 3.33; N 17.36.

5,6-Dibromo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones IIIa and IIId and 5-bromo-6-chloro-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones VIIa and VIId (*general procedure***).** A solution of 2 mmol of bromine in 0.6 ml of glacial acetic acid was added in portions to a solution of 1.5 mmol of imidazopyridine **Va**, **Vd**, **VIa**, or **VId** and 3 mmol of fused sodium acetate in 15 ml of glacial acetic acid. The mixture was heated for 5 h on a boiling water bath and evaporated to dryness under reduced pressure, and the residue was dissolved in 5 ml of water and neutralized with 25% aqueous ammonia. The precipitate was filtered off, dried, and recrystallized from appropriate solvent (Table 1).

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