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SYNTHESIS OF DIHALOPICOLINE N-OXIDES AND THEIR 4-NITRO DERIVATIVES

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Three aminohalo-substituted α- and β-picolines, six dihalo-substituted α- and β-picolines, six dihalo-substituted α- and β-picoline N-oxides and six respective dihalo-4-nitropicoline N-oxides were synthesized in excellent yields. Some properties of the products were reported.

Electrophilic and nucleophilic substitutions proceed for N-oxides more easily than for parent compounds. Furthermore, N-oxides exhibit rich reactivity, i.e., deoxidative substitution, cycloaddition, and photorearrangement. It is therefore not surprising that these derivatives are often useful intermediates in organic synthesis.

Heterocyclic N-oxides can be used as auxiliary agents that are later eliminated in the course of the reaction, yielding the desired product, and as an N-protecting group that are removable by hydrogenolysis.

Heterocyclic N-oxides are useful as oxidants. Typical examples include dehydrogenation of diphenylethane to stilbene derivatives [1], aromatization of hydroaromatic and heterocyclic compounds, as well as cyclic dehydrogenation of 2-hydroxychalcones to flavones.

Heterocyclic N-oxides form complexes through the oxygen atom with various metals though they are not as strongly coordinating as the corresponding bases, which act through the nitrogen atom.

Heterocyclic N-oxides also have an important role as catalysts. In a two-phase reaction, N-oxides work as phase-transfer catalysts for the selective transport of organic or metallic compounds. Reported effects include the acceleration of nucleophilic substitution of alkyl and aryl halides and particularly of reactions involving transfer of acyl, sulfonyl, and phosphoryl groups. Many heterocyclic compounds have found application as pharmaceuticals, fungicides, herbicides, and insecticides (see monograph [1] for further literature).

Wide applications of pyridine N-oxide derivatives prompted us to study the synthesis of 2,3- or 2,5-dihalo-4-nitropicoline N-oxides. Within extensive investigations on the reactivity and structure of pyridine N-oxide performed in our department it was interesting to examine the spectroscopic properties of studied compounds and to compare with previous results [1-15]. The present paper deals with the synthesis of the above mentioned compounds and with determination of their chemical structures.

2-Halo-3(or 5)-nitropicolines were obtained in three-step synthesis, which is described previously [16]. These compounds readily undergo reduction with hydrazine hydrate in the presence of Raney nickel to amino derivatives (I-III). The diazotization of 2-halo-3(or 5)-aminopicolines leads to 2,3-(or 2,5)-dihalopicolines (IVa,b-Va,b) (Scheme 1).

Dihalopicolines (IVa, b-VIa, b) were oxidized to corresponding N-oxides using the procedure previously developed in our department [17]. In this way six new compounds (VIIa, b-IXa, b) were obtained. Nitro derivatives (Xa, b-XIIa, b) were obtained from N-oxides during the nitration reaction (Scheme 2).

All six 4-nitrodihalopicoline N-oxides (Xa, b-XIIa, b) are new compounds. Some properties and results of analyses of the investigated compounds are summarized in Table 1.

IR spectra of pyridine N-oxides are characterized by two strong absorption bands within the region 1200-1300 cm^{-1} (1265 cm^{-1} in CS_2) and at 835 cm^{-1} [18-20]. The position and nature of a substituent in the pyridine ring influence the

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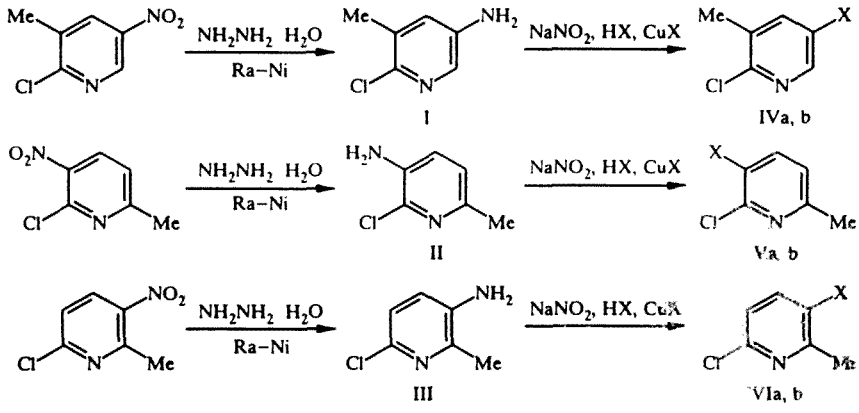
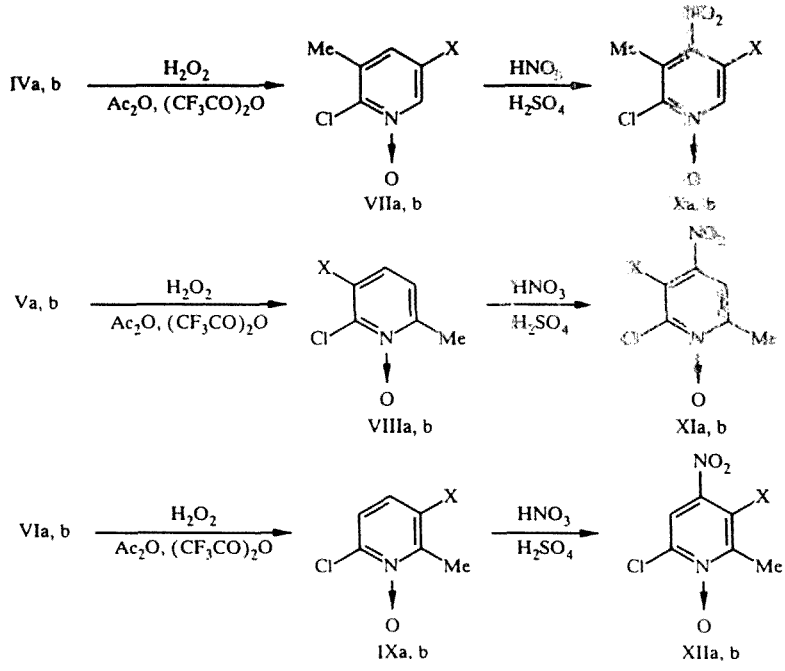
stretching frequency of the N-oxide group. In 2- and 4-picoline N-oxides the frequency of the stretching vibration of the N → O group is by 5 cm^{-1} lower than in pyridine N-oxide, which results from the electron-releasing properties of the methyl grup [18, 19]. The IR spectra of mono-substituted pyridine N-oxides had been previously described by Katritzky [19, 20] and Szafran [18, 21], however, the IR spectra of disubstituted pyridine N-oxides have not been reported so far.

Scheme 1



IV–VI a X = Cl, b X = Br

Scheme 2



IV — XII a X = Cl, b X = Br

IR spectra of 2-halopicoline N-oxides, 2,4-dihalopicoline N-oxides, and 2-halo-4-nitropicoline N-oxides have been reported in a previous paper [8]. The frequency of stretching vibrations of the N-oxide group is lower in 2,4-dihalopicoline N-oxides than in 2-halo-4-nitropicoline N-oxides and increases together with the increase of electron-withdrawing properties of substituents. The introduction of the chlorine into position 5 of 2-chloro-3-methylpyridine N-oxide results in the absorption shift towards the shorter wavelength (1253 → 1285 cm^{-1}) and testifies the complementarity of the interaction (resonance effect) between halogen in position 2 and halogen in position 5. As seen from Table 1, the withdrawing effect of bromine in position 5 is smaller than that of chlorine in the same position of 2,5-dihalo-3-methylpyridines. The spectra of 2,5-dichloro- and 2-chloro-5-bromo-6-methyl derivatives are shifted to lower wavenumbers as compared with 3-methyl derivatives, due to the electron-releasing properties and the position of the methyl group (1265, 1248 → 1285, 1280 cm^{-1}). Comparing IR spectra

TABLE 1. 5-Amino-2-chloro-3- or -6-picoline and 3-Amino-2-chloro-6-picoline, 2,3- or 2,5-Dihalopicolines, 2,3- or 2,5-Dihalopicoline N-Oxides and Products of Their Nitration

Compound, empirical formula (molecular weight)	mp, °C or bp, °C/mm Hg	Found, %/ Calculated, %			IR, cm^{-1}	Yield, % (cryst. from)
		C	H	N		
1	2	3	4	5	6	7
2-Chloro-3-methyl-5-aminopyridine (I), $C_6H_7N_2Cl$ (142,60)	93	51,20 50,53	4,87 4,96	19,87 19,65	1040 Cl, 1385 CH_3, 1470 CH_3, 1600 ν ring, 1660 NH_2, 3320 NH_2	68,55 (B + P)
2-Chloro-3-amino-6-methylpyridine (II), $C_6H_7N_2Cl$ (142,60)	158	49,93 50,53	4,48 4,96	18,95 19,65	1035 Cl, 1380 CH_3, 1478 CH_3, 1595 ν ring, 1640 NH_2, 3150 NH_2	80,5 (B + P)
2-Chloro-3-amino-6-methylpyridine (III), $C_6H_7N_2Cl$ (142,60)	94	50,55 50,53	4,80 4,96	19,66 19,65	1072 Cl, 1405 CH_3, 1454 CH_3, 1578 ν ring, 1630 NH_2, 3325 NH_2, 3480 NH_2	84 (B + P)
2,5-Dichloro-3-methylpyridine (IVa), $C_6H_5NCl_2$ (162,03)	52/2	48,90 48,48	3,01 3,11	9,01 8,65	1035 Cl, 1395 CH_3, 1460 CH_3, 1585 ν ring	45
5-Bromo-2-chloro-3-methylpyridine (IVb), C_6H_5NBrCl (206,48)	78/3	34,20 34,90	2,21 2,44	6,34 6,78	880 Br, 1064 Cl, 1395 CH_3, 1455 CH_3, 1550 ν ring	76
2,3-Dichloro-3-methylpyridine (Va), $C_6H_5NCl_2$ (162,03)	52...54/2	48,02 48,48	3,04 3,11	8,28 8,65	1035 Cl, 1378 CH_3, 1433 CH_3, 1575 ν ring	67,5
3-Bromo-2-chloro-6-methylpyridine (Vb), C_6H_5NBrCl (206,48)	68/2	35,10 34,90	2,50 2,44	7,01 6,78	825 Br, 1018 Cl, 1380 CH_3, 1430 CH_3, 1575 ν ring	60,0
2,5-Dichloro-6-methylpyridine (VIa), $C_6H_5NCl_2$ (162,03)	58/2	44,20 44,48	2,99 3,11	8,42 8,65	1060 Cl, 1378 CH_3, 1435 CH_3, 1580 ν ring	58
5-Bromo-2-chloro-6-methylpyridine (VIb), C_6H_5NBrCl (206,48)	80...84/2	34,72 34,90	2,28 2,44	6,50 6,78	828 Br, 1060 Cl, 1388 CH_3, 1430 CH_3, 1575 ν ring	54
2,5-Dichloro-3-methylpyridine N-oxide (VIIa), $C_6H_5NOCl_2$ (178,03)	159	40,48 40,48	2,83 2,83	7,69 7,87	1065 Cl, 1285 N—O, 1380 CH_3, 1460 CH_3	50 (B + P)
5-Bromo-2-chloro-3-methylpyridine N-oxide (VIIb), $C_6H_5NOBrCl$ (222,48)	158	32,52 32,39	2,11 2,26	6,16 6,30	985 Br, 1040 Cl, 1280 N—O, 1380 CH_3, 1455 CH_3	91 (B + P)
2,3-Dichloro-6-methylpyridine N-oxide (VIIIa), $C_6H_5NOCl_2$ (178,03)	104	40,24 40,48	2,72 2,83	7,62 7,87	1010 Cl, 1275 N—O, 1385 CH_3, 1487 CH_3	75 (B + P)
5-Bromo-2-chloro-6-methylpyridine N-oxide (VIIIb), $C_6H_5NOBrCl$ (222,48)	116	32,42 32,39	2,10 2,26	6,12 6,30	985 Br, 1040 Cl, 1240 N—O, 1380 CH_3, 1482 CH_3	60 (B + P)
2,5-Dichloro-6-methylpyridine N-oxide (IXa), $C_6H_5NOCl_2$ (178,03)	83	40,82 40,48	2,66 2,83	7,78 7,87	1025 Cl, 1265 N—O, 1375 CH_3, 1470 CH_3	78 (B + P)
5-Bromo-2-chloro-6-methylpyridine N-oxide (IXb), $C_6H_5NOBrCl$ (222,48)	112	32,58 32,39	2,16 2,26	6,18 6,30	860 Br, 998 Cl, 1248 N—O, 1370 CH_3, 1430 CH_3	68 (B + P)
2,5-Dichloro-3-methyl-4-nitropyridine N-oxide (Xa), $C_6H_4N_2O_3Cl_2$ (223,02)	140	32,41 32,31	1,67 1,81	12,41 12,56	846 NO_2, 1060 Cl, 1300 N—O, 1370 CH_3, 1450 CH_3, 1550 NO_2	65 (W + DMF)
5-Bromo-2-chloro-3-methyl-4-nitropyridine N-oxide (Xb), $C_6H_4N_2O_3BrCl$ (267,47)	160	27,21 26,94	1,41 1,51	10,34 10,47	898 NO_2, 1030 Br, 1060 Cl, 1295 N—O, 1350 CH_3, 1450 CH_3, 1550 NO_2	60 (W + DMF)

TABLE 1. (Continued)

Compound, empirical formula (molecular weight)	mp, °C or bp, °C/mm Hg	Found, %/ Calculated, %			IR, cm^{-1}	Yield, % (cryst. from)
		C	H	N		
1	2	3	4	5	6	7
2,3-Dichloro-6-methyl-4-nitropyridine N-oxide (XIa), $C_6H_4N_2O_3Cl_2$ (223,02)	125	32,18 32,31	1,65 1,81	12,42 12,56	850 NO_2, 1005 Cl, 1290 N—O, 1390 CH_3, 1440 CH_3, 1548 NO_2	77 (W + DMF)
3-Bromo-2-chloro-6-methyl-4-nitropyridine N-oxide (XIb), $C_6H_4N_2O_3BrCl$ (267,47)	108	26,41 26,94	1,30 1,51	10,09 10,47	890 NO_2, 970 Br, 1015 Cl, 1285 N—O, 1360 CH_3, 1440 CH_3, 1500 NO_2	90 (W + DMF)
2,5-Dichloro-6-methyl-4-nitropyridine N-oxide (XIIa), $C_6H_4N_2O_3Cl_2$ (223,02)	103	32,38 32,31	1,64 1,81	12,38 12,56	849 NO_2, 1035 Cl, 1283 N—O, 1385 CH_3, 1455 CH_3, 1560 NO_2	76 (W + DMF)
5-Bromo-2-chloro-6-methyl-4-nitropyridine N-oxide (XIIb), $C_6H_4N_2O_3BrCl$ (267,47)	105	26,69 26,94	1,33 1,51	10,24 10,47	840 NO_2, 950 Br, 1015 Cl, 1285 N—O, 1387 CH_3, 1455 CH_3, 1555 NO_2	80 (W + DMF)

*Note. B) benzene; P) petroleum ether; W) water; DMF) dimethylformamide.

of 4-nitro derivatives of the above-mentioned compounds shows smaller differences in wavenumbers between isomeric compounds than those occuring in derivatives without nitro group (1240-1285 cm^{-1}). This fact can be explained by the presence of 4-nitro group because an electron-withdrawing substituent in the 4-position favors the back donation of the N → O group and shifts this band to higher wavenumbers [15].

EXPERIMENTAL

The IR spectra were obtained on a Specord IR 75 instrument in KBr pellets or as film.

The elemental analyses were carried out using the Elemental Analyzer CHN + O Model 1104 Carlo Erba. Melting points were determined with a Büchi SMP-20 apparatus and uncorrected.

2-Halo-3(or 5)-aminopicolines (I-III). A solution of 0.1 mole (17.2 g) of corresponding chloronitropicoline in 150 ml of ethanol was added to a solution of 40 ml 80% of hydrazine hydrate in 60 ml ethanol with Raney nickel catalyst. Then the reaction mixture was heated to 70°C for 10 min and then the mixture was left standing for half an hour at room temperature. After filtering off nickel, the solvent was removed on a rotary evaporator under reduced pressure. Then water (100 ml) was added and the mixture was extracted with ether. The extract was dried with anhydrous magnesium sulfate, ether was removed, and residue was recrystallized from benzene + petroleum ether. Yields of products: 68-84%.

2,3-(or 2,5-)Dichloropicolines (IVa-VIa). 2-Chloro-(3 or 5)-aminopicoline 4.3 g (0.003 mole) was added to freshly prepared solution of CuCl in HCl (12 g $CuSO_4$ were dissolved in 50 ml of hot water and 8 g NaCl with 4 g $NaHSO_3$ were added). The reaction mixture was cooled down to 5-10°C and treated with small portions of saturated $NaNO_2$ solution. The temperature was kept ~10°C. After addition of $NaNO_2$ solution, the reaction mixture was heated to 50°C and kept at this temperature for 10 min. After heating, the mixture was alkalized with 50% KOH and distilled off water steam. The product of distillation was extracted with ether, the extract was dried with anhydrous sodium sulfate, ether removed, and the residue was used to reaction of N-oxidation. Yields of products: 45-67.5%.

2-Chloro-3-(or 5)bromopicolines (IVb-VIb). The bromo derivatives were obtained analogously to the above described 2,3- or 2,5-dichloro derivatives using freshly prepared solution of CuBr (20 g $CuSO_4$, 15 g KBr, 50 ml H_2O, 4 g $NaHSO_3$) in HBr instead of CuCl in HCl. Yields of products: 54-76%.

Dihalopicoline N-oxides (VIIa, b-IXa, b). Acetic anhydride (40 ml) was cooled to 0°C and then was treated in portions with 30% hydrogen peroxide (50 ml). The mixture was left standing in ice and then 10 ml of cooled trifluoroacetic

anhydride was added in small portions in 1 hour's time. Then corresponding dihalopicoline 0.07 mole was added slowly. The reaction mixture was left standing at room temperature for 1 h and then heated for 4 h at 75-80°C. The excess acetic acid was distilled off under reduced pressure and the residue alkalized with K_2CO_3 and extracted with ether–chloroform mixture, the extracted was dried with anhydrous sodium sulfate, solvents were removed. The reaction products were recrystallized from benzene-peltroleum ether. The properties and yields are summarized in Table 1.

Dihalo-4-nitropicoline N-oxides (Xa, b-XIIa, b). A solution of 0.05 mole of dichloro- (8.9 g) or bromochloropicoline N-oxides (11.1 g) in 30 ml of sulfuric acid was cooled and the resulting solution was added in small portions to nitrating mixture (20 ml of HNO_3, d = 1.52 + 40 ml of concentrated H_2SO_4). Nitration was carried out at 100°C for 3 hrs. After cooling the reaction mixture to room temperature it was poured on ice, neutralized with solid ammonium carbonate and finally with ammonia up to an alkaline reaction (litmus). Dihalo-4-nitropicoline N-oxide was filtered off. The filtrate was extracted with chloroform, the extract was dried with anhydrous sodium sulfate, chloroform was removed and the residue was combined with the above separated product. Dihalo-4-nitropyridine N-oxides formed are light yellow crystalline substances. They were recrystallized from water + dimethylformamide. Their properties and yields are summarized in Table 1.

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