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BROMINATION OF 1-ALKYL-2-PYRIDONES

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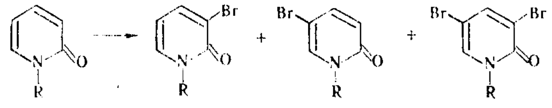
The corresponding monobromides were obtained in the bromination of 1-alkyl-2-pyridones with bonded bromine (with N-bromosuccinimide and dioxane dibromide). The conditions under which the yields of the mixtures of isomers were 60-80%, and almost no dibromides were obtained, were found. It was established that the ratios of the 3- and 5-bromo isomers depend on the character of the brominating agent.

It is known from the literature data that the bromination of 2-pyridones generally leads to 3,5-dibromo-substituted compounds [1, 2]. Up until now, the monobromination of 1-alkyl-2-pyridones has not been accomplished.* In the present research we studied the bromination of 1-alkyl-2-pyridones [1-methyl-, 1-ethyl-, and 1-butyl-2-pyridone (I-III)] by means of various brominating reagents, viz., bromine, dioxane dibromide, and N-bromosuccinimide, in order to investigate the orientation and also to obtain monobromides with the goal of subjecting them to further functionalization. Considerable amounts of dibromopyridones are formed along with monobromides in the reaction of bromine with alkylpyridones even at negative temperatures (see Table 1). Only bromination with bonded bromine (using dioxane dibromide and N-bromosuccinimide) completely excludes the formation of dibromides. We have shown that the bromination of pyridones I-III with dioxane dibromide and N-bromosuccinimide under various temperature conditions gives mixtures of 3-bromo-1-alkylpyridones (IVa-c) and 5-bromo-1-alkylpyridones (Va-c) (in 60-80% overall yields), which were isolated in individual form by means of column chromatography.



I-III IVa-c Va-c VIa-b

I, IV-VIa R = CH_3; II, IV-VIb R = C_2H_5; III, IV-Vc R = C_4H_9

It is apparent from the data in Table 1 that approximately equal amounts of 3- and 5-monobromides (IVa and Va) are formed when dioxane dibromide is used. Bromination with a more selective reagent — N-bromosuccinimide — gives primarily 5-bromo isomers V and can be used for the preparative synthesis of these compounds. A change in the temperature conditions had almost no effect on the overall yields of the bromination products and the ratios of 3- and 5-bromo isomers IV and V, which were determined by means of gas–liquid chromatography (GLC). The assignment of the signals of the protons of the pyridone ring in the PMR spectra of the bromination products was made on the basis of their multiplicities and also on the basis of the spin–spin coupling constants (SSCC), which, in agreement with the literature data [4], are larger for J_{34} than for J_{45} (see Table 2).

The results show that despite the calculated data [5], the 5 position of the pyridone ring is more reactive in bromination than the 3 position.

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*The 3- and 5-bromo-substituted pyridones described in the literature were obtained from the corresponding bromoaminopyridines [3].

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TABLE 1. Bromination of 1-Alkyl-2-pyridones

Starting pyridone	Brominating agent	Reaction temp., °C	Yields of bromination products							
			monobromides						dibromides	
			overall yield, %	3-Br		5-Br		ratio of the 3- and 5-bromo isomers	compound	%
				compound	%	compound	%			
1-Methyl-2-pyridone (I)	Dioxane dibromide	10	73	IVa	33	Va	40	1 : 1,3	VIa	8
	N-Bromosuccinimide	−10	76	IVa	16	Va	60	1 : 4	VIa	2
	N-Bromosuccinimide	10	70	IVa	14	Va	56	1 : 4	VIa	0
1-Ethyl-2-pyridone (II)	Br_2/CCl_4	−10	43	IVb	14	Vb	29	1 : 2	VIb	18
	Dioxane dibromide	10	80	IVb	39	Vb	41	1 : 1	VIb	5
	N-Bromosuccinimide	−10	60	IVb	10	Vb	50	1 : 5	VIb	3
	N-Bromosuccinimide	10	63	IVb	9	Vb	54	1 : 6	VIb	0
	N-Bromosuccinimide	50	65	IVb	13	Vb	52	1 : 4	VIb	0
1-Butyl-2-pyridone (III)	N-Bromosuccinimide	−10	76	IVc	18	Vc	58	1 : 3	VIc	0
	N-Bromosuccinimide	10	81	IVc	20	Vc	61	1 : 3	VIc	0

TABLE 2. PMR Spectra of the Products of Bromination of 1-Alkyl-2-pyridones

Compound	Chemical shift, ppm				SSCC, Hz			
	3-H	5-H	4-H	6-H	J_{34}	J_{45}	J_{56}	J_{46}
IVa	—	6,16 t	7,80	7,80	—	7,5	7,5	2
Va	6,43 d	—	7,45	7,82	9,3	—	—	3
IVb	—	6,16 t	7,60	7,60	—	7,3	7,3	2
Vb	6,50 d	—	7,47	7,82	9,5	—	—	3
IVc	—	5,94 t	7,35	7,71	—	7,2	7,2	3
Vc	6,30 d	—	7,30	7,61	9,7	—	—	2,5

These data, as well as the fact that the temperature has no effect on the site of incorporation of the substituent, make it possible to conclude that the prior coordination of the electrophilic particle at the CO group of the pyridone ring that evidently occurs in the nitration of 1-alkyl-2-pyridones [6] and determines incorporation of the nitro group preferably in the 3 position does not take place in the case of bromination with N-bromosuccinimide.

EXPERIMENTAL

The PMR spectra were recorded with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. Gas–liquid chromatography (GLC) was carried out with a Tsvet-104 chromatograph with a 3 m by 2 mm column containing 5% SE-30 on Chromaton NAW as the stationary phase and equipped with a flame-ionization detector; the carrier gas was nitrogen, the flow rate was 40 ml/min, and the column temperature was 170°C. Thin-layer chromatography (TLC) was carried out on activity II Al_2O_3 in ethyl acetate. The bromination products were separated by chromatography of the mixtures with a column (l = 750 mm, d = 40 mm) filled with Al_2O_3.

Bromination of 1-Alkyl-2-pyridones. A) Bromination with Dioxane Dibromide. A solution of 0.008 mole of dioxane dibromide in 20 ml of dioxane was added dropwise with stirring to a cooled (to 10°C) solution of 0.008 mole of 1-alkyl-2-pyridone I-III in 4 ml of dioxane at such a rate that the temperature of the reaction mixture did not exceed 10-12°C. After all of the dioxane dibromide had been added, stirring was continued at the same temperature for another hour. The reaction mixture was then poured into 30 ml of ice water, and the aqueous mixture was neutralized with 2 N NaOH solution and extracted with chloroform. The chloroform solution was dried and chromatographed with a column filled with Al_2O_3 (elution with ethyl acetate) to give, successively, 3,5-dibromo-1-alkyl-2-pyridones (VIa, b), 3-bromo-1-alkyl-2-pyridones (IVa, b), 5-bromo-1-alkyl-2-pyridones (Va, b), and the starting 1-alkyl-2-pyridones (I, II; ∼20%).

3-Bromo-1-methyl-2-pyridone (IVa). This compound was obtained in 33% yield and had R_f 0.57, bp 278-280°C (750 mm), and n_D^{25} 1.6619. PMR spectrum (CCl_4): 6.16 (1H, t, J_{45} = 7.5 Hz, 5-H) and 7.80 ppm (2H, m, 4-H, 6-H). Found: C 38.5; H 3.4; Br 42.3%. C_6H_6BrNO. Calculated: C 38.3; H 3.2; Br 42.5%.

5-Bromo-1-methyl-2-pyridone (Va). This compound was obtained in 40% yield and had R_f 0.49 and mp 52-53°C (from petroleum ether) [mp 53°C (ether–petroleum ether) [7]].

3,5-Dibromo-1-methyl-2-pyridone (VIa). This compound was obtained in 8% yield and had R_f 0.72 and mp 175-176°C (from ethanol) (mp 176°C [8]).

3-Bromo-1-ethyl-2-pyridone (IVb). This compound was obtained in 39% yield and had R_f 0.62, bp 282-284°C (750 mm), and n_D^{25} 1.6714. PMR spectrum (CCl_4): 6.16 (1H, t, J_{45} = 7.3 Hz, 5-H) and 7.60 ppm (2H, m, 4-H, 6-H). Found: C 41.3; H 4.1; Br 39.3%. C_7H_8BrNO. Calculated: C 41.4; H 4.1; Br 39.6%.

5-Bromo-1-ethyl-2-pyridone (Vb). This compound was obtained in 41% yield and had R_f 0.55 and mp 62-63°C (from hexane) (bp 242-245°C [9]).

3,5-Dibromo-1-ethyl-2-pyridone (VIb). This compound was obtained in 5% yield and had R_f 0.75 and mp 106-108°C (from ethanol) [mp 109°C (from ethanol) [2]].

B) Bromination with N-Bromosuccinimide. A solution of 0.01 mole of N-bromosuccinimide in 5 ml of dimethylformamide (DMF) was added dropwise with stirring at the appropriate temperature (−10, +10, and +50°C) to a solution of 0.01 mole of 1-alkyl-2-pyridone I-III in 30 ml of DMF, after which stirring was continued for 4 h at the predesignated temperature. The reaction mixture was then poured into 50 ml of ice water, and the aqueous mixture was extracted with methylene chloride. The extract was dried with magnesium sulfate. According to the results of TLC (on Al_2O_3 in ethyl acetate), mixtures of monobromo-substituted pyridones IVa-c and Va-c containing very small amounts of dibromides VIa, b and starting pyridones I and II are formed as a result of bromination. The residues after removal of the solvent by distillation were analyzed by GLC.

Monobromo-1-butyl-2-pyridones III were isolated in individual form by chromatography of solutions of the reaction mixtures in methylene chloride with a column filled with Al_2O_3 (elution with ethyl acetate).

3-Bromo-1-butyl-2-pyridone (IVc). This compound was obtained in 18% yield and had R_f 0.86, bp 130-132°C (5 mm), and n_D^{25} 1.6535. PMR spectrum (CCl_4): 5.94 (1H, t, J_{45} = 7.2 Hz, 5-H), 7.35 (1H, t, 4-H), and 7.71 ppm (1H, t, 6-H). Found: C 46.8; H 5.3; N 6.0%. $C_9H_{12}BrNO$. Calculated: C 47.0; H 5.2; N 6.0%.

5-Bromo-1-butyl-2-pyridone (Vc). This compound was obtained in 58% yield and had R_f 0.78, bp 128-129°C (3 mm), and n_D^{25} 1.6515. PMR spectrum (CCl_4): 6.30 (1H, d, J_{34} = 9.7 Hz, 3-H), 7.30 (1H, q, 4-H), and 7.61 ppm (1H, t, 6-H). Found: C 47.1; H 5.1; N 6.2%. $C_9H_{12}BrNO$. Calculated: C 47.0; H 5.2; N 6.0%.

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