BROMINATION OF 2-(2'-FURYL)IMIDAZO[1,2-a]PYRIDINE AND ITS DERIVATIVES

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The action of bromine and N-bromosuccinimide on 2-(2'-furyl)imidazo[1,2-a]pyridine and its 3-nitroso, 5'-bromo, and 5'-nitro derivatives was studied.

According to the NMR spectrum, imidazo[1,2-a]pyridine is brominated in the 3 position [1]. The bromination of 2-phenylimidazo[1,2-a]pyridine also occurs in the 3 position without involving the phenyl group [2, 3]. In addition, it might have been assumed that the bromination of 2-(2'-furyl)imidazo[1,2-a]pyridine (I) could occur not only in the imidazole ring but also in the free α position of the furan ring, in analogy with the bromination of 2-(2'-thienyl)imidazo[1,2-a]pyridine [3].

We have used thin-layer chromatography (TLC) to establish that 3-bromo-2-(2'-furyl)imidazo[1,2-a]-pyridine (V) is formed exclusively when a solution of 1 mole of bromine in chloroform or glacial acetic acid is added slowly to a cooled solution of I in the same solvent and the hydrobromide of the bromo derivative formed is neutralized, while 3-bromo-2-(5'-bromo-2'-furyl)imidazo[1,2-a]pyridine VII) is also obtained along with V in small amounts when the bromine is added more rapidly and the mixture is not cooled. The 3-bromo derivative (V) was extracted from the mixture with boiling n-octane. In contrast to VI, which we have previously described [4], V has a lower melting point and is more unstable – it darkens rapidly in light and is converted to a light-colored insoluble product in alcohol and ether solutions even in the dark. The structure of 3-bromo derivative V was proved indirectly by the fact that it was impossible to nitrosate it with n-butyl nitrite.

The action of 2 moles of bromine on I gives the hydrobromide of the dibromo derivative (III), in which the position of one of the bromine atoms in the furan ring was proved by alternative synthesis of III from VI.

The action of 3 or more moles of bromine on I in the same solvents without heating gives the perbromide of the hydrobromide of the dibromo derivative (IV). The latter is also formed when the hydrobromide of the dibromo derivative (III) is treated with bromine in chloroform.

The action of aqueous alkali and alkali metal carbonates or acetates on III and IV gives 3-bromo-2-(5'-bromo-2'-furyl)imidazo[1,2-a]pyridine (VII), while heating IV with dioxane brings about cleavage of a molecule of bromine and formation of the hydrobromide of the dibromo derivative (III).

According to the results of TLC, the bromination of I with 1 mole of N-bromosuccinimide (NBS) leads to a mixture of monobromo derivative V and dibromo derivative VII. Only VII is formed in the reaction of I with 2 moles of NBS.

Compound VII is also formed by the action of 2 moles of NBS on 3-nitroso-2-(2'-furyl)imidazo[1,2-a]-pyridine (VIII). A small amount of 3-nitroso-2-(5'-bromo-2'-furyl)imidazo[1,2-a]pyridine (IX), along with VII, was detected by chromatography in the products of the reaction of VIII with 1 mole of NBS. We have previously obtained IX by the nitrosation of VI [5]. A similar case of displacement of a nitroso group by bromine was noted in the action of bromine on 3-nitroso-2-(2'-thienyl)imidazo[1,2-a]pyridine [6].

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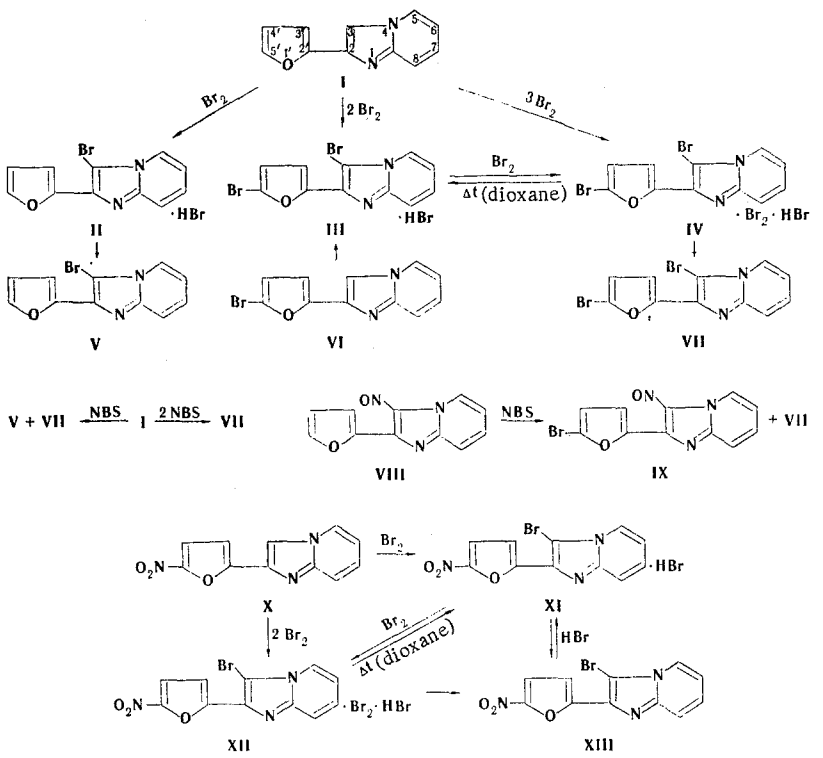


The structures of the products of the bromination of I (V, VI, and VII) were confirmed by PMR spectroscopy (Table 1). Three groups of signals are observed in the spectrum of I. The character of the first group of signals (δ 7.59, 6.89, and 6.56 ppm) makes it possible, according to [7], to assign it to the absorption of the furyl group. The singlet at weak field (8.05 ppm) is due to the 3-H proton. The third group of signals – a complex multiplet of the ABCD type at 6.7-7.6 ppm and two quartets at 8.49 and 8.39 ppm – arises due to absorption of the pyridine ring of the molecule. It is easy to follow the disappearance of one or the other signal, as well as the change in the character of the furyl multiplet, in the spectra of the bromination products and to unambiguously establish substitution by the bromine atom.

2-(5'-Nitro-2'-furyl)imidazo[1,2-a]pyridine (X) reacts with 1 mole of bromine to give the hydrobromide of the monobromo derivative (XI), which is converted to base XII not only on treatment with alkaline agents but also by the action of water, alcohol, or dimethylformamide, as well as by prolonged storage in air. As in the case of I, the action of excess bromine on X leads to the formation of the perbromide of the hydrobromide of XII, which is converted to XI on heating in dioxane and to the base (XIII) on refluxing with alcohol.

In contrast to the starting 2-(2'-furyl)imidazo[1,2-a]pyridine, which gives a carmine-red color with concentrated sulfuric acid, its 3-bromo derivative induces a bright dark-blue color, its 5'-bromo derivative causes a dark-blue color that gradually is converted to blue-violet, its 3,5'-dibromo derivative gives initially a lemon-yellow color that changes rapidly to stable malachite green, while 3-bromo-2-(5'-nitro-2'-furyl)imidazo[1,2-a]pyridine gives a yellow color. The color vanishes on dilution with water.

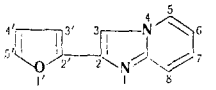
EXPERIMENTAL

The UV spectra of alcohol solutions (c $5 \cdot 10^{-5}$ M) were recorded with an SF-4A spectrophotometer. The PMR spectra of 20% solutions in acetone were obtained with a Perkin-Elmer R-12 A spectrometer (60 MHz) with cyclohexane as the internal standard relative to the δ scale.

Thin-layer chromatography was accomplished on Silufol UV_{254} plates with the following solvent mixtures: benzene–ethyl acetate (2:3) (system 1), benzene–ethyl acetate (1:2) (system 2), and chloroform–methanol–acetic acid (15:4:1) (system 3). The R_f values of the compounds obtained and the color of the fluorescence of their spots on the chromatograms are presented in Table 2.

3-Bromo-2-(2'-furyl)imidazo[1,2-a]pyridine (V). A. A solution of 6.2 g (39 mmole) of bromine in 20 ml of $CHCl_3$ was added in the course of 1 h with stirring and cooling to a solution of 7.2 g (39 mmole) of I

TABLE 1. Parameters of the PMR Spectra of 2-(2'-Furyl)imidazo-[1,2-a]pyridine and Its Bromo Derivatives



Compound	Chemical shifts, δ, ppm					
	3'-H	4'-H	5'-H	3-H	5-H	6-H, 7-H, 8-H
I	6,89	6,56	7,59	8,05	8,44	6,7—7,6
V	7,04	6,61	7,59	—	8,28	6,9—7,7
VI	6,85*	6,57*	—	8,10	8,44	6,8—7,7
VII	7,01*	6,60*	—	—	8,28	6,9—7,7

*Doublet, $^3J_{3',4'}$ - 3.3 Hz.

TABLE 2. Thin-Layer Chromatography of the Products of Bromination of 2-(2'-Furyl)imidazo[1,2-a]pyridine and Its Derivatives

Compound	$R_f \times 100$			Fluorescence color
	system 1	system 2	system 3	
I	27	23	50	Bright-blue
V	53	41	87	Blue
VI	42	31	73	Blue
VII	62	50	92	Blue
VIII	35	23	85	Light-green
IX	54	—	88	Light-green
X	35	26	86	Light-green
XIII	50	39	90	Light-green

in 60 ml of $CHCl_3$, and the precipitate was removed by filtration after 1 h and washed with chloroform to give 10.88 g (81%) of the crude hydrobromide (II) of V with mp 175-177°. Recrystallization from absolute alcohol–ether gave a product with mp 184-185°. Found: C 37.6; H 2.5; Br 45.2%. $C_{11}H_7BrN_2O \cdot HBr \cdot 0.5H_2O$. Calculated: C 37.4; H 2.6; Br 45.3%. UV spectrum: λ_{max} 250, 325 nm, log ε 4.46, 3.87.

A 5.44 g sample of II was dissolved in 25 ml of water and neutralized with 3.5 ml of 20% sodium hydroxide, and the precipitate was removed by filtration, washed with water, and dried to give 3.53 g (85%) of crude V with mp 90-93°. Recrystallization from n-octane or aqueous alcohol gave a product with mp 102-103°. Found: C 49.8; H 2.7; Br 29.9%. $C_{11}H_7BrN_2O$. Calculated: C 50.5; H 2.7; Br 30.4%.

When bromine was added in the course of 30 min without cooling, VII was detected by chromatography in the crude product – the base with mp 85-88°. Pure V was extracted from the mixture with hot n-octane and recrystallized from aqueous alcohol to give a product with mp 102-103°.

B. A solution of 1.56 ml (30 mmole) of bromine in 10 ml of glacial acetic acid was added in the course of 30 min at 50-60° to 5.62 g (30 mmole) of I in 50 ml of glacial acetic acid, and the mixture was stirred, cooled, and diluted with 150 ml of ether. The precipitated II was removed by filtration to give 9.13 g (88%) of product. A 6.5 g sample of II was neutralized with aqueous alkali, the oily layer was separated, and V was extracted from it with 300 ml of boiling n-octane. The octane extract was cooled to 0°, and 1.5 g of V with mp 88-90° was removed by filtration. Vacuum distillation of the octane from the filtrate gave an additional 1 g of V with mp 102-103° (from n-octane). Found: C 51.1; H 3.1; N 10.8%. $C_{11}H_7BrN_2O$. Calculated: C 50.5; H 2.7; N 10.7%. UV spectrum: λ_{max} 255, 327 nm, log ε 4.32, 3.79.

Hydrochloride of V. This was obtained by the action of alcoholic hydrogen chloride on V with precipitation by the addition of absolute ether to give a product with mp 180-184°. UV spectrum: λ_{max} 250, 324 nm, log ε 4.43, 3.87.

Perchlorate of V. This was obtained as colorless needles with mp 170-173° by the action of 57% perchloric acid on the base. Found: C 36.3; H 2.5; N 7.6%. $C_{11}H_7BrN_2O \cdot HClO_4$. Calculated: C 36.3; H 2.2; N 7.7%.

Picrate of V. This had mp 185-187° (from alcohol). Found: C 41.8; H 2.4%. $C_{11}H_7BrN_2O \cdot C_6H_3N_3O_7$. Calculated: C 41.5; H 2.1%.

3-Bromo-2-(5'-bromo-2'-furyl)imidazo[1,2-a]pyridine Dibromide Hydrobromide (IV). A. Solutions of 3.68 g (20 mmole) of I in 20 ml of chloroform or glacial acetic acid and of 3.1 ml (60 mmole) of bromine

in 15 ml of the same solvent were mixed, and the green precipitate was washed with chloroform to give 11.11 g (95%) of a product with mp 155° (dec.). Found: C 23.2; H 1.5; N 5.1%. $C_{11}H_6Br_2N_2O \cdot Br_2 \cdot HBr$. Calculated: C 22.7; H 1.2; N 4.8%.

B. The compound was also obtained as yellow-green crystals with mp 155-157° (dec.) by the action of a solution of bromine in chloroform on III in chloroform. This product did not depress the melting point of the sample obtained by method A. Found: N 5.0%. $C_{11}H_6Br_2N_2O \cdot Br_2 \cdot HBr$. Calculated: N 4.8%.

3-Bromo-2-(5'-bromo-2'-furyl)imidazo[1,2-a]pyridine (VII). A. A solution of 2.08 ml (40 mmole) of bromine in 10 ml of chloroform was added gradually to a solution of 3.68 g (20 mmole) of I in 20 ml of chloroform, and the precipitate was removed by filtration after 2 h to give 6.93 g (82%) of the hydrobromide (III) of VII. Crystallization from absolute alcohol–ether gave colorless crystals with mp 237°. Found: C 31.0; H 2.0; Br 56.1; N 6.8%. $C_{11}H_6Br_2N_2O \cdot HBr$. Calculated: C 31.2; H 1.7; Br 56.2; N 6.6%.

Neutralization of a solution of 1.0 g of III in 10 ml of water with 25% NH_4OH or KOH precipitated 0.46 g (57%) of VII with mp 136° (from water). Found: N 8.1%. $C_{11}H_6Br_2N_2O$. Calculated: N 8.2%. UV spectrum: λ_{max} 261, 325 nm, log ε 4.47, 4.00.

B. A 1.0 g sample of IV was triturated with 5 ml of 10% NH_4OH, and the solid product was separated and recrystallized from aqueous methanol to give a product with mp 135-136°. Found: C 38.8; H 2.0; Br 46.4%. $C_{11}H_6Br_2N_2O$. Calculated: C 38.6; H 1.7; Br 46.4%.

C. The base, with mp 136° was obtained in 75% yield by the action of an equimolecular amount of bromine on VI in chloroform and subsequent neutralization. The product was chromatographically identical to VII prepared from III and IV.

D. A mixture of 1.84 g (10 mmole) of I, 3.58 g (20 mmole) of NBS, and 40 ml of chloroform was refluxed for 1 h and allowed to stand for 24 h at room temperature. The precipitate was removed by filtration and washed with 35 ml of chloroform. The chloroform extract was washed with aqueous NaOH and water, and the solvent was evaporated to give 2.76 g (80%) of VII with mp 134-135.5° (from aqueous alcohol). The product was chromatographically identical to VII prepared by the methods described above (see Table 2).

E. A mixture of 2.12 g (10 mmole) of 3-nitroso-2-(2'-furyl)imidazo[1,2-a]pyridine (VIII) [5], 3.58 g (20 mmole) of NBS, and 50 ml of CCl_4 was refluxed for 2 h, during which nitrous gases were evolved. The reaction mixture was allowed to stand for 3 days, and the precipitate was separated and washed with 30 ml of CCl_4 and 50 ml of $CHCl_3$. Evaporation of the filtrate and the wash liquids gave 1.76 g of a reaction product, which according to TLC, contained along with VII,3-nitroso-2-(5'-bromo-2'-furyl)imidazo[1,2-a]-pyridine (IX) with mp 128-132° (from aqueous alcohol, three times).

Hydrochloride of VII. This was obtained from VII and alcoholic HCl and had mp 198-201° (dec., from alcohol–ether). Found: C 32.1; H 2.7; N 6.7%. $C_{11}H_6Br_2N_2O \cdot HCl \cdot H_2O$. Calculated: C 32.2; H 2.3; N 7.1%. λ_{max} 255, 260, 325 nm, log ε 4.45, 4.46, 3.99.

Perchlorate of VII. This was obtained from VII and 57% $HClO_4$ and had mp 234° (dec., from alcohol–ether). Found: C 29.6; H 2.0; N 6.6%. $C_{11}H_6Br_2N_2O \cdot HClO_4$. Calculated: C 29.9; H 1.6; N 6.3%.

Picrate of VII. This had mp 193-194° (from alcohol). Found: C 36.1; H 1.8; Br 28.3%. $C_{11}H_6Br_2N_2O \cdot C_6H_3N_3O_7$. Calculated: C 35.8; H 1.6; Br 28.0%.

3-Bromo-2-(5'-nitro-2'-furyl)imidazo[1,2-a]pyridine Dibromide Hydrobromide (XII). A. A 2.1 ml (40 mmole) sample of bromine in 30 ml of chloroform was added in the course of 30 min to a solution of 2.29 g (10 mmole) of X in 500 ml of chloroform, and the light-yellow precipitate was removed by filtration and washed with chloroform to give 5.46 g (almost quantitative) of a product with mp 165-168°. Found: C 22.6; H 1.4; Br 56.5; N 7.4%. $C_{11}H_6BrN_3O_3 \cdot Br_2 \cdot HBr \cdot H_2O$. Calculated: C 23.4; H 1.6; Br 56.7; N 7.5%.

B. A 0.5 g sample of XI was triturated with a solution of bromine in chloroform, and the precipitate was removed by filtration to give a product with mp 166-168° that did not depress the melting point of the sample prepared by method A. Found: C 23.3; H 2.0; Br 56.0%. $C_{11}H_6BrN_3O_3 \cdot Br_2 \cdot HBr \cdot H_2O$. Calculated: C 23.4; H 1.6; Br 56.7%.

3-Bromo-2-(5'-nitro-2'-furyl)imidazo[1,2-a]pyridine Hydrobromide (XI). A. A solution of 0.52 ml (10 mmole) of bromine in $CHCl_3$ or CH_3COOH was added to a solution of 2.29 g (10 mmole) of X in 500 ml of the same solvent, and the precipitate was removed by filtration to give a product with mp 208-211° (dec.). Found: N 10.5%. $C_{11}H_6BrN_3O_3 \cdot HBr$. Calculated: N 10.8%.

B. Compound XII was refluxed for 15 min in dioxane, and the precipitate was removed by filtration to give a product with mp 213-215° (dec.). Found: C 34.4; H 2.3; N 10.9%. $C_{11}H_6BrN_3O_3 \cdot HBr$. Calculated: C 34.0; H 1.8; N 10.8%.

C. Compound XIII was triturated with 40% HBr, and the product was washed with acetone to give a substance with mp 208-210° (dec.).

3-Bromo-2-(5'-nitro-2'-furyl)imidazo[1,2-a]pyridine (XIII). This was obtained by heating XI with pyridine, dimethylformamide, alcohol, or water and had mp 248-249°. Found: C 43.0; H 2.1; N 13.8%. $C_{11}H_6BrN_3O_3$. Calculated: C 42.9; H 1.9; N 13.6%. UV spectrum: λ_{max} 235, 278, 295, 365 nm, log ε 4.60, 4.03, 3.97, 4.25.

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