Furopyridines. II. Bromination and Nitration of Furo[2,3-*b*]-, Furo[3,2-*b*]-, Furo[2,3-*c*]- and Furo[3,2-*c*]pyridine

Shunsaku Shiotani* and Hiroyuki Morita

College of Liberal Arts, University of Toyama,
Gofuku 3190, Toyama 930, Japan

Masatoshi Inoue and Toshimasa Ishida

Osaka College of Pharmacy, Kawai 2-10-65, Matsubara,
Osaka 580, Japan

Yoichi Iitaka and Akiko Itai

Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo Bunkyo-ku, Tokyo 113, Japan

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In order to reveal the reactivities of furopyridines, we undertook bromination and nitration of four furopyridines (**1**, **2**, **3** and **4**) whose chemical properties had been almost unknown. Bromination of **1**, **2**, **3** and **4** gave the corresponding *trans*-2,3-dibromo-2,3-dihydro derivatives **6**, **8**, **10** and **12**, respectively, which were converted to 3-bromofuropyridines **7**, **9**, **11** and **13** by treatment with sodium hydroxide in aqueous methanol. Nitration of **1** with a mixture of fuming nitric acid and sulfuric acid afforded a mixture of addition products **14a**, **14b** and **14c** and 2-nitro derivative **15**. Both **14a** and **14b** were easily converted to **15** by treatment with sodium bicarbonate. Compound **2** was nitrated to give a mixture of *cis*- and *trans*-2-nitro-3-hydroxy-2,3-dihydro derivative **16a** and **16b** and 2-nitro derivative **17**. The *cis* isomer **16a** was transformed to the *trans* isomer **16b** by refluxing on silica gel in ethyl acetate. Compound **16b** was dehydrated with acetic anhydride to give **17**. Nitration of **3** gave a nitrolic acid derivative **20**. Nitration of **4** gave a mixture of 2-nitro derivative **22** and 3-(trinitromethyl)pyridin-4-ol (**23**). The structures of **20** and **23** were established by single crystal X-ray analysis. The differences of behavior observed in these reactions are discussed in connection with the results of the determination of p*K*a values and the relative reactivities of deuteriodeprotonation of these furopyridines.

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Furopyridines are of chemical interest because of their similarity to quinoline, isoquinoline and benzofuran which are important nuclei in many biologically active compounds. While derivatives of six possible systems and five of the parent structures **1** [1], **2** [2], **3** [3], **4** [4] and **5** [5] are known from the literature, there are very few studies on the chemical properties of these systems.

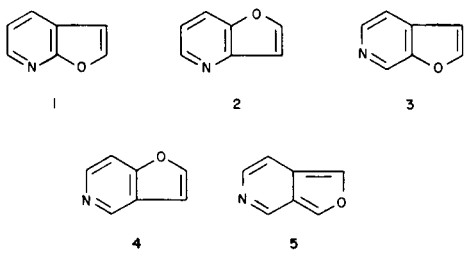
Furopyridines consist of an electron rich five-membered furan ring fused to an electron poor pyridine ring. This raises the question of how annelation will perturb the electronic structure of each individual ring and how this will be manifested in the reactivity of these substrates. In order to reveal the actual chemical reactivities, we undertook several typical electrophilic reactions of furopyridines. In this paper we report the bromination, nitration and hydrogen exchange of furo[2,3-*b*]- (**1**), furo[3,2-*b*]- (**2**),

Table I

^{1}H NMR (60 MHz) Data for 3-Bromo- and 2-Nitrofuropyridines in Deuteriochloroform [a]

Compound	H - 2	H - 3	H - 4	H - 5	H - 6	H - 7
7	7.70 (s)	—	7.85 (dd)	7.27 (dd)	8.35 (dd)	—
			($J_{4,5}$ = 7.6)	($J_{5,6}$ = 4.8)	($J_{4,6}$ = 1.6)	
9	7.85 (s)	—	—	8.61 (dd)	7.20 (dd)	7.70 (dd)
				($J_{5,6}$ = 4.4)	($J_{6,7}$ = 8.0)	($J_{5,7}$ = 1.2)
11	7.75 (s)	—	7.52 (dd)	8.52 (d)	—	8.86 (d)
			($J_{4,5}$ = 5.2)			($J_{4,7}$ = 0.8)
13	7.63 (s)	—	8.86 (d)	—	8.55 (d)	7.40 (dd)
			($J_{4,7}$ = 0.8)		($J_{6,7}$ = 5.6)	
15	—	7.57 (s)	8.19 (dd)	7.45 (dd)	8.62 (dd)	—
			($J_{4,5}$ = 7.8)	($J_{5,6}$ = 4.6)	($J_{4,6}$ = 1.6)	
17	—	7.77 (d)	—	8.73 (dd)	7.47 (dd)	7.92 (ddd)
		($J_{3,7}$ = 0.8)		($J_{5,6}$ = 4.6)	($J_{6,7}$ = 8.4)	($J_{5,7}$ = 1.2)
22 [b]	—	7.65 (d)	9.02 (d)	—	8.62 (d)	7.48 (ddd)
		($J_{3,7}$ = 0.8)	($J_{4,7}$ = 0.9)		($J_{6,7}$ = 5.4)	

[a] Abbreviations: s, singlet; d, doublet; dd, double doublet; ddd, doublet of double doublet. Chemical shifts (δ values) are in parts per million from tetramethylsilane. Coupling constants (J) are in Hz. [b] See reference [6].



furo[2,3-*c*]- (**3**) and furo[3,2-*c*]pyridine (**4**).

The bromination of **1** with 1.2 moles of bromine in carbon tetrachloride afforded *trans*-2,3-dibromo-2,3-dihydrofuro[2,3-*b*]pyridine (**6**) in 95% yield as a sole product. The *trans* configuration was confirmed by the coupling constant between H-2 and H-3, J = 0.0 Hz, in its nmr spectrum [6]. The treatment of **6** with sodium hydroxide in aqueous methanol gave a monobromo compound **7**. The chemical shift of the proton in the furan ring, at δ 7.70 (pure singlet), in its nmr spectrum strongly suggested the position of the bromine atom to be at C-3. This suggestion was confirmed as follows. 2-Deuteriofuro[2,3-*b*]pyridine (**1-D**) obtained by the reaction of **1** with sodium deuteroxide in methanol-d_4 was brominated to give the addition product **6-D**. Compound **6-D** was dehydrobrominated with sodium hydroxide in aqueous methanol to afford 2-deuterio-3-bromo derivative **7-D**. In the nmr spectrum compound **7-D** showed no signal at δ 7.70 appeared in that of **7**.

Treatment of **2** with 1.2 moles of bromine gave an unstable yellow solid product which was suggested to be the perbromide **2-Br$_2$** of **2** by the fact that its nmr spectrum was much similar to that of **2** and that this compound gave **2** by treatment with sodium hydroxide in methanol. The bromination of **2** with 3 moles of bromine afforded *trans*-2,3-dibromo-2,3-dihydrofuro[3,2-*b*]pyridine (**8**) in 92% yield, which was converted to 3-bromo derivative **9** by dehydrobromination with sodium hydroxide. Their structures were established by the nmr spectroscopy (Table I).

Furo[2,3-*c*]pyridine (**3**) also gave the perbromide **3-Br$_2$** as unstable yellow solid by the reaction with 1.2 moles of bromine. The bromination of **3** with 3 moles of bromine gave a mixture of the perbromide **3-Br$_2$** and *trans*-2,3-dibromo-2,3-dihydro compound **10** from which 3-bromo derivative **11** was obtained in 20% yield accompanying the recovery of **3** (60%) by treatment with sodium hydroxide.

Table II

Ionization Constants of Furopyridines

Compounds	p*Ka*/20°
1 [a]	0.87 [f]
2 [b]	4.11 [g]
3 [c]	5.43 [g]
4 [d]	5.79 [g]
7	−0.23 [f]
9	2.38 [f]
11	4.54 [f]
13	4.93 [f]
4-(2-Me) [e]	6.41 [f]
quinoline	5.01 [f]
	4.91 [g]
	4.94 [h]

[a] See reference [1a]. [b] See reference [2a]. [c] See reference [3]. [d] See reference [4a]. [e] See reference [6]. [f] Uv absorption method. [g] Titration method. [h] See reference [16].

Scheme I

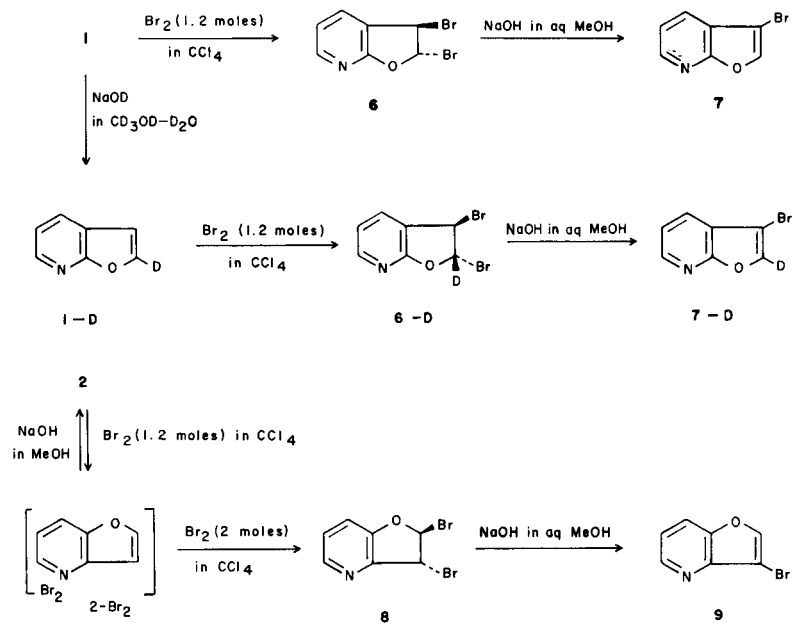


Table III

Atomic Coordinates with Their Estimated Standard Deviations

Compound **18**

Atom	x	y	z
Cl	0.9749(2)	9.2439(1)	0.3381(1)
N(1)	1.1457(4)	0.0585(1)	0.6834(2)
C(2)	0.9674(4)	0.0887(1)	0.5479(3)
C(3)	1.0449(4)	0.1141(1)	0.5159(3)
O(3)	0.7231(3)	0.0597(1)	0.4674(2)
C(4)	1.3026(4)	0.1689(1)	0.6156(2)
C(5)	1.4642(4)	0.1372(1)	0.7450(3)
C(6)	1.3886(4)	0.0847(1)	0.7721(3)
C(7)	0.8680(4)	0.1758(1)	0.3745(2)
N(8)	0.6394(3)	0.1509(1)	0.2876(2)
O(9)	0.4797(3)	0.1813(1)	0.1585(2)
N(10)	0.9903(3)	0.0704(1)	1.0967(2)
O(11)	1.0342(3)	0.1137(1)	1.0193(2)
O(12)	1.1668(3)	0.0583(1)	1.2274(2)
O(13)	0.7612(3)	0.0406(1)	1.0479(3)

Compound **20'**

Atom	x	y	z
N(1)	1.0475(3)	−0.0417(1)	0.7037(1)
C(2)	1.0903(3)	0.0184(2)	0.7413(1)
C(3)	1.0795(3)	0.1159(2)	0.7359(1)
C(4)	1.0227(3)	0.1535(1)	0.6897(1)
C(5)	0.9778(3)	0.0915(2)	0.6504(1)
C(6)	0.9911(3)	−0.0054(2)	0.6591(1)
O(7)	0.9278(3)	0.1288(1)	0.6055(1)
C(8)	1.0196(3)	0.2569(1)	0.6804(1)
N(9)	1.1380(3)	0.3211(1)	0.6867(1)
O(10)	1.2986(2)	0.2882(1)	0.7057(1)
N(11)	0.8500(3)	0.2969(1)	0.6593(1)
O(12)	0.7096(2)	0.2568(1)	0.6697(1)
O(13)	0.8585(3)	0.3681(2)	0.6329(1)
N(14)	0.8033(3)	0.0319(2)	0.5284(1)
C(15)	0.7740(4)	0.0985(2)	0.4926(1)
C(16)	0.7040(4)	0.0795(2)	0.4449(1)
C(17)	0.5885(4)	−0.0660(3)	0.3911(1)
C(18)	0.5842(5)	−0.1578(3)	0.4055(1)
O(19)	0.6478(3)	−0.1708(2)	0.4553(1)
C(20)	0.7642(4)	−0.0586(2)	0.5183(1)
C(21)	0.6946(3)	−0.0816(2)	0.4714(1)
C(22)	0.6625(3)	−0.0146(2)	0.4341(1)

Compound **23**

Atom	x	y	z
C(1)	0.2217(2)	0.0157(1)	0.6180(3)
C(2)	0.2307(2)	0.0329(1)	0.4169(3)
C(3)	0.1761(2)	−0.0300(1)	0.2488(3)
C(4)	0.1208(3)	−0.1097(1)	0.3134(3)
C(5)	0.1188(2)	−0.1230(1)	0.5160(3)
C(6)	0.2910(2)	0.1154(1)	0.3569(3)
N(1)	0.1671(2)	−0.0602(1)	0.6660(3)
N(2)	0.1911(2)	0.1575(1)	0.1612(3)
N(3)	0.4330(2)	0.1040(1)	0.3018(3)
N(4)	0.3200(2)	0.1869(1)	0.5311(3)
O(1)	0.0707(2)	0.1624(1)	0.1693(3)
O(2)	0.2390(2)	0.1830(1)	0.0183(3)
O(3)	0.4646(2)	0.0299(1)	0.2642(3)
O(4)	0.5000(2)	0.1710(2)	0.3001(4)
O(5)	0.4124(2)	0.1670(1)	0.6849(3)
O(6)	0.2518(2)	0.2520(1)	0.5041(3)
O(7)	0.1787(2)	−0.0133(1)	0.0628(2)

Table IV

Bond Lengths (Å)

Compound **18**

Atom 1	Atom 2	Length	Atom 1	Atom 2	Length
C(1)	C(7)	1.709(8)	N(1)	C(2)	1.429(11)
N(1)	C(6)	1.339(11)	C(3)	O(3)	1.352(9)
C(2)	C(3)	1.380(10)	C(3)	C(4)	1.408(10)
C(4)	C(7)	1.478(10)	C(4)	C(5)	1.384(11)
C(5)	C(6)	1.307(10)	C(7)	N(8)	1.274(10)
N(8)	O(9)	1.365(8)	N(10)	O(11)	1.250(8)
N(10)	O(12)	1.244(9)	N(10)	O(13)	1.253(8)

Compound **20'**

Atom 1	Atom 2	Length	Atom 1	Atom 2	Length
N(1)	C(2)	1.340(3)	N(1)	C(6)	1.336(3)
C(2)	C(3)	1.380(3)	C(3)	C(4)	1.387(3)
C(4)	C(5)	1.391(3)	C(4)	C(8)	1.472(3)
C(5)	C(6)	1.386(3)	C(5)	O(7)	1.342(3)
C(8)	N(9)	1.267(3)	C(8)	N(11)	1.485(3)
N(9)	O(10)	1.370(3)	N(11)	O(12)	1.214(3)
N(11)	O(13)	1.219(3)	N(14)	C(15)	1.342(4)
N(14)	C(20)	1.334(4)	C(15)	C(16)	1.383(4)
C(16)	C(22)	1.387(4)	C(17)	C(18)	1.350(5)
C(17)	C(22)	1.446(5)	C(18)	O(19)	1.405(5)
O(19)	C(21)	1.368(3)	C(20)	C(21)	1.376(4)
C(21)	C(22)	1.376(4)			

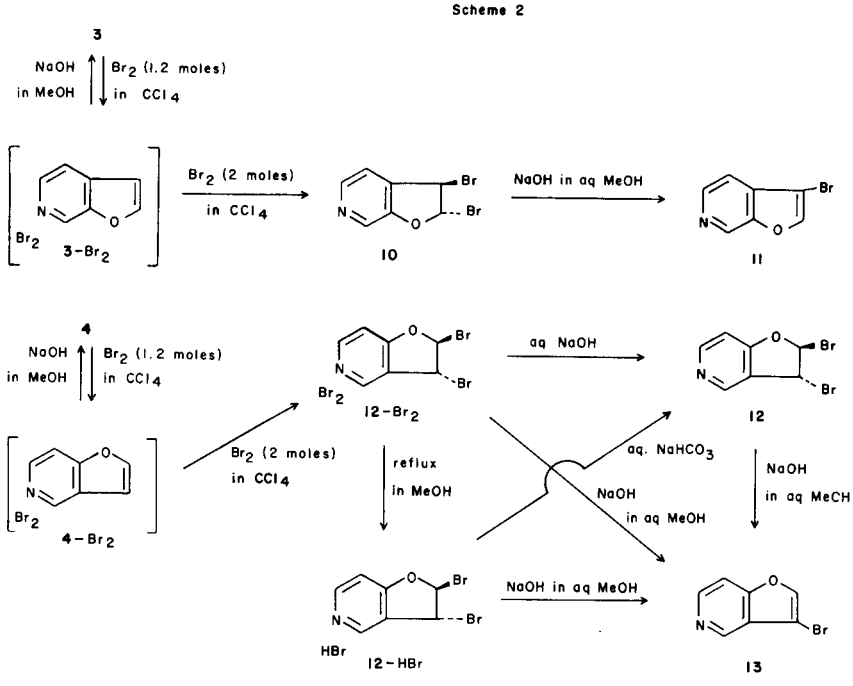
Compound **23**

Atom 1	Atom 2	Length	Atom 1	Atom 2	Length
C(1)	C(2)	1.369(3)	C(1)	N(1)	1.339(3)
C(2)	C(3)	1.453(3)	C(2)	C(6)	1.478(3)
C(3)	C(4)	1.430(3)	C(3)	O(7)	1.253(2)
C(4)	C(5)	1.355(3)	C(5)	N(1)	1.361(3)
C(6)	N(2)	1.547(3)	C(6)	N(3)	1.547(3)
C(6)	N(4)	1.537(3)	N(2)	O(1)	1.208(3)
N(2)	O(2)	1.215(3)	N(3)	O(3)	1.204(3)
N(4)	O(6)	1.192(3)			

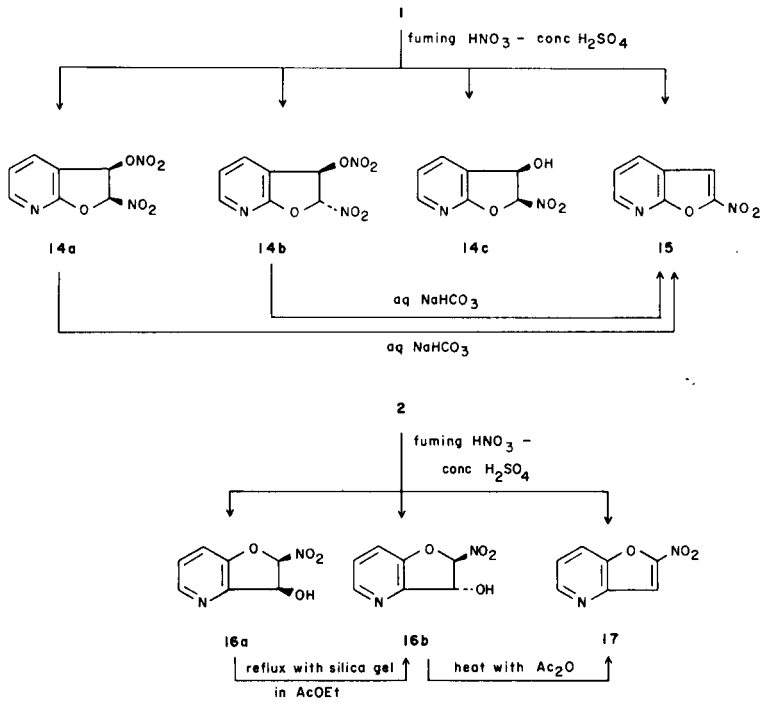
Though compound **10** could not be isolated because of its instability, signals at δ 5.67 (H-3) and δ 6.86 (H-2) (singlets) in the spectrum of the bromination product indicated the formation of **10**. The same reaction in chloroform gave better yield (50%) of **11**.

McFarland and his coworkers reported that the bromination of **4** gave *trans*-2,3-dibromo-2,3-dihydro compound **12** as a final product [6]. We reexamined the bromination of **4** expecting to obtain the similar result as in the cases of **1, 2** and **3**. Treatment of **4** with 1.2 moles of bromine gave similarly furo[3,2-*c*]pyridine perbromide **4-Br$_2$** as an unstable yellow crystalline powder. The reaction, however, did not proceed further and afforded neither 2,3-dibromo compound **12** nor bromofuropyridine (**13**) under this condition. When compound **4** was treated with 3 moles of

Scheme 2



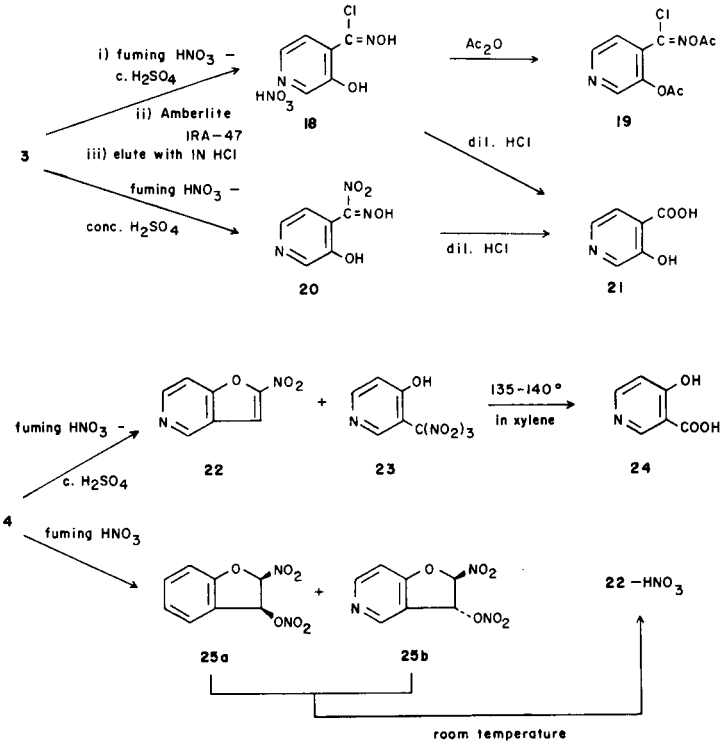
Scheme 3



bromine in carbon tetrachloride, the perbromide **12-Br$_2$** of **12** was obtained, which was transformed to the hydrobromide **12-HBr** by refluxing in methanol. Treatment of **12-Br$_2$** and **12-HBr** with sodium hydroxide in methanol afforded the 3-bromo derivative **13**.

These results resemble the bromination of benzofuran [7] rather than those of the thieno analogs, such as thieno-[2,3-*c*]- and thieno[3,2-*c*]pyridine, in which no bromination took place in the reaction with bromine in carbon tetrachloride or chloroform [8]. While, in the case of thieno-[2,3-*b*]pyridine, the bromination was reported to proceed to give 2,3-dibromo derivative in poor yield [9].

Scheme 4



The nitration of **1** with a mixture of fuming nitric acid (d, 1.50) and sulfuric acid gave a mixture of *cis*-**14a** and *trans*-2-nitro-2,3-dihydrofuro[2,3-*b*]pyrid-3-yl nitrate (**14b**), 2-nitro-2,3-dihydro[2,3-*b*]pyridin-3-ol (**14c**) and 2-nitrofuro[2,3-*b*]pyridine (**15**) (approximate ratio: 2:20:5:1, determined by the integration of the ^{1}H nmr signals). The hydroxyl compound **14c** was isolated by treatment of the mixture with ether as the ether-insoluble material. The main product **14b** was isolated by concentration of the ethereal solution as colorless prisms. Compound **14b** and the mixture of **14a** and **14b** were easily converted to 2-nitro derivative **15** by treatment with sodium bicarbonate solution. The position of the nitro group at C-2 was confirmed by comparison of the nmr chemical shift of H-3 (δ 7.63, pure singlet) with those of the parent compound and other nitro compounds **17** and **22** (Table I).

The nitration of **2** under similar conditions gave a mixture of *cis*-**16a** and *trans*-2-nitro-2,3-dihydrofuro[3,2-*b*]pyridin-3-ol (**16b**) and 2-nitrofuro[3,2-*b*]pyridine (**17**) (approximate ratio: 1:3:2). Compound **17** was isolated from the mixture by dissolving in chloroform. The mixture of the chloroform-insoluble hydroxyl compounds was recrystallized from acetone to isolate the *trans* isomer **16b**. The *cis* isomer **16a** was converted to **16b** by refluxing on silica gel in ethyl acetate. Compound **16b** was converted to the 2-nitro derivative **17** by heating with acetic anhydride. The position of the nitro group at C-2 was confirmed by

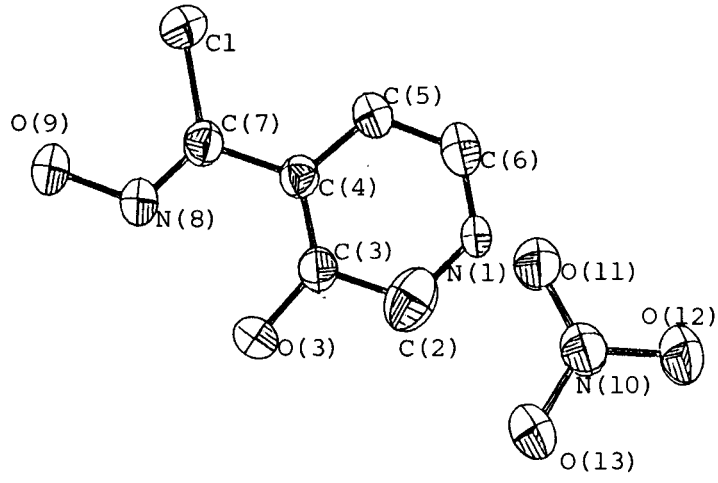


Figure 1. ORTEP drawing of 3-hydroxy-4-(1'-chloro-1'-hydroximinomethyl)pyridinium nitrate (**18**).

the disappearance of coupling between H-2 and H-3 and the retention of zig-zag coupling between H-3 and H-7 [2a], in its nmr spectrum.

The reaction of **3** with a mixture of fuming nitric acid and sulfuric acid gave an unexpected result. When the reaction mixture was extracted with ether, chloroform or ethyl acetate after neutralization with sodium bicarbonate, no organic compound was extracted. Thus, the acidic

Table V

Bond Angles (°)

Compound **18**			
C(2)-N(1)-C(6)	118.3(7)	N(1)-C(2)-C(3)	119.4(7)
C(2)-C(3)-O(2)	114.3(7)	C(2)-C(3)-C(4)	118.9(7)
O(3)-C(3)-C(4)	126.2(7)	C(3)-C(4)-C(7)	120.5(6)
C(5)-C(4)-C(7)	120.5(6)	C(3)-C(4)-C(5)	118.7(7)
C(4)-C(5)-C(6)	121.3(7)	N(1)-C(6)-C(5)	123.3(7)
Cl-C(7)-C(4)	118.9(5)	Cl-C(7)-N(8)	123.4(6)
C(4)-C(7)-N(8)	117.7(7)	C(7)-N(8)-O(9)	116.3(6)
O(11)-N(10)-O(12)	120.3(6)	O(11)-N(10)-O(13)	120.5(6)
O(12)-N(10)-O(13)	119.1(6)		
Compound **20′**			
C(2)-N(1)-C(6)	118.4(2)	N(1)-C(2)-C(3)	122.6(2)
C(2)-N(1)-C(4)	118.9(2)	C(3)-C(4)-C(5)	118.9(2)
C(3)-C(4)-C(8)	121.6(2)	C(5)-C(4)-C(8)	119.5(2)
C(4)-C(5)-C(6)	118.4(2)	C(4)-C(5)-O(7)	118.2(2)
C(6)-C(5)-O(7)	123.3(2)	N(1)-C(6)-C(5)	122.8(2)
C(4)-C(8)-N(9)	132.3(2)	C(4)-C(8)-N(11)	116.7(2)
N(9)-C(8)-N(11)	111.0(2)	C(8)-N(9)-O(10)	113.6(2)
C(8)-N(11)-O(12)	117.5(2)	C(8)-N(11)-O(13)	118.6(2)
O(12)-N(11)-O(13)	123.9(2)	C(15)-N(14)-C(20)	119.5(2)
N(14)-C(15)-C(16)	124.1(3)	C(15)-C(16)-C(22)	116.8(3)
C(18)-C(17)-C(22)	105.7(3)	C(17)-C(18)-O(19)	112.0(3)
C(18)-O(19)-C(21)	104.5(2)	N(14)-C(20)-C(21)	118.8(3)
O(19-C(21)-C(20)	125.6(2)	O(19)-C(21)-C(22)	111.7(2)
C(20)-C(21)-C(22)	122.8(3)	C(16)-C(22)-C(17)	135.8(3)
C(16)-C(22)-C(21)	118.1(3)	C(17)-C(22)-C(21)	106.1(3)
Compound **23**			
C(2)-C(1)-N(1)	121.1(2)	C(3)-C(2)-C(1)	120.3(2)
C(3)-C(2)-C(6)	116.6(2)	C(4)-C(3)-C(2)	115.0(2)
C(1)-C(2)-C(6)	123.0(2)	C(4)-C(3)-O(7)	124.2(2)
C(2)-C(3)-O(7)	120.8(2)	C(5)-C(4)-C(3)	121.3(2)
N(1)-C(5)-C(4)	120.9(2)	N(2)-C(5)-C(2)	110.6(2)
N(2)-C(6)-N(3)	106.3(2)	N(2)-C(6)-N(4)	106.9(2)
C(2)-C(6)-N(3)	114.9(2)	C(2)-C(6)-N(4)	113.6(2)
N(3)-C(6)-N(4)	103.9(2)	O(1)-N(2)-C(6)	114.8(2)
O(1)-N(2)-O(2)	126.6(2)	C(6)-N(2)-O(2)	118.6(2)
O(3)-N(3)-C(6)	116.7(2)	O(3)-N(3)-O(4)	127.1(2)
C(6)-N(3)-O(4)	116.2(2)	O(5)-N(4)-C(6)	114.4(2)
O(5)-N(4)-O(6)	127.0(2)	C(6)-N(4)-O(6)	118.6(2)
C(1)-N(1)-C(5)	121.2(2)		

aqueous solution was treated with basic ion-exchange resin (Amberlite IRA-47), and the organic compound absorbed on the resin was eluted with 1*N* hydrochloric acid to give a crystalline compound **18** of mp 136-140° in 24% yield. The ^{1}H nmr spectrum showed only the signals of three protons on the pyridine ring. The ^{13}C nmr spectrum indicated the presence of six carbon atoms (three singlets and three doublets in the off-resonance decoupled spectrum). In the mass spectrum compound **18** showed a pair of peaks at m/e 172 and 174, indicating the presence of a chlorine atom in the molecule. The elemental analysis suggested the molecular formula $C_6H_6ClN_3O_5$. When compound **18** was refluxed with 10% hydrochloric acid, 3-hydroxyisonicotinic acid (**21**) was obtained which was identified by comparison of the ir and nmr spectra and melting point with those of the authentic sample [10]. These data, however, did not give any more information about the structure of **18** particularly about the arrangement of a chlorine, two nitrogen and four oxygen atoms in **18**. Thus, the final structure was determined by a single crystal X-ray analysis performed by the Osaka group of the authors, which showed the structure to be 3-hydroxy-4-(1′-chloro-1′-hydroximinomethyl)pyridinium nitrate. Acetylation of **18** yielded 3-acetoxy-4-(1′-chloro-1′-acetoximinomethyl)pyridine (**19**).

On the other hand, when the reaction mixture of **3** with the mixed acid was diluted, neutralized with sodium bicarbonate and extracted with ethyl acetate after addition of 0.5 moles of **3**, a crystalline compound (**20′**) of mp 110-112° was obtained in about 42% yield. The ^{1}H nmr spectrum in methanol-d_4 indicated the presence of eight protons unexchangeable with deuterium in methanol-d_4, and the ^{13}C nmr spectrum thirteen carbons (five singlets and eight doublets in the off-resonance decoupled spectrum). The elemental analysis suggested the molecular formula $C_{13}H_{10}N_4O_5$. When this compound was treated with aqueous ammonia and extracted with chloroform, compound **3** was obtained. Evaporation of the aqueous solution gave a syrup from which no compound could be isolated. Refluxing of **20′** with 10% hydrochloric acid gave 3-hydroxyisonicotinic acid. These results suggested the compound **20′** to be furo[2,3-*c*]pyridinium salt of an acidic compound of $C_6H_5N_3O_4$ (**20**). Agian, the structure of **20′** was unequivocally determined by a single crystal X-ray analysis performed by the Osaka group of the authors, which exhibited the structure of **20′** to be furo[2,3-*c*]pyridinium 3-hydroxypurine-4-nitrolate.

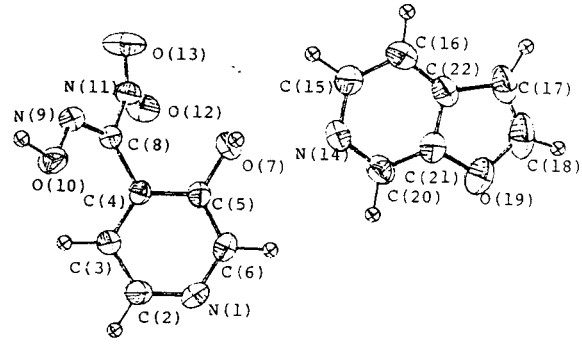


Figure 2. ORTEP drawing of furo[2,3-*c*]pyridinium-3-hydroxypyridine-4-nitrolate (**20′**).

McFarland and his coworkers reported the nitration of **4**, in which 2-nitro derivative **22** was isolated as a sole product [6]. Our reexamination, however, gave somewhat different result from that of them. The nitration of **4** gave two compounds, one was ether-soluble 2-nitro derivative **22**

(33% yield), another ether-insoluble compound **23** of mp 130-132° (20% yield). The ^{1}H nmr spectrum of **23** showed signals of three protons of the pyridine ring. The ^{13}C nmr spectrum indicated the presence of six carbon atoms (three singlets and three doublets in the off-resonance decoupled spectrum). The elemental analysis suggested the molecular formula $C_6H_4N_4O_7$. Compound **23** was converted to 4-hydroxynicotinic acid (**24**) [11] by heating at 135-140°. On the basis of common spectroscopic methods it is difficult to estimate the real structure of **23**. This question was resolved by an X-ray structural analysis performed by the Tokyo group of the authors, which showed the structure of **23** to be 3-(trinitromethyl)pyridin-4-ol. Since it was assumed that compound **23** could be formed by further oxidation and nitration of **22**, compound **22** was reacted with a nitrating mixture at 45-55°. However, only starting material was recovered in almost quantitative yield.

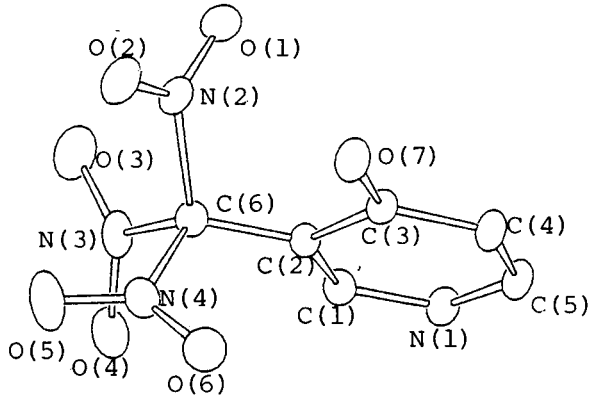


Figure 3. ORTEP drawing of 3-(trinitromethyl)pyridin-4-ol (**23**).

Whereas, the nitration of **4** with fuming nitric acid at 0° gave a mixture of *cis*-**25a** and *trans*-2-nitro-2,3-dihydrofuro[3,2-*c*]pyrid-3-yl nitrate (**25b**) in 42% yield which rapidly changed to 2-nitrofuro[3,2-*c*]pyridinium nitrate **22**-**HNO$_3$** at room temperature.

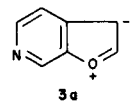
The nitration of furopyridines also resemble that of benzofuran [12] rather than those of thienopyridines which yielded the 3-nitro derivatives [13].

From both a theoretical and practical point of view, hydrogen exchange in acidic media is considered to be the simplest electrophilic reaction. At 85° the H-D exchange reaction of **1, 2, 3** and **4** in 96% sulfuric acid-d_2 were followed by ^{1}H nmr technique. After 9 hours, 87% of 3-hydrogen of **4**, 95% of 3-hydrogen of **3**, 70% of 3-hydrogen of **2** and 54% of 3-hydrogen of **1** were exchanged without any noticeable change of the intensity of the 2-hydrogen or other ring hydrogen signal.

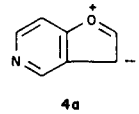
The H-D exchange reactions of **1, 2, 3** and **4** for deuterium in 20% sodium deuteroxide in methanol-d_4 at 55° were also studied, in which the proton would be abstracted from the neutral molecule of the substrate in the rate-determining step, *i.e.* by a carbanion pathway. After 1.5 hours, 61%, 68%, 90% and 68% of 2-hydrogen, and 5%, 10%, 20% and 5% of 3-hydrogen of **1, 2, 3** and **4** were exchanged, respectively.

The ionization constant is a fundamental index for the reactivity and the electron distribution of a molecule. Thus, the p*K*a values for the parent compounds **1, 2, 3** and **4**, the 3-bromo derivatives **7, 9, 11** and **13** and 2-methylfuro[3,2-*c*]pyridine [4a] were measured by titration or uv absorption method. The values are summarized in Table II. Though the basicity of each furopyridine is comparable to the corresponding thienopyridine, furopyridines **1, 2** and **3** are weaker than the corresponding thienopyridine [14]. The stronger basicity of **4** than that of thieno[3,2-*c*]-pyridine (p*K*a 5.67 [14c]) may suggest that the *para*-quinoide structure highly contributes to the resonance of the molecule. It should be pointed out that the quinoline isosteres are weaker in basicity than pyridine (p*K*a 5.23 [15]) and quinoline (p*K*a 4.94 [16]), and isoquinoline isosteres are stronger than pyridine and isoquinoline (p*K*a 5.40 [17]). Furthermore, the bromine atom at C-3 lowers the basicity of each furopyridine.

We have presented here results of typical electrophilic reactions, *i.e.* bromination, nitration and hydrogen exchange, of four furopyridines. It is apparent that these furopyridines are reactive toward electrophilic addition and an electrophile attacks the double bond between C-2 and C-3 to form an addition product. The quinoline isosteres react with strong electrophiles (NO_2^+ and Br^+) smoothly to give the addition products as in the case of an aliphatic double bond. These facts and weaker basicity suggest that the electron density on the double bond between C-2 and C-3 is high and the electrons in the pyridine ring are withdrawn to the furan ring by the inductive effect of the oxygen atom. Thus, the contribution of the charge separated forms to the resonance is small. On the other hand, isoquinoline isosteres form 2,3-dibromo-2,3-dihydro derivatives more slowly, exchange 3-hydrogen (in acidic medium) and 2-hydrogen (in alkaline medium) faster, and are greater in basicity as compared to quinoline isosteres. These facts indicate that the charge separated resonance form such as **3a** and **4a** are more important. Thus, formation of nitrolic acid derivative **20** from **3** and trinitromethyl compound **23** from **4** can be explained by the initial attack of NO_2^+ at 3-position of **3** and **4** and the subsequent oxidation, decarboxylation and nitration [18].



3a



4a

EXPERIMENTAL

Melting points were determined by using Yanagimoto micro melting point apparatus. All melting points are uncorrected. Infrared (ir) spectra were taken on a JASCO A-102 spectrometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a JEOL JNM-PMX 60 spectrometer. Carbon 13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Varian XL-200 and JEOL FX90Q instruments. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi RMU-6MG spectrometer.

Bromination of Furo[2,3-*b*]pyridine (**1**).

To a solution of 110 mg (0.92 mmole) of **1** in 2 ml of carbon tetrachloride at −15° was added 160 mg (1.0 mmole) of bromine in 2 ml of carbon tetrachloride dropwise over 10 minutes with stirring. After the addition was complete, the mixture was stirred for 10 minutes at this temperature. The solvent was removed under reduced pressure at room temperature to yield a yellow solid (245 mg, 95%). The crude product was recrystallized from ether to give pure *trans*-2,3-dibromo-2,3-dihydrofuro[2,3-*b*]pyridine (**6**) as colorless needles; mp 80-83°; ^{1}H nmr (deuteriochloroform): δ 5.73 (s, 1H, H-3), 6.84 (s, 1H, H-2), 7.09 (dd, J = 7.2, 5.0 Hz, 1H, H-5), 7.84 (dd, J = 7.2, 1.7 Hz, 1H, H-4), 8.25 (dd, J = 5.0, 1.7 Hz, H-6).

Anal. Calcd. for $C_7H_5Br_2NO$: C, 30.14; H, 1.81; N, 5.02. Found: C, 30.09; H, 1.73; N, 5.08.

3-Bromofuro[2,3-*b*]pyridine (**7**).

To a solution of 256 mg (0.92 mmole) of **6** in 5 ml of methanol was added 0.5 ml of 20% sodium hydroxide solution. After stirring for 10 minutes at room temperature, the mixture was evaporated to give a yellow semi-solid which was treated with water and extracted with ether. After drying (magnesium sulfate), the solvent was evaporated to give 157 mg (86%) of **7** as colorless needles; mp 90-94°. Recrystallization from aqueous methanol raised the melting point to 93-95°.

Anal. Calcd. for C_7H_4BrNO: C, 42.46; H, 2.04; N, 7.07. Found: C, 42.38; H, 2.01; N, 7.15.

2-Deuterio-3-bromofuro[2,3-*b*]pyridine (**7-D**).

A mixture of 25 mg (0.21 mmole) of **1**, 0.1 ml of 40% sodium deuteroxide solution, 0.3 ml of deuterium oxide and 0.5 ml of methanol-d_4 was heated at 65° for 6 hours. After evaporation of the solvents, the residual syrup was taken up in carbon tetrachloride, dried (magnesium sulfate) (the ^{1}H nmr spectrum taken on this solution indicated the disappearance of 90% of H-2 (δ 6.68 (almost s, 1H, H-3), 7.10 (dd, J = 7.4, 4.4 Hz, 1H, H-5), 7.63 (d, J = 2.4 Hz, 0.1H, H-2), 7.80 (dd, J = 7.4, 0.9 Hz, 1H, H-4), 8.21 (dd, J = 4.4, 0.9 Hz, 1H, H-6))). To this solution was added bromine (32 mg, 0.2 mmoles) in 1 ml of carbon tetrachloride at −10°. After stirring for 10 minutes at room temperature, the solvent was evaporated under reduced pressure to give 55 mg of **6-D**; ^{1}H nmr (methanol-d_4): δ 5.72 (s, 1H, H-3), 6.85 (s, 0.1H, H-2), 7.10 (dd, J = 7.2, 5.0 Hz, 1H, H-5), 7.83 (dd, J = 7.2, 1.7 Hz, 1H, H-4), 8.25 (dd, J = 5.0, 1.7 Hz, 1H, H-6).

Compound **6-D** (55 mg) was dissolved in 0.5 ml of methanol containing 3 drops of 20% sodium hydroxide solution, and stirred for 10 minutes at room temperature. After evaporation of the solvent, the residual syrup was taken up in ether. Drying (magnesium sulfate) and evaporation of the solution yielded 30 mg (72%) of **7-D**, mp 89-93°; ^{1}H nmr (deuteriochloroform): δ 7.27 (dd, J = 7.6, 4.8 Hz, 1H, H-5), 7.70 (s, 0.1H, H-2), 7.85 (dd, J = 7.6, 1.8 Hz, 1H, H-4), 8.35 (dd, J = 4.8, 1.8 Hz, 1H, H-6).

Bromination of Furo[3,2-*b*]pyridine (**2**).

a) To a solution of 44 mg (0.37 mmole) of **2** in 2 ml of carbon tetrachloride at −10° was added 50 mg (0.31 mmole) of bromine in 1 ml of carbon tetrachloride. The yellow crystalline precipitate **2-Br$_2$** (mp 60-62°) was filtered and dissolved in methanol-d_4. The ^{1}H nmr spectrum taken on this solution exhibited signals of five protons, δ 7.25 (dd, J = 2.4, 1.0 Hz, 1H, H-3), 7.72 (dd, J = 7.8, 5.0 Hz, 1H, H-6), 8.39 (d, J = 2.4 Hz, 1H, H-2), 8.46 (ddd, J = 7.8, 1.2, 1.0 Hz, 1H, H-7), 8.68 (dd, J = 5.0, 1.2 Hz, 1H, H-5). To the deuteriomethanol solution was added 0.5 ml of 10% sodium hydroxide solution and evaporated the solvent under reduced pressure at room temperature. The residue was taken up in chloroform, washed with water and dried (magnesium sulfate). Evaporation of the solvent afforded 30 mg of a yellow oil, the ir spectrum of which was identical with that of **2**. From these results, compound **2-Br$_2$** was judged to be the perbromide of **2**.

b) To a stirred solution of 250 mg (6.25 mmoles) of **2** in 30 ml of carbon tetrachloride at −15° was added 1.0 g (6.25 mmoles) of bromine in 10 ml of carbon tetrachloride during 10 minutes. After being stirred for 15 hours, the red-brown solution was evaporated under reduced pressure to give 545 mg of pale yellow crystals. Recrystallization from ether afforded pure colorless sample of **8**, mp 88-89; ^{1}H nmr (deuteriochloroform): δ 5.78 (s, 1H, H-3), 6.93 (s, 1H, H-2), 7.20 (dd, J = 8.0, 4.0 Hz, 1H, H-6), 7.33 (dd, J = 8.0, 2.2 Hz, 1H, H-7), 8.37 (dd, J = 4.0, 2.2 Hz, 1H, H-5).

Anal. Calcd. for $C_7H_5Br_2NO$: C, 30.14; H, 1.81; N, 5.02. Found: C, 30.16; H, 1.83; N, 5.41.

3-Bromofuro[3,2-*b*]pyridine (**9**).

A mixture of 285 mg (1.02 mmoles) of **8**, 1 ml of 10% sodium hydroxide solution and 4 ml of methanol was stirred at room temperature for 5 minutes. After evaporation of the solvents, the residue was taken up in ether, washed with water and dried (magnesium sulfate). Evaporation of the solvent gave 195 mg (96%) of **9** as a nearly colorless solid. The analytical sample was obtained by recrystallization from ether as colorless needles, mp 53-55°.

Anal. Calcd. for C_7H_4BrNO: C, 42.46; H, 2.04; N, 7.07. Found: C, 42.18; H, 2.02; N, 7.24.

Bromination of Furo[2,3-*c*]pyridine (**3**) and the Preparation of 3-Bromofuro[2,3-*c*]pyridine (**11**).

a) To a stirred solution of 110 mg (0.92 mmole) of **3** in 1 ml of carbon tetrachloride at −10° was added 170 mg (1.06 mmoles) of bromine in 2 ml of carbon tetrachloride over 5 minutes. After being stirred for 10 minutes at −10°, the yellow-orange crystalline powder **3-Br$_2$** (mp 87-90°) was filtered and dissolved in 1 ml of methanol-d_4. The ^{1}H nmr spectrum of this solution showed signals of five protons, δ 7.41 (dd, J = 2.0, 1.0 Hz, 1H, H-3), 8.32 (dd, J = 6.5, 0.8 Hz, 1H, H-4), 8.58 (d, J = 6.5 Hz, 1H, H-5), 8.61 (d, J = 2.0 Hz, 1H, H-2), 9.35 (dd, J = 1.0, 0.8 Hz, 1H, H-7). To the methanol-d_4 solution was added 1 ml of 10% sodium hydroxide solution and the mixture was evaporated under reduced pressure to give a colorless syrup which was taken up in chloroform. Evaporation of the solvent afforded 80 mg of a nearly colorless oil, the ir spectrum of which was identical with that of **3**.

b) To a stirred solution of 330 mg (2.77 mmoles) of **3** in 40 ml of carbon tetrachloride at −10° was added 1.4 g (8.85 mmoles) of bromine in 14 ml of carbon tetrachloride over 15 minutes. After being stirred for 18 hours at room temperature, the solvent and the excess bromine were evaporated under reduced pressure to give a yellow-orange solid. The ^{1}H nmr spectrum in methanol-d_4 (signals at δ 5.67 (s, 1H, H-3) and 6.86 (s, 1H, H-2)) indicated the formation of *trans*-2,3-dibromo-2,3-dihydro derivative **10** (or its perbromide) in 30% yield. Attempts to isolate this compound by recrystallization or silica gel chromatography were unsuccessful because compound **10** was decomposed by these treatments.

To a solution of the above solid in 5 ml of methanol was added 2 ml of 10% sodium hydroxide solution. After standing for 5 minutes, the solution was diluted with 20 ml of water and extracted with chloroform. Evaporation of the dried (magnesium sulfate) chloroform solution gave 370 mg of semi-solid, from which 120 mg (22%) of 3-bromo derivative **11** was obtained as colorless needles by recrystallization from ether, mp 133-135°.

Anal. Calcd. for C_7H_4BrON: C, 42.46; H, 2.04; N, 7.07. Found: C 42.63; H, 2.10; N, 7.19.

Distillation of the mother liquor gave 200 mg (61%) of **3**. The bromination of **3** in chloroform afforded compound **11** in 50% yield.

Bromination of Furo[3,2-*c*]pyridine (**4**).

a) To a stirred solution of 120 mg (1.0 mmole) of **4** in 1 ml of carbon tetrachloride at −10° was added a solution of 180 mg (1.13 mmoles) of bromine in carbon tetrachloride over 5 minutes. After being stirred for 10 minutes, the yellow crystalline powder **4-Br$_2$** (mp 72-73°) was filtered and dissolved in 1 ml of methanol-d$_4$. The ^{1}H nmr spectrum showed signals of five protons, δ 7.18 (dd, J = 2.5, 0.8 Hz, 1H, H-3), 7.92 (dt, J = 6.0, 0.8 Hz, 1H, H-7), 8.10 (d, J = 2.5 Hz, 1H, H-2), 8.53 (d, J = 6.0 Hz, 1H, H-6), 9.08 (d, J = 0.8 Hz, 1H, H-4). The deuteriomethanol solution was made alkaline with 1 ml of 10% sodium hydroxide solution, diluted with water, extracted with chloroform and dried (magnesium sulfate). Evaporation of the solvent gave 100 mg of **4**.

b) To a solution of 600 mg (5.05 mmoles) of **4** in 30 ml of carbon tetrachloride at −10° was added 2.4 g (1.5 mmoles) of bromine in 24 ml of carbon tetrachloride over 10 minutes. After being stirred for 12 hours at room temperature, the solvent and the excess bromine were evaporated under reduced pressure to give 1.51 g of yellow-orange solid. Recrystallization of the solid from methanol without heating above 30° gave 0.2 g (9%) of **12-Br$_2$** as red-orange prisms, mp 102-104°; ^{1}H nmr (deuteriomethanol): δ 6.25 (s, 1H, H-3), 7.42 (s, 1H, H-2), 7.57 (d, J = 8.0 Hz, 1H, H-7), 8.83 (d, J = 8.0 Hz, 1H, H-6), 8.96 (s, 1H, H-4). Decomposition occurred resulting in a poor elemental analysis (*Anal.* Calcd. for $C_7H_5Br_4NO$: C, 19.16; H, 1.15; N, 3.19. Found: C, 21.10; H, 1.19; N, 3.58). The mother liquor was diluted with 30 ml of methanol, refluxed for 3 hours, concentrated to about 1 ml and cooled. The nearly colorless crystals formed was recrystallized from methanol to give 744 mg (41%) of **12-HBr** as colorless cubes, mp 115-117°; ^{1}H nmr (deuteriomethanol): δ 6.33 (s, 1H, H-3), 7.55 (s, 1H, H-2), 7.82 (d, J = 6.5 Hz, 1H, H-7), 8.87 (d, J = 6.5 Hz, 1H, H-6), 9.14 (s, 1H, H-4).

Anal. Calcd. for $C_7H_6Br_3NO$: C, 23.36; H, 1.68; N, 3.89. Found: C, 23.46; H, 1.49; N, 3.89.

A solution of 200 mg (0.46 mmole) of **12-Br$_2$** in 10 ml of methanol was refluxed for 2 hours, concentrated to about 0.5 ml and cooled. The ir spectrum of the crystals obtained was identical with that of **12-HBr**. Compound **12-HBr** (100 mg, 0.28 mmole) was dissolved in water, made alkaline with sodium bicarbonate solution, extracted with chloroform and dried (magnesium sulfate). Evaporation of the solvent yielded 66 mg (85%) of **12**, mp 88-91° (literature [6], mp 91-92°).

Anal. Calcd. for $C_7H_5Br_2NO$: C, 30.14; H, 1.81; N, 5.02. Found: C, 30.29; H, 1.78; N, 5.32.

3-Bromofuro[3,2-*c*]pyridine (**13**).

a) A mixture of 360 mg (1.0 mmole) of **12-HBr**, 2 ml of 10% sodium hydroxide solution and 10 ml of methanol was stirred for 15 minutes at room temperature. After being evaporated to dryness, the residue was treated with water and extracted with chloroform. Evaporation of the solvent yielded 188 mg (95%) of **13**. The analytical sample was obtained by recrystallization from ether as colorless crystals, mp 78-79°.

Anal. Calcd. for C_7H_4BrNO: C, 42.46; H, 2.04; N, 7.07. Found: C, 42.43; H, 2.15; N, 7.32.

The same procedure with a 100 mg (0.23 mmole) sample of **12-Br$_2$** afforded **13** in 92% yield.

b) Compound **4** (1.2 g, 10 mmoles) was brominated with 4.5 g (28 mmoles) of bromine as described above. The crude brominated product in 50 ml of methanol was treated with 5 ml of 10% sodium hydroxide solution to give 1.04 g (52%) of **13** and 0.48 g (40%) of the starting material **4**.

Nitration of Furo[2,3-*b*]pyridine (**1**).

To compound **1** (500 mg, 4.2 mmoles) at −15° was added 2 ml of sulfuric acid dropwise over 15 minutes. A mixture of 5 ml of fuming nitric acid (d, 1.50) and 1.5 ml of sulfuric acid was then added at such a rate as to maintain the temperature at 0-5°. After being stirred at room temperature for 5 hours, the slightly yellow mixture was poured onto 100 g of ice and neutralized with small portions of solid sodium bicarbonate (*p*H *ca.* 6). The solution was extracted with ethyl acetate and the extract dried (magnesium sulfate). Removal of the solvent under reduced pressure gave 0.9 g of semi-solid. The crude product was treated with 20 ml of ether, filtered off the nearly colorless insoluble material and the filtrate evaporated to give 0.8 g of slightly yellow solid. The ^{1}H nmr spectrum indicated the ether-soluble solid to be a mixture of **14a, 14b** and **15** (approximate ratio: 2:20:1). A portion of the mixture was recrystallized from ether to give **14b** as colorless needles, mp 110-115°; ^{1}H nmr (deuteriochloroform): δ 6.27 (d, J = 0.8 Hz, 1H, H-3), 6.53 (slightly broad s, 1H, H-2), 7.13 (dd, J = 7.4, 4.8 Hz, 1H, H-5), 7.87 (ddd, J = 7.5, 1.8, 0.8 Hz, 1H, H-4), 8.42 (dd, J = 4.8, 1.8 Hz, 1H, H-6).

Anal. Calcd. for $C_7H_5N_3O_6$: C, 37.01; H, 2.22; N, 18.50. Found: C, 37.25; H, 2.27; N, 18.67.

A solution of 0.7 g of the ether-soluble solid in chloroform was shaken with 5% sodium bicarbonate solution for 15 minutes, dried over magnesium sulfate and evaporated to give 0.5 g (73%) of **15**. Analytical sample was obtained by recrystallization from ether as slightly yellow crystals, mp 132-135°.

Anal. Calcd. for $C_7H_4N_2O_3$: C, 51.23; H, 2.46; N, 17.07. Found: C, 51.34; H, 2.44; N, 17.25.

Compound **14b** was treated with sodium bicarbonate solution to give compound **15** in 98% yield.

Though compound **14a** could not be isolated by recrystallization or silica gel chromatography, signals at δ 6.53 (d, J = 6.4 Hz, H-3) and 6.95 (d, J = 6.4 Hz, H-2) in the nmr spectrum of the ether-soluble product supported the formation of compound **14a**.

Recrystallization of the ether-insoluble material from acetone gave 60 mg of **14c**, mp 153-157°; ^{1}H nmr (deuteriomethanol): δ 5.86 (broad d, J = 6.8 Hz, 1H, H-3), 6.50 (d, J = 6.8 Hz, 1H, H-2), 7.14 (dd, J = 7.2, 5.0 Hz, 1H, H-5), 7.85 (ddd, J = 7.2, 1.6, 1.0 Hz, 1H, H-4), 8.17 (ddd, J = 5.0, 1.6, 0.8 Hz, 1H, H-6).

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.02; H, 3.30; N, 15.48.

Nitration of Furo[3,2-*b*]pyridine (**2**).

Sulfuric acid (2 ml) was added to 490 mg (4.12 mmoles) of **2** at −15° over 15 minutes. To this solution was added a mixture of 5 ml of fuming nitric acid (d, 1.50), and 1.5 ml of sulfuric acid dropwise to maintain the temperature at 0-5°. After being stirred for 5 hours at room temperature, the mixture was poured onto 100 g of ice, made alkaline with sodium bicarbonate, extracted with ethyl acetate, dried (magnesium sulfate) and evaporated the solvent under reduced pressure to give 580 mg of light brown semi-solid. The ^{1}H nmr spectrum indicated the product to be a mixture of **16a, 16b** and **17** (approximate ratio: 1:3:2). The crude product was suspended in 20 ml of chloroform, stirred for 30 minutes at room temperature and filtered. Evaporation of the filtrate gave 210 mg of yellow solid, which was recrystallized from methanol to give 170 mg (25%) of **17** as slightly yellow crystals, mp 144-147°.

Anal. Calcd. for $C_7H_4N_2O_3$: C, 51.23; H, 2.46; N, 17.07. Found: C, 51.11; H, 2.59; N, 17.00.

The filter cake (350 mg) from the chloroform suspension was recrystallized several times from methanol to afford 205 mg (27%) of **16b** as nearly colorless crystals, mp 165-167°; ^{1}H nmr (deuteriomethanol): δ 5.39 (d, J = 6.2 Hz, 1H, H-3), 6.37 (d, J = 6.2 Hz, 1H, H-2), 7.43 (dd, J = 8.2, 4.0 Hz, 1H, H-6), 7.61 (dd, J = 8.2, 1.8 Hz, 1H, H-7), 8.28 (dd, J = 4.0, 1.8 Hz, 1H, H-5).

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 45.98; H, 3.47; N, 15.23.

The combined mother liquors were evaporated to dryness, and the residual yellow solid (130 mg), which mainly contained **16a** and **16b** in the ratio of 2:1 (determined from the nmr spectrum by integration of signals of H-2 and H-3), was dissolved in 20 ml of ethyl acetate and stirred with 2 g of silica gel under reflux for 4 hours, and filtered. Evaporation of the solvent gave 120 mg of yellow solid, which was found to be a mixture of **16a** and **16b** in the ratio of 1:1 (determined by the nmr spectrum). Recrystallization of the solid product from methanol gave pure **16b** (95 mg), mp 164-167°.

A solution of 26 mg (0.14 mmole) of **16b** in 2 ml of acetic anhydride

was heated on a boiling water bath for 3 hours. After removal of the acetic anhydride under reduced pressure, the residual syrup was dissolved in chloroform, washed with 5% sodium bicarbonate solution, dried (magnesium sulfate) and evaporated the solvent to give 18 mg (77%) of **17**. Recrystallization from methanol gave a pure sample, mp 143-146°.

Though attempts to isolate **16a** by fractional recrystallization or silica gel chromatography were unsuccessful, the signals at δ 5.77 (d, J = 7.0 Hz, H-3), and 6.52 (d, J = 7.0 Hz, H-2) in the nmr spectrum of the chloroform-insoluble product supported the formation of **16a**.

Nitration of Furo[2,3-*c*]pyridine (**3**).

a) Compound **3** (1.5 g, 12.6 mmoles) was cooled at −10°, then 7.5 ml of sulfuric acid was added dropwise over 20 minutes. To this solution was added a mixture of 15 ml of fuming nitric acid (d, 1.50) and 6 ml of sulfuric acid at such a rate as to maintain the temperature below 5° with stirring. After being stirred for 1.5 hours, the yellow mixture was poured onto 300 g of ice. Ion-exchange resin (Amberlite IRA-47) was added to the solution until no sulfate ion was detected (about 350 ml of the resin), and filtered and washed the resin with five portions of 100 ml of water. The filtrate and the washings were combined, passed through a column of 500 ml of Amberlite IRA-47 and then the organic compound absorbed was eluted with 1*N* hydrochloric acid (2.9 ℓ). Evaporation of the eluate under reduced pressure below 50° afforded 900 mg of nearly colorless semi-solid. Recrystallization from methanol gave 705 mg (24%) of **18**, mp 138-141°; ^{1}H nmr (deuteriomethanol): δ 8.16 (d, J = 6.0 Hz, 1H, H-5), 8.35 (d, J = 6.0 Hz, 1H, H-6), 8.50 (s, 1H, H-2); ^{13}C nmr (dimethylsulfoxide-d_6): 125.28 (d, C-5), 131.21 (s, C-4), 132.66 (d, C-2 or C-6), 133.21 (s, C-3), 133.92 (d, C-6 or C-2), 153.63 (s, *C*=NOH); ms: m/e 174, 172 (relative ratio of intensities of these peaks: 1:3), 136, 120; ir (potassium bromide): 3200-2400 (broad, s), 3050 (s), 2800 (s), 1638 (w), 1590 (w), 1515 (s), 1400 (m), 1378 (m), 1320 (s), 1270 (m), 1200 (s), 1140 (m), 1070 (w), 1040 (s), 950 (m), 900 (w), 818 cm^{-1} (s).

Anal. Calcd. for $C_6H_6ClN_3O_5$: C, 30.59; H, 2.57; N, 17.84. Found: C, 30.76; H, 2.49; N, 17.34.

b) Compound **3** (1.0 g, 8.4 mmoles) in 4 ml of sulfuric acid was nitrated with a mixture of 10 ml of fuming nitric acid (d, 1.50) and 3 ml of sulfuric acid by the same procedure as above. The mixture was poured onto 150 g of ice, neutrallized with small portions of solid sodium bicarbonate after addition of 0.5 g (4.2 mmoles) of **3**, and extracted with ethyl acetate. After drying (magnesium sulfate), the solvent was removed under reduced pressure below 35° to give 1.15 g of a pale brown semi-solid. Recrystallization from acetone gave 1.05 g (41%) of **20′**, mp 110-112°; ^{1}H nmr (deuteriomethanol): δ 6.93 (dd, J = 2.2, 0.8 Hz, 1H, H-3′), 7.37 (dd, J = 5.0, 0.8 Hz, 1H, H-5), 7.66 (dd, J = 5.4, 1.0 Hz, 1H, H-4′), 7.96 (dd, J = 2.2 Hz, 1H, H-2′), 8.11 (d, J = 5.0 Hz, 1H, H-6), 8.22 (broad s, 1H, H-2), 8.28 (broad d, J = 5.4 Hz, 1H, H-5′), 8.78 (broad s, 1H, H-7′); ir (potassium bromide): 3140 (w), 3060 (2), 2900-2300 (broad, m), 2000-1700 (broad, w), 1640 (w), 1615 (w), 1600 (w), 1540 (s), 1520 (m), 1470 (w), 1415 (s), 1345 (s), 1315 (m), 1260 (s), 1233 (w), 1210 (m), 1190 (m), 1180 (m), 1150 (m), 1110 (w), 1070 (w), 1040 (s), 1020 (s), 900 (w), 890 (w), 875 (m), 865 (m), 825 (s), 810 (s), 780 (m), 740 (m), 705 cm^{-1} (m); ^{13}C nmr (deuteriomethanol): δ 107.22 (d), 117.94 (d), 122.68 (s), 126.37 (d), 133.97 (d), 136.45 (s), 139.16 (d), 140.45 (d), 142.41 (d), 151.02 (d), 153.02 (s), 153.59 (s), 156.89 (s).

Anal. Calcd. for $C_{13}H_{10}N_4O_5$: C, 51.65; H, 3.33; N, 18.54. Found: C, 51.77; H, 3.59; N, 18.38.

3-Acetoxy-4-(1′-chloro-1′-acetoximinomethyl)pyridine (**19**).

A mixture of 105 mg (0.45 mmole) of **18** and 1 ml of acetic anhydride was heated on a boiling water bath for 30 minutes. After being removed the excess acetic anhydride, the residual syrup was dissolved in chloroform, washed with 5% sodium bicarbonate solution and water, and dried (magnesium sulfate). Removal of the solvent gave a pale yellow syrup, which was chromatographed on 10 g of silica gel. Elution with chloroform yielded 75 mg (65%) of the diacetate **19**. Recrystallization from ether gave a pure sample of mp 78-82°; ^{1}H nmr (deuteriochloroform): δ 2.20 (s, 3H, -CH_3), 2.31 (s, 3H, -CH_3), 7.68 (d, J = 5.4 Hz, 1H, H-5), 8.48 (s, 1H, H-2), 8.60 (d, J = 5.4 Hz, 1H, H-5), 8.48 (s, 1H, H-2), 8.60 (d, J = 5.4 Hz, 1H, H-6); ir (potassium bromide): 1780 (C=O), 1760 cm^{-1} (C=O); ms: m/e 258, 256 (M$^+$), 216, 214, 174, 172, 137, 43.

Anal. Calcd. for $C_{10}H_9ClN_2O_4$: C, 46.80; H, 3.53; N, 10.92. Found: C, 46.88; H, 3.52; N, 11.12.

Hydrolysis of 3-Hydroxy-4-(1′-chloro-1′-hydroximinomethyl)pyrimidinium Nitrate (**18**) and Furo[2,3-*c*]pyridinium 3-Hydroxypyridine-4-nitrolate (**20′**).

a) A mixture of 60 mg (0.25 mmole) of **18** and 6 ml of 10% hydrochloric acid was refluxed for 16 hours. After evaporation of the hydrochloric acid, the crystalline mass was recrystallized from methanol to give 28.3 mg (80%) of 3-hydroxyisonicotinic acid (**21**) which was identified by comparison of the ir spectrum with that of the authentic sample prepared by the method of Crum [10].

b) A solution of 30 mg (0.13 mmole) of **20′** in 1 ml of water was made alkaline with 10% ammonium hydroxide solution, extracted with chloroform. The extract was dried (potassium carbonate) and evaporated to give 10 mg (85%) of a pale yellow oil. The ir spectrum of this oil was identical with that of **3**. The aqueous layer was evaporated under reduced pressure, the residue dissolved in 1 ml of 10% hydrochloric acid and refluxed for 16 hours. Evaporation of the solvent and recrystallization of the residue from methanol gave 11 mg (80%) of **21** which was identified by comparison of the ir and nmr spectra with those of the authentic sample [10].

Nitration of Furo[3,2-*c*]pyridine (**4**).

a) Compound **4** (1.18 g, 10 mmoles) was dissolved in 5.4 ml of sulfuric acid by slow addition of the acid keeping the temperature below −5°. A mixture of 17.6 ml of fuming nitric acid (d, 1.52) and 6 ml of sulfuric acid was added to this solution at such a rate as to maintain the temperature below 0°. After being stirred for 5 hours at room temperature, the reaction mixture was poured onto 100 g of ice, neutralized with solid sodium bicarbonate and extracted with ethyl acetate. After drying (magnesium sulfate), evaporated the solvent to give 1.0 g of a yellow solid. The solid product was suspended in 30 ml of chloroform, stirred for 15 minutes at room temperature and filtered. The chloroform-insoluble pale yellow crystalline powder was recrystallized from methanol to give 0.84 g (20%) of **23**, mp 135-137° (Decomposed with foaming; after decomposition, new crystals appeared at this temperature, which melted at 246° dec); ^{1}H nmr (deuteriomethanol): δ 6.51 (d, J = 7.0 Hz, 1H, H-5), 7.86 (dd, J = 7.0, 1.5 Hz, 1H, H-6), 8.12 (d, J = 1.5 Hz, 1H, H-2); ^{13}C nmr (dimethylsulfoxide-d_6, containing bis(acetylacetonato)copper(II)): δ 116.99 (s, C-3), 122.44 (d, C-5), 137.95 (d, C-6), 140.38 (d, C-2), 170.08 (s, *C*(NO$_2$)$_3$), 172.66 (s, C-4); (in dimethylsulfoxide-d_6): δ 111.27 (s, C-3), 118.73 (d, C-5), 139.99 (d, C-6), 142.47 (d, C-2), 174.65 (s, C-4), signal of -*C*(NO$_2$)$_3$ could not be detected; ir (potassium bromide): 3200-2400 (broad, m), 1650 (s), 1607 (s), 1595 (s), 1540 (s), 1503 (s), 1403 (w), 1370 (w), 1350 (w), 1300 (s), 1280 (s), 1180 (s), 1150 (m), 1030 (w), 975 (w), 940 (w), 880 (w), 855 (w), 825 (s), 795 (s), 785 cm^{-1} (s).

Anal. Calcd. for $C_6H_4N_4O_7$: C, 29.52; H, 1.65; N, 22.95. Found: C, 29.56; H, 1.63; N, 23.21.

The chloroform solution was evaporated to give 0.53 g (33%) of 2-nitrofuro[3,2-*c*]pyridine (**22**), mp 96-99° (literature [6], 99-101.5°). The ^{1}H nmr spectrum was identical with that reported [6].

b) A mixture of 2.0 g (16.8 mmoles) of **4** and 35 ml of fuming nitric acid (d, 1.50) prepared at −5° was stirred at 10° for 2.5 hours, poured onto 100 g of ice, neutralized with solid sodium bicarbonate, extracted with ethyl acetate and dried (magnesium sulfate). Evaporation of the solvent under reduced pressure at 20° yielded 1.64 g of a yellow semi-solid. The ^{1}H nmr spectrum in deuteriochloroform indicated the product to be a mixture of *cis*-(**25a**) and *trans*-2-nitro-2,3-dihydrofuro[3,2-*c*]pyrid-3-yl nitrate (**25b**) and 2-nitrofuro[3,2-*c*]pyridinium nitrate (**22-HNO$_3$**) (approximate ratio: 1:2:1, determined by integration of the signals at δ 6.37 (s, H-3 of **25b**), 6.52 (d, J = 7.0 Hz, H-2 of **25a**), 6.68 (s, H-3 of **25b**), 6.99 (d, J = 7.0 Hz, H-3 of **25a**) and 9.14 (s, H-4 of **22-HNO$_3$**)). The mixture gradually solidified and became insoluble in chloroform. Recrystallization of the solid from methanol yielded 1.4 g (37%) of **22-HNO$_3$**, mp 175-177°; ^{1}H nmr (deuteriomethanol): δ 8.29 (d, J = 0.8 Hz, 1H, H-3),

8.34 (dt, J = 6.6, 0.8 Hz, 1H, H-7), 8.95 (d, J = 6.6 Hz, 1H, H-6), 9.54 (d, J = 0.8 Hz, 1H, H-4).

Anal. Calcd. for $C_7H_5N_3O_6$: C, 37.01; H, 2.22; N, 18.50. Found: C, 37.03; H, 2.35; N, 18.76.

Conversion of **23** to 4-Hydroxynicotinic Acid (**24**).

A suspension of 50 mg (0.22 mmole) of **23** in 2 ml of xylene was heated at 135-140° for 5 minutes with stirring. After cooling, the mixture was evaporated under reduced pressure, and the residue was recrystallized from methanol to give 20 mg (70%) of **24**, mp 257-264° (literature [11] mp 245-247°). The ir spectrum was identical with that of the sample prepared by the method of Taylor [11].

Determination of Ionization Constants.

a) Titration Method.

The 240 mg samples of analytically pure **2, 3** and **4** were weighed on a micro analytical balance and dissolved in ion free water in a 200 ml volumetric flask. While stirring the solution magnetically at 20.0±0.1°, 0.10*N* hydrochloric acid was added from a burette to the solution in small increments. The resulting *p*H readings were observed on a digital *p*H meter (Toko Chemical Laboratories, Model TP-1000) using a combination glass electrode (PCE 108C). The meter was calibrated in 0.01 *p*H units, allowing estimation to 0.001 *p*H units. It was standardized with aqueous buffer (*p*H 4.01±0.01° @ 20°, *p*H 6.86±0.01 @ 20°) supplied by Toko Chemical Laboratories and the standardization was rechecked after titrations.

b) The UV Absorption Method.

The ionization constants of **1, 7, 9, 11, 13** and 2-methylfuro[3,2-*c*]pyridine [4a] were determined by this method. Eight solutions of different *p*H values were prepared in acetate buffer (**9, 11** and **13**), in hydrochloric acid (**1** and **7**) or phosphate buffer (2-methylfuro[3,2-*c*]pyridine). The extinction coefficient *(E)* of the substance was measured at *p*H values corresponding to the range from 15% to 85% ionization. The p*K*a was determined from the equation $pKa = pH - \log(E_{BH^+} - E)/(E - E_B)$, where E_{BH^+} and E_B are the extinction coefficient of the cation and the neutral molecule, respectively.

Deuteriodeprotonation.

a) In Sulfuric Acid-d_2.

These experiments were carried out with 50 mg samples of freshly distilled **1, 2, 3** and **4**, dissolved in 1.0 ml of 96% sulfuric acid-d_2. The exchange was carried out in an external thermostat at 85°. The tubes were cooled to room temperature before measuring the nmr spectrum and time of measurement (*ca.* 5 minutes) was negelected. The ratio of deuteriodeprotonation was determined by integration over 3-hydrogen resonance, using the resonance of hydrogens of the pyridine ring as internal standard.

b) In Sodium Deuterioxide-Methanol-d_4.

These experiments were carried out with 50 mg samples of freshly distilled **1, 2, 3** and **4**, dissolved in 1.00 g of sodium deuteroxide in methanol-d_4 (prepared by mixing 2.51 g of 40% sodium deutroxide in deuterium oxide with 2.60 g of methanol-d_4). The exchange was carried out in an external thermostat at 45°. The ratio of deuteriodeprotonation was determined by integration over 2-hydrogen resonance, using the resonance of hydrogens of the pyridine ring as internal standard.

X-Ray Structural Determination of **18, 20'** and **23**.

A single crystal of **18** ($C_6H_6ClN_3O_5$), **20'** ($C_{13}H_{10}N_4O_5$) or **23** ($C_6H_4N_4O_7$) was recrystallized by slow evaporation of a methanol or an acetone solution at room temperature. Cell parameters were measured on a Rigaku automatic four-circle diffractometer for **18** and **20'** and a Philips PW 1100 automatic four-circle diffractometer for **23** with a graphite-monochromated CuKα radiation (λ = 1.5418 Å) and refined by least-squares method. The crystallographic data are as follows: **18**, M_r = 253.6, monoclinic, space group $P2_1/c$, a = 4.688(1), b = 23.161(6), c = 8.647(3) Å, β = 105.24(2)°, V = 905.8(5) Å^3, D_m (by flotation in carbon tetrachloride/benzene mixture) = 1.723(3), D_x = 1.727 g cm^{-3}, z = 4; **20'**, M_r = 302.2, orthorhombic, space group Pbca, a = 7.394(5), b = 14047(9), c = 26.206(23) Å, V = 2722(4) Å^3, D_m = 1.474(1), D_x = 1.475 g cm^{-3}, z = 8; **23**, M_r = 244.1, monoclinic, space group $P2_1/n$, a = 9.896, b = 15.114, c = 6.560 Å, β = 104.60°, V = 949.5 Å^3, D_x = 1.707 g cm^{-3}, z = 4. By means of the $\omega-2\theta$ scanning mode, a total of 1541 (**18**), 2316 (**20'**) or 1714 (**23**) independent reflections ($\sin\theta/\lambda \leq 0.588$ Å^{-1}) were collected at a rate of 4°/minutes in 2θ; the background was counted for 5s at the edges of the reflections. The intensities of four standard reflections, measured at every 100 reflection intervals, did not change during the data collection. Corrections were made for the Lorentz and polarization factors, but not for the absorption effects because of the smallness of the used crystal size (0.2 × 0.1 × 0.1 mm for **18**, 0.4 × 0.4 × 0.3 mm for **20'** and 0.4 × 0.3 × 0.2 mm for **23**). The structure was solved by Patterson-Fourier (**18**) or direct methods (**20'** and **23**) [19] and refined by block-diagonal least-squares methods with anisotropic thermal parameters for all non-hydrogen atoms. From a difference Fourier map, the hydrogen atom of **20'** and **23** were located in idealized positions, but **18** did not show these hydrogen atoms clearly. The obtained hydrogen atoms of **20'** and **23** were included in the further refinements with anisotropic temperature factors. The structure was refined down to final values of R_1 = 11.0% and R_2 = 10.7% for **18**, R_1 = 6.0% and R_2 = 7.1% for **10'** or R = 6.1% for **23**. The scattering factors were taken from the literature [20].

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