NUCLEOPHILIC SUBSTITUTION IN A SERIES OF 4-NITRONICOTINIC ACID 1-OXIDE DERIVATIVES

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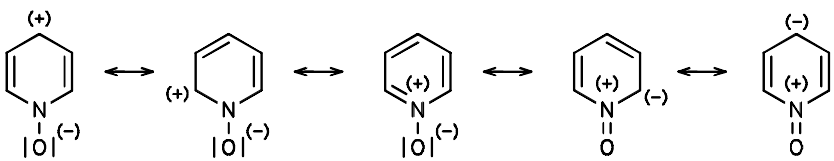
Received February 16, 1995
Accepted May 18, 1995

Dedicated to Professor Otakar Cervinka on the occasion of his 70th birthday.

Nucleophilic substitution of the nitro group in 4-nitro-3-pyridinecarboxanilide 1-oxide (*IIa*) afforded 4-hydroxy- (*IIb*), 4-chloro- (*IIc*), 4-methoxy- (*IId*), 4-ethoxy- (*IIe*), and 4-dimethylamino-3-pyridinecarboxanilide (*IIf*). The ^{1}H and ^{13}C NMR chemical shifts of the pyridine moiety were correlated with the Hammett constants of the substituent in position 4, with the exception of compound *IIb*. The reason of this phenomenon is discussed.

In the course of preparation of 4-aminonicotinates from methyl 4-nitropyridine-3-carboxylate 1-oxide[1] we found a very simple substitution of the nitro group by the methoxy group under conditions of acid-catalyzed esterification[2]. This brought us to a more detailed study of nucleophilic aromatic substitution in the series of pyridine-1-oxide derivatives.

Pyridine 1-oxide is an interesting molecule, with positions 2 and 4 activated for either electrophilic or nucleophilic substitution[3,4] (Scheme 1).



SCHEME 1

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It is generally known that nucleophilic substitution at the aromatic ring is facilitated by the presence of an electron-withdrawing group. In our case, a modified carboxyl group is present in position 3. Using different *C*-, *N*-, *O*- and *S*-nucleophiles we found[5] that the reaction of methyl 4-nitropyridine-3-carboxylate 1-oxide proceeds under very mild conditions (low concentration, laboratory temperature) within very short reaction periods (seconds) and with a 100% conversion of the reactant (determined by TLC). The electron donor–electron acceptor complex[6] formation was accompanied by an immediate color change.

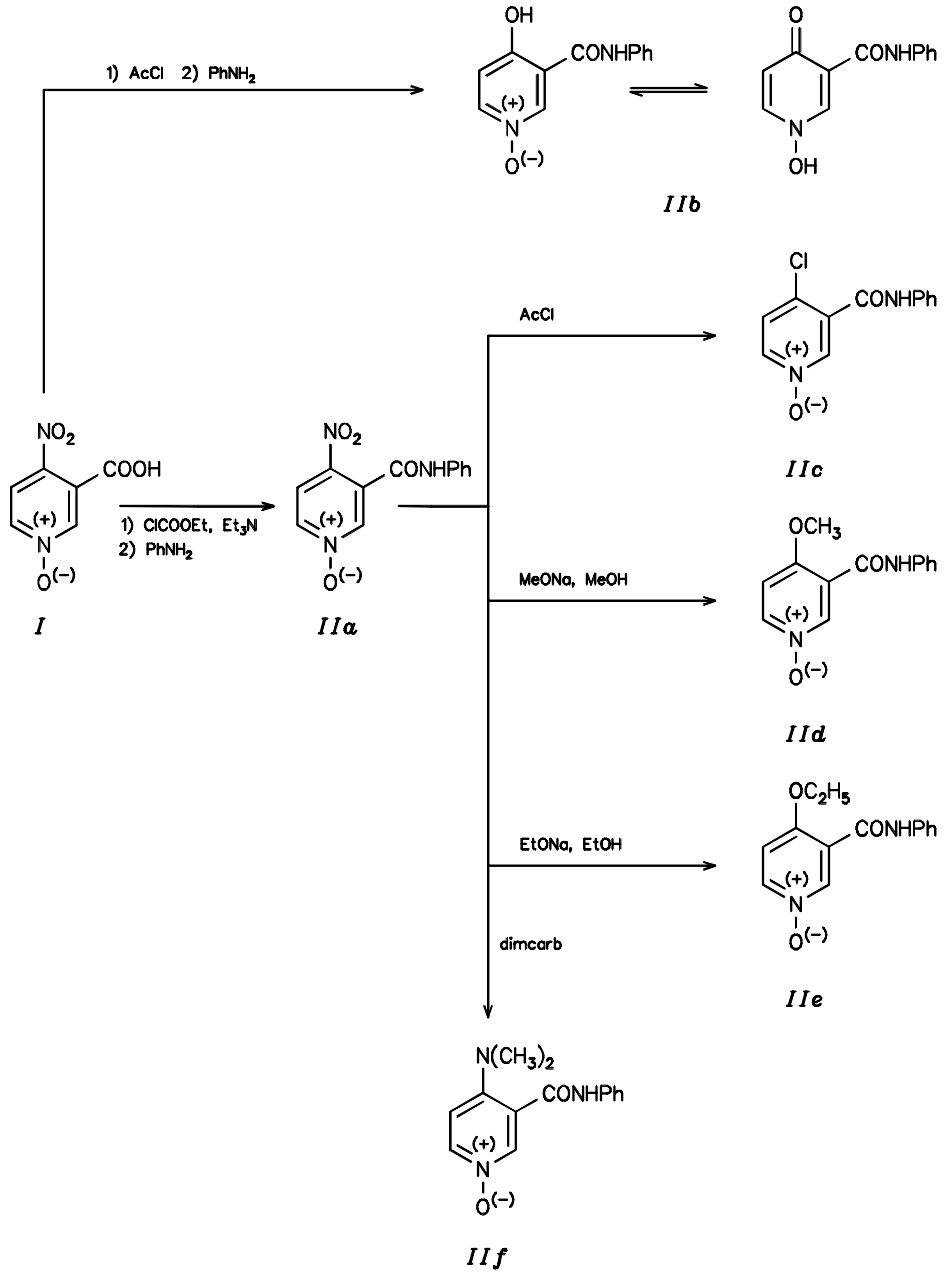
Nucleophilic substitution of the nitro group bonded to pyridine 1-oxide derivatives was first described almost 50 years ago[7]. Since that time the preparation of 4-anilino[8], 4-chloro[9], 4-hydroxy[9], 4-methoxy[10] and 4-bromo derivative[10] starting from the 4-nitronicotinic acid 1-oxide has been reported. We extend now this kind of substitution to other 4-nitronicotinic acid derivatives.

4-Nitronicotinic acid 1-oxide (*I*) was prepared by a three-step procedure from 3-methylpyridine, the first step being the oxidation by hydrogen peroxide to the corresponding 1-oxide[11]. The 1-oxide was then nitrated with 100% nitric acid in concentrated sulfuric acid to 3-methyl-4-nitropyridine 1-oxide[12]. The oxidation of the methyl group leading to compound *I* was done with sodium dichromate in sulfuric acid[13]. 4-Nitro-3-pyridinecarboxanilide 1-oxide (*IIa*) was obtained by the method[14] described for 4-nitronicotinamide 1-oxide via a mixed anhydride intermediate. The hydroxy derivative *IIb* was formed in two steps from acid *I*, the intermediate being the non-isolated chloride of 4-chloronicotinic acid *N*-oxide. By the nucleophilic substitution of the nitro group in *IIa* we obtained 4-chloro- (*IIc*), 4-methoxy- (*IId*), 4-ethoxy- (*IIe*) and 4-dimethylamino-3-nitropyridinecarboxanilide 1-oxide (*IIf*) (Scheme 2).

We found the following interesting dependences in the ^{1}H NMR spectra of compounds *II* (Table I): While the proton signals of the benzene ring are not influenced by the substituent in position 4 of the pyridine oxide ring, all the other protons are linearly dependent on the Hammett substituent σ_p constants (see Fig. 1; the line slopes and positions were calculated by linear regression); the range of chemical shifts of H-2 being 0.67 ppm, H-5 1.39 ppm, H-6 0.50 ppm and NH (the signal position is independent of concentration) 0.47 ppm. One compound, however, behaves differently, viz. the hydroxy derivative *IIb* (Table I, Fig. 1), whose signals H-2, H-5 and H-6 were not included in the correlation analysis.

A similar dependence can be found in the analysis of ^{13}C NMR spectral data (Table II). The different nature of *IIb* is especially obvious from the C-4 chemical shift: while the C-4 peaks of compounds *IIa*, *IIc–IIf* lie in the range of 134–153.5 ppm, the corresponding signal of *IIb* occurs at 175 ppm, which indicates a strong deshielding effect.

The double-bond region of the IR spectrum of the hydroxy derivative *IIb* is slightly different from the spectra of all other compounds *II*: There appeared a new band of


1) AcCl 2) PhNH2
OH
CONHPh
O
CONHPh
N
O(–)
OH
IIb
NO2
COOH
(+)
N
O(–)
I
1) ClCOOEt, Et3N
2) PhNH2
NO2
CONHPh
IIa
AcCl
Cl
CONHPh
IIc
MeONa, MeOH
OCH3
CONHPh
IId
EtONa, EtOH
OC2H5
CONHPh
IIe
dimcarb
N(CH3)2
CONHPh
IIf

SCHEME 2

TABLE I
^{1}H NMR spectral data of compounds *II*

Compound	Chemical shift, ppm							Coupling constant *J*(H,H), Hz							
	NH	2	5	6	*o*	*m*	*p*	2,6	6,2	6,5	5,6	*o*,*m*	*m*,*o*	*m*,*p*	*p*,*m*
IIa	10.76	8.75	8.22	8.50	7.61	7.37	7.14	1.9	2.0	7.1	7.1	7.6	7.7	15.8	16.8
IIb	12.80	8.75	6.53	8.11	7.69	7.37	7.10	3.0	2.9	7.7	7.8	7.8	7.6	15.8	14.8
IIc	10.73	8.60	7.68	8.32	7.68	7.37	7.15	2.1	2.1	7.2	–	–	7.8	15.9	15.0
IId[a]	10.35	8.27	7.24	8.27	7.67	7.34	7.11	–	–	–	7.2	8.1	7.8	15.3	14.4
IIe[b]	10.29	8.29	7.23	8.25	7.67	7.35	7.11	2.4	2.4	7.2	7.5	7.5	7.2	15.9	15.0
IIf[c]	11.03	8.08	6.83	8.00	7.67	7.34	7.11	2.1	2.1	7.2	8.1	8.1	7.8	16.2	15.0

[a] Chemical shift of the methoxy group: 3.90 ppm. [b] Ethoxy group: 4.19 q (CH_2), 1.34 t (CH_3). [c] Dimethylamino group: 2.91 ppm.

ν(C=C) at 1 640 cm^{-1} (see Table III), which can be assigned to the carbon–carbon double bond conjugated to the oxo group of the pyridone tautomer.

From the results of all the mentioned analyses it is possible to conclude that the hydroxy derivative *IIb*, formed by nucleophilic substitution of the nitro group, occurs exclusively in the 1-hydroxy-4-pyridone form.

EXPERIMENTAL

The melting points were determined on a Boetius block and are uncorrected. The IR spectra were recorded on a Bruker IFS 88 spectrometer in KBr pellets. The ^{1}H NMR spectra (δ, ppm; *J*, Hz) were measured on a Gemini-300HC instrument (300.075 MHz, digital resolution 0.3 Hz/point), the ^{13}C NMR

TABLE II
^{13}C NMR spectral data (δ, ppm) of compounds *II*

Compound	C=O	C-2	C-3	C-4	C-5	C-6	*i*	*o*	*m*	*p*
IIa	159.48	140.56	130.72	139.52	122.37	139.19	138.26	128.39	119.72	124.39
IIb	161.48	141.20	117.15	175.30	119.60	139.66	138.42	129.00	119.64	123.67
IIc	160.20	140.36	126.44	134.93	127.55	138.49	138.28	128.87	119.69	124.35
IId[a]	160.17	140.60	124.27	153.52	110.51	138.39	138.47	128.78	119.76	124.09
IIe[b]	160.07	140.72	124.02	152.94	111.22	138.61	138.43	128.85	119.62	124.08
IIf[c]	163.56	138.72	121.04	145.94	111.85	137.66	138.80	128.75	119.78	123.96

[a] Chemical shift of the methoxy group: 59.92 ppm. [b] Ethoxy group: 65.47 (CH_2), 14.14 (CH_3). [c] Dimethylamino group: 41.41 ppm.

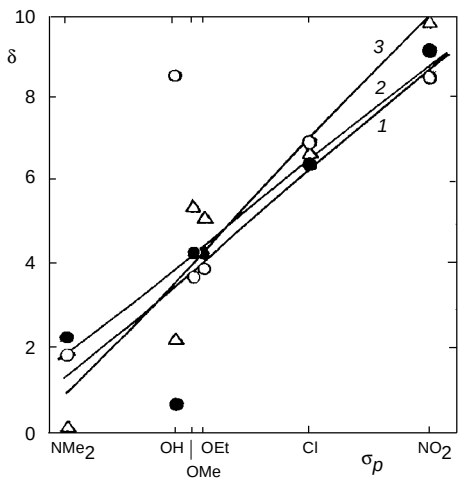


FIG. 1
The pyridine moiety ^{1}H NMR chemical shift dependence on the Hammett substituent constants for compounds *II* (*1*, H-2, the range of δ being 7.9–8.9 ppm; *2*, H-5, 6.4–8.4 ppm; *3*, H-6, 8.0–8.5 ppm). The hydroxy derivative *IIb* was not included in the correlation analysis

spectra (δ, ppm) on a Bruker-400 instrument (100.614 MHz, digital resolution 1 Hz/point, APT technique, pulse sequence) in hexadeuteriodimethyl sulfoxide. For the concentration dependence study solutions were measured at 0.07, 0.14 and 0.21 mol l^{-1}. Flash column chromatography was performed on Merck silica gel 40 in dichloromethane followed by acetone, TLC on Silufol plates (Kavalier, Czech Republic) in a mixture of chloroform–methanol 4 : 1. Dimethylammonium *N,N*-dimethylcarbamate (dimcarb) was a gift from Professor W. Schroth, Martin-Luther University, Halle, Germany.

4-Nitro-3-pyridinecarboxanilide 1-Oxide (*IIa*)

A suspension of 4-nitronicotinic acid 1-oxide (*I*, 0.5 g, 2.7 mmol) in dry dioxane (6.8 ml) and dry tetrahydrofuran (8.2 ml) was combined with freshly distilled triethylamine (0.76 ml, 5.4 mmol). The resulting solution was then cooled to –15 °C and ethyl chloroformate (0.52 ml, 5.4 mmol) was added dropwise at such a rate that the temperature of the reaction mixture did not exceed –12 °C. The resulting suspension was then stirred at –15 °C for 3 h, aniline (1.0 ml, 11 mmol) was added in one portion and the mixture was stirred at room temperature for 30 min. Water (5 ml) was then added, the organic layer was evaporated to dryness, dissolved in dichloromethane (5 ml) and column-chromatographed. The amorphous red solid was recrystallized from water, and 90 mg (13%) of *IIa* was obtained, m.p. 168–170 °C, R_F 0.56. For $C_{12}H_9N_3O_4$ (259.2) calculated: 55.60% C, 3.50% H, 16.21% N; found: 55.89% C, 3.68% H, 16.07% N. ^{1}H NMR spectra are given in Table I, ^{13}C NMR spectra in Table II and IR spectra in Table III.

4-Hydroxy-3-pyridinecarboxanilide 1-Oxide (*IIb*)

A suspension of 4-nitronicotinic acid 1-oxide (*I*, 0.2 g, 1.1 mmol) in acetyl chloride (5.0 ml, 70 mmol) was refluxed for 5 h. Acetyl chloride was then distilled off and aniline (5.0 ml, 55 mmol) was added

TABLE III
IR spectra of compounds *II* (s strong, br broad, w weak)

Compound	ν(NH)	Amide I	Amide II	ν(CH-arom.)
IIa	3 258(w) 3 111(w)	1 679(s)	1 554(s)	756 689
IIb[a]	3 448(br) 3 252(br)	1 683(s)	1 551(s)	759 692
IIc	3 400(br) 3 240 3 180	1 681 (br,s)	1 552(s)	692
IId	3 447(br) 3 353(s)	1 677(s)	1 559(s)	763(s)
IIe	3 438(br) 3 344(s) 3 223(br) 3 117(s)	1 676(s)	1 558(s)	765 778(s)[b]
IIf	3 336(br)	1 676(s)	1 562(s)	764 695

[a] ν(C=C) 1 640 cm^{-1}, ν(C=O) 1 592 cm^{-1}. [b] Rocking vibration of the ethyl group.

dropwise. After 1 h stirring at room temperature the precipitated solid was filtered, washed with toluene and, after dissolving in water, alkalified to pH 8. The remaining aniline was washed off with ethyl acetate, the residue after evaporation of the water portion was dissolved in acetone (25 ml) and filtered. After evaporation of acetone 40 mg (15%) of *IIb* was obtained, m.p. 282–286 °C, R_F 0.52. For $C_{12}H_{10}N_2O_3$ (230.2) calculated: 62.61% C, 4.35% H, 12.17% N; found: 62.58% C, 4.40% H, 12.08% N. ^{1}H NMR spectra are given in Table I, ^{13}C NMR spectra in Table II and IR spectra in Table III.

4-Chloro-3-pyridinecarboxanilide 1-Oxide (*IIc*)

4-Nitro-3-pyridinecarboxanilide 1-oxide (*IIa*, 50 mg, 0.2 mmol) was suspended in acetyl chloride (2 ml) and refluxed for 4 h. Acetyl chloride was then distilled off and the solid residue was washed with acetone, filtered and recrystallized from water. After drying a quantitative yield of *IIc* was obtained, m.p. 172–175 °C, R_F 0.52. For $C_{12}H_9ClN_2O_2$. 1.5 H_2O (275.7) calculated: 52.28% C, 4.38% H, 10.16% N; found: 52.32% C, 3.80% H, 9.70% N. ^{1}H NMR spectra are given in Table I, ^{13}C NMR spectra in Table II and IR spectra in Table III.

4-Methoxy-3-pyridinecarboxanilide 1-Oxide (*IId*)

4-Nitro-3-pyridinecarboxanilide 1-oxide (*IIa*, 100 mg, 0.4 mmol) and 7% sodium methoxide in methanol (3 ml, 2.6 mmol) were stirred at room temperature for 0.5 h. The mixture was diluted with acetone and filtered through a silica gel layer. After evaporation of the filtrate compound *IId* was obtained (60 mg, 55%), m.p. 160–162 °C, R_F 0.37. For $C_{13}H_{12}N_2O_3$. 1.5 H_2O (271.3) calculated: 57.56% C, 5.57% H, 10.33% N; found: 57.52% C, 5.80% H, 10.33% N. ^{1}H NMR spectra are given in Table I, ^{13}C NMR spectra in Table II and IR spectra in Table III.

4-Ethoxy-3-pyridinecarboxanilide 1-Oxide (*IIe*)

4-Nitro-3-pyridinecarboxanilide 1-oxide (*IIa*, 100 mg, 0.4 mmol) and 7% sodium ethoxide in ethanol (5 ml) were stirred at room temperature for 0.5 h. The solvent was then evaporated under reduced pressure and the residue was triturated with water. The resulting crystalline compound was the pure anilide *IIe* (35 mg, 30%), m.p. 153–154 °C, R_F 0.41. For $C_{14}H_{14}N_2O_3$. 2 H_2O (294.3) calculated: 57.14% C, 6.16% H, 9.52% N; found: 57.51% C, 6.52% H, 9.67% N. ^{1}H NMR spectra are given in Table I, ^{13}C NMR spectra in Table II and IR spectra in Table III.

4-Dimethylamino-3-pyridinecarboxanilide 1-Oxide (*IIf*)

4-Nitro-3-pyridinecarboxanilide 1-oxide (*IIa*, 100 mg, 0.4 mmol) and freshly distilled dimethylammonium *N*,*N*-dimethylcarbamate (2 ml, 15 mmol) in water (2 ml) were stirred at room temperature for 5 h. The solvent was then evaporated under reduced pressure and codistilled with toluene; the residue was column chromatographed (eluent chloroform–methanol 9 : 1) to give the anilide *IIf* (80 mg, 68%), m.p. 230–233 °C, R_F 0.34. For $C_{14}H_{15}N_3O_2$. 2 H_2O (293.3) calculated: 57.33% C, 6.53% H, 14.33% N; found: 57.56% C, 6.01% H, 14.26% N. ^{1}H NMR spectra are given in Table I, ^{13}C NMR spectra in Table II and IR spectra in Table III.

The authors are indebted to Dr Antonin Holy from the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, for valuable advice and discussions. Their thanks are also due to Mrs Zdenka Hladikova for excellent technical assistance. This work was supported by

the Grant Agency of the Czech Republic (Grant No. 93/203/0118) and the Ministry of Education of the Czech Republic (Grant No. 93/0766).

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