STRUCTURE AND PROPERTIES OF QUATERNIZED 2- AND 4-AMINONICOTINAMIDES

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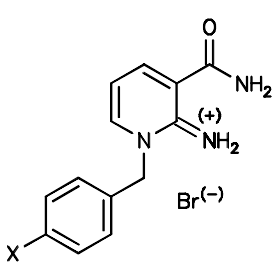
Compounds 2- and 4-aminonicotinamide were quaternized with eight 4-substituted 1-bromomethylbenzenes to form 1-(4-substituted benzyl)-3-carbamoyl-1,2(1,4)-dihydropyridin-2(4)-iminium bromides. The optimal reaction conditions were found and the resulting iminium salts were characterized by ^{1}H and ^{13}C NMR spectra. No transmission of electronic effect of the substituent at the benzene ring on the spectral properties of dihydropyridine moiety was observed. The possible reason is discussed.

In our previous communication[1] we have found ^{13}C NMR spectroscopy as a suitable tool for the proof of the structure of aminopyridine quaternary salts. We concluded that salts derived from 2- and 4-aminopyridine occur exclusively in the iminium form with dihydropyridine structure. This fact may be important from the biological point of view: dihydropyridiniminium structure behaves rather as an 1,4-dihydropyridine derivative than as a pyridinium quaternary salt and the hydride-donor properties are lost. This fact can be a reason of both the CNS activity of the alkaloid clitidin[2] and the powerful competitive inhibition of NAD by aminonicotinamide, which is by NADase catalyzed base-exchange reaction transformed into a coenzyme analog[3]. The chance to be therapeutically useful let us to the synthesis of 2- and 4-aminonicotinamides substituted in the position 1 with modified benzyl group. These compounds are interesting also from the chemical point of view, regarding the study on the substituent effects.

The starting 2-aminonicotinamide was prepared from nicotinamide by oxidation to its *N*-oxide, chlorination with a mixture of phosphorus pentachloride and phosphorus oxychloride to 2-chloronicotinonitrile, reaction with alcoholic ammonia at 180 °C and hydrolysis according to the described procedure[4]. 4-Aminonicotinamide was obtained from the 3-methylpyridine-1-oxide by its nitration[5], oxidation[6] to 4-nitronicotinic acid 1-oxide, catalytic hydrogenation[7] to 4-aminonicotinic acid and amide preparation via the anhydride intermediate[8]. The 1-substituted 2- and 4-aminonicotinamides *I* and *II* were prepared by reaction of the base with the corresponding 4-substituted 1-bromomethylbenzene in dimethylformamide or acetonitrile.

The physico-chemical characteristics of prepared compounds are given in Table I, the ^{1}H NMR and ^{13}C NMR spectra of compounds *I* and *II* in Tables II–V, respectively.

The aim of our work was to find how is the electronic structure of dihydropyridiniminium moiety influenced by a relatively remote substituent. In continuation of a systematic study[9–11] of substituent effects of pyridine derivatives carried out earlier in our laboratory we tried to detect any relationship between the substituent on the benzyl group and the pyridine moiety. Although the mentioned studies were focused mainly on the polarographic reduction, the ^{1}H NMR signals given show some dependences on the nature of the substituent, e.g. in the case of the 1-(4-substituted phenyl) derivatives[10] the difference of the chemical shifts of H-2 is $\Delta\delta$ = 0.60 ppm (Table VI); in our compounds *II* the value is only 0.20 ppm (Table IV), for H-4 $\Delta\delta$ = 1.0 ppm (in our case – compounds *I* – $\Delta\delta$ = 0.05 ppm; Table II), for H-5 $\Delta\delta$ = 0.5 ppm (0.05 and 0.07 ppm), and for H-6 $\Delta\delta$ = 0.44 ppm (0.05 and 0.08 ppm, see Tables VI, II and IV, respectively). Also in the 1-(4-substituted benzyl) derivatives[9] the substituent effect is more prominent when no amino group is present. The isolation of the aminopyridine moiety is even more obvious from the ^{13}C NMR spectra (Tables III and V) where, even the $\Delta\delta$ value of C-4′ being both in compounds *I* and in compounds *II* more than 35 ppm, almost no change in chemical shifts is observed. As a plausible explanation for the absence of electronic substituent effect transfer in quaternized 2- and 4-aminopyridine derivatives we suggest their dihydropyridine-like structure, which lacks aromaticity of pyridinium compounds and thus does not possess the pronounced electron-acceptor properties. Absence of these properties causes probably the powerful inhibition of NAD in the respiratory chain, and thus the biological activity of aminopyridine derivatives.



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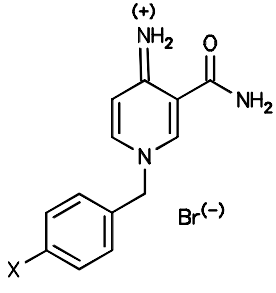

II

I, *II*	X
a	H
b	Br
c	CF_3
d	COOH
e	CN
f	NO_2
g	$C(CH_3)_3$
h	F

TABLE I
Characteristic data for the compounds *I* and *II*

Compound	M.p., °C Yield, %	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
Ia	246–250	$C_{13}H_{14}BrN_3O$	50.67	4.58	13.64
	67	(308.2)	49.84	4.54	13.38
Ib	238–240	$C_{13}H_{13}Br_2N_3O \cdot H_2O$	38.55	3.74	10.37
	41	(405.1)	38.53	3.94	10.43
Ic	222–226	$C_{14}H_{13}BrF_3N_3O \cdot 1.5\ H_2O$	41.70	4.00	10.42
	85	(403.2)	41.57	3.78	10.41
Id	289–292	$C_{14}H_{14}BrN_3O_3 \cdot 0.5\ H_2O$	46.57	4.19	11.60
	95	(361.2)	46.97	4.13	11.10
Ie	238–242	$C_{14}H_{13}BrN_4O \cdot 0.5\ H_2O$	49.14	4.12	16.37
	72	(342.2)	48.94	4.08	15.81
If	245–247	$C_{13}H_{13}BrN_4O_3 \cdot H_2O$	42.07	4.07	15.09
	55	(371.2)	42.14	4.05	14.69
Ig	208–211	$C_{17}H_{22}BrN_3O \cdot C_3H_7NO$[a]	54.92	6.68	12.81
	72	(437.4)	54.80	6.90	12.78
Ih	234–236	$C_{13}H_{13}BrFN_3O \cdot 2\ H_2O$	43.11	4.70	11.66
	52	(362.2)	43.37	4.30	12.15
IIa	231–232	$C_{13}H_{14}BrN_3O \cdot 0.5\ H_2O$	49.18	4.73	13.24
	65	(317.2)	49.05	4.94	13.35
IIb	186–190	$C_{13}H_{13}Br_2N_3O \cdot H_2O$	38.55	3.74	10.37
	66	(405.1)	38.06	3.86	10.31
IIc	190–192	$C_{14}H_{13}BrF_3N_3O \cdot H_2O$	42.66	3.84	10.66
	75	(394.2)	42.91	3.94	10.34
IId	319–320	$C_{14}H_{14}BrN_3O_3 \cdot 2\ H_2O$	43.31	4.67	10.82
	56	(388.2)	43.16	4.33	10.47
IIe	194–195	$C_{14}H_{13}BrN_4O \cdot 0.5\ H_2O$	49.09	4.09	16.36
	81	(342.2)	49.22	4.29	16.09
IIf	255–256	$C_{13}H_{13}BrN_4O_3$	44.21	3.71	15.86
	39	(353.2)	44.01	3.89	15.62
IIg	252–253	$C_{17}H_{22}BrN_3O \cdot H_2O$	53.41	6.33	10.99
	60	(382.3)	53.55	6.19	10.62
IIh	234–236	$C_{13}H_{13}BrFN_3O \cdot 1.5\ H_2O$	44.16	4.53	11.89
	71	(353.2)	44.02	4.18	11.56

[a] Solvate with one molecule of dimethylformamide.

EXPERIMENTAL

The melting points were determined on a Boetius block and are uncorrected. The NMR spectra (δ, ppm; *J*, Hz) were measured on a Gemini-300HC instrument in hexadeuteriodimethyl sulfoxide. Experimental parameters: for ^{1}H 300.075 MHz, digital resolution 0.3 Hz/point; for ^{13}C 75.462 MHz, digital resolution 0.6 Hz/point; APT technique. The thin layer chromatography was performed on the

TABLE II
^{1}H NMR spectra of iminium bromides *I*

Compound	H-4	H-5	H-6	2-NH_2	H_a	H_b	CH_2	*o*	*m*	*J*(6,5)	*J*(4,5)	*J*(*o*,*m*)	*J*(*m*,*o*)
Ia	8.45	7.12	8.55	9.33	8.09	8.59	5.61	7.40	7.28[a]	7.6	6.5	7.3	7.1
Ib	8.43	7.12	8.53	9.32	8.09	8.58	5.57	7.24	7.62	7.6	6.7	8.6	8.4
Ic	8.46	7.16	8.55	9.35	8.10	8.59	5.71	7.45	7.79	7.7	6.6	8.2	7.7
Id	8.44	7.14	8.54	9.32	8.10	8.58	5.67	7.33	7.96	7.2	6.6	8.2	8.2
Ie	8.47	7.15	8.57	9.35	8.10	8.60	5.73	7.42	7.89	7.7	6.7	6.7	7.5
If	8.48	7.17	8.57	9.38	8.10	8.60	5.77	7.49	8.26	7.5	6.6	6.9	8.7
Ig	8.45	7.14	8.54	9.30	8.08	8.58	5.57	7.21	7.42	7.6	6.7	7.7	7.1
Ih	8.43	7.12	8.52	9.33	8.09	8.58	5.57	7.38	7.26	7.1	6.1	7.0	8.8

[a] Signal dd, 3 H (m+p).

TABLE III
^{13}C NMR spectra of iminium bromides *I*

Compound	C-2	C-3	C-4	C-5	C-6	CO	CH_2	C-1′	C-2′	C-3′	C-4′	Subst.
Ia	153.2	115.7	143.6	112.0	143.0	167.0	55.6	132.9	127.4	128.9	128.4	–
Ib	153.2	115.9	143.6	112.2	143.0	167.0	55.1	121.8	129.7	131.9	132.3	–
Ic	153.4	115.9	143.9	112.2	143.2	167.0	55.2	128.6	125.6	128.1	137.7	–[a]
Id	153.3	115.8	143.8	112.1	143.1	166.8	55.4	130.7	127.3	129.7	137.8	167.0
Ie	153.4	115.9	143.8	112.1	143.1	166.9	55.3	118.3	128.1	132.7	138.5	111.1
If	153.4	116.0	143.8	112.2	143.2	166.9	55.2	140.5	123.8	128.4	147.3	–
Ig	153.1	115.6	143.6	112.0	142.9	166.9	55.3	129.9	127.3	125.6	151.0	34.1[b]
Ih	153.2	115.7	143.5	112.0	143.0	166.9	54.9	129.1	130.1	115.7	163.6	–

[a] Signal not found. [b] Chemical shift of the methyl group: 30.1 ppm.

Silufol plates (Kavalier, The Czech Republic); all products had R_F 0.0 in the mixture 2-propanol–aqueous ammonia–water (90 : 5 : 5). Starting 4-substituted 1-bromomethylbenzenes were purchased from Fluka. Dimethylformamide was purified by drying over potassium hydroxide, twice vacuum distilled and stored over molecular sieves. Traces of dimethylamine were removed by evacuation immediately before reaction. Acetonitrile was five times rectified from phosphorus pentoxide.

TABLE IV
^{1}H NMR spectra of iminium bromides *II*

Compound	H-2	H-5	H-6	4-NH_2	H_a	H_b	CH_2	*o*	*m*	*J*(5,6)	*J*(6,5)	*J*(*o*,*m*)	*J*(*m*,*o*)
IIa	9.16	7.04	8.29	8.93	7.90	8.32	5.41	7.45[a]	7.45[a]	7.3	7.7	–	–
IIb	9.01	7.00	8.23	8.91	7.89	8.24	5.36	7.42	7.64	7.2	6.6	8.1	8.1
IIc	9.01	7.02	8.26	8.94	7.89	8.26	5.50	7.65	7.81	7.3	6.0	8.1	8.2
IId	9.10	7.04	8.27	8.95	7.89	8.29	5.50	7.54	7.97	7.1	7.2	8.2	8.1
IIe	9.16	7.05	8.29	8.97	7.90	8.28	5.54	7.65	7.91	7.4	6.2	8.3	8.1
IIf	9.11	7.05	8.27	8.98	7.90	8.28	5.58	7.71	8.29	7.5	8.4	8.6	8.8
IIg	8.96	6.99	8.23	8.87	7.88	8.26	5.31	7.36	7.43	7.3	7.6	8.3	8.4
IIh	9.15	6.98	8.21	8.82	7.85	8.57	5.38	7.57	7.25	5.9	4.9	8.0	8.2

[a] Multiplet (5 H).

TABLE V
^{13}C NMR spectra of iminium bromides *II*

Compound	C-2	C-3	C-4	C-5	C-6	CO	CH_2	C-1′	C-2′	C-3′	C-4′	Subst.
IIa	144.5	110.7	157.7	112.5	142.3	166.4	60.0	135.1	128.3	129.0	128.8	–
IIb	144.5	110.8	157.7	112.5	142.3	166.3	59.2	122.1	130.6	131.9	134.3	–
IIc	144.6	111.1	157.7	112.5	142.4	166.2	59.4	129.0	125.8	128.9	139.5	–[a]
IId	144.6	110.9	157.7	112.5	142.5	166.3	59.6	131.0	128.2	129.8	139.6	166.8
IIe	144.7	110.9	157.7	112.5	142.4	166.3	59.2	118.2	129.0	132.8	140.3	111.4
IIf	144.7	111.0	157.8	112.5	142.5	166.3	59.1	142.3	124.0	129.5	147.6	–
IIg	144.4	110.6	157.7	112.5	142.3	166.4	59.8	132.1	128.0	125.7	151.3	34.3[b]
IIh	144.3	111.0	158.0	112.9	142.0	166.4	59.0	131.4	130.7	115.8	163.9	–

[a] Signal not found. [b] Chemical shift of the methyl group: 30.9 ppm.

1-(4-Substituted Benzyl)-3-carbamoyl-1,2-dihydropyridin-2-iminium Bromides *I*. General Procedure

The solution of 2-aminonicotinamide (0.1 g, 0.73 mmol) and corresponding 4-substituted 1-bromomethylbenzene (0.5 g) in dimethylformamide (2 ml) was left at 15 °C for 20 days. Toluene (20 ml) was then added and the resulting white precipitate was isolated by filtration. To remove the residual dimethylformamide, the solid was dissolved in methanol–toluene (1 : 1, 60 ml) and methanol was evaporated under reduced pressure at 15 °C. The suspension formed was then filtered, the solid substance washed with acetone and dried. Yields and physical characteristics of the compounds *I* are given in Table I, ^{1}H and ^{13}C NMR spectra in Tables II and III, respectively.

1-(4-Substituted Benzyl)-3-carbamoyl-1,4-dihydropyridin-4-iminium Bromides *IIa–IId*, *IIf*, *IIg*. General Procedure

The solution of 4-aminonicotinamide (0.1 g, 0.73 mmol) and corresponding 4-substituted 1-bromomethylbenzene (0.5 g) in dimethylformamide (2 ml) was refluxed to the complete conversion of the starting base (TLC). The solvent was then evaporated under reduced pressure and the remaining oily product was co-distilled with toluene. The solid precipitate was washed with ether and dried.Yields and physical characteristics of the compounds *IIa–IId*, *IIf* and *IIg* are given in Table I, ^{1}H and ^{13}C NMR spectra in Tables IV and V, respectively.

1-(4-Cyanobenzyl)-3-carbamoyl-1,4-dihydropyridin-4-iminium Bromide (*IIe*) and
1-(4-Fluorobenzyl)-3-carbamoyl-1,4-dihydropyridin-4-iminium Bromide (*IIh*)

The solution of 4-aminonicotinamide (0.1 g, 0.7 mmol) and 4-bromomethylbenzonitrile or 1-bromomethyl-4-fluorobenzene (0.5 g) in dry acetonitrile (20 ml) was refluxed for three days. The resulting white solid was filtered and dried. Yields and physical characteristics of the compounds *IIe* and *IIh* are given in Table I, ^{1}H and ^{13}C NMR spectra in Tables IV and V, respectively.

TABLE VI
^{1}H NMR spectral data of the nicotinamide moiety for 1-(4-substituted phenyl)-3-carbamoylpyridinium perchlorates (taken from ref.[10])

Proton	Substituent									
	$(C_2H_5)_2N$	OH	OCH_3	CH_3	$NHCOCH_3$	H	Cl	Br	COOH	NO_2
H-2	9.36	9.42	9.40	9.44	9.50	9.50	9.58	9.46	9.96	9.73
H-4	8.88	8.94	8.92	8.98	8.95	9.02	9.10	8.30	9.30	9.23
H-5	8.20	8.26	8.22	8.28	8.20	8.32	8.40	8.00	8.50	8.48
H-6	9.22	9.28	9.28	9.30	9.27	9.38	9.44	9.30	9.66	9.43

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