Nuclear Magnetic Resonance Data of Pyrido[2,3-*b*]pyrazines and Their σ-Adducts with Amide Ion and Water (1)

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^{13}C nmr spectral data of the parent substance pyrido[2,3-*b*]pyrazine and several of its derivatives (containing one or more chloro, amino, oxo, bromo, fluoro, phenyl, methyl, hydrazino or *t*-butyl substituents) are reported. The ^{13}C nmr spectrum of the parent substance has been assigned conclusively by ^{13}C-labelling. Additionally we proved, the existence of anionic 1:1 σ-adducts *i.e.*, 3-amino-3,4-dihydropyrido[2,3-*b*]pyrazine, the formation of 3-amino-2-*t*-butyl-6-chloro-3,4-dihydropyrido[2,3-*b*]pyrazinide ion and by ^{1}H nmr spectroscopy 2-amino-1,2-dihydro-3-phenylpyrido[2,3-*b*]pyrazinide ion. The ^{13}C nmr data of the cation of the dihydrate 2,3-dihydroxy-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine, present in a solution of the parent compound in *N* hydrochloric acid, are given.

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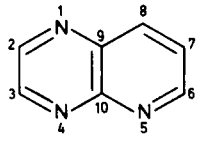
Introduction.

Recently the ^{13}C nmr spectra of pteridines and their covalent σ-adducts with ammonia and water have been analyzed (2,3). In our study on the course of the ring contraction of pyrido[2,3-*b*]pyrazines (3-deazapteridines) into 1*H*-imidazo[4,5-*b*]pyridines we suggested as initial step the formation of a σ-adduct between the pyrido[2,3-*b*]pyrazine and amide ion (3). With the aim to obtain more detailed information about the formation and structure of these σ-adducts we measured the ^{13}C nmr spectra of solutions of pyrido[2,3-*b*]pyrazine and a number of its derivatives in deuteriochloroform and compared these data with those of solutions of the compounds in liquid ammonia, containing potassium amide.



1a

Results and Discussion.

The proton coupled ^{13}C nmr spectrum of pyrido[2,3-*b*]pyrazine (**1a**) - dissolved in deuteriochloroform - shows five intense signals found at 125.7, 138.8, 146.3, 148.0 and 154.5 ppm (Table 1), associated with one bond ^{13}C-^{1}H coupling constants (^{1}JC-H) of 168, 169, 185, 185 and 181 Hz, respectively. The most downfield signal in the spectrum, at 154.5 ppm, is found to be associated with two long-range ^{13}C-^{1}H coupling constants of 8.6 and 3.5 Hz. Long-range coupling constants are found for the resonances at 125.6 ppm (9.2 Hz) and 138.8 ppm (6.4 Hz). The chemical shifts and the one bond coupling constants are in excellent agreement with those established for quinoline (C-2: 150.2 ppm, ^{1}JC-H = 178 Hz, $^{2}JC_2$-H_3 = 3.7 Hz, $^{3}JC_2$-H_4 = 7.9 Hz; C-3: 120.9 ppm, ^{1}JC-H = 165 Hz, $^{2}JC_3$-H_2 = 9.6 Hz; C-4: 135.7 ppm, ^{1}JC-H = 162 Hz, $^{3}JC_4$-H_2 = 5.4 Hz). Based on these data we assigned the signals in the ^{13}C nmr spectrum of **1a** at 154.5, 125.6 and 138.8 ppm to C-6, C-7 and C-8 respectively. The two remaining signals at 146.3 (^{1}JC-H = 185 Hz) and 148.0 ppm (^{1}JC-H = 185 Hz) are ascribed to C-2 and C-3 respectively. That this assignment is not reversed is substantiated on the increase of the signal at 146.3 ppm, when the ^{13}C nmr spectrum of [^{13}C-2]pyrido[2,3-*b*]pyrazine (**1a***) is measured (4). Two smaller signals at 138.6 ppm and 151.6 ppm were assigned to C-9 and C-10 respectively. These assignments were based on the values established for similar systems such as quinoxaline and quinazoline (5).

From the ^{13}C nmr spectral data presented in Table I some substituent effects deserve comment. Striking long-range effects are caused by amino and oxo groups. Thus the 6-amino group in **1e** causes C-2 to have an upfield shift of 6.5 ppm, while C-3 is almost unaffected. A similar effect is exerted by the 2-oxo group in **1f**, that gives rise to an upfield shift of 9.4 ppm for C-6, leaving C-7 unaffected. Apparently the electron-donating capability of the amino or oxo group enhances the electron density in those positions. When compared with **1a**, C-8 in 6-chloropyrido[2,3-*b*]pyrazine (**1d**) - *meta*-oriented to the chloro atom - is shifted more downfield (2.3 ppm) than C-6 (0.2 ppm). This is also observed with C-4 in 2-chloropteridine (2) and is apparently a general phenomenon. It reflects the somewhat enhanced reactivity of the position *meta*-oriented to the chloro atom in 2-chloroquinoline (6), 2,6-dichloropyridine (7) and 2-chloropteridine (8) towards nucleophiles, such as the amide ion.

As was reported for pteridine derivatives (2), the α-substituent effect of a *t*-butyl group was found to be

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approximately - 20 ppm, the β-substituent effect about +2 ppm.

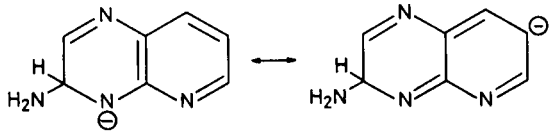
Because of the very slight difference between the chemical shifts (0.1 ppm) in the pmr spectra of pyrido[2,3-*b*]pyrazines it is not possible to assign unequivocally whether a compound is a 2- or 3-substituted derivative. However, it is now certain that ^{13}C nmr substituent effects should provide a more sound base than pmr data, in establishing such structures as **1k** and **11**.

Covalent σ-Adducts.

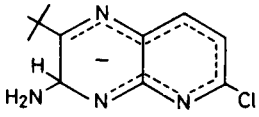
Covalent Aminination.

Close resemblance was found for the pmr spectrum of pyrido[2,3-*b*]pyrazine (**1a**), dissolved in deuteriochloroform and in liquid ammonia. This indicates that **1a**, in contrast to pteridine (8), is not able to give a σ-adduct with ammonia, not even at elevated temperature. However, the ^{13}C nmr spectrum of a solution of **1a** in liquid ammonia, containing 2 equivalents of potassium amide, completely differs from that of **1a**, dissolved in deuteriochloroform (Table 2). An enormous upfield shift of 83.7 ppm is observed for C-3, while ^{1}JC-H decreases to 150 Hz. This is ascribed to rehybridization of C-3, due to formation of the 3-amino-3,4-dihydropyrido[2,3-*b*]pyrazinide ion. Similar magnitudes of upfield shifts have been observed before, on adduct formation of pyrimidines (9) with the amide ion.

Consistent with σ-adduct formation at C-3 is the relatively large upfield shift of C-7, reflecting the enhancement of negative charge in the pyridine nucleus, caused by the contribution of the resonance structure **2a**.



2 **2a**



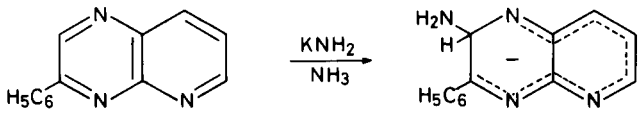
3

Similar upfield shifts for C-3 and C-7 are found for a solution of 2-*t*-butyl-6-chloropyrido[2,3-*b*]pyrazine (**11**) in liquid ammonia, containing 2 equivalents of potassium amide, indicating the formation of the stable σ-adduct 3. Recently 3-*t*-butyl-6-chloropyrido[2,3-*b*]pyrazine (**1k**) was found to be converted into 2-*t*-butyl-1*H*-imidazo[4,5-*b*]-pyridine by potassium amide in liquid ammonia. This ring contraction was explained by an initial addition of the amide ion to C-2, followed by a rearrangement with expulsion of C-2. Attempts to obtain spectroscopic evidence for the existence of a covalent σ-adduct between **1k** and amide ion failed, due to the fast occurring ring contraction. When measuring the pmr spectrum of 3-*t*-

Table I

		C-2	C-3	C-9	C-10	C-6	C-7	C-8
Pyrido[2,3-*b*]pyrazine	**1a**	146.3	148.0	138.6	151.6	154.5	125.7	138.8
^{13}C-2-Pyrido[2,3-*b*]pyrazine	**1a***	146.3*	148.0	138.6	151.6	154.5	125.7	138.8
3-Phenyl-	**1b**	144.3	154.5	135.8	150.8	154.5	124.7	138.1
3-*t*-Butyl-	**1c**	144.8	167.6	135.9	150.4	153.9	124.6	138.2
6-Chloro-	**1d**	146.3	148.6	137.7	150.9	154.7	127.5	141.1
6-Chloro[^{13}C-2]-	**1d***	146.3*	148.6	137.7	150.9	154.7	127.5	141.1
6-Amino- (a)	**1e**	139.8	146.4	134.6	152.4	161.0	117.7	138.4
Pyrido[2,3-*b*]pyrazin-2-one (a)	**1f**	154.5	155.3	127.9	143.0	145.1	125.7	124.8
2-Chloro-	**1g**	148.3	148.3	137.7	149.9	154.3	126.5	137.7
2-Chloro[^{13}C-2]-	**1g***	148.3*	148.3	137.7	149.9	154.3	126.5	137.7
2,6-Dichloro-	**1h**	148.7	148.9	136.7	149.2	154.7	128.4	140.0
2,6-Dichloro[^{13}C-2]-	**1h***	148.7*	148.9	136.7	149.2	154.7	128.4	140.0
6-Chloropyrido[2,3-*b*]pyrazin-2-one (a)	**1i**	154.5	156.3	127.5	142.1	143.7	126.3	128.4
6-Chloro-3-phenyl-	**1j**	144.3	155.2	136.0	150.3	154.8	126.5	140.6
3-*t*-Butyl-6-chloro-	**1k**	144.8	168.7	135.1	149.9	154.3	126.3	140.6
2-*t*-Butyl-6-chloro-	**11**	165.7	147.1	135.9	149.4	153.4	126.9	140.9
Pyrido[2,3-*b*]pyrazin-6-one (a)	**1m**	139.5	144.6	132.8	146.2	162.4	127.7	140.0
6-Chloro-2-hydrazino- (a)	**1n**	144.3	142.7	136.3	146.0	153.7	126.0	137.2
2,3-Diphenyl-	**1o**	154.7	156.3	136.2	149.9	154.1	125.2	138.0
2,3-Diphenyl-6-fluoro-	**1p**	154.3	156.9	135.3	148.4	163.2	114.7	143.5
2,3-Diphenyl-6-chloro-	**1q**	154.8	156.9	135.2	149.2	154.3	126.9	140.4
2,3-Diphenyl-6-bromo-	**1r**	155.0	157.0	135.5	149.7	145.5	130.4	139.9

Samples were measured for deuteriochloroform solutions. (a) Measured for DMSO-d_6 solution. *Increase found for the signal in the ^{13}C nmr spectrum of the ^{13}C-labelled compound.



1b 4

		H-2	H-6	H-7	H-8	Solvent
3-Phenylpyrido-[2,3-*b*]pyrazine	**1b**	9.35 (s)	9.08 (q)	7.51 (q)	8.37 (q)	$CDCl_3$
2-Amino-1,2-dihydro-3-phenylpyrido[2,3-*b*]-pyrazinide ion	**4**	5.52 (s)	8.05 (q)	6.62 (q)	6.94 (q)	NH_3/KNH_2

Table II

		C-2	C-3	C-9	C-10	C-6	C-7	C-8
3-Amino-3,4-dihydro-Pyrido[2,3-*b*]pyrazinide ion	**2**	148.4	64.3	125.6	159.7	149.8	102.7	132.5
3-Amino-2-*t*-butyl-6-chloro-Pyrido[2,3-*b*]pyrazinide ion	**3**	164.2	61.7	124.9	159.5	146.2	99.9	133.2
2,3-Dihydroxy-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine cation	**5**	73.3	74.5	(a)	(a)	125.4	115.9	124.2
2,3-Diaminopyridine cation	**6**			132.7 (C-5)	146.6 (C-2)	125.5	115.0 (C-5)	125.5 (C-4)

(a) Signals did not exceed signal-to-noise level.

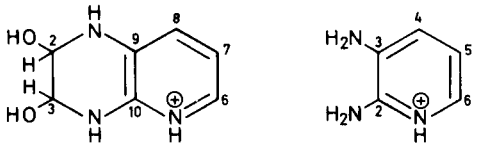
butylpyrido[2,3-*b*]pyrazine (**1c**) in the liquid ammonia potassium amide system, the spectrum of this solution was nearly the same as that of **1c**, dissolved in deuterio chloroform. The conclusion is justified that **1c** does not undergo addition of an amide ion, neither at C-2, nor at C-6. In contrast, 3-phenylpyrido[2,3-*b*]pyrazine (**1b**) was found by pmr spectroscopy to be completely converted into the 2-amino-1,2-dihydro-3-phenylpyrido[2,3-*b*]pyrazinide ion **4**, when dissolved in liquid ammonia, containing two equivalents of potassium amide. This is established by the large upfield shift for H-2 and the smaller upfield shifts for H-6, H-7 and H-8. Moreover, the coupling constants for H-6, H-7 and H-8 are found to be unchanged.

This is the first spectroscopic evidence that addition at C-2 of the pyrido[2,3-*b*]pyrazine ring system can take place. It further indicates that the previous suggestion that the ring contraction of **1k** into 2-*t*-butyl-1-*H*-imidazo[4,5-*b*]pyridine takes place by an initial addition at C-2, seems reasonable.

Attempts to establish the ^{13}C nmr spectrum of **4** were unsuccessful, due to decomposition of the concentrated solution in the time required for the measurement.

Covalent Hydration.

It is proved by pmr spectroscopy that **1a** is not hydrated in a neutral aqueous solution (10) and that in dilute aqueous acid **1a** exists to a small extent as the cationic 2:1 σ-adduct *i.e.*, 2,3-dihydroxy-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine ($5^{\oplus}$).



$5^{\oplus}$ $6^{\oplus}$

We measured ^{13}C nmr spectra of **5** and found that they resemble to a great extent those reported for the pteridine analogue *i.e.*, 6,7-dihydroxy-5,6,7,8-tetrahydropteridine cation. Moreover, the low field region of the ^{13}C nmr spectra of $5^{\oplus}$ and the cation of 2,3-diaminopyridine ($6^{\oplus}$) are strikingly similar. In order to obtain ^{13}C nmr data of the neutral peaks of **5**, we carefully nuetralized the acidic aqueous solution containing $5^{\oplus}$ with ammonia. However the ^{13}C nmr spectrum of the resulting solution, measured without delay, only showed signals due to **1a**, indicating that dehydration of **5** into **1a** is completed in the time required for the acquisition of the last free induction decay.

EXPERIMENTAL

The σ-adduct measurements were performed as described before (9). All compounds, except 2-chloropyrido[2,3-*b*]pyrazine (**1g**) were synthesized to reported procedures (11).

2-Chloropyrido[2,3-*b*]pyrazine (**1g**).

Pyrido[2,3-*b*]pyrazin-2-one (12) (**1f**) was treated with phosphoryl chloride by the usual procedure (11). Compound **1i** was recrystallized from hexane, m.p. 115-116°.

Anal. Calcd. for $C_7H_4ClN_3$: C, 50.77; H, 2.44; Found C, 50.96; H, 2.26.

REFERENCES AND NOTES

(1) Part XXII on σ-adducts of heterocycles with nucleophiles; see for part XXI A. Rykowski, H. C. van der Plas and A. van Veldhuizen, submitted to *Rec. Trav. Chim.*

(2) J. P. Geerts, A. Nagel and H. C. van der Plas, *Org. Magn. Reson.*, 8, 607 (1976).

(3) A. Nagel and H. C. van der Plas, *Tetrahedron Letters*, 2021 (1978).

(4) Compound **1a*** was available from a previous study (11), being formed as the dehalogenated by-product of the reaction of **1d*** and potassium amide in liquid ammonia.

(5) U. Ewers, H. Günther and L. Jaenicke, *Chem. Ber.*, **106**, 3951 (1973).

(6) H. J. den Hertog and D. J. Buurman, *Rec. Trav. Chim.*, **86**, 187 (1967).

(7) H. J. den Hertog, H. C. van der Plas, M. J. Pieterse and J. W. Streef, *ibid.*, **84**, 1569 (1965).

(8) A. Nagel, H. C. van der Plas and A. van Veldhuizen, *ibid.*, **94**, 95 (1975).

(9) J. P. Geerts, H. C. van der Plas and A. van Veldhuizen, *Org. Magn. Reson.*, 7, 86 (1975).

(10) T. J. Batterham, *J. Chem. Soc.* (c), 999 (1966).

(11) A. Nagel, H. C. van der Plas, G. Geurtsen and A. van der Kuilen, submitted to *Heterocyclic Chem.*

(12) A. Albert and G. Barlin, *J. Chem. Soc.*, 5737 (1963).