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Dithionite adducts of pyridinium salts: regioselectivity of formation and mechanisms of decomposition

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Abstract—^{1}H and ^{13}C NMR spectroscopy has been used to detect and to characterize the adducts formed, in alkaline solutions, by the attack of dithionite anion on 3-carbamoyl or 3-cyano substituted pyridinium salts. In all studied cases, only 1,4-dihydropyridine-4-sulfinates, formed by attack of dithionite oxyanion on the carbon 4 of pyridinium ring, were found. This absolute regioselectivity seems to suggest a very specific interaction between the pyridinium cation and the dithionite through the formation of a rigidly oriented ion pair, determining the position of attack. In weak alkaline solution, the adducts decompose according to two mechanisms S_Ni and S_Ni': the S_Ni path is operative in all studied cases and preserves the 1,4-dihydro structure yielding the corresponding 1,4-dihydropyridines, whereas the S_Ni' path involves the shift of 2,3 or 5,6 double bonds yielding 1,2- or 1,6-dihydropyridines, respectively. The formation of 1,2- or 1,6-dihydropyridines, in addition to 1,4-dihydro isomers, depends on their respective thermodynamic stabilities.

1. Introduction

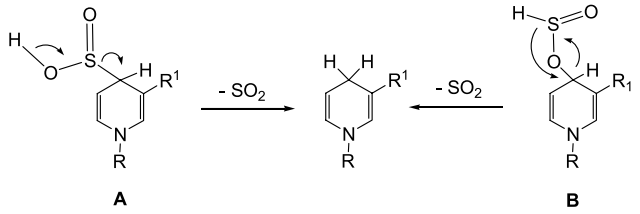
Sodium dithionite reduction has been largely applied to pyridinium salts bearing, in the 3- or 3,5-positions, electron-withdrawing groups such as –CN, –$CONH_2$, –COOR, and chiefly affords the corresponding 1,4-dihydropyridines.[1–7] Thermodynamic factors accounted for this high regioselectivity, since theoretical studies such as, for example, the calculation of the heats of formation using AM1 molecular orbital methods,[8a,b] demonstrated the greater thermodynamic stability of the 1,4-dihydropyridines in comparison with the isomeric 1,2- and 1,6-dihydroderivatives.[9] Intermediate adducts, identified by some authors[1,5,7] as sulfinate anions (Scheme 1, A), are found in the dithionite reduction. These adducts are stable at alkaline pH, while in neutral or weakly alkaline medium they undergo fast protonation and conversion to 1,4-dihydropyridines.

In a recent work[10] we have shown, in accordance with ^{1}H, ^{13}C and ^{17}O NMR spectroscopic evidence, that dithionite adducts are *S*-anions of esters of sulfinic acid (Scheme 1, B), originated by attack of the dithionite oxyanion at the carbon 4 of the pyridinium salts. We have also proposed that the decomposition of these esters, after protonation, may occur according to an intramolecular hydrogen transfer mechanism associated with sulfur dioxide evolution, leading to the formation of 1,4-dihydropyridines with high regioselectivity.

However, it has been reported[7] that in the dithionite reduction of some 4- and 4,6-methyl substituted *N*-Benzyl and *N*-(2,6-dichlorobenzyl)-nicotinamide salts, 1,2- and 1,6-dihydropyridines were formed in addition to the isomeric 1,4-dihydro derivatives.

During our studies on the dithionite reduction of pyridinium salts, in some instances we also noticed the presence of variable amounts of 1,2- or 1,6-dihydropyridines besides the predominant 1,4-dihydropyridines.

These findings led us to perform a careful examination of the dithionite reduction of a significant number of pyridinium salts in order to ascertain: (a) if the formation



Scheme 1.

Keywords: Pyridinium salts; Dithionite adducts; Adduct decomposition; S_Ni and S_Ni' mechanisms; Dihydropyridines.
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of 1,2- and 1,6 -dihydropyridines, in addition to the 1, 4-dihydroderivatives, is a common occurrence and the extent of the phenomenon; (b) if the formation of 1,2- or 1, 6-dihydropyridines follows the decomposition of corresponding dithionite adducts at position 2 or 6 of the dihydropyridine system.

2. Results and discussion

Several pyridinium salts (**1a**–**m**, Scheme 2) have been used as model compounds for the present study.

The results of an accurate ^{1}H NMR analysis (Tables 1 and 5) performed directly on the chloroform extracts obtained from dithionite reduction of salts **1a**–**m**, were compared with the ^{1}H NMR data of known dihydroderivatives reported in the literature. In this way, it was possible to ascertain that the reduction sometimes led to a 1,4-dihydropyridine as unique product, in other cases to mixtures of 1,4- and 1,2- or 1,4- and 1,6-dihydropyridines. When not previously known, the dihydroderivatives obtained, such as the 1,4-dihydropyridines **3h**,**i**,**l** and the 1,2-dihydropyridines **4h**,**i**, were unambiguously identified and their relative abundances determined by means of HPLC, ^{1}H and ^{13}C NMR analyses (Tables 1 and 2).

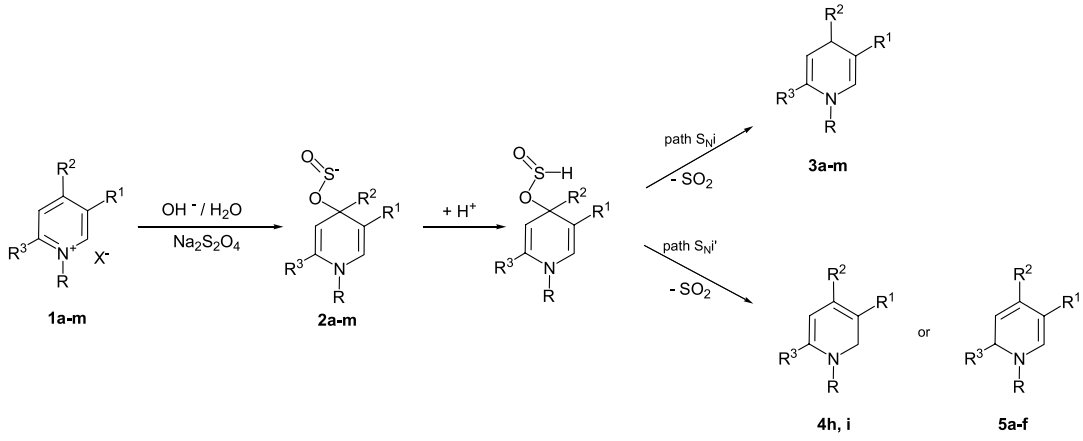
The structure of the dithionite adducts **2a**–**m** has been determined from the ^{1}H and ^{13}C NMR analyses, directly carried out on the reduction mixtures (Tables 3 and 4). In order to prevent a possible decomposition of the adducts even in strongly alkaline medium, a particular procedure has been adopted for the preparation of the samples before their submission to NMR analyses (see Section 3). As stressed previously by us,[10] ^{1}H and ^{13}C NMR spectroscopies represent highly diagnostic techniques for identifying the position of attack of the dithionite on the pyridinium cation and in all the reactions studied have allowed us to establish, beyond doubt, that the unique intermediate adduct present was the sulfinic ester (*S*-anion) formed by attack of the dithionite oxyanion at carbon 4 of the pyridinium salt. The formation of this sole adduct was always observed even when the final reduction products were, besides the 1,4-dihydropyridines, also the isomeric 1,2- or 1,6-dihydro derivatives.

Similar examples of absolute regioselectivity in the reaction of a nucleophile with a pyridinium salt were previously reported and concerned the exclusive attack of nitroalkane carbanions at the 4 position of the pyridinium rings.[11]

As we have already reported,[10] carbons 4 of the dithionite adducts are strongly deshielded with respect to the carbons in the 4 position of the corresponding 1,4-dihydropyridines. Indeed, the chemical shifts of carbons in the 4 position in adducts **2a**,**b**,**c**,**d**,**h**–**m** (Scheme 2, Table 4) are all comprised in the 62–68 ppm range, and display, in comparison with the chemical shifts of 4-position carbons in corresponding 1,4-dihydropyridines (Table 2, Ref. 12–14), a downfield shift effect variable from ca. 32 to 46 ppm. Such a downfield shift suggests that carbon atoms are directly bonded to an oxygen atom. Indeed, the downfield effect of an oxygen atom on the ^{13}C chemical shift of the carbon to which is bonded, ranges in alkane and cycloalkanes from 49 to 42 ppm ca., respectively.[15,16]

Similarly, the H4 in the adducts are significantly deshielded as well (downfield shift 0.5–0.8 ppm, Table 3) with respect to H4 in the corresponding 1,4-dihydropyridines (Table 5).

The presence of adducts deriving from the dithionite attack to carbons 2 or 6 of the pyridinium ions would give rise in



	R	R^1	R^2	R^3	X^-		R	R^1	R^2	R^3	X^-
a	Me	CN	H	H	I^-	**g**	Bn	$CONH_2$	H	Me	Br^-
b	Bn	CN	H	H	Br^-	**h**	Me	CN	Me	Me	I^-
c	Me	$CONH_2$	H	H	I^-	**i**	Bn	CN	Me	Me	Br^-
d	Bn	$CONH_2$	H	H	Br^-	**l**	Bn	$CONH_2$	Me	Me	Br^-
e	Bn;	$CONH_2$	Me	H	Br^-	**m**	2,6-DCB	$CONH_2$	Me	Me	Br^-
f	2,6-DCB	$CONH_2$	Me	H	Br^-						

Scheme 2.

Table 1. ^{1}H NMR chemical shifts of the 1,2-dihydropyridines **4h**,**i** and 1,6-dihydropyridines **5a–f**

	H2	H4	H5	H6	N–CH_3	N–CH_2	4-CH_3	6-CH_3	$J_{2,4}$	$J_{2,5}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$
4h[a]	3.92 2Hs		4.73s		2.86s		1.59s	1.95s					
4i[a, b]	3.99 2Hs		4.93s			4.51s	2.00s	2.08s					
5a[a]	6.68dd	5.79m	5.01m	4.11 2Hdd	2.80s				1.2	0.8	10.0	1.6	3.2
5b[a, b]	6.86dd	5.80m	5.00m	4.03 2Hdd		4.15s			1.6	0.8	10.0	1.6	3.2
5c[a]	7.08s	6.13m	4.99dt	4.03 2Hdd	2.84s						10.0	1.6	3.2
5d[a, b]	[c]	6.09m	4.94dt	3.93 2Hdd		4.16s			1.2	0.8	9.8	1.6	3.2
5e[b, d, e]	7.16d		4.74m	3.85m		4.20s	1.98s						5.0
5f[b, d, f]	7.17s		4.74m	3.93d		4.49s	1.96s						4.5

[a] $CDCl_3$.
[b] Aromatic proton signals are in the range 7.20–7.50 ppm.
[c] Overlapped with aromatic signals.
[d] DMSO-d_6.
[e] $CONH_2$ 5.46s, $J_{2,6}=1.5$.
[f] $CONH_2$ 5.20s.

Table 2. ^{13}C NMR chemical shifts of the 1,4-dihydropyridines **3h–m** and 1,2-dihydropyridines **4h**,**i**

	C2	C3	C4	C5	C6	N–CH_3	N–CH_2	4-CH_3	6-CH_3	CN	$CONH_2$
3h[a]	145.4d	82.1s	30.4s	105.4d	133.4s	38.6q		20.6q	20.6q	123.1s	
3i[a,b]	144.1d	80.7s	30.1s	105.2d	140.9s		53.6t	20.3q	20.3q	121.2s	
3l[b,c]	139.4d	102.4s	26.2s	105.3d	138.3s		52.6t	20.0q	20.0q		169.1s
3m[b,c]	136.1d	104.3s	27.0s	107.6d	135.4s		47.8t	18.3q	24.6q		168.8s
4h[a]	52.3d	80.6s	151.2s	100.2d	153.6s	38.1q		20.6q	20.6q	121.3s	
4i[a,b]	47.3d	80.2s	151.1s	100.9d	152.4s		52.9t	20.1q	20.1q	121.5s	

^{13}C NMR spectra were obtained with Gate decoupled pulse sequence.
[a] $CDCl_3$.
[b] Aromatic carbon signals are in the range 125–140 ppm.
[c] DMSO-d_6.

Table 3. ^{1}H NMR chemical shifts of the adducts **2a–m**

	H2	H4	H5	H6	N–CH_3	N–CH_2		4-CH_3	6-CH_3	$J_{2,6}$	$J_{4,5}$	$J_{5,6}$
						Ha	Hb					
2a[a]	7.08s	3.68d	4.92dd	6.22d	3.07s	—		—	—	—	5.7	7.6
2b[b, c]	7.16d	3.59d	4.90dd	6.23dd	—	4.42s		—	—	1.1	5.3	8.1
2c[a]	[d]	3.98d	4.93dd	6.27d	3.08s	—		—	—	—	5.6	7.7
2d[a, c]	[d]	3.85 br s	4.75m	6.05d	—	4.39s		—	—	—	[e]	[e]
2e[b, c]	7.18d	—	4.49d	6.19dd	—	4.40s		1.30s	—	1.6	—	7.9
2f[b, c]	7.24s	—	4.46d	6.26d	—	4.70s		1.35s	—	—	—	7.9
2g[b, c]	7.02s	3.99d	4.53d	—	—	4.49s		—	1.66s	—	5.4	—
2h[b]	7.15s	—	4.49s		3.15s	—		1.30s	1.90s		—	—
2i[b, c]	7.23s	—	4.56s	—	—	4.70s		1.43s	1.91s	—	—	—
2l[b, c]	7.21s	—	4.37s	—	—	4.59d[f]	4.66d	1.41s	2.65s	—	—	—
2m[b, c]	6.87s	—	4.38s	—		[g]		1.34s	2.73s	—	—	—

[a] D_2O.
[b] D_2O/DMSO-d_6 1:1.
[c] Aromatic proton signals are in the range 7.30–7.50 ppm.
[d] Exchange with D_2O.
[e] Broad signals.
[f] $J_{a,b}$ 17.0 Hz.
[g] Obscured by D_2O signal.

the ^{13}C NMR spectrum to signals in the 85–95 ppm range, with an analogous substituent downfield shift effect of ca. 30–45 ppm in comparison with the chemical shifts of carbon 2 or 6 of the corresponding 1,2- or 1,6-dihydropyridines.

In all cases examined no signals were ever observed in 85–95 ppm range of the ^{13}C NMR spectra.

Therefore, on the whole, the ^{1}H and ^{13}C NMR spectroscopic data clearly demonstrate the 1,4-dihydropyridine structure of the dithionite adducts.

The above findings leave some questions open: (a) how can it be explained the absolute regioselectivity of the dithionite attack, which, in all cases examined, leads to the formation of only 1,4-dihydro-4-pyridine sulfinates; (b) how can the

Table 4. ^{13}C NMR chemical shifts of the adducts **2a**,**c**,**d**,**h**–**m**

	C2	C3	C4	C5	C6	CN	$CONH_2$	$N–CH_2$	$N–CH_3$
2a[a]	149.5d	74.6s	66.7d	100.3d	135.0d	125.8s			43.2q
2b[b, c]	145.4d	72.9s	64.1d	98.0d	129.5d	120.2s		54.1t	
2c[b]	146.0d	96.9s	65.9d	99.4d	133.9d		174.2s		[d]
2d[a, c]	143.9d	99.6s	68.5d	101.2d	134.1d		175.4s	59.5t	
2h[b, c, e]	148.0d	80.5s	62.3s	103.2d	138.1s	123.0s			[d]
2i[b, c, e]	150.3d	82.2s	61.6s	105.1d	139.2s	121.0s		54.5t	
2l[b, c, e]	144.3d	108.1s	64.2s	109.2d	136.5s		168.7s	62.8t	
2m[b, c, e]	142.8d	105.6s	64.6s	107.8d	142.3s		173.5s	49.3t	

^{13}C NMR spectra were obtained with Gated decoupled pulse sequence.
[a] D_2O.
[b] D_2O/ DMSO-d_6 1:1.
[c] Aromatic carbon signals are in the range 128–137 ppm.
[d] Obscured by solvent signal (DMSO-d_6).
[e] The incomplete H/D exchange in 4 and 6-CH_3 gives rise to broad peaks at about 20 ppm.

Table 5. ^1H NMR chemicals shift of the 1,4-dihydropyridines **3a**–**m**

	H2	H4	H5	H6	$N–CH_3$	$N–CH_2$		$4\text{-}CH_3$	$6\text{-}CH_3$	$J_{2,4}$	$J_{2,6}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	$J_{a,b}$	J_{CH_3}, H4
						Ha	Hb									
3a[a]	6. 54dd	3.12 2Hdd	4.66m	5.70m	2.90s					0.6	1.6	3.6	1.6	8.20		
3b[a, b]	6. 41dd	3.08 2H dd	4.63m	5.61m		4.24s				0.8	1.6	3.2	1.6	8.0		
3c[a]	6.83d	3.03 2H dd	4.69m	5.73m	2.88s						1.2	3.2	1.5	8.0		
3d[a, b]	7.11d	3.12 2H dd	4.71m	5.70m		4.24s					1.6	3.4	1.6	8.0		
3e[a, b]	7.18d	3.28m	4. 85dd	5. 80dd		4.36s		1.13d			1.5	5.0		8.0		6.5
3f[b, c]	7.29	3.30m	4. 79dd	6. 05dd		4.77s		1.03d			1.5	5.0		7.7		6.0
3g[b, c]	7.15s	3.21 2Hm	4.57m			4.47s			1. 71m[d]			3.2				
3h[a]	6.48s	3.22m	4.42m		2.98s			1.18d	1.80s			3.2				6.3
3i[a, b]	6.85s	3.27m	4.91d			4.79d	4.83d	1.23d	1.75s			5.1			16.9	
3l[a, b]	7.08s	3.25m	4.52d			4.54d	4.58d	0.98d	1.70s			5.1			16.7	
3m[b, c]	6.66s	3.13m	4.54d			4.69d	4.78d	0.82d	1.92s			5.1			14.34	

[a] $CDCl_3$.
[b] Aromatic proton signals are in the range 7.20–7.60 ppm.
[c] DMSO-d_6.
[d] J_{CH_3},H5 = 2.8.

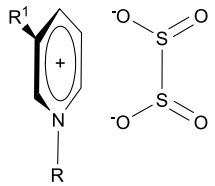
decomposition of a unique adduct also lead to the formation of 1,2- or 1,6-dihydropyridines, together with the isomeric 1,4-dihydroderivatives.

In our opinion, the absolute regioselectivity of the reaction between dithionite and pyridinium salts seems to suggest the idea of a particular orientation of the two reagents determining the position of attack. A very specific interaction between the reagents through the formation of a rigidly oriented ion pair (Fig. 1), before the nucleophilic dithionite attacks the electrophilic carbon 4, may be supposed.

In this connection, it should be born in mind that, as shown by the X-ray structure of the dithionite anion,[17] the distance between the two nucleophilic centres located on the two oxygen atoms measures 2.868 Å, which is structurally consistent with the occurrence of a strong interaction with both the ring N^+ cation and the C4 electrophilic site (calculated distance ca. 2.87 Å) but not with the analogous pairs C2-ring N^+(1.51 Å) or C6-ring N^+(1.51 Å).

The collapse of the ion pair (Fig. 1) would then give rise to the formation of the C4-sulfinate bound with elimination of SO_2.

An answer to the second question may be given bearing in mind the analogy existing between the decomposition of the dithionite adducts of the pyridinium salts and that of the allyl chlorosulfinates resulting from the reaction of allyl alcohols with thionyl chloride. Indeed, it is well known that two mechanisms, S_Ni[18,19] or S_Ni',[20] may be operative in



R = Alkyl or aralkyl
R^1 = $CONH_2$ or CN

Figure 1.

Table 6. Calculated heats of formation of all the dihydroderivatives, which could theoretically form in the dithionite reduction of salts **1a–m**; the table also lists the dihydropyridines actually formed and their relative abundances

Sale	1,2-DHP	ΔH_f (Kcal/mol)	1,4-DHP	ΔH_f (Kcal/mol)	1,6-DHP	ΔH_f (Kcal/mol)
1a	**4a** —	64.061	**3a** 92%	60.781	**5a** 8%	63.011
1b	**4b** —	91.137	**3b** 94%	87.770	**5b** 6%	90.466
1c	**4c** —	−5.022	**3c** 82%	−7.914	**5c** 18%	−5.829
1d	**4d** —	21.960	**3d** 95%	19.412	**5d** 5%	21.426
1e	**4e** —	16.026	**3e** 90%	15.973	**5e** 10%	16.345
1f	**4f** —	6.558	**3f** 50%	5.726	**5f** 50%	5.708
1g	**4g** —	17.200	**3g** 100%	14.225	**5g** —	18.560
1h	**4h** 70%	50.947	**3h** 30%	51.309	**5h** —	52.587
1i	**4i** 48%	79.869	**3i** 52%	79.782	**5i** —	80.513
1l	**4l**	9.583	**3l** 100%	8.778	**5l** —	11.634
1m	**4m**	2.031	**3m** 100%	0.432	**5m** —	1.176

such decompositions: the S_Ni mechanism leads to the preservation of the structure by the simple substitution of the sulfinate group with the chlorine atom, while the S_Ni' mechanism involves a structural rearrangement with migration of the double bond and shift of the chlorine atom to the carbon γ from the original position of the sulfinate. In both cases SO_2 is eliminated.

Path S_Ni R-CH=CH–CH_2–OSOCl → R-CH=CH–CH_2–Cl + SO_2

Path S_Ni' R-CH=CH–CH_2–OSOCl → R-CH(Cl)–CH=CH_2 + SO_2

Analogously, the decomposition of the 1,4-dihydropyridine-4-sulfinates may proceed according to the two mechanisms S_Ni or S_Ni'. In the first case, intramolecular hydrogen transfer occurs from the sulfinic SH group to the adjacent carbon atom 4 with SO_2 elimination and preservation of the 1,4-dihydropyridine structure, while the decomposition according to S_Ni' mechanism involves instead an intramolecular hydrogen transfer to atoms 2 or 6 with ensuing shift of the 2,3 or 5,6 double bonds to positions 3,4 or 4,5, respectively, and SO_2 elimination (Scheme 2). Thus, the possibility for the dithionite adducts of decomposing according to these mechanisms, may provide, in our opinion, a convincing explanation for the formation of all the three possible dihydroderivatives starting from an unique intermediate adduct. The occurrence of the decomposition mechanism S_Ni', which leads to 1,2- or 1,6-dihydropyridines, besides mechanism S_Ni, which affords 1,4-dihydropyridines, depends on the respective thermodynamic stability of the dihydroderivatives.

As may be seen from Table 6, in which the formation heats of dihydropyridines, calculated according to the AM1 molecular orbital methods,[8a,b] are summarized, 1,2- or 1,6-dihydropyridines are produced when their relative heats of formation are lower or very close to those of the corresponding 1,4-dihydro derivatives.

3. Experimental

3.1. Materials and methods

Chemical reagents and solvents were purchased from Aldrich Chemical Co. and were of analytical grade. Melting points were determined with a Tottoli apparatus and are uncorrected. IR spectra were registered with a Perkin Elmer mod. 281 spectrophotometer. ^1H and ^{13}C NMR were taken with a Bruker AVANCE 400 spectrometer, data were elaborated by using the WINNMR Bruker Daltonik GmbH, version 6.1.0.0 software. Chemical shifts are reported as ppm (δ) from TMS as internal standard when the solvent was DMSO-d_6 or $CDCl_3$ and from the D_2O signals (δ = 4.78 ppm) for D_2O solutions. Coupling constants are given in Hz. The HPLC analyses were performed with a Perkin Elmer Series 200 liquid chromatograph equipped with a Perkin Elmer series 200 diode array detector, HPLC data were elaborated by using TURBOCHROM NAVIGATOR, version 6.1.2.0.1 software. Preparative HPLC were performed on a Perkin Elmer series 3 apparatus equipped with a spectophotometric UV–vis Perkin Elmer LC55B detector and an analogic HP3390A integrator.

The column used were HPLC Lab Service Analytic Hypersil 5-NH_2 250/4.6 mm (5 μm) for the analytical determinations and 250/10 mm (5 μm) for the preparative determinations.

Formation enthalpies were calculated by AM1 molecular orbital methods[8a,b] making use of the Hyperchem version 7.0 software. Structure were minimised by using a Fletcher-Reeves algorithm with a convergence limit of 0.1 kcal/mol.

3.2. Pyridinium salts

3-Cyano-1-methylpyridinium iodide **1a**,[21] 1-benzyl-3-cyanopyridinium bromide **1b**,[22] 3-carbamoyl-1-methylpyridinium iodide **1c**,[23] 1-benzyl-3-carbamoylpyridinium bromide **1d**,[24] 1-benzyl-3-carbamoyl-4-metylpyridinium bromide **1e**,[25] 3-carbamoyl-1-(2,6-dichlorobenzyl)-4-methylpyridinium bromide **1f**,[7] 1-benzyl-3-carbamoyl-6-metylpyridinium bromide **1g**[26] and 3-carbamoyl-1-(2,6-dichlorobenzyl)-4,6-dimethylpyridinium bromide **1m**,[7] were prepared according to literature procedures and displayed the expected NMR properties.

3.3. General procedures for the preparation of pyridinium salts 1h–l

To a solution of 3-cyano-4,6-dimethylpyridine[27] (10.0 mmol) or 3-carbamoyl-4,6-dimetylpyridine[27] (10.0 mmol) in 20 ml of warm acetonitrile, 14.0 mmol of methyl iodide or 10.0 mmol of benzyl bromide was added and the mixture was refluxed for 12 h. To the cold solution,

Et_2O (50 ml) was then added: the precipitate was collected, washed with Et_2O and recrystallised from methanol.

3.3.1. 3-Cyano-1,4,6-trimethylpyridinium iodide 1h. Yield 70%, mp 228–9 °C; IR (nujol) cm^{-1}: 3175, 2245, 1650; ^1H NMR (DMSO-d_6), δ: 2.71 (3H, s, 4-CH_3), 3.31 (3H, s, 6-CH_3), 4.20 (3H, s, N-CH_3), 8.19 (1H, s, H5), 9.60 (1H, s, H2). Anal. Calcd for C_9 H_{11} N_2 I: C, 39.44; H, 4.05; N, 10.22. Found: C, 39.75; H, 3.86; N, 10.01.

3.3.2. 1-Benzyl-3-cyano-4,6-dimethylpyridinium bromide 1i. Yield 75%; mp 252–4 °C; IR (nujol) cm^{-1}: 3180, 2245, 1650; ^1H NMR (DMSO-d_6) δ: 2.74 (3H, s, 4-CH_3), 3.32 (3H, s, 6-CH_3), 5.92 (2H, s, N-CH_2), 7.30-7.45 (5H, m, Ar), 8.25 (1H, s, H5), 9.85 (1H, s, H2). Anal. Calcd for C_{15} H_{15} N_2 Br: C, 59.42; H, 4.99; N, 9.24. Found: C, 59.69; H, 5.10; N, 8.97.

3.3.3. 1-Benzyl-3-carbamoyl-4,6-dimethylpyridinium bromide 1l. Yield 95%; mp 225–7 °C; IR (nujol) cm^{-1}: 3200, 3030, 1690; ^1H NMR (DMSO-d_6) δ: 2.63 (3H, s, 4-CH_3), 2.67 (3H, s, 6-CH_3), 5.92 (2H, s, N–CH_2), 7.32-7.45 (5H, m, Ar), 8.43 (1H, s, H5), 9.30 (1H, s, H2). Anal. Calcd for C_{15} H_{17} N_2 O Br: C, 56.09; H, 5.33; N, 8.72. Found: C, 55.87; H, 5.65; N, 8.55.

3.4. General procedure for the dithionite reduction of pyridinium salts 1a–g,m

To a stirred solution of $NaHCO_3$ (2.5 mmol) and $Na_2S_2O_4$ (2.5 mmol) in H_2O (30 ml), chloroform (30 ml) and then slowly 0.5 mmol of the pyridinium salt were added at 4–5 °C and under argon flow. After 3 h, the organic phase was separated from the aqueous one, which was repeatedly extracted with chloroform (4×20 ml). The combined chloroform extracts were dried over anhydrous Na_2SO_4 and analyzed by ^1H NMR spectroscopy.

The spectral parameters listed in Tables 1 and 5, compared with the ^1H NMR data reported in literature, allowed to identify the dihydropyridine or the dihydropyridine mixture formed in every reduction run and to determine their relative abundances (Table 6).

The pyridinium salts **1a–g,m** were reduced according to the general procedure described above giving rise to the dihydropyridines listed below in the relative abundances near indicated:

Salt **1a** gave the 1,4-dihydropyridine **3a**[12] 92% and the 1,6-dihydropyridine **5a**[12] 8%. Salt **1b** afforded the 1,4-dihydropyridine **3b**[22] 94% and the 1,6-dihydropyridine **5b**[28] 6%. Salt **1c** yielded the 1,4-dihydropyridine **3c**[13] 82% and the 1,6-dihydropyridine **5c**[29] 18%. Salt **1d** gave the 1,4-dihydropyridine **3d**[25] 95% and the 1,6-dihydropyridine **5d**[25] 5%. Salt **1e** afforded the 1,4-dihydropyridine **3e**[30] 90% and the 1,6-dihydropyridine **5e**[30] 10%. Salt **1f** yielded the 1,4-dihydropyridine **3f**[7] 50% and the 1,6-dihydropyridine **5f**[7] 50%. Salt **1g** gave as unique product the 1,4-dihydropyridine **3g**.[26] Salt **1m** afforded as unique product the 1,4-dihydropyridine **3m**.[7]

3.5. Dithionite reduction of pyridinium salts 1h–l, identification of the dihydro derivatives obtained and determination of their relative abundances

3.5.1. Reduction of salt 1h. To a solution of $NaHCO_3$ (400 mg) and $Na_2S_2O_4$ (300 mg) in 40 ml of H_2O, 50 ml of $CHCl_3$ were added at 4–5 °C under argon flow and strong stirring, followed by addition of 150 mg of salt **1h**. After 3 h the chloroform layer was separated and the aqueous phase repeatedly extracted with $CHCl_3$ (4×20 ml). The combined organic extracts, after drying over Na_2SO_4, were brought to dryness and the residue was submitted to HPLC analysis employing a 90:10 hexane/CH_2Cl_2+2% MeOH mixture (flow 1 ml/min): the elution profile showed two major peaks. A preparative HPLC carried out on 20 mg of residue, adopting the same eluent (flow 5 ml/min), led to the separation of two fractions having retention time of 7.5 and 8.9 min, respectively, the purity, of which was determined as better than 97%. Both fractions were examined by ^1H and ^{13}C NMR and unambiguously identified. The first fraction (t_R=7–5 min) consisted of 3-cyano-1,4,6-trimethyl-1,2-dihydropyridine **4h** (Tables 1 and 2), while the second fraction (t_R=8.9 min) was identified as 3-cyano-1,4,6-trimethyl-1,4-dihydropyridine **3h** (Tables 5 and 2).

Anal. Calcd for C_9 H_{12} N_2: C, 72.94; H, 8.16; N, 18.90.

Compound **3h**. Found: C, 72.73; H, 7.87; N, 18.68.

Compound **4h**. Found: C, 73.41; H, 7.92; N, 18.53.

The relative abundance of dihydropyridines **3h** and **4h**, determined by ^1H NMR analysis of the crude $CHCl_3$ extract obtained directly from the reduction, resulted to be 30% and 70%, respectively (Table 6).

3.5.2. Reduction of salt 1i. From the reduction of **1i** carried out in the same conditions described above for **1h**, a crude residue was obtained, which, submitted to HPLC analysis (eluent: 90:10 hexane/CH_2Cl_2+2% MeOH, flow 1 ml/min) gave an elution profile characterized from two major peaks. A preparative HPLC carried out on 25 mg of residue using the same elution system (flow 5 ml/min), led to the separation of two fractions having retention times of 6.5 and 7.6 min, respectively, with an analytically controlled purity degree higher than 97%. Both fractions were examined by ^1H and ^{13}C NMR. The first fraction (t_R= 6.5 min) consisted of 1-benzyl-3-cyano-4,6-dimethyl-1,2-dihydropyridine **4i** (Tables 1 and 2), while the second fraction (t_R=7.6 min) was identified as the 1-benzyl-3-cyano-4,6-dimethyl-1,4-dihydropyridine **3i** (Tables 5 and 2).

Anal. Calcd for C_{15} H_{16} N_2: C, 80.32; H, 7.19; N, 12.49.

Compound **3i**. Found: C, 80.63; H, 6.97; N, 12.25.

Compound **4i**. Found: C, 80.06; H, 7.02; N, 12.18.

The relative abundance of dihydropyridines **3i** and **4i**, determined by ^1H NMR analysis of the crude $CHCl_3$ extract obtained directly from the reduction, resulted to be 30% and 48%, respectively (Table 6).

3.5.3. Reduction of salf 1l. From the reduction of salt **1l** carried out according the procedure described above for **1a**, a chloroform extract was obtained, the ^{1}H NMR analysis of which revealed the presence of a unique product, which was unambiguously identified, by ^{1}H and ^{13}C NMR spectroscopy, as 1-benzyl-3-carbamoyl-4,6-dimethyl-1,4-dihydropyridine **3l** (Tables 2 and 5).

Anal. Calcd for C_{15} H_{18} N_2 O: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.48; H, 7.27; N, 11.34.

3.6. ^{1}H and ^{13}C NMR analysis of the dithionite adducts 2a–m

In a typical procedure for the preparation of an adduct sample for NMR examination, a solution of $Na_2S_2O_4$ (0.11 mmol) in 0.25 ml of 2 M NaOD (in D_2O) or 2 M Na_2CO_3 (in D_2O) was prepared in a NMR tube and subsequently cooled down to −20 °C. Over this frozen solution, kept at −20 °C, was then stratified the pyridinium salt solution (0.06 mmol of salt in 0.25 ml of D_2O or 0.25 ml of DMSO-d_6), which was afterwords frozen. The tube was finally sealed in vacuo always keeping the temperature at −20 °C. At the moment of performing the NMR analysis, the tube temperature was increased to 20 °C in order to cause the thawing of the solutions and their mixing.

The ^{1}H and ^{13}C NMR parameters of adducts **2** are summarized in Tables 3 and 4.

It was impossible to record ^{13}C NMR spectra on adducts **2e**–**g**, because of insufficient concentrations achievable both in NaOD and Na_2CO_3 solutions. Indeed, pyridinium salts **1e**–**g** displayed extreme reactivity towards aqueous NaOH, giving rise to mixtures of dihydropyridines and pyridones.[31] On the other hand, adducts **2e**–**g** rapidly decomposed, in aqueous Na_2CO_3, yielding 1,4-dihydropyridine and 1,4- and 1,6-dihydropyridine mixtures.

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