Imination of *N*-Methylpyridinium Salts by Liquid Ammonia-Potassium Permanganate [1]. A New Synthesis of Nudiflorine

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Reaction of substituted 1-methyl(benzyl)pyridinium salts (**1**) with liquid ammonia/potassium permanganate leads to introduction of the imino group at the carbon adjacent to the nitrogen. The regiospecificity of the reaction strongly depends on substituent X: at C-6 for X = H, $CONH_2$, C_6H_5 and at C-2 for X = CH_3. 3-Aminocarbonyl-1-*t*-butylpyridinium iodide (**5**) on treatment with liquid ammonia/potassium permanganate exclusively gives the 4-imino compound **8**; ^1H nmr spectroscopy shows that **5** in liquid ammonia gives a mixture of the σ-adducts 4-amino-1,4-dihydro- and 6-amino-1,6-dihydro-3-pyridinecarbonamide (**6** and **7**). Surprisingly, an oxodemethylation reaction is observed on treatment of 3-aminocarbonyl-1,6-dimethylpyridinium iodide (**13**) with liquid ammonia/potassium permanganate, 1,6-dihydro-1-methyl-6-oxo-3-pyridinecarboxamide (**14**) being obtained. This compound can easily be converted by phosphorus oxychloride into the alkaloid nudiflorine (**15**).

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Recently it has been shown that quaternized bicyclic azines can be iminated when treated with liquid ammonia/potassium permanganate [2], as exemplified in the conversions of *N*-methylquinolinium- and *N*-methylnaphthyridinium salts into the corresponding *N*-methyl imino compounds. These imino compounds can easily be converted into the corresponding azinones by base treatment. Sometimes unexpected reactions are observed: a) treatment of the 7-methyl-1,7-naphthyridinium salt and the 6-methyl-1,6-naphthyridinium salt with liquid ammonia/potassium permanganate leads to ring contraction [3] and b) 1,2-dimethylquinolinium iodide undergoes a nearly exclusive oxodemethylation at C-2, yielding 1-methylquinolone-2 [2].

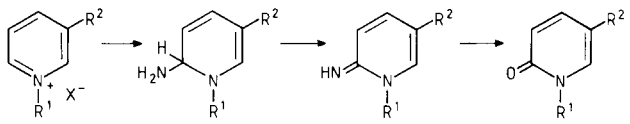
We report in this paper the results of a study on the imination of 3-substituted 1-alkylpyridinium salts **1**. This study was undertaken in order to explore the scope and regiospecificity of the imination of these salts bearing in mind that there is current interest in simple biologically active pyridones and the development of a new method for the regiospecific preparation of iminopyridines from which oxo compounds can easily be prepared, seems therefore of interest.

Results.

Two methods of imination can be applied: Method A, involving addition of **1** to a solution of liquid ammonia, containing potassium permanganate or method B, involving addition of potassium permanganate to a solution of **1** in liquid ammonia. We found that in this study method A is the most preferable one and therefore was used to carry out our reactions. Reaction of 1-methylpyridinium iodide (**1a**) gives in a good yield (80%) 1,2-dihydro-2-imino-1-methylpyridine (**3a**); its structure was established in the usual way (see experimental part) and further proved by conversion of **3a** into 1-methylpyridone-2 (**4a**) using an aqueous potassium hydroxide solution.

Since the conversion of **1a** into **3a** shows that liquid ammonia/potassium permanganate is an effective imination reagent for quaternary pyridinium salts, we investigated the regiospecificity of this reaction. Reaction of 3-aminocarbonyl-1-methylpyridinium iodide (**1b**) with liquid ammonia/potassium permanganate gave a reaction mixture from which we could isolate only the 6-imino compound **3b**. The structure of **3b** was proved by ^1H nmr spectroscopy, featuring the characteristic pattern of a 3,6-disubstituted pyridine ring (see experimental part), and further by conversion into the known 1,6-dihydro-1-methyl-6-oxo-3-pyridinecarboxylic acid (**4b**). No trace of the isomeric 2-imino compound could be detected, showing the regiospecificity of the reaction.

Scheme 1



1 2 3 4

	R^1	R^2
a)	CH_3	H
b)	CH_3	$CONH_2$
c)	CH_3	C_6H_5
d)	$CH_2C_6H_5$	$CONH_2$

	R^1	R^2
a)	CH_3	H
b)	CH_3	CO_2H
c)	CH_3	C_6H_5
d)	$CH_2C_6H_5$	CO_2H

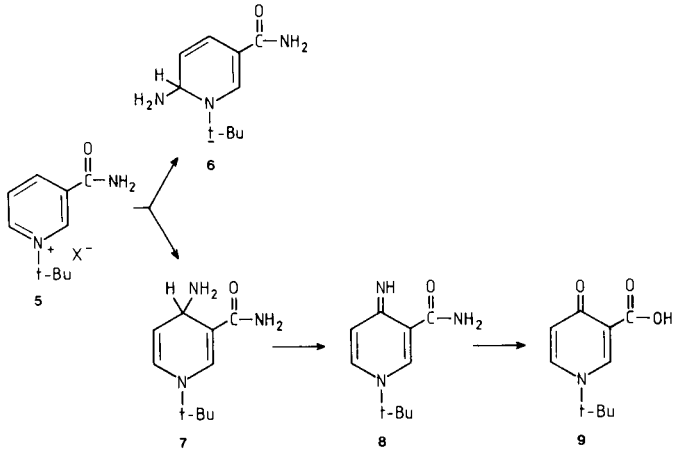
The regiospecificity of the imination is also observed in the reaction of 1-methyl-3-phenylpyridinium iodide (**1c**) and 1-benzyl-3-aminocarbonylpyridinium iodide (**1d**). In both reactions exclusively the 6-imino compounds **3c** and **3d** respectively were formed. The structures **3c** and **3d** were proved by the ^1H nmr spectroscopy and by conversion of these compounds into the corresponding pyridones

4c and **4d**.

The results obtained thus far seem to indicate that in the pyridinium salts **1** the imino group is exclusively introduced at the position adjacent to the positively charged ring nitrogen and *para* towards the electron-withdrawing group at position 3. Previous ^{1}H nmr studies have already shown that compound **1b** easily undergoes addition at position 6, *i.e.* formation of **2b**. It seems reasonable to suggest that the 6-amino σ-adducts **2** are the precursors of **3**, although by ^{1}H nmr spectroscopy no clear indication for the presence of the σ-adducts **2a,2c,2d** could be obtained; it is probably due to the fact that these adducts are apparently present in an equilibrium concentration, being too small to be detected by ^{1}H nmr techniques.

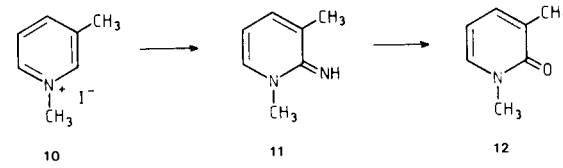
In order to establish whether the nucleophilic addition of ammonia at position 6 is sterically hindered, when a bulky group is present at position 1, we investigated the imination of 3-aminocarbonyl-1-*t*-butylpyridinium iodide (**5**). After the reaction only the 4-imino compound **8** could be isolated. The structure of **8** was proved by ^{1}H nmr spectroscopy and confirmed by conversion into the 4-pyridone **9** [5]. Interestingly, ^{1}H nmr spectroscopy of a solution of **5** in liquid ammonia unequivocally showed the formation of *two* Meisenheimer adducts *i.e.* the 6-amino adduct **6** and the 4-amino adduct **7** [4]. The ratio **6**:**7** = 6:4 indicates that the addition at C-6 is severely hindered but not completely prevented. That in the reaction mixture no indication for the formation of the 6-imino compound was found, although in the liquid ammonia its precursor **6** is clearly present, is caused by the fact that the potassium permanganate prefers attack at position 4 in **7** to the sterically crowded position 6 in **6**.

Scheme 2



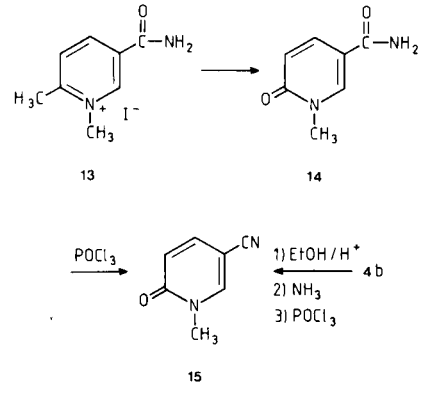
Treatment of 1,3-dimethylpyridinium iodide (**10**) with liquid ammonia/potassium permanganate surprisingly gave a regiospecific imination at position 2, 1,2-dihydro-2-imino-1,3-dimethylpyridine (**11**) being obtained. Basic hydrolysis of **14** gives 1,3-dimethylpyridone-2 (**12**).

Scheme 3



Imination of 3-aminocarbonyl-1,6-dimethylpyridinium iodide (**13**) in which position 6 is blocked does not give the 2-imino compound; instead an oxo-demethylation reaction occurred yielding 1,6-dihydro-1-methyl-6-oxo-3-pyridinecarboxamide (**14**). This surprisingly easy introduction of the 6-oxo group in the 3-aminocarbonyl-1-methyl-pyridinium salt (**1b**) opened unexpectedly a new and convenient route for synthesizing the well-known alkaloid nudiflorine (**15**) since by treatment of **14** with phosphorus oxychloride **15** was obtained in a good yield. Nudiflorine was also obtained in an independent way from **4b** by esterification, aminolysis and treatment with phosphorus oxychloride. The synthesis of **15** from **13** *via* **14** is far superior to the hexacyanoferrate oxidation of the 3-cyano-1-methylpyridinium salt, always yielding an isomeric mixture of the pyridone-6 **15** and pyridone-2.

Scheme 4



EXPERIMENTAL

Melting points are uncorrected. The ^{1}H nmr spectra are recorded on an Hitachi Perkin Elmer R-24^B or a Varian EM-390 spectrometer with TMS or DSS as internal standard (δ = 0 ppm). The mass spectra were determined using an AEI MS-902 mass spectrometer, equipped with a VG ZAB console.

Preparation of Starting Materials.

1-Methylpyridinium iodide (**1a**) [6]; 3-aminocarbonyl-1-methylpyridinium iodide (**1b**) [7]; 1-methyl-3-phenylpyridinium iodide (**1c**) [11]; 3-aminocarbonyl-1-benzylpyridinium chloride (**1d**) [7]; 3-aminocarbonyl-1-*t*-butylpyridinium chloride (**5**) [8]; 3-aminocarbonyl-1,6-dimethylpyridinium iodide (**13**) [9] and 1,3-dimethylpyridinium iodide (**10**) [10] were synthesized as described before.

Procedure of Imination of Pyridinium Salts.

To a solution of 2 mmoles of potassium permanganate in 25-30 ml liquid ammonia 2 mmoles of the starting material were added and the mix-

ture was stirred for 4 hours at -33°. The ammonia was evaporated off and the residue was extracted with water. After filtration the solvent was evaporated off to dryness. If possible the picrate and its melting point, ^{1}H nmr and mass spectrum were made of the crude products.

Procedure for Conversion of Imino Compounds into Pyridones.

For conversion of the imino compounds into the pyridones the imino compound was heated with aqueous 5 *N* potassium hydroxide during 4 hours. After neutralisation the solution was extracted with chloroform and 75-85% of a crude product could be isolated, that on crystallisation gave the pure product.

Imination of 1-Methylpyridinium Iodide (**1a**).

1,2-Dihydro-2-imino-1-methylpyridine (**3a**) was obtained in a yield of about 80%; exact mass 108.0691. Calcd. for $C_6H_8N_2$: 108.0686; ^{1}H nmr (deuteromethanol): δ 8.20 (d, H-6), 8.00 (m, H-4), 7.30 (d, H-3), 7.00 (t, H-5), 3.90 (s, CH_3); mp picrate 207-209° (lit [12] mp 201°).

Anal. Calcd. for $C_6H_8N_2.C_6H_3N_3O_7.H_2O$: C, 40.57; H, 3.69; N, 19.71; mol wt, 355.26. Found: C, 40.85; H, 3.52; N, 19.72.

Treatment of **3a** with base gave 1-methylpyridone-2 (**4a**) yield 70-75%; exact mass 109.0524. Calcd. for C_6H_7NO: 109.0528; ^{1}H nmr (deuteromethanol): δ 7.66 (d, H-6), 7.56 (dd, H-4), 6.58 (d, H-3), 6.38 (t, H-5), 3.60 (s, CH_3); mp picrate 145-146° (lit [13] mp 144-145°).

Anal. Calcd. for $C_6H_7NO.C_6H_3N_3O_7$: C, 42.61; H, 2.98; mol wt, 338.23. Found: C, 43.05; H, 3.34.

Imination of 3-Aminocarbonyl-1-methylpyridinium Iodide (**1b**).

1,6-Dihydro-6-imino-1-methyl-3-pyridinecarboxamide (**3b**) was described in an earlier publication [5], yield 70-75%; exact mass 151.0748. Calcd. for $C_7H_9N_3O$: 151.0746; ^{1}H nmr (deuterium oxide): δ 8.32 (d, H-2), 8.00 (dd, H-4), 7.00 (d, H-5), 3.87 (s, CH_3); mp picrate 312-314°.

Anal. Calcd. for $C_7H_9N_3O.C_6H_3N_3O_7$: C, 41.06; H, 3.18; N, 22.10; mol wt, 224.14. Found: C, 41.15; H, 3.09; N, 21.65.

Base treatment of **3b** and acidification gave 1,6-dihydro-1-methyl-6-oxo-3-pyridinecarboxylic acid (**4b**), yield 90%, mp 239-240° (lit [14] 240-241°); exact mass 153.0423. Calcd. for $C_7H_7NO_3$: 153.0426; ^{1}H nmr (deuteromethanol): δ 8.28 (d, H-2); 7.80 (dd, H-4); 6.36 (d, H-5); 3.38 (s, CH_3).

Anal. Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.61; mol wt, 153.13. Found: C, 54.71; H, 4.35.

Imination of 1-Methyl-3-phenylpyridinium Iodide (**1c**).

1,6-Dihydro-6-imino-1-methyl-3-phenylpyridine (**3c**) was formed in about 80%; exact mass 184.0998. Calcd. for $C_{12}H_{12}N_2$: 184.1000; ^{1}H nmr (deuteromethanol): δ 8.36 (d, H-2), 8.22 (dd, H-4), 7.80-7.50 (m, C_6H_5), 7.25 (d, H-5), 3.79 (s, CH_3); mp picrate 210-211°.

Anal. Calcd. for $C_{12}H_{12}N_2.C_6H_3N_3O_7.\frac{1}{2}H_2O$: C, 51.18; H, 3.82; N, 16.00; mol wt, 422.35. Found: C, 51.05; H, 3.89; N, 15.97.

After base treatment of **3c** 1-methyl-3-phenylpyridone-6 (**4c**), (yield 70-75%) could be isolated; exact mass 185.0840. Calcd. for $C_{12}H_{11}NO$: 185.0841; ^{1}H nmr (deuteromethanol): δ 7.80 (d, H-2), 7.59 (dd, H-4), 7.60-7.40 (m, C_6H_5), 6.56 (d, H-5), 3.56 (s, CH_3); mp picrate 135-136° (lit [15] 133-134°).

Anal. Calcd. for $C_{12}H_{11}NO.C_6H_3N_3O_7.\frac{1}{2}H_2O$: C, 51.07; H, 3.57; mol wt, 423.33. Found: C, 51.07; H, 3.70.

Imination of 3-Aminocarbonyl-1-benzylpyridinium Chloride (**1d**).

1-Benzyl-1,6-dihydro-6-imino-3-pyridinecarboxamide (**3d**) was obtained in a yield of about 80%; exact mass 227.1055. Calcd. for $C_{13}H_{13}N_3O$: 227.1059; ^{1}H nmr (deuteromethanol): δ 8.66 (br s, H-2), 8.33 (br d, H-4), 7.50-7.15 (m, C_6H_5), 7.26 (d, H-5), 5.55 (s, CH_2); mp picrate 177-178°.

Anal. Calcd. for $C_{13}H_{13}N_3O.C_6H_3N_3O_7.2H_2O$: C, 46.34; H, 4.09; N, 17.07; mol wt, 492.40. Found: C, 46.32; H, 4.37; N, 16.85.

Base treatment of **3d** gave **4d** in a yield of 70-75%; exact mass 229.0749. Calcd. for $C_{13}H_{11}NO_3$: 229.0739; ^{1}H nmr (deuteromethanol): δ 8.43 (d, H-2); 7.96 (dd, H-4), 7.32 (s, C_6H_5), 6.53 (d, H-5), 5.20 (s, CH_2); mp 209-210°.

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84. mol wt; 229.23. Found: C, 68.31; H, 4.97.

Imination of 3-Aminocarbonyl-1-*t*-butylpyridinium Iodide (**5**).

The yield of 1,4-dihydro-4-imino-1-*t*-butyl-3-pyridinecarbonamide (**8**) was 60%; exact mass 193.1220. Calcd. for $C_{10}H_{15}N_3O$: 193.1215; ^{1}H nmr (deuteromethanol): δ 8.77 (d, H-2), 8.49 (dd, H-6), 7.10 (d, H-5), 1.72 (s, *t*-C_4H_9); mp HCl salt; 256-258°, mp picrate: 197-198°.

Anal. Calcd. for $C_{10}H_{15}N_3O.C_6H_3N_3O_7$: C, 45.50; H, 4.29; N, 19.90; mol wt, 422.78. Found: C, 45.33; H, 4.00; N, 19.56.

Heating of **8** with an aqueous 5*N* potassium hydroxide solution, neutralisation and extraction gave 1,4-dihydro-4-oxo-1-*t*-butyl-3-pyridinecarboxylic acid (**9**) in a yield of 50%, mp 201-202°; exact mass 195.0889. Calcd. for $C_{10}H_{13}NO_3$: 195.0895; ^{1}H nmr (deuteromethanol): δ 8.85 (d, H-2), 8.38 (dd, H-6), 6.78 (d, H-5), 1.70 (s, *t*-C_4H_9).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; mol wt, 195.21. Found: C, 61.73; H, 6.41.

Imination of 1,3-Dimethylpyridinium Iodide (**10**).

From the reaction mixture it was possible to isolate crude 1,2-dihydro-1,3-dimethyl-2-iminopyridine (**11**) in a yield of 75-80%, exact mass 122.0840. Calcd. for $C_7H_{10}N_2$: 122.0844; ^{1}H nmr (deuteromethanol): δ 8.04 (d, H-6), 7.88 (d, H-4), 6.93 (t, H-5), 3.95 (s, N-CH_3), 2.30 (s, CH_3).

Base treatment of **10** gave 1,3-dimethylpyridone-2 (**12**); exact mass 123.0685. Calcd. for C_7H_9NO: 123.0684; ^{1}H nmr (deuteriochloroform): δ 7.14 (δ, 2H, H-4 and H-6), 6.03 (t, H-5), 3.51 (s, N-CH_3), 2.14 (s, CH_3); mp HCl-salt of 1,3-dimethylpyridone-2; 116-118° (lit [14] 120-122°).

Imination of 3-Aminocarbonyl-1,6-dimethylpyridinium Iodide (**13**).

In a yield of 80% 1,6-dihydro-1-methyl-6-oxo-3-pyridinecarbonamide (**14**) was formed; exact mass 152.0588. Calcd. for $C_7H_8N_2O_2$: 152.0586; ^{1}H nmr (deuteromethanol): δ 8.48 (d, H-2), 8.05 (dd, H-4), 6.60 (d, H-5), 3.68 (s, CH_3); mp 214-215° (lit [16] 213-215°).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; mol wt, 152.15. Found: C, 55.39; H, 5.04.

3-Cyano-1-methylpyridone-6 (**15**).

Compound **14** (0.4 g) was heated with an excess of phosphorus oxychloride at 120-125° for 2 hours. After cooling the reaction mixture was poured out on ice, neutralised with potassium carbonate and extracted with chloroform, yield 60%, mp 159-160° (lit [14] 159-160°); exact mass 134.0476. Calcd. for $C_7H_6N_2O$: 134.0480; ir (chloroform): 2250 cm^{-1} (C≡N), 1680 cm^{-1} (C=O).

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