Tetrahedron Vol. 35, pp. 2591 to 2595
Pergamon Press Ltd., 1979. Printed in Great Britain

REACTIVITY OF PSEUDOBASES FROM PYRIDINIUM SALTS COMPETITION BETWEEN HYDROGEN TRANSFER AND RING-OPENING REACTIONS

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(*Received in UK 6 June 1979*)

Abstract—The reactions of 3-cyano-1-methylpyridinium iodide (**1a**) and 1-benzyl-3-cyanopyridinium chloride (**1b**) in aqueous NaOH have been studied over a range of concentrations from N 0.5 to N 2.5 with respect to the hydroxide ion, and with the concentrations of the reactants at different ratios. It has been found that the intermediate, not isolable pseudobases can undergo, depending on the experimental conditions, two competitive reaction channels, namely, a redox process leading to the dihydropyridines **3–5** and pyridones **2, 6**, and a ring-opening reaction leading to the pentadienenitrile **7**, 2-imino-3-pyridinecarbaldehyde **8**, and 2-(aryl)alkylamino-3-pyridinecarbaldehyde **9**.

We have previously reported that 3 - cyano - 1 - methylpyridinium iodide (**1a**) by reaction with N 0.5 NaOH in the molar ratio 1:2 yields the correspondent isomeric dihydropyridines **3a–5a**, in equimolar amounts with the pyridones **2a** and **6a**, and we ascribed the formation of these products to a redox process, involving a hydrogen transfer from the intermediate 3 - cyano - α - hydroxydihydropyridines (**A** and **B**) to the electron-deficient centers of the pyridinium cation.[1] From the same reaction, we have also isolated minor amounts of sodium enolate of the glutaconaldehyde 2-cyano derivative (**10**), a product arising from a ring-opening reaction.

We have also reported[2] that **1a** by reaction with aqueous solutions of primary amines yields imino derivatives of type **8**, arising from a sequence of ring-opening and ring-closing steps. In addition, the redox process takes place as well, yielding the products **2a–6a**, whose amount decreases as the molar ratio amine/quaternary salt is increased.

It is therefore apparent that the reaction of **1a** with aqueous bases can follow two competing pathways, namely the redox process and the ring-opening process (Scheme 1). In order to evaluate the conditions that affect the dicothomic behaviour of the intermediate pseudobases in the reaction of the 3-cyanopyridinium cation with OH^- ions, **1a** and 1-benzyl-3-cyanopyridinium chloride (**1b**) have been allowed to react with NaOH aq, over a range of concentrations from N 0.5 to N 2.5 with respect to the hydroxide ion, and with the concentrations of the reactants at different ratios. In the present paper we report on the results of such investigation.

Concerning the reaction of **1a** with sodium hydroxide, the study has been carried out in N 0.5 NaOH at the following molar ratios: (i) **1a**/NaOH = 1:0.5; (ii) **1a**/NaOH = 1:2; (iii) **1a**/NaOH = 1:10. The analysis of the reaction products clearly shows that only the redox process occurs under conditions (i), both processes take place under conditions (ii) with a predominance of the redox reaction, while the ring-opening process becomes predominant in the case (iii) (Experimental). When the reaction is carried out at the same molar ratios as in cases (i) and (iii), but increasing the NaOH concentration to N 2.5, no appreciable change in the composition of the mixtures has been observed.

As a whole, these results suggest that the pseudobases (**A** and **B**), in equilibrium with the quaternary hydroxide in the reaction medium,[3] undergo preferentially the redox process with respect to the ring-opening reaction, as the available concentration of the pyridinium cation is increased.

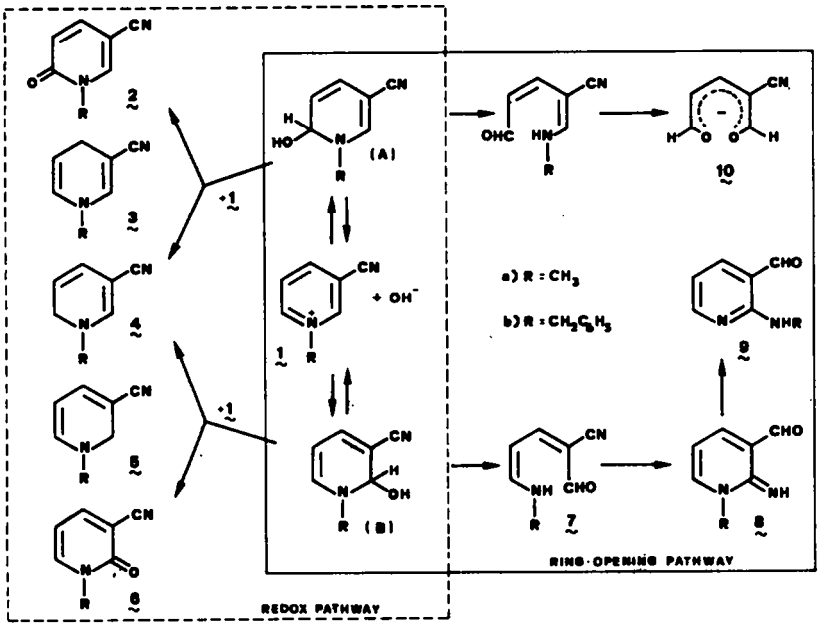
Concerning the reaction of **1b** with NaOH, the following molar ratios were used: (i) **1b**/NaOH = 1:0.5 in N 0.5 NaOH; (ii) **1b**/NaOH = 1:2 in N 0.5 NaOH; (iii) **1b**/NaOH = 1:10 in N 2.5 NaOH. The results outline a sharp discrepancy in the behaviour of two 3-cyanopyridinium salts, that are structurally strictly related: in fact, the analysis of the products (Experimental) shows that, in addition to the case (iii), the ring-opening reaction is favoured also in the case (ii). Even more surprisingly, the ring-opening reaction is a significant process in the case (i) as well, while under the same conditions, in the correspondent reaction with **1a**, only the hydrogen transfer process took place.

In this connection is worth pointing out that many hydrogen transfer reactions implying dihydropyridines have been studied as biomimetic model for redox process involving the nicotinamide coenzymes,[4] but the problem concerning the detailed mechanism of these class of reactions remains as yet open.

Recently, the sensitivity to steric effects of the hydrogen exchange rate between dihydropyridines and pyridinium salts has been related to a close association of the reacting molecules in the transition state.[5] Our results can provide further support to this hypothesis, since the higher steric hindrance of the benzyl group, with respect to the methyl group, should hamper the possibility of association between the pseudobase and the pyridinium cation, thus favouring the ring-opening reaction.

EXPERIMENTAL

The m.ps were taken upon a Tottoli apparatus, and are uncorrected. The UV spectra were recorded on a Perkin–Elmer 402 spectrophotometer and the IR spectra, as nujol mull or liquid films, on a Perkin–Elmer 177 grating spectrophotometer. The



Scheme 1.

^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer, and the chemical shifts are reported as δ units from TMS, used as internal standard. The *m/e* values were measured with a Hewlett-Packard 5980 A low-resolution mass spectrometer. Column chromatography was carried out on Merck silica gel 70–230 mesh. All known compounds were identified by comparison with authentic samples. All new compounds gave elemental analyses (C, H, N) within ±0.3% of the theoretical values.

General procedure. The pyridinium salt was added to NaOH aq, and the soln stirred 2 hr at room temp. (in the reactions carried out with the salt 1b, a gummy ppt was formed as soon as the salt was added). The mixture was extracted with CH_2Cl_2, the organic layer separated, dried (Na_2SO_4), and evaporated under vacuum at room temp. The residue was resolved by column chromatography: with a mixture AcOEt–MeOH 9:1 were eluted in the order 3–5, 9, 2, 6, 7. The imino derivative 8 was eluted with a mixture AcOH–H_2O 1:1, and recovered from the acidic soln by careful alkalinisation with Na_2CO_3, followed by several extractions with CH_2Cl_2.

Reactions between 1a *and* NaOH

(a) *Reactions in* N 0.5 NaOH. (i) *Molar ratio* 1a/NaOH 1:0.5. 3.07 g (12.5 mmol) of 1a and 12.5 ml (6.25 mmol) of N 0.5 NaOH gave a residue (0.75 g), from which the following products were isolated: 3a–5a (0.27 g), 2a (0.24 g) and 6a (0.08 g).

(ii) *Molar ratio* 1a/NaOH 1:2. 3.07 g (12.5 mmol) of 1a and 50 ml (25 mmol) of N 0.5 NaOH gave a residue (0.75 g), from which the following products were isolated: 3a–5a (0.23 g), 9a (0.05 g), 2a (0.20 g), 6a (0.07 g), 8a (0.13 g).

(iii) *Molar ratio* 1a/NaOH 1:10. 3.07 g (12.5 mmol) of 1a and 250 ml (125 mmol) of N 0.5 NaOH gave a residue (1.0 g) from which the following products were isolated: 3a–5a (0.02 g), 9a (0.52 g), 2a (0.01 g), 6a (0.02 g), 8a (0.15 g).

(b) *Reactions in* N 2.5 NaOH. (i) *Molar ratio* 1a/NaOH 1:0.5. 3.07 g (12.5 mmol) of 1a and 2.5 ml (6.25 mmol) of N 2.5 NaOH gave a residue (0.90 g) from which the following products were isolated: 3a–5a (0.24 g), 2a (0.19 g), 6a (0.07 g). (ii) *Molar ratio* 1a/NaOH 1:10. 3.07 g (12.5 mmol) of 1a and 50 ml (125 mmol) of N 2.5 NaOH gave a residue (0.90 g) from which the following products were isolated: 3a–5a (0.01 g), 9a (0.56 g), 2a (0.01 g), 8a (0.04 g).

Reactions of 1b *with* NaOH

(i) *Molar ratio* 1b/NaOH 1:0.5 *in* N 0.5 NaOH. 2.88 g (12.5 mmol) of 1b and 12.5 ml (6.25 mmol) of N 0.5 NaOH gave a residue (1.4 g) from which the following products were isolated: 3b–5b (0.29 g), 2b (0.24 g), 6b (0.09 g), 7b (0.29 g), 8b (0.10 g).

1-*Benzyl-5-cyano-2-pyridone* (2b): m.p. 112–13° (2-propanol); mol wt calcd 210.23, found 210 (from mass spectrum); UV max (EtOH) 310 nm; IR (Nujol) 2220, 1690, 1680, 1615, 1530 cm^{-1}; NMR ($CDCl_3$) δ 7.84 (s, 1, H–2), 7.5–7.2 (group of signals, 6, H–4 + aromatic protons), 6.61 (d, 1, H–5) and 5.13 ppm (s, 2, N–CH_2).

1-Benzyl-3-cyano-2-pyridone (6b): m.p. 120–21° (2-propanol); mol wt calcd 210.23, found 210 (from mass spectrum); UV max (EtOH) 345 nm; IR (Nujol) 2225, 1665, 1605, 1550 cm^{-1}; NMR ($CDCl_3$) δ7.79 (dd, 1, H–6, $J_{6,5}$ = 6.7 Hz, $J_{6,4}$ = 1.8 Hz), 7.66 (dd, 1, H–4, $J_{4,5}$ = 6.7 Hz), 7.36 (s, 5, aromatic protons), 6.25 (t, 1, H–5) and 5.16 ppm (s, 2, N–CH_2).

5 - *Benzylamino* - 2 - *formyl* - 2,4 - *pentadienenitrile* (7b): m.p. 112–13° (AcOEt); mol wt calcd 212.24, found 212 (from mass spectrum); UV max (EtOH) 250,385 nm; IR (Nujol) 3250, 2205, 1645, 1605, 1595 cm^{-1}; NMR (CD_3COCD_3) δ 9.20 (d, 1, CHO, J = 1.5 Hz), 8.7–8.0 (bs, 1, NH) 7.9–7.5 (group of signals, 2, H–3 + H–5), 7.35 (s, 5, aromatic protons), 5.90 (t, 1, H–4) and 4.59 ppm (s, 2, N–CH_2).

1 - *Benzyl* - 1,2 - *dihydro* - 2 - *imino* - 3 - *pyridinecarbaldehyde* (8b): m.p. 130–35° (AcOEt); mol wt calcd 212.24, found 212 (from mass spectrum); UV max (EtOH) 266,415 nm, (H_2O) 260,337,410 nm; IR (Nujol) 3340,1650, 1640, 1575, 1530 cm^{-1}; NMR ($CDCl_3$) δ 9.65 (s, 1, CHO), 9.0–8.0 (bs, 1, NH), 7.5–7.0 (group of signals, 7, H–4 + H–6 + aromatic protons), 5.82 (t, 1, H–5) and 5.19 ppm (s, 2, N–CH_2).

(ii) *Molar ratio* 1b/NaOH 1:2 in N 0.5 NaOH. 2.88 g (12.5 mmol) of 1b and 50 ml (25 mmol) of N 0.5 NaOH gave a residue (2.0 g) from which the following products were isolated: 3b–5b (0.20 g), 9b (0.10 g), 2b (0.16 g), 6b (0.06 g), 7b (0.12 g), 8b (0.70 g).

2 - *Benzylamino* - 3 - *pyridinecarbaldehyde* (9b): m.p. 53–54° (light petroleum ether); mol wt calcd 212.24, found 212 (from mass spectrum); UV max(EtOH) 270,370 nm; IR (Nujol) 3330, 1670, 1600, 1580 cm^{-1}; NMR ($CDCl_3$) δ 9.83 (s, 1, CHO), 9.0–8.5 (bs, 1, NH), 8.36 (dd, 1, H–6, $J_{6,5}$ = 6.0 Hz, $J_{6,4}$ = 1.5 Hz), 7.73 (dd, 1, H–4, $J_{4,5}$ = 7.5 Hz), 7.5–7.1 (group of signals, 5, aromatic protons), 6.63 (dd, 1, H–5) and 4.79 ppm (d, 2, N–CH_2).

(iii) *Molar ratio* 1b/NaOH 1:10 *in* N 2.5 NaOH. 2.88 g (12.5 mmol) of 1b and 50 ml (125 mmol) of N 2.5 NaOH gave a residue (2.0 g) from which the following products were isolated: 3b–5b (0.04 g), 9b (0.50 g), 2b (0.04 g), 6b (0.02 g), 8b (0.96 g).

Conversion of 7b *to* 8b.[6] A mixture of 7b (0.1 g) and N 0.5

NaOH (2 ml) was stirred 2 hr at room temp., extracted with CH_2Cl_2, the organic layer was separated, dried (Na_2SO_4), and evaporated, to give a mixture (0.06 g) of **8b** and minor amount of **9b**. From the aqueous layer, the sodium salt of the enolate **10** (0.02 g) was recovered.

Rearrangement of **8b** *to* **9b**. A mixture of **8b** (0.1 g), N 2.5 NaOH (4 ml), and EtOH (4 ml) was stirred 2 hr at room temp., diluted with H_2O (50 ml), and extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4) and evaporated to give essentially pure **9b** (0.07 g).

Acknowledgement—The authors thank Prof. V. Carelli for helpful discussions. This work was supported by a research grant from CNR, Rome, Italy.

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[5]See ref. 4*h*.

[6]This conversion, and the rearrangement of the imino derivative **8** to the aminopyridinecarbaldehyde **9** (see also ref. 2) provide the experimental proof of the reaction pathway from **1** to **9** postulated by Blanch *et al.*[7]

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