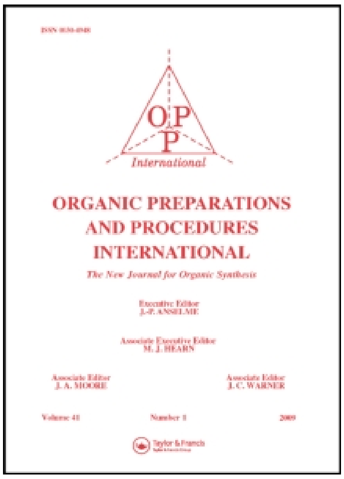

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SYNTHESIS OF PHENYLENE 1,3- AND 1,44*bis*(METHYLENE)-3-CARBAMOYL PYRIDINIUM BROMIDES

Feng Zhou[a]; Chi-Hua Wang[a]; John C. Warner[a]
[a] Department of Chemistry, University of Massachusetts, Boston, MA

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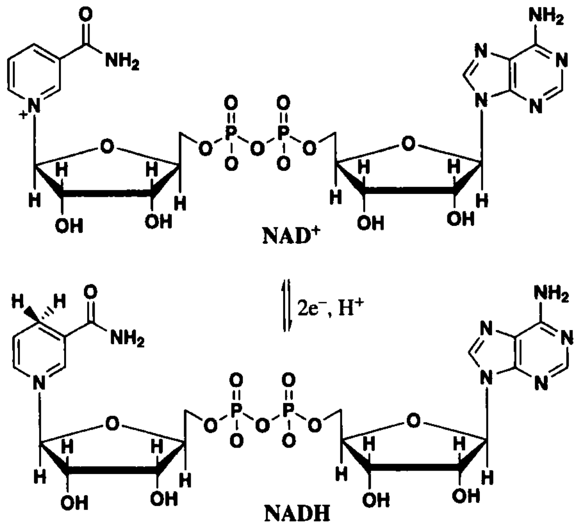
SYNTHESIS OF PHENYLENE 1,3- AND 1,4-*bis*(METHYLENE)-3-CARBAMOYLPYRIDINIUM BROMIDES

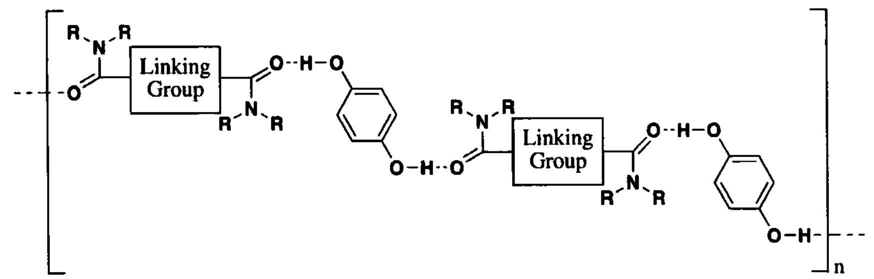
Submitted by Feng Zhou, Chi-Hua Wang and John C. Warner*
(3/23/01)

Department of Chemistry, University of Massachusetts Boston
100 Morrissey Blvd., Boston, MA 012125-3393

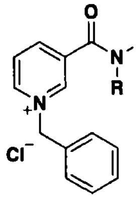
The B3 vitamin nicotinate (niacin) is needed by organisms for the synthesis of nicotinamide adenine dinucleotide (NAD^+) and its reduced form, NADH. These compounds are important nucleotide coenzymes in biotic electron transfer systems. There have been many studies of the biological oxidation and reductions related to the NAD^+/NADH pair.



These studies show that NAD$^+$ ultimately acquires two electrons and a proton (equivalent to a hydride). Whether the process involves a one-step hydride transfer[1] or multi-step electron transfer[2] has received a lot of debate. It has also been suggested that both of these two mechanisms might occur simultaneously.[3] In order to study electron transfer processes in constrained media, a family of single and binary nicotinamide derivatives has been prepared and, to permit entry into extended hydrogen bonding chain systems, bisnicotinamide derivatives containing two amide groups were synthesized. These compounds would allow us to apply the information learned from previous experiments with hydroquinone and various *bis*-amides.[4]



Nicotinamide derivatives of toluene **1**, *m*-xylene **2**, and *p*-xylene **3**, have been prepared. In order to control intermolecular hydrogen bonding, these systems have been synthesized both with and without hydrogens on the amide nitrogens.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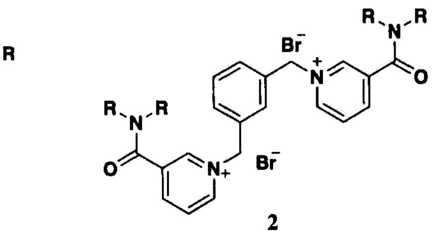
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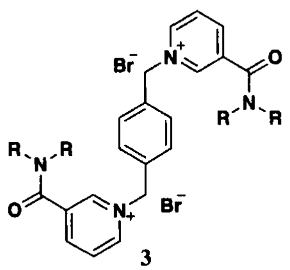
a) R = H b) R = Et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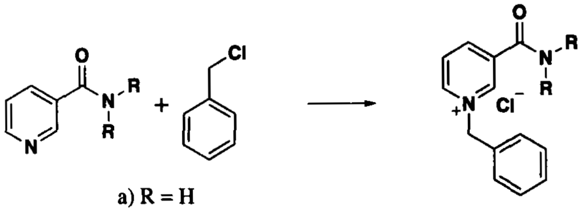
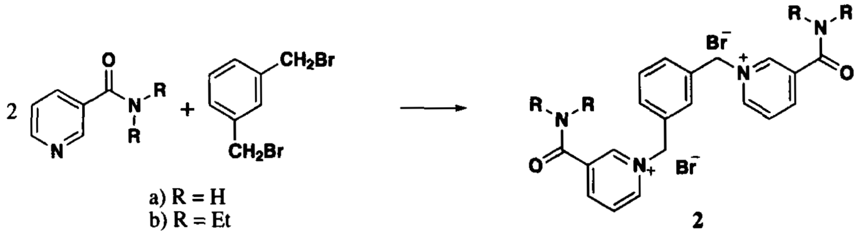
The parent 1-benzyl-1,4-dihydronicotinamide (**1a**) was prepared according to the method of Karrer and Stare,[5] in which a neat mixture of benzyl chloride and nicotinamide is heated to reflux at about 140°C. When this procedure was applied to the preparation of 1-benzyl-3-(*N,N*-diethyl)carbamoylpyridinium chloride (**1b**), a dark red tar was formed. This compound was obtained when the reaction was performed at lower temperatures in acetonitrile at reflux.



1

Based on our success with benzyl chloride in the previous system, we investigated the synthesis of xylene derivatives. The first system investigated was based on α,α'-dibromo-*o*-xylene. While we were unable to synthesize these derivatives, possibly due to the proximity of the substituents, we were successful in the synthesis of the *meta* (**2a** and **2b**) and *para* (**3a** and **3b**) derivatives.



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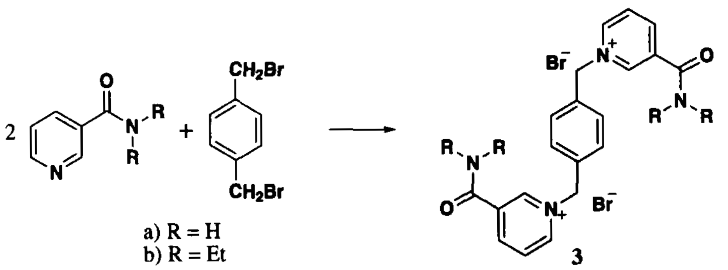

3

EXPERIMENTAL

Proton NMR spectra were recorded in deuterium oxide on a Bruker AC300 spectrometer or a Varian Gemini 400 Spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to TMS. Melting points were obtained using a Mel-Temp capillary melting point apparatus and are uncorrected. Elemental analyses were carried out by the Microanalysis Laboratory at University of Massachusetts at Amherst. Reagents were obtained commercially and used without further purification.

1-Benzyl-3-carbamoylpyridinium Chloride (1a).- This material was prepared according to the method of Karrer and Stare.[5] Nicotinamide (10.50 g, 86 mmol) and benzyl chloride (100 mL, 0.869 mol) were refluxed for 3 hrs. The mixture was cooled to room temperature and the white powdery product was collected and washed with ether twice to give 19.06 g (89%) product. A sample of the crude product was recrystallized from acetone/water to give pure product, mp 242-246°C, *lit.*[5] 235°C.

^{1}H NMR: δ 9.02 (s, 1 H); 8.90 (d, J = 6 Hz, 1 H); 8.72 (d, J = 8 Hz, 1 H); 8.01 (t, J = 7 Hz, 1 H); 7.36 (s, 5 H); 5.75 (s, 2 H).

Anal. Calcd for $C_{13}H_{13}ClN_2O$: C, 62.78; H, 5.27; N, 11.26; Cl, 14.25
Found: C, 62.90; H, 5.30; N, 11.29; Cl, 14.40

1-Benzyl-3-(*N,N*-diethyl)carbamoylpyridinium Chloride (1b).- *N,N*-diethylnicotinamide (5.1 g, 29 mmol) and benzyl chloride (3.9 g, 31 mmol) were refluxed in 40 mL of acetonitrile for 3 hrs. The colorless crystals formed upon cooling to room temperature were recrystallized from acetonitrile to give 4.0 g (46%) final product, mp 141-142°C.

^{1}H NMR: δ 9.98 (d, J = 6 Hz, 1 H); 9.36 (s, 1 H); 8.32 (d, J = 7 Hz, 1 H); 8.18 (t, J = 6.5 Hz, 1 H); 7.70 (s, 2 H);), 7.36 (s, 3 H); 6.48 (s, 2 H); 3.44 (2 q, J = 7 Hz, 4 H); 1.20 (2 t, J = 7 Hz, 6 H).

Anal. Calcd for $C_{17}H_{21}ClN_2O$: C, 66.99; H, 6.94; N, 9.19; Cl, 11.63
Found: C, 66.88; H, 6.79; N, 9.16; Cl, 11.58

1,3-Phenylenebis(methylene)[3-carbamoylpyridinium Bromide] (2a).- A solution of α,α'-dibromo-*m*-xylene (4.0 g, 15 mmol) and nicotinamide (4.0 g, 33 mmol) in 50 mL of a mixture of 3:7 acetonitrile and ethanol was heated at reflux for 1.5 hrs. The product precipitated from the solution as a gummy solid which, upon drying, became a white solid 5.6 g (73%). A 0.2 g sample was recrystallized from ethanol/water mixture to afford 0.14 g (70%), mp: 245-247°C.

^{1}H NMR: δ 9.217 (s, 2 H); 8.94 (d, J = 6.0 Hz, 2 H); 8.79 (d, J = 8.0 Hz, 2 H); 8.06 (t, J = 7 Hz, 2 H); 7.495 (s, 1 H); 7.458 (s, 3 H); 5.808 (s, 4 H).

Anal. Calcd: for $C_{20}H_{20}Br_2N_4O_2$: C, 47.27; H, 3.97; N, 11.02; Br, 31.45
Found: C, 47.04; H, 3.95; N, 10.93; Br, 31.66

1,3-Phenylenebis(methylene)[3-(*N,N*-diethyl)carbamoylpyridinium Bromide] (2b).- To a solution of α,α'-dibromo-*m*-xylene (1.32 g, 5 mmol) in acetonitrile (10 mL) was added *N,N*-diethylnicotinamide (1.8 g, 10 mmol). This solution was refluxed for 18 hrs. After evaporation of the acetonitrile, the residue was dissolved in about 3 mL water and extracted with ether (2 x 10 mL). The aqueous layer was evaporated and the residue was dried in a vacuum oven overnight at 150°C. A glass-like solid, (2.92 g, 94%) was obtained after cooling, mp 86-90°C.

^{1}H NMR: δ 9.10 (m, 4 H); 8.68 (d, J = 8 Hz, 2 H); 8.22 (t, J = 7 Hz, 2 H); 7.67 (s, 1 H); 7.60 (s, 3 H); 5.94 (s, 4 H); 3.56 (q, J = 7 Hz, 4 H); 3.26 (q, J = 7 Hz, 4 H); 1.24 (t, J = 7 Hz, 6 H); 1.05 (t, J = 7 Hz, 6 H).

Anal. Calcd. for $C_{28}H_{36}Br_2N_4O_2$: C, 53.43; H, 5.93; N, 8.90; Br, 25.4

Found: C, 53.38; H, 5.87; N, 8.92; Br, 25.5

1,4-Phenylenebis(methylene)[3-carbamoylpyridinium Bromide] (3a).- α,α'-Dibromo-*p*-xylene (4.0 g, 15 mmol) and nicotinamide (3.82 g, 31 mmol) were refluxed in 40 mL of a mixture of 3:5 acetonitrile and ethanol for 1.5 hrs. Evaporation of the solvent gave a white foamy solid, (5.88 g, 75%) which was recrystallized from water to yield 2.31 g (40%) of a colorless solid, mp 315°C.

^{1}H NMR: δ 9.22 0(s, 2 H); 8.92 (d, J = 6.0 Hz, 2 H); 8.77 (d, J = 8.0 Hz, 2 H); 8.05 (t, J = 7 Hz, 2 H); 7.433 (s, 4 H); 5.797 (s, 4 H).

Anal. Calcd for $C_{20}H_{20}Br_2N_4O_2{\bullet}0.5H_2O$: C, 47.27; H, 3.97; N, 11.02; Br, 31.45

Found: C, 47.06; H, 4.12; N, 10.95; Br, 31.77

1,4-Phenylenebis(methylene)[3-(*N,N*-diethyl)carbamoylpyridinium Bromide] (3b).- *N,N*-diethylnicotinamide (5.33 g, 30 mmol) and α,α'-dibromo-*p*-xylene (3.94 g, 15 mol) were refluxed in 40 mL of acetonitrile for 1.5 hrs. The foamy white powder formed was purified by dissolution in water and then precipitation by addition of acetone (twice) to give 7.9 g (85%) of a white powder, mp 242-246°C. *lit.*[6] 267.4-268.1°C.

^{1}H NMR: δ 8.94 (m, 4 H); 8.52 (d, J = 7.8 Hz, 2 H); 8.07 (t, J = 7.8 Hz, 2 H); 7.446 (s, 4 H); 5.787 (s, 4 H); 3.4 (q, J = 7.3 Hz, 4H); 3.1 (q, J = 7.0 Hz, 4H); 1.09 (t, J = 7.0 Hz, 6H); 0.85 (t, J = 7.0 Hz, 6H).

Anal. Calcd. for $C_{28}H_{36}Br_2N_4O_2$: C, 54.21; H, 5.84; N, 9.03; Br, 25.76.

Found: C, 53.91; H, 5.78; N, 8.99; Br, 26.00

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