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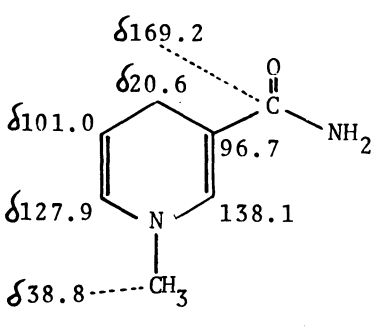
REACTIONS OF SEVERAL NUCLEOPHILES WITH QUATERNARY SALTS OF NICOTINAMIDE

Hiroshi MINATO*, Eiji YAMAZAKI, and Michio KOBAYASHI
Department of Chemistry, Tokyo Metropolitan University, Setagaya, Tokyo 158

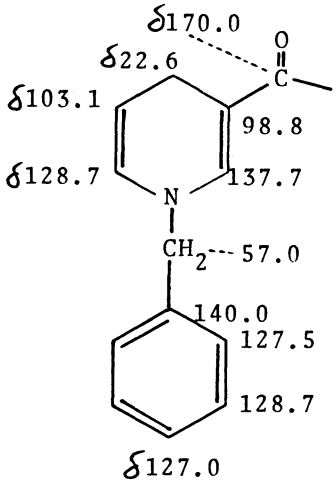
Reactions between 1-benzyl-3-carbamoylpyridinium chloride(1) and several nucleophiles were investigated by use of ^{13}C-NMR spectroscopy. The reaction with $OH^{\ominus}$ in EtOH-H_2O yielded a trimer of the deprotonated 1, and the positions 4 and 6 were the ring-connecting sites. The $MeO^{\ominus}$ in MeOH removed a benzyl proton, and yielded an N-ylide. The $MeS^{\ominus}$ in H_2O added at the position 4. The reaction with HgO and Et_2NH resulted in the oxidation at the position 2, yielding a pyridone.

Nicotinamide adenine dinucleotide (NAD^+) participates in a large number of enzyme-catalyzed reactions, and undergoes a two-electron reduction to form the reduced form, NADH, which is formally the product of addition of $H^{\ominus}$ at the position 4 of the pyridine ring. Reactions between some nucleophiles and quaternary salts of nicotinamides were studied,[1-2] but there are some ambiguities. We have investigated reactions between some nucleophiles and quaternary salts of nicotinamides with the aid of ^{13}C-NMR spectroscopy, and wish to describe the results in this communication.

First the ^{13}C-NMR spectra of several reference compounds were determined, and their chemical shifts were assigned by using the chemical shifts of related known compounds and the off-resonance proton decoupling technique. All the spectra were determined with a JEOL NMR spectrophotomer FX-60. Chemical shifts were determined relative to TMS dissolved in the solvent ($CDCl_3$, etc), or TMS in a capillary inserted into D_2O solutions.



(in $CDCl_3$)



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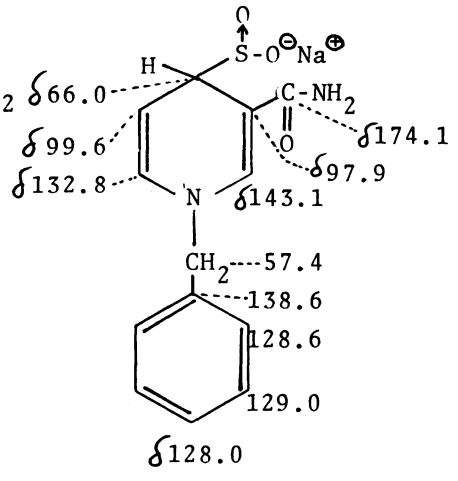
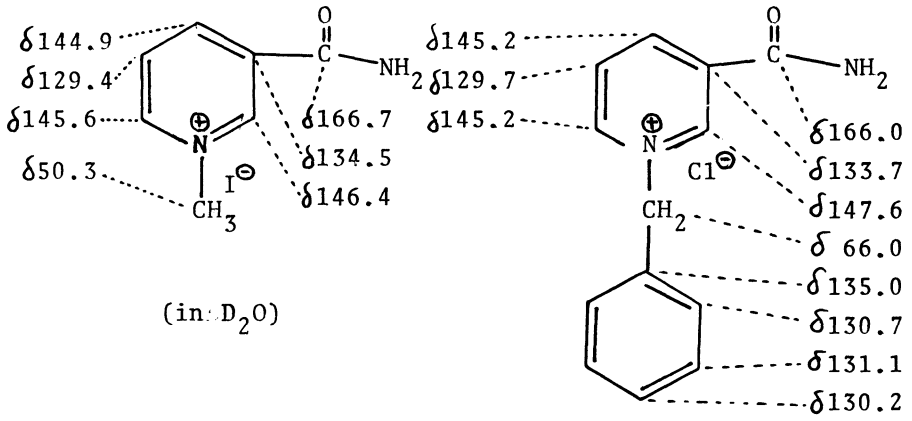
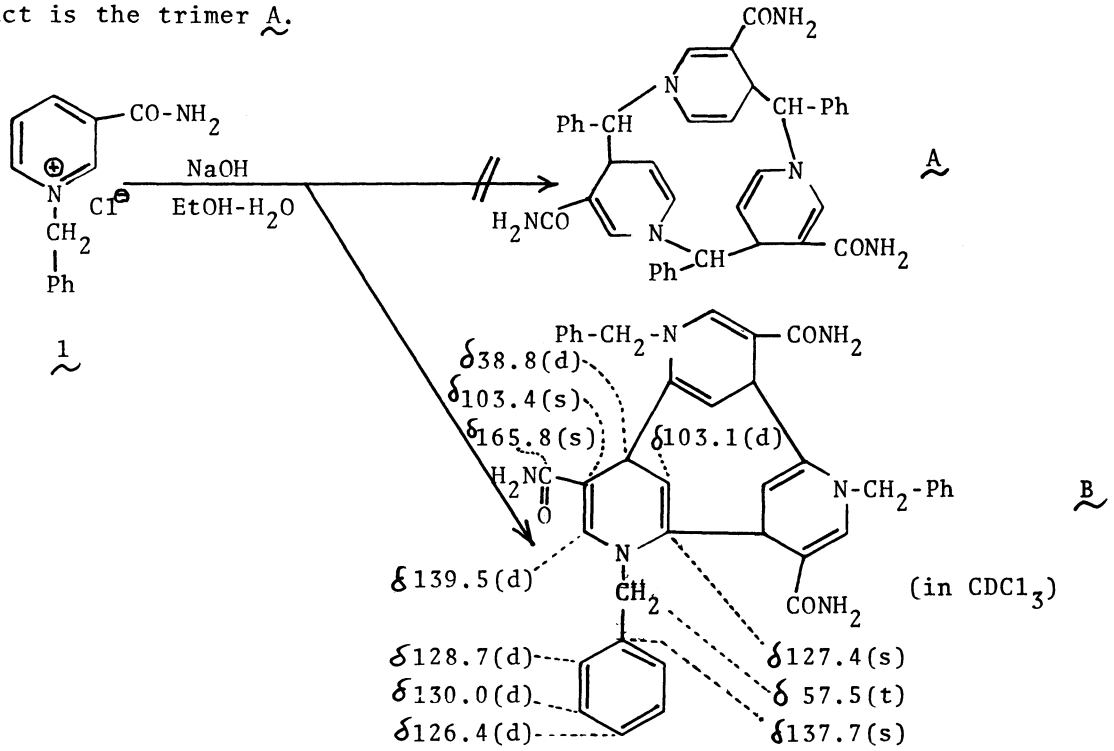


(in D_2O)



Dittmer and Kolyer[1] treated 1-benzyl-3-carbamoylpyridinium chloride (1) with NaOH in an EtOH-H_2O mixture (v/v, 72/28) at room temperature, and reported that the product is the trimer A.

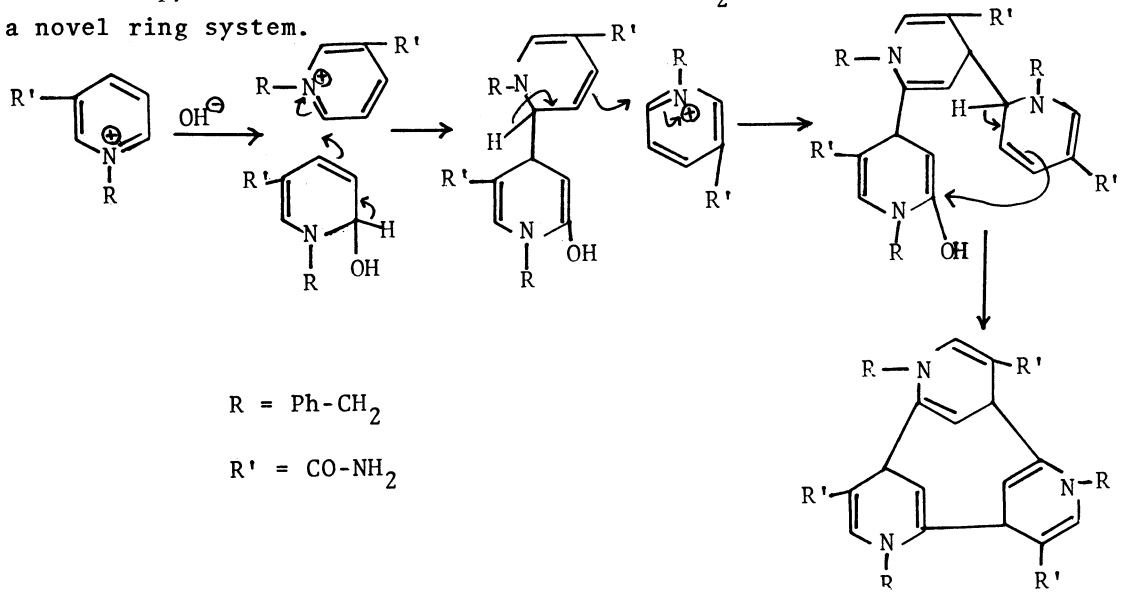


We repeated their experiment and obtained the same crystals. However, when we determined the ^{13}C-NMR spectrum, we found that the structure cannot be A, and a plausible structure appears to be B. The absorption at δ57.5 ppm is a triplet in the off-resonance proton decoupled spectrum. The doublets at δ139.5 ppm and 103.1 ppm are assignable to C-2 and C-5, respectively. The singlet at δ127.4 ppm is assigned to C-6. Thus the ring-connecting sites are C-4 and C-6. The assignments of the ^{1}H-NMR absorptions are: δ4.1(2H, $PhCH_2$), 4.9(1H, -CH of C-4), 6.0(2H,NH_2) and 7.2-7.6 ppm (7H; H's of C-2, C-5 and ArH).

Another plausible structure for this trimer is the one formed by the connection between C-6 and the benzyl carbon. However, the C-4 of N-benzyl-1,4-dihydronicotinamide absorbs at δ22.6 ppm(t), and its ^{1}H-NMR spectrum shows absorptions at δ3.1

(CH_2 of C-4) and 4.2 ppm($PhCH_2$).[3] It is probably difficult to assign the absorptions at δ4.1 (^{1}H-NMR) and at δ57.5 ppm (^{13}C-NMR) of the trimer to the CH_2 of C-4 and the C-4, respectively. Therefore, the structure B appears to be most favorable.

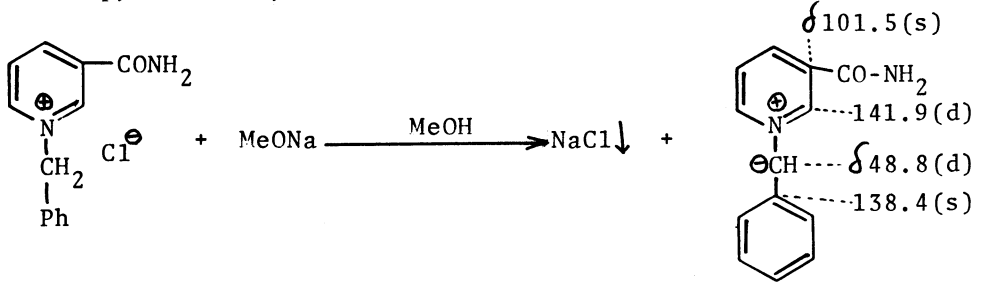
A plausible mechanism is shown below. It is of interest that a simple treatment of a pyridinium ion with alkali in EtOH-H_2O results in the formation of such a novel ring system.



R = Ph-CH_2

R' = CO-NH_2

It appears to be of interest to investigate the reaction between 1 and $MeO^{\ominus}Na^{\oplus}$. After sodium (8.70 mmol) was dissolved in methanol (10 ml), it was added to a mixture of 1 (8.04 mmol) and methanol (10 ml). White solids of NaCl immediately precipitated. The yellow solution was evaporated under reduced pressure, and the residue was extracted with CH_2Cl_2. Evaporation of the extracts yielded yellow powder (1.45 g). Its ^{1}H-NMR spectrum in $CDCl_3$ had absorptions at δ5.7 (1H) and 7.1-7.5(9H)ppm. Since it slowly reacted with $CDCl_3$, its ^{13}C-NMR spectrum was determined in dimethyl sulfoxide. Its benzyl carbon absorbed at δ48.8 ppm which was a doublet at its off-resonance proton decoupled spectrum. Other absorptions observed were δ101.5, 126.3-128.5, 138.4, and 141.9 ppm. Its benzyl carbon absorbed at δ 49.7 ppm (off-resonance, doublet) in hexamethylphosphoramide and at δ49.7 ppm (off-resonance, doublet) in dichloromethane. These data suggest that this yellow solid is a pyridinium ylide shown below.

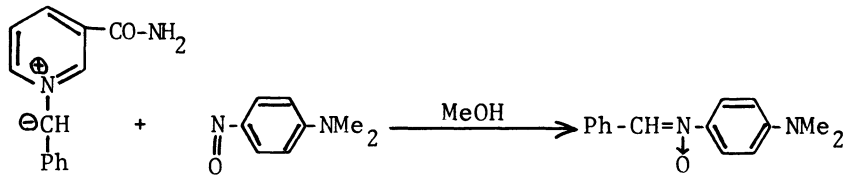


(^{13}C-NMR, in DMSO)

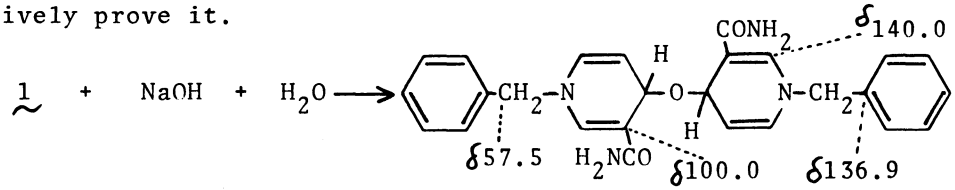
This compound is unstable, especially in solution. The solids could be stored at 0°C for 1 day. The results of its elemental analysis were C, 69.02; H, 5.64; N, 12.31%. Calcd for $C_{13}H_{13}ON_2$, C, 73.56; H, 5.70; N, 13.17%. Kröhnke[4] treated benzyl-

pyridinium halides with aqueous NaOH solutions, but the pyridinium ylides formed in solution were immediately let to react with other reagents and he did not isolate the ylides.

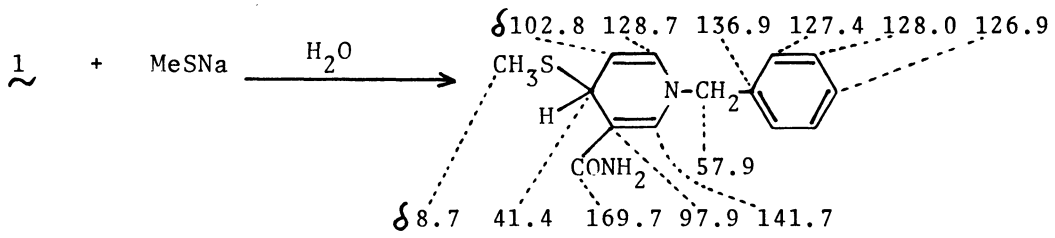
When the ylide (5.61 mmol) and p-dimethylaminonitrosobenzene (6.67 mmol) were allowed to react in methanol at room temperature for 16 h, phenyl-N-(p-dimethylaminophenyl)nitrone[3] was obtained in a 19% yield.



Dittmer and Kolyer[1] reported that the reaction between 1 and aquous NaOH yielded white crystals to which they assigned the dimolecular ether structure shown below. We repeated their experiment, and determined the ^{13}C-NMR spectrum of the product (in $CDCl_3$, δ 57.5, 100.0, 103.1, 126.4-130.0, 136.9, 140.0, 171.5 ppm). However, because of its instability the spectrum was poorly resolved, and it was not possible to determine its off-resonance spectrum. The ^{13}C-NMR data obtained appear to be consistent with the proposed structure, although they do not positively prove it.

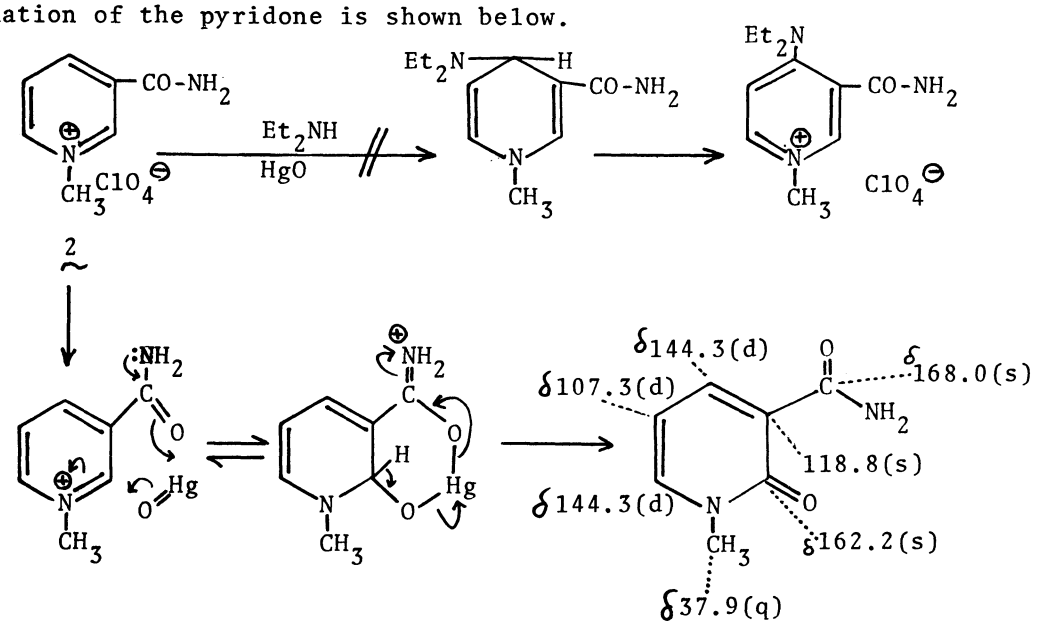


Then the reaction between 1 and $MeS^{\ominus}Na^{\oplus}$ in water was examined. 1(10 mmol) and MeSNa (20 mmol) was mixed in water (20 ml) and the mixture was extracted with dichloromethane. From the dichloromethane extracts, a product was obtained, and its ^{13}C-NMR spectrum was determined. Its ^{13}C chemical shifts show that this compound is the product of addition of $MeS^{\ominus}$ at the position4 of 1 (58 mol% yield).



Then the reaction among 1-methyl-3-carbamoylpyridinium perchlorate (2), diethylamine, and mercury(II) oxide in methanol was investigated. The N-methyl salt was used because of greater solubility in methanol and easier assignment of

^{13}C-NMR absorptions. Nucleophilic addition of diethylamine to C-2, C-4, or C-6 and subsequent oxidation with HgO were the reactions expected, but the product found was different. After a mixture of 2 (12.8 mmol), diethylamine(38.8 mmol), HgO (38.8 mmol) and methanol (60 ml) was refluxed with stirring for 44 h, the product found from the mixture was N-methyl-2-pyridone[5] shown below in a 60% yield. In the absence of diethylamine no reaction took place, and the deprotonation appears to be rate-determining. It is of interest that the attack of HgO takes place exclusively on the C-2. It is most likely that the positively charged Hg(II) is weakly bonded to the carbonyl oxygen atom of the nicotinamide and thus the attack of HgO to the C-2 is favored. A plausible mechanism for the formation of the pyridone is shown below.



It is not certain how diethylamine functions. It may simply removes a proton from the addition product shown above; or with the pyridinium ion it may form a charge-transfer complex, which is then oxidized with HgO.

The reactions between various nucleophiles and quaternary salts of nicotinamide can be summarized as follows. In an EtOH-H_2O mixture, $HO^{\ominus}$ attacks the C-6 of 1, and subsequently the trimer B is formed; in MeOH, $MeO^{\ominus}$ deprotonates the benzyl proton of 1; in H_2O, $HO^{\ominus}$ appears to attack the C-4 of 1 and forms a dimolecular ether; in H_2O, $MeS^{\ominus}$ attacks the C-4 of 1; the nagatively-charged oxide of HgO attacks the C-2 of 1-methyl-3-carbamoylpyridinium ring. The reactions between nucleophiles and quaternary salts of nicotinamide are very complex, and further work is necessary for complete understanding of these reactions. ^{13}C-NMR spectroscopy has proved to be a useful method for studies of these reactions.

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