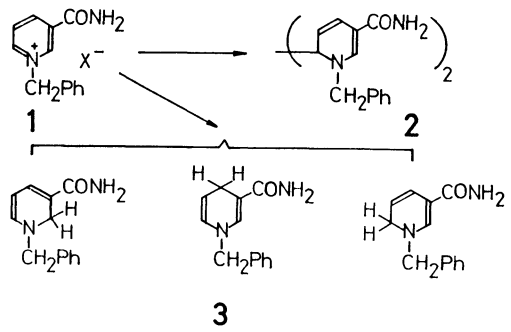
Photoreduction of 1-Benzyl-3-carbamoylpyridinium Chloride in Aqueous Ammonia[1)]

Teruo MATSUURA,* Toshio ITAHARA, Toshiaki OTSUKI, and Isao SAITO
Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606
(Received April, 18 1978)

Irradiation of 1-benzyl-3-carbamoylpyridinium chloride (BNA$^+$Cl$^-$) in the presence of ascorbic acid in 28% aqueous ammonia gives the corresponding 1,4-dihydronicotinamide as the major product. The spectroscopic behavior of BNA$^+$ in aqueous ammonia and the adduct formation between BNA$^+$ and chloroform are also described.

Among various reactions of *N*-alkylpyridinium salts containing electronwithdrawing groups as models for the biological oxido-reductions involving nicotinamide coenzymes, NAD(P)$^+$, the chemical or electrochemical reduction of 1-alkyl-3-carbamoylpyridinium salts has received considerable attention, where 1,2-,[2)] 1,4-,[3,4)] and 1,6-dihydronicotinamides[5)] are formed two-electron transfer and a 6,6′-dihydro dimer[3)] by one-electron transfer. Relatively few attention has been drawn to



the photochemical reduction of NAD$^+$ or its analogs, which may serve as a model for the electron transport in photosynthetic system. Earlier workers have shown that photolysis of NAD$^+$ or its analog, 1-benzyl-3-carbamoylpyridinium chloride (**1**; BNA$^+$Cl$^-$), in the presence of ascorbic acid appreciably gives a reduced nicotinamide detected by its absorption spectrum, only in aqueous pyridine containing ammonia[6,7)] or in the presence of NADP reductase in aqueous solution.[8,9)] Kano and Matsuo have recently found that BNA$^+$Cl$^-$ (**1**) is photoreduced in the presence of diethylamine and/or ethylenediaminetetraacetic acid in aqueous solution to give 6,6′-dihydrodimer **2** as the main product(15—19%).[10,11)] We now report that the photoreduction of **1** in the presence of ascorbic acid in aqueous ammonia gives 1-benzyl-3-carbamoyl-1,4-dihydropyridine (**3**).

Results and Discussion

Irradiation of a 2×10^{-2} M solution of BNA$^+$Cl$^-$ (**1**) in 28% aqueous ammonia in the presence of an excess of ascorbic acid with a high-pressure mercury lamp (Pyrex) under nitrogen for 12 h gave the known 1,4-dihydro compound **3**[12)] in 22% yield, as the major component of the chloroform extract of the reaction mixture. TLC analysis of the chloroform extract revealed the presence of a trace of nicotinamide (**4**), but no other dihydronicotinamides and dihydrodimers. The aqueous layer contained a complex mixture of products from which no pure compound could be isolated. The photoreaction of **1** under various conditions was examined (Table 1). The characteristic features of the photoreduction are as follows. (1); Catechol could be used as a reducing agent instead of ascorbic acid, although the yield of **3** was lower. (2); The kind of the counter anion of BNA$^+$ appears to give no effect; the photolysis of BNA$^+$Br$^-$ under the same conditions gave virtually the same result. (3); When various amines were used instead of ammonia, only a trace of **3** was detected and the yield of **4** somewhat increased. Upon irradiation in 30% aqueous trimethylamine under similar conditions, **3** was found to be recovered almost unchanged. This result indicates that **3**

TABLE 1. PHOTOREACTION OF 1-BENZYL-3-CARBAMOYLPYRIDINIUM SALTS
(Irradiated with a high pressure mercury lamp (Pyrex) for 12 h.)

Pyridinium salt	Solvent	Reducing agent	Yield of products (%)[a)]	
			3	Nicotinamide (**4**)
BNA$^+$Cl$^-$	28% aq NH_3	ascorbic acid	22	trace[b)]
BNA$^+$Br$^-$	28% aq NH_3	ascorbic acid	20	trace
BNA$^+$Cl$^-$	28% aq NH_3	pyrocatechol	9	4
BNA$^+$Cl$^-$	30% aq $MeNH_2$	ascorbic acid	trace	3
BNA$^+$Cl$^-$	30% aq Me_2NH	ascorbic acid	trace	5
BNA$^+$Cl$^-$	30% aq Me_3N	ascorbic acid	trace	5
BNA$^+$Cl$^-$	30% aq $EtNH_2$	ascorbic acid	trace	4
BNA$^+$Cl$^-$	30% aq Et_2NH	ascorbic acid	trace	5
BNA$^+$Cl$^-$	H_2O[c)]	ascorbic acid	—	—
BNA$^+$Cl$^-$	5.7 M NaOH[d)]	ascorbic acid	trace	—

a) Based on the starting BNA$^+$ salt. b) Detected on TLC. c) Almost no reaction was observed. d) A complex mixture of products was obtained.

might not be formed in the photolysis of **1** in the presence of trimethylamine. (4); Replacemnet of ammonia by sodium hydroxide gave a complex mixture of products including a trace of **3**. These results indicate that the presence of ammonia are essential for the photochemical formation of the 1,4-dihydronicotinamide **3**.

Recently, Ohnishi has reported that treatment of **1** with aqueous ammonia in the dark gives **3** in small yield.[13] This finding prompted us to carry out a control experiment under similar conditions. Thus, when **1** was treated with 28% aqueous ammonia for 12 h in the dark, **3** was found to form in 7% yield in a complex mixture of products. This result indicates that the major portion of the compound **3** formed under the irradiation is resulted from a photochemical process.

In order to gain informations on the role of ammonia in the photochemical formation of **3**, the spectroscopic and chemical behaviors of BNA$^+$Cl$^-$ (**1**) in aqueous ammonia were examined. At a low concentration (4×10^{-5} M), **1** apparently undergoes chemical transformation at least with three steps. The ultraviolet absorption spectra of **1** with or without ammonia in aqueous solution are shown in Fig. 1. The absorption maximum at 258 nm of **1** in aqueous solution increased with increased amount of added ammonia and a new maximum appeared at 323 nm (stage I). The intensity of the latter absorption strongly depends upon ammonia concentration, as shown by the fact that the 323 nm maximum does not appear at ammonia concentrations of below 15% w/v. Acidification of the strong ammonia solution of **1** with hydrochloric acid gave rise to a spectrum identical with that of **1** in aqueous solution, indicating that the change into stage I is reversible.

When the ammonia solution at stage I was kept on standing at room temperature for several hours, a spectral change occurred gradually to reach a new spectrum having a maximum at 345 nm (stage II) with three isosbestic points at 273, 294, and 334 nm (Fig. 2). The spectral change of stage I to stage II

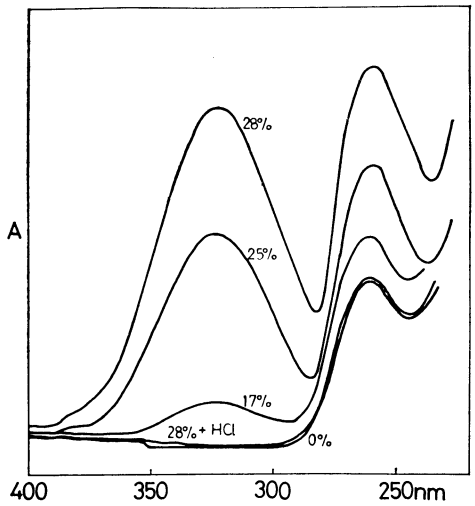


Fig. 1. UV spectra of BNA$^+$Cl$^-$ (**1**) in aqueous solution and in aqueous ammonia solution with different concentrations. BNA$^+$Cl$^-$: 4.0×10^{-5} M. Ammonia concentrations are shown by w/v %.

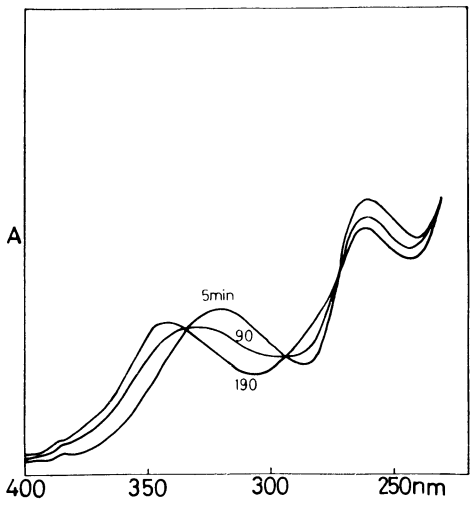


Fig. 2. UV spectral change of a solution of BNA$^+$Cl$^-$ (**1**) in 23% aqueous ammonia at 5, 90, and 190 min after dissolution. BNA$^+$Cl$^-$: 4.0×10^{-5} M.

was highly sensitive to the concentration of **1**. Thus, at higher concentrations of **1** the change became obscure, suggesting the occurrence of bimolecular reactions of the transient species having the 345 nm maximum. In fact, a 0.16 M solution of **1** in 28% aqueous ammonia became turbid and deposited an yellowish brown precipitate in a few hours (stage III). Figure 3 shows the spectra of the freshly prepared precipitate and the aqueous filtrate, suggesting a complex nature of stage III. These results may be simply summarized as the following scheme:

$$\text{NBA}^+\text{Cl}^- + \text{NH}_3\ \text{aq} \rightleftharpoons \text{stage I} \rightarrow \text{stage II} \rightarrow \text{stage III}$$

Since the photolysis of **1** in aqueous ammonia was done at a relatively high concentration (2×10^{-2} M), the reduction product **3** seems to originate from some of the intermediate species corresponding to these three stages.

Various attempts were made to isolate the species formed in the stages I, II, and III, but were unsuccessful because of their instability. During these attempts, it was found that when a 0.27 M solution of **1** in 28%

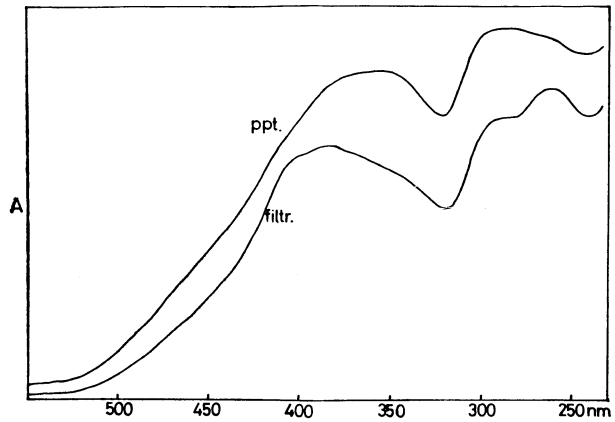
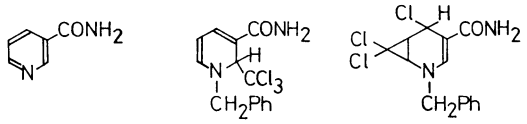


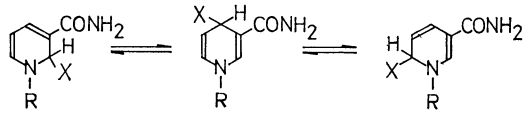
Fig. 3. UV spectra of the precipitate and the filtrate obtained from a solution of BNA$^+$Cl$^-$ (**1**) in 28% aqueous ammonia after standing for 12 hr. BNA$^+$Cl$^-$ (2.0 g) in 28% aqueous ammonia (50 ml).

aqueous ammonia is stirred with chloroform for 3 h, two adducts between BNA^+ and the trichloromethanide anion, **5** (19%) and **6** (15%) are obtained from the chloroform layer. The structure of the latter product was assigned as **6** which had already been reported by Gündel.[14] The structure **5** was assigned by comparing its spectral data with those of the known 2,6-dichlorobenzyl analog.[14] Similar adduct formation between pyridinium salts and the trihalomethanide anions has been reported.[14-16]



4 **5** **6**

Because of the failure to identify any of the intermediate species in stages I, II, and III, the nature of the present photoreduction remains unknown. However, on the basis of the probable equilibrium of ammonia in water, $NH_3+H_2O \rightleftarrows NH_4^+ + OH^-$ ($K_B=[NH_4^+][OH^-]/[NH_3]_t=1.75\times10^{-5}$ (25°)), where $[NH_3]_t$ denotes the total concentration of ammonia,[17] NH_3 would be able to act as a nucleophile rather than OH^-. Therefore, it seems reasonable to assume that adducts, **7a**, **8a**, and **9a**, which are formed between **1** and ammonia, play a role in the formation of the 1,4-dihydronicotinamide **3**. Comparing the absorption maxima at stages I (323 nm), II (345 nm), and III (350—400 nm) in Figs. 2 and 3 with those of *N*-(2,6-dichlorobenzyl)dihydronicotinamides, **7b** (ca. 420 nm), **8b** (350 nm), and **9b** (355 nm),[2,5] *N*-(2,6-dichlorobenzyl)-2-trichloromethyl-1,2-dihydronicotinamide (**7c**) (364 nm),[14] *N*-benzyl-4-trichloromethyl-1,4-dihydronicotinamide (**8d**) (365 nm),[14] and **5** (360 nm), there appeared rather difficult to assign the structures of the adducts in stages I, II, and III. However, considering from the difference between stages I and II in their absorption maxima, the adducts in stage I and II may be assigned as **8a** and **7a** (or **9a**) respectively. The precipitates of stage III may be very likely to consist of a mixture of the adducts and/or their decomposition products. The relatively low yield of the 1,4-dihydronicotinamide **3** may have resulted from the simultaneous occurence of side reactions of the adducts. A similar formation of the unstable adducts from **1** or its analogs by the action of a nucleophile such as the hydroxide anion,[18,19] amines,[13] and formate,[20] has been claimed. Such adducts are considered to be interconvertible, although the nature of the reaction is usually complex.



7 **8** **9**

a: X=NH_2 R=$PhCH_2$
b: X=H; R=2,6-$Cl_2C_6H_3CH_2$
c: X=CCl_3; R=2,6-$Cl_2C_6H_3CH_2$
d: X=CCl_3; R=$PhCH_2$

Experimental

All the melting points are uncorrected. UV, IR, NMR, and mass spectra were measured on a Shimadzu UV-200, a JASCO IRA-1, an NEVA T-60 (TMS, internal standard), and a Hitachi RMS-4 spectrometers, respectively. BNA^+ (**1**) was prepared by the known method.[21]

Photoreduction of 1-Benzyl-3-carbamoylpyridinium Chloride (1). A solution of **1** (1.0 g) and ascorbic acid (1.0 g) in 28% aqueous ammonia (180 ml) was irradiated internally with a 100 W high-pressure mercury lamp (Pyrex housing) under nitrogen for 12 h. The photolysate was extracted with chloroform. Evaporation of the chloroform extracts gave a solid (0.19 g) which on TLC (silica gel; chloroform) showed a major spot of *N*-benzyl-1,4-dihydronicotinamide (**3**) and a minute spot of nicotinamide (**4**). Recrystallization of the solid from aqueous ethanol gave crystals which were identical with an authentic sample of **3**[12] (NMR, IR, and TLC). Attempts to isolate pure products from the aqueous layer were unsuccessful.

Photolysis of **1** and the corresponding bromide (BNA^+Br^-) was carried out (Table 1). A solution of the pyridinium salts (1.0 g) and ascorbic acid or pyrocatechol (1.0 g) in a given solvent (180 ml) was irradiated under similar conditions. The photolysate was worked up as above.

Dark Reaction of 1 with Aqueous Ammonia. A solution of **1** (1.0 g) in 28% aqueous ammonia (180 ml) was kept on standing at room temperature under nitrogen for 12 h. After evaporating ammonia *in vacuo*, the mixture was extracted with chloroform. The chloroform layer was dried (Na_2SO_4) and evaporated to give a reddish brown solid (419 mg), which was found to contain **3** by TLC (silica gel; EtOAc–MeOH (10:1)). The NMR analysis of the solid with *t*-butyl alcohol as an internal standard showed that the yield of **3** was less than 7%.

Reaction of 1 with Chloroform in Aqueous Ammonia. A solution of **1** (2.0 g) in 28% aqueous ammonia (30 ml) was stirred with chloroform (60 ml) at room temperature for 3 h. The chloroform layer was dried (Na_2SO_4) and evaporated to give an yellowish brown solid (1.65 g), which was chromatographed on a silica gel column (Wakogel C-200). Elution with chloroform–ethyl acetate (2:3) yielded *N*-benzyl-2-trichloromethyl-1,2-dihydronicotinamide (**5**) as a pale yellow solid (0.50 g; 19%), which was recrystallized from benzene–cyclohexane as pale yellow crystals; mp 118—123 °C; λ_{max}^{EtOH} 360 nm (ε 5500); MS, *m/e* (rel int.) 213 (41) (M^+-CCl_3), 91 (65) ($PhCH_2^+$), 85 (100), 83 (65); NMR ($CDCl_3$), δ 4.80 (s, 2H, benzyl protons), 5.27 (dd, 1H, 5-H, J=6.6, 6.6 Hz), 5.70 (broad, 2H, NH_2, D_2O-exchangeable), 5.73 (d, 1H, 2-H, J=1.8 Hz), 6.58 (dd, 1H, 6-H, J=6.6, 1.8 Hz), 7.03 (d, 1H, 4-H, J=6.6 Hz), 7.32 (m, 5H, phenyl protons).

Found: C, 51.28; H, 4.05; Cl, 30.83; N, 8.27%. Calcd for $C_{14}H_{13}Cl_3N_2O$: C, 50.70; H, 3.95; Cl, 32.08; N, 8.45%.

Further elution with the same solvent yielded 5,7,7-trichloro-4-carbamoyl-2-benzyl-2-azabicyclo[4.1.0]hept-3-ene (**6**) as a pale yellow solid (0.41 g; 15%), which was recrystallized from ether–petroleum ether as colorless needles; mp 55—60 °C (containing 1 equivalent mole of ether of crystallization) (lit,[14] mp 130—131 °C, from dichloromethane); λ_{max}^{EtOH} 263 nm (ε 4400), 313 (4400); MS, *m/e* (rel int.) 213 (54) (M^+-CCl_3), 91 (100) ($PhCH_2^+$), 85 (23), 83 (35); NMR ($CDCl_3$), δ 1.20 (t, 6H, CH_2-CH_3, J=6 Hz), 3.49 (q, 4H, -O-CH_2-CH_3, J=6 Hz), 4.53 (s, 2H, benzyl protons), 4.55 (d, 1H, 5-H, J=6 Hz), 5.21 (dd, 1H, 6-H, J=6, 7.2 Hz), 5.60 (broad, 2H, NH_2, D_2O-exchangeable), 6.38 (dd, 1H, 1-H, J=7.2, 1.2 Hz), 7.24 (m, 5H, phenyl protons), 7.33 (d, 1H, 3-H,

J=1.8 Hz). (Found: C, 53.03; H, 5.65; N, 7.04; O, 8.19%. Calcd for $C_{14}H_{13}Cl_3N_2O \cdot C_2H_5OC_2H_5$: C, 53.28; H, 5.71; N, 6.90; O, 7.89%.)

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education.

References

1) Photoinduced Reactions, Part 105.
2) K. Wallenfels and M. Gellrich, *Chem. Ber.*, **92**, 1406 (1959).
3) D. Mauzerall and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 77 (1955).
4) J. N. Burnett and A. L. Underwood, *J. Org. Chem.*, **30**, 1154 (1965); A. J. Cunningham and A. L. Underwood, *Biochemistry*, **6**, 266 (1967).
5) K. Wallenfels and H. Schultz, *Angew. Chem.*, **67**, 517 (1955); **69**, 505 (1957); *Justus Liebigs Ann. Chem.*, **621**, 106 (1959).
6) A. A. Krasnovskii and G. P. Brin, *Dokl. Acad. Nauk. SSSR*, **67**, 325 (1949); A. A. Krasnovskii, G. P. Brin, and N. N. Drozdova, *ibid.*, **150**, 1157 (1963); G. P. Brin and A. A. Krasnovskii, *Biokhimiya*, **24**, 1085 (1959).
7) G. R. Seely, *J. Phys. Chem.*, **69**, 2779 (1965).
8) T. T. Bannister and J. E. Bernardini, *Biochem. Biophys. Acta*, **59**, 188 (1962).
9) L. P. Vernon, A. S. Pietro, and D. A. Limbach, *Arch. Biochem. Biophys.*, **109**, 92 (1965).
10) K. Kano and T. Matsuo, *Tetrahedron Lett.*, **1975**, 1389.
11) K. Kano and T. Matsuo, *Bull. Chem. Soc. Jpn.*, **49**, 3269 (1976).
12) D. Mauzerall and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 2261 (1955).
13) Y. Ohnishi, *Tetrahedron Lett.*, **1977**, 2109.
14) W.-H. Gündel, *Z. Naturforsch.*, **30b**, 616 (1975).
15) A. Lambardo and D. C. Dittmer, *Bioorganic Chemistry*, **1**, 400 (1971).
16) V. Mann, G. Schneider, and F. Kröhnke, *Tetrahedron Lett.*, **1973**, 683.
17) Kagaku Daijiten (Encyclopedia Chimica), Kyoritsu Publ. Co. (1960), Vol. 1, p. 532.
18) F. M. Maracci, A. Casini, F. Liberatore, and V. Carelli, *Tetrahedron Lett.*, **1976**, 3723.
19) H. Minato, E. Yamazaki, and M. Kobayashi, *Chem. Lett.*, **1976**, 525.
20) Y. Onishi and S. Tanimoto, *Tetrahedron Lett.*, **1977**, 1909.
21) P. Karrer and F. J. Stare, *Helv. Chim. Acta*, **20**, 418 (1937).