

excess ammonia was then allowed to escape, with intermittent stirring, and the resulting solid was filtered and dried *in vacuo* for 24 hr. This procedure gave 8.25 g. (60%) of a slightly brown material which was recrystallized three times from benzene to give *n*-octylurea, m.p. 100–101°.

*Anal.* Calcd. for  $C_8H_{20}N_2O$ : C, 62.70; H, 11.62; N, 16.27. Found: C, 62.47; H, 11.62; N, 16.29.

The ureas which were prepared from the isocyanates,

resulting from the ozonolysis of the various isocyanides are listed in Table II.

*Acknowledgment.* We are indebted to the Purdue Research Foundation and the Office of Naval Research for the financial support of this work.

LAFAYETTE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

## Action of Base on Certain Pyridinium Salts<sup>1,2</sup>

ARTHUR G. ANDERSON, JR., AND GERALD BERKELHAMMER

Received January 23, 1958

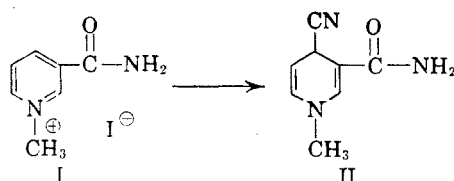
The action of ethoxide, hydroxide, and cyanide ions on a number of 1-alkyl-3-substituted pyridinium salts has been studied and interpreted. Evidence for the formation of pseudo bases and, in one case, the dimolecular ether of a hydroxy pseudo base has been obtained.

Among the properties of di- and triphosphopyridine nucleotides (DPN and TPN) which have been attributed to the nicotinamide portion of the molecule is the reaction with nucleophilic species to give a change in the ultraviolet absorption similar to that observed on reduction to the dihydro compounds. This behavior was first noted with cyanide and bisulfite by Meyerhof *et al.*<sup>3</sup> More recently the reaction with cyanide has been studied in some detail with the coenzymes and also with model compounds including a number of 3-substituted 1-methylpyridinium iodides.<sup>4</sup> From deuterium exchange experiments San Pietro<sup>5</sup> concluded that the reaction involved the addition of cyanide to the 4-position of DPN to form a pseudo cyanide. Recently a stable, crystalline cyanide addition product (II) has been isolated from I.<sup>6</sup> Also the spectral changes observed with the model compounds<sup>4</sup> seem to correspond best to 4-cyano deriva-

tives. Other reactions which probably involve addition of a nucleophilic group at the 4-position are those with acetone,<sup>7</sup> negatively substituted methyl ketones,<sup>8</sup> and hydroxylamine.<sup>9</sup>

The transient existence of pseudo bases has long been suspected in the formation of pyridones from *N*-alkylpyridinium halides<sup>10</sup> and in the reaction of strong alkali with DPN,<sup>11</sup> but there is very little evidence in support of this hypothesis.<sup>10,12</sup>

In connection with the preparation of a number of 1-alkyl-3-substituted-1,4-dihydropyridines as model compounds of DPNH,<sup>13</sup> it was observed that the aqueous solution of the quaternary pyridinium halide and sodium carbonate became yellow before the introduction of the sodium dithionite. In the case of one compound, 1-benzyl-3-acetylpyridinium chloride, a yellow solid also precipitated. Accordingly, the effect of base on the absorption spectra of ethanolic solutions of the substituted pyridinium halides was qualitatively measured and it was found that a similar spectral change occurred for all of the model compounds (Table I). Each of these had a substituent attached *via* a carbonyl group to the 3-position. The spectrum of a compound having no such group, 1-benzylpyridinium chloride, was essentially the same in neutral, basic, and acidic solutions.



(1) From the Ph.D. thesis of Gerald Berkelhammer.

(2) Supported in part by a research grant (No. RG-3844) from the National Institutes of Health, Public Health Service.

(3) O. Meyerhof, P. Ohlmeyer, and W. Mohle, *Biochem. Z.*, **279**, 113 (1938).

(4) S. P. Colowick, N. O. Kaplan, and M. M. Ciotti, *J. Biol. Chem.*, **191**, 447 (1951); M. R. Lamborg, R. M. Burton, and N. O. Kaplan, *J. Am. Chem. Soc.*, **79**, 6173 (1957). The latter paper appeared after the completion of the present work.

(5) A. San Pietro, *J. Biol. Chem.*, **217**, 579 (1955).

(6) M. Marti, M. Viscontini, and P. Karrer, *Helv. Chim. Acta*, **39**, 1451 (1956). This publication appeared after our work had been completed.

(7) J. W. Huff, *J. Biol. Chem.*, **167**, 151 (1947).

(8) R. M. Burton and N. O. Kaplan, *J. Biol. Chem.*, **206**, 283 (1954).

(9) R. M. Burton and N. O. Kaplan, *J. Biol. Chem.*, **211**, 447 (1954).

(10) H. S. Mosher, *Heterocyclic Compounds*, edited by R. C. Elderfield, Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 415.

(11) N. O. Kaplan, S. P. Colowick, and C. C. Barnes, *J. Biol. Chem.*, **191**, 461 (1951).

(12) E. M. Kosower, *J. Am. Chem. Soc.*, **77**, 3883 (1955).

(13) A. G. Anderson and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958).

TABLE I  
BASE-INDUCED CHANGES IN THE ULTRAVIOLET SPECTRA OF  
MODEL COMPOUNDS OF DPN IN 95% ETHANOL

Compound	$\lambda_{\max}$ (m $\mu$ ) in Ethanol	$\lambda_{\max}$ (m $\mu$ ) in Basic Ethanol <sup>a</sup>
1-Benzyl-3-carbamoylpyridinium chloride	266	259, 318
1-n-Propyl-3-carbamoylpyridinium bromide	266	259, 315
1-Benzyl-3-carbomethoxy-pyridinium chloride	264	258, 316 <sup>b</sup>
1-Benzyl-3-acetylpyridinium chloride	264	271, 323
1-Benzyl-3-(N-phenylcarbamoyl)pyridinium chloride	End absorption	260-275, 325
1-Benzylpyridinium chloride	259	259

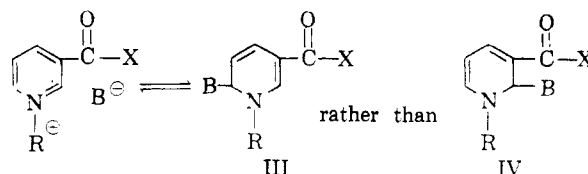
<sup>a</sup> One drop (about 0.04 ml.) of 3*N* aqueous sodium hydroxide added to the ethanolic solution of the compound in a 1-cm. Cary cell. <sup>b</sup> These peaks were unstable and eventually disappeared, leaving the 264 m $\mu$  maxima found in neutral solution. This behavior probably is due to hydrolysis to the zwitter ion, which is not attacked by base to an observable extent.

A reasonable explanation of the spectral changes found is the addition of a basic species (*e.g.*, ethoxide ion) to the ring in a reversible process. If so, the band at the shorter wave length (*ca.* 260 m $\mu$ ) would be the (displaced) absorption of the pyridinium ion. Also, increasing the basicity of the solution would be expected to increase the ratio of the intensity of the long wave length peak (314-325 m $\mu$ ) to that of the short wave length peak. This was found to occur. Similar spectral changes were observed with 1-benzyl-3-carbamoylpyridinium chloride and 1-benzyl-3-acetylpyridinium chloride in water, although the solutions had to be considerably more basic to give ratios of intensities comparable in magnitude to those obtained in ethanol. This is in keeping with the postulated equilibrium since the higher dielectric constant of water would cause a displacement in favor of the more ionic species (substituted pyridinium hydroxide) rather than the covalently bonded pseudo base.

It was noted that the long wave length absorption bands were 35-48 m $\mu$  shorter than those of the corresponding 1,4-dihydro compounds. This was in contrast to the results cited above for products obtained with other anions and suggested that the addition of the ethoxide or hydroxide ion did not take place at the 4-position. Of the two other likely possibilities (2 and 6), the 6-position was judged the more probable (III) since addition at position 2 would result in a chromophore having a nitrogen atom conjugated through two double bonds to a carbonyl (IV) and this would be expected<sup>14</sup> to absorb at considerably longer wave lengths than those observed. It is possible that with

(14) K. Bowden, E. A. Braude, E. R. H. Jones, and B. Weedon, *J. Chem. Soc.*, 45 (1946).

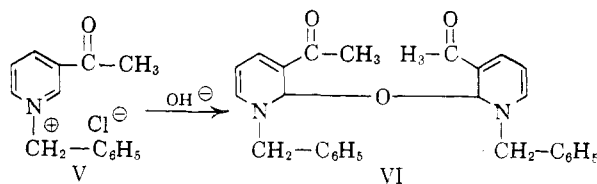
other substituted pyridinium salts, including those with different substituents in the 3-position, addition may occur predominantly, or even solely, at the 2-position. This would account for the formation



of different  $\alpha$ -pyridones as the main products from, for example, the ferricyanide oxidation of the quaternary salts of nicotinic acid and nicotinamide.<sup>10,15</sup> The selection of the 6-position in the present case is in opposition to the postulated formation (on the basis of the wave length of absorption) of a pseudo base of DPN by reaction at the 4-position.<sup>11</sup>

The finding that the spectrum of 1-benzylpyridinium chloride was unchanged in basic ethanol or in 3*N* aqueous sodium hydroxide is in agreement with the conductivity studies of Hantzsch and Kalb<sup>16</sup> who found no evidence of pseudo base formation by quaternary pyridinium salts. Thus apparently the presence of a substituent capable of imparting resonance stabilization to the pseudo base by conjugation with the ring nitrogen causes a significant increase in the stability of the product relative to that of the quaternary salt.

When the yellow solid obtained from the action of sodium hydroxide on 1-benzyl-3-acetylpyridinium chloride (V) in aqueous solution was treated with acid, V was recovered in quantitative yield. This result was that expected from a pseudo base and efforts were made to characterize the compound. The material was stable in a refrigerator but darkened at room temperature. It could not be crystallized or otherwise further purified. Elementary analysis showed, however, that it was most probably not the pseudo base but rather a dimolecular ether of it, possibly VI. Precedent for this structure is found in analogous derivatives of



other nitrogen heterocycles<sup>16,17</sup> and in the product of the reaction of the tropylium cation with base.<sup>18</sup>

(15) W. Holman and C. Wiegand, *Biochem. J.*, 43, 423 (1948); H. Bradlow and C. Vanderwerf, *J. Org. Chem.*, 16, 73 (1951); J. W. Huff, *J. Biol. Chem.*, 171, 639 (1947).

(16) A. Hantzsch and M. Kalb, *Ber.*, 32, 3109 (1899).

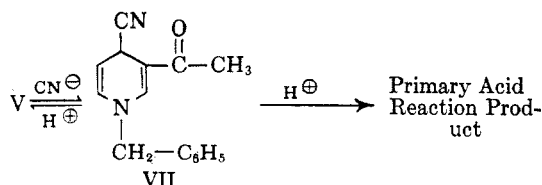
(17) J. G. Aston and P. Lasselle, *J. Am. Chem. Soc.*, 56, 426 (1934); W. La Coste, *Ber.*, 15, 186 (1882); J. G. Aston, *J. Am. Chem. Soc.*, 53, 1448 (1931).

(18) W. E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, 76, 3203 (1954).

To our knowledge no other example in the pyridine series has been reported.

Just as the addition of ethoxide or hydroxide ion to form the pseudo base was postulated from the position of the ultraviolet absorption maximum to take place at the 6-position, the absorption of the ether at 278 and 351  $m\mu$  (dioxane)<sup>19</sup> suggested the 2-position for the attachment of the ether bridge. A second possibility would be that the rings are joined through the oxygen at the 4-positions. This might also account for the band at 351  $m\mu$ , though 1-benzyl-3-acetyl-1,4-dihydropyridine is known to absorb at 371  $m\mu$  in ethanol.<sup>13</sup> The peak at 278  $m\mu$  is less easy to explain. It seems unlikely that this represents pyridinium ion since the latter would be expected to absorb nearer to 270  $m\mu$  and, in addition, ionization would not be particularly favored in dioxane. When the dimolecular ether was dissolved in ethanol the initial absorption at 270 and 362  $m\mu$  was rapidly replaced by the maxima of the ethoxide addition compound (323  $m\mu$ ) and the pyridinium alcoholate (270  $m\mu$ ), the intensity of which increased with time. The formation of the latter products can be readily explained from either VI or the 4-isomer by displacement *via* nucleophilic attack at the 6-position. Whether the initial absorption at 270  $m\mu$  in ethanol represents some immediate ionization of the ether or corresponds to the peak at 278  $m\mu$  in dioxane (if this is not caused by ionization) is not known. Treatment of the dimolecular ether with acid regenerated the original pyridinium salt.

The reaction with cyanide ion was also investigated and found to alter the spectra of aqueous solutions of the model compounds. In particular, treatment of a dilute solution of 1-benzyl-3-acetylpyridinium chloride (V) with a small amount of sodium cyanide resulted in the gradual disappearance of the absorption at 265  $m\mu$  and concurrent growth of a peak at 355  $m\mu$ . Acidification of the solution caused the loss of the maximum at 355  $m\mu$  and the appearance of a new peak at 298  $m\mu$ <sup>20</sup> along with increased intensity at 270  $m\mu$ . When excess cyanide ion was then introduced, the 298  $m\mu$  peak was unchanged, some increase in absorption occurred at 355  $m\mu$  and the intensity at 270  $m\mu$

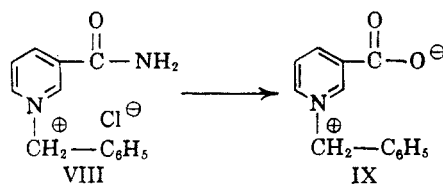


(19) These maxima correspond closely to those of a product obtained from the x-ray induced reduction of 1-methyl-3-carbamoylpyridinium iodide by G. Stein and G. Stiasny, *Nature*, 176, 734 (1955) which was thought to be the 1,2- or 1,6-dihydro compound.

(20) This behavior is very similar to that associated with the so-called primary acid reaction on the 1,4-dihydro forms of the model compounds.<sup>13</sup>

decreased. These results are consistent with the formation of VII and the conversion of this by acid both back to V and to the product of the "primary acid reaction." VII was isolated as a relatively stable crystalline material which showed, in ethanol, a single absorption maximum at 351  $m\mu$ . Thus the compound is essentially completely covalent whereas the corresponding product (II) obtained by Karrer<sup>6</sup> apparently is partially ionized in ethanol since it displayed a peak at 265  $m\mu$  (as well as at 340  $m\mu$ ) which was absent in dioxane solution. Explanation for this difference is afforded by the stronger electron-withdrawing resonance interaction with the ring unsaturation of the acetyl group as compared with the carbamoyl group.

Observations of the action of base on aqueous solutions of 1-benzyl-3-carbamoylpyridinium chloride (VIII) at room temperature indicated hydrolysis of the amide group. The odor of ammonia was evident soon after addition of the base and, after two hours, a *ca.* 40% yield of zwitter ion (IX), characterized by comparison with a sample prepared by quaternization of nicotinic acid, was isolated. After a reaction period of only 10 min. a 15% yield of IX was realized. Extraction of the reaction mixture after three minutes gave only a yellow-brown resinous product (30–40%) which showed absorption at 262 and 350  $m\mu$  and thus may have arisen from attack on the ring. Its nature discouraged further investigation.



#### EXPERIMENTAL<sup>21,22</sup>

*Pyridinium salts.* 1-Benzyl-3-carbamoylpyridinium chloride, 1-*n*-propyl-3-carbamoylpyridinium bromide, 1-benzyl-3-carbomethoxypyridinium chloride, 1-benzyl-3-acetylpyridinium chloride, and 1-benzyl-3-(*N*-ethyl-*N*-phenylcarbamoyl)-pyridinium chloride were prepared from the corresponding 3-substituted pyridines and benzyl or *n*-propyl halides as previously described.<sup>13</sup>

*Dimolecular pseudo base ether from 1-benzyl-3-acetylpyridinium chloride.* To a solution of 1.24 g. (5 mmoles) of 1-benzyl-3-acetylpyridinium chloride in 200 ml. of water was added 50 ml. of 0.2*N* sodium hydroxide. After 45 min. the lemon yellow solid which had precipitated was collected in a sintered glass funnel, washed four times with 5-ml. portions of water, and placed while still wet over phosphorus pentoxide in a desiccator under vacuum and in a refrigerator. The solid came to constant weight (1.02 g., 93%) in 6 hr. It sintered at 74°, darkened and softened at 80–95° and melted at 95–98°. A qualitative ultraviolet spectrum showed maxima ( $m\mu$ ) at 277 and 346 (chloroform), and 278 and 350

(21) Melting points are corrected unless otherwise stated. Boiling points are uncorrected. Elementary analyses were performed by B. J. Nist and C. H. Ludwig.

(22) Ultraviolet spectra were determined with a Cary Model 115 Recording Spectrophotometer and/or a Beckman Model DU Spectrophotometer.

(dioxan). An ethanol solution exhibited maxima at 270 and 362  $m\mu$  immediately after preparation but after a few minutes the peaks were at 270 and 323  $m\mu$  and both increased in intensity with time.

*Anal.* Calcd. for  $C_{23}H_{23}N_2O_3$ : C, 76.35; H, 6.39; N, 6.36. Found: C, 76.73; H, 6.20; N, 6.06.

*1-Benzyl-3-acetylpyridinium chloride from the dimolecular pseudo base ether.* Hydrogen chloride was passed into a solution of the dimolecular pseudo base ether (229 mg., 0.52 mmole) in 20 ml. of methanol for one minute. Evaporation of the solvent left a brown solid (235 mg., 91%) the infrared spectrum of which was identical with that of 1-benzyl-3-acetylpyridinium chloride. Recrystallization from methanol-ethyl acetate gave a 64% recovery of tan crystals which melted at 183.5–184° alone and when mixed with an authentic sample.

*1-Benzyl-3-acetyl-4-cyano-1,4-dihydropyridine* (VII). A solution of 3.25 g. (0.05 mole) of potassium cyanide in 10 ml. of water was added to a solution of 1.24 g. (0.005 mole) of 1-benzyl-3-acetylpyridinium chloride in 10 ml. of water. There was an immediate separation of a yellow oil. The supernatant solution was decanted from the oil and the latter washed with water and taken up in 5 ml. of hot ethanol. The yellow needles (0.87 g., 77%) which separated from the cooled solution melted at 114–115.5° with decomposition. An ethanol solution showed absorption at 351  $m\mu$  ( $\epsilon$  9,500).

*Anal.* Calcd. for  $C_{15}H_{14}N_2O$ : C, 75.60; H, 5.92. Found: C, 75.61; H, 5.99.

*1-Benzylpyridinium-3-carboxylate* (IX). 1-Benzyl-3-carboxypyridinium chloride (2.49 g., 0.01 mole) was dissolved in 100 ml. of 0.1*N* carbonate-free sodium hydroxide. The odor of ammonia was soon evident. After 2 hr. the solution was extracted with three 50-ml. portions of chloroform and then seven 50-ml. portions of 1-butanol. The combined butanol extracts were washed with 25 ml. of water, dried over sodium sulfate, and concentrated to a volume of 20 ml. Addition of a large excess of ether precipitated an orange solid (1.29 g., 60%). Purification by extraction with cold chloroform, chromatography on acid-washed alumina with methanol, treatment with Norit, and recrystallization from ethanol-ethyl acetate gave 0.8 g. (37.5%) of IX as colorless crystals, m.p. 183–184.5° dec.;  $\lambda_{max}$  (ethanol) 264  $m\mu$ . Treatment of this product with hydrochloric acid gave 1-benzyl-3-carboxypyridinium chloride, identical with a sample prepared from benzyl chloride and nicotinic acid. Acidification of the aqueous layer from the 1-butanol extraction with hydrochloric acid, extraction with chloroform and then 1-butanol (two 60-ml. portions), and evaporation of the butanol solution afforded 227 mg. of somewhat impure 1-benzyl-3-carboxypyridinium chloride.

SEATTLE 5, WASH.

[CONTRIBUTION FROM THE ROHM & HAAS CO.]

## Nitrile Groups. V. Substituted Aminoacetamidoximes<sup>1</sup>

CHARLES S. HOLLANDER, ROBERT A. YONCOSKIE, AND PETER L. DE BENNEVILLE

Received February 26, 1958

The reaction of substituted aminoacetonitriles with hydroxylamine hydrochloride gave, after neutralization, substituted aminoacetamidoximes. The reaction is interpreted to reflect activation of the nitrile group by the ammonium ion. *N*-Benzyl-*N*-cyanomethyl-*N,N*-dimethylammonium chloride similarly gave a quaternary ammonium substituted acetamidoxime by reaction with free hydroxylamine. Aminonitriles derived from isobutyraldehyde and from cyclohexanone failed to give the reaction, and instead amine displacement reactions occurred. Tetrakis(cyanomethyl)ethylenediamine gave the corresponding tetrakisamidoxime.

Other papers in this series have shown that a nitrile group in a position near to an electron-withdrawing substituent undergoes reaction with amines with unusual ease.<sup>1,2</sup> The reactions to be described illustrate how a proximate cation (substituted ammonium group) favors the addition of hydroxylamine to the nitrile function.

The usual conditions for the formation of amidoximes require treating the corresponding nitrile with free hydroxylamine in aqueous alcoholic solution for an extended period of time. It is significant that unusually rapid reactions have been reported for succinonitrile,<sup>3</sup> cyanogen,<sup>4</sup> and tribromoacetonitrile.<sup>5</sup>

(1) For the previous paper in this series, see P. L. de Benneville, C. L. Levesque, L. J. Exner, and E. Hertz, *J. Org. Chem.*, **21**, 1072 (1956).

(2) (a) L. J. Exner, M. J. Hurwitz, and P. L. de Benneville, *J. Am. Chem. Soc.*, **77**, 1103 (1955); (b) M. J. Hurwitz, L. J. Exner, and P. L. de Benneville, *J. Am. Chem. Soc.*, **77**, 3251 (1955).

(3) F. Sembritzki, *Ber.*, **22**, 2958 (1899).

(4) E. Fischer, *Ber.*, **22**, 1930 (1899).

(5) W. Steinkopf and H. Grünupp, *Ber.*, **41**, 3571 (1908).

When, in this study, hydroxylamine was added to substituted aminoacetonitriles, it was not necessary, and not desirable, to free the hydroxylamine from its hydrochloride by the addition of a base. The reaction of the nitrile with hydroxylamine hydrochloride proceeded rapidly with evolution of heat to give the hydrochloride of the corresponding aminoacetamidoxime. The addition of sodium carbonate in equivalent amount then freed the amidoxime for isolation. The data for a number of aminoacetamidoximes are given in Table I.

The aminonitrile is believed to take part in the reaction in its ammonium form, by equilibration with the hydroxylamine hydrochloride. The provision in this way of a highly electron-withdrawing substituent then activates the nitrile group. This substituent could also be provided in the form of a quaternary ammonium ion, in which case it would be necessary to add base to free the hydroxylamine for reaction. *N*-Benzyl-*N,N*-dimethyl-*N*-cyanomethylammonium chloride was prepared, and to it was added an equivalent amount of hydroxylamine