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REACTIONS OF NUCLEOPHILES WITH PYRIDINIUM IONS.

CYANIDE ION REACTIONS WITH SOME PYRIDINIUM IONS.

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The reaction of substituted pyridinium ion with a nucleophile usually occurs with the formation of a 1,2-1,6-, or 1,4-dihydropyridine.[1] These dihydropyridines correspond in structure to the proposed intermediates in nucleophilic substitution of nitrobenzenes and heteroaromatics.[2] Due to the stability of these dihydropyridines the reaction of nucleophiles with pyridinium ions offers an excellent substrate for the investigation of nucleophilic substitution reactions since the addition and elimination steps can be studied independently.

In an attempt to summarize the information recorded in the literature relative to the reaction of nucleophiles with pyridinium ions, Kosower related the position of attack of a nucleophile on a pyridinium ion with the possible intermediacy of a "charge transfer complex" in the reaction

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mechanism.[3] Thus reactions with nucleophiles which have a low ionization (oxidation) potential were presumed to proceed *via* a charge transfer complex and form 1,4-dihydropyridines. In view of the structural assignment of 1,4-dihydropyridines to the products of reactions of cyanide ion with various substituted pyridinium ions it was assumed that this reaction proceeded *via* a charge transfer complex, and this mechanistic path was consistent with the orientation of the cyano group in the product.[4] Since the cyano addition reactions have been shown to be reversible[5], the previous results suggested that the 1,4-dihydropyridine was the product of kinetic *and* thermodynamic control. Recent investigation of this reaction in this laboratory clearly demonstrated that the reaction of cyanide ion with a number of pyridinium ions occurs with initial attack predominantly at the 6-position of the pyridinium ion.* This initial product is slowly converted by recrystallization or standing in solution in alcohol to an equilibrium mixture composed largely of the 1,4-dihydropyridine. In chloroform the conversion is very slow and in carbon tetrachloride the decomposition of the 1,6-dihydropyridine does not take place readily.

On mixing alcoholic solutions of the pyridinium ion and cyanide ion the ultraviolet absorption of the pyridinium ion rapidly disappears and new bands appear. Using I as an

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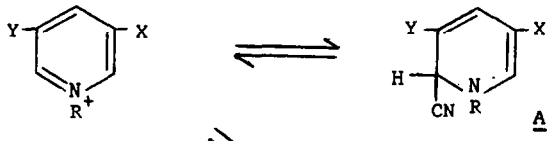
*The reaction of cyanide ion with 1-alkoxy pyridinium ions, probably an irreversible reaction, usually gives 2- or 6-substituted pyridines.[6]

example: Py^+, 287 mμ (ε 3.72); $Py^+ + CN^-$, 262 (4.18), 319 (4.04); on standing 60 min. 263 (3.61), 343 (4.04). Most significant is the absorption band in the 260-280 mμ region which must be associated with the 1,6-dihydropyridine chromophore.[4,5,7] Some of the reactions gave evidence of formation of the 1,2-dihydropyridine isomer by showing a small but definite absorption band in the visible region (400-430 mμ) of the spectrum. As the solutions were allowed to stand the spectra changed further with a loss of the 260-280 mμ band and a shift of the 300-350 mμ band. These changes are indicative of the formation of the 1,4-dihydropyridine system. Since clean isosbestic points were observed in the spectra, it is evident that simple equilibria were involved.



A

I. X= $COOC_2H_5$
Y= Br
R= CH_3-

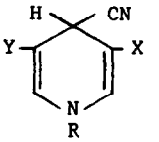
Y= H
R= CH_3-, $C_6H_5CH_2$-, or $2,6\text{-}Cl_2C_6H_5CH_2$-

II. X= C_6H_5CO-

III. X= CH_3CO-

IV. X= CN

V. X= $-CONH_2$



B

To support the structural assignment of the kinetically controlled products, aqueous solutions of cyanide ion and 1-methyl-5-bromo-3-ethoxycarbonylpyridinium bromide (I) were mixed and the oily cyanide-addition product which precipitated was dissolved in carbon tetrachloride and fractionally recovered by evaporation of the carbon tetrachloride to give the corresponding, crystalline 1,6-dihydropyridine (IA)* (λ_{max} 262, 320 mμ).

A solution of the 1,6-dihydropyridine (IA) in chloroform was slowly converted to a mixture of IA and 5-bromo-3-ethoxycarbonyl-4-cyano-1-methyl-1,4-dihydropyridine (IB) (λ_{max}^{MeOH} 343 mμ). The rearrangement could be followed easily by the changes in the n.m.r. spectrum with time. The assignment of bands corresponds well with those recently reported for similar compounds.[8] The chemical shifts of the protons in the spectra are consistent only with the structures indicated,** and the change with time is indicative of a conversion of the 1,6-dihydropyridine (IA) to the isomer, the 1,4-dihydropyridine (IB), of greater stability under these conditions. Similar observations were made with the products from the reactions of 1-benzyl-3-cyanopyridinium bromide (IV) and 1-benzyl-3-benzoylpyridinium bromide (II) with cyanide ion.

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*All isolated products gave correct elemental analyses.

**The correctness of the assignment of the 1,6-dihydropyridine structure to IA is supported by the fact that the vinyl hydrogens appear at lower field than those of the 1,4-dihydro isomer IB, consistent with the observation that the proton cis to an acid carbonyl is more deshielded than a trans or other hydrogens.[9] The sp^3 proton in the 1,6-dihydropyridine is at lower field than the 1,4-dihydropyridine as expected.[8]

The reaction of cyanide ion with most pyridinium ions by attack of a position adjacent to the quaternary nitrogen and subsequent rearrangement to the 4-position suggests that this reaction is controlled by the same factors which govern the orientation of attack of most nucleophiles with pyridinium ions, the relative electron density at the carbon under attack. The cyanide ion reaction differs from those which lead largely to 1,2- or 1,6-dihydropyridines only in being reversible. Thus we propose that the reaction of cyanide ion with 3-substituted-pyridinium ions should be considered as leading to the 1,6-dihydropyridine by a kinetically controlled step, but due to the reversibility of the reaction, this kinetically formed product is converted to the 1,4-dihydropyridine due to the greater thermodynamic stability of the latter under most reaction conditions. These findings eliminate the necessity, with cyanide ion at least, of postulating that some nucleophilic reactions proceed via a charge transfer complex while others form sigma bonds from a tight ion pair.

The apparent inconsistency in the structure of the product of cyclopentadienyl anion with pyridinium ion[10] may result from a lack of reversibility in the initial attack with the procedure of Hafner.[11] If the rate of oxidation of the dihydropyridine is greater than the reverse of the nucleophilic attack, products from attack at the 2-position would be expected. The importance of steric factors in directing the position of nucleophilic attack on pyridinium ions is indicated elsewhere.[12]

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