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THE REACTION OF CYANOPYRIDINES WITH SODIUM BOROHYDRIDE IN APROTIC SOLVENTS

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In previous papers[1], the authors have reported the reduction of 2-, 3-, or 4-cyanopyridine with sodium borohydride in protic solvent and we found that reduction of pyridine nucleus took place for 3-cyanopyridine, while in case of 2- and 4-cyanopyridines only the cyano group was reduced to the corresponding amine without nuclear reduction.

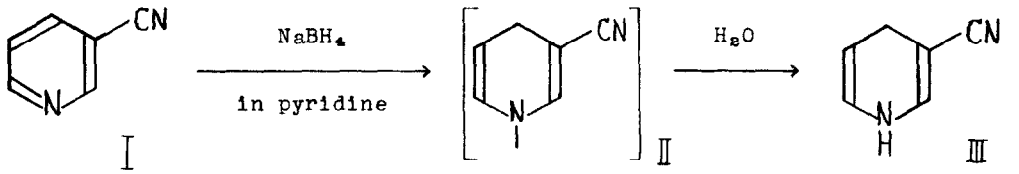
This paper deals with the reduction of 2-, 3-, or 4-cyanopyridine with sodium borohydride in aprotic solvents such as pyridine and diglyme. Sufficiently different results from those in protic solvent were obtained.

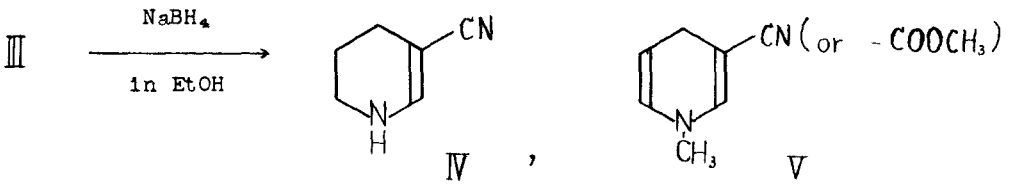
General Procedure——A solution of cyanopyridine (5.2 g, 0.05 mole) and sodium borohydride (5.7 g, 0.15 mole) in anhydrous pyridine (150 ml) or diglyme (100 ml) was refluxed for 8 hrs. After the reaction was completed, the solvent was removed in vacuo under N_2 atmosphere. The residue was dissolved in water, an aqueous layer obtained was extracted with chloroform, which was washed with NaCl saturated water and dried over anhyd. Na_2SO_4. Evaporation of the solvent under N_2 atmosphere in vacuo gave the residue which was purified by column chromatography.

Reduction of 3-Cyanopyridine

Under the procedure described above, 3-cyanopyridine I was easily reduced in 52% yield to a dihydro compound (mp. 74-75°C), 3-cyano-1,4-dihydropyridine III, which showed the following spectral data, λ_{max} (EtOH) 330 mμ (ε 5600) ; ν_{max}

(KBr) 3380 (NH), 2220 (C≡N), 1690 (C=C), 1630 cm^{-1} ($\rangle$N-CH=$\overset{|}{C}$-CN) ; n.m.r., τ ($CDCl_3$) 3.41 (1H), 4.20 (2H. This 2H was decreased to 1H when N-H was deuterated), 5.40 (1H), 6.90 (2H). 3-Cyano-1,4,5,6-tetrahydropyridine IV was not obtained. It was the main product in the reduction of I with sodium borohydride in ethanol[1a]. However, III was again reduced in ethanol with sodium borohydride to give IV.





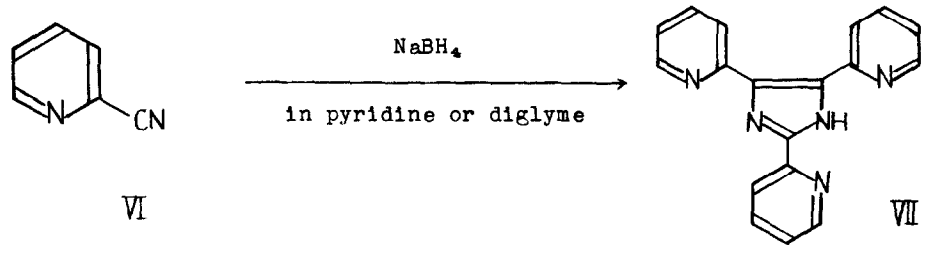
In this reduction, the first attack of hydride anion was readily proven to be in position 4 of I and further reduction of dihydropyridine (II) did not proceed in aprotic solvent. On the structure of II, it is not clear now whether ring nitrogen forms sodium salt or boron derivative. However, III which has N-H bond, was found to be reduced in protic solvent. It is of interest to compare these findings with reports that on the reduction of quarternary pyridinium salts, $BH_4^{\ominus}$ anion first attacks in position 2 or 6 of pyridine nucleus[2], and N-methyl-1,4-dihydropyridine derivatives V are not reduced in protic solvent with sodium borohydride[3]. The explanation of these differences will be published soon.

The synthesis of 3-substituted 1,4-dihydropyridine (III) is very difficult except this method.

Reduction of 2-Cyanopyridine

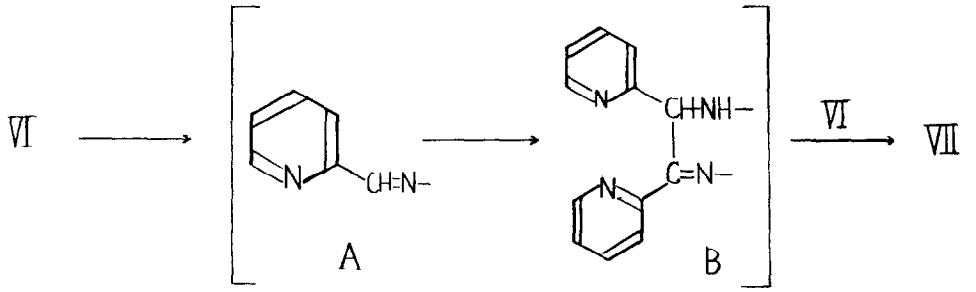
The reduction of 2-cyanopyridine VI was examined by the conditions described in general procedure. The expected product, 2-aminomethylpyridine was

not found in the reaction mixture[1b], but surprisingly, although in low yield (about 10%), 2,4,5-tris(2-pyridyl)imidazole VII (mp. 113-4°C, $C_{18}H_{13}N_5$) was obtained and yield was improved up to 20% yield when the reaction was performed in diglyme at 100°C. The structure of compound VII was confirmed by the following spectral data ; λ_{max} (EtOH) 320 mμ (ε 51800), ν_{max} (KBr) 3430 (NH), 3050 (aromatic CH), 1587 cm^{-1} (aromatic C=C) ; n.m.r., τ(CDCl$_3$) 1.45 (4H), 1.80 (2H), 2.35 (3H), 2.80 (3H) ; mass spectrum, m/e 299 (M^+). The structure was also confirmed by the chromic anhydride oxidation which gave α-picolinamide in poor yield[4].



VI VII

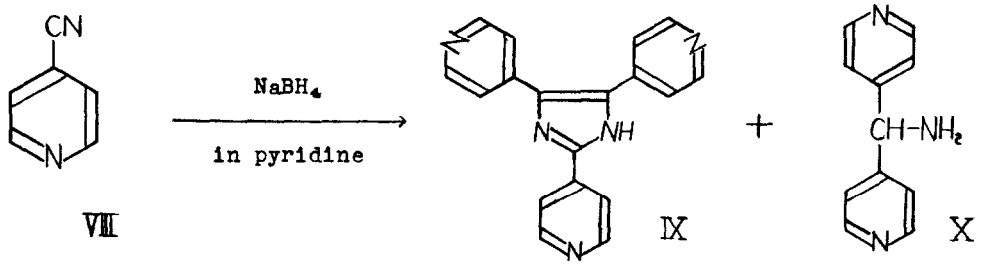
The mechanism of this reaction is not clearly understood, but it might be assumed that the benzoin type condensation of two moles of aldimine A which is the first reduced product on the nitrile group, would give the compound B and further reaction of B with one mole of VI could form VII[5].



Reduction of 4-Cyanopyridine

In this case, the definite reduction product was not obtained. However, two compounds could be isolated, with difficulty, from the brown reaction mixture by the column chromatography, that is, 2,4,5-tris(4-pyridyl)imidazole IX

(mp. >300°C, $C_{18}H_{18}N_6$) and 1,1-bis(4-pyridyl)methylamine X (mp. 92-93°C, $C_{11}H_{11}N_3$) in yields of 2.1% and 1.5%, respectively. The spectral data, compound IX, λ_{max} (EtOH) 315 mμ (ε 54600) ; ν_{max} (KBr) 3440 (NH), 3040, 2980 (aromatic CH), 1605 cm^{-1} (aromatic C=C) ; n.m.r., τ(CF_3COOH) 1.07 (8H), 1.57 (4H) ; mass spectrum, m/e 299 (M^+). Compound X, λ_{max} (EtOH), 265 (ε 2900), 278 mμ (ε 2240) ; ν_{max} (KBr) 3380 (NH_2), 3000 (aromatic CH), 1595 cm^{-1} (aromatic C=C) ; n.m.r., τ ($CDCl_3$) 1.41 (4H), 2.65 (4H), 4.80 (1H), 7.97 (2H. This peak vanished by addition of D_2O) ; mass spectrum, m/e 185 (M^+). The expected 4-aminomethylpyridine which was obtained in the reduction using ethanol as a solvent[1b] was not detected.



VIII IX X

Studies on the scope and limitation of this reduction on other cyano-substituted heterocycles are in progress.

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