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CATALYTIC HYDROGENATION OF PYRIDINIUM SALTS

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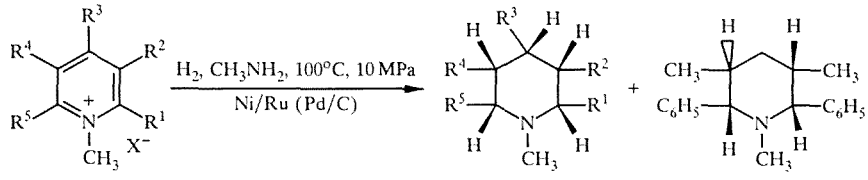
Catalytic hydrogenation of polysubstituted pyridinium salts leads to piperidines and their condensed analogs. The spatial properties and conformational properties of the saturated azaheterocycles have been determined by ^{13}C NMR spectroscopy. It was shown that hydrogenation of the pyridinium salts occurs stereoselectively to form cis isomers in most cases.

Quaternary pyridinium salts are known to undergo ready reduction (including catalytic [1-4]). There are literature reports concerning basic hydrogenation of mono- and di-substituted pyridinium salts.

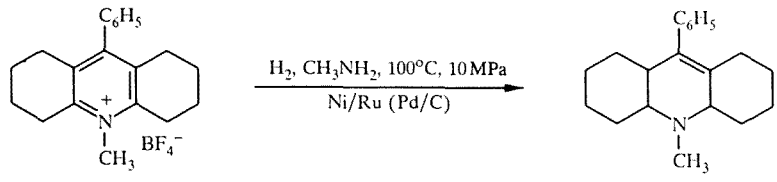
This work was undertaken to study the behavior of polyaryl-(alkyl)pyridinium salts under catalytic hydrogenation conditions. We have studied the hydrogenation of the tetra-, penta-, and hexa-substituted salts I-VII and shown that the reaction proceeds successfully at 100°C with 10 MPa pressure of hydrogen in the presence of nickel modified by ruthenium (or 10% palladium on carbon), and an equimolar amount of methylamine. The piperidines VIII-X, perhydroquinolines XI, XII, and perhydrocaridine XIII were obtained in good yields (78-96%).



I – VI VIII – XIII Xa

I, VIII $R^1 = R^3 = R^5 = C_6H_5$; II, IX $R^1 = R^3 = R^5 = C_6H_5$, $R^2 = CH_3$; III, X $R^1 = R^5 = C_6H_5$, $R^2 = R^4 = CH_3$; IV, XI $R^1 = C_6H_5$, $R^4 + R^5 = -(CH_2)_4-$; V, XII $R^1 = R^3 = C_6H_5$, $R^4 + R^5 = -(CH_2)_4-$; VI, XIII $R^1 + R^2 = R^4 + R^5 = -(CH_2)_4-$; where not indicated R = H; $X^- = BF_4^-$; VI $X^- = I^-$

A peculiarity of the hydrogenation of 9-phenyl-10-methyl-sym-octahydroacridine tetrafluoroborate (VII) is the formation of a product with an incompletely hydrogenated pyridine ring, viz. 9-phenyl-10-methyl-$\Delta^{9,9a}$-dodecahydrocridine (XIV), in 68% yield.



VII XIV

Retention of the double bond is possible due to conjugation with the phenyl group and through steric shielding.

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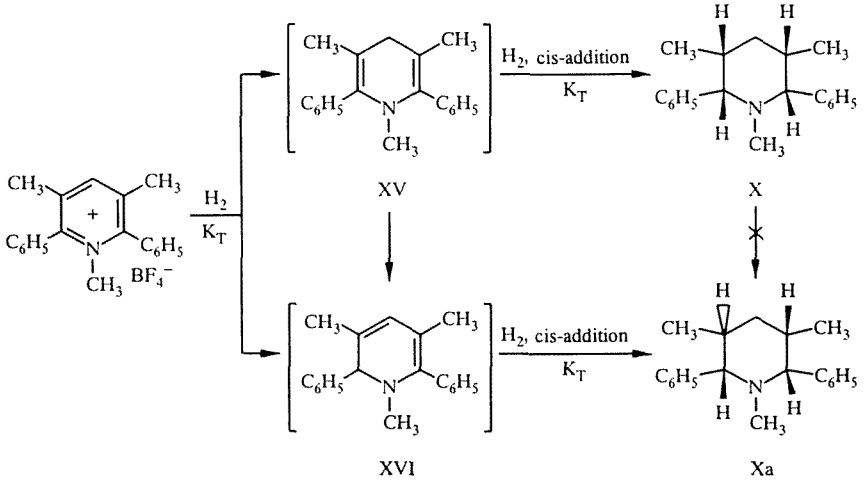
TABLE 1. ^{13}C NMR Spectral Data for Piperidines VIII-XIV

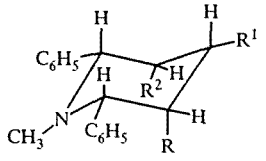
Compound	Chemical shift, ppm						
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	N—CH_3	Others
VIII	70,80	44,85	42,52	44,85	70,80	41,89	
IX	74,88	45,84	42,70	34,55	71,42	42,28	7,61 ($C_{(3)}$—CH_3)
X	74,50	34,89	38,88	34,89	74,50	43,85	18,26 ($C_{(3)}$—CH_3, $C_{(5)}$—CH_3)
Xa	73,12	35,29	41,12	32,19	78,62	43,00	14,31 ($C_{(3)}$—CH_3), 19,84 ($C_{(5)}$—CH_3)
XI	71,58	32,54	31,14	26,60	27,30	39,89	19,97 ($C_{(7)}$), 30,76 ($C_{(8)}$), 63,38 ($C_{(9)}$), 37,68 ($C_{(10)}$)
XII	71,15	35,82	45,76	21,05	26,18	39,50	20,18 ($C_{(7)}$), 30,84 ($C_{(8)}$), 64,53 ($C_{(9)}$), 44,50 ($C_{(10)}$)
XIII	22,68	25,66	25,98	25,98	25,66	39,20	22,68 ($C_{(7)}$), 32,34 ($C_{(8)}$), 32,34 ($C_{(1)}$), 26,85 ($C_{(9)}$), 61,03 ($C_{(4a)}$, $C_{(10a)}$), 37,73 ($C_{(8a)}$, $C_{(9a)}$)
XIV	—	—	—	—	19,78	38,59	135,62 ($C_{(9)}$), 133,92 ($C_{(9a)}$), 66,63 ($C_{(4a)}$), 58,54 ($C_{(10a)}$), 44,73 ($C_{(8a)}$), 35,47, 30,38, 29,47, 28,31, 27,83, 26,55, 25,68 ($C_{(1)}$...$C_{(5)}$, $C_{(7)}$, $C_{(8)}$)

At lower temperature (50-70°C), the yields of the piperidine bases are decreased to 55-70%. Exchange of nickel modified by ruthenium for 10% palladium on carbon has no effect on the yield of piperidines or cyclanopiperidines. In the absence of methylamine, hydrogenation of α,α'-diarylpyridinium salts I-III lead to formation of mixtures of non-nitrogenous products of ring opening. The cause is apparently hydrogenolysis of the C—N bond to form substituted piperidinium salts containing a tertiary amino group at the benzylic carbon atom [5].

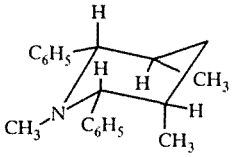
Study of the stereoisomeric composition of the hydrogenation products showed that the reaction occurs stereoselectively to form cis-isomers. Only in the case of 1,3,5-trimethyl-2,6-diphenylpyridinium tetrafluoroborate was a cis—trans—trans isomer Xa noted with the cis—cis—cis isomer X. Formation of the cis—cis isomers based on X can arise as a result of cis addition of hydrogen to the intermediate 1,4-dihydropyridine XV. Formation of Xa may result from isomerization of initially formed, sterically hindered all cis isomer. However, specific experiments have shown that isomerization of X to Xa does not occur under these reaction conditions (100°C, 10 MPa, Ni/Ru). It is likely that the cis—trans—trans isomer is formed by stepwise hydrogenation at the 2,3- and 4,5- bonds of the intermediate 1,2-dihydropiperidine (XVI), which is formed by initial reduction of the pyridinium ring C—N bond or as a result of migration of the double bond to the 1,4-dihydropyridine A.



The stereochemistry of the piperidines and cyclanopiperidines VIII-XIV was proved using ^{13}C NMR spectroscopy (Table 1). Assignment of signals was made using off resonance spectra and with the aid of increments taken from [6-9].



VIII – X

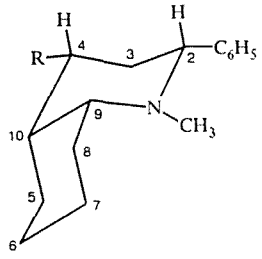


Xa

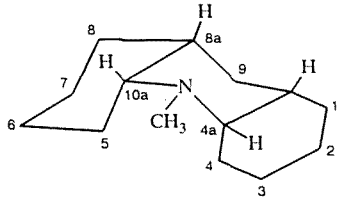
The number of signals in the spectrum of VIII points to the symmetry of the molecules and their position to the equatorial disposition of all the substitutents. The appearance of a high field signal at 7.61 ppm in the spectrum of IX confirms the axial orientation of the methyl group at position 3. This methyl group orientation causes a significant upfield shift of $C_{(5)}$ (34.55 ppm compared with 44.85 ppm in compound VIII).

The ^{13}C NMR spectrum of pure X contains five signals (besides those for the phenyl ring) pointing to its symmetry. The ^{1}H NMR spectrum has a doublet at 3.34 ppm assigned to an α-hydrogen atom. The spin–spin coupling $J_{2,3} = 3.78$ Hz is characteristic of cis related protons at $C_{(2)}$ and $C_{(3)}$. The high field shift for the $C_{(3)}$ and $C_{(5)}$ atoms in the ^{13}C NMR spectrum (34.89 ppm) points to an interaction with an axially oriented methyl groups. The data obtained showed X to have the configuration shown above.

Isomer Xa can be determined in a mixture with X. The protons on carbons $C_{(2)}$ and $C_{(6)}$ appear in the ^{1}H NMR at 3.34 and 2.61 ppm (doublets). The spin–spin interaction between $H_{(6)}$ and $H_{(5)}$ (9.8 Hz) points to their axial orientation. The ^{13}C NMR spectrum of Xa shows signals for an axial $C_{(3)}$ methyl at 14.31 ppm an equatorial $C_{(5)}$ methyl at 19.84 ppm. The interaction of $C_{(5)}$ with an axial CH_3 group causes a high field shift (32.14 ppm) when compared with atom $C_{(3)}$ (35.29 ppm), in the γ-position to which is configured an equatorial substituent. Thus Xa can be assigned the structure cis–trans–trans-1,3,5-trimethyl-2,6-diphenylpiperidine.



A



B

In agreement with known work [6], decahydroquinolines XI and XII have a cis fusion of rings and are stabilized in conformation A. According to spectral properties (see [10]), N-methylperhydroacridine XIII exists as the cis–syn–cis isomer and is fixed in conformation B.

The spectrum of XIV shows a signal at 19.78 ppm, pointing to a cis fusion of the carbo- and heterocycles. By an off resonance method it was shown that $C_{(4a)}$, $C_{(8a)}$, and $C_{(10a)}$ occurred at 66.63, 44.73, and 58.54 ppm respectively and the $N-CH_3$ group as a quartet signal at 38.59 ppm. The presence of the double bond was confirmed by the appearance of low field signals at 135.62 and 133.92 ppm (besides four peaks for the phenyl ring carbon atoms).

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were measured on Varian FT-80A and Bruker CXP-200 instruments using $CDCl_3$ solvent and TMS internal standard.

Pyridinium tetrafluoroborates I-V and VII were prepared by treatment of the corresponding pyrilium salts with excess methylamine in methanol. The iodide VI was synthesized by reaction of sym-octahydroacridine with methyl iodide.

TABLE 2. Parameters for the Synthesized Compounds

Compound	Empirical formula	Mp, °C	Yield, %	Compound	Empirical formula	Mp, °C	Yield, %
VIII	$C_{24}H_{25}N$	83...85	82	XII	$C_{22}H_{27}N$	117...118	80
IX*	$C_{25}H_{28}NCl$	261...263	96	XIII	$C_{14}H_{25}N$	55...57	78
X*[2]	$C_{20}H_{25}N$	85...86	85*[3]	XIV	$C_{20}H_{27}N$	62...63	68
XI	$C_{16}H_{23}N$	62...64	88				

*Compound separated and characterized as the hydrochloride.

*[2]mp given for the pure cis–cis–cis isomer of X.

*[3]Overall yield of X and Xa given. According to GLC, the yield of isomer X was 62% and of Xa 23%.

Hydrogenation of Pyridinium Salts I-VII. Into an autoclave of volume 150 ml there were added the pyridinium salt (0.01 mole), methanol (80 ml) saturated with methylamine (0.01 mole), and catalyst (Ni/Ru or Pd/C, 10% of the mass of substance). The initial hydrogen pressure was 10 MPa and the temperature 100°C. After 5-7 h the reaction mixture was cooled, the catalyst filtered off, and the methanol distilled off. Bases VIII-XIV were extracted with ether. After evaporation of ether, VIII, X-XIII were recrystallized from ethanol and XIV from ethyl acetate. By treatment with dilute HCl, base IX was converted to the hydrochloride which was recrystallized from ethanol. After removal of piperidine X, the remaining mixture of isomers X and Xa was an oil which could be purified on an Al_2O_3 column (activity grade III, eluent hexane). The yields and melting points for VIII-XIV are given in Table 2.

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