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Stereochemical Studies of the Electrolytic Reactions of Organic Compounds. IV.* Electrolytic Reduction of Optically-active 1-Pyridylalkanols to the Corresponding Substituted-alkyl Pyridines

Tsutomu NONAKA, Tetsuro OTA,** and Toshio FUCHIGAMI

Department of Electronic Chemistry, The Graduate School, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227

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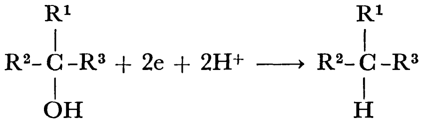
The mechanism of electrolytic reduction of 1-pyridylalkanol to the corresponding substituted-alkyl pyridine was examined by electrolyzing several optically-active 1-pyridylalkanols in an aqueous sulfuric acid solution in the vicinity of a mercury cathode. The alkyl pyridine from 1-(2-pyridyl)alkanol showed optical rotation, while that from 1-(4-pyridyl)alkanol was almost racemized.

Alcoholic hydroxyl groups are generally difficult to reduce electrolytically.[1–3] In a previous work,[4] it was found that 1-(2-pyridyl)- and (4-pyridyl)alkanols are electrolytically reduced to the corresponding substituted-alkyl pyridines in high yields and current efficiencies with a mercury cathode in an aqueous sulfuric acid solution. Also a tentative mechanism for the reductive elimination of the hydroxyl group of 1-pyridylalkanols was proposed on the basis of their adsorption on a cathode surface and the steric hindrance effect of their substituents. Namely, the two electrons required for the reduction were supposed to be introduced from the cathode to a carbon atom adjacent to the hydroxyl group following the route of the conjugated π-electron system of a pyridine nucleus.

In order to discuss the stereochemical aspects of the reaction mechanism, the starting 1-pyridylalkanol and the alkyl pyridine formed must be chiral. In this work, the three kinds of optically-active 1-pyridylalkanols (**1**, **2**, and **3**) studied are electrolytically reduced to the corresponding substituted-alkyl pyridines.



$$R^2\text{-}\underset{\displaystyle OH}{\overset{\displaystyle R^1}{C}}\text{-}R^3 + 2e + 2H^+ \longrightarrow R^2\text{-}\underset{\displaystyle H}{\overset{\displaystyle R^1}{C}}\text{-}R^3$$

1 : R^1=4-Pyridyl, R^2=Methyl, R^3=Ethyl
2 : R^1=4-Pyridyl, R^2=Methyl, R^3=Phenyl
3 : R^1=2-Pyridyl, R^2=Ethyl, R^3=Phenyl

Results and Discussion

Although a number of racemic 1-pyridylalkanols were synthesized, only 2-(4-pyridyl)-2-butanol (**1**), 1-(4-pyridyl)-1-phenylethanol (**2**), and 1-(2-pyridyl)-1-phenyl-1-propanol (**3**) could be optically resolved by fractional recrystallization of their salts with optically-active acids, such as (+)-camphor-10-sulfonic acid or (+)-tartaric acid.

Electrolysis was carried out at a constant cathodic potential, for which the initial cathodic current density was 6 A/dm^2 and no hydrogen evolution was observed. The electrolytic results are summarized in Table 1.

Optically-active 1-(4-pyridyl)alkanols (**1** and **2**) were reduced to the corresponding alkylpyridines, which were almost racemized, in high yields. On the other hand, the reduction of optically-active 1-(2-pyridyl)alkanol (**3**) afforded the optically-active alkylpyridine in a low yield, and two by-products were detected by gas chromatograph. The amount of these by-products increased steadily with increasing electric charge passed, while the amount of alkylpyridine reached a maximum of 3 to 4×10^5 C/mol of electric charge passed.[5] This fact indicates that the alkylpyridine formed was further reduced to the by-products. Although the by-products could not be isolated, their molecular weights were both determined to be 201 using a gas chromatograph-mass spectrometer. Therefore, they may be two isomers of 2-(1-phenylpropyl)tetrahydropyridine, though the position of the double bond was undetermined. Polymeric substances insoluble in ether were also formed upon the reduction of **3**.

No optical yield of the alkylpyridines could be estimated because the attempt to determine the optical purities of both the starting 1-pyridylalkanols and the alkylpyridines formed using an optically-active NMR shift reagent, such as europium tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorate,[6] was unsuccessful.

The absolute steric configurations of the 1-pyridylalkanols and the alkylpyridines are unknown. Therefore, the change in relative configuration in the course of the reduction was investigated on the basis of an empirical rule, the so-called Freudenberg displacement rule.[7] The rule states that, when two similarly constituted dissymmetric compounds are chemically changed in the same way and the change produces a considerable shift in optical rotation in the same direction, then the two compounds probably have the same configuration. In order to apply the rule to determining the relative configuration of the 1-pyridylalkanols and the corresponding alkylpyridines, their derivatives were prepared by the same way. As shown in Table 2, for 1-substituted pyridinium halides from **3** and the corresponding alkylpyridine, the shifts were in the same direction. This fact suggests that the configurations of **3** and the alkylpyridine are the same, *i.e.*, in the reduction of **3** to the alkylpyridine, retention of the configuration is predominant over inversion. On the other hand, the free base and N-oxide of either **3** or the alkylpyridine may not fall in the category of the displacement rule, since the intramolecular hydrogen bonding in these compounds should give a rather different contribution

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** Present address: Chemical Administration, Asahi Chemical Industry Co., Ltd., 1-3-1 Yakoo, Kawasaki-ku, Kawasaki 210.

TABLE 1. RESULTS OF THE ELECTROLYSIS OF OPTICALLY-ACTIVE 1-PYRIDYLALKANOLS

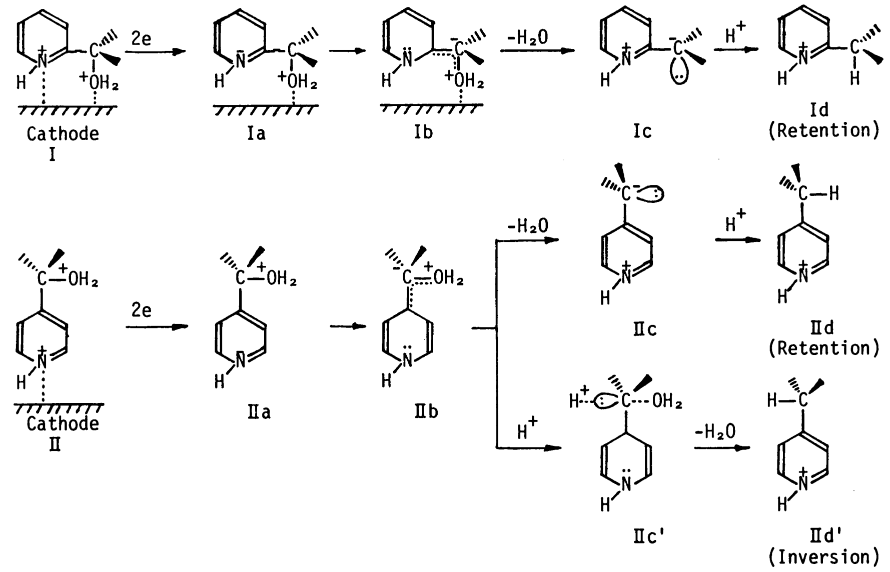
	1-Pyridylalkanol	Cathodic potential	Charge passed	Alkylpyridine	
	$[\alpha]^{20}_{D}$ (degree)	(V *vs.* SCE)	($\times 10^5$ C/mol)	Yield (%)	$[\alpha]^{20}_{D}$ (degree)
1	-1.7 ± 0.4[a)]	-1.22	1.88	92	-0.1 ± 0.1[a)]
2	$+2.4\pm0.4$[b)]	-1.25	1.96	94	$+0.1\pm0.1$[b)]
3	$+8.8\pm0.2$[b)]	-1.36	3.09	62	-5.0 ± 0.2[b)]

a) Measured in ethanol. b) Measured in methanol.

TABLE 2. MOLECULAR OPTICAL ROTATIONS OF THE DERIVATIVES OF 1-PYRIDYLALKANOLS AND ALKYLPYRIDINES

	$[M]^{20}_{D}$ (degree)						
	Original base	Hydrochloride	Hydroiodide	1-Phenacylpyridinium bromide	1-Methylpyridinium iodide	1-Benzylpyridinium bromide	1-Oxide
1	-2.6 ± 0.6[a)]	-0.6 ± 0.2[a)]	-1.8 ± 0.5[b)]				
Alkylpyridine from **1**	-0.1 ± 0.1[a)]	-0.2 ± 0.2[a)]	-0.1 ± 0.2[b)]				
2	$+4.3\pm0.2$[c)]	$+10.5\pm0.5$[c)]	$+11.0\pm0.5$[b)]	$+1.0\pm0.1$[c)]			
Alkylpyridine from **1**	$+0.2\pm0.2$[c)]	-0.2 ± 0.5[c)]	-0.2 ± 0.5[b)]	-0.0 ± 0.1[c)]			
3	$+18.8\pm0.4$[c)]	$+248.8\pm1.6$[c)]	$+258.8\pm1.4$[d)]		-205.9 ± 1.6[d)]	-38.4 ± 0.3[d)]	-14.4 ± 0.1[c)]
Alkylpyridine from **3**	-9.9 ± 0.5[c)]	$+19.9\pm0.5$[c)]	$+35.8\pm0.5$[d)]		-11.9 ± 0.1[d)]	$+7.4\pm0.2$[d)]	$+12.1\pm0.1$[c)]

a) Measured in ethanol. b) Measured in water. c) Measured in methanol. d) Measured in acetone.



Scheme.

to their optical activities. Such an exception to the displacement rule is acceptable.[7)]

In the cases of **1** and **2**, the optical rotations of not only the original alkylpyridines, but also their derivatives, were so small that the displacement rule could not be applied.[8)] Such small optical rotations may indicate that racemization occurs almost exclusively in the reduction of **1** and **2**.

Although the reductive elimination of the hydroxyl group of a 1-pyridylalkanol is formally similar to that of the halo group of an alkyl halide, it is doubtful that these eliminations proceed *via* similar mechanisms. If the reduction of a 1-pyridylalkanol proceeds *via* a mechanism similar to that for the reduction of an optically-active alkyl halide,[9)] the formation of configurationally inverted alkylpyridine is expected, since an intermediate radical formed by the first one-electron transfer appears to be sufficiently planar in its steric form to result in an inverted carbanion as a result of the second electron transfer. The planarity of a pyridylmethyl radical is thought to be due to the interaction between an unpaired electron and the π-electrons of a pyridine nucleus.

The electrolytic results, however, indicate that the reduction involves configurational retention and racemization in the cases of 1-(2-pyridyl)- and (4-pyridyl)-

alkanols, respectively. A mechanism involving the pyridylmethyl radical as an important intermediate should also be inadequate to explain such a difference between the electrolytic results of 1-(2-pyridyl)- and (4-pyridyl)alkanols.

According to the mechanism proposed in a previous paper[4] two electrons are supplied to a pyridine nucleus *via* a pyridinium nitrogen atom adsorbed on the cathode surface and then migrate to an asymmetric carbon atom through the π-electron system of the pyridine nucleus. As is shown in the scheme, a protonated 1-(2-pyridyl)-alkanol molecule (I) promotes adsorption at a pyridinium nitrogen, on which a positive charge would be localized to some degree, and at a hydroxonium oxygen. The orientation perpendicular to the cathode surface of the adsorbed pyridine nucleus may contribute to relaxing the steric hindrance between the cathode and I. Two electrons are transferred to the pyridine nucleus from the cathode. Excess electrons in the resulting intermediate (Ia), which should be substantially regarded as an unstable dihydropyridine such as Ib, are sequentially introduced into the bonding σ orbital of the C–O bond lengthened by the attachment of a positive hydroxonium group, and then water is eleminated from the asymmetric carbon. Consequently, a carbanion (Ic), the configuration of which is retained, is formed by the restoration of the completely conjugated system of the pyridine nucleus. The sequence of processes from I to Ic may be regarded as a multi-centered reaction involving two adsorption sites on the cathode.

On the other hand, a protonated 1-(4-pyridyl)-alkanol molecule (II) should promote adsorption only at its pyridinium nitrogen, which has an electron density lower than that of the hydroxonium oxygen, because of the rigidity of the molecule. In the course of the formation of the carbanion from IIb, an electron should be introduced not only into the bonding σ orbital of the C–O bond but also into the antibonding σ^* orbital. The latter process may be accelerated by a proton approaching to the asymmetric carbon from the opposite side of the hydroxonium group. Racemization in the reduction of 1-(4-pyridyl)alkanols should be rationalized as being due to the almost even competition between the above two processes, one of which results in configurational inversion and the other of which results in retention. In the above discussion, it is tacitly assumed that the configurations of the carbanions (Ic and IIc) are stable enough not to be racemized before undergoing protonation. Such an assumption should be acceptable, especially in a strongly acidic medium, since it is known that no recemization occurs in the reduction of optically-active alkyl halides to the corresponding alkanes in neutral media,[9,11,12] which involves a carbanion as an intermediate.[10]

In conclusion, the mechanism proposed in a previous paper[4] is consistent with the stereochemical data obtained in this work.

Experimental

Materials. *Optically-active 2-(4-Pyridyl)-2-butanol (**1**)*: Racemic **1** was prepared from 4-cyanopyridine using the method of Nakajima.[13] Yield 12%, mp 103—104 °C (lit,[13] 113—114 °C), and *m/e* 151 (M+). Found: C, 71.46; H, 9.01; N, 8.94%. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.64; N, 9.25%. After 30 g (0.2 mol) of racemic **1** and 46 g (0.2 mol) of (+)-camphor-10-sulfonic acid ($[\alpha]^{20}_D$ +22.1° in water) were dissolved in 90 ml of absolute ethanol at 60 °C, the mixture was slowly cooled to room temperature. The resulting crystals were repeatedly recrystallized (three times) from ethanol. Optically-active **1** was finally obtained: Yield 6.4 g with $[\alpha]^{20}_D$ −1.7° (in ethanol).

*Optically-active 1-(4-Pyridyl)-1-phenylethanol (**2**)*: Racemic **2** was synthesized from 4-pyridyl pheny ketone and methylmagnesium iodide in benzene. Yield 80 g, mp 146—148 °C (lit,[14] 148—150 °C), and *m/e* 199 (M+). Found: C, 77.76; H, 6.48; N, 6.82%. Calcd for $C_{13}H_{13}NO$: C, 78.46; H, 6.58; N, 7.03%. The compound, **2**, was optically resolved using the method of Thakar and Pathak.[11] $[\alpha]^{20}_D$ +2.4° (in methanol) (lit,[14] $[\alpha]^{31}_D$ +1.567°).

*Optically-active 1-(2-Pyridyl)-1-phenyl-1-propanol (**3**)*: The synthesis and optical resolution of **3** were carried out by the method of Davies.[15] Mp 84—85 °C (lit,[15] 80—81 °C) and *m/e* 213 (M+). Found: C, 78.61; H, 7.33; N, 6.42%. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57%. $[\alpha]^{20}_D$ +80.0° (in chloroform) (lit,[12] $[\alpha]^{23}_D$ +65.9°).

Electrolytic Procedure. Electrolysis was carried out using a method similar to that used in previous work.[4] The products were analyzed by a gas chromatograph (OV-1 column at 150 °C) and were isolated by fractional distillation.

Alkylpyridines. *4-(2-Butyl)pyridine*: Bp 36—37 °C/1.5 Torr (lit,[13] 93—97 °C/15 Torr) and *m/e* 135 (M+). Picrate: Mp 145—146 °C. Found: C, 49.37; H, 4.42; N, 15.07%. Calcd for $C_{15}H_{16}N_4O_7$: C, 49.45; H, 4.43; N, 15.38%.

4-(α-Methylbenzyl)pyridine: Bp 96—98 °C/1 Torr and *m/e* 183 (M+). Picrate: Mp 153—154 °C. Found: C, 55.32; H, 3.93; N, 13.29%. Calcd for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.59%.

2-(1-Phenylpropyl)pyridine: Bp 89—90 °C/1 Torr (lit,[16] 104—106 °C/0.01 Torr) and *m/e* 197 (M+). Picrate: Mp 144—145 °C. Found: C, 56.53; H, 4.38; N, 12.78%. Calcd for $C_{20}H_{18}N_4O_7$: C, 56.34; H, 4.26; N, 13.14%.

N-Substituted Derivatives of 1-Pyridylalkanols and Alkylpyridines. *4-(1-Hydroxy-1-phenylethyl)-1-phenacylpyridinium Bromide*: Compound **1** was heated at 70 °C in an excess amount of phenacyl bromide for 2.5 h. Yield 45% and mp 220—222 °C. Found: C, 63.16; H, 5.15; N, 3.22%. Calcd for $C_{21}H_{20}NO_2Br$: C, 63.33; H, 5.06; N, 3.52%.

4-(α-Methylbenzyl)-1-phenacylpyridinium Bromide: This compound was prepared by a method similar to that described above. Yield 70% and mp 228—229 °C. Found: C, 65.86; H, 5.36; N, 3.43%. Calcd for $C_{21}H_{20}NOBr$: C, 65.98; H, 5.27; N, 3.66%.

2-(1-Hydroxy-1-phenylpropyl)-1-methylpyridinium Iodide: Compound **3** was heated with an excess amount of methyl iodide at 50—60 °C for 3 days in a sealed tube. Yield 40% and mp 119—120 °C. Found: C, 50.57; H, 5.40; N, 3.56%. Calcd for $C_{15}H_{18}NOI$: C, 50.72; H, 5.11; N, 3.94%.

2-(1-Phenylpropyl)-1-methylpyridinium Iodide: 4-(1-Phenylpropyl)pyridine was reflexed in an excess amount of methyl iodide for 5 h and the separated oil was solidified by treatment with diethyl ketone. The titled compound was obtained in a form including three molecules of diethyl ketone as a solvent of crystallization. Yield 36%, mp 100 °C, and $\nu_{C=O}$ 1690 cm^{-1} Found: C, 60.41; H, 7.75; N, 1.97%. Calcd for $C_{15}H_{18}NI \cdot 3C_5H_{10}O$: C, 60.30; H, 8.09; N, 2.34%.

2-(1-Hydroxy-1-phenylpropyl)-1-benzylpyridinium Bromide: An equimolar mixture of **3** and acetic acid was heated at 90 °C in an excess amount of benzyl bromide for 12 h. Yield 70% and mp 97—100 °C. Found: C, 65.70; H, 5.58; N, 3.50%.

Calcd for $C_{21}H_{22}NOBr$: C, 65.63; H, 5.77; N, 3.64%.

2-(1-Phenylpropyl)-1-benzylpyridinium Bromide: 2-(1-Phenylpropyl)pyridine was heated in an excess amount of benzyl bromide at 90 °C for 4 h. Yield 60% and mp 121—123 °C. Found: C, 68.30; H, 6.18; N, 3.61%. Calcd for $C_{21}H_{22}NBr$: C, 68.48; H, 6.21; N, 3.80%.

2-(1-Hydroxy-1-phenylpropyl)pyridine 1-Oxide: Two grams of **3** and 4 ml of 30% hydrogen peroxide were heated in 10 ml of acetic acid at 80 °C for 24 h. Yield 74%, mp 119—120 °C, and m/e 229 (M^+). Found: C, 73.02; H, 6.59; N, 5.83%. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11%.

2-(1-Phenylpropyl)pyridine 1-Oxide: This compound was prepared by a method similar to that described above. Yield 78%, mp 99—101 °C, and m/e 213 (M^+). Found: C, 78.48; H, 7.17; N, 6.37%. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.17; N, 6.59%.

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