Notes

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Radical Methylation and Radical Hydroxymethylation of Nicotine and Quinine[1)]

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Radical methylation and radical hydroxymethylation of N-substituted quinoline derivatives were applied to natural products, especially to nicotine and quinine. In both cases, methyl derivatives were obtained in high yield than hydroxymethyl derivatives.

Nicotine was substituted preferentially at C-6 position and quinine was substituted preferentially at C-2 position.

Keywords——radical methylation; radical hydroxymethylation; nicotine; quinine; 6-hydroxymethylnicotine; 2-hydroxymethylquinine

We have reported about radical hydroxymethylation, hydroxyethylation, hydroxypropylation, and methylation of N-substituted quinolines (>N$^+$–Me, >N$^+$–O$^-$, >N$^+$–NH$^-$).[3)] In this note, we applied these results to nicotine and quinine.

For methylation was used the methyl radical produced by using *t*-BuOOH–$FeSO_4 \cdot 7H_2O$ system in 7% sulfuric acid solution. For hydroxymethylation was used the hydroxymethyl

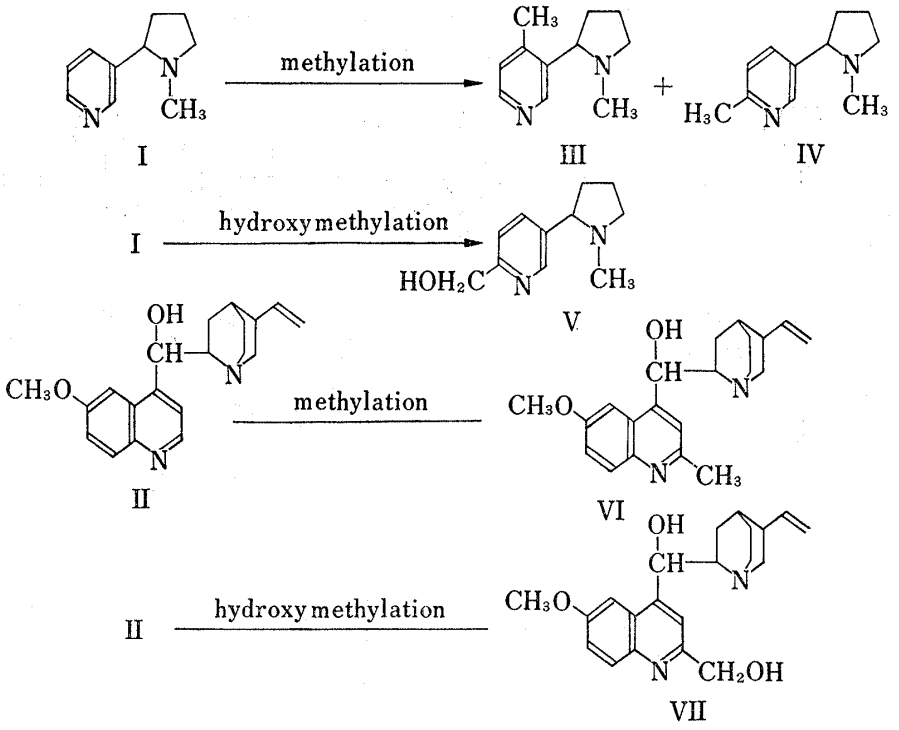

Chart 1

1) Presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April, 1975.
2) Location: *1432–1, Horinouchi, Hachioji, Tokyo, 192–03, Japan.*
3) H. Itokawa, Sh. Kameyama, T. Inaba, T. Tazaki, R. Haruta, Y. Kawazoe, and M. Maeda, *Chem. Pharm. Bull.* (Tokyo), **26**, 1015 (1978).

Table I. Recoveries of Reaction Products

Substrate	Substituted group	Product yield (%) Position 2	Position 3	Position 6	Recovery	Total recovery	Reagent/mol
Nicotine (I)	Methyl	—	III 5.5	IV 23.2	71.9	100.6	2
		—	III 6.5	IV 28.6	63.7	98.8	3
	Hydroxymethyl	—	—	V 12.6	60.9	73.5	2
Quinine (II)	Methyl	VI 26.2			60.8	87.0	2
	Hydroxymethyl	VII 17.8			51.6	69.4	2

radical produced by using 30% H_2O_2–$FeSO_4 \cdot 7H_2O$ system in 7% sulfuric acid solution. The results are illustrated in Chart 1.

Generally, methylation had higher reactivity than hydroxymethylation in both cases of nicotine and quinine. Substitution was not occurred at C-2 and/or C-4 of nicotine by hydroxymethylation, but it occurred only at C-6, which was marked contrast to its methylation.

This result suggested that most nucleophilic site was C-6 position in nicotine molecule because of the steric hindrance at C-2 and C-4 positions by pyrrolidine group at C-3 indicated by arrows as shown in Chart 2.

In the case of quinine, methylation and hydroxymethylation occurred preferentially at C-2 position.

This reaction mechanism was also suggested in Chart 2. Neighbouring position to N, *i. e.*, C-2 was the most nucleophilic position from the view of the distribution of electron density.

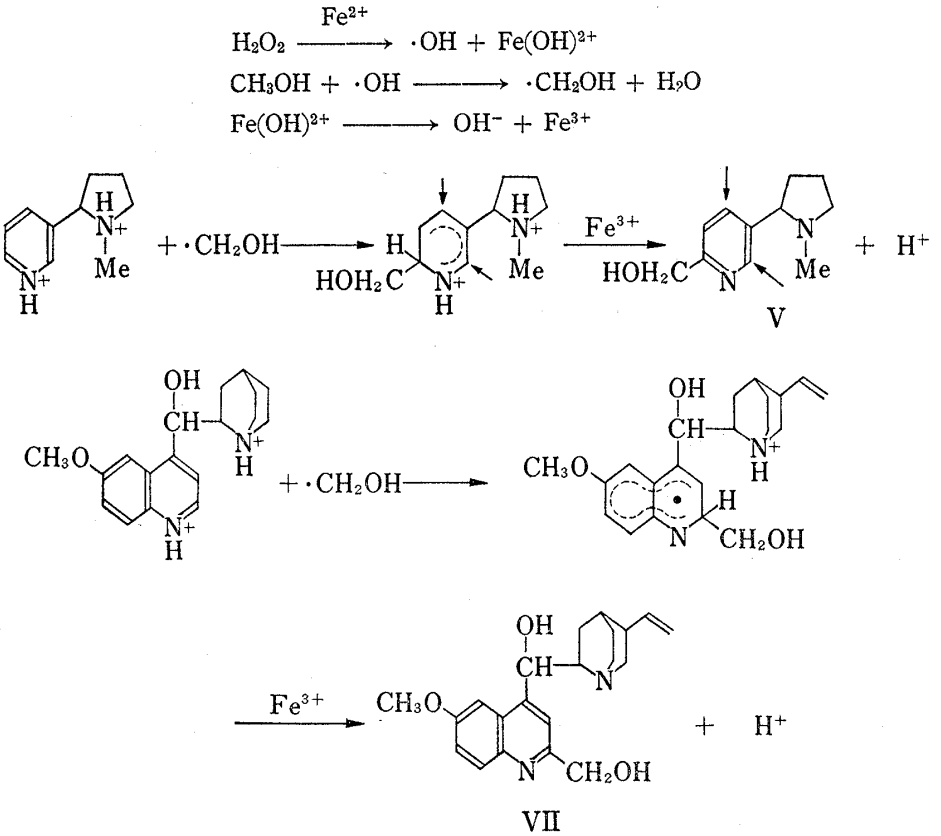

Chart 2

Consequently, it was suggested that this reaction was very useful for selective modification of some natural products.

Experimental

Methylation of Nicotine (I)——I 500 mg (3.09 mmol) was dissolved in 30 ml H_2O, added H_2SO_4 1 ml and $FeSO_4 \cdot 7H_2O$ 1.72 g stirred by adding *t*-BuOOH 555.6 mg for 20 min. After stirring for more 20 min, reacted solution was extracted with $CHCl_3$, aqueous layer was alkalified with NaOH and extracted with $CHCl_3$. III: MS: *m/e* 162 (M^+), *Anal.* Calcd. $C_{10}H_{14}N_2$: C, 74.07; H, 8.64; N, 17.28. Found: C, 73.24; H, 8.79; N, 17.03. NMR ($CDCl_3$) ppm: 1.47—3.40 (7H, m, proton of pyrrolidine ring); 7.72 (1H, d, ring proton at C-4); 8.45 (1H, s, ring proton at C-2); 8.47 (1H, d, ring proton at C-6). IV: MS: *m/e* 176 (M^+), NMR ($CDCl_3$) ppm: 2.53 (3H, s, ring-Me).

Hydroxymethylation of I——I 500 mg (3.09 mmol) was dissolved in conc. H_2SO_4 1 ml and MeOH 30 ml, and added $FeSO_4 \cdot 7H_2O$ 1.72 g, stirred by adding 30% H_2O_2 699.7 mg for 20 min. After stirring for more 20 min, reacted solution was extracted with $CHCl_3$, $CHCl_3$ sol. was concentrated and submitted to column chromatography on alumina. From benzene fr. was obtained I 304.7 mg; from $CHCl_3$: MeOH (40: 1) was obtained 6-hydroxymethylnicotine (V) 74.5 mg as oil. V: MS: *m/e* 192 (M^+), *Anal.* Calcd. $C_{11}H_{16}N_2O$: C, 68.75; H, 8.33; N, 14.58. Found: C, 67.77; H, 8.24; N, 3.97. NMR ($CDCl_3$) ppm: 1.43—3.43 (7H, m, proton of pyrrolidine ring); 2.20 (3H, s, N–Me); 4.77 (2H, s, $-CH_2-OH$); 7.35 (1H, d, ring proton at C-5); 7.78 (1H, d, ring proton at C-4); 8.62 (1H, s, ring proton at C-2).

Methylation of Quinine Hydrochloride (II)——II 1 g (2.77 mmol) was dissolved in H_2O 60 ml, conc. H_2SO_4 2 ml and $FeSO_4 \cdot 7H_2O$ 1.72 g, and added *t*-BuOOH 555.6 mg for 20 min by stirring. After stirring for 20 min, to the reacted sol. was added H_2O 20 ml, and extracted with $CHCl_3$. Aq. layer was alkalified with NaOH sol., and extracted with $CHCl_3$. Basic sol. was concentrated and submitted to column chromatography on alumina. From benzene fr. was obtained quinine 634.5 mg; from $CHCl_3$ fr. 2-methylquinine (VI) 273.3 mg. VI: MS: *m/e* 338 (M^+), NMR ($CDCl_3$) ppm: 2.48 (3H, s, ring-Me); 7.13—7.76 (4H, m, aromatic proton); the signal (8.42 ppm) of the ring proton at C-2 was not observed.

Hydroxymethylation of Quinine Hydrochloride (II)——To a sol. of II 500 mg (1.39 mmol) in conc. H_2SO_4 1 ml and MeOH 30 ml sol. was added $FeSO_4 \cdot 7H_2O$ 858 mg and was stirred by adding 30% H_2O_2 314.4 mg for 20 min. To the reaction mixture was added H_2O 20 ml, and the solution was extracted with $CHCl_3$. Aq. layer was alkalified with NaOH and extracted with $CHCl_3$. $CHCl_3$ sol. was concentrated and was submitted to column chromatography on alumina. From $CHCl_3$: MeOH (50: 1) quinine 257.8 mg, from $CHCl_3$: MeOH (40: 1) 2-hydroxymethylquinine (VII) 97.5 mg. VII: colorless plates, mp 94.5—95°, MS: *m/e*: 354 (M^+), NMR ($CDCl_3$) ppm: 1.27—3.53 (11H, m, ring proton of quinuclidine); 3.90 (3H, s, aromatic-OMe); 4.77 (s, 2H, $-CH_2-OH$); 4.80 (1H, broad, –CH–OH); 5.03 (2H, t, $>C=C<^{H}_{H}$); 5.60 (1H, m, $^{H}\!\!>C=C$); 7.14—7.97 (4H, m, aromatic proton).

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