Chem. Pharm. Bull. 24(8)1704—1707(1976)

UDC 547.834.2.04 : 547.22.04

Studies on the Reaction of Heterocyclic Compounds. XV.[1] N-Alkylation of 1,2,3,4-Tetrahydro-5-methyl-1,6-naphthyridine[2]

Yoshiro Kobayashi, Itsumaro Kumadaki, and Hiroshi Hamana

Tokyo College of Pharmacy[3]

(Received September 5, 1975)

Alkylation of 1-position of 5-methyl-1,2,3,4-tetrahydro-1,6-naphthyridine (I) does not proceed in ordinary methods. I shows quite peculiar behavior in ultraviolet spectrum; absorption maximum shows bathochromic shift on protonation. Based on these data alkylation was successfully carried out in the presence of sodium amide.

As a part of our studies on 1,6-naphthyridine derivative,[4] we are investigating its derivation to allomatridine, which is the skeleton of allomatrine. During this work, we found that 1-alkylation of 1,2,3,4-tetrahydro-5-methyl-1,6-naphthyridine (I) was fairly difficult and that the behavior in the ultraviolet (UV) spectrum was abnormal. The UV spectra of I and those of 4-amino-α-picoline (II), and 4-methylamino-α-picoline (III), which have π-systems similar to that of I, were abnormal in the same way. On the basis of the investigation, concerning the behavior, we partly succeeded in the alkylation under a more drastic condition. In this paper, we report these results in detail.

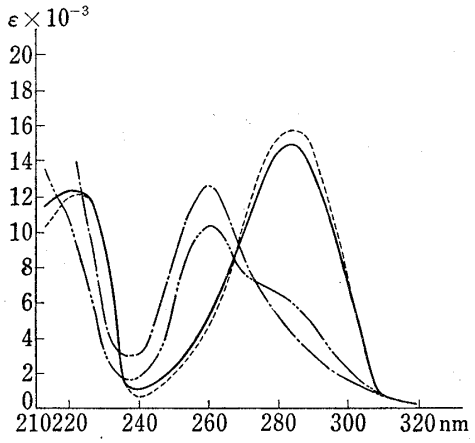


Fig. 1. UV Spectra of 1,2,3,4-Tetrahydro-5-methyl-1,6-naphthyridine (I)

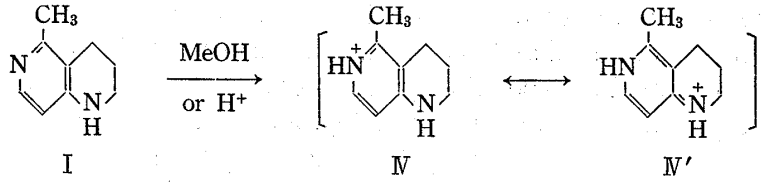
———: MeOH
----------: 0.01N HCl in MeOH
———: 0.01N NaOH in MeOH
— — — —: EtOH

When alkylation of I at 1-position was attempted by the conventional method in the presence and absence of an alkali, the starting material was completely recovered.

The UV spectra of I in methanol and ethanol are quite different; the former agrees with that in hydrochloric acid-methanol, while the latter with those in sodium hydroxide-methanol and in tetrahydrofuran (Fig. 1). The fact shows that I exists as a completely protonated form (IV) in methanol and mostly as a free form in ethanol. The noteworthy point is that, while the absorption of aromatic amines generally shows a hypsochromic shift in acid,[5] these spectra show a bathochromic shift. The phenomenon may be due to the following resonance of IV and IV′.

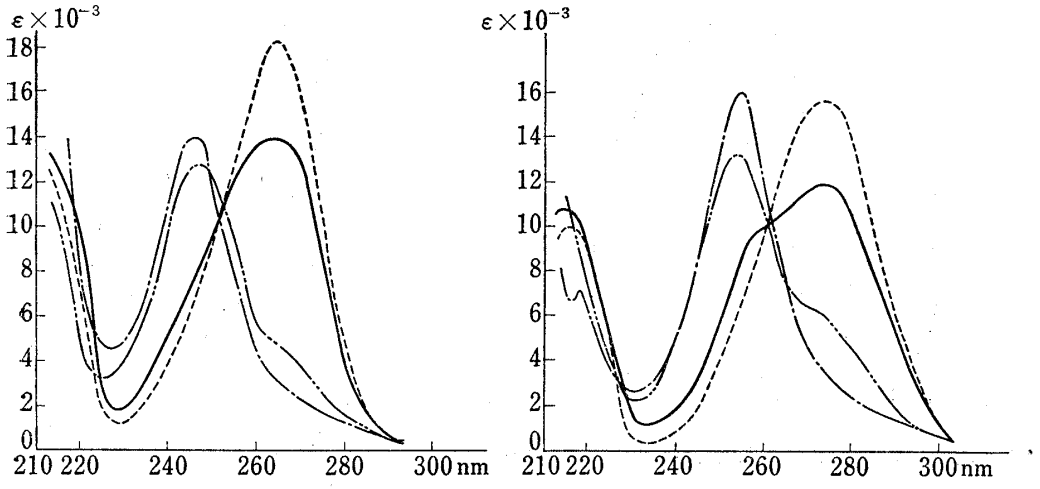
Similar results were obtained with II and III (Fig. 2); the fact that I shows the longest bathochromic shift means that the lone-pair of the nitrogen atom at 1-position is parallel to π-system of the pyridine part and ready to conjugate with it, owing to the hindrance on free

1) Part XIV: Y. Kobayashi, I. Kumadaki, Y. Sekine, Y. Naito, and T. Kutsuma, *Chem. Pharm. Bull.* (Tokyo), **23**, 566 (1975).
2) Presented at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April 1974.
3) Location: *Horinouchi, Hachioji-shi, Tokyo, 192-03, Japan.*
4) Y. Kobayashi, I. Kumadaki, H. Sato, Y. Sekine, and T. Hara, *Chem. Pharm. Bull.* (Tokyo), 22, 2097 (1974).
5) A.E. Gillam and E.S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold Publishers Ltd., London, 2nd ed., 1957, p. 140.



I Ⅳ Ⅳ′

Chart 1



UV Spectra of 4-Amino-α-picoline (II) UV Spectra of 4-Methylamino-α-picoline (III)

Fig. 2

———: MeOH
– – – – –: 0.01N HCl in MeOH
———·———: 0.01N NaOH in MeOH
·····: EtOH

rotation of C–N bond by the presence of the tetrahydropyridine ring. In other words, the lone-pair electrons of the nitrogen atom at 1-position were delocalized and hardly subject to alkylation. Alkylation of this group, therefore, must need a strong base. Consequently, N-alkylation of I with various kinds of alkyl halides in the presence of sodium amide in liquid ammonia was investigated. As the result, various products were obtained according to the kind of alkyl halide used, as shown in Chart 2.

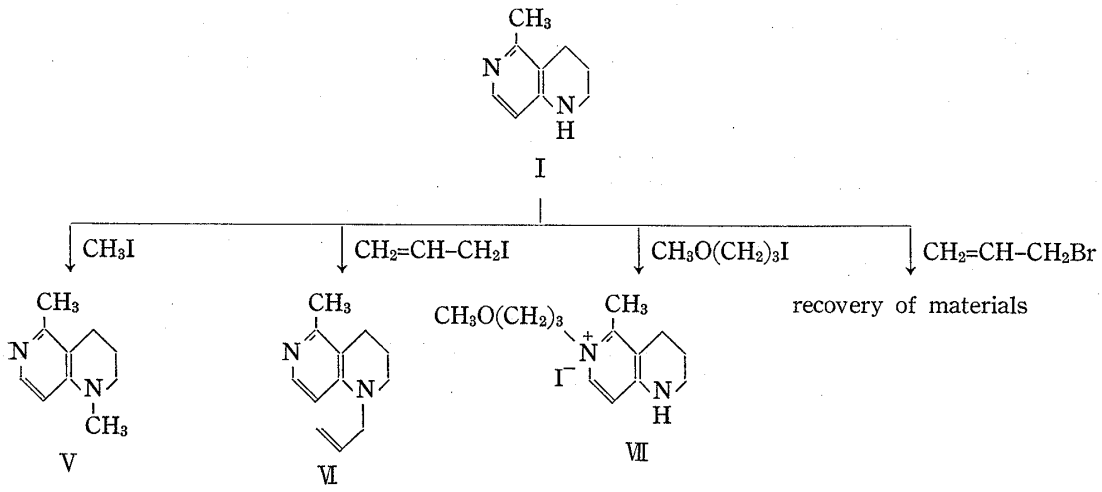


Chart 2

When methyl iodide or allyl iodide was used, N-alkylation of I in the presence of sodium amide in liquid ammonia occurred at 1-position. On the other hand, when 1-iodo-3-methoxypropane was used, it occurred at 6-position, giving a quaternary salt. UV spectra of 1-methyl compound and 6-alkyl compound are shown in Fig. 3 and 4. Comparison of these data with those in Fig. 1 and 2 shows that the assumption concerning the resonance structures is correct.

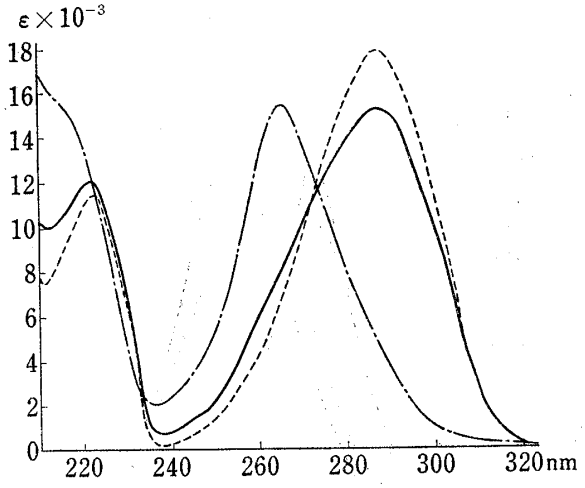


Fig. 3. UV Spectra of 1,2,3,4-Tetrahydro-1,5-dimethyl-1,6-naphthyridine

———: MeOH
– – – – –: 0.01N HCl in MeOH
———: 0.01N NaOH in MeOH

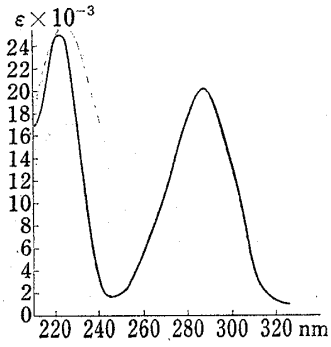


Fig. 4. UV Spectra of 1,2,3,4-Tetrahydro-5-methyl-6-(3-methoxypropyl)-1,6-naphthyridinium Iodide

Even in the case of a considerably active alkyl bromide like allyl bromide, the starting material was recovered. The result may be due to the predominance of the reaction of the bromide with excess ammonia to the reaction with 1-sodio derivative, because 1-sodio derivative was presumably produced with sodium amide. However, the reason why methylation and allylation take place at 1-position, while methoxy propylation does at 6-position, is not yet clear.

The fact that the slight difference in acidity of the solvent between methanol and ethanol causes great difference in the spectra shows that I might be utilized as an indicator for distinguishing the minute difference between these weakly acidic substances.

Experimental[6]

1,2,3,4-Tetrahydro-5-methyl-1,6-naphthyridine (I)——A solution of 5-methyl-1,6-naphthyridine (1 g) in CH_3OH (20 ml) was shaken in the presence of 0.2 g of Pd-$CaCO_3$ (15%) in the atmosphere of hydrogen. After absorption of hydrogen (0.305 liter), the catalyst was filtered off and the solvent was removed. The residue was recrystallized from benzene to give pale yellow plates of 1,2,3,4-tetrahydro-5-methyl-1,6-naphthyridine (I), mp 123—125°; yield, 0.85 g (80%). IR cm^{-1}; ν_{N-H} 3300 (KBr). NMR (in $CDCl_3$) τ: 2.12 (1H, d, J=3.0 Hz, 7-H), 3.78 (1H, d, J=3.0 Hz, 8-H), 5.43 (1H, broad, 1-NH), 6.72 (2H, m, 2-CH_2), 7.37 (2H, t, J=6 Hz, 4-CH_2), 7.64 (3H, s, 5-CH_3), 8.05 (2H, m, 3-CH_2). Mass Spectrum *m/e*: 148 (M^+). *Anal.* Calcd. for $C_9H_{12}N_2$: C, 72.93; H, 8.16; N, 18.90. Found: C, 72.36; H, 8.28; N, 18.75.

General Procedure of $NaNH_2$ Solution——$NaNH_2$ was freshly prepared by adding Na (0.165 g) in liq. NH_3 (15—20 ml) containing $Fe(NO_3)_3$ (0.1 g).

1,2,3,4-Tetrahydro-1,5-dimethyl-1,6-naphthyridine (V)——To a solution of $NaNH_2$ (from Na (0.165 g)) in liq. NH_3 (15 ml), a solution of I (0.740 g) in THF (10 ml) was added dropwise and stirred for 2 hr. Then a solution of methyl iodide (0.7 g) in THF (10 ml) was added and stirred for 2 hr. NH_3 was evaporated and the residue was treated with ice water; the insoluble substance was filtered off. The H_2O layer was extracted

6) UV spectra were recorded on Hitachi-124-spectrophotometer. Spectral Grade methanol and freshly distilled JP VIII ethanol were used as solvents.

with CH_2Cl_2. After the CH_2Cl_2 solution was dried over Na_2SO_4, CH_2Cl_2 was evaporated and the residue in CH_2Cl_2 solution was passed through Al_2O_3-column. Effluent with CH_2Cl_2 gave crude crystals, which were recrystallized from *n*-hexane to give colorless granules of 1,2,3,4-tetrahydro-1,5-dimethyl-1,6-naphthyridine (V), mp 78—80°; yield, 0.42 g (50%). NMR (in CCl_4) τ: 7.18 (3H, s, 1-CH_3). Mass Spectrum *m/e*: 162 (M^+). *Anal.* Calcd. for $C_{10}H_{14}N_2$: C, 74.02; H, 8.70; N, 17.28. Found: C, 73.84; H, 8.79; N, 17.30.

1,2,3,4-Tetrahydro-1-allyl-5-methyl-1,6-naphthyridine (VI)——To a solution of I (0.74 g), which was treated with $NaNH_2$ (from Na (0.165 g)) as in the case of V, a solution of allyl iodide (1 g) in THF (10 ml) was added dropwise and stirred for 2 hr. The residue which was obtained as in the case of V was passed through Al_2O_3-column. The first effluent gave yellow oil. Yield, 550 mg (58%). IR cm^{-1}: $\nu_{C=C}$ 1645 (film). NMR (in CCl_4) τ: 4.22 (1H, m, >═<H), 4.78 (2H, broad d, J=5 Hz, H\ /H C=C /\ ), 8.80 (2H, m, \ H / C-C-N). Mass Spectrum *m/e*: 188 (M^+). High Mass Spectrum *m/e* for $C_{12}H_{16}N_2$: Calcd.: 188.131. Found: 188.129.

1,2,3,4-Tetrahydro-6-(3-methoxypropyl)-5-methyl-1,6-naphthyridinium Iodide (VII)——To a solution of I (0.74 g) which was treated with $NaNH_2$ (from Na (0.165 g)) as in the case of V, a solution of 1-iodo-3-methoxypropane (3 g) in THF (20 ml) was added dropwise and stirred for 2 hr. The residue which was obtained as in the case of V was passed through Al_2O_3-column. The second effluent gave crude crystals, which were recrystallized from acetone to give colorless granules of 1,2,3,4-tetrahydro-6-(3-methoxypropyl)-5-methyl-1,6-naphthyridinium iodide (VII), mp 131—132°; yield, 0.110 g (15.1%). NMR (in $CDCl_3$) τ: 6.63 (3H, s, -OCH_3). *Anal.* Calcd. for $C_{13}H_{20}ON_2I$: C, 44.97; H, 5.81; N, 8.01. Found: C, 44.94; H, 6.23; N, 8.35.