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Studies on Tertiary Amine Oxides. XLIX.[1] Reactions of Pyridine and Quinoline N-Oxides with 1(10)-Dehydroquinolizidine

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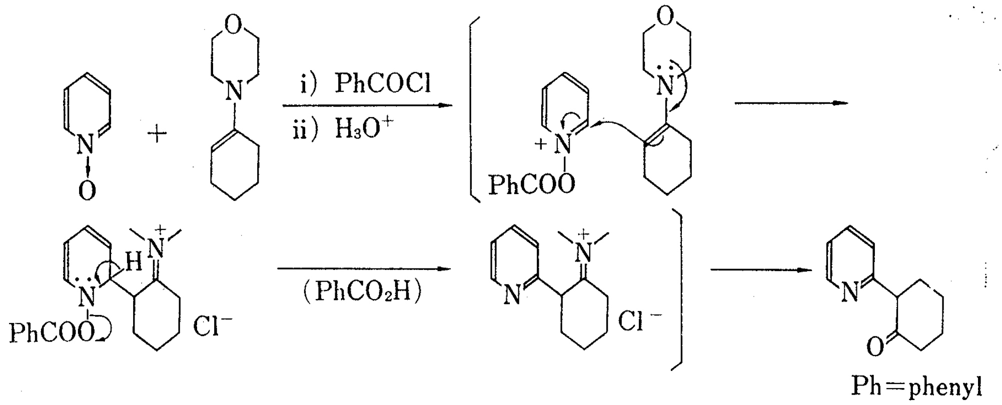
As an extension of reaction of acyl-adducts of aromatic N-oxides with enamines, 1(10)-dehydroquinolizidine (II), a heterocyclic enamine, has been applied to pyridine and quinoline N-oxides. Reaction of N-benzoyloxypyridinium chloride (I) with II proceeds at room temperature in dichloromethane to give 1-(2-pyridyl)quinolizidine (III) in 26% yield after treatment of the reaction mixture with sodium borohydride. Quinoline N-oxide (VI) reacts similarly with II in the presence of benzoyl chloride and 1-(2-quinolyl)-quinolizidine (VII) has been obtained in 14% yield, however, the reaction seems rather complicated.

The reaction of aromatic N-oxide with enamine in the presence of an acylating agent proceeds very readily by the course exemplified below, and many interesting results have been obtained by using various derivatives of pyridine and benzopyridine N-oxides.[3]



With an aim to extend this line of research to heterocyclic enamines, 1(10)-dehydroquinolizidine[4] was applied to pyridine and quinoline N-oxides in the presence of acylating agents.

A dichloromethane solution of 1(10)-dehydroquinolizidine (II) and 2 equivalents of N-benzoyloxypyridinium chloride (I) preliminary prepared from pyridine N-oxide and benzoyl chloride was stirred at room temperature for 48 hr. The brown reaction mixture was evaporated under reduced pressure, and the residue was taken up in anhydrous ethanol and treated with a small excess of sodium borohydride to give 1-(2-pyridyl)quinolizidine (III) as a brownish oil, bp 170—175° (0.02 mmHg), in 26% yield. It forms a dipicrate with the empirical formula $C_{14}H_{20}N_2 \cdot 2C_6H_3O_7N_3$, yellow needles, mp 243° (decomp.). The free base regenerated from the purified dipicrate exhibited Bohlmann bands[5] at 2830—2870 cm^{-1} and a C=N band at

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[1] Part XLVII: M. Hamana, K. Funakoshi and, Y. Kuchino, *Chem. Pharm. Bull.* (Tokyo), **22**, 1806 (1974).

[2] Location: *Katakasu, Higashi-ku, Fukuoka.*

[3] *a*) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **13**, 912 (1965); *b*) *Idem, ibid.*, **14**, 762 (1966); *c*) *Idem, ibid.*, **15**, 474 (1967); *d*) *Idem, Yakugaku Zasshi*, **89**, 641 (1969).

[4] N.J. Leonard, A.S. Hay, R.W. Fulmer, and V.W. Gach, *J. Am. Chem. Soc.*, **77**, 439 (1955).

[5] *a*) F. Bohlmann, *Chem. Ber.*, **31**, 2157 (1958); *b*) J. Skolik and P.J. Krueger, *Tetrahedron*, **24**, 5439 (1968).

1620 cm^{-1} in infrared (IR) spectrum. Its nuclear magnetic resonance (NMR) spectrum showed a one-proton, a three-proton and a ten-proton multiplets at τ 1.55—1.40, 3.00—2.30 and 9.00—6.95, which are reasonably assigned to an α-proton of pyridine ring, two β- and one γ-protons of pyridine ring, and ten protons of quinolizidine ring, respectively.

In further confirmation of the structure III, 1-(2-piperidyl)quinolizidine (V) prepared from 1-(2-pyridyl)-3-ethoxycarbonyl-4-quinolizinone (IV) by the procedure of Sato[6] was dehydrogenated by heating at 250° in the presence of 40% palladium asbestos to yield an oil, bp 170—175° (0.02 mmHg), which afforded a dipicrate, mp 243° (decomp.) and was proved identical with III by comparison of their IR and NMR spectra and by admixture of their dipicrates.

The presence of Bohlmann bands in its IR spectrum and the fact that III can be obtained from V under a rather drastic condition of catalytic dehydrogenation indicate that the quinolizidine ring in III is trans-fused and the bond between pyridine and quinolizidine rings has the stable equatorial conformation[7] (III′) as shown in Chart 1.

The reaction can be visualized by the course formulated in Chart 1.

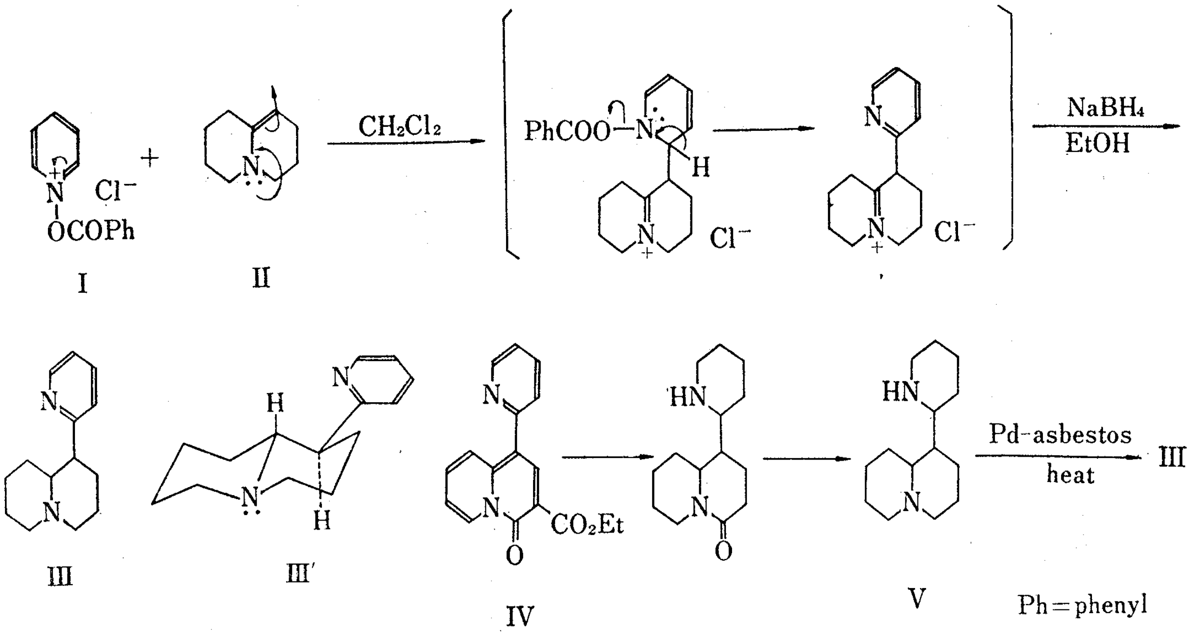

Chart 1

In order to increase the yield of III, examinations using tosyl chloride, dimethyl sulfate or acetyl chloride instead of benzoyl chloride were carried out in dichloromethane, dioxane or acetonitrile, but no satisfactory result was obtained.

Subsequently, the reaction of quinoline N-oxide (VI) was carried out under the similar condition. As quinoline N-oxide of naphthoid structure is known to be generally more reactive than benzenoid pyridine N-oxide towards nucleophilic reactions, the usual procedure using one molar equivalent of benzoyl chloride was applied. A dichloromethane solution of benzoyl chloride was slowly added under ice-cooling to a solution of VI and II in the same solvent, and the reactants were stirred for 3 days, followed by reduction with sodium borohydride in the same way as the foregoing reaction. Chromatography on silica gel furnished three oily products (VII, VIII and IX) in small yields of 14, 2 and 1%, respectively, and a trace of crystalline one (X) (Chart 2).

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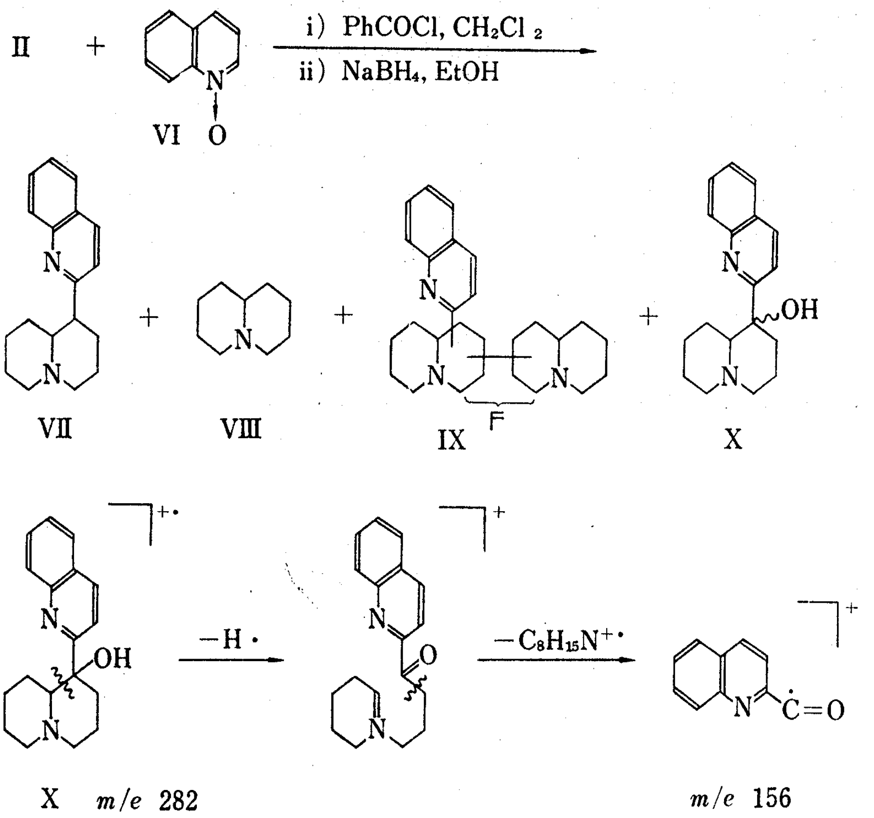
[6] Y. Sato, *Chem. Pharm. Bull.* (Tokyo), **5**, 412 (1957).

[7] *a*) E. Ochiai, S. Okuda, and H. Minato, *Yakugaku Zasshi*, **72**, 781 (1952); *b*) E.W. Garbish, Jr., *J. Org. Chem.*, **27**, 3363 (1962).



Ph=phenyl

Chart 2

The yellow columnar dipicrate of VII melted at 240—241° and gave analytical values in agreement with the empirical formula $C_{18}H_{22}N_2 \cdot 2C_6H_3O_7N_3$. The IR spectrum of the free VII liberated from the dipicrate exhibited Bohlmann bands at 2700—2800 cm^{-1} as well as a C=N band at 1600 cm^{-1}. Its NMR spectrum showed a couple of multiplets at τ 1.75—3.04 and 7.00—8.75 which were assignable to six quinoline protons and sixteen protons of quinolizidine ring, respectively, but no signal due to the α-proton of quinoline ring was noticed. From these data and also by analogy with the reaction of I, the product VII can be assumed to be 1-(2-quinolyl)quinolizidine, and its stereochemistry may probably be the same with that of III.

The compound VIII was identified as quinolizidine by comparison of their IR spectra and by admixture of their picrates (mp 198—199°).

The product IX affords a dipicrate with the empirical formular $C_{27}H_{35}N_3 \cdot 2C_6H_3N_3O_7$, yellow columns, mp 233—234° (decomp.). The free base obtained from the purified dipicrate displayed Bohlmann bands at 2700—2800 cm^{-1} and a C=N band at 1600 cm^{-1} in the IR spectrum. Its NMR spectrum showed one proton of a vinyl group as a singlet at τ 4.72 and six aromatic protons as a multiplet at τ 1.85—2.75. These observations demonstrate that IX consists of one quinoline and two quinolizidine nuclei, and one of the latter contains a vinyl group bearing one proton. Its structure is not yet elucidated because of the lack of the sample.

The crystalline product X formed pale brown columns, mp 173—174°, from acetone, and its analytical values agreed with the empirical formula $C_{18}H_{22}ON_2$. The mass spectrum shows the parent peak at *m/e* 282 and two characteristic peaks at *m/e* 264 (M^+—18) and *m/e* 156 (M^+—126); the last peak corresponds to the α-quinolyl carbonyl ion formed by cleavage of the C_1-C_{10} bond of the parent radical and by successive loss of $C_8H_{15}N$ radical ion as shown in Chart 2. From these observations, X may presumably be deduced to be 1-hydroxy-1-(2-quinolyl)quinolizidine, but its detailed structural elucidation also remains to be explored.

Thus it was disclosed that 1(10)-dehydroquinolizidine II is able to react with acyl-adducts of aromatic N-oxides in the similar way to usual enamines such as those of cyclohexanone[3a–c] and isobutyroaldehyde.[3d] The reaction with quinoline N-oxide was unexpectedly rather complicated, but further examinations should permit establishment of the optimal reaction condition. Of particularly interesting is the formation of III in a fair yield from the reaction with pyridine N-oxide. This appears to promise a new route to matrine type alkaloids by usage of appropriate 9-substituted derivatives of II, and the results obtained from studies along this line will be published in the near future.

Experimental[8]

1(10)-Dehydroquinolizidine (II)——1(10)-Dehydroquinolizidine (II) was prepared from quinolizidine by $Hg(OAc)_2$ dehydrogenation in AcOH according to Leonard, *et al.*[4] and stored as the stable perchlorate, colorless needles, mp 234°. A suspension of II-perchlorate in a small amount of H_2O was treated with 40% NaOH and extracted with ether which was dried over Na_2SO_4. After evaporation of the solvent, a residual oil (II) was distilled under reduced pressure and a colorless oil of bp 60° (4 mmHg) was collected. Fresh II thus obtained was used for each run.

Reaction of II with N-Benzoyloxypyridinium Chloride (I)——A CH_2Cl_2 solution of I was prepared by mixing 227 mg (2.5 mmole) of pyridine N-oxide and 340 mg (2.5 mmole) of PhCOCl in 20 ml of CH_2Cl_2. To this solution was added with ice-cooling and stirring 170 mg (1.2 mmole) of II dissolved in 10 ml of CH_2Cl_2, and the whole was stirred at room temperature for 48 hr. The solvent was evaporated under reduced pressure, and the residue was taken up in 100 ml of anhydrous EtOH and treated with 180 mg of $NaBH_4$ with ice-cooling for 4 hr. After evaporation of the solvent, the residue was dissolved in 10% HCl and washed several times with ether in order to remove benzoic acid. The residual solution was made alkaline with K_2CO_3, extracted with ether and the ether layer was dried over Na_2SO_4. Evaporation of the solvent gave an oil which was purified by chromatography on alumina (Woelm, neutral, grade 1). Elution with petr. ether–ether (1: 1) afforded 100 mg (26%) of 1-(2-pyridyl)quinolizidine (III), a brown oil, bp 170—175° (0.02 mmHg). Dipicrate: yellow needles, mp 243° (decomp.) (acetone). *Anal.* Calcd. for $C_{26}H_{26}O_{14}N_8$: C, 46.29; H, 3.85; N, 16.61. Found: C, 46.31; H, 3.75; N, 16.24.

The free base (III) obtained from the dipicrate: bp 170—175° (0.02 mmHg). IR ν_{max} cm^{-1}: 2830—2780 (Bohlmann bands), 1620 (C=N). NMR τ ($CDCl_3$): 9.00—6.95 (10H, m, quinolizidine-protons), 3.00—2.30 (3H, m, C_3–H, C_4–H and C_5–H of pyridine), 1.55—1.40 (1H, m, C_2–H of pyridine).

Dehydrogenation of 1-(2-Piperidyl)quinolizidine (V)——A mixture of 150 mg of V[6] and 50 mg of 40% Pd-asbestos was heated at 250° until the evolution of hydrogen gas had ceased. The reaction mixture was extracted with ether to give 110 mg of an oil. It formed a dipicrate, yellow needles, mp 243° (decomp.) (acetone), and was proved to be identical with the sample of III obtained from I and II by comparison of their IR and NMR spectra and also by admixture of their dipicrates.

Reaction of II with Quinoline N-Oxide (VI) in the Presence of Benzoyl Chloride——To a solution of 406 mg (2.7 mmole) of quinoline N-oxide (VI) and 400 mg (2.8 mmole) of II in 40 ml of CH_2Cl_2, a solution of 400 mg (2.8 mmole) of PhCOCl in 20 ml of CH_2Cl_2 was added with ice-cooling, and the whole was stirred at room temperature for 3 days. The solvent was evaporated under reduced pressure and the residue was treated with 270 mg of $NaBH_4$ in 45 ml of EtOH under stirring for 12 hr. After evaporation of EtOH, the residue was treated with a small amount of H_2O and extracted with ether. The ether layer was shaken with 10% HCl and the HCl solution was made alkaline with K_2CO_3 and extracted again with ether. The extracted fractions were submitted to chromatography on silica gel (Wako Gel C-200). From fractions eluted with petr. ether–ether (1: 1), three oily substances, VII, VIII and IX, were obtained. Further, a trace of crystalline substance (X) was isolated as the fourth product by eluting with MeOH.

The first fraction VII afforded a dipicrate, yellow columns, mp 240—241° (acetone). *Anal.* Calcd. for $C_{30}H_{28}O_{14}N_8$: C, 49.72; H, 3.86; N, 15.44. Found: C, 49.88; H, 3.87; N, 15.17. The free VII was obtained as a pale yellow oil in 14% yield from the purified dipicrate. IR ν_{max} cm^{-1}: 2800—2700 (Bohlmann bands), 1600 (C=N). NMR τ ($CDCl_3$): 7.00—8.75 (16H, m, quinolizidine-protons), 1.75—3.04 (6H, m, aromatic protons). From these data, VII was inferred to be 1-(2-quinolyl)quinolizidine.

A picrate of VIII melting at 198—199° was not depressed in admixture with an authentic specimen of quinolizidine picrate. The IR and NMR spectra of the free VIII was further found to be practically the same with those of authentic quinolizidine.

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8) All melting and boiling points are uncorrected. IR spectra were recorded on a JASCO IR-E spectrophotometer. NMR spectra were taken at 60 MHz with TMS as an internal standard using a C-60H NMR spectrometer. Mass spectra were measured on a JMS-O1SG mass spectrometer.

The third oily fraction IX (1%) formed a dipicrate, yellow columns, mp 233—234° (decomp.) (acetone). *Anal.* Calcd. for $C_{39}H_{41}O_{14}N_9$: C, 54.48; H, 4.77; N, 14.78. Found: C, 54.76; H, 3.80; N, 14.14. The free IX showed the following spectral data. IR ν_{max} cm^{-1}: 2800—2700 (Bohlmann bands), 1600 (C=N). NMR τ ($CDCl_3$): 4.72 (1H, s, a vinyl proton), 1.85—2.75 (6H, m, aromatic protons).

The fourth product X was recrystallized from acetone to give pale brown columns, mp 173—174°. *Anal.* Calcd. for $C_{18}H_{22}ON_2$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.57; H, 7.86; N, 9.86. IR ν_{max}^{Nujol} cm^{-1}: 1600 (C=N). Mass Spectrum *m/e*: 282 (M^+), 264 (M^+-H_2O), 156 ($M^+-C_8H_{15}N$). From these observations, X was deduced to be 1-hydroxy-1-(2-quinolyl)quinolizidine.

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