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Studies on the Reaction of Heterocyclic Compounds. XII.[1] N-Oxidation of Diazabenzene and Diazanaphthalene[2]

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Application of N-oxidation using sodium tungstate as a catalyst was attempted with diazines and diazanaphthalenes, some of which are labile to peracids, and found to be especially useful. N-Oxides of quinazoline and pyrimidine were obtained from the bases by this method. Pyrazine and quinoxaline were oxidized stepwise to the dioxides through monooxides.

We previously reported that oxidation of 1,6-naphthyridine (I) with hydrogen peroxide and acetic acid, or with monoperphthalic acid, afforded 1,6-naphthyridine 6-oxide (II), 1,6-naphthyridin-2(1*H*)-one (III), and 1-hydroxy-1,6-naphthyridin-2(1*H*)-one (IV). In those cases 1-oxide (VI) and 1,6-dioxide (V) were not obtained and the yield of II was poor. On the other hand, V was obtained by the oxidation of I with 30% hydrogen peroxide in the presence of catalytic amount of sodium tungstate. VI was obtained by catalytic hydrogenation of V using Raney nickel (Chart 1).[4]

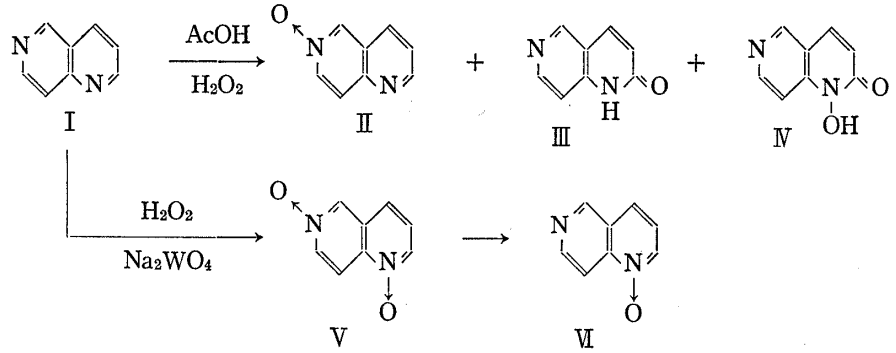

Chart 1

The main difference in the two cases of oxidation shown above is that by-products (III and IV), which are oxidized at the ring carbon atom, are obtained by the former method; therefore, the latter method seems to be a useful one for N-oxidation involving no by-product. We examined this method concerning N-oxidation of diazines and diazanaphthalenes. Selective N-oxidation of diazines was possible and this method was especially useful for N-oxidation of the amines where ring-carbon atoms had been oxidized by the peracid-N-oxidation. The results will be discussed in detail.

First, we tried N-oxidation of I in dilute hydrogen peroxide at a lower temperature and obtained only II, without any VI. This shows that I was oxidized selectively at 6-position. I and VI were converted to V in higher concentration of hydrogen peroxide, but in both cases

1) Part XI: Y. Kobayashi, I. Kumadaki, H. Sato, C. Yokoo, and T. Mimura, *Chem. Pharm. Bull.* (Tokyo), **21**, 2066 (1973).
2) Presented at the 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July 1970.
3) Location: *Kitashinjuku 3-chome, Shinjuku-ku, Tokyo.*
4) Y. Kobayashi, I. Kumadaki, and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **17**, 1045 (1969).

none of the products which had been attacked at the ring-carbon atom were obtained. This fact shows that the N-oxidation method using sodium tungstate as catalyst is useful for selective N-oxidation of aromatic amines, which are very sensitive to peracids and easily oxidized at the ring-carbon atom. Most of the diazines and diazanaphthalenes are susceptible to peracids in that sense. For example, quinazoline N-oxides have not been obtained from quinazoline (VII) by N-oxidation with peracid. By the control of the reaction temperature and concentration of hydrogen peroxide, however, quinazoline 1-oxide (VIII) and quinazoline 3-oxide (IX) were obtained by this method. IX had been synthesized[5] by ring closure, but VIII had not been obtained by any method. In the present case, 30% hydrogen peroxide gave only quinazolin-(3*H*)4-one (X) which was obtained in low yield with dilute hydrogen peroxide.

Further, we tried N-oxidation of 1,8-naphthyridine, from which no N-oxide had been obtained with peracid, to give 1,8-naphthyridine 1-oxide (XII) in 48% yield. As regards the above compound, Hamana and others applied this method independently of us and obtained similar results.[6]

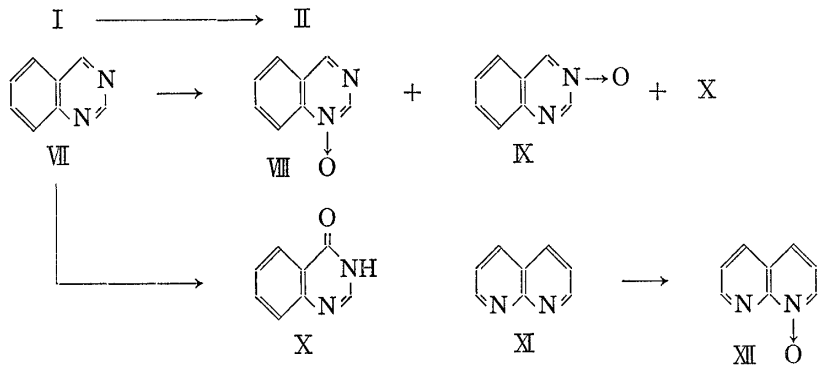

Chart 2

Next, we tried N-oxidation of diazines, which are interesting since they have two nitrogen atoms, making monooxidation and dioxidation possible, and are very difficult to be converted to N-oxides with peracids.

Pyridazine 1-oxide (XIV) was the only product obtained in 50% yield when pyridazine (XIII) was treated by this method using 30% hydrogen peroxide at 100° for 8 hours; even when the reaction was prolonged for a longer period of time, 1,2-dioxide could not be obtained.

Pyrimidine 1-oxide (XVI) was obtained in 17% yield when pyrimidine (XV) was heated at 60° for 9 hours by this method, but when the reaction conditions were made more drastic than the above, XV was decomposed with ring opening, and neither the yield was raised nor dioxide was produced.

Pyrazine 1-oxide (XVIII) was solely obtained in 47% yield when pyrazine (XVII) was heated at 40° for 3 hours by this method, while only pyrazine 1,4-dioxide (XIX) was obtained in 17% yield when XVII was heated at 70° for 6 hours.

These results show that this method is superior to the ordinary method using a peracid; the yield of XVI is twice as much as that by the latter method and XVIII or XIX can be selectively obtained by choosing reaction conditions. These characteristics were observed with quinoxaline (XX); XX gave quinoxaline 1-oxide (XXI) in 50% yield at 40° for 1.5 hours, while 1,4-dioxide (XXII) was obtained in 54% yield at 50° for 6 hours. Phenazine (XXIII) gave 9-oxide (XXIV) in 21% yield with trace of the 9,10-dioxide (XXV).

5) K. Adachi, *Yakugaku Zasshi*, **77**, 507 (1957).
6) Private Communication.

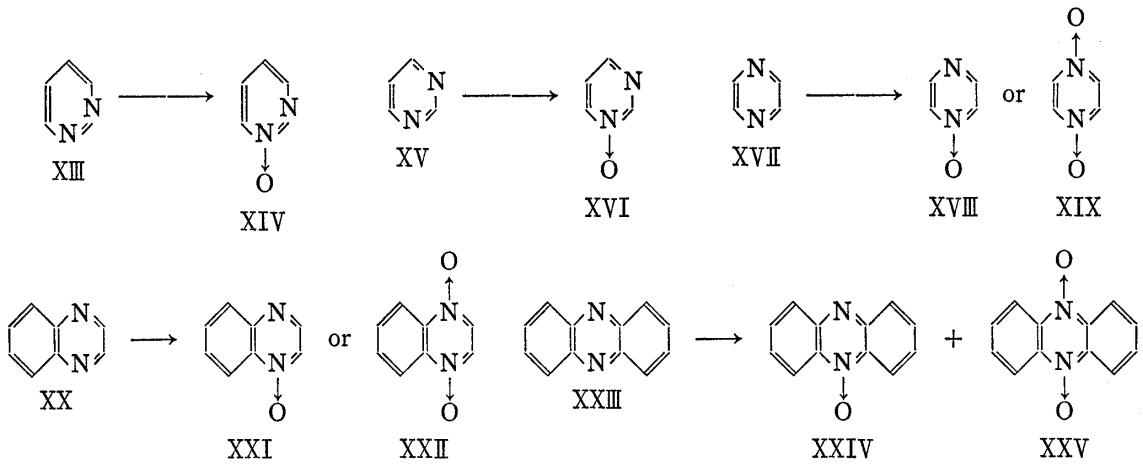

Chart 3

In conclusion, this N-oxidation method using sodium tungstate as a catalyst shows wide applicability, especially for diazines which are much liable to be oxidized at the ring-carbon atom in the N-oxidation method using a peracid. This method is also useful for obtaining the mono- or dioxide of diazines selecting the right reaction conditions.

Experimental

General Procedure of Oxidation with Hydrogen Peroxide and Na_2WO_4——The starting material was dissolved in a solution of a given concentration of hydrogen peroxide with the catalytic amount of sodium tungstate. The mixture was heated at a given temperature for designated hours. After the reaction was over, the solution was diluted with water to about twice the original volume and then a small amount of sodium carbonate or sodium bicarbonate was added; then it was concentrated to half the volume *in vacuo* and this process was repeated several times. After decomposition of almost all the hydrogen peroxide, which was tested by KI-starch, the solution was evaporated to dryness *in vacuo* at 30°. The residue was dissolved in CH_2Cl_2 and separated by column chromatography using silica gel, unless otherwise stated. Effluent with CH_2Cl_2–CH_3OH gave monooxide and dioxide.

1,6-Naphthyridine 6-Oxide (II)——1,6-Naphthyridine, 1.62 g; 10% hydrogen peroxide, 13 ml; Na_2WO_4, 0.1 g; 40°, 6 hr; light-yellow prisms from acetone, mp 150°; yield, 26%. IR cm^{-1}: ν_{N-O} 1312 (KBr). This product was identified with the authentic sample[4] by comparing infrared (IR) spectra and mixture melting point. (The authentic sample was prepared with 30% hydrogen peroxide and acetic acid.)

1,6-Naphthyridine 1,6-Dioxide (V) from 1,6-Naphthyridine 1-Oxide (VI)——1,6-Naphthyridine 1-oxide, 0.2 g; 30% hydrogen peroxide, 2 ml; Na_2WO_4, 0.05 g; 60°, 9 hr. The product was purified by alumina chromatography. Elution with CH_2Cl_2–CH_3OH (10: 1) afforded pale yellow needles (0.06 g); yield, 30%. This product was identified with the authentic sample by comparing IR spectra and mixture melting point.

Quinazoline 1-Oxide (VIII) and Its 3-Oxide (IX)——Quinazoline (VII), 1 g; 6.8% hydrogen peroxide, 11.5 ml; Na_2WO_4, 0.1 g; 40°, 6 hr. Quinazoline 1-oxide and its 3-oxide were separated from the first effluent by preparative thin-layer chromatography on a silica plate with a mixed solvent of CH_2Cl_2, ethyl acetate, and acetone (3: 1: 1). Recrystallization of VIII from ether gave colorless prisms, mp 68.5°; yield, 5.5%. IR cm^{-1}: ν_{N-O} 1243 (KBr). NMR (in $CDCl_3$) τ: 0.83 (1H, s, 2-H), 1.13 (1H, s, 4-H), 1.37 (1H, d, J=8.75 cps, 8-H), 2.14 (3H, m, 5-H, 6-H, 7-H). *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.59; H, 4.06; N, 18.98. Recrystallization of IX from acetone gave colorless needles, mp 153°; yield, 4.7%. IR cm^{-1}: ν_{N-O} 1336 (KBr).

Recrystallization of the second effluent from benzene and *n*-hexane gave quinazolin-(3*H*)4-one (X), colorless needles, mp 217°; yield, 9.4%. IX and X were identified with the authentic samples[5] by comparing IR spectra and mixture melting point.

1,8-Naphthyridine 1-Oxide (XII)——1,8-Naphthyridine (XI), 1.2 g; 30% hydrogen peroxide, 10 ml; Na_2WO_4, 0.2 g; 40°, 10 hr; colorless needles from benzene, mp 98°; yield, 4.8%. IR cm^{-1}: ν_{N-O} 1229 (KBr). NMR (in $CDCl_3$) τ: 0.09 (1H, q, $J_{6,7}$=5 cps, $J_{5,7}$=2.5 cps, 7-H), 1.23 (1H, d, J=7.5 cps, 2-H), 1.66 (1H, q, $J_{5,6}$=10 cps, $J_{5,7}$=2.5 cps, 5-H), 2.39 (3H, m, 3-H, 4-H, 6-H). *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.31; H, 4.28; N, 18.93.

Pyridazine 1-Oxide (XIV)——Pyridazine (XIII), 2.1 g; 30% hydrogen peroxide, 16 ml; Na_2WO_4, 0.2 g; 55°, 8.5 hr; oil: bp_4 138—140°; yield, 8.5%. IR cm^{-1}: ν_{N-O} 1315 (film); mp 38—39°. This product was

identified with the authentic sample[7] by comparing IR spectra and mixture melting point. (The authentic sample was prepared with 30% hydrogen peroxide and acetic acid.)

Pyrimidine 1-Oxide (XVI)——Pyrimidine (XV), 1 g; 30% hydrogen peroxide, 30 ml; Na_2WO_4, 0.2 g; 60°, 9 hr; colorless needles from cyclohexane (mp 95—96°); yield, 17%. IR cm^{-1}: ν_{N-O} 1263 (KBr). NMR (in $CDCl_3$): 0.94 (1H, s, 2-H); 1.54 (1H, d, J=6.75 cps, 6-H); 1.69 (1H, d, J=5 cps, 4-H); 2.63 (1H, q, $J_{5,6}$= 6.75 cps, $J_{4,5}$=5 cps, 5-H). High Mass Spectrum *m/e*: Calcd. for $C_4H_4ON_2$: 96.0323. Found: 96.0310 (M^+).

Pyrazine 1-Oxide (XVIII)——Pyrazine (XVII), 0.5 g; 35% hydrogen peroxide, 4 ml; Na_2WO_4, 0.1 g; 40°, 3.5 hr; colorless needles from benzene after extracting it with benzene without submitting to chromatography, mp 113—114°; yield, 47%. IR cm^{-1}: ν_{N-O} 1316 (KBr). This product was identified with the authentic sample[8] by comparing IR spectra and mixture melting point. (The authentic sample was prepared with 30% hydrogen peroxide and acetic acid.)

Pyrazine 1,4-Dioxide (XIX)——XVII, 1 g; 30% hydrogen peroxide, 8 ml; Na_2WO_4, 0.1 g; 70°, 6 hr; colorless needles from methanol without submitting to chromatography, mp 285—295°; yield, 17% IR cm^{-1}: ν_{N-O} 1260 (KBr). This product was identified with the authentic sample[8] by comparing IR spectra and mixture melting point. (The authentic sample was prepared with 30% hydrogen peroxide and acetic acid.)

Quinoxaline 1-Oxide (XXI)——Quinoxaline (XX), 0.5 g; 35% hydrogen peroxide, 2.5 ml; Na_2WO_4, 0.1 g; 40°, 1.5 hr; colorless needles from cyclohexane without submitting to chromatography, mp 122—123°; yield, 50%. IR cm^{-1}: ν_{N-O} 1320 (KBr). This product was identified with the authentic sample[8] by comparing IR spectra and mixture melting point. (The authentic sample was prepared with 30% hydrogen peroxide and acetic acid.)

Quinoxaline 1,4-Dioxide (XXII)——XX, 3 g; 32% hydrogen peroxide, 16 ml; Na_2WO_4, 0.1 g; 50°, 6 hr; golden yellow needles from ethanol, mp 241—243°; yield, 54%. IR cm^{-1}: ν_{N-O} 1285 (KBr). This product was identified with the authentic sample[8] by comparing IR spectra and mixture melting point. (The authentic sample was prepared with 30% hydrogen peroxide and acetic acid.)

Phenazine 9-Oxide (XXIV) and Its 9,10-Dioxide (XXXV)——Phenazine (XXIII), 1 g; 34% hydrogen peroxide, 12 ml; ethanol, 30 ml; Na_2WO_4, 0.1 g; 70°, 16 hr. Recrystallization of its 9-oxide from ethanol gave yellow needles, mp 225°; yield, 21%. IR cm^{-1}: ν_{N-O} 1353 (KBr). Recrystallization of its 9,10-dioxide from ethanol gave orange needles, mp 204°; yield, 0.8%. IR cm^{-1}: ν_{N-O} 1353 (KBr). These products were identified with the authentic samples[9] by comparing IR spectra and mixture melting point. (The authentic samples were prepared with 30% hydrogen peroxide and acetic acid.)

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7) C.F. Koelsch and W.H. Gumprecht, *J. Org. Chem.*, **23**, 1603 (1958).
8) J.K. Landquist, *J. Chem. Soc.*, **1953**, 2816.
9) Y.S. Rozum and N.N. Lisouskaya, *Zh. Obshch. Khim.*, **29**, 228 (1959) [*Chem. Abstr.*, **53**, 21990 (1959)].