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Studies on the Reactions of Heterocyclic Compounds. II.[1] Syntheses and Some Reactions of 1,6-Phenanthroline N-Oxides

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1,6-Phenanthroline was synthesized from 4-aminoquinoline by the Skraup reaction using sulfo–mix, and N-oxidation was carried out in various ways to obtain 6-oxide and 1,6-dioxide. Reactions of 6-oxide with acetic anhydride and with phosphoryl chloride and the Reissert reaction were carreid out and the results were compared with those in the case of 1,6-naphthyridine.

In the previous paper[1] we reported on N-oxidation of 1,6-naphthyridine which was obtained by Paudler's method,[3] that is, using sulfo–mix in the Skraup reaction, and the reactions of its N-oxides. In this paper we report on 1,6-phenanthroline obtained from 4-aminoquinoline by applying the Skraup reaction using sulfo–mix, its N-oxidation, and some reactions of its N-oxides.

In the presence of sulfo–mix, 1,6-phenanthroline (I), mp 95—96°, was obtained from 4-aminoquinoline in 49% yield by the Skraup reaction. The structure of I was determined

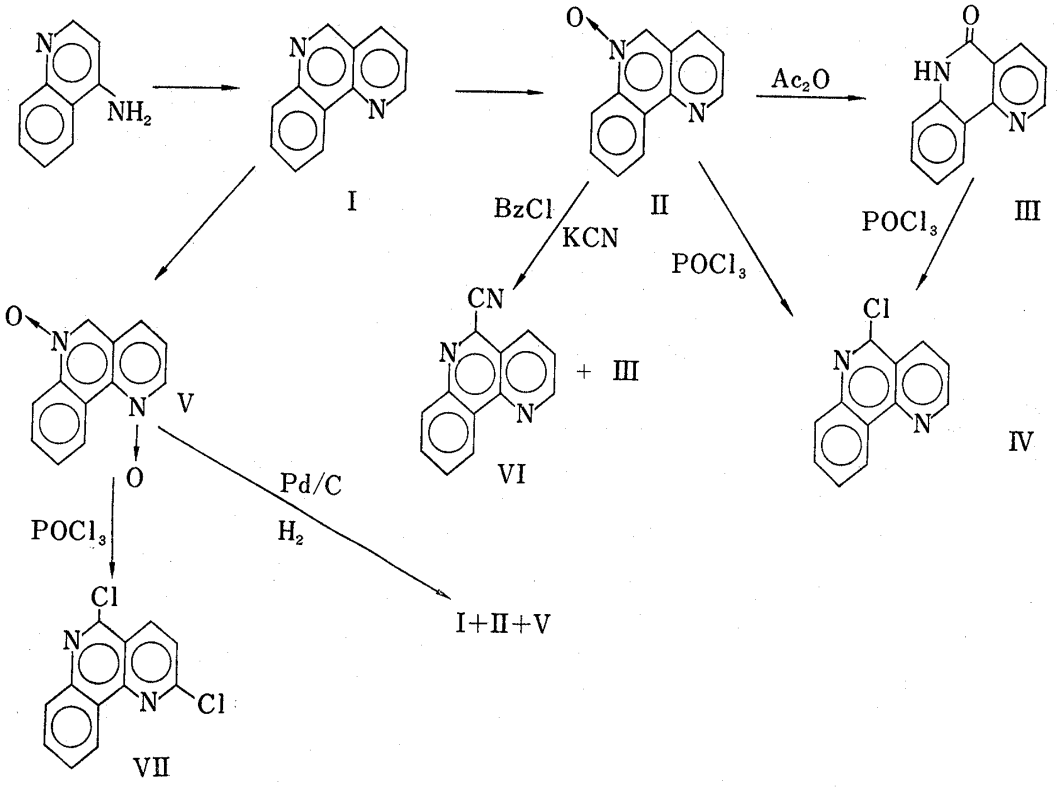

Chart 1

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[1] Part I: Y. Kobayashi, I. Kumadaki, and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **17**, 1045 (1969).

[2] Location: *Kashiwagi 4-chome, Shinjuku-ku, Tokyo.*

[3] T.J. Kress and W.W. Paudler, *Chem.Commun.*,**1967**, 3.

by its elemental analysis, infrared (IR) spectrum, and nuclear magnetic resonance (NMR) spectrum.

Next, in comparison with N-oxidation of 1,6-naphthyridine in the previous paper, that of 1,6-phenanthroline and the reactions of its N-oxides were carried out. Oxidation of I with acetic acid and a limited amount of hydrogen peroxide at 50° gave 1,6-phenanthroline 6-oxide (II) in 61.5% yield. The fact that no α-oxo compound was obtained in this case shows the fused benzene ring has a stabilizing effect for ring oxidation, which was observed in the case of 1,6-naphthyridine. Oxidation at a higher temperature (88—90°) gave 1,6-phenanthrolin-5(6*H*)-one (III) in 31% yield instead of II. The structure of II was deduced from reactions shown later. As III was found to be $C_{12}H_8ON_2$ from its elemental analysis and the carbonyl absorption band appeared at 1678 cm^{-1} in its IR spectrum, it was presumed to be 5(6*H*)-one derivative or 2(1*H*)-one one; it was determined as 5(6*H*)-one derivative from the fact that the signal of 5-H did not appear in the NMR spectrum when III was converted to its chloro derivative (IV) by boiling it with phosphoryl chloride. Oxidation of I at 50° with more hydrogen peroxide than before gave 51% of II and 5% of III.

As oxidation of I with acetic acid and hydrogen peroxide did not give 1-oxide, we tried oxidation with monoperphthalic acid. But only II and III were obtained in 30.5% and 41% yields, respectively. Therefore, N-oxidation was attempted with hydrogen peroxide in the presence of sodium tungstate,[4] whose presence gave dioxide in the case of 1,6-naphthyridine, and, similarly, 1,6-phenanthroline 1,6-dioxide (V), mp 280—281°, was obtained in 66% yield. V was found to be $C_{12}H_8O_2N_2$ from its elemental analysis and determined as 1,6-dioxide from the facts that N-O stretching band appeared at 1217 cm^{-1} and 1253 cm^{-1} with no carbonyl absorption band in its IR spectrum, and that treatment with phosphoryl chloride gave its dichloro derivative, as shall be described later.

In order to convert 1,6-dioxide obtained as above to 1-oxide, as in the cases of 1,6-naphthyridine 1,6-dioxide, partial reduction over Raney nickel was attempted, but the object was not produced though I was obtained in 57% yield and 32% of V was recovered. Applying the method of Itai and others,[5] therefore, we attempted partial reduction of 1,6-dioxide in the presence of hydrochloric acid over paladium-charcoal. After the absorption of 1 mole equivalent fo hydrogen, chromatographic separation of the reduction products afforded 21.5% of 6-oxide (II), 17.5% of I, and 28% of V but no 1-oxide. Such a difference as above can be explained in the case of 1,6-phenanthroline as caused by the fact that the oxygen atom at 1-position was readily eliminated, owing to the steric effect of the hydrogen atom at 10-position. Reactions with phosphorus trichloride and triphenyl phosphite were also attempted, and only a little amount of I was obtained while most of the starting materials were recovered in both cases.

Reactions of the oxides obtained as above were examined. First, when 1,6-phenanthroline 6-oxide (II) was boiled in acetic anhydride, its 5(6*H*)-one derivative (III) (previously mentioned) was given in 75% yield. When II was boiled with phosphoryl chloride, its 5-chloro derivative (IV) was given in 63% yield. The above results shows that the only nucleophilically active position in II is, as with other quinolines, α-position. When the Reissert reaction was attempted with II, against our expectation, very little 5-cyano derivative was obtained in the usual condition and the product was mostly 5(6*H*)-one derivative (III). This is presumed to be caused by the strong activity of 5-position in the benzoyl adduct of II under the effect of the nitrogen atom at 1-position, thereby reacting with water before attacking CN^-. Considering that prevention of its reaction with water by keeping the temperature lower should increase the yield of cyano derivative, the Reissert reaction under cooling in an ice-salt bath was carried out with the increased yield of 29% of 5-cyano-1,6-phenanthroline

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[4] R.C. Witmann, U. S. Patent 3047579 [*Chem. Abstr.*, **58**, 7916].

[5] T. Itai and H. Ogura, *Yakugaku Zasshi*, **75**, 292 (1955).

(VI). The fact is considered to support the above assumption. The structure of VI was found to be $C_{13}H_7N_3$ from its elemental analysis, from the fact that nitril absorption band appeared at 2250 cm^{-1} in its IR spectrum, and from the fact that no 5–H absorption was observed in NMR spectrum.

On the other hand, dioxide (V), when boiled with acetic anhydride, decomposed becoming resinous; but, when boilded with phosphoryl chloride, it gave 2,5-dichloro-1,6-phenanthroline (VII). The structure of VII was determined from the empirical formula $C_{12}H_6N_2Cl_2$ by its elemental analysis and from the facts that its Beilstein test was positive, and that no absorption was observed at 2-H and 5-H in NMR spectrum. The fact shows that α-position is reactive to nucleophilic reagents, as in the cases of other N-oxides generally.

To conclude from the above facts, 1,6-phenanthroline is more stable against oxidation than 1,6-naphthyridine and its 6-oxide is obtained in a good yield. Its 1-oxide is hard to obtain, which may be due to the effect of the hydrogen atom at 10-position in addition to the electronic effect. Its 1,6-dioxide is produced and the oxygen at 1-position is more readily reduced than that at 6-position. In the nucleophilic reaction of 6-oxide, 5-position is reactive in all the cases, but in the Reissert reaction, an abnormal result attributable to the effect of the nitrogen at 1-position is observed.

Experimental

Synthesis of 1,6-Phenanthroline (I)——To a sulfo-mix[6] (prepared from 50 ml of conc. H_2SO_4, 50% oleum (60 g), and nitrobenzene (28.6 g)), glycerine (33.2 g) was added under ice cooling. This solution was poured on 4-aminoquinoline (17 g), and after the addition of ice water (17 ml), the mixture was gently refluxed at 130—135° for 20 hr with stirring. After the reaction was completed, nitrobenzene was removed from the mixture by steam distillation. And when the solution was basified to pH 10 with 50% NaOH, the steam distillation was resumed. The distillate (30 liter) was salted out with NaCl and extracted with $CHCl_3$. After the extract was dried over Na_2SO_4, $CHCl_3$ was removed and the residue was recrystallized from *n*-hexane to afford colorless needles (I), mp 95—96°. Yield, 10.4 g (49%). NMR (in $CDCl_3$) δ[7]: 9.28 (1H, singlet, 5–H); *ca.* 9.15 (2H multiplet, 2–H, 10–H); 8.26 (2H, doublet, 4–H, 7–H); *ca.* 7.8 (2H, multiplet, 8–H, 9–H); 7.57 (1H, doublet-doublet, 3–H). *Anal* Calcd. for $C_{12}H_8N_2$: C, 80.01; H, 4.48; N, 15.55. Found: C, 79.97; H, 4.52; N, 15.47.

Reaction of 1,6-Phenanthroline with AcOH-H_2O_2——a) A mixture of I (0.9 g) with AcOH (3 ml) and 30% H_2O_2 (1 ml) was warmed at 50° for 2 hr. After the addition of 30% H_2O_2 (0.5 ml), warming was continued for 3 hr. The solution was concentrated *in vacuo* to half the volume, and the same amount of water was added; the same procedure was repeated twice. After being neutralized with Na_2CO_3, the mixture was extracted with $CHCl_3$ and dried over Na_2SO_4; then $CHCl_3$ was distilled off to afford yellow powder (0.8 g).

By fractional recrystallization from EtOH, colorless needles (II), mp 209—210° (yield: 0.5 g, 51%), and colorless needles (III), mp 275—276° (yield: 0.05 g, 5%), were obtained. II: IR cm^{-1}: ν_{N-O} 1220 (KBr). *Anal.* Calcd, for $C_{12}H_8ON$ (1,6-phenanthroline 6-oxide): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.33; H, 4.20; N, 14.32. III: IR cm^{-1}: $\nu_{C=O}$ 1678 (KBr). *Anal.* Calcd. for $C_{12}H_8ON$ (1,6-phenanthrolin-5(6*H*)-one): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.49; H, 4.10; N, 14.85.

b) A mixture of I (0.9 g) with 30% H_2O_2 (0.7 ml) and AcOH (3 ml) was warmed at 50° for 10 hr. After the addition of 30% H_2O_2 (0.4 ml), warming was continued for additional 11 hr. After the treatment mentioned above, 0.6 g (61.5%) of II was obtained but III was not found at all.

c) A mixture of I (0.9 g) with 30% H_2O_2 (1 ml) and AcOH (3 ml), was heated at 88—90° for 3 hr. The treatment described above afforded 0.3 g of III, but none of II.

d) To a solution of I (0.9 g) in ether (5 ml), a solution (7.4 ml, 10.5%) of monoperphthalic acid in ether was added under ice cooling. After 13 days' cooling in an ice box, conc. NH_4OH was added to the mixture and the precipitate was collected by filtration. The filtrate was evaporated *in vacuo*. The precipitate and the residue were recrystallized from MeOH. Two crops of crystals were obtained: III (0.4 g, 41%) and II (0.3 g, 30.5%) in that order.

1,6-Phenanthrolin-5(6*H*)-one (III)——A solution of II (0.4 g) in Ac_2O (10 ml) was refluxed for 5 hr. After the evaporation of Ac_2O *in vacuo*, the residue was treated with H_2O, neutralized with Na_2CO_3, and extracted with $CHCl_3$. After being dried with Na_2SO_4, the solvent was evaporated, and the residue was recrys-

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[6] W.P. Utermohlen, Jr., *J. Org. Chem.*, **8**, 544 (1943).

[7] Internal standard: TMS.

tallized from MeOH to give colorless needles, mp 273—274°. Yield, 0.3 g (75%). The crystals were identified with III obtained in the above reaction by the mixture melting point and comparing IR spectra.

5-Chloro-1,6-phenanthroline (IV)——a) A solution of III (0.3 g) in $POCl_3$ (2 ml) was refluxed for 4 hr, followed by the evaporation of $POCl_3$ *in vacuo*. The residue was treated with ice water, neutralized with Na_2CO_3, and extracted with $CHCl_3$. After being dried over Na_2SO_4, the solvent was evaporated and the residue was recrystallized from *n*-hexane to give pale yellow prisms, mp 102—103°. Yield, 0.2 g (61%). Beilstein test, (+). NMR spectrum has no signal of 5-H (δ 9.28). *Anal.* Calcd. for $C_{12}H_7N_2Cl$: C, 67.14; H, 3.30; N, 13.05. Found: C, 66.99; H, 3.34; N, 13.29.

b) A solution of II (0.2 g) in $POCl_3$ (2 ml) was refluxed for 4 hr and treated as in a). Colorless prisms, mp 99.5—101°, were obtained. Yield, 0.138 g (63%). The crystals were identified with IV obtained by the method mentioned above, by mixture melting point and comparing IR spectra.

The Reissert Reaction of II——a) To a solution of II (0.2 g in $CHCl_3$ (8 ml)), a solution of KCN (0.2 g) in H_2O (5 ml) was added and the mixture was cooled with ice. To this solution, BzCl (0.2 g) was added under stirring. After stirring was continued for 5 hr, the precipitated crystals were collected by filtration and washed with water. The filtrate was separated to two layers and the water layer was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with 10% NaOH and dried over Na_2SO_4. After the evaporation of $CHCl_3$, the residue was chromatographed over Al_2O_3. The first elute with C_6H_6–$CHCl_3$ (1:1) gave a trace of colorless needles, mp 163—164.5°. It was identified as 5-cyano-1,6-phenanthroline (VI), whose data will be described later. The second elute with $CHCl_3$–MeOH (20:1) and filtered crystals gave III (0.115 g).

b) To a solution of II (0.2 g) in $CHCl_3$ (8 ml), a mixture of KCN (0.2 g) in H_2O (10 ml) was added and the mixture was chilled in an ice-salt bath. To this solution BzCl (0.2 g) was added under stirring, and stirring was continued for 3 hr. When it was treated as above, colorless needles (from *n*-hexane) of VI, mp 163—164.5°, (yield: 0.61 g, 29%) and III (yield: 0.11 g, 55%) were obtained. VI: IR cm^{-1}: $\nu_{C\equiv N}$ 2250 (KBr). 5-H signal in I (9.28) disappeared in NMR spectrum. *Anal.* Calcd. for $C_{13}H_7N_3$: C, 76.08; H, 3.44; N, 20.28. Found: C, 75.97; H, 3.68; N, 20.16.

1,6-Phenanthroline 1,6-dioxide (V)——To a solution of I (1.8 g) in 30% H_2O_2 (12 ml), Na_2WO_4 (0.1 g) was added and the mixture was warmed at 50° for 15 hr under stirring. After the same volume of water was added to the reaction mixture, water was evaporated *in vacuo* to half the volume. This procedure was repeated four times. Precipitated crystals were collected by filtration and the filtrate was treated as above. The first and second crops of crystals were treated together and recrystallized from MeOH to give yellow needles, mp 280—281° (decomp.). Yield, 1.4 g (66%). IR cm^{-1}: ν_{N-O} 1217, 1253 (KBr). *Anal.* Calcd. for $C_{12}H_8O_2N_2$: C, 67.29; H, 3.80; N, 13.20. Found: C, 68.08; H, 3.92; N, 13.39.

Deoxidation of V——a) A solution of V (0.62 g) in MeOH (700 ml) was shaken with Reney Ni (from Ni-Al alloy (0.5 g)) in H_2 atmosphere. After H_2 (140 ml) was absorbed, Ni was filtered off, the solvent was evaporated, and the residue was chromatographed over silica gel. The first elute with $CHCl_3$ gave I (0.3 g, 57%). The second elute with $CHCl_3$–MeOH (10:1) gave V (0.2 g, 32%).

b) To a solution of V (0.521 g) in conc. HCl (2 ml), 5% Pd-C (0.55 g) and H_2O (30 ml) were added, and the mixture was shaken in H_2 atmosphere. After H_2 (52 ml, 0.96 equivalent) was absorbed, the catalyst was filtered off. The filtrate was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. After the extract was dried over Na_2SO_4, the solvent was evaporated. Recrystallization of the residue from MeOH gave V, which was identified by mixture melting point.

The solvent was evaporated from the mother liquor, and the residue was chromatographed over silica gel. The first elute with $CHCl_3$ gave I (0.078 g, 17.5%), and the second elute with MeOH–$CHCl_3$ (1:100) gave II (0.104 g, 21.5%). The third elute with MeOH–$CHCl_3$ (1:20) and the crystals obtained in the above reaction gave V (0.145 g, 28%).

c) To a solution of V (0.193 g) in $CHCl_3$ (50 ml), PCl_3 (0.137 g) was added under cooling, and the mixture was kept at 2° in an ice box for 13 hr. The reaction mixture was treated with ice water, neutralized with Na_2CO_3, and extracted with $CHCl_3$. After it was dried over Na_2SO_4, $CHCl_3$ was evaporated and the residue was recrystallized to recover V (0.131 g).

d) To a solution of V (0.212 g) in $(CH_3)_2NCHO$ (15 ml), $P(OC_6H_5)_3$ (0.40 g) was added and the mixture was heated at 145—155° for 5 hr. After the evaporation of $(CH_3)_2NCHO$ *in vacuo*, the residue was dissolved in $CHCl_3$ (5 ml) and the base was extracted with $CHCl_3$. After it was dried over K_2CO_3, $CHCl_3$ was evaporated and the recrystallization of the yellow residue from MeOH gave III (0.104 g) and I (0.015 g), which were identified by mixture melting point and comparing IR spectra.

2,5-Dichloro-1,6-phenanthroline (VII)——A solution of V (0.40 g) in $POCl_3$ (3 ml) was refluxed for 4 hr. After the evaporation of the excess $POCl_3$ *in vacuo*, the residue was treated with $CHCl_3$. After it was dried with Na_2SO_4, $CHCl_3$ was evaporated and the residue was recrystallized from *n*-hexane to give colorless prisms of VII, mp 174—175°. Yield, 0.32 g (68%). Beilstein test. (+). *Anal.* Calcd. for $C_{12}H_6N_2Cl_2$: C, 57.88; H, 2.43; N, 11.25. Found: C, 58.38; H, 2.71; N, 11.63.

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