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Studies on Ring-opening of Heterocyclic Compounds. III.[1] Alternative Preparation of Isoquinoline N-Oxide and N-Imine[2]

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Isoquinoline N-oxide (**5**) and N-imine (**8**) were prepared by ring-opening reactions of quarternary isoquinolinium salts and successive ring-closures. The ring-opening reaction of N-(2,4-dinitrophenyl)isoquinolinium chloride (**1**) with hydroxylamine gave *o*-[2-(2,4-dinitroanilino)vinyl]benzaldehyde oxime (**2**), which cyclized by refluxing in concentrated hydrochloric acid–ethanol (3:40) to isoquinoline N-oxide (**5**) in 53% yield from isoquinoline. This method was applied to the preparation of isoquinoline N-imine (**8**). An equimolar mixture of N-(2,4-dinitrophenyl)isoquinolinium chloride (**1**) and hydrazine hydrate in dioxane–water (4:1) was heated under reflux to give isoquinoline N-imine (**8**) in 50% yield from isoquinoline.

In the previous paper,[1] we reported the preparation of pyridine N-oxides and N-aminopyridinium chlorides by the ring-cleavage of N-(2,4-dinitrophenyl)pyridinium chloride followed by the ring-closure of the resulted azatriene. The present paper extends this method to the preparation of isoquinoline N-oxide (**5**) and N-imine (**8**).

Synthesis of Isoquinoline N-Oxide(5)

Isoquinoline N-oxide(**5**) can be prepared by the direct oxidation[4] of isoquinoline with peracid. The formation[5] of **5** from homophthalaldehyde with hydroxylamine is of interest as a route without oxidizing reagent, but it has never been established as a preparative method. We applied the method for pyridine N-oxides and N-aminopyridinium chlorides reported in the previous paper[1] to preparation of isoquinoline N-oxide(**5**) and N-imine(**8**) and established the following method *via* cyclization of homophthalaldehyde derivatives as shown in Chart 1.

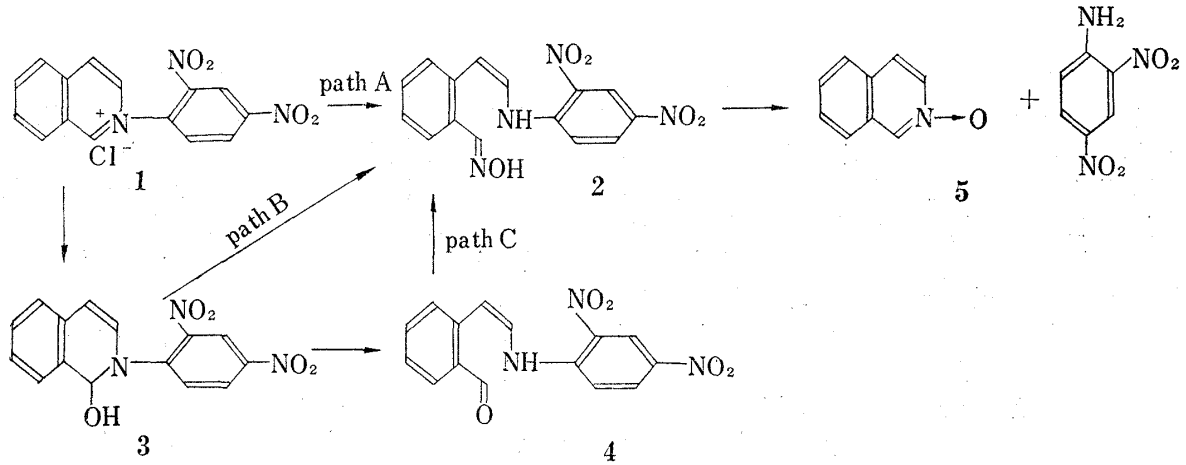

Chart 1

1) Part II: Y. Tamura, N. Tsujimoto and M. Mano, *Chem. Pharm. Bull.* (Tokyo), **19**, 130 (1971).
2) Y. Tamura and N. Tsujimoto, *Chem. and Ind.*, **1970**, 926.
3) Location: *Toneyama, Toyonaka, Osaka.*
4) J. Meisenheimer, *Ber.*, **59**, 1848 (1926).
5) C. Schopf, A. Hartmann and K. Koch, *Ber.*, **69**, 2766 (1936); W.E. Doering and J.A. Berson, *J. Am. Chem. Soc.*, **72**, 1118 (1950).

N-(2,4-Dinitrophenyl)isoquinolinium chloride(1)[6] was prepared by keeping an equimolar mixture of isoquinoline and 2,4-dinitrochlorobenzene at 40° for 5 hr in quantitative yield. Treatment of **1** (0.01 mole), hydroxylamine hydrochloride (0.02 mole) and triethylamine (0.03 mole) in methanol at room temperature gave *o*-[2-(2,4-dinitroanilino)vinyl]benzaldehyde oxime(**2**) in 71% yield (path A). Two other routes, path B and C, from **1** to **2** were also investigated. The path B is the following two step route; treatment of **1** with 5% sodium carbonate in water afforded a high yield of 1-hydroxy-2-(2,4-dinitrophenyl)-1,2-dihydroisoquinoline(**3**),[7] which was converted into **2** with hydroxylamine hydrochloride and triethylamine in methanol. Over-all yield of the path B was 68% from **1**. The path C is as follows. Refluxing **3** in 20% aqueous acetone gave *o*-[2-(2,4-dinitroanilino]vinyl]benzaldehyde(**4**),[7] which was treated with hydroxylamine hydrochloride in the presence of triethylamine to give **2**. The path C afforded 70% yield of **2** from **1**. From these experimental results the path A was proved to be most excellent as a preparative method especially from simple operations.

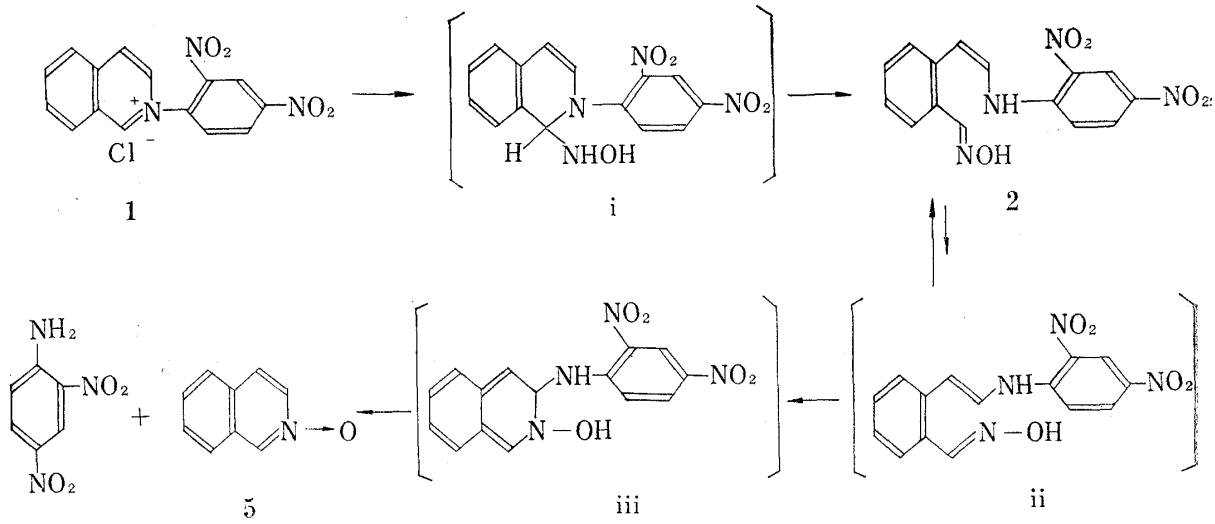

Chart 2

The conformation of **2** is assumed to be *cis* conformer from its nuclear magnetic resonance (NMR) spectrum (Chart 2). Kuhn[8] examined the NMR spectrum of *β*-(4-nitrobenzylideneamino)-2-formylstyryl, produced by the ring opening of N-(*α*-benzyloxy-4-nitrobenzyl)-isoquinolinium chloride with kalium hydroxide, and assigned the coupling constant of J 8.2 cps of the two vinyl protons for the *cis* configuration of the double bond. The NMR spectrum of **2** exhibits the coupling constant of $J_{3,4}$ 9 cps, and this coupling constant is in good accord with that assigned for the *cis* double bond by Kuhn.

Cyclization of **2** to **5** by heating in various solvents, such as HCl–EtOH, HCl, AcOH, TsOH–EtOH and dioxane–H_2O, were investigated and the results shown in Table I. Heating in concentrated hydrochloric acid–ethanol gave the highest yield (75%).

As to the mechanism for the ring-cleavage and subsequent ring-closure reactions from **1** to **5**, we suppose a sequence of reaction as shown in Chart 2. The ring opening of **1** would proceeded *via* i to give the *cis* vinylbenzaldehyde oxime(**2**). Heating of **2** in concentrated hydrochloric acid–ethanol (3:40) causes conversion to the *trans* conformer ii, which undergoes cyclization to iii followed by removal of 2,4-dinitroaniline to give **5**.

6) Th. Zincke and G. Weisspfenning, *Ann.*, **396**, 103 (1913).
7) D. Beke and C. Szantay, *Ann.*, **640**, 127 (1961).
8) R. Kuhn and E. Teller, *Ann.*, **715**, 106 (1968).

Table I. Cyclization of *o*-[2-(2,4-Dinitroanilino) vinyl]benzaldehyde Oxime(2) to Isoquinoline N-Oxide(5)

Solvent	Temperature (°C)	Yield of isoquinoline N-oxide(5) (as picrate) (%)
Ethanol–conc.HCl (3:40)	65	81
Ethanol–conc.HCl (1:4)	65	81
Ethanol–TsOH	65	78
Water–conc.HCl (3:40)	105	72
Acetic acid	105	17
Dioxane–water (4:1)	105	1

Synthesis of Isoquinoline N-Imine(8)

Huisgen reported[9] the preparation of isoquinoline N-imine(8) by the Gösl' smethod. This report establishes an alternative method for isoquinoline N-imine(8). The method is essencially the same as that for **5** except in using hydrazine hydrate in place of hydroxylamine. Treatment of **1** with hydrazine hydrate gave crude *o*-[2-(2,4-dinitroanilino)vinyl]-benzaldehyde hydrazone(**6**), which was converted to N-aminoisoquinolinium chloride(**7**) by heating in concentrated hydrochloric acid–ethanol (3:40) for 4 hr. However, the yield of the latter cyclization step, **6** to **7**, was poor. The over-all yield was improved by the following modification; hydrazine hydrate was added drowpise to an ice-cooled solution of **1** in water and then dioxane was added to the mixture. The mixture, after being kept overnight at room temperature, was heated under reflux for 7 hr. The product was obtained as N-aminoisoquinolinium chloride(**7**) in 50% yield from isoquinoline. An ethanolic solution of **7** was passed through a column of anion exchange resin (Amberlite IRA-410) to give N-iminoisoquinolinium betaine (**8**). The Mass spectrum of **8** (Chart 3) exhibits the molecular ion at *m/e* 228, whose values insists strongly that the structure of **8** is in dimer form.

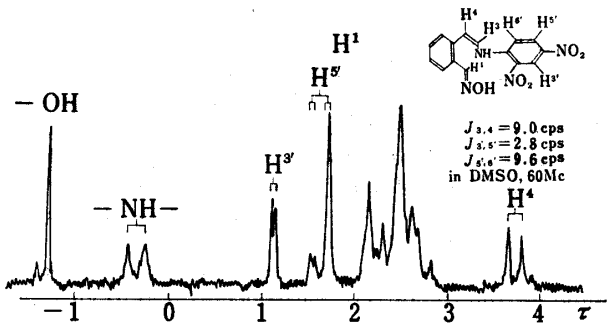

Fig. 1

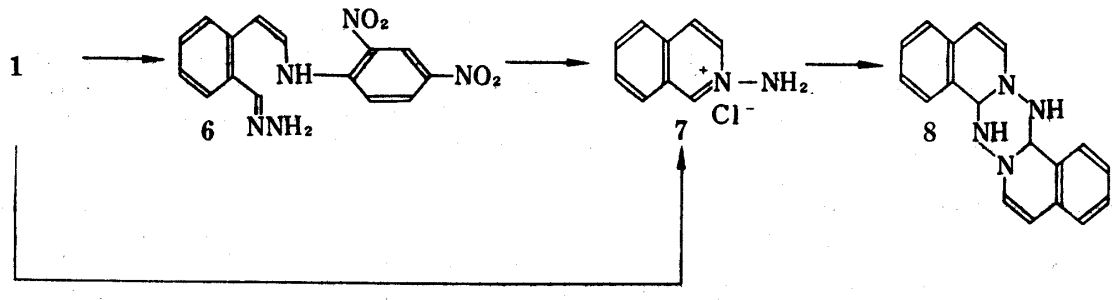

Chart 3

Experimental

The NMR spectrum was measured with a Hitachi Perkin-Elmer H-60 type (60 Mc). The mass spectrum was measured with a Hitachi RMU-6D mass spectrometer. Melting points are uncorrected.

9) R. Huisgen, R. Grashey and R. Krishke, *Tetrahedron Letters*, **1962**, 387.

N-(2,4-Dinitrophenyl)isoquinolinium Chloride (1)——A mixture of isoquinoline (1.65 g, 0.013M) and 2,4-dinitrochlorobenzene (2.61 g, 0.013M) was warmed at 40° for 5 hr. After cooling, the whole mixture solidified. The solid was triturated in dry CH_3COCH_3, collected and washed thoroughly with dry CH_3COCH_3 and dry ether. Recrystallization from EtOH–ether gave light yellow hygrosscopic crystals of **1** (3.96 g, 93% yield), mp 180—181° (decomp.) (lit.[6] mp 130°).

***o*-[2-(2,4-Dinitroanilino)vinyl]benzaldehyde Oxime** (2)——a) To an ice-cooled solution of **1** (3.32 g, 0.01M) in MeOH (5 ml) was added dropwise a solution of $NH_2OH \cdot HCl$ (1.39 g, 0.02M) and Et_3N (2.03 g, 0.02M) in MeOH (15 ml) with stirring. Triethylamine (1 g, 0.01M) was added to the mixture. The mixture was stirred at room temperature for 5 hr, during which time color of the mixture gradually changed from colorless to red-violet to precipitates. The precipitates were collected and washed thoroughly with MeOH, H_2O, MeOH and ether to give reddish-violet crystals of **2** (2.33 g, 71% yield), mp 159—160°. *Anal.* Calcd. for $C_{15}H_{12}O_5N_4$: C, 54.88; H, 3.68; N, 17.07. Found: C, 54.96; H, 3.48; N, 17.14. NMR (in DMSO) τ: 3.74 (1H, doublet, $J_{3,4}=9.0$ cps, H^3 or H^4), 1.50—2.75 (multiplet, H^3, $H^{6'}$, $H^{5'}$, H^1, $H^{3'}$), −0.35 (1H, doublet, $J_{NH-H^3}=12$ cps, –NH–), −1.28 (1H, singlet, –OH).

b) To a suspension of 1-hydroxy-2-(2,4-dinitrophenyl)-1,2-dihydroisoquinoline (**3**) (3.13 g, 0.01M, mp 89.5—90°; lit.[7] 95—105°), prepared from **1** and 5% Na_2CO_3 solution in 94% yield according to the procedure of Beke, *et al.*,[7] in MeOH (6 ml) was added a solution of NH_2OH HCl (1.39 g, 0.02M) and Et_3N (2 g, 0.02M) in MeOH (14 ml). The mixture was heated at 60° for 4 hr, during which time the orange crystals of **3** changed to red-violet crystals. The red-violet crystals were collected and washed thoroughly with MeOH, H_2O, MeOH and ether to give reddish-violet crystals (2.12 g, 79% yield), mp 159—160°, whose infrared (IR), ultraviolet (UV) and NMR spectra and mp were completely identical with **2**.

c) To a suspension of *o*-[2-(2,4-dinitroanilino)vinyl]benzaldehyde (**4**) (3.13 g, 0.01M, mp 153—154°; lit.[7] mp 154°), prepared from **3** and 20% aqueous CH_3COCH_3 in 79% yield according to the procedure of Beke, *et al.*,[7] in MeOH (8 ml) was added a solution of $NH_2OH \cdot HCl$ (1.39 g, 0.02M) and Et_3N (2 g, 0.02M) in MeOH (12 ml). The reaction mixture was stirred at room temperature for 16 hr. The precipitates were collected and washed thoroughly with MeOH, H_2O, MeOH and ether to give reddish-violet crystals (3.10 g, 94% yield), which identified with the IR, UV and NMR spectra and mp of **2**.

Isoquinoline N-Oxide (5)——a) Cyclization in conc. HCl–EtOH (3:40): To a suspension of **2** (3.28 g, 0.01M) in EtOH (40 ml) was added conc. HCl (3 ml, 0.03M). The mixture was heated at 65° for 15 min, during which time the mixture changed to a light yellow solution. Water (80 ml) was added to the cooled light-yellow solution to give yellow precipitates of 2,4-dinitroaniline. The yellow precipitates (1.8 g) were filtered off and the filtrate was concentrated to yield light yellow residue, which was treated with an ethanolic solution of picric acid to give a picrate of **5** (3.01 g, 81% yield), mp 167—167.5° (lit.[4] mp 165°).

b) Cyclization in conc. HCl–EtOH (1:4): To a suspension of (**2**) (3.28 g, 0.01M) in EtOH (40 ml) was added a solution of conc. HCl (10 ml, 0.1M). The reaction mixture was heated at 65° for 5 min. The mixture was treated in a similar manner to that described above in a) to give a picrate of **5** (3.03 g, 81% yield).

c) Cyclization in TsOH–EtOH: To a suspension of **2** (3.28 g, 0.01M) in EtOH (40 ml) was added TsOH (5.16 g, 0.03M). The mixture was heated at 65° for 5 min. The mixture was treated in a similar manner to that described above in a) to give a picrate of **5** (2.91 g, 78%).

d) Cyclization in conc. HCl–H_2O (3:40): To a suspension of **2** (3.28 g, 0.01M) in H_2O (40 ml) was added a solution of conc. HCl (3 ml, 0.03M). The mixture was heated at 105° for 7 hr. The mixture was treated in a similar manner to that described above in a) to give a picrate of **5** (2.70 g, 72%).

e) Cyclization in AcOH: A suspension of **2** (3.28 g, 0.01M) in AcOH (40 ml) was heated at 105° for 30 min. The mixture was treated in a similar manner to that described above in a) to give a picrate of **5** (0.65 g, 17%).

f) Cyclization in Dioxane–H_2O (4:1): A suspension of **2** (3.28 g, 0.01M) in dioxane–H_2O (4:1) (40 ml) was refluxed at 105° for 10 hr. After cooling, the solvent was removed at reduced pressure to give the residue. Water (80 ml) and conc. HCl (1 ml, 0.01M) were added to the residue. The precipitates were filtered off and the filtrate was concentrated to give the residue. The residue was treated with an ethanolic solution of picric acid to give a picrate of **5** (0.53 g, 1.4%).

N-Iminoisoquinolinium Betaine (8)——a) From *o*-[2-(2,4-Dinitroanilino) vinyl] benzaldehyde Hydrazone (**6**): To an ice-cooled solution of **1** (3.32 g, 0.01M) in MeOH (20 ml) was added dropwise a solution of $NH_2NH_2 \cdot H_2O$ (1 ml, 0.02M), during which time color of the solution changed colorless to red. The red mixture was allowed to stand at room temperature for 2 hr with stirring. The precipitates were collected and washed with MeOH, H_2O, MeOH and ether to give an orange product of crude **6** (2.74 g), mp 149—150°. A suspension of crude **6** (2.74 g) in dioxane–H_2O (4:1) (40 ml) was heated under reflux for 10 hr. After cooling, the reaction mixture was acidified with 10% HCl (3.2 ml, 0.009M). The solvent was removed at reduced pressure. The precipitates were filtered off and the filtrate was concentrated to give crude **7**. The crude **7** was treated with an ethanolic solution of picric acid to give a picrate of **8** (0.01 g, 3% yield), yellow needles, mp 182—184°. *Anal.* Calcd. for $C_{15}H_{11}O_6N_5$: C, 48.26; H, 2.97; N, 18.76. Found: C, 49.13; H, 3.39; N, 17.97.

b) From N-(2,4-Dinitrophenyl)isoquinolinium Chloride (**1**): To a solution of **1** (3.32 g, 0.01M) in H_2O (8 ml) was added dropwise a solution of $NH_2NH_2 \cdot H_2O$ (0.5 ml, 0.01M) in ice-cooling, during which time the

solution gave precipitates. The mixture was allowed to stand at room temperature for 1 hr and then dioxane (32 ml) was added to the mixture. The mixture was heated under reflux for about 10 hr until the mixture changed to clear. After cooling, the mixture was acidfied with 10% HCl (3.6 ml, 0.01M). The solvent was removed at reduced pressure and H_2O (50 ml) was added to the residue. The precipitates were filtered off and the filtrate was concentrated to yield white hygroscopic needles of crude **7**. The crude **7** was treated with an ethanolic solution of picric acid to give a picrate of **8** (1.86 g, 50% yield), yellow needles, mp 182—184°. HI salt of **8**: yellow needles, mp 177—178° (decomp.). *Anal.* Calcd. for $C_9H_9N_2I$: C, 39.73; H, 3.33; N, 10.30. Found: C, 39.93; H, 3.42; N, 10.13. An ethanolic solution of **7**, picrate of **8** or HI salt of **8** was passed through the anion exchange resin using EtOH as the eluent to give white needles of **8** in quantitative yield, mp 147—148. *Anal.* Calcd. for $C_{18}H_{16}N_4$: C, 74.97; H, 5.59; N, 19.43. Found: C, 75.18; H, 5.46; N, 19.42. UV λ_{max}^{EtOH} mμ (log ε): 219 (4.67), 231 (4.63), 245 (4.63). Mass Spectrum *m/e* 288. (M^+)