[Chem. Pharm. Bull. 22(8)1921—1922(1974)]

UDC 547.822.3'546.04.057

Synthesis of Nitrophenylpiperidine N-Oxides and Their Reductive Intramolecular Ring-Closure

Hiroshi Takahashi, Shiro Sato, and Hirotaka Otomasu

Hoshi College of Pharmacy[1]

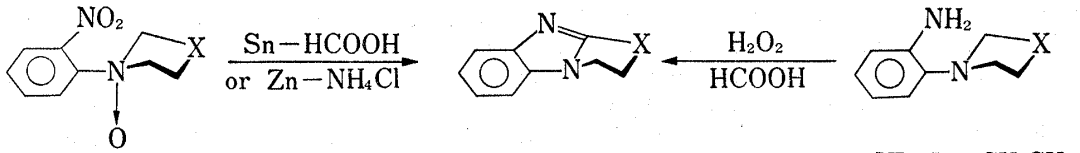
(Received February 1, 1974)

Few studies of N-oxides of piperidine and its related compounds have been reported. Only 1-phenylpiperidine 1-oxide,[2] 1-(2-nitrophenyl)piperidine 1-oxide[2] and 1-(pentafloro-phenyl)piperidine 1-oxide[3] have been synthesized.

We have synthesized the N-oxide (II) from 1-(4-nitrophenyl)piperidine using hydrogen peroxide in formic acid. N-Oxide (II) formed light yellow pillar shaped crystals (mp 120—123°). N-Oxide (III) which formed a light yellow crystals (mp 93°) was also synthesized from 1-(2-nitrophenyl)pyrrolidine. In both cases the yields were good. The structure of II and III were identified with infrared (IR), nuclear magnetic resonance (NMR), and mass (MS) spectra.

It is known that when 1-(2-aminophenyl)piperidine (VI) is treated with hydrogen peroxide in formic acid, it causes ring closure between the amino group and position 2 in the piperidine ring forming 1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (IV).

We have synthesized benzimidazole derivative (IV) by reducing 1-(2-nitrophenyl)piperidine 1-oxide (I) by tin in formic acid or by zinc with ammonium chloride. This may indicate that under these weak reduction condition, a nitro group in an organic nitro compound could be reduced to a hydroxyamino group. With the same reaction conditions of I, we have synthesized 1*H*-2,3-dihydropyrrolo[1,2-*a*]benzimidazole (V) from 1-(2-nitrophenyl)pyrrolidine 1-oxide (III). This also appears to be a reductive intramolecular ring closure.



I : X=CH_2CH_2
III : X=CH_2

IV : X=CH_2CH_2
V : X=CH_2

VI : X=CH_2CH_2

Chart 1

Meth-Cohn[4] reported the stnthesis of IV from 1-(2-aminophenyl)piperidine in formic acid by using hydrogen peroxide. He assumed that the piperidine N-oxide was produced as an intermediate before the ring closure to form IV, however he never isolated the N-oxide. In comparison with this report, our present work has shown that nitrophenylpiperidine N-oxide compounds (I and III) by their reductive intramolecular ring-closure gave benzimidazole compounds (IV and V). This experimental result may indicate the importance of the presence of an N-oxide group on the intramolecular ring closure of I and III.

1) Location: *Ebara 2-4-41, Shinagawa-ku, Tokyo.*
2) O. Meth-Cohn and H. Suschitzky, *J. Chem. Soc.*, **1963**, 4666.
3) M. Bellas, D. Price, and H. Suschitzky, *J. Chem. Soc.* (*C*), **1967**, 1249.
4) O. Meth-Cohn, *J. Chem. Soc.* (*C*), **1971**, 1356.

Experimental

All melting points were uncorrected. IR spectra were recorded on Hitachi Infrared Spectrophotometer, Model 215. NMR spectra were recorded on Hitachi-Perkin-Elmer Model R-20 Spectrometer and tetramethylsilane was used as an internal standard. A Hitachi Model RMS-4 Mass Spectrometer was used to take all MS spectra in this experiment.

1-(2-Nitrophenyl)piperidine 1-Oxide (I)——This N-oxide (I) was synthesized mainly by following the method of Meth-Cohn, *et al.*[2] 1-(2-Nitrophenyl)piperidine 10 g was dissolved in 60 ml of formic acid and then 30 ml of 30% H_2O_2 was added to the solution. As the mixture was heated, it reacted violently. After the violent reaction ceased, the mixture was heated 20 minutes, then it was cooled to room temperature. The reaction mixture was neutralized by aqueous ammonia and was extracted by chloroform. The chloroform was distilled and the residue was purified by column chromatography using alumina. The colorless needle crystals were obtained and they were recrystalized from benzene, mp 176° (mp 166° [2]). The yield was 8.0 g (75%). *Anal.* Calcd. for $C_{11}H_{14}O_3N_2$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.25; H, 6.10; N, 12.44. IR ν_{max}^{KBr} cm^{-1}: 1540, 1380 (NO_2). $M^+=222$ and $(M^+-O)=206$. NMR ($CDCl_3$) ppm: 1.6—1.9 (4H), 2.1—2.8 (2H), 3.8—4.0 (4H), 7.4—8.0 (4H, aromatic).

1-(4-Nitrophenyl)piperidine 1-Oxide (II)——1-(4-Nitrophenyl)piperidine 2.0 g was dissolved in 12 ml of formic acid and then 6 ml of 30% H_2O_2 was added to the solution. The same purification method as the preparation of compound I was applied. 1.7 g of light yellow pillar shaped crystals were obtained, mp 120—123° (benzene). The yield was 73%. *Anal.* Calcd. for $C_{11}H_{14}O_3N_2$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.30; H, 6.32; N, 12.48. IR ν_{max}^{KBr} cm^{-1}: 1530, 1355 (NO_2). $M^+=222$ and $(M^+-O)=206$. NMR ($CDCl_3$) ppm: 1.5—1.9 (4H), 2.3—4.0 (6H), 8.28 (4H, aromatic).

1-(2-Nitrophenyl)pyrrolidine 1-Oxide (III)——Five g of 1-(2-nitrophenyl)pyrrolidine was dissolved in 60 ml of formic acid. Then 40 ml of 30% H_2O_2 was added into the solution. The mixture was heated at 50° for 2 hours with continuous stirring. The reaction mixture was neutralized by aqueous ammonia and then extracted by chloroform. Chloroform was distilled and the residue was recrystallized by using benzene as a solvent. Light yellow needle crystals were obtained, mp 93°. The yield was 91% (5.1 g). *Anal.* Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.66; H, 5.71; N, 13.22. IR ν_{max}^{KBr} cm^{-1}: 1530, 1375 (NO_2). $M^+=208$ and $(M^+-O)=192$. NMR ($CDCl_3$) ppm: 2.1—2.5 (4H), 3.9—4.2 (4H), 7.4—7.8 (4H, aromatic).

Intramolecular Ring-Closure of I——i) Reduction with Tin in Formic Acid: The compound I, 500 mg, was dissolved in 20 ml of formic acid and 500 mg of granular tin was added. The mixture was refluxed for 3 hours, then cooled and the inorganic salts were filtered. The filtrat was concentrated under vacuum, and water was added to the concentrated filtrate. This solution was made basic by adding aqueous ammonia, and then extracted by chloroform. The chloroform was distilled and the residue was purified by column chromatography using alumina. 1-(2-Formamidophenyl)piperidine and 1,2,3,4-tetrahydropyrido[1,2-*a*]-benzimidazole (IV) were prepared by this method, and their yields were 80 mg (18%) and 320 mg (82%), respectively. The melting points of the mixture of these compounds and their authentic compounds shown no depression. Furthermore the *Rf* values on thin-layer chromatography (TLC) and IR spectra of these compounds and those of authentic compounds were identical.

ii) Reduction with Zinc and Ammonium Chloride: Eight hundred mg of ammonium chloride was dissolved into 15 ml of water. Compound I 1.0 g was dissolved in 20 ml of methanol and the aqueous ammonium chloride solution was added to it. The mixture was stirred continuously and 1.8 g of zinc powder was added over 30 minutes. The temperature of the mixture during this time was kept at 5—10°. Then the mixture was stirred for 6 hours at room temperature. The precipitation was filtered and the filtrate was concentrated and extracted by chloroform. Chloroform was distilled and the residue was purified by column chromatography using alumina. 1-(2-Aminophenyl)piperidine (VI) and 1,2,3,4-tetrahydropyrido-[1,2-*a*]benzimidazole (IV) were 300 mg (40%) and 260 mg (34%), respectively. The melting points of the mixtures of these compounds and authentic compounds shown no depression. *Rf* values on TLC and IR spectra of these and their authentic compounds were identical.

Intramolecular Ring-Closure of III in Formic Acid with Tin——One g of III was dissolved in 40 ml of formic acid and 1.0 g of granular tin was added. The mixture was refluxed for 3 hours, cooled, then filtered to remove inorganic salts. The filtrate was concentrated under the vacuum. Water was added to the concentrated filtrate and it was made basic by adding aqueous ammonia solution, then residue was purified by column chromatography using alumina. 90 mg of 1-(2-formamidophenyl)pyrrolidine and 380 mg of 1*H*-2,3-dihydropyrrolo[1,2-*a*]benzimidazole (V) were obtained. The yield of the former was 10% and the latter was 50%. The mixed melting points with their authentic compounds gave no depression. *Rf* values on TLC and IR spectra of these compounds were identical to those of authentic compounds.