Rearrangements of Tertiary Amine Oxides. XIII.* The Reactions of p-Nitrobenzenesulfenyl Chloride with Pyridine- and α-Picoline N-Oxides

By Shigeru OAE and Katuyata IKURA

Since it was discovered in Professor Ochiai's Laboratories that the reaction between pyridine N-oxides and acetic anhydride leads to the formation of 2-acetoxypyridine,[1] many investigations have been made of the reactions between heteroaromatic N-oxides and acylating agents.[2]

Recently, by the aid of the [18]O tracer technique, the mechanistic features of these reactions have gradually been uncovered and it has become quite clear that one cannot draw any single common mechanistic scheme which can explain all these apparently similar reactions. The nature of the reaction may differ with the variation in N-oxides and in acylating agents and also in other reaction conditions, such as the change in solvent. For example, 2-picoline N-oxide has been considered to react with acetic anhydride via a free radical cage process,[3] while its isomer, 4-picoline N-oxide, apparently undergoes a nucleophilic SN2'-type replacement with the same reagent.[4] The reaction between pyridine N-oxide and acetic anhydride has been presumed to proceed through the initial nucleophilic addition of acetate ion at the α-position to give α-acetoxypyridine.[5]

* Part XII. S. Oae and S. Kozuka, *Tetrahedron*, in press.
1) M. Katada, *Yakugakuzashi*, **67**, 51 (1947).
2) E. Ochiai, *Ann. Rept. ITSUU Lab.*, No. 12, 43 (1962).

3) S. Oae, T. Kitao and Y. Kitaoka, *J. Am. Chem. Soc.*, **84**, 3359 (1962).
4) S. Oae, T. Kitao and Y. Kitaoka, ibid., **84**, 3362 (1962).
5) J. H. Markgraf, H. B. Brown, Jr., S. C. Mohr and R. G. Peterson, ibid., **85**, 958 (1963).

An especially interesing reaction is that of pyridine- or isoquinoline N-oxide with p-toluenesulfonyl chloride. Here, the mechanism, suggested as the result of ^{18}O tracer experiments, is very unusual and involves an intramolecular rearrangement via the α,γ-intimate ion pair, as is shown below.[6]
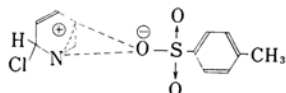
The unique feature of this reaction may arise either in the intrinsic nature of sulfur-oxgen linkages or merely in the different bond strength of the acylated N–O bond. Thus, we have attempted to find some important information on the influence of the nature of sulfur-oxygen linkages on these reactions by reacting N-oxides of pyridine bases with arylsulfenyl and arylsulfinyl chlorides. This paper will deal with the reactions of p-nitrobenzenesulfenyl chloride with pyridine and α-picoline N-oxides.

Results and Discussion

When equivalent amounts of pyridine N-oxide and p-nitrobenzenesulfenyl chloride were mixed in a benzene solution, colorless crystalline precipitates were formed immediately, with an evolution of heat. The crystals apparently has following structure (I); this structure is very hygroscopic, but it can readily be converted to its perchlorate, which has the correct analytical composition.


(I)
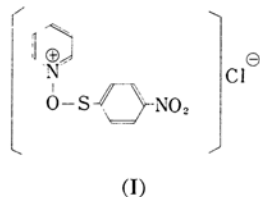
The salt I obtained after the thorough removal of the solvent benzene in a vacuum line was sealed in an ampoule; the ampoule was then heated at 150—160°C for five hours. It began to melt at around 80°C, at which point also color began to be formed, and at around 150°C the mixture became a dark, oily mass. Among the reaction products isolated were pyridine, p,p'-dinitrodiphenyl disulfide, p-nitrophenyl p-nitrobenzenethiolsulfonate and p-nitrobenzenesulfonic acid; these ingredients constituted more than 85% of the product mixture. Neither a ring-substituted

rearrangement product nor unreacted pyridine N-oxide was found among the products. The evolution of hydrogen chloride was not observed when the salt was heated in an open vessel, unlike as in the case of pyridine N-oxide with tosyl chloride or p-nitrobenzoyl chloride.[7]

If the reaction followed a path similar to that of pyridine N-oxide with tosyl chloride, one would expect some pyridine ring-substituted compound among the products mixture, for the heterolytically-cleaved species, presumably nitrobenzenesulfinate ions, is considered to be more nucleophilic than tosylate and, hence, to react more readily with the other cleaved partner, 2-chloro-2-hydropyridinium cation, to give perhaps the sulfinyl product. On the other hand, if the N–O bond is assumed to cleave homolytically, the resulting radical, p-nitrosulfinyl, may not recombine with the other partner to give any pyridine ring-substituted compound, since the radical has been known to be quite stable, due to the electron-sharing 3d orbital resonance, as is shown below,[8] and to dimerize readily eventually yielding p-nitrophenyl p-nitrobenzenethiolsulfonate.[9]
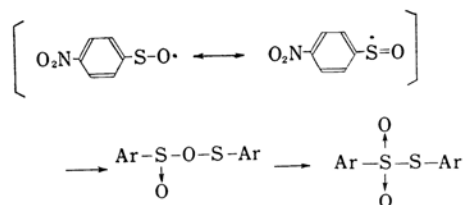
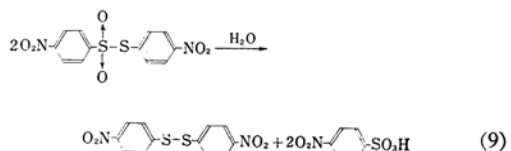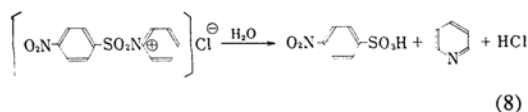
The lack of any heteroring-substituted product, together with the formation of p-nitrophenyl p-nitrobenzenethiolsulfonate, seems to favor the homolytic cleavage of the N–O bond of the salt I. Thus, the over-all reaction scheme may be formulated as is shown below:

(1)

(I)

(2)

6) S. Oae, T. Kitao and Y. Kitaoka, *Tetrahedron*, **19**, 827 (1963).
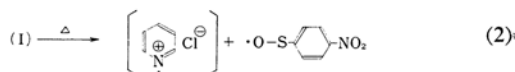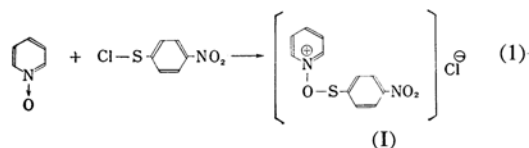
7) Our preliminary experiment suggests that p-nitrobenzoyl chloride reacts with pyridine N-oxide and similarly gives 3-acyloxypyridine as the main product.

8) S. Oae, "3d-Orbital Resonance Involving the Sulfur Atom in Organic Sulfides," in "Organic Sulfur Compounds," Vol. 4., Ed. by N. Kharasch, Pergamon Press, in press.

9) S. Oae and S. Kawamura, This Bulletin, **35**, 1156 (1962); H. J. Backer and H. Kloosterziel, *Rec. Trav. Chim.*, **73**, 129 (1954); R. N. Topping and N. Kharasch, *Chem. & Ind.*, **1961**, 178.

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$$2O_2N-\!\!\!\!\bigcirc\!\!\!\!-S-O\cdot \longrightarrow O_2N-\!\!\!\!\bigcirc\!\!\!\!-\overset{O}{\underset{O}{S}}-S-\!\!\!\!\bigcirc\!\!\!\!-NO_2 \quad (3)$$

$$\left[\bigcirc_{N}Cl^{\ominus}\right] \longrightarrow \bigcirc_{N} + Cl\cdot \quad (4)$$

$$O_2N-\!\!\!\!\bigcirc\!\!\!\!-\overset{O}{\underset{O}{S}}-S-\!\!\!\!\bigcirc\!\!\!\!-NO_2 + \bigcirc_{N} \longrightarrow$$

$$\left[O_2N-\!\!\!\!\bigcirc\!\!\!\!-SO_2N\overset{\oplus}{\bigcirc}\right]\overset{\ominus}{S}-\!\!\!\!\bigcirc\!\!\!\!-NO_2 \quad (5)$$

$$\left[O_2N-\!\!\!\!\bigcirc\!\!\!\!-SO_2N\overset{\oplus}{\bigcirc}\right]\overset{\ominus}{S}-\!\!\!\!\bigcirc\!\!\!\!-NO_2 + Cl\cdot \longrightarrow$$

$$\left[O_2N-\!\!\!\!\bigcirc\!\!\!\!-SO_2N\overset{\oplus}{\bigcirc}\right]Cl^{\ominus} + \cdot S-\!\!\!\!\bigcirc\!\!\!\!-NO_2 \quad (6)$$

$$2O_2N-\!\!\!\!\bigcirc\!\!\!\!-S\cdot \longrightarrow O_2N-\!\!\!\!\bigcirc\!\!\!\!-S-S-\!\!\!\!\bigcirc\!\!\!\!-NO_2 \quad (7)$$

$$\left[O_2N-\!\!\!\!\bigcirc\!\!\!\!-SO_2N\overset{\oplus}{\bigcirc}\right]Cl^{\ominus} \overset{H_2O}{\longrightarrow} O_2N-\!\!\!\!\bigcirc\!\!\!\!-SO_3H + \bigcirc_{N} + HCl \quad (8)$$

$$2O_2N-\!\!\!\!\bigcirc\!\!\!\!-\overset{O}{\underset{O}{S}}-S-\!\!\!\!\bigcirc\!\!\!\!-NO_2 \overset{H_2O}{\longrightarrow}$$

$$O_2N-\!\!\!\!\bigcirc\!\!\!\!-S-S-\!\!\!\!\bigcirc\!\!\!\!-NO_2 + 2O_2N-\!\!\!\!\bigcirc\!\!\!\!-SO_3H \quad (9)$$
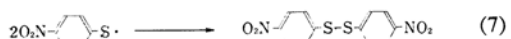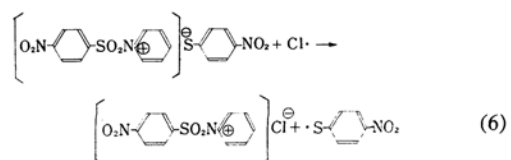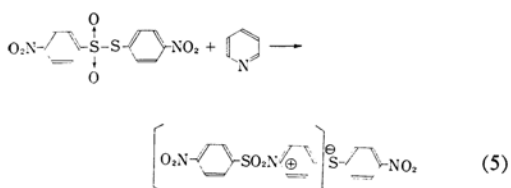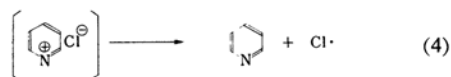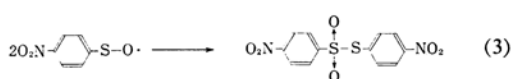
The clear-cut ESR signals seen[10] during and shortly after the reaction also appear to suport the free radical mechanism.

Previously it was shown that the *p*-nitro-benzenesulfinyl radical, once formed, readily dimerized to give stable *p*-nitrophenyl *p*-nitro-benzenethiolsulfonate. However, the amount of this compound actually isolated was rather small as compared to those of the disulfide and *p*-nitrobenzenesulfonic acid. The latter two compounds were perhaps formed through steps 5—8.

When *p*-nitrophenyl *p*-nitrobenzenethiolsulfonate was reacted with pyridine and the reaction mixture was quenched with water, both *p*-nitrobenzenesulfonic acid and *p, p'*-dinitrodiphenyl disulfide were actually obtained in substantial yields. Exactly the same compounds were also obtained when a mixture of the thiolsulfonate and pyridine hydrochloride

was heated at 150°C and then quenched with water.

Some of the thiolsulfonate probably suffered hydrolysis during the treatment and was disproportionated to the disulfide and the sulfonic acid according to step 9.
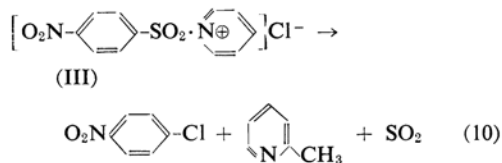
Previously there was a case where the use of a solvent did change the reaction pathway. However, in this reaction of pyridine *N*-oxide with *p*-nitrobenzenesulfenyl chloride, the use of xylene as the solvent did not change the pattern of the reaction; it yielded essentially the same products.

The same reaction was applied to *α*-picoline *N*-oxide to see if the presence of the *α*-methyl group would change the nature of the reaction as with acetic anhydride.

In this case, too, as soon as equimolar amounts of *α*-picoline *N*-oxide and *p*-nitrobenzenesulfenyl chloride was mixed in a benzene solution, white crystalline precipitates formed, with an evolution of heat. The hygroscopic crystals were changed to its perchlorate, which was found by analysis to have the correct composition as derived from the salt, II.

$$\left[\bigcirc_{\overset{\oplus}{N}}\overset{CH_3}{\underset{O-S-\bigcirc-NO_2}{}}\right]Cl^{\ominus}$$

(II)
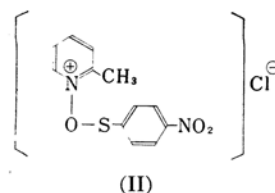
The reaction conditions were nearly the same as in the case of pyridine *N*-oxide. Here again no detectable amount of any heteroring-substituted product was obtained. There was only one difference; that is, the formation of *p*-nitrochlorobenzene was observed in this case. Otherwise, the pattern product distribution was almost the same. Therefore, reaction also seems to proceed via the homolytic cleavage of the N–O bond of the salt II and the overall reaction scheme is considered to be very similar to the one previously obtained with pyridine *N*-oxide.

$$\left[O_2N-\bigcirc-SO_2\cdot N\overset{\oplus}{\bigcirc}\right]Cl^- \rightarrow$$

(III)

$$O_2N\bigcirc-Cl + \bigcirc_{N\underset{CH_3}{}} + SO_2 \quad (10)$$

The formation of *p*-nitrochlorobenzene may be explained when one considers that this compound was formed through step 10, involving the nucleophilic attack of the chloride anion on the complex III.

10) A detailed study along this line is now underway by the group headed by Professor W. F. Forbes.

Indeed, p-nitrochlorobenzene was actually obtained when the mixture of p-nitrophenyl p-nitrobenzenethiolsulfonate and α-picoline hydrochloride was heated at around 150°C. The formation of p-nitrochlorobenzene in this case and not with pyridine N-oxide is fascinating; however, we have no way at present to explain it.

Apparently the overall pattern of the reaction was not much changed by the substitution of the α-methyl group. Even in alkaline conditions, where it was anticipated that the proton of the α-methyl group wolud be abstracted by base to form possibly an anhydrobase, there was no formation of any detectable amount of heteroring-substituted product. Thus, the reaction of the salt II in the presence of sodium ethoxide in ethanol was found to yield nearly the same compounds.

Experimental

Material. — *Pyridine N-Oxide.* — Pyridine N-oxide was prepared by the oxidation of pyridine with hydrogen peroxide in glacial acetic acid, following the procedure used by Ochiai.[11]

B. p. 150—153°C (24 mmHg); lit.[11] 138—144°C (15 mmHg).

Picoline N-Oxide.—This N-oxide was also prepared by the same method.

B. p. 108—109°C (9 mmHg); lit.[12] 123—124°C (15 mmHg).

p-Nitrosulfenyl Chloride.—At first, p,p'-dinitrodiphenyl disulfide was prepared from sodium sulfide, sulfur,and p-nitrochlorobenzene,[13] m. p. 179~180°C (recrystallized from xylene) (lit.[13] 181°C).

Then this disulfide was chlorinated with dry chlorine gas in chloroform at room temperature until the solution turned yellow. The solvent was distilled off in a vacuum to obtain the chloride, m. p. 49—51°C (lit.[13] 52°C).

The Reaction of Pyridine N-Oxide with p-Nitrobenzenesulfenyl Chloride.—The benzene solutions of both pyridine N-oxide (1.00 g.) and p-nitrobenzenesulfenyl chloride (2.00 g.) were mixed at 10°C; then the solvent was distilled off and the crystalline residue was sealed in a vaccum line. This salt was heated at 150—160°C for five hours. It began to melt at around 80°C and turned dark red, while at around 150°C the reaction mixure became a dark, oily mass. After the reaction had been completed, dilute hydrochloric acid was added and the mixture was extracted with chloroform.

The removal of the solvent gave p,p'-dinitrodiphenyl disulfide (1.15 g.) and a mixture of p,p'-dinitrodiphenyl disulfide and p-nitrophenyl p-nitrobenzenethiolsulfonate (0.30 g.), m. p. 178—179°C and 154—155°C respectively.

The presence of p-nitrophenyl p-nitrobenzenethiolsulfonate was confirmed by the use of infrared spectra.

The aqueous layer was made neutral with sodium carbonate and extracted with chloroform. The removal of the solvent gave a colored liquid; then the residual liquid was converted into picrate. From its melting point and infrared spectrum, this picrate was confirmed to be the picrate of pyridine (0.67 g.), m. p. 164—165°C (lit.[14] 167°C).

Then, a 10% ethanol solution of benzylisothiourea hydrochloride salt was added to the aqueous mother solution from which pyridine had already been recovered, and the crystals thus precipitated was collected and recrystallized from a water-ethanol mixture. This was confirmed by elemental analysis, mixed melting point, and infrared spectra to be thiuronium salt of p-nitrosulfonic acid (0.21 g.), m. p. 205—206°C.

Found: N, 9.20. Calcd. for disulfide $C_{12}H_8N_2O_4S_2$: N, 8.92%.

Found: C, 45.71; H, 4.20; N, 11.78. Calcd. for thiuronium salt: C, 45.52; H, 4.09; N, 11.37%.

The Isolation of 1-p-Nitrobenzenesulfinylpyridinium Perchlorate. — In a separate experiment the hygroscopic crystalline precipitate obtained by reacting 0.5 g. of p-nitrobenzenesulfenyl chloride on 0.25 g. of pyridine N-oxide was treated with 0.43 g. of 60% perchloric acid at 0°C. The colorless crystals which precipitated immediately were washed well with water and dried; m. p. 160—170°C with decomposition.

Found: C, 40.09; H, 2.63; N, 8.04. Calcd. for $C_{11}H_9N_2O_7SCl$: C, 41.33; H, 2.58; N, 8.03%.

The Reaction of α-Picoline N-Oxide with p-Nitrobenzenesulfenyl Chloride.—α-Picoline N-oxide (1.00 g.) and p-nitrobenzenesulfenyl chloride (2.00 g.) were used. The reaction conditions and the treatment of the reaction products were exactly the same as in the case of pyridine N-oxide. The products from the chloroform layer were p,p'-dinitrodiphenyl disulfide (1.2 g.), p-nitrochlorobenzene (0.08 g.), and a mixture of p,p'-dinitrodiphenyl disulfide and p-nitrophenyl p-nitrobenzenethiolsulfonate (0.08 g.); m. p. 165—169°C. From the aqueous layer, α-picoline (0.62 g.), (picrate m. p. 160—163°C; lit.[15] 164°C)) and p-nitrosulfonic acid (0.20 g.) (m. p. 204—205°C (thiuronium salt)) were obtained.

The Isolation of 1-p-Nitrobenzenesulfinyl-2-picolinium Perchlorate. — In a separate experiment the hygroscopic crystalline precipitate obtained by reacting 0.5 g. of p-nitrobenzenesulfenyl chloride on 0.25 g. of α-picoline N-oxide was treated with 0.42 g. of 20% perchloric acid at 0°C. The colorless crystals which precipitated immediately were washed well with water and dried; m. p. 128—150°C with decomposition.

Found: N, 8.43. Calcd. for $C_{12}H_{11}N_2O_7SCl$: N, 7.76%.

The slight discrepancy in the elemental analysis for salt II may be due to the instability of the salt, which could not be purified by recrystallization.

The Reaction of Pyridine N-Oxide with p-Nitrosulfenyl Chloride in Xylenen. — The salt I (3 g.) was placed in dry xylene (10 ml.) and refluxed

11) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).
12) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).
13) T. Zincke and S. Lenhardt, *Ann.*, **400**, 1 (1913).

14) "Daiyukikagaku," Vol. 16, Asakura, Tokyo (1959), p. 11.
15) Ibid., Vol. 16, Asakura, Tokyo (1959), p. 12.

for 5 hr. The reaction products were p, p'-dinitrodiphenyl disulfide (1.56 g.), p-nitrobenzenesulfonic acid (0.25 g.) and pyridine (0.61 g.).

The Reaction of Salt II with Sodium Ethoxide in Ethanol. — Sodium (0.26 g.) was added to anhydrous ethanol (10 ml.) and dissolved. Then the salt II (3 g.) was added at room temperature and warmed at 40°C for two hours. Finally the mixture was refluxed for three hours. The products isolated were p, p'-dinitrodiphenyl disulfide (0.91 g.), a mixture of p, p'-dinitrodiphenyl disulfide and p-nitrophenyl p-nitrobenzenethiolsulfonate (0.65 g.), and α-picoline (0.61 g.).

All the compounds were identified by mixed melting point, infrared spectra, and elemental analyses.

Summary

In the reactions of both pyridine and α-picoline N-oxides with p-nitrobenzenesulfenyl chloride, the N–O bonds of the intermediate salts appear to cleave homolytically, and the p-nitrosulfinyl radical which arises from the homolytic cleavage of the N–O bond is considered to be so stable that only the secondary reaction products from the sulfinyl radical, and no heteroring-substituted products, were obtained.

Department of Applied Chemistry
Faculty of Engineering
Osaka City University
Sumiyoshi-ku, Osaka