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THE MECHANISMS OF THE REACTIONS OF *p*-TOLUENESULFONYL CHLORIDE WITH ISOQUINOLINE- AND PYRIDINE N-OXIDES[1]

S. OAE,* T. KITAO and Y. KITAOKA
Department of Chemistry, Radiation Center of Osaka Prefecture,
Osaka, Japan

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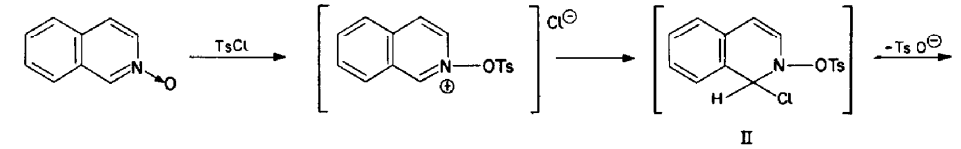
Abstract—The mechanisms of the reactions of isoquinoline- and pyridine N-oxides have been studied using oxygen-18 as a tracer. *p*-Toluenesulfonyl chloride labeled with ^{18}O was reacted with isoquinoline N-oxide, yielding 4-tosyloxyisoquinoline, a portion of which was further hydrolysed yielding 4-hydroxyisoquinoline. The analytical results suggest that the main path of this reaction proceeds *via* "intimate ion pair" as depicted by VI. In the reaction of pyridine N-oxide with *p*-toluenesulfonyl chloride, ^{18}O tracer study suggests that a similar rearrangement *via* "intimate ion pair" as VI takes place with the formation of 3-tosyloxypyridine.

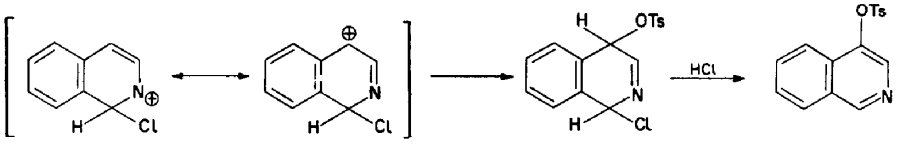
IN PREVIOUS papers,[2-4] concerning the reactions of several t-amine N-oxides with acetic anhydride, it was suggested on the basis of oxygen-18 tracer studies, that the nature of these reactions depends on the strength of the nitrogen-oxygen bond of the O-acetylated N-oxide complexes.

The reaction of quinoline N-oxide with *p*-toluenesulfonyl chloride and acetic anhydride was recently shown to give carbostyril.[5] Isoquinoline N-oxide reacts with acetic anhydride in a similar manner giving isocarbostyril, but reaction with *p*-toluenesulfonyl chloride yields 4-tosyloxyisoquinoline.

In view of the facile nucleophilic addition at the 4-position of isoquinoline N-oxide derivatives, Ochiai and Ikehara[6] postulated the following mechanism for the rearrangement of O-tosylated isoquinoline N-oxide to 4-tosyloxyisoquinoline.



II



a III b IV

* Present address: Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Japan.

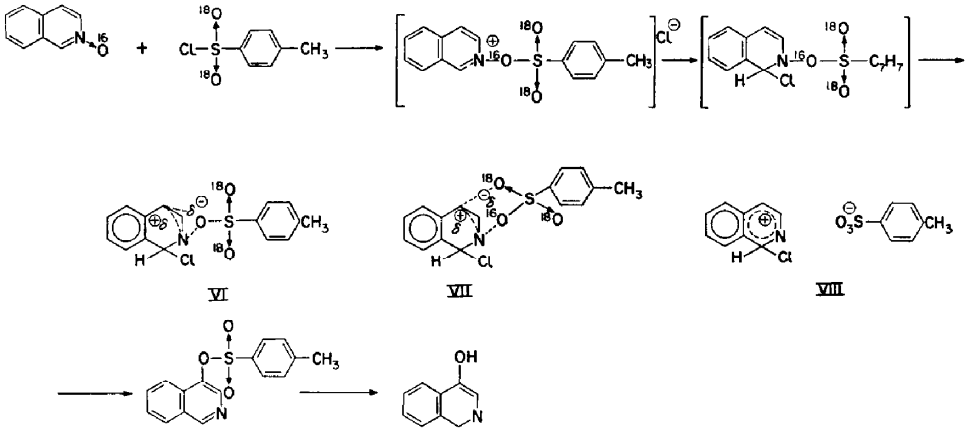
[1] Paper VI on *Rearrangements of Tertiary Amine Oxides*, paper III–V see ref. 2–4.
[2] S. Oae, T. Kitao and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3359 (1962).
[3] S. Oae, T. Kitao and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3362 (1962).
[4] S. Oae, T. Kitao and Y. Kitaoka, *J. Amer. Chem. Soc.* **84**, 3366 (1962).
[5] E. Ochiai and T. Yokokawa, *Pharm. Bull., Japan* **75**, 213 (1955).
[6] E. Ochiai and Ikehara, *Pharm. Bull., Tokyo* **3**, 454 (1955).

According to this mechanism, the reaction involved the heterogeneous cleavage of the nitrogen-oxygen bond in II to give the cation (III), resonating between IIIa and IIIb, and the subsequent nucleophilic attack of tosyloxy anion at the 4-position in III to yield an unstable intermediate (VI), which upon elimination of hydrogen chloride gives 4-tosyloxyisoquinoline.

The mechanism of this reaction has been investigated using oxygen-18 as a tracer. The oxygen-18 labeled *p*-toluenesulfonyl chloride, of which two oxygens were equally enriched by ^{18}O, was prepared by introducing *p*-toluenethiol into oxygen-18 enriched water in which dry chlorine was bubbled. The oxygen-18 labeled *p*-toluenesulfonyl chloride, reacted with a semimolar quantity of isoquinoline N-oxide in chloroform yielding 4-tosyloxyisoquinoline.

In order to determine the fate of the oxygen-18, the 4-tosyloxyisoquinoline was hydrolysed with sulphuric acid or with 20% sodium hydroxide yielding 4-hydroxyisoquinoline. Under similar conditions, there is no exchange between 4-hydroxyisoquinoline and oxygen-18 labeled sulphuric acid or labeled sodium hydroxide.

The distributions of oxygen-18 for the three possible ionic mechanisms are illustrated in Figure II.



If the intimate ion pair from I has a structural arrangement VI, the excess oxygen-18 should not be incorporated into the ether oxygen of the product but the excess will be retained in the sulphonyl oxygens. Structure VII may also be considered for another possible intimate ion pair in the intramolecular cyclic rearrangement. It requires the excess oxygen-18 in 4-tosyloxyisoquinoline to be incorporated both in the ether group and one of the sulphonyl oxygens, leaving another sulphonyl oxygen natural. The formation of 4-tosyloxyisoquinoline by the solvent separated ion pair or the intermolecular mechanism which involves nucleophilic attack by tosyloxy anion will give product in which all the oxygen atoms become equivalent by scrambling two ^{18}O-enriched oxygens and one natural, eventually giving rise to an equal value of oxygen-18 for both the ether and the sulphonyl oxygens of 4-tosyloxyisoquinoline.

The analytical values of oxygen-18 for both 4-tosyloxyisoquinoline and 4-hydroxyisoquinoline obtained by the usual analytical procedure[2] are shown in Table 1.

Inspection of the data excludes clearly both the ion pair (VII) rearrangement and the solvent separated ion pair (VIII) process for this reaction, because the latter

TABLE 1.—OXYGEN-18 ANALYTICAL RESULTS

Compound	Atom% Oxygen-18
p-CH_3-C_6H_4-SO_2Cl	0·596
4-C_9H_6N-OSO_2-C_6H_4-CH_3	0·447
4-C_9H_6N-OH	0·258
$C_9H_7N\rightarrow O$	0·204

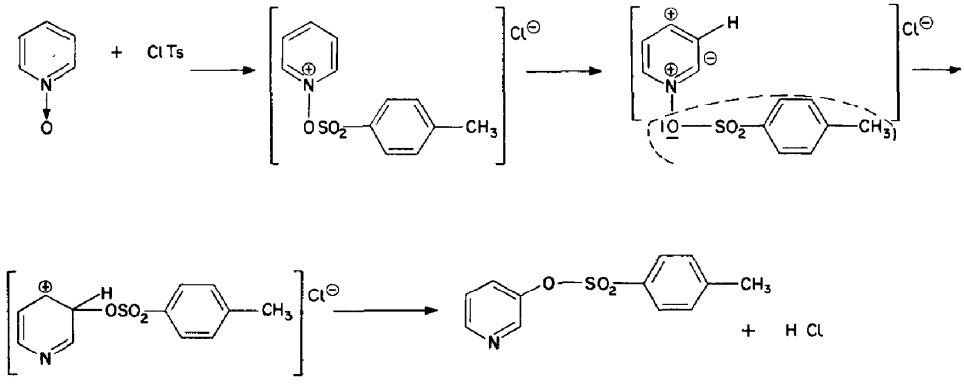
requires oxygen-18 value to be 0·45 atom% for 4-hydroxyisoquinoline while the former demands oxygen-18 concentration to be 0·60 atom% for 4-hydroxyisoquinoline. Therefore, the probable mechanism is the intimate ion pair (VI) rearrangement which requires the oxygen-18 concentration to be 0·204 atom% for 4-hydroxyisoquinoline.

The slightly higher ^{18}O value for 4-hydroxyisoquinoline over that of natural, which is beyond experimental error, may be due to some contributions from either or both ion pairs VII or VIII in the formation of the final product, although the main path of this reaction proceeds *via* the intimate ion pair as illustrated by VI. The possibility of a free radical mechanism was eliminated because this should result in the same oxygen-18 concentration as in the case of the ion pair intermediate (VIII).

As it is believed that a trace of water is essential for this rearrangement, the reaction with *p*-toluenesulfonyl chloride using ^{18}O-hydrate of isoquinoline N-oxide and 4-tosyloxyisoquinoline was investigated and the almost quantitative yield subjected to ^{18}O analysis. But there was no incorporation of excess ^{18}O in the product. This is additional evidence for the proposed mechanism, since it clearly indicates that there is no exchange of ^{18}O between the rearranging species.

The well known reaction between pyridine N-oxide and *p*-toluenesulfonyl chloride is more sluggish and 3-tosyloxypyridine is one of many products isolated such as 2,3'-dipyridyl ether, N-(2'-puridyl)-pyridone-2, N-(2'-pyridyl)-5-chloropyridone-2 and N-(2'-pyridyl)-3-chloropyridone.[7]

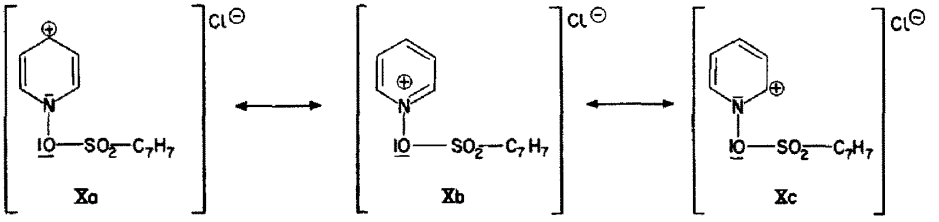
Murakami and Matumura[8] have suggested that the reaction is an intramolecular rearrangement involving cationic cleavage of tosyloxy group, leaving an electron pair on the nitrogen atom as shown below:



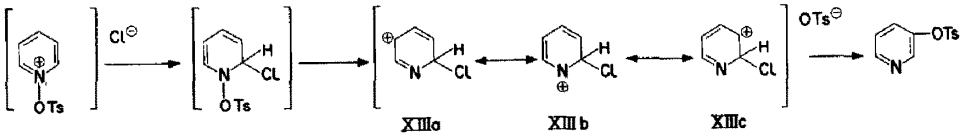
XI XII

[7] H. J. den Hertog, D. J. Buurman and P. A. de Villiers, *Rec. Trav. Chim.* **80**, 325 (1961).
[8] M. Murakami and E. Matumura, *J. Chem. Soc., Japan., Pure Chem. Soc.* **68**, 88 (1949).

The novel tosyloxy cation was suggested because it is believed that the intermediate pyridinium salt resonates between Xa, Xb and Xc.



An alternative mechanism—an adaptation of the rearrangement of isoquinoline N-oxide suggested by Ochiai *et al*,[5] is as follows:



This mechanism involves nucleophilic addition of chloride at the 2 position followed by anionic cleavage of the oxygen-nitrogen bond, giving the tosyloxy anion and the cation XIII.

In order to obtain additional information on the mechanism of this reaction oxygen-18 labeled *p*-toluenesulfonyl chloride, of which two oxygens were equally enriched by ^{18}O, was reacted in benzene with an equimolar amount of pyridine N-oxide. After removal of benzene, the resulting precipitate was heated to give 3-tosyloxypyridine together with a large amount of tarry material. The hydrolysis of the ester with sodium hydroxide, yielded 3-hydroxypyridine and the resulting sulphonic acid was also isolated as the S-benzylthiuronium salt.

The distributions of oxygen-18 required by the different mechanisms for the formation of 3-tosyloxypyridine are the same as for 4-tosyloxyisoquinoline.

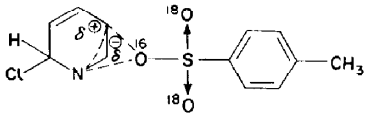
The actual oxygen-18 analysis for 3-tosyloxypyridine, 3-hydroxypyridine and S-benzylthiuronium salt of *p*-toluenesulphonic acid are listed in Table 2.

TABLE 2. ANALYTICAL RESULTS OF OXYGEN-18

Compound	Atom% ^{18}O
p-CH_3-C_6H_4-SO_2Cl	0·56
3-C_5H_4N-OSO_2-C_6H_4-CH_3	0·41
3-C_5H_4N-OH	0·21
p-CH_3-C_6H_4-SO_3H	0·41
$C_5H_5N\rightarrow O$	0·20

These results favour the intimate ion pair of type VI, and clearly excludes the other mechanisms, because the oxygen-18 concentration of 3-hydroxypyridine was natural and the excess of ^{18}O was retained in *p*-toluenesulphonic acid derived from the hydrolysis of 3-tosyloxypyridine. All these findings are in accord with the suggestion

that the pyridinium salt rearranges through the intimate ion pair to 3-tosyloxypyridine as follows:



This rearrangement is essentially similar to that of isoquinoline N-oxide, although in this case only a slight contribution from other possible pathways appears likely.

Denney and Goldstein[9] suggested a similar α, β-intimate ion pair mechanism for the rearrangement of 2-phenyl-1-propyl-*p*-bromobenzensulphonate to 1-phenyl-2-propyl-*p*-bromobenzenesulphonate.

It is quite inconceivable to assume that a bond formation or migration takes place faster than electron transfer within the close vicinity of the same group, and, therefore, the suggestions that all three oxygen atoms of the tosyloxy cation do not scramble during the rearrangement is not valid.

Further work in connection with these observations are in progress and the reactions of the *p*-toluenesulfonic acid anhydride with several t-amine N-oxides is in progress.

EXPERIMENTAL

p-*Toluenesulfonyl chloride*-CH_3-C_6H_4-$S^{18}O_2Cl$. *p*-Toluenethiol, 100 g, freshly prepared by the reduction of *p*-toluenesulfonyl chloride was suspended in 50 ml oxygen-18 enriched water (about 0·7 atom% ^{18}O) and dry chlorine bubbled through the mixture. The system was stirred with a mechanical stirrer under ice cooling. The reaction started with evolution of heat and the mixture turning yellow and then brown, and after ½ hr, the solution became transparent. If the chlorine was passed through for a while, a white solid precipitated which was filtered off, washed with water and recrystallized from benzene. This chloride (0·56 atom% ^{18}O) was obtained in a 70% yield, m.p. 69—70°.

Reaction of isoquinoline N-*oxide with oxygen*-18 *labeled* p-*toluenesulfonyl chloride*. To the solution of isoquinoline N-oxide (17 g, 0·089 mole) in 100 ml chloroform was added oxygen-18 labeled *p*-toluenesulfonyl chloride (7 g, 0·048 mole, 0·596 atom% ^{18}O), while the solution was cooled with ice. The chloride was added slowly without permitting a rise in temp. The mixture was then heated on a water bath for 2 hr. After removal of solvent *in vacuo*, the residue was washed with ether, leaving needles m.p. 186°. This solid was shaken with 20% sodium hydroxide and then extracted with ether. The ether layer was dried (Na_2SO_4) and evaporated. The resulting residue was oxygen-18 labeled 4-tosyloxyisoquinoline (0·447 atom% ^{18}O), which was recrystallized from ether, m.p. 92°, 50% yield.

Using the same quantities of isoquinoline N-oxide hydrated with two moles of ^{18}O-enriched water (1·5 atom% ^{18}O) and *p*-toluenesulfonyl chloride as above, and following the same procedure yielded 4-tosyloxyisoquinoline (0·220 atom% ^{18}O), m.p. 92°.

Acidic hydrolysis of oxygen-18 *labeled* 4-*tosyloxyisoquinoline*. Oxygen-18 labeled 4-tosyloxyisoquinoline (4·5 g, 0·015 mole) was dissolved in 85 ml 40% sulphuric acid. The solution was refluxed on an oil bath for 8 hr and diluted with an equal volume of water after cooling. The solution was made alkaline with sodium carbonate. The resulting precipitate was thoroughly washed with hot water to exclude the inorganic salt and recrystallized from ethanol, giving 4-hydroxyisoquinoline (0·258 atom% ^{18}O), 1·1 g (50% yield), m.p. 228°.

Oxygen-18 *exchange reaction between oxygen*-18 *labeled* 40% *sulphuric acid and* 4-*hydroxyisoquinoline*. A solution of 0·2 g 4-hydroxyisoquinoline in 5 ml 40% sulphuric acid (about 0·7 atom% ^{18}O) was refluxed for 8 hr. The solution was diluted to 10 ml with water and made alkaline with sodium carbonate. The resulting precipitate was washed several times with hot water and recrystallized from ethanol, m.p. 224°. The isolated 4-hydroxyisoquinoline revealed no incorporation of oxygen-18 within experimental error. Oxygen-18 analysis of 4-hydroxyisoquinoline: 0·230 atom% ^{18}O.

Reaction of pyridine N-*oxide with oxygen*-18 *labeled* p-*toluenesulfonyl chloride*. When a solution of *p*-toluenesulfonyl chloride (20 g, 0·10 mole) in benzene, was added to pyridine N-oxide (10 g, 0·11 mole) in 120 ml benzene, a solid precipitate formed with evolution of heat, After removal of solvent *in vacuo*, the residue was heated at 200–205° on an oil-bath for 2 hr. The reaction proceeded with

[9] D. B. Denney and B. Goldstein, *J. Amer. Chem. Soc.* **79**, 4948 (1957).

evolution of hydrogen chloride, resulting in tarry material. This was diluted with water, made alkaline with sodium carbonate and extracted with chloroform. The chloroform layer was dried (Na_2SO_4) and fractional distillation yielded 3-tosyloxypyridine (170–172°/3 mm). The distillate was poured into 80 ml water and cooled in a dry ice–acetone bath. After keeping the mixture for a few min at room temp, the precipitate was collected and dried overnight in a desiccator. The dried sample was recrystallized from n-hexane. The yield was about 1 g (4% yield), m.p. 78°. Analytical sample (0·41 atom% ^{18}O) was recrystallized further from n-hexane.

Hydrolysis of 3-*tosyloxypyridine*. 3-Tosyloxypyridine (1 g, 0·004 mole; 0·41 atom% ^{18}O) and sodium hydroxide (2 g, 0·05 mole) in 1 ml water was refluxed at 140–150° for ½ hr. This reaction mixture was evaporated to dryness and the residue was extracted wih ether. After removal of ether, the resulting solid was recrystallized from benzene. The 3-hydroxypyridine (0·21 atom% ^{18}O), gave a positive ferric chloride test and m.p. 124–125°. To the remaining acidic solution S-benzylthiuronium chloride was added and the resulting salt was in accord with that of *p*-toluenesulphonic acid and the ^{18}O concentration of this salt was 0·41 atom% ^{18}O.

Isotopic analysis. Oxygen-18 analysis was carried out according to the method reported in the previous paper.[2]