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REARRANGEMENT OF TERTIARY AMINE N-OXIDES—XXVII

MECHANISM OF THE REACTION OF ISOQUINOLINE N-OXIDE WITH SUBSTITUTED BENZENESULFONYL CHLORIDES

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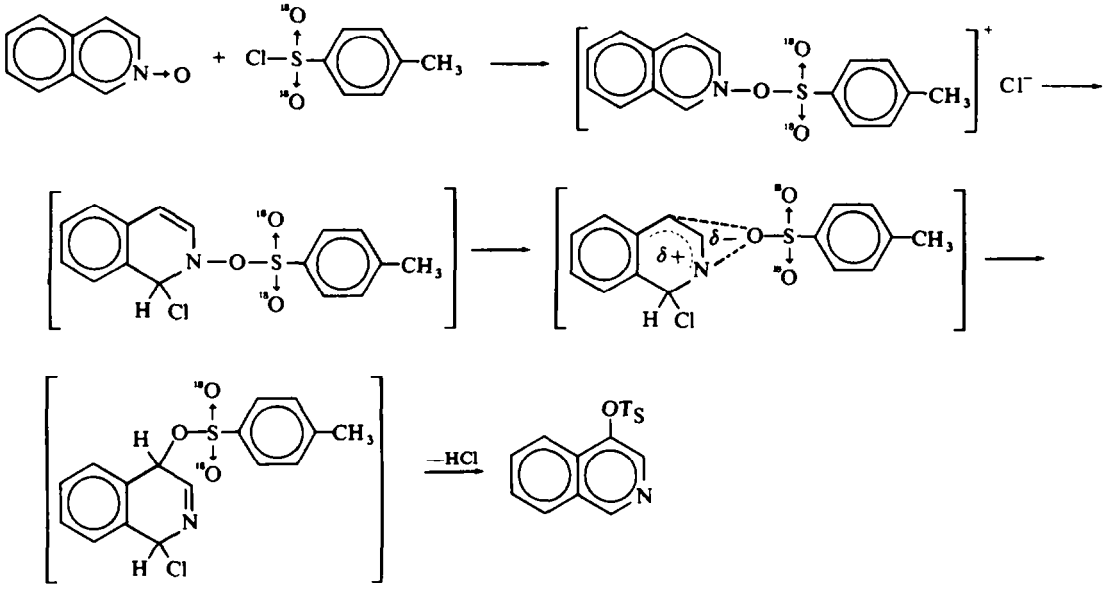
Abstract—Kinetic experiments have been carried out on the reactions of isoquinoline N-oxide with *p*-toluenesulfonyl and other substituted benzenesulfonyl chlorides, varying solvent and salt compositions. The rate was correlated by the second-order equation, i.e., $v = k_2[N \rightarrow O] \times [ArSO_2Cl]$, and was found to be accelerated in polar media. The addition of chloride ion was found to increase the rate considerably, while the rates of the over-all reaction became greater with arenesulfonyl chlorides bearing stronger electron-withdrawing substituents ($\rho = +2{\cdot}0$). By the use of 1-deuterated isoquinoline N-oxide a small kinetic isotope effect ($k_H/k_D = 1{\cdot}2$) was observed for this reaction. Based on these kinetic observations the rate-determining step of this reaction is considered to be the cleavage of N—O bond. Meanwhile, from the ^{18}O-tracer experiments in several solvents using uniformly ^{18}O-labelled *p*-toluenesulfonyl or *p*-bromobenzenesulfonyl chloride the migration of arenesulfonate was found to proceed mainly via oxygen-bridged ion pair pathway.

REACTIONS of heteroaromatic tertiary amine oxides with acylating agents to afford rearrangement products, either by intramolecular or by intermolecular processes,[2] depending upon the kinds of N-oxides and acylating agents. The reaction of isoquinoline N-oxide with *p*-toluenesulfonyl chloride to give 4-tosyloxyisoquinoline was first reported by Ochiai and Ikehara[3] and suggested to proceed through an ionic route. The previous ^{18}O-tracer work has suggested that the migration of tosyloxyl group proceeds via oxygen-bridged ion pair path as shown below (Scheme 1).[4] Although the yield is poor, the ^{18}O-tracer experiment suggests that the reaction of pyridine N-oxide with tosyl chloride to give 3-tosyloxypyridine proceeds similarly.[4] However, the reaction of quinoline N-oxide[5] with this reagent does not give any tosyloxy-migrated products. Meanwhile, in the reactions of pyridine and isoquinoline N-oxides, chloride anion has been thought to play an important role in these rearrangements since the migration of tosyloxy group was not found to occur at the 1-position which is considered to be the most active site for nucleophilic attack, but took place at γ-position. The unusual γ-migration has been rationalized by assuming that at the second step of the reaction, chloride anion attacks at the α-position of the hetero-ring and then tosyloxy group undergoes allylic type migration to the γ-position. However, the role of chloride ion has not been verified. A more important unsolved problem is which is the rate-determining step of the reaction of isoquinoline N-oxide with tosyl chloride. There are four possible steps which can be the slowest: namely, (i) the nucleophilic attack at the 1-position by chloride anion, (ii) the N—O

SCHEME 1



bond cleavage, (iii) the attack of migrating tosyloxy at γ-carbon and (iv) the elimination of hydrogen chloride. In order to verify the over-all reaction scheme and also to find out the r.d.s. of the reaction, kinetic experiments of these reactions have been carried out, examining solvent effect, salt effect, kinetic isotope effect (k_H/k_D) and substituent effect of substituted benzenesulfonyl chlorides.

Further, to check the validity of our old data and also to add supplementary data on the nature of arylsulfonate-migration, tracer experiments using ^{18}O-labelled *p*-toluenesulfonyl and *p*-bromobenzenesulfonyl chloride were also carried out. This paper will describe detailed accounts of our kinetic and ^{18}O-tracer experiments and their implications for the interpretation of the reaction.

RESULTS AND DISCUSSION

The pseudo-first order rate constants were obtained by following the decrease of remaining N-oxide spectrophotometrically (λ_{max} 297 mμ; $\varepsilon = 9{\cdot}200$ in water), although the rate of this reaction was correlated by the second-order rate equation; i.e. $v = k_2$ [N-oxide] × [TsCl]. The kinetic dependency (order) of tosyl chloride concentration was examined by plotting the observed rates against various concentrations of tosyl chloride and found to be of the first order. Reaction rates were followed only until 30–40% conversion, since from Eq. 4 hydrogen chloride was expected to be produced and to serve as a proton donnor to protonate the N-oxide while chloride anion formed was found to effect the rate.

The first step of this reaction is undoubtedly the formation of the salt (II), N-tosyloxyisoquinolinium chloride (Eq. 1). Evidence for the formation of II may be found both in the characteristic UV spectrum (λ_{max} 301 mμ in acetonitrile) and the successful isolation of the perchlorate salt (II') corresponding to II when tosyl chloride was added into acetonitrile solution of the N-oxide and lithium perchlorate

under cooling with an ice bath. These salts, (II and II') revert to the N-oxide when treated in alkaline media. The equilibrium of the formation of the salt is believed to be inclined toward the right hand side (Eq. 1) on the basis of the NMR study; namely when an excess of tosyl chloride was added into $CDCl_3$ solution containing the N-oxide, the proton signals of II and no proton signal corresponding to the free N-oxide were observed. Therefore, the reaction is considered to start from the formation of II. Pseudo-first order rate constants are summarized in Table 1. Activation energy (*Ea*) and activation entropy ($\Delta S^{\ddagger}$) are calculated as $Ea = 9{\cdot}6$ Kcal/mole and $\Delta S^{\ddagger} = -40{\cdot}2$ e.u. respectively (in dioxan at 35·0°).

TABLE 1. PSEUDO-FIRST ORDER RATE CONSTANTS OF THE REACTION OF N-OXIDE AND TOSYL CHLORIDE

Solvent	Salt[c]	rate const. $k \times 10^5$ sec^{-1}
CH_3CN	—	26·1[a]
CH_3CN	$LiClO_4$	30·4
CH_3CN	TsONa	28·1
CH_3CN	n-Bu_4NCl	42·0
HMPA	—	13·3
$CHCl_3$	—	10·4
dioxan	—	3·0[b]
dioxan	$LiClO_4$	6·25
dioxan	n-Bu_4NCl	11·1
$[N \rightarrow 0] = 2{\cdot}3 \times 10^{-3}$ M,		$[TsCl] = 9{\cdot}1 \times 10^{-3}$ M

[a] at 30·0°;
[b] at 35·0°;
[c] $[salt] = 1{\cdot}1 \times 10^{-3}$ M

The effect of solvent is shown in Table 1 and the rate constant increases as the solvent polarity increases in the following order: dioxan < chloroform < HMPA < acetonitrile. This observation suggests the reaction to be of ionic character. Salt effect was then examined. As the data in Table 1 indicate the addition of lithium perchlorate increases the rate only slightly, however, the addition of tetra-n-butylammonium chloride was found to enhance the rate, i.e., a nearly three fold increase with $1{\cdot}1 \times 10^{-3}$ M of $[n\text{-}Bu_4N^+Cl^-]$ and $2{\cdot}3 \times 10^{-3}$ M of the N-oxide in dioxan. Whereas, the addition of tosylate anion which is also a common anion in this reaction did not affect the rate at all, as would be expected from the intimate ion pair nature of the tosyloxy migration. These data of the salt effects of litium perchlorate and tetra-n-butyl ammonium chloride are summarized in Figs 1 and 2.

In both the Reissert reaction[6] and treatment[7] of isoquinoline N-oxide with acetic anhydride to give isocarbostyril, the 1-position of N-substituted isoquinolinium cation is attacked by nucleophiles to give the final products. In this reaction also the next step is considered to be the nucleophilic attack of chloride anion at the 1-position. In keeping with this postulate the rate was found to increase by the addition of an excess chloride anion into the system.

Deuterium isotope effects were measured using 1-deuterated and 1,3,4-trideuterated isoquinoline N-oxides in the reaction with an excess tosyl chloride at 35·0°. These data are listed in Table 2. The values of kinetic isotope effect (k_H/k_D) were rather

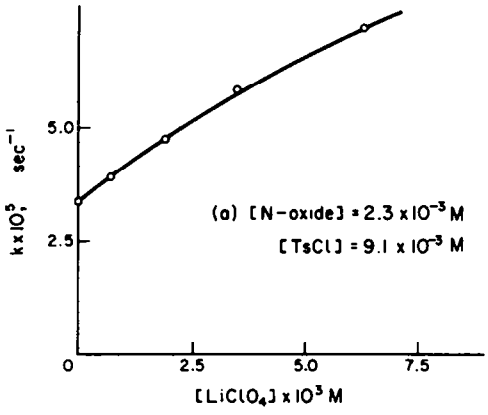


FIG. 1

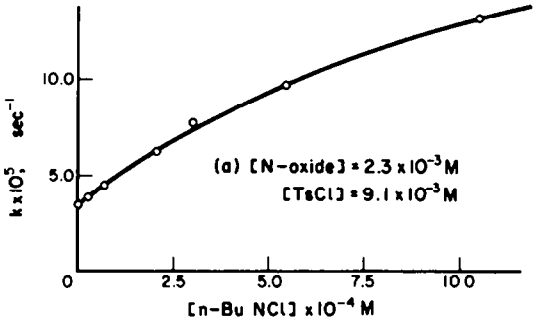


FIG. 2

TABLE 2. RATE CONSTANTS OF ISOQUINOLINE AND THE ANOMOLOUS N-OXIDE IN DIOXAN

N-oxide	$k \times 10^5$ sec^{-1}	k_H/k_D
isoquinoline	3·36 ± 0·10	—
1-deuterated isoquinoline	2·96 ± 0·24	1·16
1,3,4-trideuterated isoquinoline	2·75 ± 0·16	1·22
[N → 0] = 2·3 × 10^{-3} M	[TsCl] = 9·1 × 10^{-3} M	

small. The magnitude of the observed values, however, resemble those of the secondary isotope effect at the β-position, such as in the reaction[8] of the acetolysis of cyclopentyl tosylate. Therefore if the cleavage of tosylate ion from the intermediate, 1-chloro-N-tosyloxy-1,2-dihydroisoquinoline (III), is involved in the rate-determining step, these values are considered to be quite reasonable.

Meanwhile, if the rate-determining step would be the nucleophilic attack of chloride anion at the 1-position of the salt (II) (Eq. 2) or that of tosyloxy anion at the 4-position (Eq. 3), the value of the kinetic isotope effect (k_H/k_D) would be less than unity (about the reciprocals of the observed values). The possibility of the elimination of hydrogen chloride (Eq. 4) as the rate-determining step is also ruled out, since it

would require the isotope effect to be substantially larger than the obtained values, (at least twice). If the rate-determining step of the reaction is the heterolysis of the N—O bond of the intermediate (III), then one can expect the rate to be enhanced with a better leaving arylsulfonate. In fact it was found to be the case in the reaction of the N-oxide with benzenesulfonyl chloride in which a large positive ρ-value ($\rho = +2{\cdot}0$) was obtained with various *p*-substituted benzenesulfonyl chlorides. Thus the large ρ-value of the reaction seems to support that the rate-determining step is the N—O bond cleavage. The straight line plot of the pseudo-first order rate constants against σ-values is shown in Fig. 3. A question may arise, since the acylation

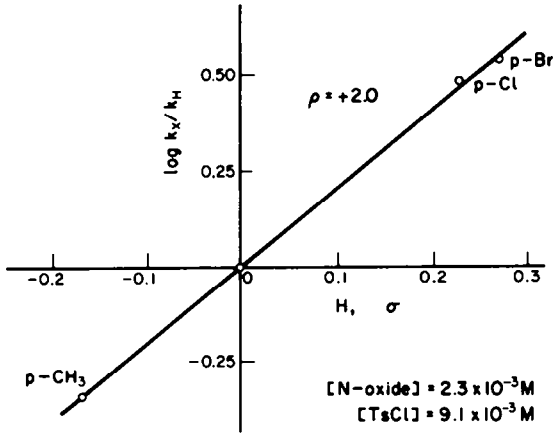


FIG. 3

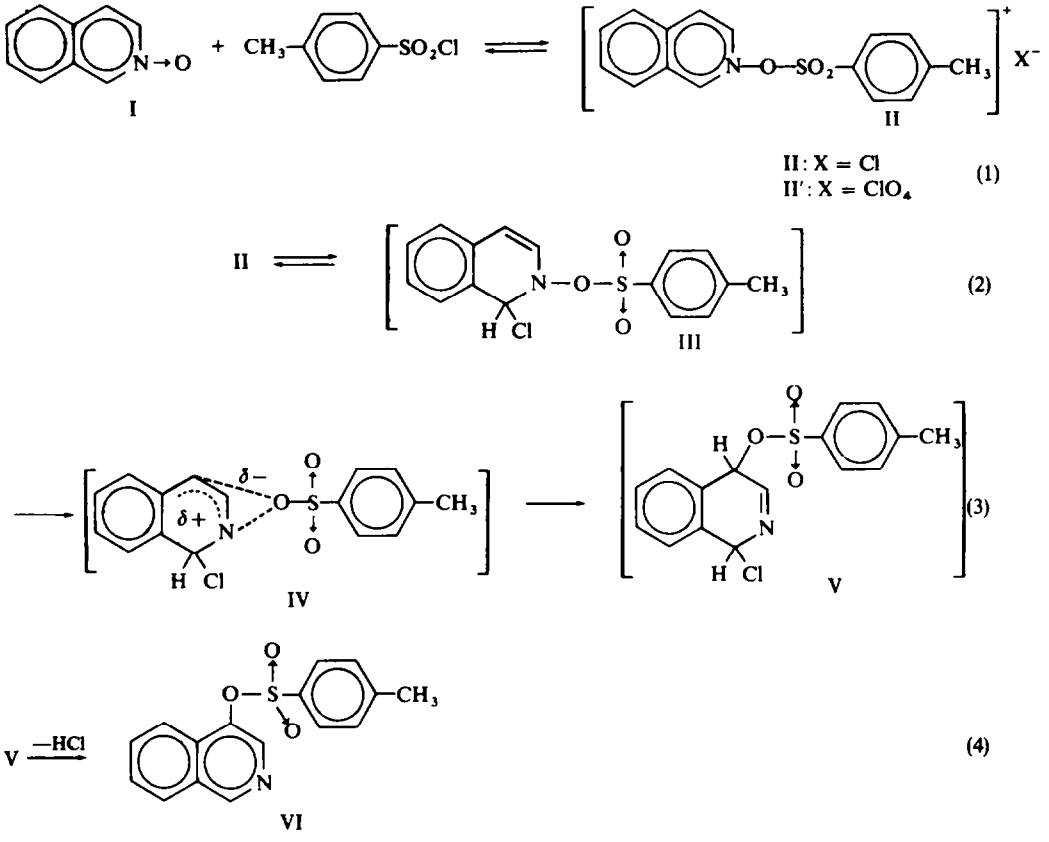
step of the pre-equilibrium reaction (Eq. 1) is also considered to be accelerated by the substitution of an electron-withdrawing group into benzenesulfonyl chloride. However, in the light of the rapid forward reaction of the first equilibrium and the size of the isotope effect, it is quite unlikely. The isotope effect would be less than unity if the acylation should be the slow step. Corollary to this large positive ρ-value, the Hammett-plot[9] of the rate constants of solvolysis of *p*-substituted benzenesulfonyl chloride is also known to give large ρ-values ($\rho = +1{\cdot}4 - 0{\cdot}6$). From these observations the following scheme may be formulated for this reaction (Scheme 2).

Mode of sulfonyloxy migration

On the basis of the tracer experiments using uniformly ^{18}O-labelled tosyl chloride, in the reactions of isoquinoline and pyridine N-oxide with tosyl chloride, the migration of tosylate proceeds via the oxygen-bridged ion pair (IV). For this migration three different types of ionic processes as illustrated in Scheme 3, are conceivable.

In the case of one oxygen-bridged ion pair mechanism (IV), none of the excess ^{18}O should be incorporated into the etheral oxygen of 4-tosyloxyisoquinoline (VI). The mechanism involving the 6-membered cyclic transition complex (VII) requires the excess ^{18}O to be incorporated into the etheral oxygen of the product (VI). Another possible mechanism is the one involving the solvent separated ion pair (VIII), or the intermolecular nucleophilic attack by outer tosyloxy anion. In this case, all of the

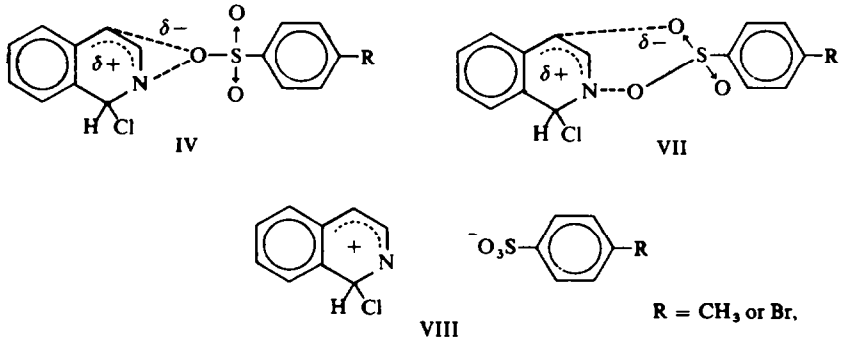
SCHEME 2



O atoms of the product (VI) should become equivalent by scrambling two ^{18}O-enriched oxygens and one natural.

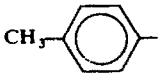
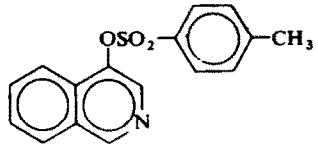
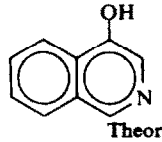
In our previous experiments a slight incorporation of ^{18}O in the etheral oxygen was observed and this was taken to suggest a minor contribution of the pathway involving the solvent separated ion pair. In order to clarify the contribution of the

SCHEME 3



other possible routes, the ^{18}O-tracer experiments were reinvestigated under various reaction conditions using different solvents such as HMPA and acetonitrile which are more polar than chloroform since the solvent separated ion pair process would become more favored in more polar media. The ^{18}O-tracer experiments were carried out with a more electron-withdrawing *p*-bromobenzenesulfonyl (brosyl) chloride, as it is also expected that the better leaving *p*-brosylate should enhance the ion-pair separation. Thus the ^{18}O-labelled sulfonyl chlorides were reacted separately with the N-oxide and 4-tosyloxy and 4-brosyloxyisoquinoline were obtained respectively. The hydrolysis of these products were performed by treatment with dilute sulfuric acid and 4-hydroxyisoquinoline was obtained. There was no exchange of the oxygen of 4-hydroxyisoquinoline under the same condition, as was found previously. Tables 3 and 4 show the analytical values of the excess atom % of ^{18}O for tosyl and brosyl chlorides, the rearranged products, and the hydrolyzed compounds respectively.

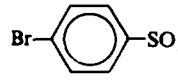
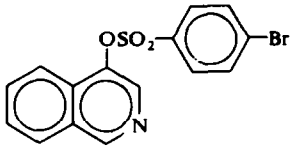
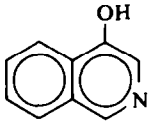
TABLE 3. ^{18}O ANALYTICAL RESULTS
Solvent: HMPA Temp: 80–90°C

Compound	Excess atom % of ^{18}O
	1·33
	0·89
	0·01
Theoretical value for the transition	IV: 0·00 VII: 1·33 VIII: 0·89

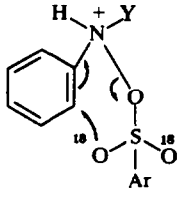
The data thus obtained are in best accord with the mechanism involving the oxygen-bridged ion pair process (IV) regardless of the reaction condition, as was found in our previous investigation, and the other two possibilities (VII and VIII) are excluded. However, in the reaction of the N-oxide with *p*-bromobenzenesulfonyl chloride in acetonitrile, the solvent separated ion pair process (VIII) appears to be contributing to this rearrangement though in minor extent.

A somewhat similar α-, γ-migration of arylsulfonate may be found in the reaction of N-benzoylphenylhydroxylamine with *p*-nitrobenzenesulfonyl chloride to give 2(*p*-nitrobenzenesulfonyloxy) benzanilide.[10] However, the ^{18}O-tracer study revealed that a concerted process (IX) is involved in this reaction unlike the present case of isoquinoline N-oxide. These different modes of arylsulfonate migration could be due to the different conformational rigidities. In the transition complex of IX for the reaction of N-benzoylphenylhydroxylamine, the N atom is combined with benzene

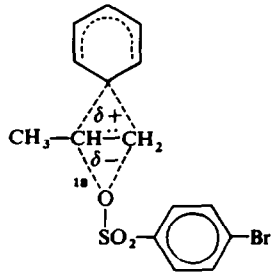
TABLE 4. ^{18}O ANALYTICAL RESULTS

Solvent, condition compound	Chloroform, reflux excess atom % of ^{18}O	Acetonitrile, reflux excess atom % of ^{18}O
	1·20	1·20
	0·78 (calc. 0·80)	0·79 (calc. 0·80)
	0·04	0·06
Theoretical value for the path via IV: 0·00 VII: 1·20 VIII: 0·80		

ring by a single bond and all the connecting linkages can rotate freely. Therefore, one terminal O atom of the sulfonyl group can always come right above the migrating ortho C atom. Whereas in the case of the complex (IV) for the reaction of isoquinoline, the N atom is in a rigid hetero-ring system and combined to the planar double bond; therefore the terminal O atoms have no chance to come right above the benzylic C atom, and hence the concerted process becomes unfavourable while perhaps the sliding type intimate ion pair process may prevail. This intimate ion pair process may be similar to X in which 2-phenyl-1-propyl-*p*-bromobenzenesulfonate[11] rearranges to 1-phenyl-2-propyl isomer or to that in the reaction of acridine N-oxide with acetic anhydride.[12]



IX



X

EXPERIMENTAL

Materials. The preparation of isoquinoline N-oxide was according to the report.[13] 1-Deuterated isoquinoline N-oxide (XI)[14] was obtained by heating the mixture of N-oxide (2·0 g, 0·11 mole), D_2O (3 g, 0·17 mole) and Et_3N (0·5 g, 5 mmole) at 80–90° in a sealed tube for about 24 hr. 1,3,4-Trideuterated N-oxide

was prepared by heating in a sealed tube containing the mixture of the N-oxide (2·40 g, 0·11 mole) and ab. 2% NaOD–D_2O (5·0 g, 0·28 mole) at 120–130° for 5 days. The isotopic contents of these N-oxides were analysed by means of integration of NMR spectra and found to contain 90% (XI) and 93% deuterium (XII) for 1-d N→O, and 1,3,4-d_3 N→O at their positions, respectively. *p*-Toluenesulfonyl chloride and other salts were purified by recrystallization for several times before use and chloroform, HMPA, acetonitrile and dioxan were used after purification by the usual method.

p-Toluenesulfonyl and *p*-bromobenzenesulfonyl chloride ^{18}O-labelled were prepared similarly according to the method reported in the previous paper.[4]

Kinetic runs. The kinetic measurements were performed by a similar method as reported,[15] namely following the UV absorption peak of the N-oxide (λ_{max} 297 mμ; ε = 9200 in H_2O) after quenching the reaction mixture. A good pseudo-first order kinetic behaviour was obsevred in each case, and a typical run is shown in Fig. 4. The order of tosyl chloride was determined by changing its concentration and the result is illustrated in Fig. 5.

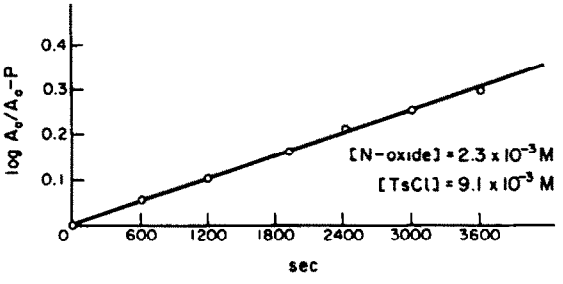
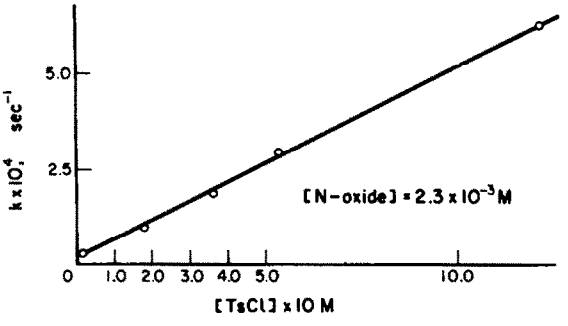


FIG. 4



^{18}O-Tracer study. The reactions of isoquinoline N-oxide with ^{18}O-labelled *p*-toluenesulfonyl and *p*-bromobenzenesulfonyl chloride in several solvents were carried out as in the previous experiments,[4] while the ^{18}O-analysis of the products were also performed as in the previous case. A typical run is as follows; isoquinoline N-oxide 2-hydrate (3·0 g, 0·16 mole) and ^{18}O-labelled *p*-bromobenzenesulfonyl chloride (4·0 g, 0·16 mole) were dissolved in 50 ml of acetonitrile and the mixture was refluxed for 3 hr. After the solvent was distilled off, water was added into the residue and then extracted with chloroform. After drying over Na_2SO_4 and removal of the solvent, the crude solid was obtained in about 6 g. 4-brosyloxyisoquinoline m.p. 121–122·5° (3·5 g) was obtained from the material after recrystallization from MeOH. The identification of the product was made by means of IR, UV and NMR spectroscopic determinations.

Hydrolysis of the ester. Hydrolysis of 4-broxyloxyisoquinoline (2·5 g, 0·007 mole) was carried out under refluxing in 25 ml of 40% H_2SO_4 for about 8 hr. Then the soln was neutralized with Na_2CO_3 and extracted with ether. After removal of the solvent from the extract, recrystallization from EtOH gave 4-hydroxyisoquinoline 0·8 g m.p. 220–222° (lit. 228°[16]). The ^{18}O-analytical results of these esters and hydrolyzed compounds are listed in Tables 3 and 4.

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