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# Reaction of Sulfoxides with Acylating Reagents. II. Mechanism of the Reactions of Aryl Benzyl Sulfoxides with Acetic Anhydride[1]

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Aryl benzyl sulfoxides undergo oxygen exchange and racemization reaction with acetic anhydride, and the rate is dependent on the concentration of both the sulfoxide and acetic anhydride. The reaction proceeds faster in a more polar solvent. Addition of sodium perchlorate or acetic acid accelerates the reaction. In this case, the rate of oxygen exchange is not exactly half of that of racemization. As an example, the ratio, $k_{ex}/k_{rac}$, is 0.36 when the reaction was carried out at 100°C. Under the same condition, both the Pummerer reaction and thermal racemization are negligible. Similar to diaryl sulfoxides the effects of phenyl group are small. Implication of the ratio is discussed.

In previous papers,[2] dealing with the reaction of diaryl sulfoxides with acetic anhydride, we focused our attention only on the oxygen exchange. In this reaction with an optically active diaryl sulfoxide, the rate of racemization $k_{rac}$, was found to be twice that of oxygen exchange and the effect of polar substituents was rather small. Based on these and related observations, we suggested that the reaction proceeds through an $S_N2$ type Walden inversion at the rate determing step. As an extension of this oxygen exchange reaction with acetic anhydride, we have chosen aryl benzyl sulfoxides, with the intention of comparing the rate of the oxygen exchange with that of possible Pummerer rearrangement, since the rate-determining removal of proton from benzylic carbon in the Pummerer reaction is considered to be easier with these sulfoxides. Thus we have prepared a few *p*-substituted phenyl benzyl sulfoxides and subjected them to the reaction with acetic anhydride. This paper will describe detailed accounts of our kinetic experiments and the mechanistic implications of the data obtained.

## Results and Discussion

When optically active *p*-tolyl benzyl sulfoxide was heated with a large excess of acetic anhydride at 100°C, the sulfoxide recovered from time to time was found to have lost its activity. The $^{18}$O-labeled *p*-tolyl benzyl sulfoxide, under the same reaction condition, was found to undergo oxygen exchange reaction. The rate of the Pummerer rearrangement was quite small under the same reaction condition as compared to the rates of both oxygen exchange and racemization. The kinetic order of the racemization of *p*-tolyl benzyl sulfoxide was examined. When the reaction was carried out in chlorobenzene, the rate was found to be first order in each component *i. e.*, $v=k_2[\rangle S \rightarrow O][Ac_2O]$ (Table 1, Fig. 1).

However, as in the case of diaryl sulfoxides, the kinetics of racemization did not follow the second order equation but satisfied the third order equation, $v=k_3[\rangle S \rightarrow O][Ac_2O]^2$ when the reaction was

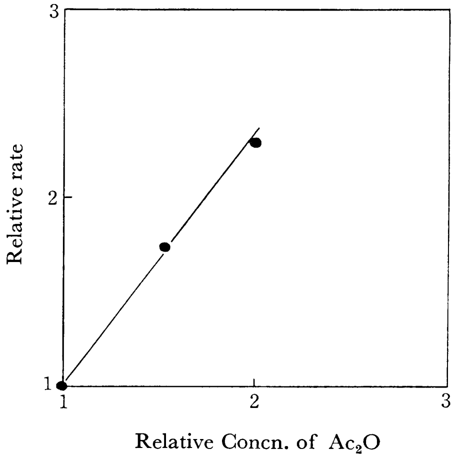

Fig. 1. The determination of kinetic order of racemization reaction in chlorobenzene. The relation between relative rate of racemization and concentration of acetic anhydride.

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[1] Paper XXIX on Sulfoxide, XXVIII on sulfoxide S. Oae and M. Kise, This Bulletin, **43**, 1416 (1970).

[2] a) S. Oae and M. Kise, *Tetrahedron Lett.*, **1967**, 1409; b) S. Oae and M. Kise, This Bulletin, and related references cited in this paper.

Table 1. Determination of kinetic order of racemization reaction in chlorobenzene solvent[a)]

| No. | $Ac_2O$(gr) | $k^{b)}\times 10^5$ ($sec^{-1}$) | Rel. concn. $Ac_2O^{c)}$ | Relative rate |
|---|---|---|---|---|
| 1 | 10.7797 | 7.30 | 1 | 1 |
| 2 | 16.5660 | 12.0 | 1.53 | 1.74 |
| 3 | 21.5522 | 16.7 | 2.00 | 2.29 |

a) The reaction was carried out at 100°C in a sealed tube. Sulfoxide, $10^{-3}$ mol, was dissolved in 20 m*l* reaction mixture of chlorobenzene and acetic anhydride.
b) Pseudo lst order rate constant.[2)]
c) Relative concentration of acetic anhydride in 20 m*l* reaction mixture of acetic anhydride and chlorobenzene.

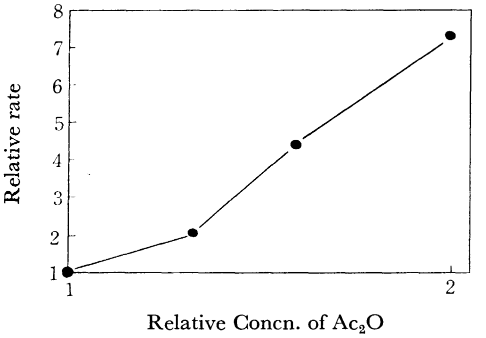


Fig. 2. The determination of kinetic order of racemization reaction in dioxane solvent. The relation between relative rate of racemization and concentration of acetic anhydride.

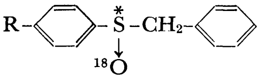
performed in dioxane (Table 2, Fig. 2). Since dioxane is a nucleophilic solvent, it would interact with acetic anhydride and the interaction might reduce the rate of the reaction notwithstanding the fact that the reaction is expected to be faster in a more polar solvent, acetic anhydride, than in nonpolar dioxane.

Table 2. Determination of kinetic order of racemization reaction in dioxane solvent[a)]

| No. | $Ac_2O$(gr) | $k\times 10^5$ ($sec^{-1}$) | Rel. concn. $Ac_2O$ | Rel. *k* rate |
|---|---|---|---|---|
| 1 | 10.8228 | 2.30 | 1 | 1 |
| 2 | 14.3722 | 4.68 | 1.33 | 2.03 |
| 3 | 17.2515 | 10.1 | 1.60 | 4.39 |
| 4 | 21.5522 | 16.7 | 2.00 | 7.26 |

a) The reaction was carried out at 100°C in a sealed tube. Sulfoxide, $10^{-3}$ mol, was dissolved in 20 m*l* reaction mixture of dioxane and acetic anhydride.

Table 3. Kinetic data on oxygen exchange and racemization reaction on aryl benzyl sulfoxide[a)]



in acetic anhydride at 100°C

| Substituent (R) | Added salt | $k_{ex}$ $\times 10^5$ | $k_{rac}$ $\times 10^5$ | $k_{ex}/k_{rac}$ |
|---|---|---|---|---|
| $OCH_3$ | | 4.70 | | |
| $CH_3$ | | 4.75 | 13.4 | 0.36 |
| $CH_3$ | AcONa[b)] | | 3.58 | |
| H | | 5.49 | | |
| Cl | | 4.28 | | |
| $NO_2$ | | 6.01 | | |

a) Sulfoxide $10^{-3}$ mol in $Ac_2O$ 20 m*l* soln.
b) NaOAc $10^{-3}$ mol in $Ac_2O$ 20 m*l* soln.

The effect of substituents on phenyl group in the oxygen exchange reaction of *p*-substituted phenyl benzyl sulfoxide was examined in acetic anhydride at 100°C and the results are tabulated in Table 3. (Table 3). As in the case of *p*-substituted diphenyl sulfoxides, the substituent effect is rather small, suggesting that the main path of the reaction is $S_N2$ type oxygen exchange process in which the effect of substituent is largely cancelled. We see, however, that the rate constant of racemization is more than two-fold that of oxygen exchange, *viz.*, the ratio, $k_{ex}/k_{rac}$ was 0.36 when the reaction was carried out at 100°C. Apparently other processes cause additional racemization in addition to the main reaction of the oxygen exchange process of $S_N2$ type nucleophilic substitution which is the only path observed in the case of diaryl sulfoxides. Other processes responsible for the racemization may include thermal racemization of sulfoxide itself, nucleophilically assisted heterolysis of S–C bond of either non-acetylated or acetylated sulfoxide by acetate ion and Pummerer rearrangements. All these processes are illustrated as shown below (Fig. 3).

The first possibility, namely, the thermal racemization (path a), by either the direct inversion of the pyramidal structure of the sulfoxide[3,4)] or the double rearrangements involving the incipient formation of benzyl arylsulfenate as the intermediate, is quite unlikely, since these aryl benzyl sulfoxides undergo very little thermal racemization at this temperature (at 100°C) in any of the common solvents, chlorobenzene, acetonitrile, dioxane, and dimethyl sulfoxide without acetic anhydride.

The second possible path for racemization (path b) which does not necessarily accompany oxygen exchange, namely, the acetic acid-catalyzed racemization appears plausible but is not likely, since the

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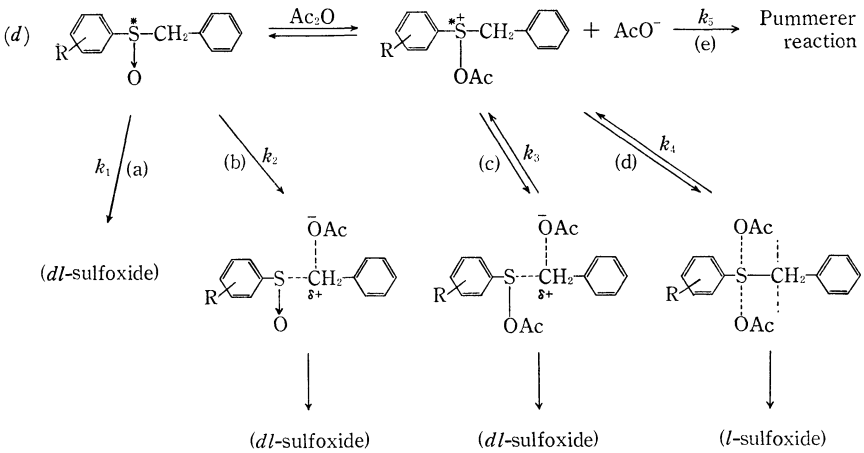
[3)] a) D. R. Rayner, E. D. Miller and K. Mislow, *J. Amer. Chem. Soc.*, **88**, 3138 (1966). b) D. R. Rayner, A. L. Gordon and K. Mislow, *ibid.*, **90**, 4854 (1968).
[4)] E. G. Miller, D. R. Rayner, H. T. Thomas and K. Mislow, *ibid.*, **90**, 4861 (1968).



$$k_{\mathrm{rac}} = k_1 + k_2 + k_3 + k_4 + k_5$$

Fig. 3

rate of racemization of any of aryl benzyl sulfoxides in acetic acid alone is negligible as compared to that in acetic anhydride ($k_{\mathrm{Ac_2O}}/k_{\mathrm{AcOH}} \gg 100$). Acetic anhydride undoubtedly takes part in facilitating the racemization.

The third possible path (path c) that takes the role of acetic anhydride into consideration is plausible. It involves the heterolysis of S–C bond following the prior acetylation of the sulfoxide function. Since benzylic sulfoxide compounds are known to undergo homolytic C–S bond cleavage in solvents of low polarities,[4] the heterolysis of benzyl acetoxysulfonium acetate would be more facile because of the substitution of more electronegative acetoxy group at the sulfur atom.

This path is very likely to contribute in the excess racemization during oxygen exchange. If the heterolysis always leads to a complete racemization, the contribution of path (c) in the racemization is calculated to be 29% from the value of 0.36 for $k_{\mathrm{ex}}/k_{\mathrm{rac}}$, and the rest of the racemization is ascribed to the $\mathrm{S_N2}$ type process as illustrated by path (d).

Undoubtedly path (d) is the main reaction pathway for racemization, since the racemization is accompanied by a substantial oxygen exchange though not as completely as in the case of diaryl sulfoxides.

Another path which is responsible for reducing optical rotation of the original solution of the sulfoxide is the Pummerer rearrangement (path e) which eventually results in the conversion of the sulfoxide to α-acetoxybenzyl aryl sulfides. However, this reaction is negligible. Thus, the first two paths (a and b) can be ruled out and path (c) also appears to be negligible. The pathways (c) and (d) are the remaining possible paths for racemization and responsible for the apparent anomaly of the ratio of the rates of oxygen exchange and racemization, *i. e.* $k_{\mathrm{ex}}/k_{\mathrm{rac}}=0.36$. These reactions are interwoven to make the overall kinetic rates of the racemization complicated.

In order to clarify the relative importance of three different pathways at different temperatures, kinetic experiments were carried out in the range of temperatures between 60 and 120°C and the results are shown in Table 4. The Arrhenius plot of the kinetic data is shown in Fig. 4. The data

TABLE 4. VALUES OF THE RATE CONSTANTS OF REACTION AT TEMPERATURES FROM 60 °C TO 120 °C[a)]

| Temp. °C | $T$°K | $1/T\times10^3$ | $k\times10^5$ (sec$^{-1}$) | log $k$+5 |
|---|---|---|---|---|
| 60 | 333 | 3.003 | 0.50 | −0.292 |
| 80 | 353 | 2.833 | 3.66 | 0.562 |
| 85 | 358 | 2.793 | 5.22 | 0.718 |
| 90 | 363 | 2.755 | 7.93 | 0.800 |
| 100 | 373 | 2.681 | 16.7 | 1.223 |
| 110 | 383 | 2.611 | 43.3 | 1.636 |
| 120 | 393 | 2.545 | 119 | 2.076 |

a) The reaction was carried out in a sealed tube.

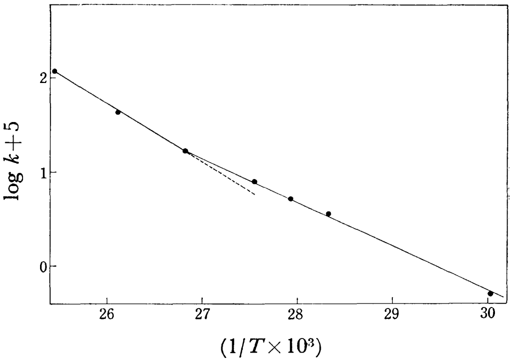


Fig. 4. The Arrhenius plot of the reaction between *p*-tolyl benzyl sulfoxides and acetic anhydride.

Table 5. Influences of acetic acid on the racemization reaction tolyl benzyl sulfoxides at 55°C

| No. | AcOH (gr) | $Ac_2O$ (gr) | $k_{rac}\times 10^5$ $(sec)^{-1}$ | Relative rate |
|---|---|---|---|---|
| 1 | 0 | | 0.400 | 1 |
| 2 | 1.2898 | 9.4233 | 1.24 | 3.1 |
| 3 | 3.1357 | 7.5550 | 5.36 | 13.4 |
| 4 | 5.7052 | 4.9275 | 7.19 | 18.0 |
| 5 | 7.9020 | 2.5956 | 2.66 | 6.65 |
| 6 | 8.3702 | 2.2307 | 2.12 | 5.3 |

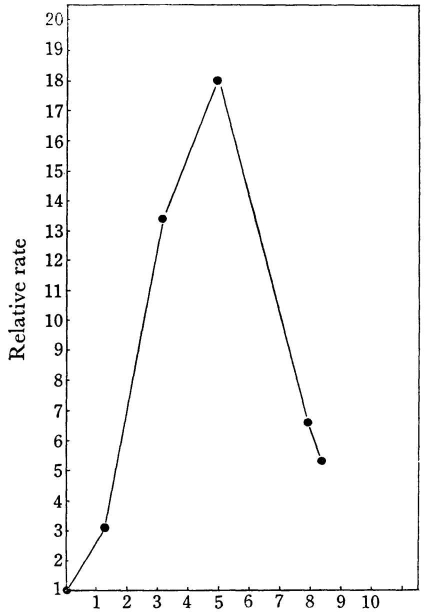


Fig. 5. The influences of acetic acid to the racemization reaction tolyl benzyl sulfoxides at 55°C.

in Table 4 and Fig. 4 reveal that the Arrhenius plot of the rate gives a curve instead of a straight line.

At 90°C the energy and entropy of activation of the overall racemization of the sulfoxide was estimated to be 21.8 kcal/mol and −17.24 e.u., while those at 110°C were calculated as 28.5 kcal/mol and 0.0 e.u. respectively. Apparently, there in a gradual change of mechanistic pathways around 100°C, where the curve of the Arrhenius plot makes a turn. We expected that the $S_N2$ type process would be the predominant path at a low temperature and the value of $k_{ex}/k_{rac}$ would approach 0.5 while at a higher temperature other paths would participate giving rise to the reduction of the $k_{ex}/k_{rac}$ value.

At a low temperature, *e. g.* 80°C, the Pummerer rearrangement is negligible. However, the value of $k_{ex}/k_{rac}$ was found to be 0.35 suggesting that the $S_N2$ type oxygen-exchange process (path d) is not the only route but another path, very likely path (c), is participating in the racemization. The small activation energy and entropy factor suggest that the main reaction for the racemization is the nucleophilic substitution process (path d).

Table 6. Influence of mercuric chloride on the racemization reaction of tolyl benzyl sulfoxide at 25°C

| No. | $HgCl_2$ (mg) | Relative concn. $HgCl_2$ | $k_{rac}\times 10^4$ $(sec^{-1})$ | Relative rate |
|---|---|---|---|---|
| 1 | 0 | 0 | 0.0014 | 1 |
| 2 | 60.4 | 1 | 3.29 | 2350 |
| 3 | 115.4 | 1.91 | 4.73 | 3380 |
| 4 | 272.0 | 4.53 | 8.89 | 6350 |
| 5 | 447.7 | 7.41 | 13.8 | 9890 |

Table 7. Influence of sodium perchlorate on the racemization reaction of sulfoxide[a]

| No. | $NaClO_4$ (mg) | $[NaClO_4]$ | $k_{rac}\times 10^5$ $(sec^{-1})$ | Relative rate |
|---|---|---|---|---|
| 1 | 8.8 | 0.00120 | 0.650±0.005 | 1 |
| 2 | 44.6 | 0.00607 | 2.31 ±0.04 | 3.31 |
| 3 | 89.3 | 0.01220 | 5.11 ±0.18 | 7.86 |
| 4 | 187.2 | 0.02550 | 10.7 ±0.1 | 16.5 |
| 5 | 307.5 | 0.04180 | 17.8 ±0.6 | 27.4 |
| 6 | 556.1 | 0.0757 | 24.1 ±0.7 | 37.1 |
| 7 | 961.7 | 0.1309 | 29.3 ±0.4 | 45.1 |
| 8 | 987.7 | 0.1344 | 31.3 ±1.2 | 48.2 |

a) The reaction was carried out at 55°C. The sulfoxide, $3\times 10^{-4}$ mol, was reacted in acetic anhydride of 6 ml soln. containing sodium perchlorate.

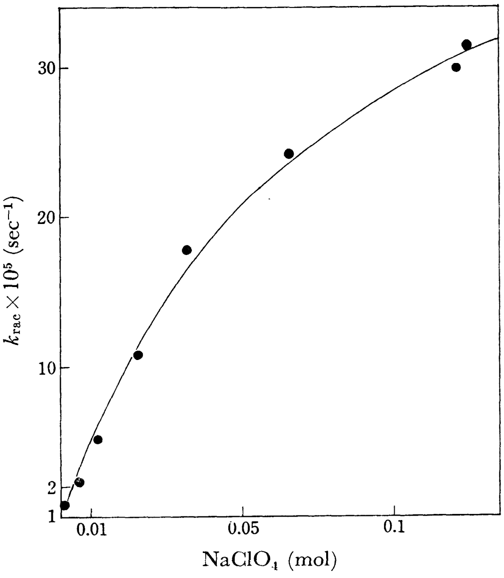


Fig. 6. The influences of sodium perchlorate to the racemization reaction of sulfoxides.

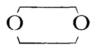
The racemization of the sulfoxide in this reaction was catalyzed markedly in the presence of acetic acid (Table 5, Fig. 5).

The rate of racemization increases remarkably with the increase of the concentration of acetic acid up to the concentration of acetic anhydride. It falls off gradually with further increase of the concentration. In a low concentration acetic acid it would solvate effectively only at the carbonyl groups of both acetic anhydride and the acetoxysulfonium intermediate, thus increasing the rate. Excess acetic acid would solvate sulfoxide oxygen either by hydrogen bonding or protonation and the initial acetylation would be retarded, though both the heterolysis of O–S and C–S bonds will be facilitated.

As in the case of diaryl sulfoxides, the addition of mercuric chloride or Lewis acid increases the rate of racemization remarkably (Table 6) as also is the case with sodium perchlorate (Table 7, Fig. 6).

Addition of the Lewis acid facilitates both the acetylation and heterolysis of both S–O and C–S bonds substantially while the addition of sodium perchlorate would increase the ionic strength of the medium and also shift the equilibrium of acetylation step to the right to increase the rate of racemization.

TABLE 8. KINETIC DATA OF THE RACEMIZATION OF *p*-TOLYL BENZYL SULFOXIDE WITH ACETIC ANHYDRIDE IN SEVERAL SOLVENTS AT 100°C[a]

| Run | Used solvent | $k_{rac}\times10^5$ (sec$^{-1}$) at 100°C | $Ac_2O$ (g) |
|---|---|---|---|
| 1 | $C_6H_5Cl$ | 7.20 | 10.7797 |
| 2 | $CH_3CN$ | 17.2 | 10.7936 |
| 3 |  | 2.30 | 10.8228 |
| 4 | $(CH_3)_2NCHO$ | 2.16 | 10.7573 |

a) Sulfoxide, $10^{-3}$ mol, was reacted with acetic anhydride in 20 m*l* reaction soln.

Solvent effect was examined with four different solvents and the results are summarized in Table 8. Apparently the reaction is slow in two nucleophilic solvents, dioxane and dimethyl formamide (DMF) but is faster in less nucleophilic and polar solvents, chlorobenzene and acetonitrile. Undoubtedly nucleophilic solvents interact with acetic anhydride to retard the initial acetylation of the sulfoxide group while both acetylation and the succeeding heterolysis would be facilitated in less nucleophilic but polar media to result in the increase of the over-all rate of the racemization.

We might conclude that the apparent over-all racemization of aryl benzyl sulfoxides in acetic anhydride or acetic anhydride containing media is caused by two participating reactions, *i. e.*, pathways (c) and (d) in which (d) is the predominant route. At low temperatures below 100°C, the contribution of S–C bond cleavage pathway (c) is small but becomes substantial as the reaction temperature is raised.

## Experimental

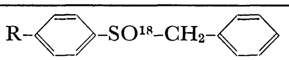
**Material.** *Optically Active p-Tolyl Benzyl Sulfoxide.* The sulfoxide was prepared by the method of Anderson[5] in which (−)-menthyl (−)-*p*-toluenesulfinate was treated with benzylmagnesium chloride in ether. Mp 167°C $[\alpha]_D$+250° (in ethanol), lit,[6] mp 169—170°C $[\alpha]_D$ +252°.

*p-Substituted Phenyl Benzyl Sulfoxides $^{18}O$-Labeled.*[7] Each of the corresponding sulfide was oxidized with bromine in the presence of pyridine in acetic acid and $H_2{}^{18}O$, according to the usual procedure. All the sulfoxides had S–O stretching bonds in their infrared spectra at about 1050 cm$^{-1}$. Their melting points, $^{18}O$-concentration (atom %) and chemical shift of methylene are summarized in Table 9.

*Dioxane*, obtained commercially, was purified according to the usual procedure, finally dried with sodium and distilled (bp 101.5°C).

*Acetic Acid*, obtained commercially was treated with chromic anhydride and after refluxing for several hours, was distilled (bp 117.5—118°C).

TABLE 9. PHYSICAL PROPERTIES AND $^{18}O$-CONCENTRATION OF $^{18}O$-LABELED *p*-SUBSTITUTED ARYL BENZYL SULFOXIDES

| R in  | Melting point (ref) | $^{18}O$-Concentration (atom%) | Chemical shift of methylene (ppm) |
|---|---|---|---|
| $OCH_3$ | 126C° (−) | 1.08 | 3.99, 4.04 |
| $CH_3$ | 140−141°C (140−141°C)[6] | 1.08 | 4.03 |
| H | 127°C (127°C)[8] | 1.06 | 4.03 |
| Cl | 135°C (135°C)[9] | 1.34 | 4.03 |
| $NO_2$ | 168°C (168—169°C)[10] | 1.15 | 4.11 |

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5) K. K. Anderson, *Tetrahedron Lett.*, **1962**, 93.

6) C. J. M. Stirling, *J. Chem. Soc.*, **1963**, 5741.

7) S. Oae, Y. Ohnishi, S. Kozuka and W. Tagaki, This Bulletin, **39**, 364 (1966).

8) M. Nishio and T. Ito, *Chem. Pharm. Bull.* (Tokyo), **13**, 1392 (1965).

9) J. D. M. Tiecco and A. Tundo, *Gazz. Chim. Ital.*, **1913**, 92.

10) G. L. A. Mangini and R. Passerini, *J. Chem. Soc.*, **1957**, 1386.

*Acetic Anhydride*, obtained commercially, was treated with anhydrous sodium acetate and after refluxing for several hours, was distilled (bp 139.5—140°C).

**Kinetic Procedure I (Oxygen Exchange Reaction).** The oxygen exchange reaction was carried out at $100\pm0.05$°C in sealed tubes into which aliquotes of a solution containing *p*-substituted phenyl benzyl sulfoxide ($10^{-3}$ mol) in 20 m*l* of acetic anhydride were placed. From time to time a sealed tube containing 5 m*l* of the solution of the reaction mixture was withdrawn and placed in an ice bath in order to stop the reaction. The sulfoxide separated out was extracted with carbon tetrachloride, then carbon tetrachloride was distilled off and the resulting sulfoxide was recovered. The recovered sulfoxide was dried throughly and subjected to $^{18}$O-analysis.[11]

**Kinetic Procedure II (Racemization Reaction).** The racemization reaction was carried out at a set temperature ranging from 60 to 120°C in sealed tubes in each of which a portion of the reaction mixture containing optically active *p*-tolyl benzyl sulfoxide ($10^{-3}$ mol) in 20 m*l* of acetic anhydride was placed without using other solvents. At suitable time intervals sealed tubes each containing 3 m*l* of reaction mixture were drawn out and placed into an ice bath to stop the reaction. 3 m*l* of dioxane was then added into the tube and the whole solution was subjected to the determination of specific rotation. The constants obtained are usually in good agreement with those obtained by isolating the product under kinetic procedure I.

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[11] S. Oae and N. Kunieda, This Bulletin, **41**, 696 (1968).