Reinvestigation of the Mechanism of the Reaction of *N*,*N*-Dimethylaniline *N*-Oxide with Acetic Anhydride

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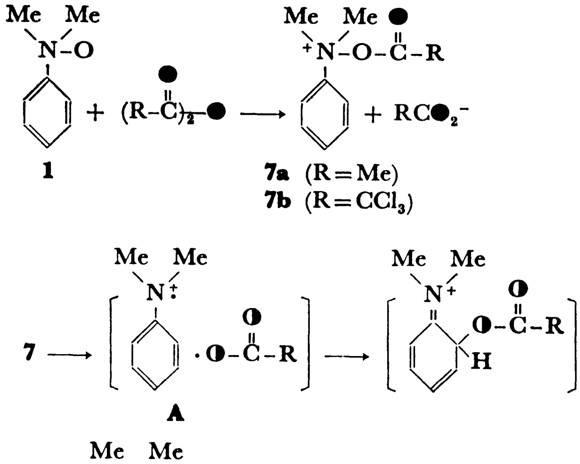
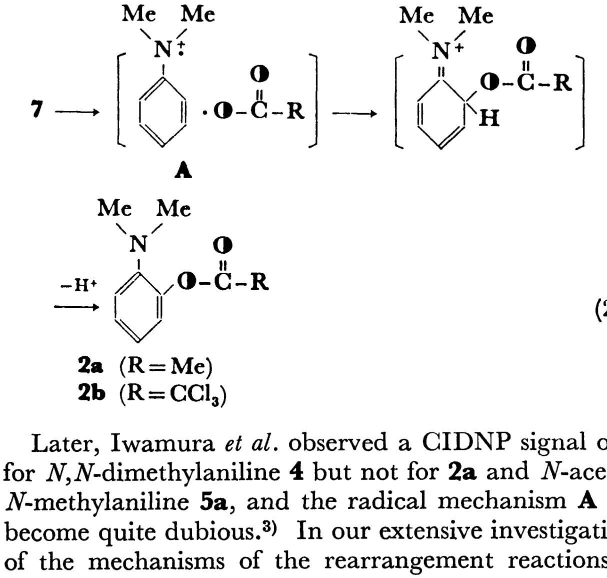
The mechanism of the reaction between *N*,*N*-dimethylaniline *N*-oxide **1** and acetic anhydride to give 2-acetoxy-*N*,*N*-dimethylaniline **2a** has been reinvestigated by means of our more refined ^{18}O-tracer experiments. Other products of the reaction are 4-acetoxy-*N*,*N*-dimethylaniline, *N*,*N*-dimethylaniline **4**, *N*-methylacetanilide, and bis(4-dimethylaminophenyl)methane. The reaction of **1** with ^{18}O-labeled acetic anhydride is considered to involve the initial formation of carbonyl-^{18}O-labeled *N*-acetoxy-*N*,*N*-dimethylanilinium ion **7a** and the subsequent intramolecular rearrangement of **7a** into **2a** in which the original ^{18}O-label in **7a** is unequally partitioned into two oxygen atoms of **2a** (phenolic oxygen: ethereal oxygen=*ca.* 4: 1). The reaction of **1** with trichloroacetic anhydride gave solely 2-trichloroacetoxy-*N*,*N*-dimethylaniline but not any **4** which should be formed *via* the free radical mechanism. These observations suggest the occurrence of the two concerted path *via* polarized six-(major) and four-(minor) membered cyclic transition states and rule out the free radical pair mechanism which was proposed ealier by us.[2]

The reaction between *N*,*N*-dimethylaniline *N*-oxide **1** and acetic anhydride was first investigated in somewhat detail by Huisgen *et al.*[1] Soon after, we also investigated the mechanism by ^{18}O-tracer technique and proposed the radical pair mechanism (**A**) for the formation of 2-acetoxy-*N*,*N*-dimethylaniline **2a** based on the observation that both carbonyl and ethereal oxygen atom in **2a** was nearly completely equilibrated in the course of the rearrangement from **7a** to **2a**.[2]



1 **7a** (R=Me) **7b** (R=CCl$_3$) (1)



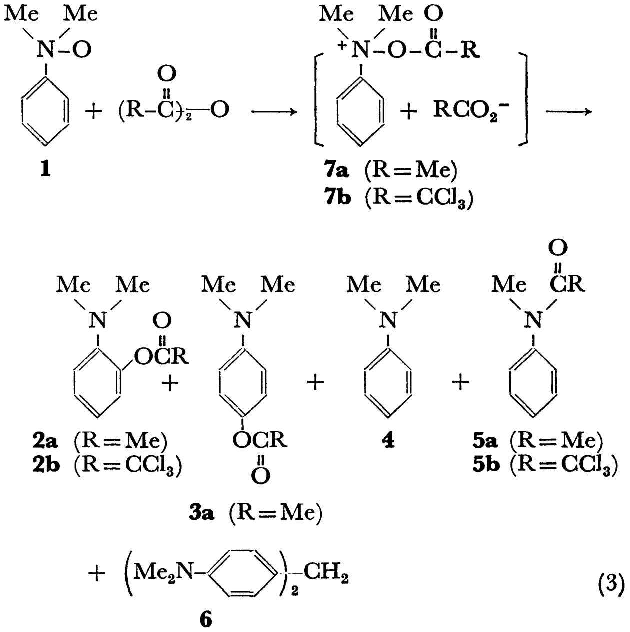
A

2a (R=Me)
2b (R=CCl$_3$) (2)

Later, Iwamura *et al.* observed a CIDNP signal only for *N*,*N*-dimethylaniline **4** but not for **2a** and *N*-acetyl-*N*-methylaniline **5a**, and the radical mechanism **A** has become quite dubious.[3] In our extensive investigations of the mechanisms of the rearrangement reactions of tertiary amine *N*-oxides with acylating agents by means of ^{18}O-tracer technique, we have seldom encountered the case in which the reaction proceeded solely *via* radical mechanistic path.[4] Thus, the reaction between **1** and acetic anhydride has been reinvestigated by aid of our more sophisticated ^{18}O-tracer technique.

Results and Discussion

The reaction between *N*,*N*-dimethylaniline *N*-oxide **1** and acetic anhydride was found to give products **2**—**4**, while the distribution of products clearly depends on the solvent as seen in Table 1.



1 **7a** (R=Me) **7b** (R=CCl$_3$)

2a (R=Me) **2b** (R=CCl$_3$) **3a** (R=Me) **4** **5a** (R=Me) **5b** (R=CCl$_3$) **6** (3)

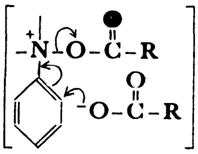
TABLE 1. PRODUCTS OF THE REACTION OF *N*,*N*-DIMETHYLANILINE *N*-OXIDE **1** WITH ACETIC ANHYDRIDE OR TRICHLOROACETIC ANHYDRIDE

Acid anhydride	Solvent	Yield(%) 2	3	4	5	6
Acetic anhydride (R=Me)	H$_2$O$^{a)}$	84	—	3	0	0
	50% MeCN-H$_2$O	66	1	11	2	—
	MeCN	6	0	0.4	48	3
Trichloroacetic anhydride (R=CCl$_3$)	MeCN	90	0	0	0	0

a) Ref. 1.

In such an aprotic solvent as acetonitrile, demethylation by Polonovski reaction giving **5a** was predominant, however, the rearrangement to afford **2a** was the major course of the reaction in protic media. The first step of the reaction has been believed to be the acetylation of **1** to form *N*-acetoxy-*N*,*N*-dimethylanilinium ion **7** which is then partitioned to go through the different paths (Eq. 1). In acetonitrile, the acetate anion is considered to be a base strong enough to abstract proton from the *N*-methyl group of **7a** to promote the Polonovski reaction eventually to give **5a**; whereas in protic media, the basicity of acetate anion should be markedly reduced by the solvation, and hence the alternative rearrangement reaction becomes predominant.[1,2)]

Upon the usual treatment of the *N*-oxide with ^{18}O-labeled acetic anhydride in protic media, **2a** was isolated from the mixture, purified and allowed to react with phenylhydrazine to give crystalline products, *i.e.* 2-hydroxy-*N*,*N*-dimethylaniline and 1-acetoxy-2-phenylhydrazine, which were carefully purified and then subjected to the routine ^{18}O-analysis (Table 2).[5)] Meanwhile all the conceivable intermediates and/or transition states of this rearrangement may be illustrated from **A** to **K**.



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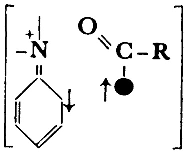

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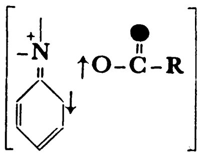

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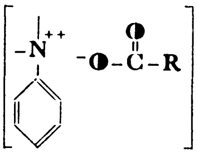

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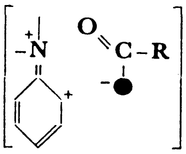

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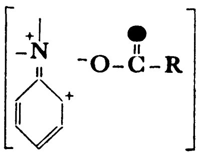

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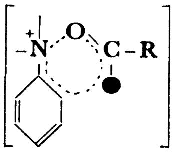

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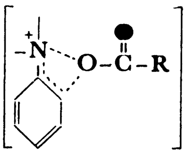

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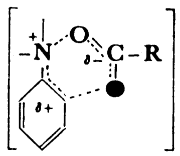

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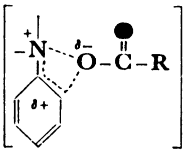


K

TABLE 2. ^{18}O-TRACER RESULT OF THE REACTION BETWEEN **1** AND $(\mathrm{Me}\overset{\overset{^{18}\mathrm{O}}{\|}}{\mathrm{C}})_2{}^{18}\mathrm{O}$

Compound	^{18}O-Content of the compd (excess atom %)[a)]	
	in 50% MeCN–H_2O	in H_2O
1-Acetyl-2-phenylhydrazine[b)]	0.854	0.854
2-Hydroxy-*N*,*N*-dimethylaniline	0.668	0.718
1-Acetyl-2-phenylhydrazine	0.178	0.133

a) ±0.005 atom %. b) Derived from the starting acetic anhydride.

When the calculated ^{18}O-distributions in **2a** resulted from all these possible mechanistic routes are compared with the observed values in Table 3, the mechanism involving the attack of external acetate anion *via* **B** is obviously ruled out, in keeping with our original argument suggested earlier.[2)] Although the observed ^{18}O-data cannot be explained by the radical mechanism **A** (Eq. 2), the possibility of homolytic cleavage of N–O bond of **7a** cannot be rejected completely. Namely, if the radical pair would be a very short lived singlet radical pair such as either **C** or **D**, as suggested by Iwamura *et al.*,[3)] the ^{18}O-label may not be completely scrambled in **2a**, since the two oxygens of the acetoxyl radical formed incipiently should be sterically unequal. The formation of **4** which has been confirmed as the radical reaction product by CIDNP study[3)] must be produced *via* homolytic cleavage of **7a**. Indeed the reaction of **1** with acetic anhydride initiates the polymerization of styrene.[1,6)] These observations seem to imply the involvement of these singlet radical pairs **C** and **D** at least partially.

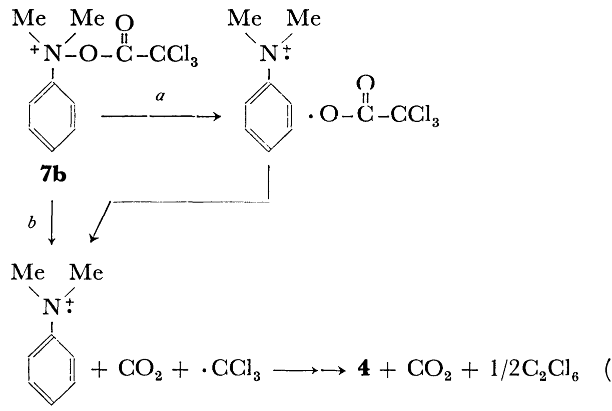
In order to examine the possible involvement of such a homolytic cleavage, trichloroacetic anhydride was allowed to react with **1**. If the intervention of radical pairs **C** or **D** or both would be responsible for the formation of **2**, the yield of radical reaction product, **4**, should markedly increase in the reaction of **1** with trichloroacetic anhydride (Eq. 4),[7)] since the decarboxylation of trichloroacetoxyl radical is well known to be very fast.[8)] However, since the reaction of **1** with trichloroacetic anhydride gave only **2b**, but neither any **4** nor hexachloroethane, all the free radical mechanisms **A**, **C**, and **D** cannot be responsible for the major path of the rearrangement.[9)]

Thus the ionic mechanisms **E**—**K** still remain. Among these, however, the ion pair mechanisms seem to be highly unlikely, since the ionic cleavage of the N–O bond of **7a** leads to the formation of a highly

TABLE 3. THEORETICAL AND EXPERIMENTAL ^{18}O-DISTRIBUTION IN **2a** OBTAINED FROM **1** AND ^{18}O-LABELED ACETIC ANHYDRIDE[a)]

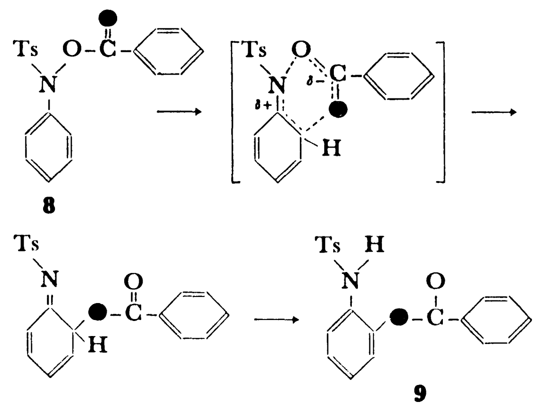
Oxygen	Experimental		Theoretical			
	in 50% MeCN–H_2O	in H_2O	**B**	**A,E**	**C,F,H,J**	**D,G,I,K**
Phenolic	79%	84%	100%	50%	100%	0%
Carbonyl	21	16	100	50	0	100

a) Original ^{18}O-content of carbonyl oxygen of **7a** is defined as 100%.



(4)

energetic double cation species of **4**. Indeed, the ion pair mechanism **E** cannot be accepted since the ^{18}O-distribution in **2a** is uneven and the oxygen scrambling in **2a** decreases with the increase of solvating power of the medium. Only in the case if the ion pair is a very short lived intimate one as illustrated by **F** or **G**, the two oxygen atoms of the acetate anion might not be sterically equal and could give **2a** in which ^{18}O-label is not completely equilibrated. The mechanisms *via* **F** and **G** may also be eliminated in view of the highly unstable *N*,*N*-dimethylaniline double cation. Meanwhile product ratio **2a** *vs*. the radical product **4** from **7a** was found to increase with the increase of the polar nature of the solvent.[10] Whereas when acetic anhydride was changed to trichloroacetic anhydride, no free radical products were obtained despite the facile homolytic bond cleavage of **7a** by concerted two bond fission to give cation radical of **4**, CO_2, and trichloromethyl radical.[7] All these observations do not seem to be in accordance with the mechanism involving the sigmatropic shift such as **H** or **I**, however, can be best explained in terms of the concurrent heterolytic cleavage of N–O bond of **7a** and a new C–O bond forming *via* such transition states as illustrated by **J** (major path) and **K** (minor path) which are represented as a hybrid of canonical forms, **C**, **F**, and **H** for **J** and that of canonical forms, **D**, **G**, and **I** for **K**. The contribution of each of these canonical forms is considered to depend on the nature of solvent and R group of the acid anhydride used. Similar polarized cyclic transition state has been suggested for the rearrangement of *O*-benzoyl-*N*-(*p*-tolylsulfonyl)-*N*-arylhydroxylamine **8** to 2′-benzoyloxy-*p*-toluenesulfonanilide **9** as shown in Eq. 5.[11]



(5)

Experimental

N,*N*-Dimethylaniline *N*-oxide **1** was prepared by oxidation of *N*,*N*-dimethylaniline **4** with hydrogen peroxide in methanol according to the method of Huisgen, Bayerlein, and Hegkamp.[1]

Oxygen-18-labeled acetic anhydride was prepared by the method reported by Oae, Kitao, and Kitaoka;[12] bp 137.5—139 °C. By treatment with phenylhydrazine, a small amount of the acetic anhydride was converted to crystalline 1-phenyl-2-acetylhydrazine which was recrystallized from benzene; mp 129—129.5 °C, and subjected to the ^{18}O-analysis (0.854 excess atom %).

Reaction between 1 and Acetic Anhydride in 50%(v/v) CH_3CN–H_2O. Acetic anhydride (1.3 g, 13 mmol) was added dropwise into a solution of **1** (1.0 g, 7.3 mmol) in 14 ml of 50%(v/v) CH_3CN–H_2O with stirring at 0 °C under nitrogen atmosphere. The mixture was stirred for 2 h at 0 °C, then the reaction mixture was treated with an aqueous solution of sodium carbonate under cooling in an ice bath, then extracted with ether and dried. To the solution, 725 mg of 2,4-dichloronitrobenzene was added as the internal standard for the analysis by a GLPC equipped with 2 m stainless steel column packed with 5% PEG-20M on 80 mesh celite. The chromatogram was recorded on Shimadzu GC-6A GLPC instrument.

Reaction between 1 and Acetic Anhydride in CH_3CN. The reaction and product analysis were carried out in a same manner described for the reaction in 50%(v/v) CH_3CN–H_2O.

Reaction between 1 and Trichloroacetic Anhydride. *N*,*N*-Dimethylaniline *N*-oxide **1** (100 mg, 0.73 mmol) in 3 ml of dry CH_3CN was treated dropwise with trichloroacetic anhydride (430 mg, 1.4 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was treated with aqueous solution of sodium carbonate and extracted with ether and dried over sodium sulfate. Into this solution, tetralin (102 mg) was added as the internal standard for GLPC analysis through a stainless steel column packed with 5% SE-30 on 80 mesh celite. The gas chromatogram of the sample solution was recorded on Hitachi 163 GLPC instrument, and only one peak of 2-hydroxy-*N*,*N*-dimethylaniline was observed.

Oxygen-18-tracer Experiment of the Reaction between 1 and Acetic Anhydride. *In 50%(v/v) CH_3CN–H_2O*: The reaction between 1.0 g of **1** and 1.36 g of ^{18}O-labeled acetic anhydride was carried out in a similar manner which was applied for the product analysis. 2-Acetoxy-*N*,*N*-dimethylaniline **2a** was separated by preparative TLC (Kieselgel G_{254}) at 5 °C with 5% acetone–hexane as an eluent (isolated yield 0.567 g). The product **2a** was treated with 0.377 g of phenylhydrazine and the mixture was allowed to stand overnight at room temperature. A solid mass, separated, was collected and washed with benzene, gave 0.33 g of 1-phenyl-2-acetylhydrazine, which was recrystallized from benzene and subjected to the ^{18}O-analysis; mp 129—129.5 °C. The filtrate was washed with water to remove unreacted phenylhydrazine, dried and solvent was removed. Preparative TLC (Kieselgel GF_{254}) of the residue with 5% acetone–dichloromethane as an eluent gave 0.406 g of 2-hydroxy-*N*,*N*-dimethylaniline which was distilled under reduced pressure and subjected to the ^{18}O-analysis, mp 44—44.5 °C.

In H_2O: The reaction was carried out in a same manner described above.

Control Experiment on Dilution of ^{18}O-Label in Acetic Anhydride during the Reaction. A solution of 500 mg (4.9 mmol) of ^{18}O-labeled acetic anhydride and 400 mg (0.33 mmol) of **1** in 1 ml of 50%(v/v) CH_3CN–H_2O was stirred for 2 h at 0 °C under nitrogen atmosphere. Into this solution 520 mg of *N*-methylaniline was added and the solution was stirred for addtional 1 h at room temperature. After the solvent was removed, the residue was washed with benzene to obtain 240 mg of *N*-methylacetanilide which was recrystallized from benzene; mp 102—102.5 °C. Since ^{18}O-content of the *N*-methylacetanilide (0.855 excess atom %) was found to be same to that of 1-acetyl-2-phenylhydrazine (0.854 excess atom %) which was derived from starting ^{18}O-labeled acetic anhydride (Table 2), there is no ^{18}O-dilution of acetic anhydride during the reaction with **1** in the presence of H_2O.

Determination of Oxygen-18 Content. ^{18}O-analysis was carried out by the method developed by Rittenberg-Ponticorbo.[5] Twenty mg of sample was pyrolyzed with 300 mg of purified $HgCl_2$ and $Hg(CN)_2$ respectively, in an evacuated, sealed silica tube at 550 °C for 12 h. Then the tube was broken in a vacuum line and CO_2 formed was purified by distillation and the mass peaks *m/e* 44 and 46 which correspond to $C^{16}O_2$ and $C^{16}O^{18}O$, respectively, were recorded on Hitachi RMU-6MG mass spectrometer. An error of ^{18}O-content was within ±0.005 atom %. $HgCl_2$ was purified by sublimation under reduced pressure and $Hg(CN)_2$ was purified by recrystallization from absolute ethanol before use.

References

1) R. Huisgen, F. Bayerlein, and W. Hegkamp, *Chem. Ber.*, **92**, 3223 (1959).

2) S. Oae, T. Kitao, and Y. Kitaoka, *J. Am. Chem. Soc.*, **84**, 3366 (1962).

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6) V. Boekelheide and D. L. Harrington, *Chem. Ind. (London)*, **1955**, 1423.

7) T. Koenig, *J. Am. Chem. Soc.*, **88**, 4045 (1966). Based on the fact that the homolytic decomposition of both *t*-butyl trichloroperacetate and trichloroacetyl peroxide proceeds *via* concerted multi bond cleavage to form trichloromethyl radical, CO_2 and *t*-butoxyl radical, and trichlormethyl radical and CO_2, respectively,[8a,b] the homolytic cleavage of **7b** is expected to be a concerted process as denoted in Eq. 4b.

8) a) P. D. Bartlett and R. R. Hiatt, *J. Am. Chem. Soc.*, **80**, 1398 (1958); b) J. E. Leffler and H. H. Gibson, Jr., *ibid.*, **90**, 4117 (1968).

9) Since the rearrangement product, 2-trichloroacetoxy-*N,N*-dimethylaniline **2b** is very sensitive to moisture and is hydrolyzed very easily to give 2-hydroxy-*N,N*-dimethylaniline and trichloroacetic acid during the treatment of the reaction mixture, ^{18}O-tracer study for the reaction between **1** and trichloroacetic anhydride could not be made.

10) Table 1 of this work and Ref. 1.

11) S. Oae and T. Sakurai, *Tetrahedron*, **32**, 2289 (1976).

12) S. Oae, T. Kitao, and Y. Kitaoka, *J. Am. Chem. Soc.*, **84**, 3359 (1962).