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The Mechanism of the Reaction of N,N-Dimethylaniline Oxide with Acetic Anhydride[1]

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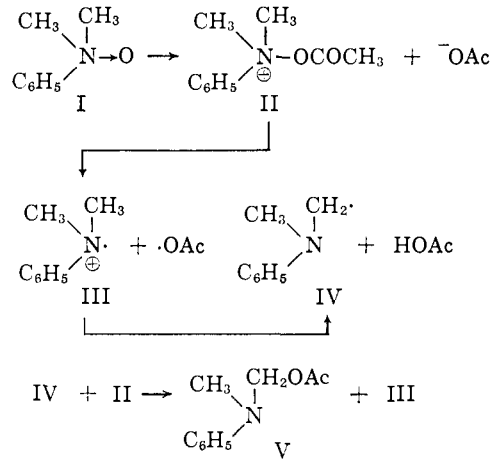
N,N-Dimethylaniline oxide was allowed to react with acetic anhydride, of which three oxygen atoms were equally enriched with oxygen-18 both with and without solvent water. The *o*-acetoxy-N,N-dimethylaniline and N-methylacetanilide formed were subjected to oxygen-18 analysis. From the data on oxygen-18 distributions in these compounds, together with previous results, a radical pair mechanism is suggested for the initial formation of both compounds. The nature of *o*-acetoxy migration *vs.* demethylation is briefly discussed.

In the previous papers[1,2] we have suggested, on the basis of the oxygen-18 tracer studies and other evidences, that the nature of the reaction of 4-picoline N-oxide with acetic anhydride is different from that of 2-picoline N-oxide; the former proceeds through an intermolecular rearrangement involving nucleophilic attack of acetate anion while the latter proceeds by a radical cage process. In this communication, we wish to report our observations on the reaction of N,N-dimethylaniline oxide with acetic anhydride.

The small amounts of tertiary amine oxides in both animals and plants have been considered to function as intermediates in some biochemical reaction sequence rather than to occur merely as the terminal products of amine oxidation.[3]

Horning and his co-workers[3c,4] have shown that the rearrangements of various *tert*-amine oxides containing at least one methyl group take place in aqueous solution at *p*H 2–7 in the presence of a transition metal ion such as ferric ion under mild conditions yielding the corresponding *sec*-amines and formaldehyde. They have also suggested that this reaction would provide a possible pathway for the biological dealkylation of *tert*-amine oxides.[5] Another possible pathway which could lead to the oxidative demethylation in biological systems is the acetylation of *tert*-amine oxides, known as the Polonovski reaction[6] whereby *tert*-amine oxides containing at least one N-methyl group are converted by acetic anhydride into *sec*-amines and formaldehyde, since acetic anhydride could be substituted by other strong acetylating agents which are present in biological systems, such as acetyl phosphate; moreover, the reaction is very rapid even in the cold.

Earlier, Boekelheide and Harrington[7] have suggested that the demethylation reaction of N,N-dimethylaniline oxide with acetic anhydride is a free radical chain process, from their observation that the rearrangement of N,N-dimethylaniline oxide in boiling benzene was effective in causing polymerization of styrene. Their postulated mechanism can be illustrated as



Recently, this demethylation reaction and the rearrangement have been studied in detail by Huisgen and his co-workers[8] using various N,N-dimethylarylamine oxides. They have shown[8a] that the acylation of N,N-dimethylarylamine oxides yields mainly *o*-acyloxy-N,N-dimethylarylamines and acylated arylamines together with small amounts of formaldehyde, N,N-dimethylarylamine, *p,p'*-bis-dimethylaminodiarylmethane and others, and also that the ratio of the reaction products depends largely on the solvent and on the nature of the acyl group. Thus the acetylation of N,N-dimethylaniline oxide without solvent gave 33% of *o*-hydroxy-N,N-dimethylaniline, 29% of N-methylacetanilide, 9% of N,N-dimethylaniline and a small amount of *p,p'*-bis-dimethylaminodiphenylmethane, while in water the same reaction gave almost exclusively *o*-acetoxy-N,N-dimethylaniline. In both cases, the reaction was very rapid and exothermic. Here again, the initial intermediate of the reaction was presumed to be N-acetoxy-N,N-dimethylanilinium ion (II).

The reaction leading to *o*-acetoxy-N,N-dimethylaniline was presumed to take place by an intramolecular cyclic electron shift as shown below, which is closely similar to that postulated for the rearrangement of 2-picoline N-oxide by Traynelis and Martello.[9]

As for the demethylation reaction, they have considered that the first step is the base-catalyzed E_2

(1) Paper V on "Rearrangements of Tertiary Amine Oxides"; paper IV, S. Oae, T. Kitao and Y. Kitaoka, *J. Am. Chem. Soc.*, **84**, 3362 (1962).

(2) S. Oae, T. Kitao and Y. Kitaoka, *ibid.*, **84**, 3359 (1962).

(3) (a) C. C. J. Culvenor, *Rev. Pure Appl. Chem.*, **3**, 84 (1953); (b) M. S. Fish, N. M. Johnson and E. C. Horning, *J. Am. Chem. Soc.*, **77**, 5892 (1955); (c) J. C. Craig, F. P. Dwyer, A. N. Glazer and E. C. Horning, *ibid.*, **83**, 1871 (1961).

(4) C. C. Sweeley and E. C. Horning, *ibid.*, **79**, 2620 (1957).

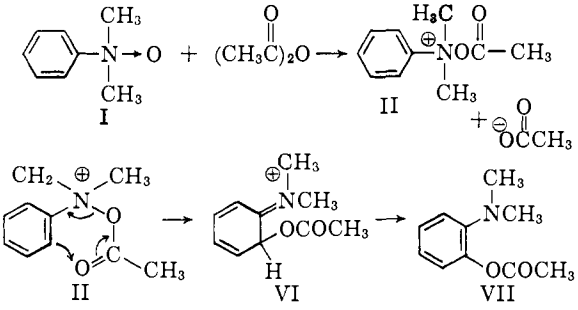
(5) M. S. Fish, C. C. Sweeley and E. C. Horning, *Chemistry & Industry*, 24 (1956).

(6) M. Polonovski and M. Polonovski, *Bull. soc. chim.*, **41**, 1190 (1927).

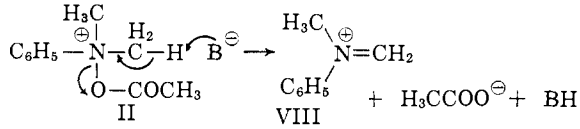
(7) V. Boekelheide and D. L. Harrington, *Chemistry & Industry*, 1423 (1955).

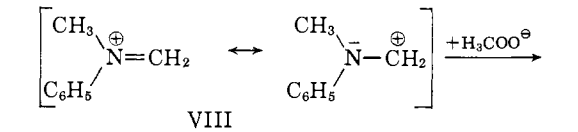
(8) (a) R. Huisgen, F. Bayerlein and W. Heydkarp, *Chem. Ber.*, **92**, 3223 (1959); (b) F. Bayerlein and R. Huisgen, *ibid.*, **92**, 3241 (1959).

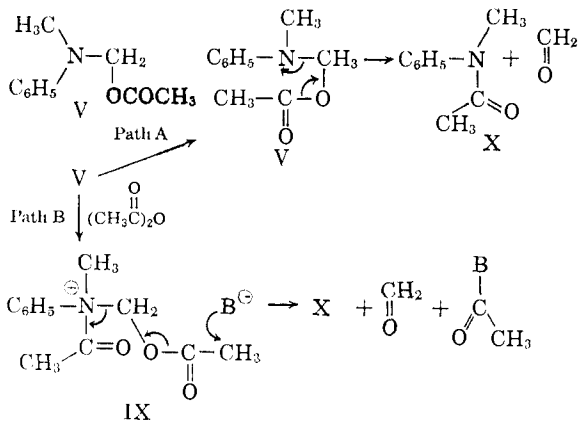
(9) V. J. Traynelis and R. F. Martello, *J. Am. Chem. Soc.*, **80**, 6590 (1958).



elimination to form the intermediate VIII, to which acetate anion adds giving unstable N-methyl-N-acetoxymethylaniline (V). Once N-methyl-N-acetoxymethylaniline is formed, this unstable compound will give N-methylacetanilide and formaldehyde either by an internal cyclic mechanism (path A) or by reacting with acetic anhydride (path B). The presence of the immonium ion VIII as an intermediate was suggested on the basis of the observation that the addition of *tert*-amines or tetramethylammonium acetate facilitates the demethylation reaction and suppresses the acetoxy rearrangement.

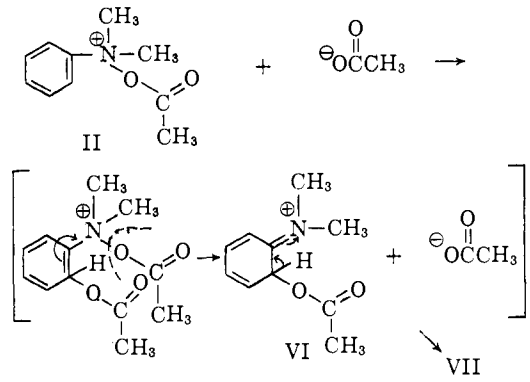






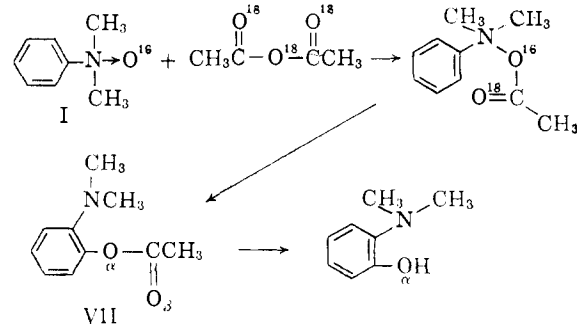
Although the formation of N,N-dimethylaniline and the polymerization of styrene seemed to be in accord with a free radical mechanism, the evidence available did not allow us to make a clear choice between an ionic mechanism and one involving free radicals. Moreover, it was uncertain whether the change of product components with the change of solvent is in any way related to the reaction mechanism.

Granting that the intermolecular rearrangement involving an initial nucleophilic attack of acetate anion would produce *p*-acetoxy compound preferentially or both *p*- and *o*-isomers, we cannot completely exclude the following intermolecular rearrangement, similar to the Bamberger rearrangement.[10]



We have extended our oxygen-18 tracer studies to shed further light on the mechanism of this reaction. Oxygen-18 labeled acetic anhydride,[2] of which all three oxygens were equally enriched by O^{18}, was allowed to react with an 0.55 molar amount of N,N-dimethylaniline oxide below −30°, obtaining N-methylacetanilide in about 26% yield and a small amount of *o*-acetoxy-N,N-dimethylaniline. Meanwhile, the same reaction of the amine oxide with the acetic anhydride was carried out in water at 0° and *o*-acetoxy-N,N-dimethylaniline was obtained in about 80% yield but not N-methylacetanilide. The *o*-acetoxy-N,N-dimethylaniline was hydrolyzed by refluxing it with methanolic potassium hydroxide to give *o*-hydroxy-N,N-dimethylaniline in about 80% yield. In separate control experiments, we confirmed that there is no exchange of oxygen-18 in each step of the reaction process.

The distribution of oxygen-18 required by the different mechanisms for the formation of *o*-acetoxy-N,N-dimethylaniline is



Intramol. cyclic rearrangement	$\alpha = O^{18}$, $\beta = O^{16}$, total $= (\alpha + \beta)/2$
Intermol. nucleophilic attack by AcO^-	$\alpha = \beta = (O^{18} \times 3 \times 1.8 + O^{16})/6.4 =$ total
Radical pair process	$\alpha = \beta = (O^{18} + O^{16})/2 =$ total

If the rearrangement of the acetoxy group to the *o*-position proceeds through an intramolecular cyclic shift as Huisgen and his co-workers have postulated, all the excess oxygen-18 for *o*-acetoxy-N,N-dimethylaniline should be found in the ether group and the carbonyl oxygen will not be enriched. The intermolecular rearrangement will require

(10) See C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, New York, 1953, pp. 621–624.

both carbonyl and ether oxygens to be completely scrambled with the oxygens of external acetate anion and to have a mean average concentration of oxygen-18 in the reaction mixture, while the radical pair process will produce acetoxy compound in which the two oxygens of the acetoxy radical are scrambled and both oxygen atoms contain the average concentration of natural and of oxygen-18 of the acetic anhydride used.

The oxygen-18 analyses of *o*-acetoxy-N,N-dimethylaniline and *o*-hydroxy-N,N-dimethylaniline are listed in Table I.

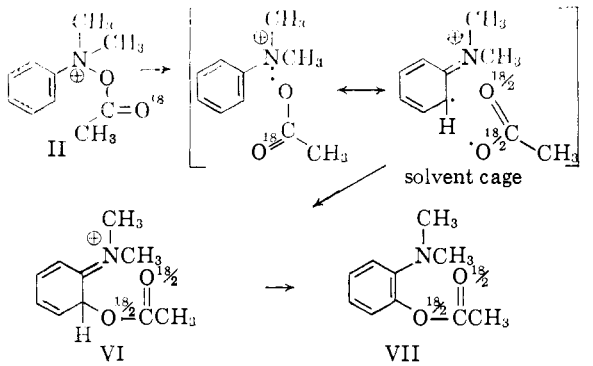
TABLE I

OXYGEN-18 ANALYTICAL RESULTS

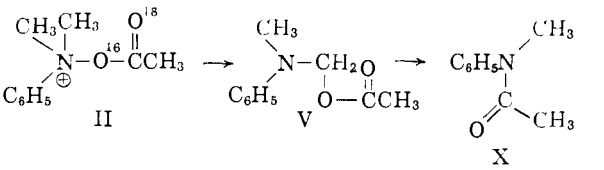
Compound	Atom % oxygen-18
$CH_3COOCOCH_3$	0.91
o-$(CH_3)_2NC_6H_4OCOCH_3$	.53, 0.52[a]
o-$(CH_3)_2NC_6H_4OH$	.49, 0.52[a]

[a] The products from the reaction which was carried out in water.

The results eliminate both the intermolecular mechanism and the intramolecular cyclic shift for the acetoxy rearrangement, because the intermolecular mechanism requires both the ester and the phenol to be incorporated by 0.80 atom % of oxygen-18 while the intramolecular cyclic process demands oxygen-18 concentrations to be 0.56 atom % for the acetoxy compound and 0.91 atom % for *o*-hydroxy-N,N-dimethylaniline. Since the radical pair process requires oxygen-18 concentration to be 0.56 atom % for both the ester and the aminophenol, this mechanism accords very well with the results. The oxygen-18 distribution pattern did not change even when the reaction was carried out in water under mild condition, indicating that the reaction is quite insensitive to solvent change. These observations together with the earlier findings that N,N-dimethylaniline and bis-N,N-dimethylaminophenylmethane are among the byproducts and that styrene polymerizes in the reaction, suggest that this *o*-acetoxy rearrangement is a radical pair reaction in a solvent cage as



For the formation of N-methylacetanilide, different mechanisms call for different distributions of oxygen-18, as illustrated in the following



Ionic, path A (II ⟶ VIII ⟶ V ⟶ X)
oxygen-18 in X = $(O^{18} \times 3 \times 1.8 + O^{16})/6.4$

Ionic, path B (II ⟶ VIII ⟶ V ⟶ IX ⟶ X)
oxygen-18 in X = $\{O^{18} + (O^{18} \times 3 + O^{16})/4\}/2$

Radical, path A (II ⟶ III ⟶ IV ⟶ V ⟶ X)
oxygen-18 in X = $(O^{18} + O^{16})/2$

Radical, path B (II ⟶ III ⟶ IV ⟶ V ⟶ IX ⟶ X)
oxygen-18 in X = $\{O^{18} + [(O^{18} + O^{16})/2 + O^{18} \times 2]/3\}/2$

If the reaction proceeds through an intermolecular rearrangement following path A, all the oxygen atoms in the reaction system become completely scrambled by recyclization of acetate ion, while ionic path B requires all the oxygen atoms other than that of formaldehyde to be scrambled, leaving that of formaldehyde to contain the same amount of oxygen-18 demanded by the path A. If both paths A and B proceed through a radical process, instead of an ionic path, the oxygen-18 value will be as shown in the above table.

The analytical value of oxygen-18 for N-methylacetanilide is shown in Table II.

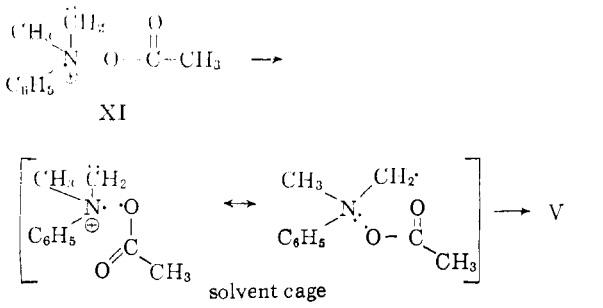
TABLE II

OXYGEN-18 ANALYTICAL RESULTS

Compound	Atom % oxygen-18
$CH_3COOCOCH_3$	0.91
$C_6H_5N(CH_3)COCH_3$	0.85

The results are compatible with any of the three conceivable mechanisms. Even the radical path A cannot be neglected, because the unstable intermediate V would exchange with external acetate ion so rapidly[11] that the acetoxy group in V would be completely scrambled before collapsing to form the final product.

Although the present data cannot clearly indicate the best mechanism, our previous work on 2-picoline N-oxide[2] and other studies[1] favor the idea that the initial migration of acetoxy group from XI to V is a radical cage process.



(11) In our unpublished work, we found that similar exchange in α-acetoxymethyl methyl sulfide takes place readily. In view of the larger electron-releasing conjugative effect of nitrogen atom than that of sulfur,[12] V is presumed to exchange far faster (at least 10^4) than the sulfur counterpart.

(12) M. Murakami and S. Oae, *Proc. Japan Acad.*, **25**, No. 11, 12 1949); *J. Chem. Soc. Japan*, **72**, 595 (1951).

o-Acetoxy Rearrangement *vs.* Demethylation.—As earlier work has shown, this reaction is a combination of two competitive reactions, *i.e.*, *o*-acetoxy rearrangement leading to *o*-acetoxy-N,N-dimethylaniline and a demethylation to form N-methylacetanilide. The common intermediate for both reactions is undoubtedly N-acetoxy-N,N-dimethylaniline. The existing data indicate that the addition of nucleophiles such as *tert*-amines and tetramethylammonium acetate facilitates the demethylation, whereas in neutral medium such as in water the *o*-acetoxy rearrangement predominates. This means that, in this reaction, the free radical cleavage of the N→O linkage competes with the elimination of a proton followed by facile acetoxy cleavage. A substantial portion of this reaction is initiated by the direct cleavage of the N→O bond of N-acetoxy-N,N-dimethylaniline leading to the *o*-acetoxy substitution whereas in the 2-picoline N-oxide the cleavage of the N→O linkage occurs only after the elimination of a proton to give the anhydrobase, which dissociates to radicals more readily than the original protonated N-acetoxy compound.[13] In this connection, it is interesting to compare the bond strengths of these two compounds from infrared data. The N→O stretching frequency of N,N-dimethylaniline oxide is 960 $cm.^{-1}$, which corresponds to a force constant of 4.05×10^5 dyn./cm., whereas that of 2-picoline N-oxide is 1200 $cm.^{-1}$, with force constant 6.35×10^5 dyn./cm.

The extremely facile reaction of N,N-dimethylaniline oxide, the successful competition of the direct cleavage–*o*-substitution of acetoxy radicals with the elimination of proton–acetoxy migration, and the mechanistic nature of this reaction are all in accord with this weakness of the N→O bond.

Acknowledgment.—The authors are grateful to Professor S. Okazaki of Nara Women's College for the generous gift of O^{18}-enriched water. Appreciation is also addressed to Dr. S. Mima of Govt. Ind. Research Inst., Osaka, for his collaborations in mass-spectroscopic analyses.

Experimental

N,N-Dimethylaniline Oxide Hydrochloride.—N,N-Dimethylaniline oxide and its hydrochloride were prepared by the oxidation of N,N-dimethylaniline with hydrogen peroxide in methanol following the procedure used by Huisgen and his co-workers.[8a] Freshly distilled N,N-dimethylaniline, b.p. 195°, 50 g., in 500 ml. of methanol was treated dropwise with stirring at room temperature with 350 ml. of 30% hydrogen peroxide and the mixture was shaken for 24 hours at room temperature. The excess of hydrogen peroxide in solution was decomposed with manganese dioxide under cooling. After the precipitate which formed was filtered off, the filtrate was diluted with 3.5-fold volumes of water, washed with ether, and then acidified with concd. hydrochloric acid. The acidic solution was carefully evaporated at 60° using a rotary evaporator. The residue was collected and was recrystallized from acetone. Recrystallization gave 39 g. (51.7% yield) of N,N-dimethylaniline oxide hydrochloride, m.p. 124–125° (lit.[8a] m.p. 124–125°).

N,N-Dimethylaniline Oxide.—N,N-Dimethylaniline oxide hydrochloride (20 g.) was dissolved in 2 l. of water and the solution was passed through 500 ml. of Amberlite-IR-4B at 1 drop/sec. The column (3.5 × 100 cm.) was washed with 1 l. of water. The combined eluates were carefully evaporated below 60° *in vacuo* to give slightly yellow hygroscopic solid (15.5 g.).

Oxygen-18 Labeled Acetic Anhydride.—The method of preparation was similar to that reported in the previous papers.[1,2] The acetic anhydride obtained had 0.91 atom % O^{18} and b.p. 137–139°.

Determination of Oxygen-18 Content of Carbonyl Oxygen in the Acetic Anhydride.—The method of determination was described in the previous paper.[2] The results obtained by analyzing oxygen-18 were identical for both acetanilide and acetamide, 0.91 atom % O^{18}, and indicated equal concentration of oxygen-18 at both carbonyl and ether oxygens of the acetic anhydride.

The Reaction of N,N-Dimethylaniline Oxide with Oxygen-18 Labeled Acetic Anhydride.—N,N-Dimethylaniline oxide, freshly prepared (7 g., 0.051 mole) was dissolved in oxygen-18 labeled acetic anhydride (9.5 g., 0.092 mole), (0.91 atom % O^{18}) below −30°. The reaction took place violently with evolution of heat and gases to give a dark green solution. After the initial vigorous reaction ceased, the mixture was allowed to stand overnight in a refrigerator. The acetic acid and acetic anhydride were removed *in vacuo* below 45° and then a trace of acetic anhydride was decomposed with warm *N* hydrochloric acid solution. After cooling, the acidic solution was extracted continuously with ether for 10 hours. The extract was dried with potassium carbonate and was distilled obtaining 2.0 g. (26% yield) of oxygen-18 labeled N-methylacetanilide, b.p. 116–118° (12 mm.), m.p. 98–99° (recrystallized from cyclohexane).

The remaining acidic aqueous solution was made alkaline with 20% solution of sodium carbonate and then extracted continuously with ether. Distillation of the residue from the extract gave 0.5 g. (6% yield) of oxygen-18 labeled *o*-acetoxy-N,N-dimethylaniline, 110–114° (12 mm.).

Alternatively, N,N-dimethylaniline hydrochloride (10 g., 0.058 mole) in 75 ml. of water containing 6 g. of sodium carbonate was treated at 0° with stirring during 0.5 hour with 11 g. (0.104 mole) of oxygen-18 labeled acetic anhydride (0.91 atom % O^{18}) and stirred for 2 hours. The dark green reaction mixture was treated with cooling with an aqueous solution of sodium carbonate and then extracted with ether. The extract was dried, filtered and distilled. Distillation gave 7.5 g. (80% yield) of oxygen-18 labeled *o*-acetoxy-N,N-dimethylaniline, b.p. 115–117° (12 mm.).

Hydrolysis of Oxygen-18 Labeled *o*-Acetoxy-N,N-dimethylaniline.—A mixture of 4.5 g. of oxygen-18 labeled *o*-acetoxy-N,N-dimethylaniline (0.52 atom % O^{18}) and 2.6 g. of potassium hydroxide in 40 ml. of methanol was refluxed for 15 minutes. After solvent was removed, the residue was neutralized with *N* hydrochloric acid and extracted with ether. Removal of ether gave 2.9 g. (80% yield) of oxygen-18 labeled *o*-hydroxy-N,N-dimethylaniline (0.52 atom % O^{18}), which was recrystallized from petroleum ether; m.p. 43–44°.

Control Experiments of Oxygen-18 Exchange.—Oxygen-18 labeled N-methylacetanilide (0.85 atom % O^{18}) or *o*-acetoxy-N,N-dimethylaniline (0.52 atom % O^{18}), 2 g., was dissolved in 30 ml. of acetic acid and acetic anhydride (1:1) solution, and then warmed at 60° for 30 minutes. The recovered N-methylacetanilide and *o*-acetoxy-N,N-dimethylaniline revealed no incorporation of natural oxygen: oxygen 18 analysis of N-methylacetanilide, 0.81 atom %; oxygen-18 analysis of *o*-acetoxy-N,N-dimethylaniline, 0.49 atom %.

Infrared Spectra.—A Perkin–Elmer model 221 spectrophotometer equipped with sodium chloride optics was used to obtain the spectra by the Nujol mull method.

Isotopic Analysis.—The experimental procedure and calculation were similar to those reported in the previous paper.[2]

(13) The radical acetoxy cleavage of XI would occur more readily than that of N-acetoxy-N,N-dimethylaniline because the resulting radical from the former, $R\ddot{N}(CH_3)CH_2\cdot$, has an additional resonance contribution of $R\ddot{N}(CH_3)CH\cdot_2$.