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The Reaction of Azoxybenzene with Acetic Anhydride1)

Shigeru Oae, Tetsuya Maeda, and Seizi Kozuka
Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Sumiyoshiku, Osaka

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When azoxybenzene was allowed to react with equimolar amount of acetic anhydride, a mixture of azobenzene, acetanilide, and acetic acid was obtained along with such gaseous products as carbon dioxide, carbon monoxide and methane. In the reaction of azoxybenzene with an excess acetic anhydride, however, azobenzene was not isolated, and only acetanilide was obtained. Acetanilide and acetic acid were also obtained in the reaction of azobenzene with acetic anhydride. The results suggest the initial formation of azobenzene which is eventually converted to acetanilide in the subsequent reaction with an excess acetic anhydride. The formation of acetanilide was inhibited by the addition of such radical scavengers as iodine, hydroquinone, and nitrobenzene. A free radical mechanism is suggested for the reaction. Phenazine *N*-oxide also apparently undergoes similar reaction.

The reactions of tertiary amine *N*-oxides such as pyridine or picoline *N*-oxides with acetic anhydride have been investigated extensively by means of product analyses,2) kinetics,3) and tracer studies.4) The first step of the reactions are considered to proceed throughout initial acylation of oxygen of the *N*-oxides.5) Thus, the reactivity of *N*-oxide in the reaction with acetic anhydride depends primarily on the basicity of the *N*-oxide oxygen. Dimethylaniline *N*-oxide, a more basic *N*-oxide ($pK_a=4.21$6)), reacts smoothly with acetic anhydride even below 0°C7)), while the reaction of pyridine *N*-oxide, a less basic *N*-oxide ($pK_a=0.56$8)), requires a few hours of refluxing for the completion of the reaction with the same reagent. Very little study has been made on the reaction of azoxybenzene with acetic anhydride,9) presumably due to its poor reactivity. The reaction, however, did occur under prolonged heating at relatively high temperatures to give an unusual product, acetanilide, as the main product. This paper deals with the details of preliminary investigation of the reaction studied mainly by means of product analysis.

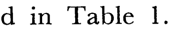
Results and Discussion

Reaction of Azoxybenzene with Acetic Anhydride. Since the basicity of azoxybenzene is very small ($pK_a=6.45$10)), the reaction of azoxybenzene with acetic anhydride is considered to be sluggish. Thus, the reaction was carried out at 190°C in an autoclave under nitrogen atmosphere, and a mixture of azobenzene and acetanilide was obtained. The yield of acetanilide was less than 100% based on the amount of azoxybenzene used. That is, only a half of azoxybenzene used is apparently converted to acetanilide. Under the same conditions, azoxybenzene underwent no thermal deoxygenation. Gaseous components were analyzed by means of gas chromatography. Carbon dioxide, carbon monoxide, and methane were detected as the main gaseous products. When *N*-oxide was treated with an excess acetic anhydride, no detectable amount of azobenzene was found, whereas acetanilide was obtained along with acetic acid and gaseous products. The reaction conditions and the yield of the products are listed in Table 1.

Table 1. Reaction of azoxybenzene with acetic anhydride under N_2 atmosphere in autoclave

Reaction system	Reaction condition Molar ratio	Product (%)
$\mathrm{Ph\underset{\underset{O}{\downarrow}}{N}{=}NPh+Ac_2O}$	190°C, 15 hr 1 : 1	PhN=NPh (60) $PhNHCOCH_3$(13) CH_3CO_2H(63) CO_2(95), CH_4(2) CO(14)
$\mathrm{Ph\underset{\underset{O}{\downarrow}}{N}{=}NPh+Ac_2O}$	190°C, 15 hr 1 : 5	$PhNHCOCH_3$(78) CH_3CO_2H(70)
$\mathrm{Ph\underset{\underset{O}{\downarrow}}{N}{=}NPh+AcOH}$	190°C, 15 hr 1 : 1	no reaction

The first step of the reaction is considered to be the formation of the *N*-acetoxyammonium salt (A) as in the



(A)

reactions of pyridine- and the related *N*-oxides with acylating agents.5) No oxygen exchange reaction was found between the *N*-acyloxy compound of pyridine

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1) Part XXVI on Rearrangement of *t*-Amine Oxides.

2) a) M. Katada, *Yakugaku Zasshi*, **67**, 51 (1947). b) S. Okuda, *Pharm. Bull.*, **3**, 316 (1955). c) V. Bockelheide and W. Linn, *J. Amer. Chem. Soc.*, **76**, 1286 (1954).

3) a) T. H. Markgraf, H. B. Brown, Jr., S. C. Morre, and R. G. Peterson, *J. Amer. Chem. Soc.*, **85**, 958 (1963). b) J. H. Markgraf and M. K. Ahn, *ibid.*, **86**, 2699 (1964).

4) a) S. Oae, T. Kitao, and Y. Kitaoka, *Tetrahedron*, **19**, 827 (1963). b) S. Kozuka, S. Tamagaki, T. Negoro, and S. Oae, *Tetrahedron Lett.*, **1968**, 923.

5) C. W. Muth and R. S. Darlak, *J. Org. Chem.*, **30**, 1909 (1965).

6) M. Colonna, *Boll. Sci. Fac. Chim. Ind. Bologna*, **15**, 1 (1957).

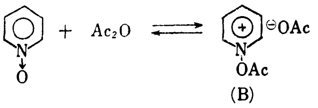
7) R. Huisgen, F. Bayerleine, and W. Heydkamp, *Chem. Ber.*, **93**, 363 (1960).

8) T. Kubota and H. Miyazaki, *Nippon Kagaku Zasshi*, **79**, 924 (1958).

9) M. M. Shemyakin, T. E. Agadzhanyan, V. I. Maimind, R. V. Kudryavtsev, and D. N. Kursanov, *Proc. Nat. Acad. Sci, U.S.*, **135**, 1295 (1960).

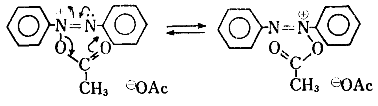
10) Chi-Sun Harn and H. H. Jaffe, *J. Amer. Chem. Soc.*, **84**, 949 (1962).

bases such as (B) in our earlier ^{18}O-tracer experiments,[11]

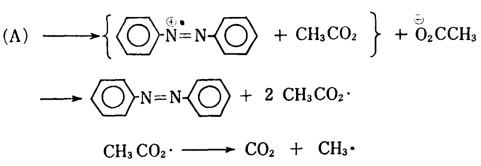


(B)

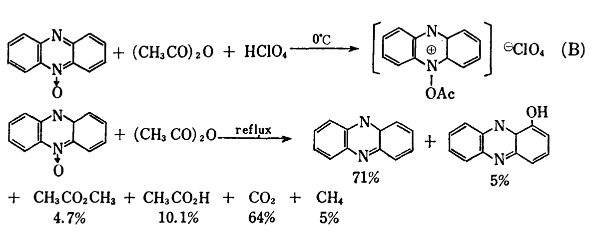
but a somewhat different oxygen exchange could be expected in this case through the following five membered cyclic migration. This supposition is based on



the observation with ^{15}N-labeled azoxybenzene by Shemyakin *et al.*[12] who showed that there is an intramolecular oxygen migration within the Wallach rearrangement. In order to examine the possible oxygen equilibration during the reaction, azoxybenzene was treated with equimolar amount of ^{18}O-labeled acetic anhydride and recovered when the reaction was about half completed . If the migration of the acetoxy group from one nitrogen atom to the other occurs during the reaction, a substantial incorporation of ^{18}O in the recovered *N*-oxide is expected. However, no noticeable amount of ^{18}O was found in the recovered *N*-oxide. Thus, the possibility of such a migration can be ruled out. For further insight into the nature of the reaction, the effect of atmosphere on the reaction was examined and the results are tabulated in Table 4. In view of the large amounts of carbon dioxide, carbon monoxide and methane, the mechanism of the reaction seems to involve the homolytic fission of the N–O bond of the *N*-acyloxy compound at the initial stage of the reaction. Acetanilide obtained in the reaction with an excess acetic anhydride is considered to be



formed *via* azobenzene. A similar reaction involving the formation of the salt (A) and subsequent homolytic fission of the N–O bond seems to take place with phenazine *N*-oxide which in the presence of acetic anhydride



gives salt (B) of perchloric acid, and generates large amounts of methane and carbon dioxide yielding mainly the reduced compound, phenazine, under refluxing with acetic anhydride.

Reaction of Azobenzene with Acetic Anhydride. Examination of the data shows that the reaction of an equimolar amount of azoxybenzene and acetic anhydride gives azobenzene along with a small amount of acetanilide while the reaction with excess acetic anhydride gave only acetanilide in a better yield. In order to examine the formation of the intermediate,

TABLE 2. REACTION OF AZOBENZENE WITH ACETIC ANHYDRIDE UNDER N$_2$ ATMOSPHERE IN AUTOCLAVE

Reaction system	Reaction condition Molar ratio	Product (%)
PhN=NPh+Ac$_2$O	190°C, 15 hr 1 : 1	PhNHCOCH$_3$(83) CH$_3$CO$_2$H(60) CO$_2$(29), CO(7)
PhN=NPh+AcOH	200°C, 15 hr 1 : 1	no reaction
p-CH$_3$C$_6$H$_4$N=NPh +Ac$_2$O	200°C, 12 hr 1 : 1	*p*-CH$_3$C$_6$H$_4$N=NPh (30 recovered) *p*-CH$_3$C$_6$H$_4$NHCOCH$_3$ (13) PhNHCOCH$_3$(15)

TABLE 3. REACTION OF AZOBENZENE WITH ACETIC ANHYDRIDE UNDER N$_2$ ATMOSPHERE EFFECT OF RADICAL ACCEPTORS

Reaction system	Reaction condition Molar ratio	Yield of PhNHCOCH$_3$
PhN=NPh+Ac$_2$O	200°C, 15 hr 1 : 5	83%
PhN=NPh+Ac$_2$O +*p*-hydroquinone	200°C, 15 hr 1 : 5 : 0.2	40%
PhN=NPh+Ac$_2$O+I$_2$	200°C, 15 hr 1 : 5 : 0.2	42%
PhN=NPh+Ac$_2$O +PhNO$_2$	200°C, 15 hr 1 : 5 : 0.1	0%

TABLE 4. EFFECT OF ATMOSPHERE IN AUTOCLAVE

Reaction system	Reaction condition	Yield of PhNHCOCH$_3$
PhN=NPh+Ac$_2$O	200°C, 15 hr, 1 : 5 under N$_2$ atm.	83%
PhN=NPh+Ac$_2$O	200°C, 19 hr, 1 : 5 under H$_2$ atm.	68%
PhN=NPh+Ac$_2$O	200°C, 15 hr, 1 : 5 under O$_2$ atm.	70%
$\underset{\overset{\downarrow}{O}}{\mathrm{PhN}}$=NPh+Ac$_2$O	200°C, 15 hr, 1 : 5 under N$_2$ atm.	78%
$\underset{\overset{\downarrow}{O}}{\mathrm{PhN}}$=NPh+Ac$_2$O	200°C, 15 hr, 1 : 5 under air	47%

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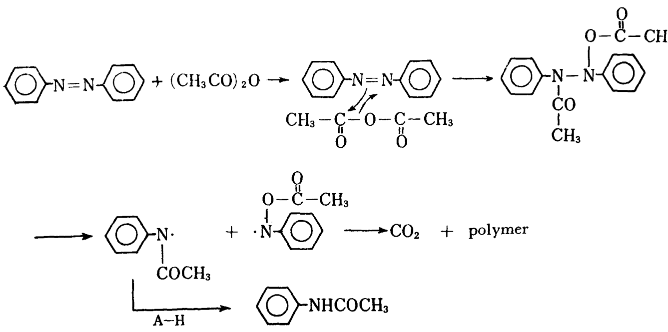
[11] Unpublished work from our laboratory.

[12] M. M. Shemyakin, V. I. Maimind, and B. K. Vaichunaite, *Zh. Obshch. Khim.*, **28**, 1708 (1958).

azobenzene, the reaction of azobenzene with acetic anhydride was studied. As was expected, acetanilide was obtained in good yield from the reaction mixture along with moderate amounts of acetic acid and gaseous products. Acetic acid was found to undergo no reaction with azobenzene. The effects of radical scavengers and atmosphere in an antoclave were also examined, the results of which are in Tables 2—4. The reaction with an unsymmetrical azobenzene, 4-methylazobenzene, gave nearly the same amount of both acetanilide and 4-methylacetanilide. No symmetrical azobenzene was found in the recovered reaction mixture in which only 4-methylazobenzene was found. The results clearly rule out the possibility of crossover and the return of the fragments to the original compound. The yield of acetanilide was apparently decreased not only by the presence of oxygen but also by the addition of radical scavengers such as hydroquinone, iodine and, nitrobenzene, suggesting a free radical mechanism for the reaction. The mechanism of the reaction of azobenzene with acetic anhydride to give acetanilide may be formulated as follows.



Experimental

Materials. Azoxybenzene was prepared by the reduction of nitrobenzene[13] (mp 35—36°C from methanol). Azobenzene was prepared by the usual method[14] (mp 66—67.5°C from ethanol). 4-Methylazobenzene was prepared by the process reported by Godger[15] (mp 71—72°C from ethanol). Preparation of ^{18}O-labeled acetic anhydride and the method of its isotope analysis were described previously.[16] Phenazine *N*-oxide was synthesized from aniline and nitrobenzene with sodium hydroxide.[17]

The reaction of Azoxybenzene with Acetic Anhydride. A mixture of azoxybenzene (7.0 g, 0.035 mol) and acetic anhydride (3.8 g 0.037 mol) was heated in an autoclave at 190°C for 15 hr under N_2 atmosphere. Distillation of the reaction mixture gave acetic acid (1.4 g). The residue was extracted first with *n*-hexane three times and then with benzene three times. From the hexane layer, azobenzene (3.8 g, 66—68°C) was obtained along with a small amount of acetanilide (0.04 g). Separation was performed by recrystallization from *n*-hexane. Acetanilide (0.6 g, mp 114—115°C) was obtained from the benzene layer. The residue which did not dissolve in these solvents, was chromatographed through an active alumina column with chloroform as an eluent. A small amount of acetanilide (0.05 g) was obtained. The gaseous components were directly transferred from the autoclave into a gas sampler and analyzed by gas chromatography (H_2 carrier, temp.: 60°C, active carbon 4 m); carbon dioxide, methane and carbon monoxide were detected. These compounds were identified by comparing their retention times with those of the corresponding authentic samples. Quantitative analysis of carbon dioxide was performed by the measurement of the amount of barium carbonate absorbed in saturated $Ba(OH)_2$ aq. solution. Carbon monoxide and methane were determined by comparing the peak areas with that of carbon dioxide, taking the relative intensities of the respective gaseous products into consideration hydrogen being used as a carrier gas.

Reaction of Azoxybenzene with ^{18}O-Labeled Acetic Anhydride. A mixture of azoxybenzene (2.0 g, 0.01 mol) and ^{18}O-labeled acetic anhydride (1.1 g, 0.01 mol, 0.89 atom% ^{18}O) was heated in an autoclave at 175°C for 10 hr under N_2 atmosphere. Distillation under reduced pressure gave crude azoxybenzene (1.2 g, bp 195—200°C/16 mmHg) along with small amounts of azobenzene (0.13 g) and acetanilide (trace). The recovered *N*-oxide was then purified by recrystallization from ethanol (mp 34—35°C). No incorporation of any excess ^{18}O was found in the recovered azoxybenzene (0.20 atom% ^{18}O).

Reaction of Phenazine N-*Oxide with Acetic Anhydride.* A mixture of phenazine *N*-oxide (5.0 g, 0.026 mol) and acetic anhydride (14.0 g, 0.14 mol) was refluxed for 5 hr. The low boiling point fractions trapped in acetone - dry ice bath and gaseous products were analyzed by gas chromatography. After any residual acetic anhydride was driven off, the residue was chromatographed on active alumina with methylene chloride as an eluent. The eluent was evaporated and the residue was hydrolyzed with 20% NaOH aq. solution. The precipitate was collected and recrystallized from ethanol (mp 171—172°C). This compound was identified as phenazine (3.3 g). The filtrate was acidified with HCl and the precipitate was recrystallized from isopropyl alcohol. Thus 1-hydroxy phenazine (0.25 g, mp 155—157°C) was obtained. All these compounds were determined by comparison with the authentic samples.

The isolation of N-*Acetoxyphenazinium Perchlorate.* The compounds was prepared by the process reported by Muth and Daolak[5] An ice cold solution of 0.7 g of 70% $HClO_4$ in 3 m*l* acetic anhydride was added dropwise to a stirred, ice-cold solution of 0.5 g of phenazine *N*-oxide in 5 m*l* of acetic acid and 10 cc of acetic anhydride. Orange colored crystals were separated by filtration. The crystals of *N*-acetoxyphenazinium perchlorate (mp 274—275°C, dec.) weighed 0.6 g. Found: C, 49.97; H, 3.38; N, 8.12%. Calcd for $C_{14}H_{11}ClN_2O_6$: C, 49.71; H, 3.26; N, 8.29%.

Reaction of Azobenzene with Acetic Anhydride. A mixture of azobenzene (6.4 g, 0.035 mol) and acetic anhydride (17.5 g, 0.175 mol) was heated at 190°C for 15 hr in an autoclave under N_2 atmosphere similarly and both acetanilide (3.88 g, 0.029 mol) and acetic acid (1.3 g) were isolated. Through gas-chromatographic analysis of the gaseous products, carbon dioxide and carbon monoxide were detected but not methane. The reaction 4-methylazobenzene (2.0 g, 0.013 mol) with acetic anhydride (1.1 g, 0.011 mol) was also carried out similarly and a mixture (0.41 g) of acetanilide and 4-methylacetanilide was obtained. The ratio of the mixture components was determined by integrating the NMR chemical shifts of methyl protons, *i.e.*, the 4-methyl signal of N-acetyl-*p*-toluidine *vs.* acetyl methyl protons of acetanilide. The results are given in Table 2. All the other experiments were carried out under corresponding conditions.

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