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REARRANGEMENTS OF TERTIARY AMINE OXIDES—XXIII

REACTION OF α, N-DIPHENYLNITRONE WITH ACETIC ANHYDRIDE

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Abstract—The reaction of the α, N-diphenylnitrone with acetic anhydride has been investigated using homogeneously ^{18}O-labelled acetic anhydride. The amount of ^{18}O incorporated into the carbonyl group of the resulting benzamide suggests an intramolecular reaction. The rates of the reaction were measured by changing the solvent and the substituents.

The large reactivity of the nitrones having electron-releasing substituents and others suggests that the N—O bond cleavage is the rate-determining step of the reaction.

THE aldonitrones are readily converted to the corresponding isomeric amides by treatment with a variety of reagents, such as, acetic anhydride, phosphorus pentachloride, phosphorus trichloride, phosphorus oxychloride, thionyl chloride.[1] These reactions are similar to those between pyridine or quinoline N-oxide with various acylating agents.[2] Meanwhile, Krohenke[3] suggested earlier, a rearrangement mechanism for these reactions involving the addition-elimination on the C=N double bond as shown below,

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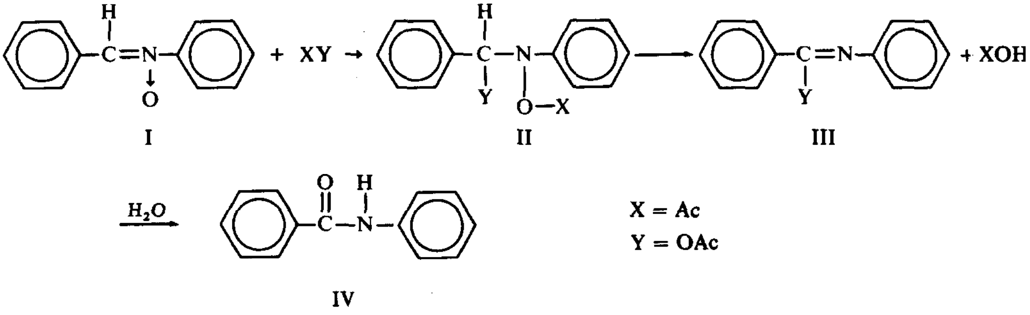
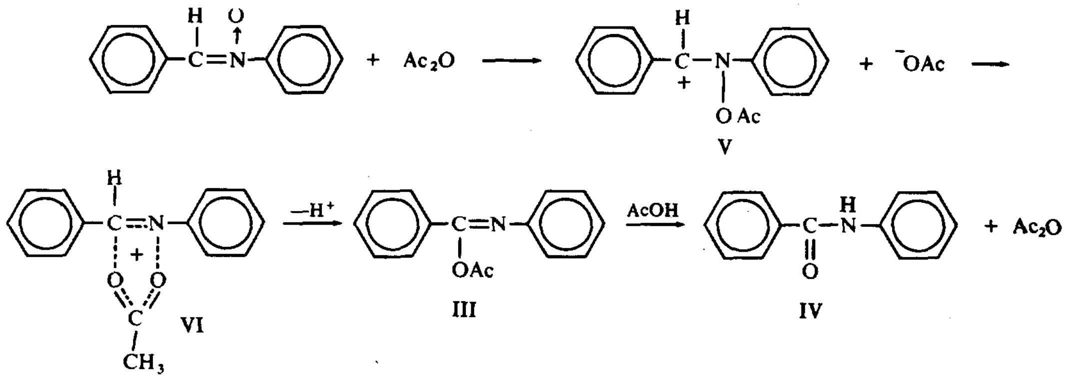


This mechanism is by no means general, since it cannot be applied to acylating reagents, such as, phosphoryl chloride and sulfur dioxide which do not dissociate readily and hence are not capable of adding to a double bond. Recently, Umesawa *et al.*[4] studied a number of reactions between various nitrones and acylating reagents and suggested a mechanism involving the cyclic migration as shown below.

But in the case of acetic anhydride, they did not make any choice between the two conceivable mechanisms, i.e., the cyclic and the other involving the addition-elimination.

Usually these acylating reagents convert aldonitrones to the corresponding amides

SCHEME 2



in good yields. For example, treatment of acetic anhydride or benzoyl chloride, with α,N-diphenylnitrone gave benzanilide in a yield ranging from 70% to 95%.

The reactions with acyl chlorides, such as benzoyl, benzenesulfonyl and phosphoryl chlorides are very facile and take place at room temperature, however, the reaction with acetic anhydride requires heating on a boiling water bath for 2–3 hr in order to complete the reaction.

As an extension of our studies on rearrangements of tertiary amine oxides,[5] we have made a detailed study of these reactions by means of kinetic investigations and ^{18}O tracer experiments. This paper details the results of our investigations, and their implications in the interpretation of the mechanisms of these reactions.

RESULTS AND DISCUSSION

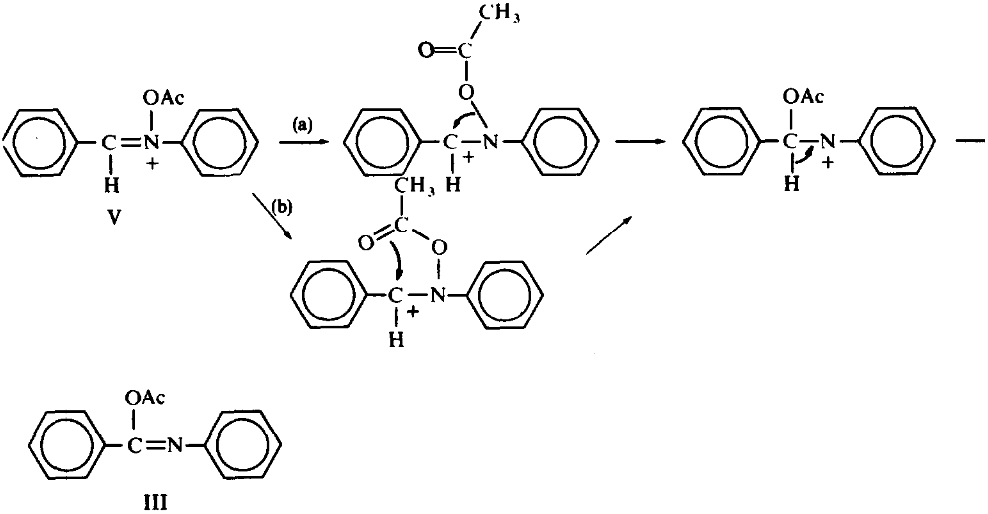
According to the mechanism suggested by Krohenke the intermediate (II) initially formed by the reaction with acetic anhydride is decomposed to α-acetoxy imine by elimination of acetic acid. Therefore, when α,N-diphenylnitrone (I) reacts with homogeneously ^{18}O-labelled acetic anhydride, the carbonyl oxygen of benzanilide (IV) should incorporate as much as three-fourths of the ^{18}O concentration of the acetic anhydride employed while the final product benzanilide should be obtained only in the presence of water.

The alternative mechanism suggested by Umesawa for the reactions of phosphoryl chloride and sulfur dioxide with nitrones, shown in the introduction, suggests that the intermediate (V) undergoes an intramolecular rearrangement to give another intermediate (III), which is then attacked by an acetate anion to give rise to benzanilide and acetic anhydride. In this case, too, the ^{18}O-content of the amide oxygen should be the average value of all the ^{18}O scrambled in the whole reaction system when the same ^{18}O-labelled acetic anhydride is used.

In another possibility (Scheme 3), the reaction proceeds via an intramolecular path in which the resulting intermediate (III) is stable and remains in the system as the final reaction product and only upon quenching with water this intermediate (III) is converted to the amide.

In this case the amount of ^{18}O incorporated in the amide should be in the range of the value between natural and that of the labelled acetic anhydride, depending upon

SCHEME 3



the extent of the participation of the following two rearrangements, i.e., cyclic (a) and bridging (b) processes.

According to this mechanism the initial intermediate (V) does not accept the nucleophilic addition of acetate anion to the C-atom, but undergoes an intramolecular rearrangement of acetoxy group, followed by the proton removal.

A rough profile of the reaction scheme was based on the results of ^{18}O tracer experiments using homogeneously ^{18}O-labelled acetic anhydride. Thus, α,N-diphenylnitrone was treated with ^{18}O-labelled acetic anhydride, and the amide isolated was subject to ^{18}O-analysis as described.[6] The results are summarized in Table 1.

TABLE 1. ^{18}O-ANALYTICAL RESULTS OF THE REACTION OF α, N-DIPHENYLNITRONE WITH ^{18}O-LABELLED ACETIC ANHYDRIDE IN CHLOROFORM REFLUXED

Exptl. No.	Ac_2O/N—O mole ratio	$Ac_2{}^{18}O$ used	Benzanilide
		excess atom %	
1	1·4	0·850	0·508
2	1·8	0·850	0·500
3	3·7	0·910	0·520

Inspection of the data reveals that the ^{18}O-distribution in the amide is nearly constant irrespective of the molar ratio of acetic anhydride to aldonitrone, variation of ^{18}O-contents due to the change of molar ratio (1·4 to 3·7) being very small.

From the ^{18}O-analytical data, the intermolecular rearrangement process, e.q., scheme (1) can be excluded since it would demand the ^{18}O contents in the amide to increase regularly with an increase of molar ratio and require 0·90 excess atom % incorporation when the molar ratio is 3·7 and the labelled acetic anhydride of 0·91 excess atom % is used. The cyclic mechanism (2) can be also eliminated, since the mechanism requires the carbonyl oxygen of the amide to contain ^{18}O of that of the ^{18}O labelled acetic anhydride originally employed.

Thus, the mechanism involving the intramolecular rearrangement process is the only plausible one. In this case, however, one has to assume that the second step, i.e., the intramolecular migration proceeds through two competing pathways, namely "cyclic" and "bridging" processes, and the former is slightly favoured (58 %) over the latter (42 %).

Fig. 1 shows the NMR spectrum of α,N-diphenylnitrone in acetic anhydride, before initiation of the reaction while Fig. 2a and 2b gives the NMR spectrum of the reaction product which was obtained after α,N-diphenylnitrone in acetic anhydride was warmed for 2 hr at 120°. Fig. 3 gives the NMR spectrum of the nitrone in dioxan in order to make a comparison with that in acetic anhydride. The fact that the NMR chemical shift and the spectral pattern in acetic anhydride does not differ from that in dioxan within the error of the NMR measurement illustrates that in the acetic

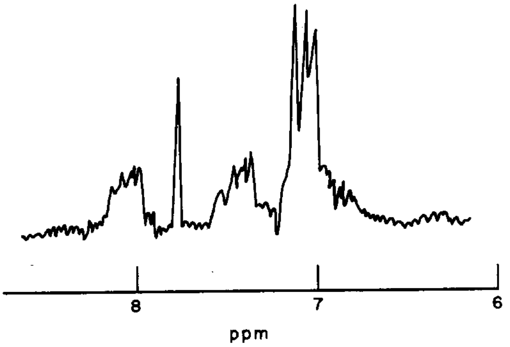


FIG. 1

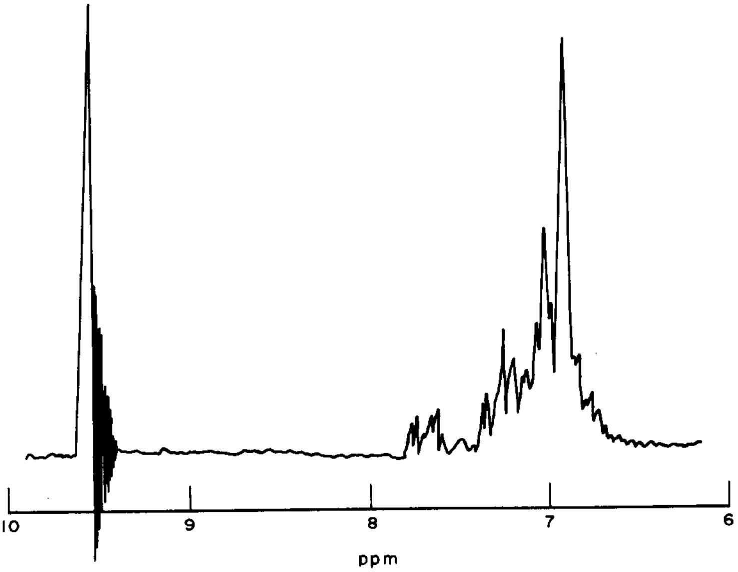


FIG. 2a

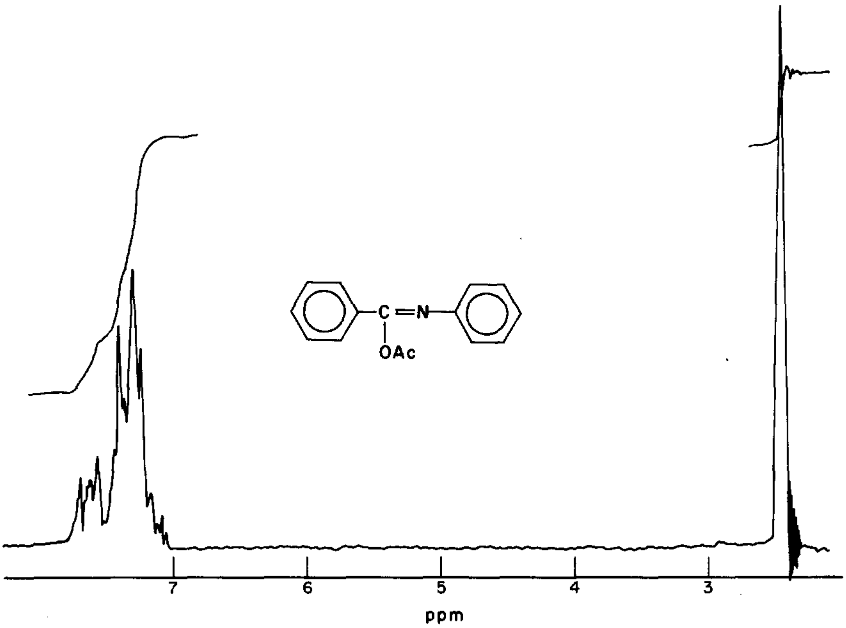


Fig. 2b

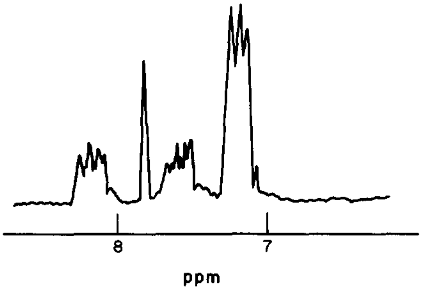


Fig. 3

anhydride the nitrone is not present in the form of acetylated intermediate (V). The peak at 9·5 in Fig. 2 is undoubtedly due to the ionizable proton of acetic acid, which is not present before the reaction.

The isolated acetic acid is probably liberated during the reaction of the nitrone with acetic anhydride and the intermediate (III) is obviously present in the reaction mixture in view of the NMR spectra. The structure of this intermediate was elucidated with IR, NMR, mass spectra and elemental analysis together with the chemical conversion to the amide by allowing the compound to react with moisture. In order to shed further light on the nature of the reaction, kinetic experiments have been carried out for the reaction of aldonitrone with acetic anhydride following the decrease of UV absorbance of π–π^* band at 300–350 mμ of aldonitrones in acetic anhydride solution at 50°. It was found to be correlated by the pseudo-first-order kinetic equation and Lambert's law was obeyed within our experimental conditions. Fig. 4 shows a straight-line plot, i.e. the reaction is expressed by the first-order rate formula with

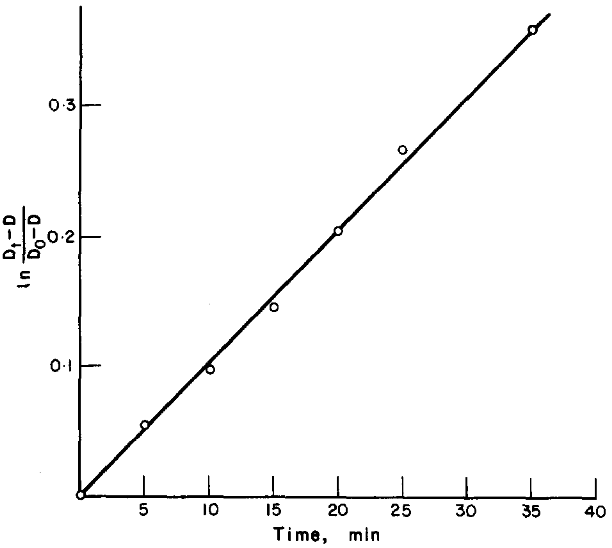


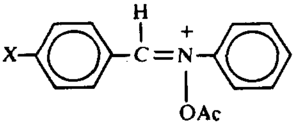
FIG. 4

respect to aldonitrone, and a linear change in rate constants with an increase in the concentration of acetic anhydride, indicates that the reaction is first-order dependent on acetic anhydride.

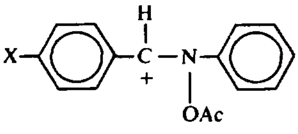
The kinetic data relating to ring-substituted benzaldonitrones are recorded in Table 2 and Fig. 5.

TABLE 2. SUBSTITUENT EFFECT FOR THE REACTIONS OF α-RING SUBSTITUTED α, N-DIPHENYLNITRONES WITH ACETIC ANHYDRIDE AT 50°

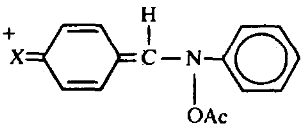
Substituent	Pseudo-first-order rate constant, 10^5k_1, sec^{-1}
m-NO_2	3·92
p-Cl	24·4
H	40·3
p-Me	69·9
p-MeO	103
p-Me_2N	ca. 705



A



B



C

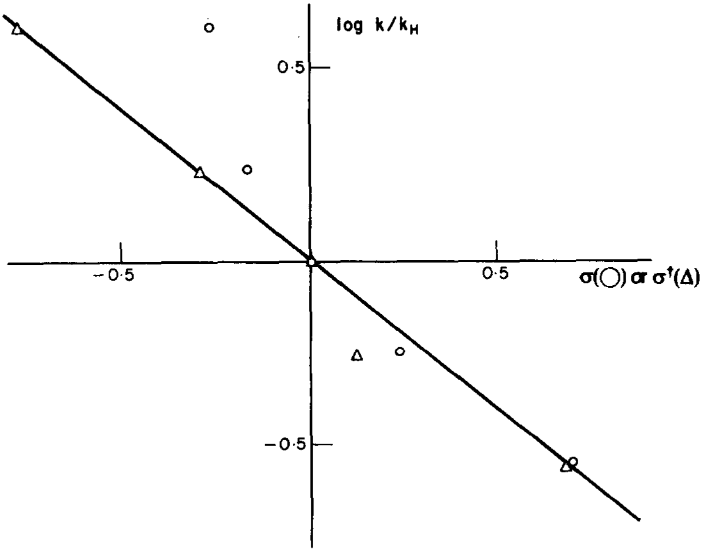


FIG. 5

The rate of the reaction is considerably accelerated by an electron-releasing *p*-methoxy and *p*-dimethylamino group due to the resonance hydride like **A**, **B** and **C**, while a *m*-nitro group strongly surpresses the rate.

It appears that the reaction involves the fast equilibrium acetylation of the N—O function of the aldonitrone with acetic anhydride followed by the slow N—O bond cleavage, since the ρ-value obtained by the correlation with σ^+-value was found to be −0·79 and the acetylation and/or the N—O bond cleavage steps results in a large separation of the charge and the large delocalization of a plus charge on a α-phenyl group would be required. The rate was in some way solvent dependent (Table 3). The effect of the solvent polarity on the rate may be also understood in terms of the above interpretation. A more polar solvent would increase the rate over a less polar solvent when the charge separation is involved in the rate determining step of the reaction.

TABLE 3. EFFECT OF SOLVENT CHANGE ON THE RATE CONSTANTS FOR THE REACTION OF α, N-DIPHENYLNITRONE WITH ACETIC ANHYDRIDE AT 50° Ac_2O = 3·72M

Solvent	Pseudo-first-order rate constant, 10^5k_1, sec^{-1}
Dioxan	4·34
Acetonitrile	18·2

The fact that an extraordinary salt effect was observed when lithium perchlorate was added to the reaction mixture (Table 4) suggests that the first step of this reaction is important, because the step is catalyzed by the presence of the salt.

A similar catalytic effect has also been observed in the reaction of quinaldine

TABLE 4. EFFECT OF LITHIUM PERCHLORATE ON RATE CONSTANTS FOR THE REACTION OF α, N-DIPHENYLNITRONE WITH ACETIC ANHYDRIDE AT 30°

Concn. of $LiClO_4$	Pseudo-first-order rate constant, 10^5k_1, sec^{-1}
0	40·2
0·59	67·4
1·89	126
3·57	314
22·2	614
49·7	966

N-oxide with acetic anhydride where the rate-determining step was proved to be the deprotonation of the Me group from the determination of the hydrogen–deuterium kinetic isotope effect,[7] and yet the addition of an equimolar amount of lithium perchlorate to the N-oxide increases the rate as much as in the case of the nitrone. However, the addition of large amounts of the salt in the case of quinaldine N-oxide gradually depresses the rate, while in the case of the nitrone the rate is linearly accelerated by further addition of the salt and no rate-decreasing effect was observed. These different behaviours must be explained by postulating two different rate-determining structures for the two reactions. Table 5 shows the activation parameters for the reaction.

TABLE 5. ACTIVATION ENERGY AND ENTROPY FOR REACTION OF α, N-DIPHENYLNITRONE WITH ACETIC ANHYDRIDE AT 50°

Temperature, T K	Pseudo-first-order rate constant, 10^5k_1, sec^{-1}	Calcd. activation parameter
323	40·4	$\Delta F\ddagger$ = 24·3 kcal/mole
318	32·6	$\Delta S\ddagger$ = −58·6 eu
313	23·3	$\Delta E\dagger$ = 11·8 kcal/mole

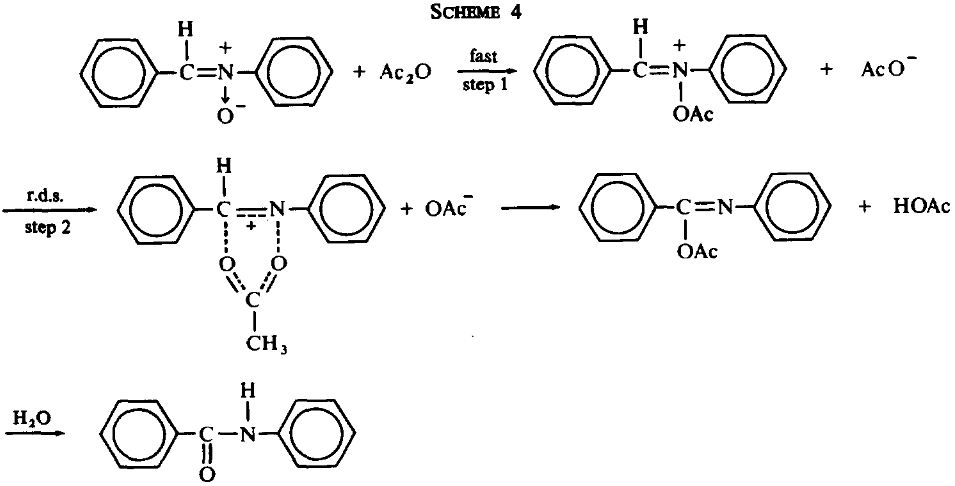
It is seen that the measured activation energy is very low but compensated by the large negative activation entropy and these values may be compared with those of the reaction of acridine N-oxide with acetic anhydride which has been suggested to proceed via a similar intramolecular rearrangement.[8] The large negative entropy of activation indicates that the transition state complex assumes a rigid structure **D** in which the degree of freedom is considerably lost.

From all these data the following scheme is considered as the most plausible pathway for the rearrangement reaction of the nitrone to the amide.

The rate-determining step cannot be assigned conclusively, but on the grounds of the activation parameter step 2 is the most attractive and more favourable than step 1 for the rate-determining step of the reaction.

In addition, the substituent effect is not inconsistent with this suggestion because the ionic scission of the N—O bond would create a large demand of electron localization at the reaction site.

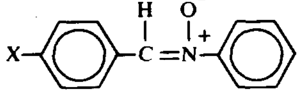
SCHEME 4



EXPERIMENTAL

Materials. α-Phenylhydroxylamine was prepared from the reduction of nitrobenzene.[9] An equimolar mixture of substituted benzaldehyde and phenylhydroxylamine dissolved in a small volume of EtOH was kept at room temp. The reaction mixture gradually crystallized and was kept over night. Solids were filtered off and recrystallized from benzene. The yields were nearly quantitative. The structure of these compounds was characterized by means of NMR, IR, mass and UV spectra.

TABLE 6. M.PS AND IR STRETCHING FREQUENCIES OF α-RING SUBSTITUTED α,N-DIPHENYLNITRONES



X	m.p., °C	N—O stretching frequency, cm^{-1}
m-NO_2	151 -152	1064·8
p-Cl	154 -154·5	1072·3
H	112 -113	1069·0
p-CH_3	92·5- 93	1067·0
p-OCH_3	118 -118·5	1065·9
p-$N(CH_3)_2$	142 -143	1062·3

Reaction of α,*N-diphenylnitrone with acetic anhydride.*[10–11] α,N-diphenylnitrone (2·0 g) and Ac_2O (5 g) with or without $CHCl_3$ was heated at 120° for 1·5 hr on an oil bath. Excess Ac_2O was removed. The distillation of the reaction mixture under reduced press gave 2·25 g of slightly yellow viscous oil, b.p. 100–135° /1mmHg. The oil was kept until it crystallized. The crystals were filtered off from the residual oil. The white solids were recrystallized from n-hexane (m.p. 72–73°), yield 0·80 g (C-acetoxy-α-phenyl-N-phenylimine). The identification of the compound was carried out by elemental analyses, IR, mass and NMR. (Found: C, 75·64; H, 5·59; N, 6·03 calc. for $C_{15}H_{13}NO$: C, 75·31; H, 5·44; N, 5·89%); IR bands: 1670, 1558, 1495, 1370, 1200–1300 cm^{-1}; mass spectrum (a main sequence) *m/e* $239 \xrightarrow[163 \cdot 5]{*} 197 \rightarrow 105 \rightarrow 77 \rightarrow 51$ (*: metastable peak).

If the reaction mixture was subjected to the chromatography on alumina and eluted with benzene without distillation, the resulting solid was benzamide: yield 70%, m.p. 163°. The main products of the reaction were not altered irrespective of the α-ring substituent.

^{18}O-*Analytical experiment.* α, N-Diphenylnitrone and ^{18}O-labelled Ac_2O were treated as described in the preceding section. The reaction mixture was directly separated by the chromatography on an alumina column as the control experiment indicated that during the column chromatography the exchange reaction of the carbonyl oxygen of benzanilide with natural water oxygen was negligibly small.

Kinetic experiments. As a typical kinetic run, the reaction solns were prepared by mixing the dioxan stock soln containing aldonitrones with Ac_2O. The reaction vessel was maintained at constant temp (50·00° ± 0·03°) during the reaction. The solns were pipetted out at constant intervals, quenched to the constant volume with cold dioxan soln and the disappearance of the aldonitrone was followed by the π–π^* band of the nitrone.

Duplicate or more runs were usually made using the same stock acetic anhydride.

REFERENCES

[1] J. Hamer and A. Maclaluso, *Chem. Rev.* **64**, 473 (1964).

[2] S. Oae and S. Kozuka, *Tetrahedron* **20**, 2671 (1964); M. Katada, *Yakugaku Zasshi* **67**, 51 (1947).

[3] F. Krohenke, *Liebigs Ann.* **604**, 203 (1957).

[4] B. Umesawa, *Chem. Pharm. Bull. Tokyo* **8**, 698, 967 (1960).

[5] Paper XXIV: Rearrangements of Tertiary Amine Oxides.

[6] See Ref. 5.

[7] [a] S. Oae, S. Tamagaki and S. Kozuka, *Tetrahedron Letters* No. 46, 7765 (1968);
[b] Paper XXIV contributed to *Tetrahedron.*

[8] J. H. Markgraf and M. K. Ann, *J. Am. Chem. Soc.* **86**, 2699 (1964).

[9] *Organic Synthesis* Collect. Vol. 1; p. 445. Wiley, London (1956).

[10] O. H. Wheeler and P. H. Gore, *J. Am. Chem. Soc.* **78**, 2160 (1956).

[11] T. Kubota, M. Yamakawa and Y. Mori, *Bull. Chem. Soc. Japan* **36**, 1522 (1963).