UDC 547.829.07

161. **Bunsuke Umezawa**: Studies on Tertiary Amine Oxides. VII. Some Reactions of Several Nitrones.

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It was reported in a previous paper[1] that the aldonitrone function of α-(1-oxido-2-pyridyl)-N-(*p*-dimethylaminophenyl)nitrone (I) underwent facile rearrangement with various reagents. The fact that (I) underwent rearrangement even by sulfur dioxide seemed to be probably ascribable to the configuration and highly negative oxygen atom of the aldonitrone, and to the presence of dimethylamino group in (I). In order to clarify the correlation between the reactivity and nature of the bond of nitrone, reaction of several nitrones with five typical reagents was carried out under somewhat milder conditions than that employed in the case of (I).

As a model compound of nitrone having *cis*-configuration in regard to C-H and N-O bonds in aldonitrone function, 3,4-dihydroisoquinoline 2-oxide[2] was chosen. Other nitrones used in this experiment have been assumed to have a *trans*-configuration.[3] Although comparison of the reaction of N-(*p*-dimethylaminophenyl)-α-(2-pyridyl)nitrone with that of (I) was of great significance, preparation of the former was unsuccessful. The results of the reaction of eight kinds of nitrones are shown in Table I. That the products obtained, especially from (V), (VI), and (VIII), were of low yield appeared to be due to their instability towards the reagents.

Examination of the results in Table II revealed that deoxygenation and rearrangement were the main reaction which might be parallel to the N-O bond character of nitrones. From this view-point, the results in Table II was re-tabulated in regard to deoxygenation and rearrangement as shown in Table I, on which the following discussion was based.

TABLE I. Main Reaction of Nitrones with Five Typical Reagents

Reagent / Nitrone	SO_2	$PO(OPh)_3$	$POCl_3$	PCl_3	Ac_2O
(II)	—	—	R	A & R	R
(III)	—	—	R	R	R
(IV)	—		R	R	R
(V)	A	—	R	A	R
(VI)			R	R	
(VII)	A & R	R	R	A & R	R
(I)	R	R	R	R	R
(VIII)		—			

— : No change; A : Formation of anil; R : Rearrangement.

Reaction with Sulfur Dioxide

The first three compounds, (II), (III), and (IV) were unaffected by the reagent, undergoing neither deoxygenation nor rearrangement. This result seemed to show that the nature of the N-O bond in these nitrones was very similar to that of aromatic N-oxides and the lone-pair electrons of the oxygen atom in these nitrones were able to conjugate with the aromatic ring.

In the case of N,α-diphenylnitrone (V) and N-phenyl-α-(2-pyridyl)nitrone (VI), the

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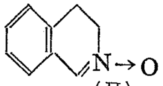
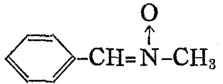
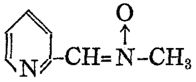
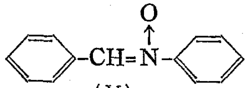
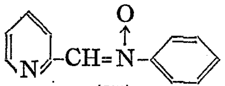
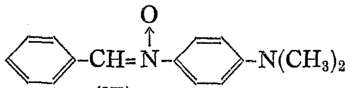
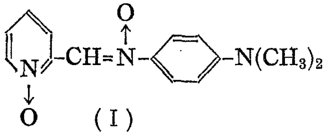
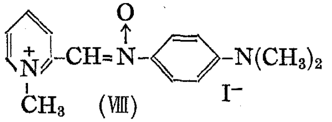
[*1] Katakasu, Fukuoka (梅沢文輔).

[1] Part IV. B. Umezawa: This Bulletin, 8, 698(1960).

[2] E. Schmitz: Chem. Ber., **91**, 1488(1958).

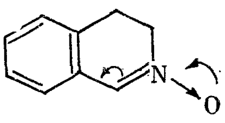
[3] J. Thesing, W. Sirrenberg: *Ibid.*, **91**, 1978(1958).

Table II. Reaction of Nitrones with Five Typical Reagents

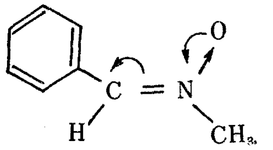
Nitrone \ Reagent	SO$_2$	PO(OPh)$_3$	POCl$_3$	PCl$_3$	Ac$_2$O
 (II)	No change (61)	No change (53.3) Isoquinoline (trace)	Acid amide (73) Isoquinoline (17)	Acid amide (40) Anil (12) Isoquinoline (4)	Acid amide (70)
 (III)	No change (67)	No change (80)	Acid amide (44;57)	Acid amide (30)	Acid amide (55)
 (IV)	No change (15)	—	Acid amide (72)	Acid amide (42)	Acid amide (44)
 (V)	Anil (17.4)	No change (30)	Acid anilide (13)	Anil (17.4)	Acid anilide (36)
 (VI)	(decomp.)	—	Acid anilide (?)	Acid anilide (2)	(decomp.)
 (VII)	Anil (13.4) Acid anilide (3.8)	Anil (15)[a] Acid anilide (2)	Acid anilide (10)	Anil (a small amount) Acid anilide (15)	Acid anilide (30)
 (I)	Acid anilide (50)	Acid anilide (15.6)	Acid anilide (13.8) (4.6)[b]	Acid anilide (82)[b]	Acid anilide (36)
 (VIII)	(decomp.)[c]	No change (87)	—	—	—

Yield is given in parentheses in per cent. The corresponding deoxygenated or rearranged product is given as anil or acid amide/anilide.

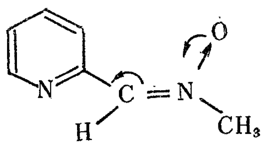
a) At room temp. : Anil (38.6) + *p*-ONPhN(CH$_3$)$_2$ (31.2). *b*)  *c*) Reaction period, 10 min. : No change (23).



(II)



(III)



(IV)

presence of cross conjugation, which involves both the same chromophore as in N-methyl-α-phenylnitrone (III) and N-methyl-α-(2-pyridyl)nitrone (IV), and the N-benzylideneaniline-type chromophore or its pyridine analog, appeared to affect the nature of the N-O bond in (V) and (VI). The fact that (V) gave the deoxygenated product with sulfur dioxide indicated the nature of the N-O bond to be similar to that of aliphatic tertiary amine N-oxides.

N-(*p*-Dimethylaminophenyl)-α-phenylnitrone (VII) mainly gave the corresponding anil accompanied with a small amount of the corresponding anilide. The presence or absence of dimethylamino group was the only difference between (V) and (VII). In the case of (V), sulfur dioxide would first add to the oxygen atom in the nitrone function and then eliminate as sulfur trioxide to leave the deoxygenated product (anil). The positive nitrogen atom, therefore, was neutralized with the bonding electron pair of the N-O bond as shown in (V′) (Chart 1). The nitrogen atom, such as in (VII′), would have been partly neutralized with an electron-donating *p*-dimethylaminophenyl group and thus the normal electron shift effecting deoxygenation would be unfavored to afford a chance for rearrangement.

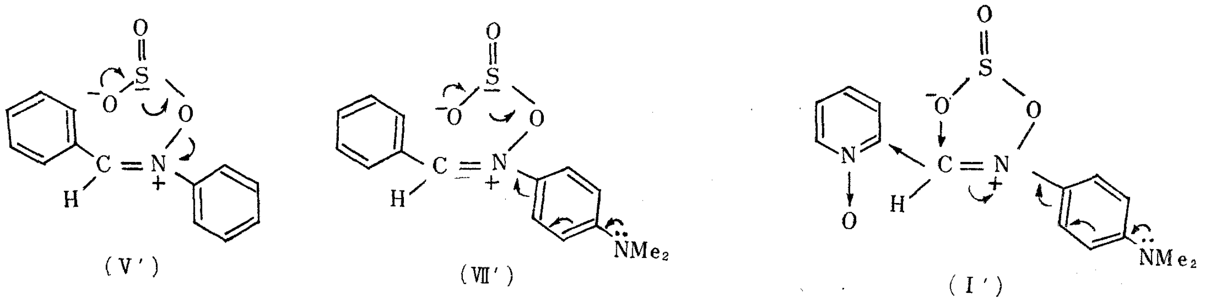


Chart 1. Electron Shift in the assumed Sulfur Dioxide Adduct of (V), (VII), and (I)

The fact that (I) readily underwent rearrangement showed the importance of -I effect of N-oxide group, which made the carbon atom adjacent to the pyridine ring positive and facilitated the rearrangement. Consequently, nitrones cited here may be classified into two groups, A and B. Group A, which includes (II), (III), and (IV), are unaffected by sulfur dioxide, while group B compounds, including (V), (VI), (VII), (I), and (VIII), are sensitive to the reagent to give deoxygenated or rearrangement product.

Reaction with Triphenyl Phosphate and Phosphoryl Chloride

(II), (III), (V), and (VIII) were unaffected when refluxed with triphenyl phosphate, but (VII) gave a small amount of the corresponding anilide (2%), together with N-benzylidene-*p*-dimethylaminoaniline (15%). Formation of the latter appeared to be due to a side reaction, the hydrolysis of (VII) followed by the condensation of benzaldehyde and *p*-dimethylaminoaniline produced from the disproportionation of *p*-dimethylaminophenylhydroxylamine,[4] as shown below. The isolation of both *p*-nitrosodimethylaniline (31.2%) and N-benzylidene-*p*-dimethylaminoaniline (38.6%) in the same reaction at room temperature supported

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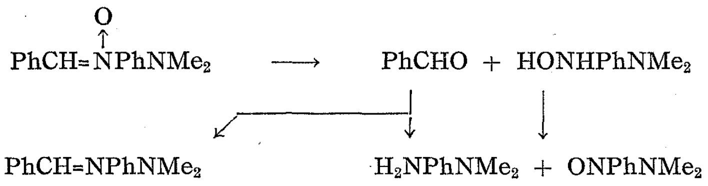
[4] M. Hamana, B. Umezawa, Y. Gotoh: Yakugaku Zasshi, **80**, 1519(1960); I. Tanasesen, M. Ruse: Chem. Ber., **92**, 1265(1959).



$$\begin{array}{ccc} \mathrm{PhCH{=}\overset{\overset{O}{\uparrow}}{N}PhNMe_2} & \longrightarrow & \mathrm{PhCHO} + \mathrm{HONHPhNMe_2} \\ & \swarrow \quad \downarrow & \downarrow \\ \mathrm{PhCH{=}NPhNMe_2} & & \mathrm{H_2NPhNMe_2} + \mathrm{ONPhNMe_2} \end{array}$$

the above route. When (I) was treated with triphenyl phosphate, the rearrangement product was obtained in 15.6% yield.[1] The electron density of the oxygen atom in (II) and (III) in group A may be too low for the oxygen to attack the phosphorus atom of the reagent, while it is high enough in (VII) and (I) in group B to do so to effect the rearrangement. The N-oxide function of (I) would promote the rearrangement as in the case of sulfur dioxide. N-(*p*-Dimethylaminophenyl)-*α*-(2-pyridyl)nitrone methiodide was recovered unchanged by this reagent. The presence of N-methylpyridinium group in (VIII) appeared to strongly promote the electron shift through the conjugated system between the pyridine and benzene rings, and to be unfavorable to the rearrangement. Moreover, the deoxygenation of (VIII) with triphenyl phosphate was not likely to occur.

With phosphoryl chloride, all nitrones cited here underwent the rearrangement irrespective of their configuration. The result was probably due to the fact that the phosphorus atom of phosphoryl chloride (strong -I effect of chlorine atom) was much more positive than that of triphenyl phosphate and was therefore attacked even by the oxygen

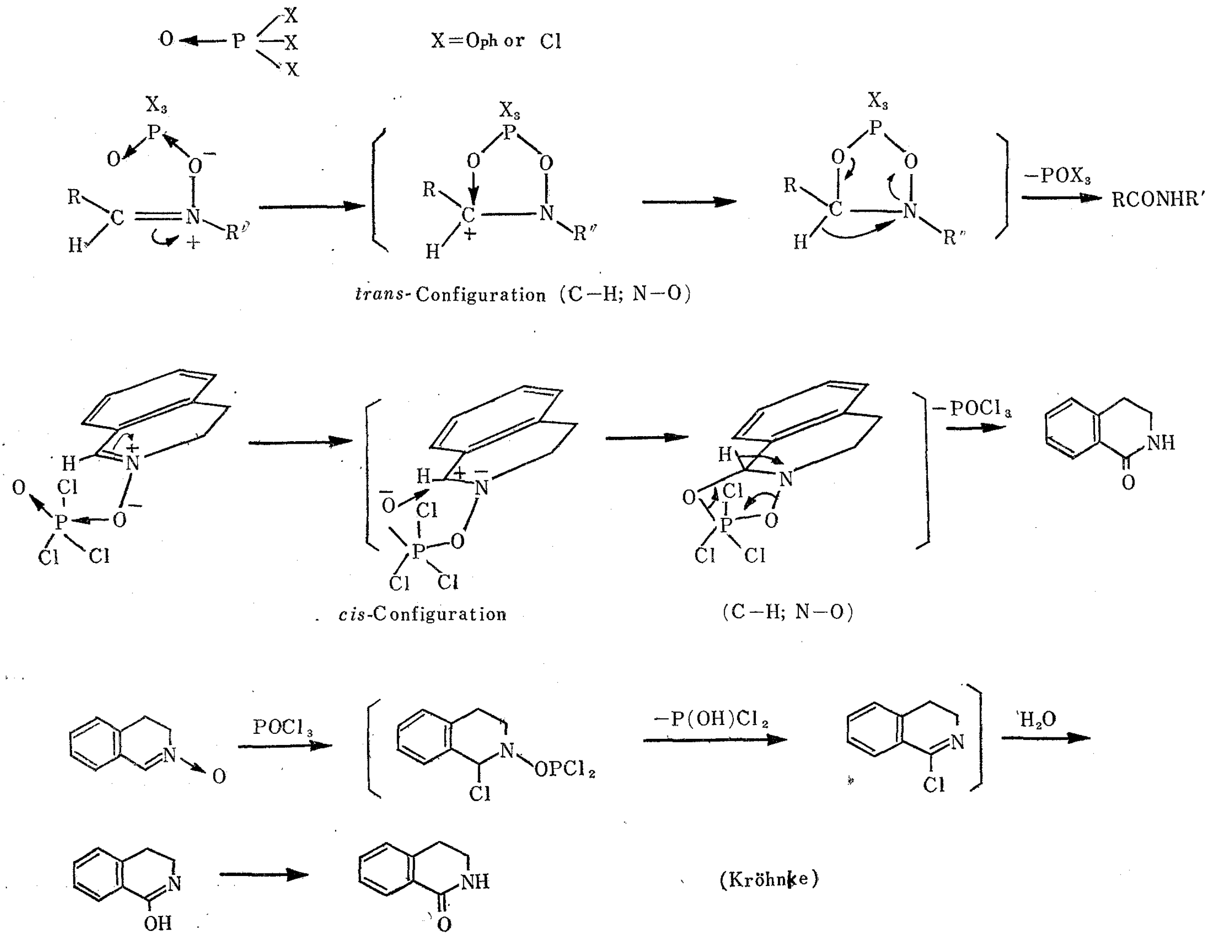
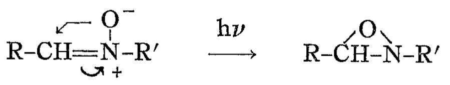


Chart 2.

atom in nitrones of group A. The rearrangement of (II) with phosphoryl chloride[*2] was assumed to proceed through a cyclic intermediate.[1] However, it may also be explained by Kröhnke's mechanism as shown in Chart 2 but the true detail remains unsolved at present.

TABLE III. Ultraviolet Spectra of Nitones (Group B)



	λ_{max} mμ (ε_{max})			
	E_1 Bands	E_2 Bands	K Bands	$\Delta\varepsilon$
(V)	231 (10,000)		312 (16,600)	+3,320
	231 (9,960)		*314 (19,920)*	
(VI)	228 (9,100)		317 (13,280)	+7,920
	223 (9,060)		*317 (21,200)*	
(VII)	255 (12,060)	310 (7,860)	411 (16,520)a)	− 220
	255 (12,670)	*310 (7,750)*	*412 (16,300)*	
(I)	261 (15,800)	320 (11,200)	423 (11,680)	+6,120
	241 (12,120)			
	262 (12,740)	*324 (11,340)*	*426 (17,800)*	
(VIII)	b)	344 (7,900)	477 (17,900)	+ 200
		347 (7,600)	*482 (18,100)*	

Ultraviolet spectra were obtained in 95% EtOH (concentration : $2\times10^{-4}M$) with Beckman DK 2 spectrophotometer. Values given in italics indicate that dilution was carried out in the dark.

a) K Band shifted notably towards a longer wave-length as expected by the introduction of dimethylamino group.

b) Absence of E_1 bands seemed to indicate that no individual aromatics were present in the original state.

Kamlet and Kaplan[5] indicated the K bands of phenylnitrones to completely disappear on exposure of its methanolic solutions to bright sunlight for 1 hour and attributed this change to the formation of the corresponding oxaziridines[6] or isonitrones.[7] Recently, Splitter and Calvin[8] also confirmed the photochemical isomerization of nitrone to oxaziridine. Neutralization of the positive nitrogen atom with the π-electron pair of the C=N double bond followed by the formation of a new bond between the positive carbon atom and negative oxygen appeared to be the course of isomerization.[9] In order to obtain some information on the rôle of dimethylamino group in nitrones, ultraviolet spectra of (V), (VI), (VII), (I), and (VIII) were measured in two different ways; the one (method 1) involving the preparation of the solution in a normally lighted room and the other (method 2) in the dark. The results are shown in Table III. In the case of (V) and (VI), the marked reduction of the value of ε_{max} of the K band (method 1) showed that photochemical isomerization took place. The fact that $\Delta\varepsilon_{max}$ value in (VI) was larger than that in (V) was assumed to be due to the electron-attracting effect of the pyridine ring, making its

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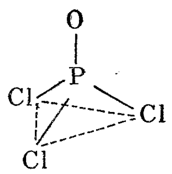
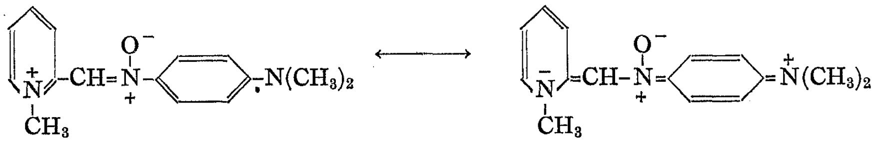
[*2] The structure of phosphoryl chloride is shown here. Therefore, the nucleophilic attack on the phosphorus atom from the rear side of the P-O bond seems possible without any stereochemical interference in the transition state as shown in Chart 2.



5) M. J. Kamlet, L. A. Kaplan : J. Org. Chem., **22**, 576(1957).
6) W. E. Emmons : J. Am. Chem. Soc., **79**, 5739(1957).
7) H. Krimm : Chem. Ber., **91**, 1057(1958).
8) J. S. Splitter, M. Calvin : J. Org. Chem., **23**, 651(1958).
9) G. Ed. Utzinger, F. A. Regenass : Helv. Chim. Acta, **37**, 1892(1954).

adjacent carbon atom more positive and facilitating the formation of a C–O bond. The fact that the values of ε_{max} of (Ⅶ) were almost equal in methods 1 and 2 indicated that the electron shift from the π-electron pair of C=N double bond to the positive nitrogen atom is interfered by electron supply from the benzene ring having *p*-dimethylamino group (strong +M effect). On the other hand, the value of (I) in method 1 was lower than that obtained in method 2. The effect of *p*-dimethylamino group was overcome by that of N-oxide group (–I effect) which strongly favored the isomerization as in (Ⅵ). No appreciable difference between the values of ε_{max} in methods 1 and 2 was observed in the case of (Ⅷ). The cooperative effect of both the N-methylpyridinium (strong –I effect) and the dimethylamino groups in (Ⅷ) may make the anil-type conjugation exclusively predominant and be entirely unfavorable to isomerization. The deep color of (Ⅷ)[10] also showed the compound to have such a mesomeric form as shown below. These results clearly indicated the significance of dimethylamino as well as N-oxide group on the rearrangement of (Ⅶ) and (I) with sulfur dioxide or triphenyl phosphate as discussed above.



Reactions with Phosphorus Trichloride

The rearrangement of nitrones with the reagent is probably due to phosphoryl chloride produced in the course of the reaction.[1] Therefore, it was anticipated that some deoxygenated products would be formed and mixed with the corresponding rearranged ones in every case. The results (Table Ⅱ) showing no apparent agreement of the anticipation were probably ascribable to the degree of stability of these products in the reaction medium.

Reactions with Acetic Anhydride

Nitrones underwent rearrangement with this reagent. Their configurations or the nature of the N–O bond had no critical effect. N-Oxides themselves are susceptible to rearrangement with acetic anhydride[11] and aldonitrones seem to have the same tendency. Summarizing these observations, following conclusions may be made.

(1) The leading factor in these reactions is the inherent nature of the N–O bond. The N–O bond of aromatic N-oxide has a double-bond character owing to its conjugation with aromatic ring, while the character of the N–O bond of nitrone is changed (partial or complete inhibition of the above conjugation) and more or less resembles that of aliphatic tertiary amine oxide. Nitrones[*3] (groups A and B), therefore, constitute a transitory group located between aromatic and aliphatic tertiary amine oxides. Group A, with only one conjugated system, is more closely related to aromatic N-oxide, while group B, with cross-conjugation, resembles aliphatic tertiary amine oxide.

(2) Nitrones which undergo rearrangement with sulfur dioxide or triphenyl phosphate are included in group B and are greatly affected by molecular environment, especially the electronic character of the group attached to aldonitrone grouping.

(3) Configurational influence, if any, is not marked, contrary to expectations. Analytical results of the nature of N–O bond in these nitrones by means of infrared spectra will be published elsewhere.

[*3] Nitrones without any conjugated system were omitted in this work.

10) F. Kröhnke, H. Leister, I. Vogt : Chem. Ber., **90**, 2792(1957).

11) E. Ochiai : J. Org. Chem., **18**, 534(1953); K. Thomas, D. Jerchel : Angew. Chem., **70**, 719(1958).

Experimental

Unless otherwise noted, chromatography was carried out over alumina. All m.p.s are uncorrected.

Preparation of the Starting Materials—The preparation of 3,4-dihydroisoquinoline 2-oxide (II) was made by Schmitz's method.[2] The condensation of BzH with methylhydroxylamine or phenylhydroxylamine gave N-methyl- (III)[12] or N-phenyl-α-phenylnitrones[13] (V). The reaction of 1-benzylpyridinium bromide with *p*-nitroso-N,N-dimethylaniline gave N-*p*-dimethylaminophenyl-α-phenylnitrone[14] (VII).

N-Methyl-α-(2-pyridyl)nitrone (IV)—To a suspension of 3 g. of 2-picolinealdehyde in 2*N* NaOH, a solution of 2.6 g. of methylhydroxylamine hydrochloride in 5 cc. of H_2O was added and the mixture was shaken for 5 min. Extraction with $CHCl_3$ and usual treatment followed by chromatography (elution with $CHCl_3$) gave an oil which, on addition of a small amount of petr. benzine and storage in a refrigerator, gradually crystallized to (IV) as colorless needles. Picrate, m.p. 147~148°. *Anal.* Calcd. for $C_7H_8ON_2 \cdot C_6H_3O_7N_3$: C, 42.74; H, 3.01; N, 19.18. Found : C, 43.01; H, 3.18; N, 18.97.

Owing to its high deliquescency, the crude crystals were used without further purification.

N-Phenyl-α-(2-pyridyl)nitrone (VI)—A solution of 5.5 g. of 2-picolinealdehyde and 5.5 g. of phenylhydroxylamine in 100 cc. of benzene was refluxed for 1.5 hr.. Concentration to a small volume and addition of petr. benzine caused precipitation of crystals which were collected and dried on a piece of clay to remove oily impurities. Treatment with activated charcoal and recrystallization from a mixture of benzene and petr. benzine gave (VI), colorless long plates, m.p. 73~74°; yield, 3.3 g. (32.5%). *Anal.* Calcd. for $C_{12}H_{10}ON_2$: C, 72.71; H, 5.09; N, 14.13. Found : C, 72.43; H, 5.26; N, 13.83.

Reactions of 3,4-Dihydroisoquinoline 2-Oxide (II)—a) With SO_2 : Through a solution of 490 mg. of (II) in 20 cc. of $CHCl_3$, dried SO_2 was passed for 15 min. under ice-cooling and for additional 3 hr. at room temperature. The solution was extracted with 50 cc. of conc. HCl which was basified with KOH and the base was extracted continuously with Et_2O. Usual treatment gave an oil of b.p$_3$ 140~150° (bath temp.); picrate, m.p. 143~144° (from MeOH); 300 mg. (61% yield). No depression of mixed m.p. with (II) picrate, m.p. 143~144°.

b) With PCl_3 : To a solution of 490 mg. of (II) in 20 cc. of $CHCl_3$, a solution of 500 mg. of PCl_3 in 5 cc. of $CHCl_3$ was added dropwise under stirring and ice-cooling. The mixture was refluxed for 1 hr. and added with 50 cc. of 3*N* HCl. The $CHCl_3$ and acid layer were treated separately. The former gave an oil of b.p$_3$ 160~180° (bath temp.), 170 mg. (40% yield), which slowly changed to a solid of m.p. 60~64°. The solid was refluxed in excess of Ac_2O for 40 min. and gave 2-acetyl-3,4-dihydroisocarbostyril as white plates, m.p. 100~102°. Basification of the latter layer with 5*N* KOH, extraction with Et_2O followed by chromatography (elution with Et_2O) gave two fractions. One, easily eluted, gave an oil; picrate (from MeOH), m.p. 221° (decomp.); 50 mg. (4% yield). It was identified as isoquinoline picrate, m.p. 222~223° (decomp.), by mixed fusion. The other, less easily eluted, gave an oil; picrate, m.p. 176~177° (from MeOH); 140 mg. (12% yield). On admixture with 3,4-dihydroisoquinoline picrate, m.p. 176~177°, no depression of m.p. was observed.

c) With $POCl_3$: To a solution of 490 mg. of (II) in 20 cc. of $CHCl_3$, 600 mg. of $POCl_3$ was added. The mixture was refluxed for 1 hr. and extracted with 50 cc. of 3*N* HCl. Usual treatment of the acid layer gave an oil; picrate (isoquinoline picrate), m.p. 222~223°; 200 mg. (17% yield), and of the $CHCl_3$ layer gave another oil, b.p$_3$ 160~180° (bath temp.); 320 mg. (73% yield). Treatment of the latter oil with Ac_2O gave 2-acetyl-3,4-dihydroisocarbostyril, m.p. 100~101°.

d) With Ac_2O[2] : A solution of 700 mg. of (II) in 5 cc. of Ac_2O was refluxed for 20 min. and poured in 50 cc. of H_2O to deposit white crystals of 2-acetyl-3,4-dihydroisocarbostyril, which were purified by distillation, m.p. 100~101°; 600 mg. (70% yield).

e) With triphenyl phosphate : A solution of 450 mg. of (II) and 1 g. of triphenyl phosphate was refluxed for 30 min. and added with 50 cc. of 10% HCl. The basic and neutral fractions were treated separately. The basic fraction afforded a trace of isoquinoline (picrate, m.p. 222°) and (II), an oil of b.p$_6$ 175~185° (bath temp.); 240 mg. (53.3% yield); picrate, m.p. 138~140°. Distillation of the latter fraction gave an oil, b.p$_5$ 220~235° (bath temp.), which changed to white crystals, m.p. 49~50° (from a mixture of Et_2O and petr. benzine), 920 mg. No depression of mixed m.p. with triphenyl phosphate, m.p. 49~50°.

Reactions of N-Methyl-α-phenylnitrone (III)—a) With SO_2 : Through a solution of 1.35 g. of (III) in 20 cc. of $CHCl_3$, dried SO_2 was passed for 1 hr. under ice-cooling. The mixture was shaken with 30 cc. of 20% K_2CO_3 to remove acid impurities. Usual treatment of the $CHCl_3$ layer gave (III) as colorless plates of m.p. 81~82° (from a mixture of benzene and petr. benzine); 900 mg. (67% yield).

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12) O.L. Brady, F.P. Dunn, R.F. Goldstein : J. Chem. Soc., **1926**, 2386.
13) E. Beckmann : Ber., **27**, 1958(1894).
14) F. Kröhnke : *Ibid.*, **71**, 2583(1938).

b) With PCl_3 : To a solution of 1.35 g. of (III) in 15 cc. of $CHCl_3$, a solution of 1.48 g. of PCl_3 was added under ice-cooling. On standing the mixture for a short time at room temp., heat was evolved. Refluxing for 30 min. and usual treatment gave colorless plates, m.p. 76~77° (from a mixture of benzene and petr. benzine); 400 mg. (30% yield), which were identified as N-methylbenzamide, m.p. 77~78°, by mixed fusion.

c) With $POCl_3$: To a solution of 1.35 g. of (III) in 15 cc. of $CHCl_3$, a solution of 1.68 g. of $POCl_3$ in $CHCl_3$ was added cautiously at room temperature. Refluxing for 30 min., chromatography (elution with $CHCl_3$), and storage of the product in a refrigerator gave N-methylbenzamide as colorless plates of m.p. 77~78°; 600 mg. (44% yield). When the reaction was carried out under milder conditions (ice-cooling, standing over night at room temperature, and refluxing for 5 min.), the yield was raised to 57%.

d) With Ac_2O[15] : A solution of 1.35 g. of (III) in 5 cc. of Ac_2O was refluxed for 10 min. and the excess of Ac_2O was decomposed with dil. Na_2CO_3. Usual treatment gave colorless plates of N-methylbenzamide, m.p. 76~77°; 750 mg. (55% yield).

e) With triphenyl phosphate : A solution of 500 mg. of (III) in $CHCl_3$ and 700 mg. of triphenyl phosphate was refluxed for 30 min. The $CHCl_3$ layer was treated as usual to give (III) as colorless plates, m.p. 81~82°; 400 mg. (80% yield).

Reactions of N-Methyl-α-(2-pyridyl)nitrone[*4] **(IV)**—a) With SO_2 : Through a solution of 300 mg. of (IV) in 20 cc. of $CHCl_3$, dried SO_2 was passed for 1 hr. under ice-cooling. Chromatography (elution with Me_2CO) of the reaction product gave an oil of (IV); picrate, m.p. 147~148° (from MeOH), 120 mg. (15% yield).

b) With PCl_3 : To a solution of 550 mg. of (IV) in 20 cc. of $CHCl_3$, a solution of 600 mg. of PCl_3 in 5 cc. of $CHCl_3$ was added dropwise, the mixture was allowed to stand overnight at room temp., and refluxed for 30 min. Usual treatment and distillation *in vacuo* gave an oil, b.p$_3$ 100~130° (bath temp.), 230 mg. (42% yield); picrate, m.p. 151~152° (from MeOH). No depression of mixed m.p. with N-methylpicolinamide picrate, m.p. 152~153°. *Anal.* Calcd. for $C_7H_8ON_2 \cdot C_6H_3O_7N_3$: C, 42.74; H, 3.02; N, 19.18. Found : C, 42.58; H, 3.31; N, 19.09.

c) With $POCl_3$: To a solution of 470 mg. of (IV) in 20 cc. of $CHCl_3$, a solution of 550 mg. of $POCl_3$ in 5 cc. of $CHCl_3$ was added under ice-cooling. The mixture was allowed to stand for 2 days at room temperature and then refluxed for 10 min. Distillation of the product gave N-methylpicolinamide, an oil of b.p$_3$ 100~130° (bath temp.); 350 mg. (72% yield); picrate, m.p. 150~151°.

d) With Ac_2O : A suspension of 800 mg. of (IV) in 5 cc. of Ac_2O was heated in an oil bath. A violent reaction occurred at 120° (bath temp.) and then the mixture was refluxed for 10 min. Treatment as above gave N-methylpicolineamide as an oil of b.p$_3$ 100~135° (bath temp.); 350 mg. (44% yield). Picrate, m.p. 149~150°.

Reactions of N,α-Diphenylnitrone (V)—a) With SO_2 : Through a solution of 1 g. of (V) in 15 cc. of $CHCl_3$, dried SO_2 was passed for 1 hr. under ice-cooling. Chromatography (elution with benzene) of the product gave crystals, m.p. 54° (from aqueous EtOH); 160 mg. (17.4% yield). No depression of mixed m.p. with N-benzylideneaniline, m.p. 53°.

b) With PCl_3 : A solution of 500 mg. of (V) and 350 mg. of PCl_3 in 10 cc. of $CHCl_3$ was refluxed for 30 min. Chromatography (elution with $CHCl_3$) of the product gave crystals of N-benzylidineaniline, m.p. 50~51°; 80 mg. (17.4% yield).

c) With $POCl_3$: A solution of 500 mg. of (V) and 400 mg. of $POCl_3$ in 10 cc. of $CHCl_3$ was refluxed for 30 min. and the mixture was allowed to stand overnight at room temperature. Usual treatment gave crystals, m.p. 160° (from aqueous MeOH); 60 mg. (13% yield), which were identified as benzanilide, m.p. 163°, by mixed fusion.

d) With Ac_2O : A solution of 500 mg. of (V) in 10 cc. of Ac_2O was warmed at 75° for 30 min. and treated as usual. Chromatography (elution with $CHCl_3$) followed by treatment with activated charcoal gave colorless plates of benzanilide, m.p. 164°; 180 mg. (36% yield).

e) With triphenyl phosphate : A solution of 500 mg. of (V) and 500 mg. of triphenyl phosphate in 20 cc. of $CHCl_3$ was refluxed for 30 min. and basified with dil. NaOH. Usual treatment of the $CHCl_3$ layer gave crystals of (V), m.p. 110° (from hydr. MeOH); 150 mg. (30% yield).

Reactions of N-Phenyl-α-(2-pyridyl)nitrone (VI)—a) Attempted reaction with SO_2 or Ac_2O failed under a variety of conditions.

b) With PCl_3 : A solution of 1 g. of (VI) in 20 cc. of $CHCl_3$ was treated with 800 mg. of PCl_3. The mixture was allowed to stand for 2 days at room temp. and treated as usual. Standing of the distillate for more than a month finally gave white crystals, m.p. 75~76° (from petr. benzine); 20 mg. (2% yield). No depression of mixed m.p. with 2-picolineanilide, m.p. 75~76°.

c) With $POCl_3$: A solution of 990 mg. of (VI) and 900 mg. of $POCl_3$ in 30 cc. of $CHCl_3$ was refluxed

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[*4] (IV) was dehydrated before use by distillation with $CHCl_3$.

15) O.L. Brady, F.P. Dunn : J. Chem. Soc., **1926**, 2411.

for 30 min. Chromatography (elution with $CHCl_3$) of the product gave an oil (100 mg.), b.p$_3$ 165~175° (bath temp.). IR[*5] ν cm^{-1} : 3375 (NH), 1674 (amide-I), 1535 (amide-II). By examination of the infrared spectra, the product was assumed to contain some 2-picolineanilide (IR ν cm^{-1} : 3375 (NH), 1676 (amide-I), 1531 (amide II)).

Reactions of N-(*p*-Dimethylaminophenyl)-*α*-phenylnitrone (VII)—a) With SO_2 : Through a solution of 800 mg. of (VII) in 20 cc. of $CHCl_3$, dried SO_2 was passed for 1.5 hr. under ice-cooling. Chromatography (elution with $CHCl_3$) of the product gave two fractions. One, easily eluted, gave light yellow plates, m.p. 99~100° (from petr. ether); 100 mg. (13.4% yield), which were identified as N-benzylidene-*p*-dimethylaminoaniline, m.p. 100°, by mixed fusion. *Anal.* Calcd. for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found : C, 80.50; H, 7.30; N, 12.58.

The other, less easily eluted, gave crystals, m.p. 221~223° (from AcOEt); 30 mg. (3.8% yield). No depression of mixed m.p. with 4′-dimethylaminobenzanilide, m,p, 224~225°. *Anal.* Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found : C, 74.52; H, 6.79; N, 11.48.

b) With PCl_3 : A solution of 800 mg. of (VII) and 480 mg. of PCl_3 in 20 cc. of $CHCl_3$ was refluxed for 30 min. Crystallization of the product from AcOEt gave 4′-dimethylaminobenzanilide, m.p. 223~224°; 120 mg. (15% yield). Evaporation of the mother liquor and chromatography (elution with $CHCl_3$) of the residue gave a small amount (less than 10 mg.) of crystals of N-benzylidene-*p*-dimethylaminoaniline, m.p. 98~99°.

c) With $POCl_3$: A solution of 1 g. of (VII) and 640 mg. of $POCl_3$ in 20 cc. of $CHCl_3$ was refluxed for 30 min. Usual treatment gave crystals of 4′-dimethylaminobenzanilide, m.p. 223~224°, 100 mg. (10% yield).

d) With Ac_2O : A suspension of 1 g. of (VII) in 10 cc. of Ac_2O was warmed for a short time and the mixture was allowed to stand for 2 days at room temperature to deposit crystals. Chromatography (elution with $CHCl_3$) of the product gave crystals of 4′-dimethylaminobenzanilide, 300 mg. (30% yield).

e) With triphenyl phosphate : A solution of 500 mg. of (VII) and 400 mg. of triphenyl phosphate in 20 cc. of $CHCl_3$ was refluxed for 30 min. and basified with dil. NaOH. The $CHCl_3$ layer was green. Chromatography (elution with $CHCl_3$) of the product first gave N-benzylidene-*p*-dimethylaminoaniline, yellow plates, m.p. 98°; 70 mg. (15% yield), and next gave 4′-dimethylaminobenzanilide, white crystals of m.p. 224~225°, 10 mg. (2% yield).

Another solution of 500 mg. of (VII) and 400 mg. of triphenyl phosphate in 20 cc. of $CHCl_3$ was allowed to stand overnight. Chromatography (elution with $CHCl_3$) of the product gave N-benzylidene-*p*-dimethylaminoaniline, as yellow plates of m.p. 100°; 180 mg. (38.6% yield), and green crystals, m.p. 84~85° (from AcOEt); 90 mg. (31.2% yield). No depression of mixed m.p. of the latter crystals with *p*-nitroso-N,N-dimethylaniline, m.p. 85~86°, was observed.

Reactions of N-(*p*-Dimethylaminophenyl)-*α*-(2-pyridyl)nitrone Methiodide (VIII)—a) With SO_2: Through a solution of 300 mg. of (VIII) in 50 cc. of $CHCl_3$, dried SO_2 was passed for 10 min. under ice-cooling. The solvent was evaporated and the residue was extracted with warm water. Concentration of the dark red solution and standing overnight at room temperature gave wine red needles, m.p. 210° (decomp.); 70 mg. (23% yield). When the reaction time was prolonged to 40 min., no identifiable material was obtained.

b) With triphenyl phosphate : A solution of 300 mg. of (VIII) and 200 mg. of triphenyl phosphate in 50 cc. of $CHCl_3$ was refluxed for 30 min. Treatment as above gave wine red needles, m.p. 211~212° (decomp.); 260 mg. (ca. 87% yield), which were identical with the needle crystals of m.p. 210°, described above. IR ν cm^{-1} : 3433 (H_2O); UV $\lambda_{\max}^{\text{EtOH}}$ mμ (ε) : 344 (7,900), 477 (17,900).[*6] Inspection of infrared and ultraviolet spectra showed that (VIII) and this product were identical except for the latter having water of crystallization. When slowly heated, the product melted at 204~205° and was identified as (VIII), m.p. 204°, by mixed fusion.

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Summary

Reactions of several nitrones, which have one or two conjugated systems, with sulfur dioxide, triphenyl phosphate, phosphoryl chloride, phosphorus trichloride, and acetic anhydride were examined. The reactions were dependent on the nature of N-O bond of nitrones.

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[*5] Infrared spectra were taken in Nujol.

[*6] Infrared and ultraviolet spectra were obtained with Koken Model DS-301 and Beckman DK-2 spectrophotometer, respectively.