# NITRONES

JAN HAMER AND ANTHONY MACALUSO

*Department of Chemistry, Tulane University,*
*New Orleans, Louisiana 70118*

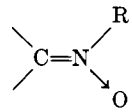
*Received February 29, 1964*

CONTENTS

## I. INTRODUCTION

### A. GENERAL INTRODUCTION

Nitrones are compounds containing the group



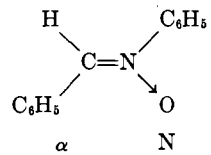
The name nitrone was contracted from nitrogen ketone in order to indicate a chemical relationship between nitrones and carbonyl compounds (212). The nitrone group bears a marked resemblance to the carbonyl group in facilitating the removal of a proton from an adjacent carbon under basic conditions, the oxidation of an adjacent methyl group to a carbonyl group by means of selenium dioxide, the addition of Grignard reagents, the addition of hydrocyanic acid, and the reduction by complex metal hydrides.

### B. SCOPE OF REVIEW

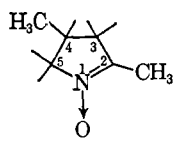
The chemistry of nitrones was previously reviewed by Smith in 1938 as one of the structural systems which undergo 1,3-addition reactions (212). The present review emphasizes publications since 1938, an attempt being made to cover the literature through 1963. Heteroaromatic N-oxides (*e.g.*, pyridine N-oxide), although formally containing the nitrone structure (61), and also isatogens have been excluded from this review.

### C. NOMENCLATURE

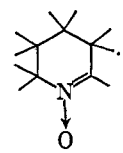
The nomenclature employed by *Chemical Abstracts* in recent years has been used throughout this review. Thus, the following compound which in the older literature was called the N-phenyl "ether" of benzaldoxime



is named $\alpha$,N-diphenylnitrone. Cyclic nitrones are named according to the parent heterocyclic structure, *e.g.*



2,4-dimethyl-$\Delta^1$-pyrroline N-oxide



$\Delta^1$-tetrahydropyridine N-oxide

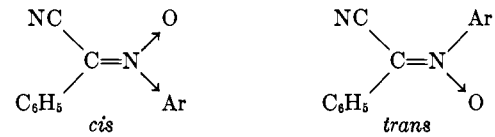
The general terms, aldonitrones and ketonitrones, have been employed occasionally. Aldonitrones contain a proton on the $\alpha$-carbon atom, RCH=N(O)R'', while in ketonitrones the $\alpha$-carbon is fully substituted with alkyl and/or aryl groups, RR'C=N(O)R''.

## II. GEOMETRIC ISOMERISM

Nitrones exhibit geometric isomerism because of the double bond in the nitrone group. The existence

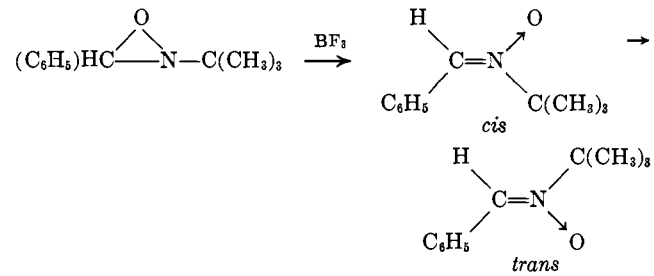
of geometric isomerism was first demonstrated in 1918 for $\alpha$-phenyl-$\alpha$-(*p*-tolyl)-N-methylnitrone (208). The configurations of the isomers were established by dipole moment studies (212).

Also, the geometrical isomers of seven $\alpha$-phenyl-$\alpha$-cyano-N-arylnitrones have been prepared, the aryl group being phenyl, *o*-, *m*-, or *p*-tolyl, or *o*-, *m*-, or *p*-chlorophenyl (17). Configurational assignments were based on dipole moment measurements. For the *cis*

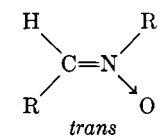


forms the dipole moments ranged between 5.6 and 6.3 D., and for the *trans* forms between 0.9 and 1.7 D. The *cis* forms were converted readily into the *trans* forms by heating (17).

The only example of geometric isomerism in aldonitrones consists of $\alpha$-phenyl-N-*t*-butylnitrone (79). The *cis* form of this nitrone was formed first when 2-*t*-butyl-3-phenyloxazirane was treated with boron trifluoride. Complete isomerization to the *trans* form occurred within 24 hr. in benzene solution.



Ultraviolet spectral studies indicate that aldonitrones exist in the stable *trans* form (225), and this has been



confirmed by nuclear magnetic resonance and infrared studies (106b).

Two resonance structures may be written for nitrones. The important contributing structure appears to be

TABLE I
ULTRAVIOLET SPECTRA OF NITRONES

| Nitrone | | λ, mμ, and ε | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| α-Substituent | N-Substituent | $E_1$ | ε | $E_2$ | ε | K | ε | Solvent | Ref. |
| $C_6H_5$ | $C_6H_5$ | 227 | 9,850 | ... | ... | 315 | 14,000 | EtOH | 236 |
| | | 236 | 9,060 | | | | | | |
| $p$-$CH_3OC_6H_4$ | $C_6H_5$ | 227 | 9,800 | 280 | 7,950 | 329 | 26,900 | MeOH | 126 |
| | | 237 | 11,800 | | | 330 | 11,800 | | |
| | | 240 | 16,700 | | | | | | |
| $p$-$NO_2C_6H_4$ | $C_6H_5$ | 228–236 | 8,500 | 251 | 8,470 | 350 | 10,400 | MeOH | 126 |
| | | 237 | 11,900 | 266–278 | 10,400 | 352 | 20,000 | | |
| | | | | 247 | 8,600 | | | | |
| | | | | 265 | 11,800 | | | | |
| $p$-$HOC_6H_4$ | $C_6H_5$ | 228 | 16,300 | 280 | 8,000 | 330 | 7,800 | MeOH | 126 |
| | | | | 310 | 9,700 | | | | |
| $C_6H_5$ | $p$-$ClC_6H_4$ | 228 | 8,480 | 254 | 7,620 | 318 | 20,900 | EtOH | 236 |
| | | 237 | 8,480 | | | | | | |
| $C_6H_5$ | $p$-$CH_3C_6H_4$ | 236 | 10,300 | 251 | 5,700 | 316 | 15,800 | EtOH | 236 |
| | | | | 257 | 5,700 | | | | |
| 2,4,4-Trimethyl-$\Delta^1$-pyrroline N-oxide | | 229 | 9,000 | | | | | EtOH | 30 |
| 4,5,5-Trimethyl-$\Delta^1$-pyrroline N-oxide | | 234 | 8,800 | | | | | EtOH | 30 |
| 5,5-Dimethyl-$\Delta^1$-pyrroline N-oxide | | 234 | 7,700 | | | | | EtOH | 30 |

TABLE II
ULTRAVIOLET SPECTRA AND GEOMETRY OF NITRONES[a]

| Compounds | λ, mμ | ε | λ, mμ | ε | λ, mμ | ε |
|---|---|---|---|---|---|---|
| 3,4-Dihydroisoquinoline (*cis*, known) | 304 | 15,956 | 228 | 12,087 | 211 | 6,414 |
| 2-Phenyl-$\Delta^1$-pyrroline N-oxide (*trans*, known) | 288 | 14,274 | 221 | 7,559 | 205 | 8,528 |
| α-Phenyl-N-methylnitrone (*trans*, deduced) | 288 | 16,540 | 221 | 6,932 | 206 | 7,455 |
| α-Phenyl-N-cyclohexylnitrone (*trans*, deduced) | 291 | 17,597 | 223 | 6,904 | 206 | 8,359 |

[a] Taken from ref. 225; solvent, methanol.

structure A, since, for instance, the dipole moment of α-phenyl-N-methylnitrone (116) is 3.55 D.

## III. Molecular Spectra

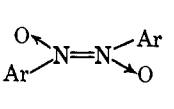
### A. Ultraviolet spectra

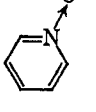
The ultraviolet spectra of many nitrones have been studied (17, 30, 84, 95, 96, 99, 108, 126, 157, 183, 223, 225, 236). The interpretation of the origin of the various regions of absorption was given by a study of the ultraviolet spectra of 13 ring-substituted α,N-diphenylnitrones (236). The E1 region falls between 227 and 237 mμ, the E2 region between 251 and 310 mμ, and the K region between 315 and 350 mμ for α,N-diphenylnitrones. These findings were generally confirmed in later studies (126, 157). A few representative data have been collected in Table I.

The ultraviolet spectra have been employed in a study (225) of the geometry of nitrones by comparing spectra of cyclic nitrones of known geometry with those of noncyclic aldonitrones. The α,N-substituents in aldonitrones were found to be in a *trans* position for two selected compounds. Table II summarizes these findings.

### B. Infrared spectra

The assignment of the N→O stretching frequency in nitrones is somewhat in a state of confusion. In a study of 34 nitrones and their isomeric O-ethers, RR′-C=N—O—R″, each of the nitrones showed an usually strong infrared absorption band which was not present in the spectra of the isomeric O-ethers in the region between 1170 and 1280 $cm.^{-1}$ (213). This is the same region to which the N→O stretching frequency has been assigned in dimeric *trans*-nitroso compounds and heteroaromatic N-oxides containing a similar nitrogen–





oxygen coordinate covalent linkage. The >C=N– stretching absorptions were in all cases close to 1600 $cm.^{-1}$. A few data from this convincing study (213)

TABLE III
INFRARED SPECTRA OF NITRONES[a]

| Nitrone | | N→O stretch, cm.$^{-1}$ |
|---|---|---|
| α-Substituent | N-Substituent | |
| $(C_6H_5)_2$ | $CH_2C_6H_5$ | 1250 |
| $(C_6H_5)_2$ | $CH(C_6H_4)_2$ | 1260 |
| $(C_6H_5)_2$ | $CH_2C_6H_4$-*p*-CN | 1265 |
| $(C_6H_5)_2$ | $CH_2C_6H_4$-*p*-$CH_3$ | 1280 |
| $(C_6H_5)_2$ | $CH_2C_6H_4$-*p*-$OCH_3$ | 1280 |
| (*p*-$CH_3OC_6H_4)_2$ | $CH_2C_6H_5$ | 1200 |
| (*p*-$NO_2C_6H_4)_2$ | $CH_2C_6H_5$ | 1270 |
| $(C_6H_5)_2$ | $CH_3$ | 1260 |
| (*p*-$CH_3OC_6H_4)_2$ | $CH_3$ | 1190 (?) |
| (*p*-$NO_2C_6H_4)_2$ | $CH_3$ | 1260 |

[a] All data from ref. 213; solvent not given.

have been collected in Table III. Also, α-butyl-N-methylnitrone, pyridine N-oxide, and trimethylamine N-oxide were found to exhibit intense bands at 1185–1250 and 920–950 cm.$^{-1}$ (209). In another recent study (210) of the infrared spectra of α-phenyl-N-methylnitrone and α,N-diphenylnitrone, the N→O stretching frequencies were assigned to, respectively, 1172 and 1088 cm.$^{-1}$, and the C=N frequencies to, respectively, 1587 and 1548 cm.$^{-1}$. Solvents capable of hydrogen bonding shifted the N→O and C=N absorptions to markedly lower, respectively, higher frequencies (210, 134, 198).

On the other hand, $\Delta^1$-pyrroline N-oxides (30, 134), a number of α,N-dialkylnitrones (85, 198), and α-phenyl-N-benzylnitrone (68) were reported to show strong absorption bands in the 1540 to 1620 cm.$^{-1}$ region ascribed by some (198) to the N→O stretching mode, and by others (68, 85, 134) to a nitrone group stretching mode. It appears more likely that this absorption band should be attributed to the C=N stretching mode (213). This assumption is further strengthened by another study (225) of the infrared spectra of seven nitrones of which two were $\Delta^1$-pyrroline N-oxides. The C=N stretching frequency was assigned to the 1560–1580 cm.$^{-1}$ region, and the strong absorption due to the N→O stretching mode to the 1150–1270 cm.$^{-1}$ region.

## IV. SYNTHESES

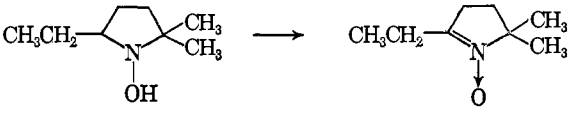
Tables IV–VI contain data on the nitrones prepared by methods A–E.

### A. BY OXIDATION OF N,N-DISUBSTITUTED HYDROXYLAMINES

The preparation of cyclic and acyclic nitrones from the corresponding N,N-disubstituted hydroxylamines has been achieved by a variety of oxidizing agents such as molecular oxygen, yellow mercuric oxide, "active" lead oxide, potassium ferricyanide, potassium permanganate, *t*-butyl hydroperoxide, and hydrogen peroxide.

$$R{-}\underset{\underset{OH}{|}}{N}{-}CHR'R'' \xrightarrow{[O]} R{-}\underset{\underset{O}{\downarrow}}{N}{=}CR'R'' + H_2O$$

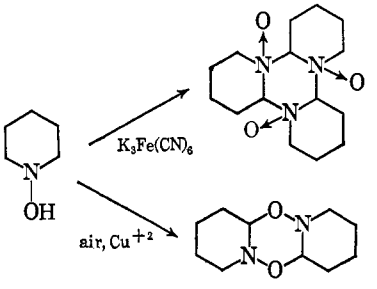
The air oxidation of secondary hydroxylamines has been known for a long time. Aqueous cupric salt solutions were shown to accelerate markedly the uptake of oxygen (124). Air oxidation of N-butyl-N-phenylhydroxylamine in the absence of catalyst required 8 weeks at −10° to yield 64% of α-propyl-N-phenylnitrone (233). On the other hand, 5-ethyl-1-hydroxy-2,2-dimethylpyrrolidine in aqueous ethanol containing cupric acetate and some ammonia yielded 90% of the nitrone when air was bubbled through the solution for a few hours (30). This method has been found very useful for the preparation of cyclic nitrones



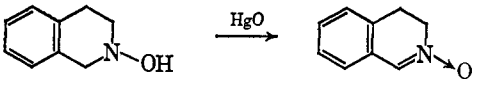
(30, 43, 222), since these nitrones are sufficiently stable to hydrolysis. In the absence of air and catalyst, disproportionation of the hydroxylamine may take place. For instance, N-ethyl-N-phenylhydroxylamine dissolved in carbon disulfide yields α-methyl-N-phenylnitrone and N-ethylaniline (186).

$$C_6H_5{-}\underset{\underset{OH}{|}}{N}{-}CH_2CH_3 \rightarrow C_6H_5{-}\underset{\underset{O}{\downarrow}}{N}{=}CHCH_3 + C_6H_5NHCH_2CH_3 + H_2O$$

Alkaline solutions of potassium ferricyanide were employed to prepare α-methyl-N-phenylnitrone (186, 233) and other nitrones (97, 221, 223) from the corresponding hydroxylamines, often in high yields. 1-Hydroxypiperidine yielded upon treatment with potassium ferricyanide the trimer of 2,3,4,5-tetrahydropyridine N-oxide (223), while the same hydroxylamine upon cupric acetate catalyzed aerial oxidation yielded the dimer of 2,3,4,5-tetrahydropyridine N-oxide (222).




The oxidation of 2-phenyl-1-hydroxypyrrolidine or 2-hydroxy-1,2,3,4-tetrahydroisoquinoline to the corresponding nitrones was achieved by yellow mercuric oxide in an aqueous acetone suspension at room temperature (223). In the absence of water no



color change of the yellow mercuric oxide was observed, even after 30 min. of shaking (223). The preparation of $\Delta^1$-pyrroline N-oxide (225) and $\alpha$-phenyl-N-benzylnitrone (83, 97, 238) was achieved by reacting the corresponding hydroxylamines with yellow mercuric oxide in anhydrous chloroform.

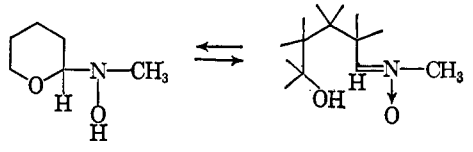
In one instance, "active" lead dioxide, freshly precipitated from a lead tetraacetate solution, was employed to oxidize N-phenyl-N-skatylhydroxylamine to the nitrone (220). In one other case, diamminosilver nitrate was used as the reagent for the preparation of $\alpha$-styryl-$\alpha$-benzyl-N-phenylnitrone from the corresponding hydroxylamine (233).

A cold alkaline solution of potassium permanganate in acetone was employed to prepare $\alpha$,N-diphenylnitrone in 60% yield from the hydroxylamine (232).

*t*-Butyl hydroperoxide oxidized N,N-dibenzylhydroxylamine to the corresponding nitrone in 90% yield. A nitrone could not be isolated by the oxidation of N,N-diethylhydroxylamine with the hydroperoxide, but the nitrone could be trapped in a 75% yield by forming an adduct with methyl methacrylate (68). The reaction appears to be general.

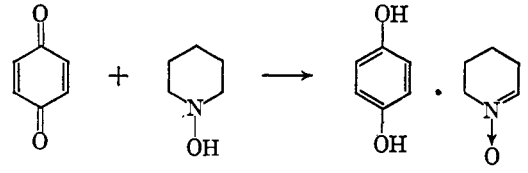
Hydrogen peroxide was employed as the oxidizing agent for the preparation of $\alpha$,N-diphenylnitrone (232), $\alpha$-(*o*-nitrophenyl)-N-phenylnitrone (232), or $\alpha$-benzyl-N-phenylnitrone (221) from the corresponding hydroxylamines.

A special case of nitrone formation consists of the tautomerization of N-(2-pyrano)-N-methylhydroxylamine (228).



Formation of similar nitrones but with different N-substituents was reported by treating the substituted hydroxylamines with hydrogen peroxide (198).

The formation of a nitrone "salt" was reported from the reaction between *p*-quinone and 1-hydroxypiperidine (40).



B. FROM N-SUBSTITUTED HYDROXYLAMINES

$$R{-}NHOH + R'R''C{=}O \rightarrow R{-}\underset{\underset{O}{\downarrow}}{N}{=}CR'R'' + H_2O$$

This reaction proceeds smoothly and in high yields when R is an alkyl or aryl group and if R′ and R″ are of small size. When R′ and R″ are bulky groups the reaction does not proceed to any extent (168).

N-Phenylhydroxylamine has been treated with a variety of aldehydes and ketones. With *n*-butyraldehyde, an 80% yield of $\alpha$-propyl-N-phenylnitrone was obtained (186), with benzaldehyde a 90% yield of the nitrone (210, 236), with *o*-, *m*-, or *p*-nitrobenzaldehyde good yields (22), with *p*-N,N-dimethylaminobenzaldehyde a 79% yield (214), and good yields with various other substituted benzaldehydes (99). N-Phenylhydroxylamine and formaldehyde appear to form N-phenylnitrone which *in situ* undergoes an intermolecular 1,3-addition following by the loss of hydrogen and the formation of a dinitrone (233).

$$C_6H_5{-}\underset{\underset{O}{\downarrow}}{N}{=}CH_2 \rightarrow C_6H_5{-}\underset{\underset{O}{\downarrow}}{\underset{\underset{H}{|}}{N}}{-}CH_2{-}CH{=}\underset{\underset{O}{\downarrow}}{N}{-}C_6H_5 \rightarrow C_6H_5{-}\underset{\underset{O}{\downarrow}}{N}{=}CH{-}CH{=}\underset{\underset{O}{\downarrow}}{N}{-}C_6H_5$$

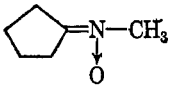
A similar 2:1 product has been observed in the reaction between N-phenylhydroxylamine and $\alpha$-bromocrotonaldehyde (233).

Twelve ring-substituted N-phenylhydroxylamines were treated with benzaldehyde dissolved in a minimum quantity of ethanol, and allowed to stand at room temperature overnight; the nitrones were isolated in 80–95% yields (236).

N-(*p*-Tolyl)hydroxylamine and 9-acridinecarboxaldehyde formed the nitrone in 73% yield (74), while the same hydroxylamine and a number of aromatic aldehydes formed the nitrones in quantitative yields (26).

Although N-diphenylmethylhydroxylamine or N-cinnamylhydroxylamine readily reacted with benzaldehyde to form the nitrone (238), the reaction between N-triphenylmethylhydroxylamine and benzophenone did not lead to a nitrone, presumably for steric reasons (67).

From N-methylhydroxylamine and cyclopentanone, heated for 3 hr. at 70°, followed by cooling to −10°, 61% of a nitrone could be isolated. This nitrone was very hygroscopic. It was instantly hydrolyzed by



water and decomposed by ethanol. In a similar fashion, nitrones were prepared from the reaction between N-methylhydroxylamine and cyclohexanone, acetone, benzophenone (80), or benzaldehyde (80, 210). Benzaldehyde also was treated with N-cyclohexylhydroxylamine (224).

N-Ethylhydroxylamine yielded the expected nitrone with 3-cyclohexenecarboxaldehyde, but with 4-cycloheptenecarboxaldehyde a nitrone was formed which *in situ* underwent an intramolecular 1,3-cycloaddition

to the olefinic double bond (161). A number of sensitive $\alpha$-alkyl-N-alkylnitrones have been formed by the reaction between an N-alkylhydroxylamine and a carbonyl compound which then were trapped *in situ* by an alkene or other unsaturated molecule in a 1,3-cycloaddition reaction in high over-all yields (100).

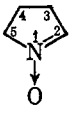
Benzaldehyde and N-(1-phenyl-2-nitroethyl)-hydroxylamine (120), or 2-hydroxyaminooctanamide (118), gave the expected nitrones in 70 and 55% yields, respectively, while *p*-nitrobenzaldehyde also formed a nitrone with N-($\beta$-phenylisopropyl)hydroxylamine (89).

The bisulfite addition compounds of aldehydes and ketones have been reported to react with N-substituted hydroxylamines, yielding nitrones quantitatively (98).

$$RR'COH\cdot SO_3Na + R''NHOH\cdot HCl \rightarrow RR'C(\rightarrow O)=NR'' + SO_2 + NaCl + H_2O$$

Five-membered cyclic nitrones have been prepared in yields ranging from 50–80% by reductive cyclization of $\gamma$-nitroketones (41, 70, 134) or $\gamma$-nitronitriles (48) by employing zinc dust and aqueous ammonium chloride, the $\gamma$-nitronitriles yielding 2-amino-$\Delta^1$-pyrroline N-oxide derivatives.

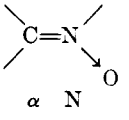
TABLE IV
$\Delta^1$-PYRROLINE N-OXIDE DERIVATIVES



| Substituents | B.p. (mm.) or m.p., °C. | Preparative method[a] | Yield, % | Ref. |
|---|---|---|---|---|
| None | 65 (0.07) | A | 72 | 225 |
| 2-Phenyl | 99–100 | A | 24 | 225 |
| 2-Phenyl | 102 | B | 49 | 224 |
| 5,5-Dimethyl | 66–67 (0.6) | B | 79 | 30 |
| 5-Carbethoxy-5-methyl | 120 (0.3) | B | 60 | 30 |
| 5-Carboxy-5-methyl | 135–136 | B | 77 | 30 |
| 2-Cyano-5,5-dimethyl | 110 (0.5) | A | 73 | 30 |
| 2,4,4-Trimethyl | 72 (0.4) | B | 75 | 30 |
| 2,5,5-Trimethyl | 98 (picrate) | A | 40 | 30 |
| 2,5,5-Trimethyl | 71–72 (2) | B | 77 | 70 |
| 2-Ethyl-5,5-dimethyl | 54–56 (0.2) | A | 90 | 30 |
| 4,5,5-Trimethyl | 80 (0.5) | B | 51 | 30 |
| 2-Cyano-4,5,5-trimethyl | 86–87 | A | 76 | 30 |
| 3,3,5,5-Tetramethyl | 32–34 | A | 72 | 30 |

[a] Method A, oxidation of hydroxylamine; method B, hydroxylamine and carbonyl compound.

TABLE V
NITRONES



| Substituents: $\alpha$ | Substituents: $\alpha$ | Substituents: N | B.p. (mm.) or m.p., °C. | Preparative method[a] | Yield, % | Ref. |
|---|---|---|---|---|---|---|
| $CH_3$ | H | $C_6H_5$ | 58–60 | A | *b* | 186, 233 |
| $n$-$C_3H_7$ | H | $C_6H_5$ | 71–74 | B | 21–80 | 186, 233 |
| $n$-$C_3H_7$ | H | $C_6H_5$ | 75 | A | 74 | 233 |
| $n$-$C_3H_7$ | H | $C_6H_5CH_2$ | 135–136 (26) | C | *b* | 174 |
| $n$-$C_7H_{15}$ | H | $C_6H_5CH_2$ | 88–90 | C | 77 | 174 |
| $n$-$C_8H_{17}$ | H | $C_6H_5CH_2$ | 91.5–92.5 | C | *b* | 174 |
| $C_6H_5$ | H | $CH_3$ | 81–82 | B | *b* | 210 |
| $C_6H_5$ | H | $CH_3$ | 84 | A | *b* | 83 |
| $C_6H_5$ | H | $C(CH_3)_3$ | 75–77 | D | 100 | 108 |
| $C_6H_5$ | H | $C_6H_5$ | 112 | A | 60 | 232, 238 |
| $C_6H_5$ | H | $C_6H_5$ | 112–114 | B | 90 | 232, 236, 237 |
| $C_6H_5$ | H | $C_6H_5$ | 112–113 | E | 25 | 110 |
| $C_6H_5$ | H | $C_6H_5CH_2$ | 81.5–83.5 | A | 90 | 67, 68, 83 |
| $C_6H_5$ | H | $C_6H_5CH{=}CH$ | 73 | B | *b* | 238 |
| $C_6H_5$ | H | $CH(C_6H_5)_2$ | 159–160 | B | 80 | 238 |
| $C_6H_5$ | H | $CH(C_6H_5)_2$ | 157–161 | C | 6–22 | 213 |
| $C_6H_5CH{=}CH$ | H | $C_6H_5$ | 150–151 | F | 20 | 233 |
| $CH_3$ | $CH_3$ | $CH_3$ | 77 (2) | B | *b* | 80 |
| $C_6H_5$ | $CH_3$ | $CH_3$ | 115 | B | *b* | 80 |
| $C_6H_5$ | $C_6H_5$ | $CH_3$ | 103 | B | *b* | 80 |
| $C_6H_5$ | $C_6H_5$ | $CH_3$ | 102–103 | C | 43 | 213 |
| $C_6H_5$ | $C_6H_5$ | $C_6H_5CH_2$ | 119–120 | B | 65 | 67, 83 |
| $C_6H_5$ | $C_6H_5$ | $C_6H_5CH_2$ | 119–122 | C | 17–22 | 213 |
| $C_6H_5$ | $C_6H_5$ | $CH(C_6H_5)_2$ | 162–166 | C | 31 | 67 |
| $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | 223–226 | E | 60–68 | 123 |
| $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | 220 | F | 18 | 73 |

[a] Method A, oxidation of hydroxylamine; B, hydroxylamine and carbonyl compound; C, alkylation of oximes; D, from oxaziranes; E, from aromatic nitroso compounds; F, miscellaneous. [b] Not reported.

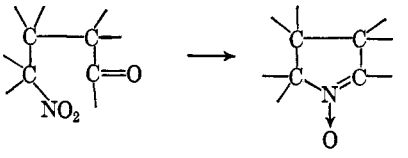
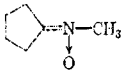
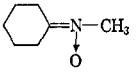
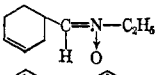
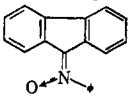
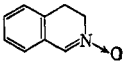


TABLE VI
NITRONES

| Compounds | B.p. (mm.) or m.p., °C. | Preparative method[a] | Yield, % | Ref. |
|---|---|---|---|---|
|  | 85 (2) | B | 61 | 80 |
|  | 96 (1) | B | .. | 80 |
|  | 99–102 (0.9) | B | .. | 161 |
|  | 194–196.5 | E | 88–96 | 123 |
|  | 56–57 | A | 94 | 223 |
|  dimer | 126–127 | A | 32 | 222 |
| trimer | 130 dec. | A | 97 | 223 |

[a] Method A, oxidation of hydroxylamine; B, hydroxylamine and carbonyl compounds; E, aromatic nitroso compounds and sulfur ylides or diazo compounds.

Nitrones have also been prepared by the generation *in situ* of the hydroxylamine in the presence of a carbonyl compound. Nitrobenzene, benzaldehyde, and zinc dust in a mixture of water, ethanol, and acetic acid at −8° for 2 hr. yielded 90% of α,N-diphenylnitrone (237). Aliphatic nitro compounds behave similarly (9, 174). Nitromethane was treated with hydrogen in the presence of a catalyst and benzaldehyde added to the resulting mixture; α-phenyl-N-methylnitrone was isolated (75). Another example is the reaction between β-naphthol, formaldehyde, and hydroxylamine, yielding N-(2-hydroxy-1-naphthylmethyl)nitrone (193).

N-Phenylhydroxylamine and benzalaniline yielded N,α-diphenylnitrone and aniline (125). Similarly,

$$C_6H_5NHOH + C_6H_5CH{=}NC_6H_5 \rightarrow C_6H_5CH{=}N(O)C_6H_5 + C_6H_5NH_2$$

N-phenylmethylhydroxylamine and benzhydrylidenimine formed α,α-diphenyl-N-benzylnitrone in 65% yield, but no nitrone formation was observed in the reaction between N-triphenylmethylhydroxylamine and benzhydrylidenimine (67), presumably for steric reasons.

Last, nitrones were formed when hydroxylamine hydrochloride was treated with potassium cyanate in the presence of an aromatic aldehyde (24, 25).

$$KOCN + HONH_3Cl + ArCHO \rightarrow ArCH{=}N(O){-}CO{-}NH_2$$

### C. FROM OXIMES

The alkylation of oximes was reviewed in 1938 (212). A disadvantage of this method is that the reaction products are mixtures of oxime ethers and nitrones, since alkylation may occur on either oxygen or nitrogen.

$$>C{=}NOH + XR \rightarrow >C{=}NOR + >C{=}N(O){-}R + HX$$

Recently a detailed study appeared concerning the factors affecting the site of alkylation of various benzophenone oxime salts (213). Lithium, sodium, potassium, or tetramethylammonium oxime salts did not show a significant difference in the product ratio of oxime ether to nitrone, although the silver salts of aldoximes have been reported as yielding exclusively the oxime ethers by earlier workers (36). The ratio of products ranged between 2.8 and 3.5 for the reaction between benzyl chloride and various salts of benzophenone oxime. A small effect was noted by employing different leaving groups. Electron-withdrawing groups in *p,p'*-disubstituted benzophenone oxime salts markedly promoted the formation of nitrones, while electron-donating substituents favored oxime ether formation. A pronounced steric effect was observed by comparing the reactions between benzophenone oxime sodium salt with methyl bromide or benzyl bromide, the small size of the alkylating reagent favoring nitrone formation; the larger size, oxime ether formation.

Heptanal oxime when treated with benzyl chloride in a solution of ethanol and sodium ethoxide yielded 77% of α-hexyl-N-benzylnitrone (174). The α-octyl and α-propyl analogs were prepared similarly (174) in good yields.

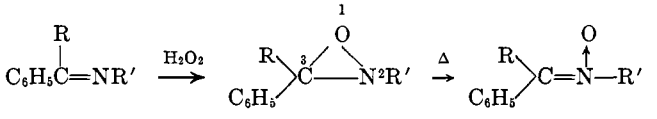
Benzophenone oxime potassium salt and diphenylbromomethane were reported to yield 31% of α,α-diphenyl-N-diphenylmethylnitrone and 54% of the oxime ether (67). The same salt and benzyl bromide showed an oxime ether to nitrone product ratio of about 5 (67).

Dimethyl sulfate was employed in the alkylation of various ketoximes. The nitrone to oxime ether product ratio ranged from 0.8–3.0. This ratio was 1.43 for acetophenone oxime, and 1.16 for benzophenone oxime (37). α-Benzaldoxime and other α-aldoximes when treated with dimethyl sulfate at room temperature for 8 months in the dark yielded the nitrone quantitatively, while β-aldoximes under similar conditions yielded mainly the nitrone and some oxime ether (35).

### D. FROM OXAZIRANES

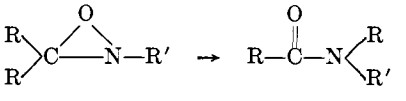
In general, oxaziranes are prepared either by the photochemical isomerization of nitrones (215) or by the reaction between imines and hydrogen peroxide (78,

79). The latter reaction was employed to synthesize a variety of 3-aryloxazirane derivatives, but 2,3-diaryloxaziranes could not be synthesized in this fashion (215).

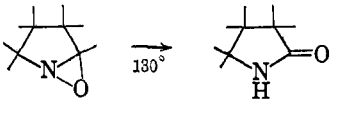


The smooth thermal rearrangement of 3-phenyloxazirane derivatives to the corresponding nitrones has been reported by various workers (78, 79, 108, 215) in yields ranging from 50–100%. The isomerization of 2-*t*-butyl-3-phenyloxazirane yielded 100% of α-phenyl-N-*t*-butylnitrone at temperatures between 60–100°. The isomerization was a first-order reaction, with an energy of activation of 28 kcal./mole and an entropy of activation of −3 kcal./mole (108).

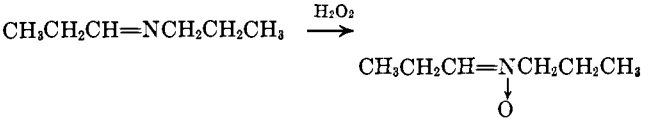
Thermal isomerizations of oxaziranes other than 3-phenyloxaziranes did not lead to nitrones but to various rearranged products, mainly amides (135).



Bicyclic oxaziranes behave similarly (31).

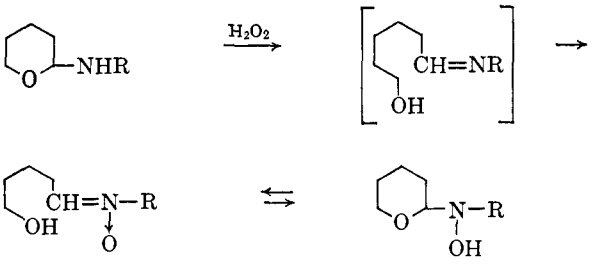


The following nitrones were claimed to be prepared by treating imines with 30% aqueous hydrogen peroxide at 5–10° in the presence of ethyl formate: α,α-pentamethylene-N-cyclohexylnitrone and the corresponding N-butylnitrone; α-methyl-N-cyclohexylnitrone and the corresponding α-ethylnitrone; and α-ethyl-N-propylnitrone (194, 198).



However, this claimed nitrone synthesis is quite similar to the synthesis of oxazirane derivatives, which also consists of treating imines with hydrogen peroxide (31, 78, 79, 108, 135, 215). It seems likely that oxazirane derivatives rather than nitrones are formed for the following additional reasons. Aliphatic noncyclic nitrones are exceedingly sensitive towards water, since they are "instantly hydrolyzed" (80). Also, isomerization of the particular oxaziranes that would be formed in this claimed nitrone synthesis should lead not to nitrones but to amides (31, 78, 79, 108, 135, 215).

Similar arguments may be used against the reported nitrone formation in a related but more complex case cited below. The structure proof of the product of this reaction was based on the infrared spectrum. A strong

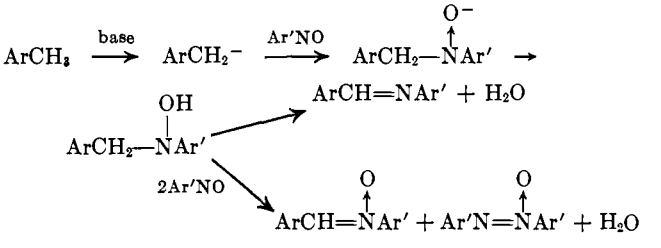


absorption band at 6.05 μ was ascribed to C=N stretching, and a medium strong band at 6.4 μ was ascribed to N→O stretching (198).

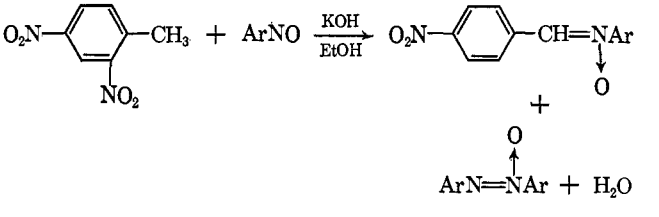
### E. FROM AROMATIC NITROSO COMPOUNDS

#### *1. With Compounds Containing Active Methyl Groups*

Aromatic nitroso compounds react readily with compounds such as 2,4,6-trinitrotoluene or 9-methylacridine, containing a sufficiently activated methyl group. The reaction products often are a mixture of anils and nitrones (71, 152, 172, 179, 180, 207). The reaction is normally catalyzed by small amounts of base such as pyridine, piperidine, and sodium carbonate. The following sequence of steps has been proposed for the reaction.



The methyl groups in mononitrotoluenes apparently were not sufficiently acidic, since a reaction was not observed with either nitrosobenzene or *p*-nitroso-N,N-dimethylaniline (217). On the other hand, 2,4-dinitrotoluene when refluxed with *p*-nitrosotoluene in ethanol, with piperidine as the catalyst, yielded the anil as the sole product, but the use of potassium hydroxide as the catalyst produced the nitrone exclusively (218). The



same nitro compound and nitrosobenzene yielded mainly the anil (16), but with *p*-nitroso-N,N-dimethylaniline the anil–nitrone ratio was found to be about 1:1 after 1 hr. reaction time at 80°, and about 50:1 after 5 hr. (55); the same nitroso compound and 3,4-dinitrotoluene yielded the anil only (55), but 2,4,6-trinitrotol-

uene yielded the nitrone, and anil formation could not be detected (219).

Lepidine N-oxide (63), quinaldine N-oxide (62, 66), and 2- and 4-picoline (71, 152) also yielded nitrones when treated with aromatic nitroso compounds. 9-Methylacridine formed the nitrone upon treatment with nitrosobenzene in 85% yield (56, 77), with *p*-nitrosophenol in 60% yield (74), and with *p*-nitrosotoluene in 33% yield (74). With *p*-nitroso-N,N-dimethylaniline the anil–nitrone product ratio was about 1:1, and with *p*-nitroso-N,N-diethylaniline about 5:1 (56, 179). 2,9-Dimethylacridine and *p*-nitroso-N,N-dimethylaniline yielded α-(2-methyl-9-acridyl)-N-(*p*-dimethylaminophenyl)nitrone under the influence of ultraviolet light (172). Other acridine derivatives yielding a mixture of nitrones and anils were 9-methyl-1,2-benzacridine (172) and 7-methyl-4,5-dihydroindeno[1,7-*bc*]acridine (195).

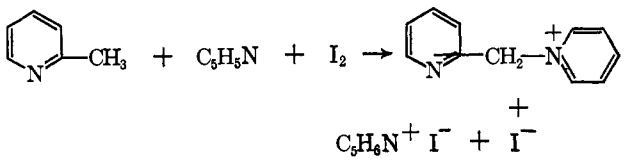
Last, 2-methylchromone (200), 2-methylthiochromone (203), and 5-methyl-1,2-dithiol-3-thione derivatives also yielded nitrones (182).

### 2. *With Compounds Containing Active Methylene Groups*

#### a. Pyridinium and Related Salts

Upon treatment with an aromatic nitroso compound, in the presence of base, pyridinium salts will give high yields of nitrones uncontaminated by anils. This reaction, known as the Kroehnke reaction, was reviewed by Kroehnke in 1953 and in 1963 (145). Quinolinium or isoquinolinium salts have been employed occasionally (142, 148, 149).

Pyridinium salts may be prepared by the King reaction or by the reaction between an appropriate halide and pyridine. The King reaction consists of the reaction between a compound containing an active methyl group with pyridine and iodine (131, 154).

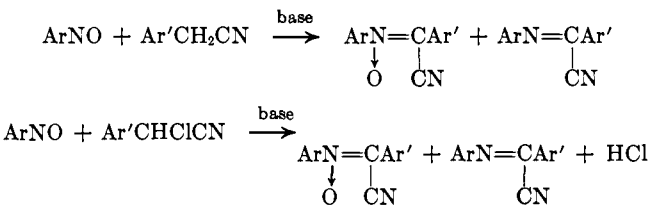


The King reaction is especially useful for preparing pyridinium salts of methyl-substituted heterocyclic aromatic compounds, α-methyl ketones (147), or dithioacetic acid (155). Thus nitrones have been prepared employing the King reaction followed by the Kroehnke reaction starting with 2- or 4-picoline (152, 205), 2-picoline 1-oxide (104), quinaldine (132, 154, 206, 207), lepidine (132, 154, 206, 207), quinaldine N-oxide (64), lepidine N-oxide (64), 4-methylcinnoline (50), 2,3-dimethylquinoxaline (112, 207), 1,2-dimethylbenzimidazole (163), 2-methylchromone (200), and methyl-substituted pyrimidines and pyrazines (190).

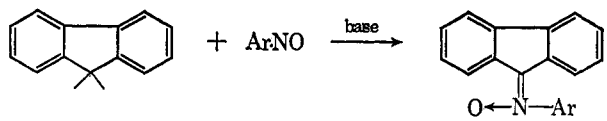
The following halides were employed to prepare nitrones *via* the pyridinium salts and the Kroehnke reactions: benzyl halides and over 30 substituted benzyl bromides (142, 144) and 2,6-disubstituted benzyl bromides (60), cinnamyl bromide (137, 146), 9-bromofluorene (122, 123, 141), 2-chloroacetylfuran (133), phenacyl bromide (136), chlorokojic acid methyl ether (164), 1,6-dibromo-2,4-hexadiene (127), γ-bromocrotonaldehyde diacetate (199), various halosteroids (171, 184), α-halocyclobutanones, and other alicyclic α-halo ketones (27).

#### b. Other Compounds

Aromatic nitroso compounds have been reported to react smoothly with benzyl derivatives such as benzyl chloride (16), α-chloro-α-cyanotoluene (17), (*p*-cyclohexylphenyl)acetonitrile (49), or benzyl cyanide (12, 16, 138). Weak bases and low reaction temperatures favored nitrone formation, while strong bases and high reaction temperatures favored anil formation (12).



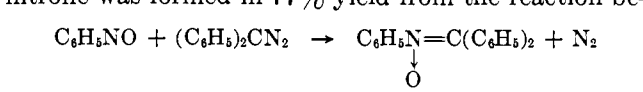
Fluorene (28) and similar compounds (65b, 151, 175, 201) yielded nitrones readily when treated with an aromatic nitroso compound in presence of base.



Nitrones were obtained from 1,3-diketones (202). In many of these reactions, however, the chief product was an azoxybenzene derivative (28). Its mode of formation is not clear.

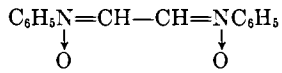
### 3. *Diazo Compounds*

This reaction, first described in the last century (65a, 212), involves the introduction of a diazo compound into a solution of an aromatic nitroso compound, causing a vigorous reaction to take place. α,α,N-Triphenylnitrone was formed in 77% yield from the reaction between nitrosobenzene and diphenyldiazomethane (123, 216), while nitrosobenzene and phenyldiazomethane yielded α,N-diphenylnitrone (216). Similarly, 9-diazofluorene yielded 88% of a nitrone with nitrosoben-



zene (123). Nitrones were also formed when *p*-nitrosotoluene or *p*-nitroso-N,N-dimethylaniline were employed, but N-nitrosoaniline derivatives did not react (216).

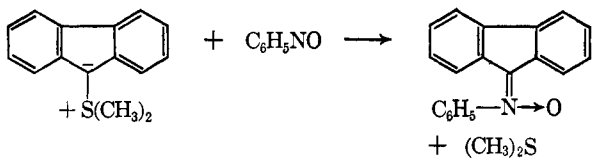
Diazomethane and nitrosobenzene did not form N-phenylnitrone, but the dinitrone of glyoxal (212, 216).



The same dinitrone was also formed in the reaction between formaldehyde and N-phenylhydroxylamine (233), and the reaction between N-phenylhydroxylamine and dibromomethane dissolved in a mixture of pyridine and ethanol (65a, 232).

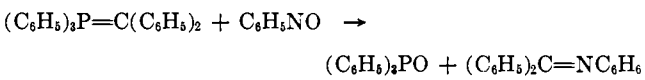
### *4. Sulfur Ylides*

Nitrosobenzene when treated with 9-dimethylsulfonium fluorenylide yields a nitrone quantitatively (122).



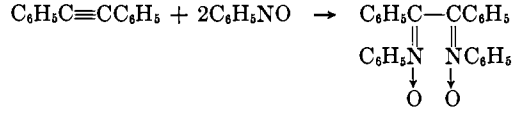
The reaction has been shown to be a general one (123). Its usefulness is limited by the availability of appropriate sulfur ylides. The reaction appears to be explained best by the formation of an un-isolable oxazirane as a very short-lived intermediate which rapidly isomerizes to a nitrone.

Phosphorus ylides and nitrosobenzene do not lead to nitrones but to anils (123, 204).

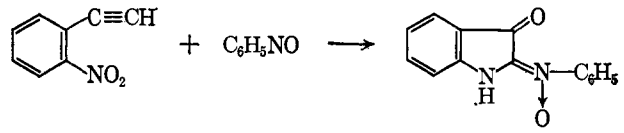


### *5. Alkenes and Alkynes*

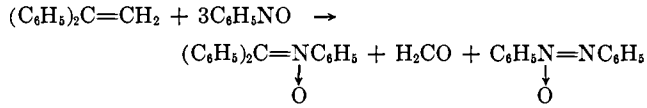
Diphenylacetylene reacted readily with 2 moles of nitrosobenzene to form a dinitrone which upon hydrolysis yielded benzil (4–6). The reaction does not appear to be general, since a dinitrone was not obtained from the reaction between acetylene and nitrosobenzene (4).



Phenylpropiolic acid and 2 moles of nitrosobenzene gave two interconvertible isomeric products, but no rigorous structural proof was given for these products (6, 7). Nitrosobenzene and *o*-nitrophenylacetylene yielded a nitrone (7, 8) of an unexpected structure.

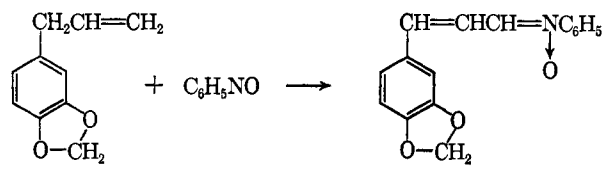


Styrene and nitrosobenzene were reported to form $\alpha$,N-diphenylnitrone (110, 121), while 1,1-diphenylethylene yields $\alpha,\alpha$,N-triphenylnitrone with nitrosobenzene (111). It is not clear at the present time what happened to the terminal methylene group, but presumably it was converted to formaldehyde since the reaction products contained large amounts of azoxybenzene (106a). The structure of the resulting ni-

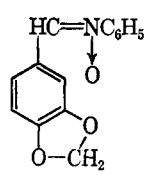


trones in these reactions was established unambiguously.

Safrole upon reaction with nitrosobenzene formed a fully conjugated nitrone (2, 11).



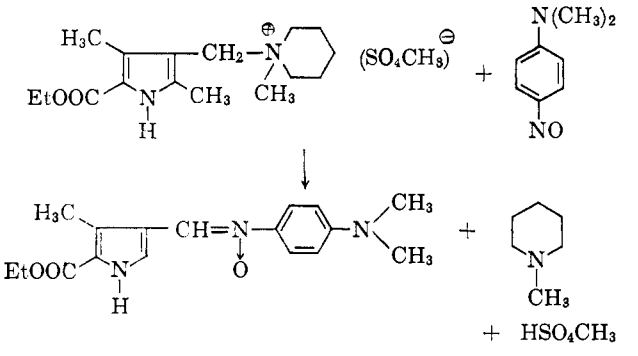
Hydrolysis of this nitrone yielded 3,4-methylenedioxycinnamaldehyde, indicating that the carbon skeleton of safrole had remained intact. Isosafrole and nitrosobenzene, on the other hand, reacted very slowly but ultimately yielded a nitrone which upon hydrolysis formed 3,4-methylenedioxybenzaldehyde, indicating the formation of a nitrone by cleavage of the side chain of isosafrole at the site of the double bond (3).



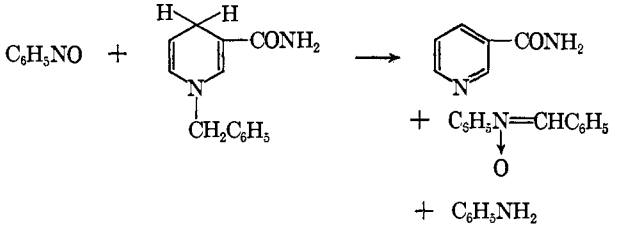
Many simple alkenes such as propylene, 1-butene, *cis*- or *trans*-2-butene, isobutene, 1-octene, 4-octene, cyclopentene, and cyclohexane reacted readily with nitrosobenzene, but thus far nitrones have not been isolated among the reaction products (106a). The reaction between aromatic nitroso compounds and alkenes or alkynes requires further investigation before it may be employed as a general synthesis of nitrones.

### F. MISCELLANEOUS

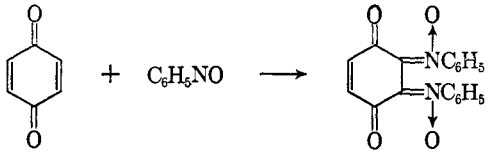
Quaternary Mannich bases when treated with an aromatic nitroso compound yielded nitrones. This reaction, although employed very seldom, was shown to be general (109, 177, 221, 226).



Aromatic nitroso compounds were shown to yield nitrones upon treatment with 1-benzyl-1,4-dihydronicotinamide (72).



Quinones yielded dinitrones upon treatment with nitrosobenzene (102), while various hydroxylamine derivatives were found to disproportionate in carbon



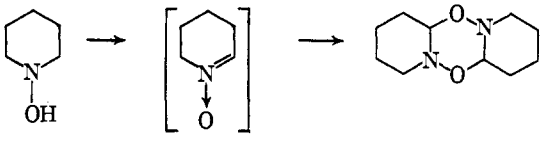
disulfide solution into nitrone and amine (186). The reaction of 1,1-dinitroethane with its salts reportedly led to the formation of $\alpha$-methyl-$\alpha$-nitro-N-(1,1-dinitroethyl)nitrone (21).

## V. REACTIONS

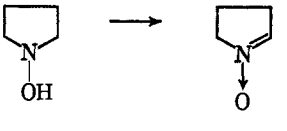
### A. DIMERIZATION

#### 1. Cyclic Dimers

The oxidation of N-hydroxypiperidine did not give the expected cyclic nitrone but a product to which a dimeric structure was assigned (41, 222).



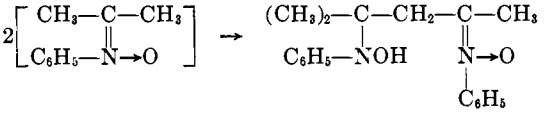
The corresponding five-membered cyclic nitrones were found to be monomeric (30).



2-Phenyl-N-hydroxypiperidine also yielded a cyclic dimer upon oxidation, but 3,4-dihydroisoquinoline N-oxide was monomeric (223).

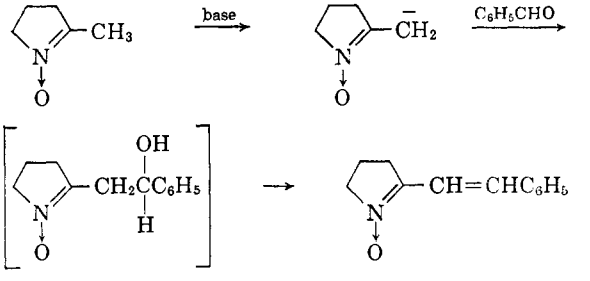
#### 2. Noncyclic Dimers

Although monomeric aliphatic nitrones have been reported (80), dimerization appeared to occur very readily. Acetone and N-phenylhydroxylamine, for instance, yielded an aldol-type dimer (41), and *n*-butyraldehyde and N-phenylhydroxylamine yielded a dimer of the same type. Dimerization of $\Delta^1$-pyrroline N-oxides to 2-(1′-hydroxypyrrolidin-2-yl)-$\Delta^1$-pyrroline N-oxide derivatives was achieved in liquid ammonia employing sodamide as the catalyst (44).

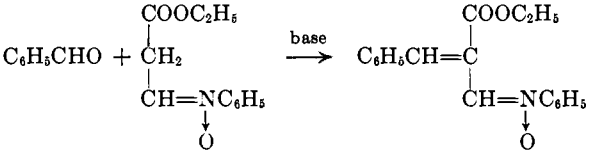


### B. ALDOL CONDENSATIONS

The nitrone group bears a marked resemblance to the carbonyl group in facilitating the removal of a proton from an adjacent carbon under basic conditions (42, 45). Thus, 2-methyl-$\Delta^1$-pyrroline N-oxide when treated with benzaldehyde in the presence of base yielded 2-styryl-$\Delta^1$-pyrroline N-oxide (30). Similarly, benzaldehyde and $\alpha$-methyl-N-phenylnitrone in the



presence of base yielded $\alpha$-styryl-N-phenylnitrone (233). This reaction was also observed employing *p*-nitro- or *p*-chlorobenzaldehyde. Another example is given below (233).



### C. ADDITION REACTIONS

#### 1. Cycloaddition Reactions

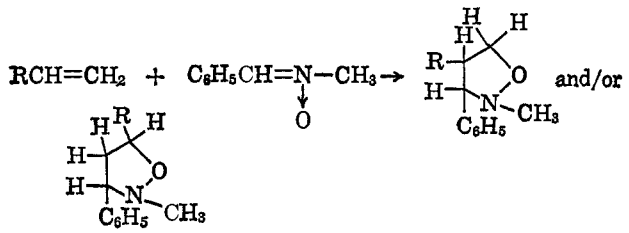
##### a. With Unconjugated Alkenes

The 1,3-cycloaddition of a nitrone to only two unconjugated alkenes, 1-heptene and safrole, have been reported (116). The reactions yielded 92 to 97% of an adduct or adducts (Table VII). The structure and stereochemistry of the isoxazolidine derivatives formed were not reported.

TABLE VII
1,3-CYCLOADDITION REACTIONS OF UNCONJUGATED ALKENES TO NITRONES

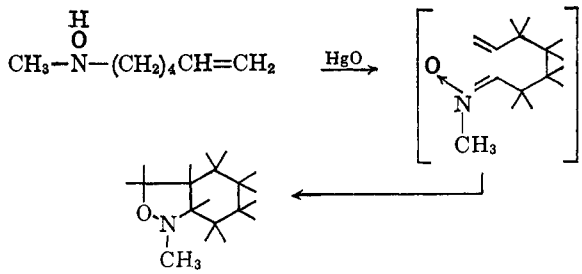
| Alkene | Nitrone | Adduct yield, % | B.p. (mm.) or m.p., °C. | Ref. | Remarks |
|---|---|---|---|---|---|
| 1-Heptene | α-Phenyl-N-methylnitrone | 92 | *a* | 116 | *b* |
| Safrole | α-Phenyl-N-methylnitrone | 97 | *a* | 116 | *b* |
| Cyclopentene | α-Phenyl-N-methylnitrone | 90 | *a* | 116 | *c* |
| Cyclohexene | α-Phenyl-N-methylnitrone | 78 | *a* | 116 | *c* |
| Cyclohexene | 4,5,5-Trimethyl-Δ¹-pyrroline N-oxide | *a* | 118–120 (16) | 39, 40 | *c* |
| Cyclohexene | N-Ethylnitrone | *a* | *a* | 39 | *d* |
| Cyclohexene | 2,3,4,5-Tetrahydropyridine N-oxide | *a* | 124 (13) | 39, 40 | *c* |
| Norbornene | α-Phenyl-N-methylnitrone | 92 | *a* | 110, 116 | *b* |
| Norbornene | α,N-Diphenylnitrone | 99 | *a* | 116 | *c* |
| Norbornene | 3,4-Dihydroisoquinoline N-oxide | 100 | *a* | 116 | *c* |
| 2-Cyano-5-norobornene | α-Phenyl-N-methylnitrone | 50 | *a* | 100 | *b* |
| 5-Norbornene-2,3-dicarboxylate | α-Phenyl-N-methylnitrone | 30 | *a* | 100 | *b*, *e* |
| 2,3-Diaza-5-norbornene | α-Phenyl-N-methylnitrone | 88 | *a* | 100 | *b* |

[a] Not specified. [b] Structure of adduct not known or not reported. [c] Stereochemistry of adduct not known or not reported. [d] Nitrone generated *in situ*. [e] Which ester was employed not reported.



Unconjugated alkenes appear to react considerably slower than conjugated unsaturated systems. The relative rates of the 1,3-cycloaddition of α-phenyl-N-methylnitrone to $RCH{=}CH_2$ in toluene at 120° were reported to be 0.67 for R = "alkyl," 3.0 for R = $C_6H_5$, and 100 for R = $CO_2Et$ (117). The cycloaddition reactions appear to have second-order kinetics, first order in the nitrone and first order in the unsaturated system.

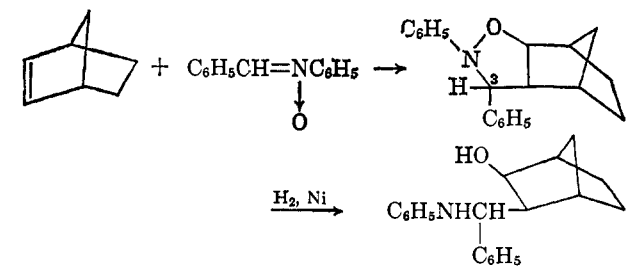
Intramolecular addition of the *in situ* generated nitrone group was also reported in the case of N-methyl-N-(5-hexenyl)hydroxylamine which upon treatment with mercuric oxide yielded an isoxazolidine derivative, presumably through a nitrone intermediate (160).



### b. With Unconjugated Cycloalkenes

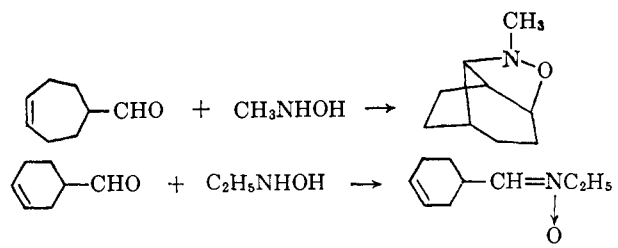
Cyclopentene, cyclohexene, norbornene, bicyclopentadiene, and other bicycloalkenes have been treated with a variety of nitrones, as summarized in Table VII.

Norbornene and α,N-diphenylnitrone yielded 99% of a mixture of two isomers, presumably epimeric at the 3-position. The isomers yielded identical β-amino



alcohols when treated with hydrogen and Raney nickel (116). The configurations of the cycloadducts of the reactions listed in Tables VII, VIII, IX, and X have not been reported for any cycloadduct for which the possibility of stereoisomerism exists.

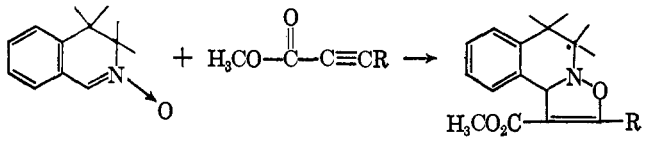
Intramolecular 1,3-cycloaddition has also been observed for cycloalkenes. When 4-cycloheptenecarboxaldehyde was treated with N-methylhydroxylamine, a single isoxazolidine derivative was obtained in 60% yield, but intramolecular addition was not observed with 3-cyclohexenecarboxaldehyde, since this yielded a nitrone instead (161).



### c. With Alkynes

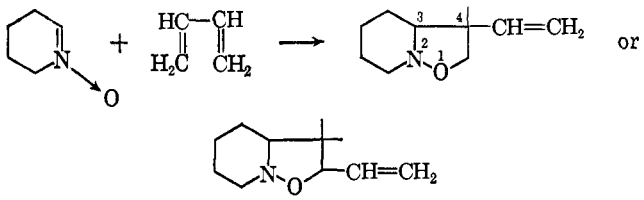
The addition of various substituted alkynes to 3,4-dihydroisoquinoline N-oxide has been described (115). For R = H, a 83% yield of the adduct was obtained at 20°, for R = $C_6H_5$, a 69% yield, but for R = $CO_2CH_3$,

further rearrangement of the formed adduct occurred *in situ* (115).

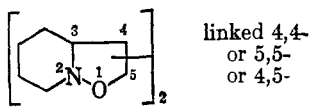


d. With Conjugated Alkenes and Dienes

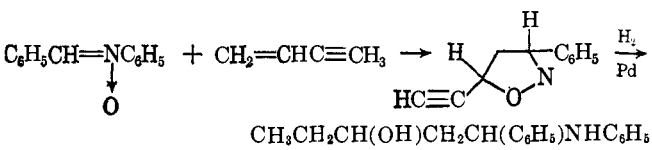
The conjugated diene, 1,3-butadiene, added to 2,3,-4,5-tetrahydropyridine N-oxide (or its dimer) in two stages to give first the 1:1 adduct which may be either of the two following structures.



Further reaction with a second mole of the N-oxide yielded a mixture of products (39, 40), which may be composed of structural isomers or diastereoisomers of the bisisoxazolidine derivatives. Similar adducts were obtained with isoprene and 2,3-dimethyl-1,3-butadiene (39, 40).

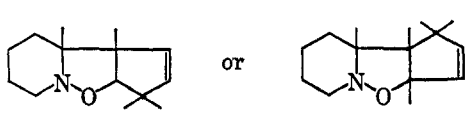


Vinyl acetylene and $\alpha$,N-diphenylnitrone yielded a 1:1 adduct (57). The presence of the unchanged triple bond was detected in the infrared spectrum of the cycloadduct. Hydrogenation of the isoxazolidine derivative over palladium–calcium carbonate catalyst yielded 1-

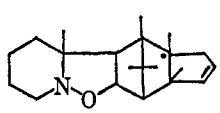


phenylamino-1-phenyl-3-hexanol. The same nitrone also added across the double bond of 1-penten-3-yne and 1-hexen-3-yne (57).

Cyclopentadiene gave a single 1:1 adduct with 2,3,-4,5-tetrahydropyridine N-oxide which was reported to be one of the following structures

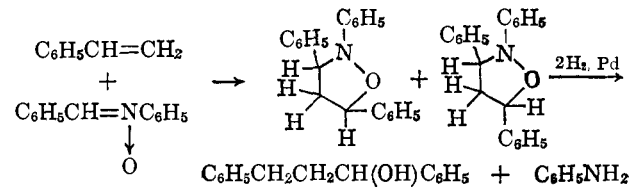


accompanied by the product from dicyclopentadiene (39, 40).



Cycloheptatriene and norbornadiene with $\alpha$-phenyl-N-methylnitrone gave cycloadducts, but the composition and structure were not reported (100).

Styrene and $\alpha$,N-diphenylnitrone yielded two isomeric adducts, presumably diastereoisomers. The products of the hydrogenolysis were found to be identical (100, 116).



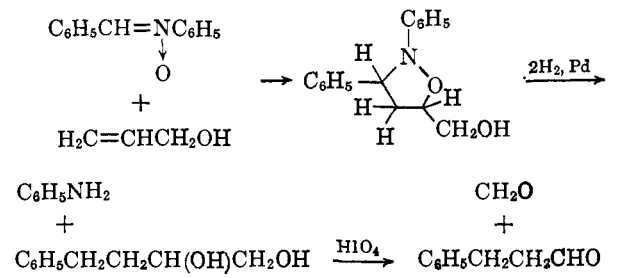
The rate of the reaction between a series of *para*-substituted styrene derivatives and $\alpha$-phenyl-N-methylnitrone was found to follow the Hammett equation, with a $\rho$-constant of +0.83 (117). The reaction between the same nitrone and 2-vinylpyridine was found to have an energy of activation of 18.3 kcal./mole and an entropy of activation of −29 e.u. (117).

The reactions between conjugated dienes and alkenes are summarized in Table VIII.

e. With Unsaturated Alcohols, Ethers, Nitriles, and Allylacetone

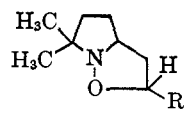
These reactions are summarized in Table IX.

The structure of the cycloadduct of the reaction between $\alpha$,N-diphenylnitrone and allyl alcohol was shown to be as indicated. Hydrogenolysis of the adduct yielded aniline and a glycol, which upon treatment with



$HIO_4$ yielded formaldehyde and 3-phenylpropionaldehyde (100). The configurations of carbons 3 and 5 of the cycloadduct were not reported.

Allyl alcohol and acrylonitrile were treated with 5,5-dimethyl-$\Delta^1$-pyrroline N-oxide; the adducts appear to have the following structure (70).



f. With Conjugated $\alpha,\beta$-Unsaturated Carbonyl Compounds

These reactions have been summarized in Table X.

TABLE VIII
1,3-CYCLOADDITION REACTIONS OF CONJUGATED ALKENES OR DIENES TO NITRONES

| Compound | Nitrone | Adduct yield, % | B.p. (mm.) or m.p., °C. | Ref. | Remarks |
|---|---|---|---|---|---|
| 1,3-Butadiene | 2,3,4,5-Tetrahydropyridine N-oxide | *a* | | 39, 40 | *d, f* |
| Isoprene | 2,3,4,5-Tetrahydropyridine N-oxide | *a* | 96–110 (20) | 39, 40 | *b, e* |
| Isoprene | 4,5,5-Trimethyl-$\Delta^1$-pyrroline N-oxide | *a* | 112–120 | 40 | *b, d* |
| 2,3-Dimethyl-1,3-butadiene | N-Methylnitrone | *a* | 60–70 (17) | 39, 40 | *b, g* |
| 2,3-Dimethyl-1,3-butadiene | N-Ethylnitrone | *a* | 70–72 (15) | 40 | *b, d, g* |
| | | *a* | 110–120 (17) | 40 | *c, d, g* |
| 2,3-Dimethyl-1,3-butadiene | 2,3,4,5-Tetrahydropyridine N-oxide | *a* | 98–97 (17) | 39, 40 | *b, e* |
| | | *a* | 120–122 | 40 | *c, d* |
| 1,4-Diphenyl-1,3-butadiene | 2,3,4,5-Tetrahydropyridine N-oxide | *a* | 185–187 | 40 | *c, d* |
| 2,3-Dimethyl-1,3-butadiene | 4,5,5-Trimethyl-$\Delta^1$-pyrroline N-oxide | *a* | 106–108 (17) | 39, 40 | *b, d* |
| 2,3-Dimethyl-1,3-butadiene | 3,4-Dihydroisoquinoline N-oxide | *a* | *a* | 39 | *b, e* |
| Vinylacetylene | $\alpha$,N-Diphenylnitrone | 12 | 103–104 | 57 | *e* |
| 1-Penten-3-yne | $\alpha$,N-Diphenylnitrone | 50 | 109–110 | 57 | *e* |
| 1-Hexen-3-yne | $\alpha$,N-Diphenylnitrone | 50 | 91–92 | 57 | *e* |
| *trans,trans*-Diethyl muconate | 4,5,5-Trimethyl-$\Delta^1$-pyrroline N-oxide | *a* | *a* | 40 | *c, d* |
| Cyclopentadiene | 2,3,4,5-Tetrahydropyridine N-oxide | 62 | *a* | 39, 116 | *b, e* |
| Cyclopentadiene | 4,5,5-Trimethyl-$\Delta^1$-pyrroline N-oxide | *a* | 120–126 (23) | 39, 40 | *b, e* |
| Cyclopentadiene | 3,4-Dihydroisoquinoline N-oxide | *a* | 98 | 40 | *b, d* |
| Cycloheptatriene | $\alpha$-Phenyl-N-methylnitrone | 83 | *a* | 100 | *d, h* |
| Norbornadiene | $\alpha$-Phenyl-N-methylnitrone | 98 | *a* | 100 | *d, h* |
| Styrene | $\alpha$-Propyl-N-phenylnitrone | 98 | *a* | 100 | *e, g* |
| Styrene | $\alpha$-Phenyl-N-methylnitrone | 95 | *a* | 100 | *e* |
| Styrene | $\alpha$,N-Diphenylnitrone | 100 | *a* | 100 | *e* |
| *p*-Methoxystyrene | $\alpha$-Phenyl-N-methylnitrone | *a* | *a* | 117 | *d* |
| *p*-Methylstyrene | $\alpha$-Phenyl-N-methylnitrone | *a* | *a* | 117 | *d* |
| *p*-Chlorostyrene | $\alpha$-Phenyl-N-methylnitrone | *a* | *a* | 117 | *d* |
| *p*-Nitrostyrene | $\alpha$-Phenyl-N-methylnitrone | *a* | *a* | 117 | *d* |
| $\alpha$-Methylstyrene | $\alpha$-Phenyl-N-methylnitrone | 85 | *a* | 100 | *d* |
| $\alpha$-Methylstyrene | $\alpha$,N-Diphenylnitrone | 71 | *a* | 116 | *d* |
| 2-Vinylpyridine | $\alpha$-Phenyl-N-methylnitrone | *a* | *a* | 117 | *d* |
| Indene | $\alpha$-Phenyl-N-methylnitrone | 92 | *a* | 100 | *d* |
| 1,2-Dihydronaphthalene | $\alpha$-Phenyl-N-methylnitrone | 97 | *a* | 100 | *d* |
| 1,1-Diphenylethylene | $\alpha$-Phenyl-N-methylnitrone | 29 | *a* | 100 | *d* |

[a] Not specified. [b] 1:1 adduct. [c] 1:2 adduct. [d] Structure of adduct not known or not reported. [e] Stereochemistry of adduct not known or not reported. [f] Mixture of adducts. [g] Nitrone generated *in situ*. [h] Composition of adduct not reported.

TABLE IX
1,3-CYCLOADDITION REACTIONS OF MISCELLANEOUS UNSATURATED SYSTEMS TO NITRONES

| Compound | Nitrone | Adduct yield, % | B.p. (mm.) or m.p., °C. | Ref. | Remarks |
|---|---|---|---|---|---|
| Dihydropyran | $\alpha$-Phenyl-N-methylnitrone | *a* | *a* | 116 | *b* |
| Allyl alcohol | $\alpha$-Phenyl-N-methylnitrone | 100 | *a* | 100, 116 | *c* |
| Allyl alcohol | 5,5-Dimethyl-$\Delta^1$-pyrroline N-oxide | 84 | 100–103 (3–4) | 69, 70 | *c* |
| Acrylonitrile | $\alpha$-Phenyl-N-methylnitrone | 91 | *a* | 100 | *b* |
| Acrylonitrile | 5,5-Dimethyl-$\Delta^1$-pyrroline N-oxide | 100 | 57–58 | 70 | *c* |
| Crotononitrile | 5,5-Dimethyl-$\Delta^1$-pyrroline N-oxide | *a* | 85 | 39, 40 | *b* |
| Allylacetone | 5,5-Dimethyl-$\Delta^1$-pyrroline N-oxide | *a* | 86–89 | 39, 40 | *b* |
| Diethyl azodicarboxylate | $\alpha,\alpha$,N-Triphenylnitrone | *d* | ... | 216 | *d* |
| Allyl isothiocyanate | $\alpha$-Phenyl-N-methylnitrone | 53 | *a* | 100 | *b, e* |

[a] Not specified. [b] Structure of adduct not known or not reported. [c] Stereochemistry of adduct not known or not reported. [d] No reaction occurred. [e] Addition presumably across the C=C bond.

In general, acrylates react faster with nitrones than methacrylates, and methacrylates faster than "crotonates," presumably the *trans*-crotonates. For the reaction between the ethyl esters of these acids and $\alpha$-phenyl-N-methylnitrone, the relative reaction rates at 120° in toluene were 100 for the acrylate, 30 for the methacrylate, and 8.4 for the "crotonate" (117). The reaction between the same nitrone and methyl methacrylate had an energy of activation of 15.7 kcal./mole and an entropy of activation of −32 e.u. (117).

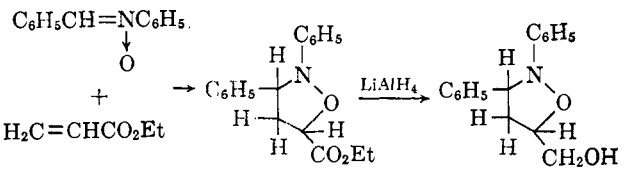
The cycloadduct of $\alpha$,N-diphenylnitrone and ethyl acrylate upon treatment with lithium aluminum hydride yielded a compound which was identical with the cycloadduct (of known structure) obtained from the

TABLE X
1,3-CYCLOADDITION REACTIONS OF α,β-UNSATURATED CARBONYL COMPOUNDS TO NITRONES

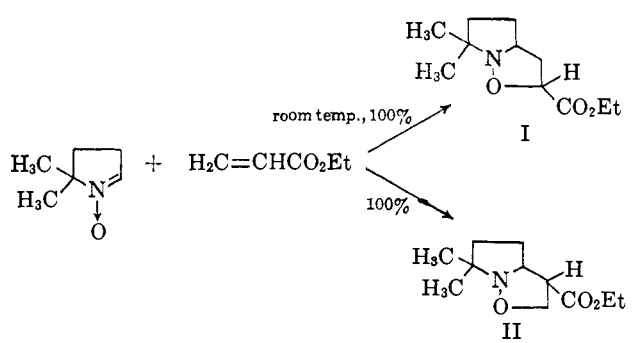
| Compound | Nitrone | Adduct yield, % | B.p. (mm.) or m.p., °C. | Ref. | Remark |
|---|---|---|---|---|---|
| Ethyl acrylate | α-Phenyl-N-methylnitrone | 99 | *a* | 100, 116, 117 | *c* |
| Ethyl acrylate | 3,3,5,5-Tetramethyl-Δ¹-pyrroline N-oxide | 60 | 100–110 (2–3) | 70 | *b* |
| Ethyl acrylate | 2,4,4-Trimethyl-Δ¹-pyrroline N-oxide | 65 | *a* | 70 | *b* |
| Ethyl acrylate | 5,5-Dimethyl-Δ¹-pyrroline N-oxide | 100 | 110–120 (1) | 70 | *c, d* |
| Ethyl acrylate | 5,5-Dimethyl-Δ¹-pyrroline N-oxide | 98 | 105–110 (0.5) | 70 | *c, d* |
| Methyl methacrylate | α-Methyl-N-ethylnitrone | 75 | *a* | 68 | *d* |
| Methyl methacrylate | α-Phenyl-N-methylnitrone | 97 | *a* | 117 | *c* |
| Methyl methacrylate | α-Propyl-N-cyclohexylnitrone | 95 | *a* | 110, 116 | *c* |
| Ethyl crotonate | α-Phenyl-N-methylnitrone | 95 | *a* | 110, 117 | *b, e* |
| Ethyl crotonate | α-Phenyl-N-(*p*-methoxyphenyl)nitrone | *a* | *a* | 117 | *b, e* |
| Ethyl crotonate | α-Phenyl-N-(*p*-chlorophenyl)nitrone | *a* | *a* | 117 | *b, e* |
| Ethyl crotonate | α,N-Diphenylnitrone | *a* | *a* | 117 | *b, e* |
| Ethyl crotonate | α-Benzoyl-N-phenylnitrone | *a* | *a* | 117 | *b, e* |
| Dimethyl fumarate | 3,4-Dihydroisoquinoline N-oxide | 100 | 89–90 | 117 | |
| Dimethyl fumarate | α-Phenyl-N-methylnitrone | *a* | *a* | 117 | *c* |
| Dimethyl maleate | 3,4-Dihydroisoquinoline N-oxide | 95 | 95–96 | 117 | |
| Dimethyl maleate | α-phenyl-N-methylnitrone | *a* | *a* | 100–117 | *c* |
| Carvone | α-Phenyl-N-methylnitrone | 85 | *a* | 100 | *b* |
| Eucarvone | α-Phenyl-N-methylnitrone | 68 | *a* | 100 | *b* |
| Mesityl oxide | α-Phenyl-N-methylnitrone | 53 | *a* | 100 | *b* |

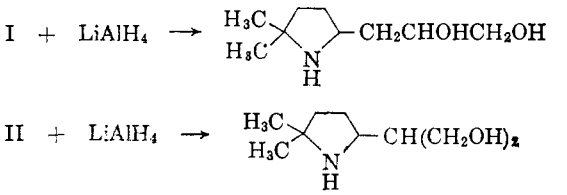
[a] Not specified. [b] Structure of adduct not known or not reported. [c] Stereochemistry of adduct not known or not reported. [d] Structural isomers. [e] Geometry of ethyl "crotonate" not reported.

same nitrone and allyl alcohol (116). The configuration of the adducts on carbon 3 and 5 were not reported.

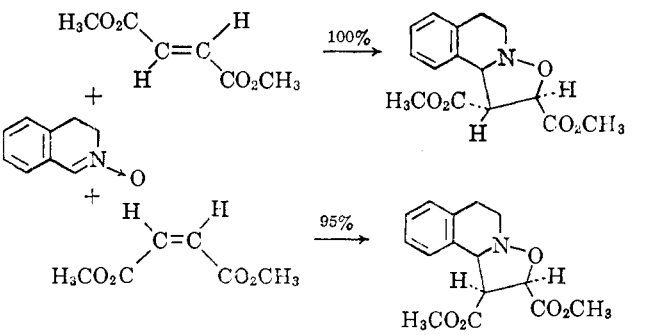


The direction of cycloaddition of nitrones may well be subject to kinetic and thermodynamic control. For instance, the addition of ethyl acrylate to 5,5-dimethyl-Δ¹-pyrroline N-oxide at room temperature yields 100% of one structural isomer, but at 100° a 98% yield of the other structural isomer was obtained, as shown below (70). Prolonged treatment of the adducts with lithium aluminum hydride provided diols whose structures were proved by synthesis (70).





Fumarates were reported to react faster with nitrones than maleates (117). With 3,4-dihydroisoquinoline N-oxide and dimethyl fumarate, an adduct was formed which was reported to be the geometric isomer of the cycloadduct formed from the same nitrone and dimethyl maleate (117). This would seem to indicate that 1,3-cycloaddition reactions are stereospecific *cis* additions as are the similar thermal 1,4-cycloaddition reactions such as the Diels–Alder reaction. Proof of the configurations of the adducts was not reported, however (117).

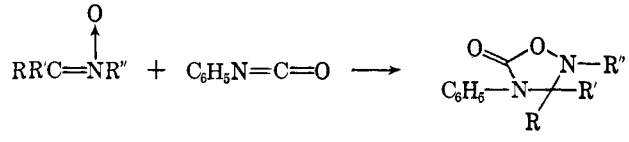


α-Acylnitrones were reported to be especially reactive. The reaction between α-benzoyl-N-phenylnitrone and ethyl "crotonate" in toluene at 100° was 110

times faster than the reaction between α,N-diphenylnitrone and the same ester (117).

### g. With Isocyanates

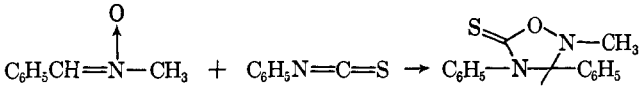
The cycloaddition of phenyl isocyanate to nitrones was first reported in 1894 (20). α,α,N-Triphenylnitrone yielded 90% of the cycloadduct (216), and a 94% yield was reported for the reaction between α-



phenyl-N-methylnitrone and phenyl isocyanate (100). The latter compound and α-styryl-N-phenylnitrone yielded 89% of 2,4-diphenyl-3-styryl-1,2,4-oxadiazolin-5-one (233).

Cyclic nitrones such as Δ¹-pyrrolidine N-oxide (225) or 3,4-dihydroisoquinoline N-oxide (116) also added phenyl isocyanate readily in quantitative yield, but no reaction occurred when dimeric nitrones such as 2,3,4,5-tetrahydropyridine N-oxide were employed (222).

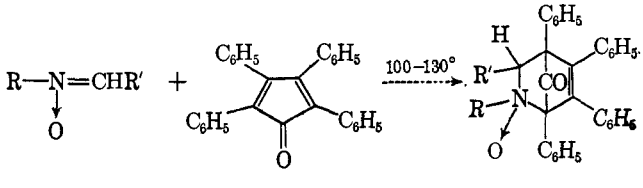
Phenyl isothiocyanate appeared to add to α-phenyl-N-methylnitrone, probably in the following fashion (116).



Reactions between nitrones and other isocyanates have not been reported.

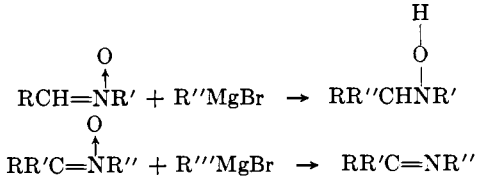
### h. 1,4-Cycloadditions

Tetraphenylcyclopentadienone was the only compound reported to yield with nitrones a 1,4-cycloadduct in respect to the conjugated diene. The following nitrones were employed: 2,3,4,5-tetrahydropyridine N-oxide, 4,5,5-trimethyl-Δ¹-pyrroline N-oxide, α-phenyl-N-benzylnitrone, α,N-diphenylnitrone, α-(*p*-methoxyphenyl)-N-phenylnitrone, and α-(*m*-nitrophenyl)-N-phenylnitrone (39, 40).

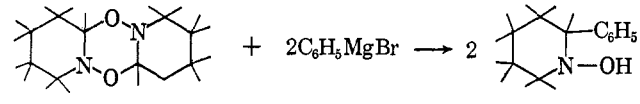


### 2. *Addition of Grignard Reagents*

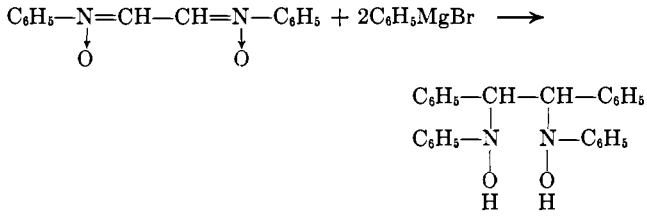
Grignard reagents were added to aldonitrones in a 1,3-fashion, but the reaction with ketonitrones led to imines (73, 233).



α,N-Diphenylnitrone reacted with phenylmagnesium bromide or ethylmagnesium iodide to form the substituted hydroxylamine (10). Phenylmagnesium bromide also was added to α-phenyl-N-benzylnitrone (10) or Δ¹-pyrroline N-oxide (225), yielding 83–90% of the hydroxylamine derivatives. An 89% yield of 1-hydroxy-2-ethyl-5,5-dimethylpyrrolidine was obtained from the reaction between ethylmagnesium bromide and 5,5-dimethyl-Δ¹-pyrroline N-oxide (30). Dimeric nitrones, which did not react with lithium aluminum hydride, sulfur dioxide, or phenyl isocyanate, readily added phenylmagnesium bromide in up to 93% yield (222, 223).

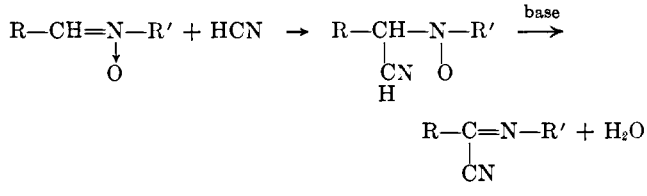


Dinitrones added 2 moles of the Grignard reagent (4).

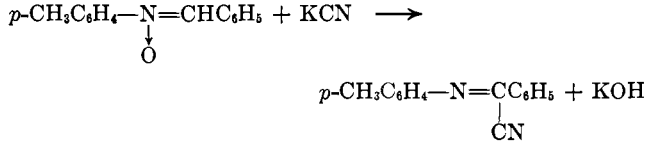


### 3. *Addition of Hydrogen Cyanide*

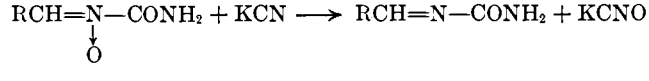
Nitrones formed a 1,3-adduct with hydrogen cyanide. In presence of base the adduct readily lost water to yield a cyanoimine.



Hydrogen cyanide and Δ¹-pyrroline N-oxide yielded 78% of 1-hydroxy-2-cyanopyrrolidine (30). α-Phenyl-N-*p*-tolylnitrone when treated with potassium cyanide in methanol formed the cyanoanil in good yields, while the intermediate hydroxylamine could not be isolated (26).



α,N-Diphenylnitrones containing nitro substituents behaved similarly (22), as was the case for a variety of α-keto-N-arylnitrones (140), but nitrones derived from hydroxyurea behaved abnormally (23, 24).



Cyanated anils may be obtained in good yields without isolating the intermediate nitrone. Thus, by treating an aromatic nitroso compound with a compound containing a suitably activated methylene group in the presence of cyanide ions, a cyanoanil was formed (152).

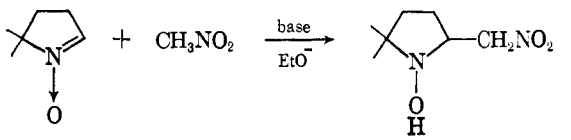
$$C_6H_5CH_2Br + C_6H_5NO + Na^+CN^- \longrightarrow C_6H_5C(CN)=NC_6H_5 + NaBr$$

Pyridinium salts (170) or $\alpha$-nitrotoluene may be employed in place of benzyl bromide (156).

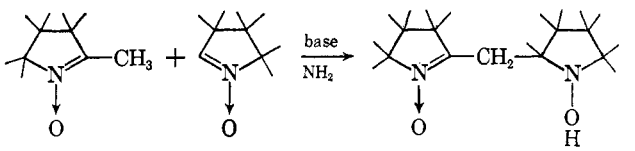
$$C_6H_5CH_2NO_2 + C_6H_5NO + NaCN \rightarrow C_6H_5C(CN)=NC_6H_5 + NaNO_2$$

*4. Miscellaneous Additions*

Good yields of $\beta$-nitrohydroxylamines have been obtained by treating $\Delta^1$-pyrroline N-oxides with nitroalkanes in presence of a base (30). In a similar fashion, 2-methyl-$\Delta^1$-pyrroline N-oxide derivatives added



to pyrroline N-oxide derivatives unsubstituted in the 2-position (43). Malonic ester also added readily to



nitrones in presence of base (233).

Dimethylsulfate alkylated the nitrone oxygen (75).

$$(CH_3)_2SO_4 + C_6H_5CH=N(\downarrow O)-CH_3 \longrightarrow [C_6H_5CH=N^+(OCH_3)-CH_3]\,[CH_3SO_4^-]$$

D. REARRANGEMENTS

*1. Isomerization to the Amide*

Aldonitrones rearranged to the isomeric amides by treatment with a variety of reagents, *e.g.*, phosphorus pentachloride, phosphorus oxychloride, thionyl chloride, sulfur dioxide, acetic anhydride, acetyl chloride, and solutions of base in ethanol (35, 80, 217–219, 229, 230). This rearrangement was reviewed in 1957 (150). Phosphorus trichloride, phosphorus oxychloride, and acetic anhydride were found to be the most effective catalysts for the rearrangement (230), although phosphorus trichloride occasionally may deoxygenate the nitrone. No marked configurational influence appeared to exist in the rearrangement of nitrones in contrast to the classical Beckmann rearrangement (230), to which this isomerization has been compared (230) on occasion. High yields of the isomeric amides have been obtained. For instance, $\alpha$-benzoyl-N-phenylnitrone upon treatment with acetic anhydride for 10 min. yielded 88% of the isomeric amide (140).

$$C_6H_5COCH=N(\downarrow O)C_6H_5 \longrightarrow C_6H_5COCONHC_6H_5$$

*2. Isomerization to the Oxime O-Ether*

This isomerization may occur either under the influence of heat or of acid. Thus, by heating $\alpha,\alpha$-diphenyl-N-diphenylmethylnitrone to 160–200°, a quantitative yield of the O-ether was obtained (67). The rearrangement was found to be first order, with an

$$(C_6H_5)_2C=N(\downarrow O)-CH(C_6H_5)_2 \xrightarrow{\Delta} (C_6H_5)_2C=N-O-CH(C_6H_5)_2$$

energy of activation of 40 kcal./mole, and an entropy of activation of +13.6 e.u. (67). The thermal rearrangement, however, was not observed for $\alpha$,N-diphenylnitrone, $\alpha$-phenyl-N-benzylnitrone, $\alpha$-phenyl-N-diphenylmethylnitrone, or $\alpha$-phenyl-N-cinnamylnitrone (238). Treatment of $\alpha$-phenyl-N-diphenylmethylnitrone with 12% aqueous hydrochloric acid yielded the O-ether (165). In a few instances, the products of the acid-catalyzed hydrolysis of nitrones may be accounted for by assuming the formation of the O-ether as an intermediate product (94, 95, 238).

*3. Behrend Rearrangement*

Ketonitrones may rearrange to aldonitrones by the catalytic influence of base (67, 183, 213).

$$(C_6H_5)_2C=N(\downarrow O)-CH_2C_6H_5 \longrightarrow (C_6H_5)_2CH-N(\downarrow O)=CHC_6H_5$$

This rearrangement has also been observed in the synthesis of nitrones (165, 213).

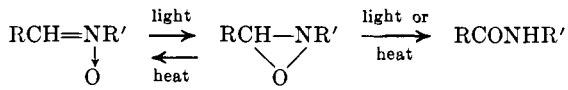
$$(C_6H_5)_2C=NOH + C_6H_5CH_2Br \longrightarrow (C_6H_5)_2CH-N(\downarrow O)=CHC_6H_5$$

*4. Miscellaneous Rearrangements*

The reaction of $\alpha$,N-diphenylnitrone with 98% sulfuric acid yielded 20% of *p*-hydroxyazobenzene. The suggested mechanism consisted of the initial hydrolysis to N-phenylhydroxylamine, followed by a disproportionation with formation of azoxybenzene and a Wallach transformation (93).

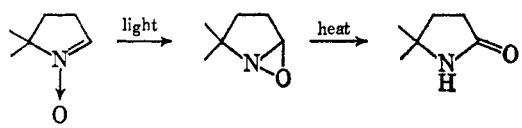
### E. PHOTOLYSIS

Irradiation of nitrones was found to lead to the isomeric oxaziranes (126, 210, 215), which were found to rearrange further thermally to the nitrones, or thermally and photochemically to amides.



Upon irradiation of α-(*p*-N,N-dimethylaminophenyl)-N-*m*-nitrophenylnitrone, the isomeric oxazirane was obtained, which upon standing for 24 hr. was reconverted to the nitrone in 60% yield, and N,N-dimethylaminobenzaldehyde in 40% yield (215). α-Phenyl-N-*t*-butylnitrone upon irradiation yielded 95% of the isomeric oxazirane (215). On the other hand, α,N-diphenylnitrone upon prolonged irradiation yielded first the isomeric oxazirane and then not only N-phenylbenzamide, but also benzaldehyde, nitrosobenzene, and benzanilide (210, 215). α-Phenyl-N-methylnitrone upon irradiation yielded first the oxazirane, which upon further irradiation yielded benzaldehyde and N-methylbenzamide (210).

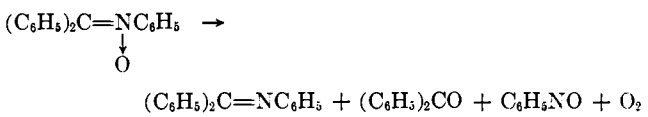
Another example consisted of the irradiation of 5,5-dimethyl-$\Delta^1$-pyrroline N-oxide forming the oxazirane which upon heating yielded an amide (31).



Oxaziranes, however, were not obtained by irradiation of 2-substituted $\Delta^1$-pyrroline N-oxides (31).

### F. PYROLYSIS

The pyrolysis of α,α,N-triphenylnitrone was reported by different workers to yield as the main product benzophenone anil with traces of nitrosobenzene and benzophenone (29, 111, 216). The pyrolysis was conducted at 200–300°.



Similarly, α,N-diphenylnitrone yielded the anil, benzaldehyde, azobenzene, nitrosobenzene, and N-phenylbenzamide (216). Detailed systematic pyrolytic studies on nitrones have not been reported.

### G. OZONOLYSIS

The ozonolysis of α,N-diphenylnitrone or α-phenyl-N-*t*-butylnitrone yielded benzaldehyde and nitrobenzene in the case of the former compound, and benzaldehyde and 2-methyl-2-nitropropane for the latter, 2 moles of ozone per mole of nitrone being absorbed. The absorption was rapid and complete, even at −78°. Throughout the ozonization the presence of a green or blue color indicated intermediate nitroso compounds. This was proved for α,N-diphenylnitrone where 25–40%

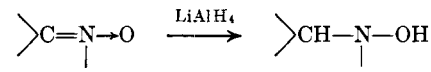
yields of nitrosobenzene were obtained by stopping the reaction after 1 mole of ozone was absorbed. The second mole of ozone oxidized the nitroso compound further to the nitro compound (187).

Oxaziranes were shown not to be intermediates in the ozonization of nitrones, since 2-*t*-butyl-3-phenyloxazirane was not attacked by ozone. The reaction was explained best by the nucleophilic attack of ozone on the carbon of the nitrone group.

α,α,N-Triphenylnitrone and ozone yielded benzophenone and nitrobenzene (216).

### H. REDUCTION

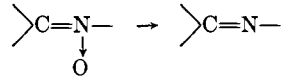
Nitrones upon treatment with either lithium aluminum hydride or sodium borohydride yielded the corresponding hydroxylamines, generally in high yields, presumably by a 1,3-addition mechanism.



α-Phenyl-N-methylnitrone or α,α-diphenyl-N-methyl nitrone for instance form the corresponding hydroxylamines in yields of 94 and 91%, respectively, when treated with lithium aluminum hydride (81–83). The same reagent and $\Delta^1$-pyrroline N-oxide formed 1-hydroxypyrrolidine (225), while α-phenyl-N-*t*-butylnitrone yielded 77% of N-benzyl-N-*t*-butylhydroxylamine (79). Dimeric nitrones, however, did not react with lithium aluminum hydride (222). Various $\Delta^1$-pyrroline N-oxide derivatives and potassium borohydride formed the corresponding 1-hydroxypyrrolidine derivatives (30, 41), but 4-keto-3,5,5-trimethyl-$\Delta^2$-pyrazoline 2-oxide yielded 4-hydroxy-3,5,5-trimethyl-$\Delta^2$-pyrazoline 2-oxide (85).

Treatment of α-hexyl-N-benzylnitrone with sodium and alcohol yielded N-heptyl-N-benzylamine (174).

Deoxygenation of nitrones



has been accomplished by zinc, tin or iron dust, phosphines, sulfur dioxide, sulfur, and catalytic hydrogenation. $\Delta^1$-Pyrroline N-oxide was converted to $\Delta^1$-pyrroline by zinc and acetic acid in 66% yield, by tin and hydrochloric acid in fair yield, and by sulfur dioxide in 15% yield (30); similar results were obtained for other cyclic nitrones (41, 134). α,α,N-Triphenylnitrone and iron powder (216), or α,N-diphenylnitrone and zinc in acetic acid (76) formed the corresponding anils. In the latter case no evidence was found indicating formation of N-phenyl-N-benzylhydroxylamine.

2,4,4-Trimethyl-$\Delta^1$-pyrroline N-oxide was smoothly deoxygenated by triphenylphosphine or triphenylarsine in yields of, respectively, 75 or 70% (1), but triphenylstibine or triphenylbismuthine gave extensive decomposition products. $\alpha$,N-Diphenylnitrone (173) and other nitrones (113) were also readily deoxygenated by triphenylphosphine. Phosphorus trichloride or phosphorus oxychloride often caused rearrangement of the nitrone besides deoxygenation (9, 22, 80, 230) which was also found to be the case with sulfur dioxide in some instances (230), but not in others (179). $\alpha$,N-Diphenyl nitrone (209) and other nitrones (25) were successfully deoxygenated by sulfur. Treatment of $\alpha$,N-diphenylnitrone with carbon monoxide at 150° and about 3000 atm. also resulted in deoxygenation (47).

Treatment of $\alpha,\alpha$-diphenyl-N-diphenylmethylnitrone with hydrogen and Raney nickel at atmospheric pressure and room temperature yielded 50% of the imine (67). Treatment of N-*o*-, -*m*-, or -*p*-nitrophenyl-$\alpha$-phenylnitrone with hydrogen and platinum black showed that the nitro group was reduced before the nitrone group (88). Because of this it is possible to prepare nitrones by reductive cyclization of nitro compounds. For instance, 4-methyl-4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone was converted to 5,5-dimethyl-4-phenyl-2-(3-pyridyl)-$\Delta^1$-pyrroline N-oxide by low pressure hydrogenation over Raney nickel in 45% yield, by zinc dust and aqueous ammonium chloride in 55% yield, and by hydrazine and Raney nickel in 75% yield (134).

### I. SOLVOLYSIS

Nitrones generally hydrolyze readily, forming an aldehyde or ketone and an N-substituted hydroxylamine (94, 145). Arylnitrones are far less susceptible to hydrolysis than alkylnitrones. For example, $\alpha,\alpha$,N-

$$RR'C{=}\underset{\underset{O}{\downarrow}}{N}R'' + H_2O \rightarrow RR'CO + R''NHOH$$

triphenylnitrone upon treatment with dilute sulfuric acid yielded benzophenone and N-phenylhydroxylamine (216). Alkyl nitrones were hydrolyzed instantly, were "decomposed" by ethanol, but were unaffected by diethyl ether (80). On the other hand, arylnitrones have commonly been recrystallized from ethanol.

Nitrones upon treatment with KCN in methanol yielded $\alpha$-methoxy anils which upon hydrolysis yielded an N-substituted amide (23, 26), while $\alpha$-cyanonitrones

$$C_6H_5CH{=}\underset{\underset{O}{\downarrow}}{N}C_6H_5 \xrightarrow[CH_3OH]{KCN} C_6H_5\underset{\underset{CH_3}{|}}{\overset{\overset{O}{|}}{C}}{=}NC_6H_5 \xrightarrow{H_2O} C_6H_5CONHC_6H_5$$

yielded $\alpha$-ketocarboxylic acids (145).

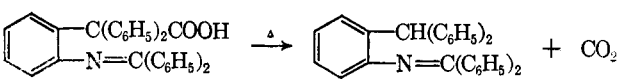
### J. MISCELLANEOUS REACTIONS

Nitrones are readily transformed into derivatives of the corresponding carbonyl compounds, *e.g.*, hydrazones (90), 4-nitrophenylhydraxones (114), 2,4-dinitrophenylhydrazones (145), semicarbazones (52), and oximes (103).

$$C_6H_5CH{=}\underset{\underset{O}{\downarrow}}{N}C_6H_5 + NH_2OH \rightarrow C_6H_5CH{=}NOH + C_6H_5NHOH$$

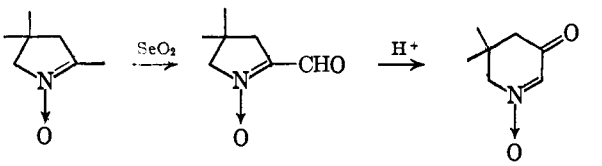
The reaction between diphenylketene and phenylnitrones, leading to Staudinger's "nitrenes" (216), was reinvestigated. Substitution of the phenyl ring appeared to occur, followed by a decarboxylation (107).

$$(C_6H_5)_2C{=}C{=}O + C_6H_5\underset{\underset{O}{\downarrow}}{N}{=}C(C_6H_5)_2 \longrightarrow$$



Treatment of $\alpha$-(2-quinolyl N-oxide)-N-phenylnitrone with quinaldine N-oxide yielded 1,2-bis(2-quinolyl N-oxide)ethylene. Lepidine derivatives exhibited a similar behavior. The mechanism for this reaction is not understood (66).

Finally, 2,4,4-trimethyl-$\Delta^1$-pyrroline N-oxide upon treatment with selenium dioxide yielded the 2-carboxaldehyde, which rearranged to 2,3,4,5-tetrahydro-3,3-dimethyl-5-ketopyridine N-oxide under the influence of acid (42).



## VI. USES

The principal use of nitrones appears to be that of a synthetic intermediate. Five-membered heterocyclic systems may be prepared by 1,3-cycloaddition reactions, as discussed in detail in that section of this review. The Kroehnke reaction has been employed to prepare by the hydrolysis of appropriate nitrones a variety of carbonyl compounds, *e.g.*, aldehydes, ketones, glyoxals, $\alpha,\beta$-unsaturated aldehydes, dialdehydes, $\alpha$-ketocarboxylic acids (140, 170), or the acids themselves, as reviewed by Kroehnke (145) in 1953.

Sensitive aliphatic aldehydes such as fumaraldehyde (114, 199), muconaldehyde (127), cyclohexylideneacetaldehyde (51, 53, 54), and acrolein (153) have been prepared by the hydrolysis of appropriate nitrones or dinitrones. The following glyoxals have been prepared similarly: aminomethylglyoxal (13) and other

aminoalkylglyoxals (14, 15, 169), aromatic aminoalkylglyoxals (32, 138), phenylglyoxal (153), substituted phenylglyoxals (211), furan-2-glyoxal (133), pyrrolylglyoxal (197), and indolylglyoxal (196).

In the benzene series, the following aldehydes were prepared by nitrone hydrolysis: 2,6-dinitro-, 2,6-dichloro-, 2-nitro-6-chloro-, and 2-nitro-6-bromobenzaldehyde (60); 4-nitrosalicylaldehyde (91, 92); α-naphthaldehyde (153); and cinnamaldehyde (153). Other aromatic aldehydes thus prepared were: (pyridine N-oxide)-2-carboxaldehyde (104); pyridazine-3-carboxaldehyde (158); quinoline-2- and -4-carboxaldehyde (132, 154); acridine-9-carboxaldehyde (77, 172, 179) and derivatives (172, 179, 195); cinnoline-4-carboxaldehyde (50); aldehydes in the pyrrole (226, 227), indole (220, 221), naphthoxazole (190), and benzselenazole series (190); benzimidazole-2-carboxaldehyde (163) and derivatives (162); thiazole-2-carboxaldehyde (231); benzthiazole-2-carboxaldehyde (129, 189); benzoxazole-2-carboxaldehyde (189); 1,3,4-thiadiazole-2-carboxaldehyde derivatives (178); and phenazine derivatives (234). Also prepared were 2-oxochrome (200), purine-6-carboxaldehyde (90), theobromine-8-carboxaldehyde (38), and theophyllin-8-carboxaldehyde (38).

Aromatic di- and tricarboxaldehydes prepared from di- and trinitrones are naphthalene-1,3-, -1,4-, -1,5-, -1,6-, -1,7-, -2,6-, and -2,7-dialdehydes (191); naphthalene-1,3,5-, -1,3,6-, and -1,3,7-trialdehydes (191); pyrazine-2,3- and -2,5-dicarboxaldehyde (190); pyrimidine-4,6-dialdehyde (190); quinoxaline-2,3-dialdehyde (112); thianaphthene-2,3-dialdehyde (188); benzthianaphthene-2,3-dialdehyde (190); and furan-2,5-dialdehyde (176).

Nitrone formation and hydrolysis have also found a use in steroid chemistry (18, 19, 185). The 21-aldehydes of cortisone, hydrocortisone, and dihydrocortisone have been prepared from the corresponding 21-methyl compounds by employing the King reaction followed by nitrone formation and hydrolysis (159, 181, 192). The 21-aldehydes of 9-(α-fluoro)- or 9-(α-chloro)hydrocortisone were prepared similarly (86, 87), as were other 21-aldehydes (58, 235) and 17-glyoxals (171, 184) in the pregnane series.

Nitrones have been used for the synthesis of neocyanine dyes (129, 130), as supersensitizers of 2,2′-cyanines (46), and in photographic plates (167).

A few scattered pharmacological experiments employing nitrones have been reported (101, 128, 166).

ACKNOWLEDGMENT.—We are indebted to the Petroleum Research Fund and the American Cancer Society for financial support.

## VII. REFERENCES

(1) Agolini, F., and Bonnett, R., *Can. J. Chem.*, **40**, 181 (1962).
(2) Alessandri, L., *Atti accad. nazl. Lincei, Sez. I*, **24**, 62 (1915); *Chem. Abstr.*, **9**, 2240 (1915).
(3) Alessandri, L., *Gazz. chim. ital.*, **51**, 129 (1921); *Chem. Abstr.*, **16**, 558 (1923).
(4) Alessandri, L., *Gazz. chim. ital.*, **52**, 193 (1922); *Chem. Abstr.*, **16**, 2504 (1922).
(5) Alessandri, L., *Gazz. chim. ital.*, **54**, 426 (1924); *Chem. Abstr.*, **19**, 45 (1925).
(6) Alessandri, L., *Gazz. chim. ital.*, **55**, 729 (1925); *Chem. Abstr.*, **20**, 1067 (1926).
(7) Alessandri, L., *Gazz. chim. ital.*, **56**, 396 (1926); *Chem. Abstr.*, **21**, 376 (1927).
(8) Alessandri, L., *Gazz. chim. ital.*, **57**, 195 (1927); *Chem. Abstr.*, **21**, 2127 (1927).
(9) Allais, A., *Bull. soc. chim. France*, **16**, 536 (1949).
(10) Angeli, A., Alessandri, L., and Alazzi-Mancini, M., *Atti accad. nazl. Lincei*, **20**, 546 (1910); *Chem. Abstr.*, **5**, 3404 (1911).
(11) Angeli, A., Alessandri, L., and Pegna, R., *Atti accad. nazl. Lincei, Sez. I*, **19**, 650 (1910); *Chem. Abstr.*, **5**, 2457 (1911).
(12) Azzazm, R. C., *Proc. Egypt. Acad. Sci.*, **9**, 89 (1953); *Chem. Abstr.*, **50**, 16,685 (1956).
(13) Balenovic, K., and Bregant, N., *J. Org. Chem.*, **17**, 1328 (1952).
(14) Balenovic, K., Cerar, D., and Filipovic, L., *J. Org. Chem.*, **18**, 686 (1953).
(15) Balenovic, K., Skaric, V., and Dvornik, D., *Croat. Chem. Acta*, **28**, 231 (1956); *Chem. Abstr.*, **51**, 11,997 (1957).
(16) Barrow, F., and Thorneycroft, F. J., *J. Chem. Soc.*, 769 (1939).
(17) Barrow, F., and Thorneycroft, F. J., *J. Chem. Soc.*, 773 (1939).
(18) Barton, D. H. R., and Beaton, J. M., *J. Am. Chem. Soc.*, **82**, 2641 (1960).
(19) Barton, D. H. R., and Beaton, J. M., *J. Am. Chem. Soc.*, **83**, 4083 (1961).
(20) Beckmann, E., *Ber.*, **27**, 1957 (1894).
(21) Belew, J. S., Gabriel, C. E., and Clapp, L. B., *J. Am. Chem. Soc.*, **77**, 1110 (1955).
(22) Bellavita, V., *Atti congr. nazl. chim. pura appl., 5th Congr. Rome, 1935*, I, 285 (1936); *Chem. Abstr.*, **31**, 3887 (1937).
(23) Bellavita, V., *Atti congr. intern. chim.*, **3**, 33 (1938); *Chem. Abstr.*, **34**, 1004 (1940).
(24) Bellavita, V., and Cagnoli, N., *Gazz. chim. ital.*, **69**, 583 (1939); *Chem. Abstr.*, **34**, 1638 (1940).
(25) Bellavita, V., and Cagnoli, N., *Gazz. chim. ital.*, **69**, 602 (1939); *Chem. Abstr.*, **34**, 1978 (1940).
(26) Bellavita, V., *Gazz. chim. ital.*, **70**, 584 (1940); *Chem. Abstr.*, **35**, 2127 (1941).
(27) Bellet, R. J., *Dissertation Abstr.*, **22**, 3391 (1962).
(28) Bergmann, E., *J. Chem. Soc.*, 1628 (1937).
(29) Blatt, A. H., *J. Org. Chem.*, **15**, 869 (1950).
(30) Bonnett, R., Brown, R. F. C., Clark, V. M., Sutherland, I. O., and Todd, A., *J. Chem. Soc.*, 2094 (1959).
(31) Bonnett, R., Clark, V. M., and Todd, A., *J. Chem. Soc.*, 2102 (1959).
(32) Borkovic, J., Michalsky, J., Rabusic, E., and Hadacek, J., *Chem. Listy*, **48**, 717 (1954); *Chem. Abstr.*, **49**, 9662 (1955).
(33) Brady, O. L., and Mehta, R. P., *J. Chem. Soc.*, **125**, 2297 (1924).
(34) Brady, O. L., and Dunn, F. P., *J. Chem. Soc.*, **129**, 2411 (1926).
(35) Brady, O. L., Dunn, F. P., and Goldstein, R. F., *J. Chem. Soc.*, **129**, 2386 (1926).
(36) Brady, O. L., and Klein, L., *J. Chem. Soc.*, **131**, 874 (1927).
(37) Brady, O. L., and Chokski, N. M., *J. Chem. Soc.*, **134**, 2271 (1929).

(38) Bredereck, H., Siegel, E., and Foehlisch, B., *Ber.*, **95**, 403 (1962).
(39) Brown, C. W., Marsden, K., Rogers, M. A. T., Tylor, C. M. B., and Wright, R., *Proc. Chem. Soc.*, 254 (1960).
(40) Brown, C. W., and Rogers, M. A. T., British Patent 850,418; *Chem. Abstr.*, **55**, 6498 (1961).
(41) Brown, R. F. C., Clark, V. M., and Todd, A., *Proc. Chem. Soc.*, 97 (1957).
(42) Brown, R. F. C., Clark, V. M., and Todd, A., *J. Chem. Soc.*, 2105 (1959).
(43) Brown, R. F. C., Clark, V. M., Sutherland, I. O., and Todd, A., *J. Chem. Soc.*, 2109 (1959).
(44) Brown, R. F. C., Clark, V. M., Lamchen, M., and Todd, A., *J. Chem. Soc.*, 2116 (1959).
(45) Brown, R. F. C., Clark, V. M., Lamchen, M., Sklarz, B., and Todd, A., *Proc. Chem. Soc.*, 169 (1959).
(46) Bruenner, R., Graf, A., and Scheibe, G., *Z. Wiss. Phot. Photophysik Photochem.*, **53**, 214 (1959); *Chem. Abstr.*, **54**, 10,606 (1960).
(47) Buckley, G. D., and Ray, N. H., *J. Chem. Soc.*, 1154 (1949).
(48) Buckley, G. D., and Elliott, T. J., *J. Chem. Soc.*, 1508 (1947).
(49) Buu-Hoi, Cagniant, P., and Mentzer, C., *Bull. soc. chim. France*, 11, 127 (1944).
(50) Castle, R. N., and Onda, M., *J. Org. Chem.*, **26**, 4465 (1961).
(51) Chaco, M. C., and Iyer, B. H., *Current Sci.* (India), **22**, 240 (1953); *Chem. Abstr.*, **47**, 240 (1953).
(52) Chaco, M. C., and Iyer, B. H., *J. Indian Inst. Sci.*, **36**, 160 (1954); *Chem. Abstr.*, **49**, 11,588 (1955).
(53) Chaco, M. C., and Iyer, B. H., *Chem. Ind.* (London), 155 (1956).
(54) Chaco, M. C., and Iyer, B. H., *J. Org. Chem.*, **25**, 186 (1960).
(55) Chardonnens, L., and Heinrich, P., *Helv. Chim. Acta*, **22**, 1471 (1939).
(56) Chardonnens, L., and Heinrich, P., *Helv. Chim. Acta*, **32**, 656 (1949).
(57) Chistokletow, V. N., and Petrov, A. A., *Zh. Obshch. Khim.*, **32**, 2385 (1962); *Chem. Abstr.*, **58**, 9040 (1963).
(58) CIBA, Ltd., British Patent 805,601; *Chem. Abstr.*, **53**, 9295 (1959).
(59) Clark, V. M., Sklarz, B., and Todd, A., *J. Chem. Soc.*, 2123 (1959).
(60) Clarke, K., *J. Chem. Soc.*, 3507 (1957).
(61) Colonna, M., *Gazz. chim. ital.*, **82**, 503 (1952); *Chem. Abstr.*, **48**, 2065 (1954).
(62) Colonna, M., *Gazz. chim. ital.*, **90**, 1179 (1960); *Chem. Abstr.*, **56**, 5930 (1962).
(63) Colonna, M., *Gazz. chim. ital.*, **90**, 1197 (1960); *Chem. Abstr.*, **56**, 5930 (1962).
(64) Colonna, M., *Gazz. chim. ital.*, **91**, 34 (1961); *Chem. Abstr.*, **56**, 12,851 (1962).
(65) (a) Colonna, M., and Risaliti, A., *Gazz. chim. ital.*, **91**, 204 (1961); *Chem. Abstr.*, **56**, 12,853 (1962); (b) Colonna, M., and Monti, A., *Gazz. chim. ital.*, **91**, 915 (1961); *Chem. Abstr.*, **56**, 15,461 (1962).
(66) Colonna, M., and Zamparella, L., *Gazz. chim. ital.*, **92**, 301 (1962); *Chem. Abstr.*, **57**, 9815 (1962).
(67) Cope, A. C., and Haven, A. C., *J. Am. Chem. Soc.*, **72**, 4896 (1950).
(68) De La Mare, H. E., and Coppinger, G. M., *J. Org. Chem.*, **28**, 1068 (1963).
(69) Delpierre, G. R., and Lamchen, M., *Proc. Chem. Soc.*, 386 (1960).
(70) Delpierre, G. R., and Lamchen, M., *J. Chem. Soc.*, 4693 (1963).
(71) De Waal, H. L., and Brink, C. v. d. M., *Ber.*, **89**, 636 (1956).
(72) Dittmer, R. C., and Kolyer, J. N., *J. Org. Chem.*, **27**, 56 (1962).
(73) Dornov, A., Gehrt, H., and Ische, F., *Ann.*, **585**, 220 (1954).
(74) Drozdov, N. S., and Yavorskaya, E. V., *Zh. Obshch. Khim.*, **30**, 3421 (1960); *Chem. Abstr.*, **55**, 18,728 (1961).
(75) du Pont de Nemours, E. I. and Co., Belgian Patent 614,730; *Chem. Abstr.*, **57**, 16,484 (1962).
(76) Earl, J. C., *Rec. trav. chim.*, **75**, 346 (1956).
(77) Eisleb, O., *Med. Chem. Abhandl. med.-chem. Forschungsstätten I. G. Farbenind.*, **3**, 41 (1936); *Chem. Abstr.*, **31**, 5802 (1937).
(78) Emmons, W. D., *J. Am. Chem. Soc.*, **78**, 6208 (1956).
(79) Emmons, W. D., *J. Am. Chem. Soc.*, **79**, 5739 (1957).
(80) Exner, O., *Collection Czech. Chem. Commun.*, 16, 258 (1951); *Chem. Abstr.*, **47**, 5884 (1953).
(81) Exner, O., *Chem. Listy*, **48**, 1543 (1954); *Chem. Abstr.*, **49**, 11,603 (1955).
(82) Exner, O., *Chem. Listy*, **48**, 1634 (1954); *Chem. Abstr.*, **49**, 14,676 (1955).
(83) Exner, O., *Collection Czech. Chem. Commun.*, **20**, 202 (1955); *Chem. Abstr.*, **49**, 11,603 (1955).
(84) Fodor, G., and Csokan, P., *Ann.*, **535**, 284 (1938).
(85) Freeman, J. P., *J. Org. Chem.*, **27**, 2881 (1962).
(86) Fried, J., and Herz, J. E., U. S. Patent 2,920,084; *Chem. Abstr.*, **54**, 11,085 (1960).
(87) Fried, J., and Herz, J. E., U. S. Patent 2,972,610; *Chem. Abstr.*, **55**, 12,357 (1961).
(88) Gandini, A., *Gazz. chim. ital.*, **72**, 28 (1942); *Chem. Abstr.*, **37**, 1399 (1943).
(89) Gilsdorf, R. T., and Nord, F. F., *J. Am. Chem. Soc.*, **74**, 1837 (1952).
(90) Ginner-Sorolla, A., Zimmerman, I., and Bendick, A., *J. Am. Chem. Soc.*, **81**, 2515 (1959).
(91) Goldberg, A. A., and Walker, H. A., *J. Chem. Soc.*, 2540 (1954).
(92) Goldberg, A. A., and Walker, H. A., British Patent 707,230; *Chem. Abstr.*, **49**, 7005 (1955).
(93) Gore, P. H., and Hughes, G. K., *Australian J. Sci.*, **13**, 23 (1950); *Chem. Abstr.*, **45**, 3818 (1951).
(94) Grammaticakis, P., *Compt. rend.*, **205**, 60 (1937).
(95) Grammaticakis, P., *Compt. rend.*, **223**, 741 (1946).
(96) Grammaticakis, P., *Bull. soc. chim. France*, **14**, 664 (1947).
(97) Grammaticakis, P., *Compt. rend.*, **224**, 1066 (1947).
(98) Grammaticakis, P., *Compt. rend.*, **224**, 1568 (1947).
(99) Grammaticakis, P., *Bull. soc. chim. France*, **18**, 965 (1951).
(100) Grashey, R., Huisgen, R., and Leitermann, H., *Tetrahedron Letters*, **No. 12**, 9 (1960).
(101) Gray, J. D. A., and Lambert, R. A., *Nature*, **162**, 733 (1948).
(102) Guendel, W., and Pummerer, R., *Ann.*, **529**, 11 (1937).
(103) Hamana, M., Umezawa, B., and Goto, Y., *Yakugaku Zasshi*, **80**, 1519 (1960); *Chem. Abstr.*, **55**, 8405 (1961).
(104) Hamana, M., Umezawa, B., Goto, Y., and Noda, K., *Chem. Pharm. Bull.* (Tokyo), **8**, 692 (1960); *Chem. Abstr.*, **55**, 18,723 (1961).
(105) Hamana, M., Umezawa, B., and Nakashima, S., *Chem. Pharm. Bull.* (Tokyo), **10**, 969 (1962).
(106) (a) Hamer, J., and Macaluso, A., *Tetrahedron Letters*, **No. 6**, 381 (1963); (b) unpublished results.
(107) Hassall, C. H., and Lippman, A. E., *J. Chem. Soc.*, 1059 (1953).
(108) Hawthorne, M. F., and Strahm, R. D., *J. Org. Chem.*, **22**, 1263 (1957).

(109) Hellman, H., and Teichmann, K., *Ber.*, **89**, 2159 (1956).
(110) Hepfinger, N. F., and Griffin, C. E., *Tetrahedron Letters*, No. 21, 1361 (1963).
(111) Hepfinger, N. F., and Griffin, C. E., *Tetrahedron Letters*, No. 21, 1365 (1963).
(112) Heuseke, G., and Baehner, K. J., *Ber.*, **91**, 1605 (1958).
(113) Horner, L., and Hoffmann, H., *Angew. Chem.*, **68**, 473 (1956).
(114) Hufford, D. L., Tarbell, D. S., and Koszalka, T. R., *J. Am. Chem. Soc.*, **74**, 3014 (1952).
(115) Huisgen, R., and Seidl, H., *Tetrahedron Letters*, No. 28, 2019 (1963).
(116) Huisgen, R., *Angew. Chem.*, **75**, 604 (1963); *Angew. Chem. Intern. Ed.*, **2**, 565 (1963).
(117) Huisgen, R., *Angew. Chem.*, **75**, 741 (1963); *Angew. Chem. Intern. Ed.*, **2**, 633 (1963).
(118) Hurd, C. D., and Longfellow, J. M., *J. Org. Chem.*, **16**, 761 (1951).
(119) Hurd, C. D., and Longfellow, J. M., *J. Am. Chem. Soc.*, **73**, 2396 (1951).
(120) Hurd, C. D., and Patterson, J., *J. Am. Chem. Soc.*, **75**, 285 (1953).
(121) Ingold, C. K., and Weaver, S. D., *J. Chem. Soc.*, **125**, 1146 (1924).
(122) Johnson, A. W., and LaCount, R. B., *J. Am. Chem. Soc.*, **83**, 417 (1961).
(123) Johnson, A. W., *J. Org. Chem.*, **28**, 252 (1963).
(124) Jonson, D. H., Rogers, M. A. T., and Trappe, G., *J. Chem. Soc.*, 1093 (1956).
(125) Jolles, E., *Gazz. chim. ital.*, **68**, 488 (1938); *Chem. Abstr.*, **33**, 543 (1939).
(126) Kamlet, M. J., and Kaplan, L. A., *J. Org. Chem.*, **22**, 576 (1957).
(127) Karrer, P., Eugster, C. H., and Perl, S., *Helv. Chim. Acta*, **32**, 1013 (1949).
(128) Kiese, M., and Platting, H. K., *Arch. Exptl. Pathol. Pharmakol.*, **233**, 484 (1958); *Chem. Abstr.*, **52**, 13,104 (1958).
(129) Kimura, S., *Bull. Chem. Soc. Japan*, **33**, 872 (1960); *Chem. Abstr.*, **55**, 3556 (1961).
(130) Kimura, S., *Bull. Chem. Soc. Japan*, **33**, 875 (1960); *Chem. Abstr.*, **55**, 3556 (1961).
(131) King, L. C., *J. Am. Chem. Soc.*, **66**, 894 (1944).
(132) King, L. C., and Abramo, S. V., *J. Org. Chem.*, **23**, 1609 (1958).
(133) Kipnis, F. and Ornfelt, J., *J. Am. Chem. Soc.*, **70**, 3948 (1948).
(134) Kloetzel, M. C., Chubb, F. L., Gobran, R., and Pinkus, J. L., *J. Am. Chem. Soc.*, **83**, 1128 (1961).
(135) Krimm, H., *Ber.*, **91**, 1057 (1958).
(136) Kroehnke, F., and Boerner, E., *Ber.*, **69**, 2006 (1936).
(137) Kroehnke, F., *Ber.*, **71**, 2583 (1938).
(138) Kroehnke, F., *Ber.*, **72**, 527 (1939).
(139) Kroehnke, F., *Ber.*, **72**, 1731 (1939).
(140) Kroehnke, F., *Ber.*, **80**, 298 (1947).
(141) Kroehnke, F., *Ber.*, **83**, 253 (1950).
(142) Kroehnke, F., *Ber.*, **84**, 388 (1951).
(143) Kroehnke, F., *Ber.*, **84**, 956 (1951).
(144) Kroehnke, F., *Ber.*, **85**, 368 (1952).
(145) Kroehnke, F., *Angew. Chem.*, **65**, 612 (1953); **75**, 181 (1963).
(146) Kroehnke, F., Kroehnke, G., and Vogt, I., *Ber.*, **86**, 1500 (1953).
(147) Kroehnke, F., Ellegast, K., and Bertram, W., *Ann.*, **600**, 176 (1956).
(148) Kroehnke, F., Ellegast, K., and Betram, W., *Ann.*, **600**, 198 (1956).
(149) Kroehnke, F., and Vogt, I., *Ann.*, **600**, 211 (1956).
(150) Kroehnke, F., *Ann.*, **604**, 203 (1957).
(151) Kroehnke, F., Leister, H., and Vogt, I., *Ber.*, **90**, 2792 (1957).
(152) Kroehnke, F., and Kroehnke, G., *Ber.*, **91**, 1474 (1958).
(153) Kroehnke, F., German Patent 755,943; *Chem. Abstr.*, **52**, 5451 (1958).
(154) Kroehnke, F., and Friedrich, K., *Ber.*, **92**, 22 (1959).
(155) Kroehnke, F., and Gerlach, F., *Ber.*, **95**, 1108 (1962).
(156) Kroehnke, F., and Steuernagel, H. H., *Ber.*, **96**, 494 (1963).
(157) Kubata, T., and Yamakawa, M., *Bull. Chem. Soc. Japan*, **35**, 555 (1962); *Chem. Abstr.*, **56**, 15,997 (1962).
(158) Kumagai, M., *Nippon Kagaku Zasshi*, **81**, 492 (1961); *Chem. Abstr.*, **55**, 6487 (1961).
(159) Leanza, W. J., Conbere, J. P., Rogers, E. F., and Pfister, K., *J. Am. Chem. Soc.*, **76**, 1691 (1954).
(160) LeBel, N. A., and Whang, J. J., *J. Am. Chem. Soc.*, **81**, 6334 (1959).
(161) LeBel, N. A., Slusarczuk, G. M. J., and Spurlock, L. A., *J. Am. Chem. Soc.*, **84**, 4360 (1962).
(162) Le Bris, M. T., and Wahl, H., *Compt. rend.*, **246**, 3472 (1958).
(163) Le Bris, M. T., Wahl, H., and Jameu, T., *Bull. soc. chim. France*, 343 (1959).
(164) Looker, J. H., and Shaneyfelt, D., *J. Org. Chem.*, **27**, 1894 (1962).
(165) Martynoff, M., *Ann. chim.*, **7**, 424 (1937).
(166) Mashbits, F. D., *Vopr. Onkol.*, **1**, 52 (1955); *Chem. Abstr.*, **51**, 2999 (1957).
(167) McQueen, D. M., U. S. Patent 2,426,894; *Chem. Abstr.*, **41**, 7289 (1947).
(168) Meisenheimer, J., and Chou, J-L., *Ann.*, **539**, 78 (1939).
(169) Michalsky, J., Borkovec, J., and Hadacek, J., *Chem. Listy*, 1379 (1955); *Chem. Abstr.*, **50**, 5681 (1956).
(170) Michalsky, J., *J. prakt. Chem.*, **8**, 186 (1959).
(171) Miescher, K., and Schmidlin, J., *Helv. Chim. Acta*, **33**, 1840 (1950).
(172) Mikhailov, B. M., and Ter-Sarkisyan, G. S., *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 656 (1954); *Chem. Abstr.*, **49**, 10,953 (1955).
(173) Mueller, E., Mayer, R., Narr, B., Schick, A., and Scheffler, K., *Ann.*, **645**, 1 (1961).
(174) Nerdel, F., and Huldschinsky, I., *Ber.*, **86**, 1005 (1953).
(175) Nohira, H., Sato, K., and Mukaiyama, T., *Bull. Chem. Soc. Japan*, **36**, 870 (1963).
(176) Novitskii, K. Yu., Volkov, V. P., and Yur'ev, Yu. K., *Zh. Obshch. Khim.*, **31**, 538 (1961); *Chem. Abstr.*, **55**, 23,486 (1961).
(177) Ogura, K., *Bull. Chem. Soc. Japan*, **35**, 420 (1962); *Chem. Abstr.*, **56**, 7166 (1962).
(178) Ohta, M., and Isowa, Y., *Nippon Kagaku Zasshi*, **79**, 1452 (1958); *Chem. Abstr.*, **54**, 5627 (1960).
(179) Perrine, T. D., and Sargent, J. L., *J. Org. Chem.*, **14**, 583 (1949).
(180) Pfeiffer, P., and Roos, H. H., *J. prakt. Chem.*, **159**, 13 (1941).
(181) Pfister, K., and Leanza, W., U. S. Patent 2,708,202; *Chem. Abstr.*, **50**, 5791 (1956).
(182) Quinion, H., *Bull. Soc. Chim. France*, 47 (1960).
(183) Ramart-Lucas, P., and Hoch, J., *Bull. Soc. Chim. France*, **5**, 987 (1938).
(184) Reich, H., and Reichstein, T., *Helv. Chim. Acta*, **22**, 1124 (1939).
(185) Reichstein, T., Wettstein, A., Anner, G., Billeter, J. R., Heusler, K., Neher, R., Schmidlin, J., Ueberwasser, H., and Wieland, P., U. S. Patent 2,904,545; *Chem. Abstr.*, **54**, 5752 (1960).
(186) Renner, G., *Z. Anal. Chem.*, **193**, 92 (1963).

(187) Riebel, A. H., Erickson, R. E., Abshire, C. J., and Bailey, P. S., *J. Am. Chem. Soc.*, **82**, 1801 (1960).
(188) Ried, W., and Bender, H., *Ber.*, **89**, 1574 (1956).
(189) Ried, W., and Bender, H., *Ber.*, **89**, 1893 (1956).
(190) Ried, W., and Gross, R. M., *Ber.*, **90**, 2646 (1957).
(191) Ried, W., Boden, H., Ludwig, U., and Neidhardt, H., *Ber.*, **91**, 2479 (1958).
(192) Rogers, E. F., Leanza, W. J., Conebere, J. P., and Pfister, K., *J. Am. Chem. Soc.*, **74**, 2947 (1952).
(193) Runti, C., and Collino, F., *Ann. chim.* (Rome), **49**, 1472 (1959); *Chem. Abstr.*, **54**, 13,071 (1960).
(194) Ruppert, W., German Patent 971,307; *Chem. Abstr.*, **54**, 12,019 (1960).
(195) Saikachi, H., Tsuge, O., and Tashiro, M., *Yakugaku Zasshi*, **80**, 584 (1960); *Chem. Abstr.*, **54**, 22,643 (1960).
(196) Sanna, G., *Gazz. chim. ital.*, **72**, 363 (1942); *Chem. Abstr.*, **37**, 6662 (1943).
(197) Sanna, G., *Gazz. chim. ital.*, **78**, 742 (1948); *Chem. Abstr.*, **43**, 4256 (1949).
(198) Sayigh, A. A. R., and Ulrich, H., *J. Org. Chem.*, **27**, 4662 (1962).
(199) Schmid, H., and Grob, E., *Helv. Chim. Acta*, **32**, 77 (1949).
(200) Schmutz, J., Hirt, R., and Lauener, H., *Helv. Chim. Acta*, **35**, 1168 (1952).
(201) Schoenberg, A., and Michaelis, R., *J. Chem. Soc.*, 627 (1937).
(202) Schoenberg, A., and Azzam, R. C., *J. Chem. Soc.*, 1428 (1939).
(203) Schoenberg, A., Sidkyand, M. M., and Aziz, G., *J. Am. Chem. Soc.*, **76**, 5115 (1954).
(204) Schoenberg, A., and Brosowski, K. H., *Ber.*, **92**, 2602 (1959).
(205) Schulze, W., *J. prakt. Chem.*, **17**, 21 (1962).
(206) Schulze, W., *J. prakt. Chem.*, **19**, 212 (1963).
(207) Schulze, A., and Williger, H. M., *J. prakt. Chem.*, **21**, 169 (1963).
(208) Semper, L., and Lichtenstadt, L., *Ber.*, **51**, 928 (1918).
(209) Shchukina, M. N., and Predvoditeleva, G. S., *Dokl. Akad. Nauk SSSR.*, **110**, 230 (1956); *Chem. Abstr.*, **51**, 4996 (1957).
(210) Shindo, H., and Umezawa, B., *Chem. Pharm. Bull.* (Tokyo), **10**, 492 (1962); *Chem. Abstr.*, **57**, 14,598 (1962).
(211) Shishido, K., Okano, K., Ishida, T., and Nozaki, H., *J. Am. Chem. Soc.*, **77**, 6580 (1955).
(212) Smith, L. I., *Chem. Rev.*, **23**, 193 (1938).
(213) Smith, P. A. S., and Robertson, J. E., *J. Am. Chem. Soc.*, **84**, 1197 (1962).
(214) Splitter, J. S., and Calvin, M., *J. Org. Chem.*, **20**, 1086 (1955).
(215) Splitter, J. S., and Calvin, M., *J. Org. Chem.*, **23**, 651 (1958).
(216) Staudinger, H., and Miescher, K., *Helv. Chim. Acta*, **2**, 554 (1919).
(217) Tananescu, J., and Nanu, J., *Ber.*, **72**, 1083 (1939).
(218) Tananescu, J., and Nanu, J., *Ber.*, **75**, 650 (1942).
(219) Tananescu, J., and Nanu, J., *Ber.*, **75**, 1287 (1942).
(220) Thesing, J., *Ber.*, **87**, 507 (1954).
(221) Thesing, J., Muller, A., and Michel, G., *Ber.*, **88**, 1030 (1955).
(222) Thesing, J., and Mayer, H., *Ber.*, **89**, 2159 (1956).
(223) Thesing, J., and Mayer, H., *Ann.*, **609**, 46 (1957).
(224) Thesing, J., and Sirrenberg, W., *Ber.*, **91**, 1979 (1958).
(225) Thesing, J., and Sirrenberg, W., *Ber.*, **92**, 1748 (1959).
(226) Treibs, A., and Fritz, G., *Angew. Chem.*, **66**, 562 (1954).
(227) Treibs, A., and Fritz, G., *Ann.*, **611**, 162 (1958).
(228) Ulrich, H., and Sayigh, A. A., *Angew. Chem.*, **74**, 468 (1962).
(229) Umezawa, B., *Chem. Pharm. Bull.* (Tokyo), **8**, 698 (1960); *Chem. Abstr.*, **55**, 18,723 (1961).
(230) Umezawa, B., *Chem. Pharm. Bull.* (Tokyo), **8**, 967 (1960); *Chem. Abstr.*, **57**, 8537 (1962).
(231) Uno, T., and Akihama, S., *Yakugaku Zasshi*, **81**, 579 (1961); *Chem. Abstr.*, **55**, 19,903 (1961).
(232) Utzinger, G. E., *Ann.*, **556**, 50 (1944).
(233) Utzinger, G. E., and Regenass, F. A., *Helv. Chim. Acta*, **37**, 1892 (1954).
(234) Westphal, O., and Jann, K., *Ann.*, **605**, 8 (1957).
(235) Wettstein, A., Auwer, G., and Schmidlin, J., U. S. Patent 2,883,378; *Chem. Abstr.*, **53**, 15,127 (1959).
(236) Wheeler, O. H., and Gore, P. H., *J. Am. Chem. Soc.*, **78**, 3363 (1956).
(237) Wiemann, J., and Glacet, C., *Bull. soc. chim. France*, **17**, 176 (1950).
(238) Wragg, A. H., and Stevens, T. S., *J. Chem. Soc.*, 461 (1959).