Synthesis and Characterization of Phenyl-Substituted C-Phenyl-N-tert-butylnitrones and Some of Their Radical Adducts

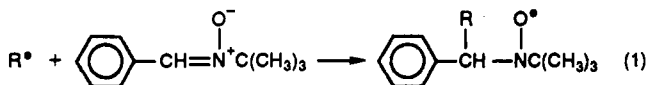Randall D. Hinton and Edward G. Janzen*,†

National Biomedical Center for Spin Trapping and Free Radicals, Molecular Toxicology Research Program, Oklahoma Medical Research Foundation, 825 N.E. 13th Street, Oklahoma City, Oklahoma 73104

Synthesis of C-phenyl-N-tert-butylnitrone (PBN) and several of its analogues with substituents in the 2-, 3-, or 4-position on the phenyl ring is described. While a one-pot reduction/condensation method proved suitable for most compounds, it was necessary to prepare some examples by direct condensation or through oxidation of the appropriate imine. The ^{1}H NMR data for the 3-X- and 4-X-PBN's can be correlated with the Hammett equation. For the 3-X series $\Delta\delta$ for the α-proton correlates best with σ^+ and has a correlation coefficient of 0.90. For the 4-X series a dual substituent parameter equation using σ_R^0 gives the best correlation with $r = 0.99$. The hyperfine splitting constants (hfsc's) of the HO$^\bullet$ and HOO$^\bullet$ adducts of several substituted PBN's are also included and their correlation with the Hammett equation is discussed.

Introduction

Stable nitrones are experiencing expanding application today as spin traps,[1] as potential therapeutic agents,[2] and as synthetic intermediates.[3] The spin-trapping capabilities of nitrones have been extensively reviewed. Nitrones have been used to trap radicals in chemical and biological systems (eq 1). The resulting aminoxyl radical is usually

$$R^\bullet + \underset{}{\bigcirc}\!\!-CH{=}N^+C(CH_3)_3 \longrightarrow \underset{}{\bigcirc}\!\!-\underset{\underset{}{|}}{\overset{R}{C}}H-\underset{\underset{}{|}}{\overset{O^\bullet}{N}}C(CH_3)_3 \quad (1)$$

persistent and can be removed from the system, if necessary, and analyzed. In biological systems this method has been used to gain information on the mechanisms of several redox processes including the free radical activation of aliphatic alcohols,[4] the injury of liver cells by CCl$_4$,[5] and the free radical reaction of 6-hydroxydopamine.[6]

In addition to detecting the presence of radicals and identifying their structures, nitrones have been used to prevent or reduce the damage thought to be caused by radicals in biological systems. Kalyanaraman et al. used PBN to inhibit oxidation of lipoproteins.[2a] Towner et al. were able to prevent the liver injury which resulted from administration of a mixture of CCl$_4$ and ethanol to rats.[2b] Hill and Thornalley used spin traps to reduce the oxidative damage to erythrocytes and the peroxidation of lipids caused by phenylhydrazine.[7]

The most common application of nitrones in synthesis involves their 1,3-cycloaddition with alkenes. This results in the formation of an isoxazolidine.[8] Padwa et al. used nitrones as an entry to β-lactams.[3g] Oxadiazolin-5-ones, and their thio analogues, have been formed in the 1,3-cycloaddition of nitrones with isocyanates and isothiocyanates.[9] Aldonitrones, but not ketonitrones, react with Grignard reagents in a 1,3-fashion to yield a hydroxylamine.[10]

One problem which arises when using nitrones as radical scavengers in biological systems is the wide variety of radicals present in many of these systems. Appropriately substituted nitrones could be used to preferentially trap desired radicals or classes of radicals. However, only a few nitrones are currently available commercially. Sigma currently sells four, none of which bear functional groups other than methyls.[11]

The practicality of selectively trapping various radicals has been explored in several papers. Janzen and co-

workers examined the amphiphilicity of a few nitrones and ranked them according to their attraction for "the most polar regions of heterogeneous media".[12] Acree et al. examined the octanol/water partition coefficients of five substituted PBN's.[13] Thus a choice could be made between spin traps which would selectively trap either lipid-soluble or water-soluble radicals. Greenstock and Wiebe studied the effect of substituents on the rate at which C-arylnitrones reacted with various radical species generated from the pulse radiolysis of water.[14] They found that the rate at which most radicals were trapped was unaffected by the substituents. However, for α-hydroxyalkyl radicals the rate was found to increase as the electron-withdrawing ability of the substituent increased. Hirota and co-workers examined reactions of substituted phenyl radicals with substituted PBN's.[15] They found

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†Alternate address: Departments of Clinical Studies and Biomedical Sciences, Ontario Veterinary College, University of Guelph, Ontario N1G 2W1, Canada.

that electron rich nitrones excelled at trapping electron poor phenyl radicals while electron poor nitrones performed better with electron rich phenyl radicals. Correlation coefficients for the radicals being trapped ranged from 0.670 to 0.991. While the effect of substituents on the rate of spin-trapping by PBN has been examined, no studies are reported on the effect of substituents on the stability of the resulting radical adducts.

Another problem which must occasionally be dealt with in the spin-trapping technique is that of short spin adduct lifetime. Certain labile radicals (e.g., HO·, HOO·, and O_2^-) when trapped by nitrones form adducts which are themselves highly unstable (though more stable than the free radical itself). A recent study by Kotake et al. showed that pH affected the stability of several nitrone/HO· adducts.[16] Increasing the pH was found to decrease the half-lives of these adducts. The stability of the HO· adducts of PBN and 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) were also compared.
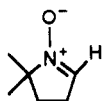
Hammett analyses of NMR data have been reported for decades.[17] Studies involving iminyl protons,[18] carbons,[19] and nitrogens[20] have been carried out. Results obtained have generally been in agreement with theory although correlation coefficients have not always been high. Other types of free energy relationships for NMR data have been examined. A recent paper by Janzen et al. described the effect of changing solvent polarity on the chemical shifts of the nitronyl proton and/or carbon of several nitrones.[12] Bennett and co-workers have compared the change in the ^{15}N chemical shifts for a series of amides with the IR frequency of their C=O bond.[21] Several groups have carried out NMR studies of substituted PBN's or their precursors. Jennings et al. examined the ^{13}C-NMR spectra of the imine and the oxaziridine analogues of several substituted PBN's.[19] Hammett correlations were found for the NC(CH₃)₃ and the ArCN carbons. Using the dual substituent parameter equation, which separates inductive/field effects from resonance effects, it was possible to obtain correlation coefficients of >0.99 in every case. For the NC(CH₃)₃ carbons a correlation coefficient of 0.989 was obtained.

Several studies on the correlation between Hammett values and hfsc's have been carried out.[22] Maki and Geske carried out the first study of substituent effects on hfsc's in 1961.[23] Although they did not attempt to correlate Hammett's σ constant with the N hfsc's of para-substituted

nitrobenzene radicals, they did note that electron-withdrawing substituents decreased the value of the N hfsc's while electron-donating groups had the opposite effect. It was left to Kolker and Waters to make that correlation in 1964.[24]

We have recently communicated on the rate of decay of the hydroxyl radical adduct of several substituted PBN's.[25] A few more nitrones have been examined and the updated results are included here. We also show the results of a Hammett analysis of the hyperfine splitting constants (hfsc's) of both the hydroxyl and peroxyl adducts of these nitrones and an analysis of the ^{1}H-NMR shifts of the nitrones themselves.

Several examples of 2-X-PBN's have been included here in order to provide a single source for the synthesis and characterization of substituted PBN's. Several of the 4-X-PBN's have been prepared before. Their syntheses and characteristics are also included for completeness.

Results and Discussion

Several methods for the synthesis of nitrones are available.[26] The first synthesis of a nitrone was accomplished by alkylating an oxime.[26g] However, this method suffers from low regioselectivity. The ratio of N-alkylation to O-alkylation varies greatly, depending on the reaction conditions and the reagent used.[26c] Other methods include the Kröhnke reaction,[26l] the condensation between an aldehyde or a ketone and an alkyl (or aryl) hydroxylamine,[26d] the oxidation of imines,[26h,j] or secondary aliphatic amines,[26e] and in situ reductions of nitro compounds to hydroxylamines followed by their condensation with aldehydes or ketones.[26b,f]

The "one-pot" synthesis (eq 2) was our method of choice due to the availability of a wide range of substituted benzaldehydes and the fact that the method is inexpensive and can be carried out overnight. One problem which
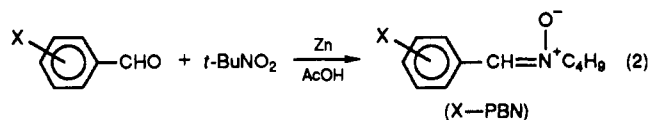
X = H, 4-CH₃, 3-CH₃, 2-CH₃, 4-F, 3-F, 4-OCH₃, 3-OCH₃, 2-OCH₃, 4-Cl, 3-Cl, 4-SCH₃, 4-CF₃, 3-CF₃, 4-Br, 3-Br, 2-Br

arises from this synthesis is that some substituents appear to be susceptible to reduction under the selected conditions. Substituents which prevented the use of this method were nitro, cyano, acetoxy, acetamido, and carboxyl. Attempts to prepare dialkylamino-substituted benzaldehydes also failed to give the nitrone under these conditions. Steric hindrance to condensation may be the reason why this method was unsuccessful with many of the 2-X-benzaldehydes which were tried. With these compounds the 2-methyl-2-nitropropane was probably over-reduced to *tert*-butylamine before the intermediate hydroxylamine

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Table I. ^{1}H NMR Chemical Shifts of Nitrones $(\delta)^a$

compound	H-α	H-t-Bu	H-2,6	H-3,5	H-4
H	7.85	1.51	8.36	7.40	7.42
4-CH$_3$	7.79	1.50	8.27	7.23	
3-CH$_3$	7.79	1.50	8.24, 8.13	7.30	7.22
2-CH$_3$	7.77	1.53	9.03	7.25, 7.25	7.25
4-OH	7.68	1.49	8.26	6.79	
3-OH	7.73	1.49	8.07, 7.55	7.20	6.81
2-OH	8.13	1.55	7.52	6.88, 7.37	6.83
4-F	7.89	1.51	8.48	7.26	
3-F	7.96	1.52	8.48, 7.97	7.47	7.25
2-F^b	7.87	1.62	9.33	7.36, 7.21	7.10
4-CN	8.06	1.53	8.52	7.88	
3-CN^c	8.15	1.26	8.38, 8.10	7.66	7.91
4-CH$_3$O	7.75	1.49	8.36	6.98	
3-CH$_3$O	7.84	1.51	8.21, 7.79	7.33	6.98
2-CH$_3$O	7.97	1.50	9.26	7.06, 7.39	6.98
4-Cl	7.92	1.52	8.42	7.49	
3-Cl	7.95	1.51	8.68, 7.46	8.15	7.46
2-COOH	7.83	1.33	7.75	7.33, 7.53	7.45
4-NO$_2$	8.15	1.55	8.60	8.28	
3-NO$_2$	8.18	1.55	9.52, 8.60	7.72	8.24
2-NO$_2$	8.17	1.48	8.20	7.99, 7.78	7.62
4-CH$_3$S	7.80	1.50	8.32	7.28	
4-C(CH$_3$)$_3$^{d}	7.80	1.50	8.29	7.43	
4-CH$_3$NH	7.74	1.55	8.31	7.63	
4-CH$_3$CO$_2$^{b}	7.51	1.61	8.19	6.87	
4-CF$_3$	8.06	1.54	8.58	7.78	
3-CF$_3$	8.09	1.54	9.00, 8.51	7.67	7.76
4-Br	7.90	1.51	8.34	7.62	
3-Br	7.93	1.51	8.82, 8.20	7.39	7.60
2-Br	8.01	1.54	9.23	7.74, 7.45	7.34
2-SO$_3^-$Na$^+$	8.91	1.54	9.31	7.86, 7.36	7.36
4-N$^+$Me$_3$	8.12	1.59	8.64	8.10	

^{a} Except where noted all samples are 0.25 M in DMSO-d_6. ^{b} This spectrum was obtained in CDCl$_3$. ^{c} This compound was impure. ^{d} This sample was <0.25 M.

could react with the aldehyde.

When the one-pot synthesis failed, recourse was made to either the condensation of N-*tert*-butylhydroxylamine with the appropriate aldehyde (eq 3) or the oxidation of
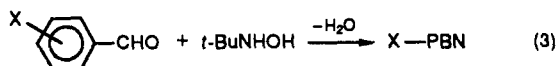
$$X = 4\text{-OH, } 3\text{-OH, } 3\text{-CN, } 2\text{-COOH, } 4\text{-NO}_2, 3\text{-NO}_2, 2\text{-NO}_2, 4\text{-AcNH, } 4\text{-AcO}$$

the appropriate imine with 3-chloroperbenzoic acid (MCPBA) followed by thermal rearrangement of the resulting oxaziridine (eq 4). When needed, imine precursors

$$X = 4\text{-CN}$$
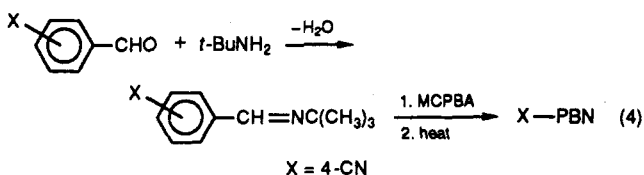
were prepared according to literature methods.[27] Most of the nitrones with the substituents mentioned above could be prepared by the condensation reaction. The 3- and 4-CN-PBN's were formed in low yield by this method. While rates were lower with 2-X-benzaldehydes, their reaction with the hydroxylamine was not impossible. Even 2,4,6-(MeO)$_3$-PBN could be prepared by this route.[28] (The purity of the product is enhanced if the reaction is carried out under an inert atmosphere.) The main drawback to this method is the cost of the hydroxylamine relative to that of the nitro compound.

Table II. Hammett Analysis of Meta-Substituted Nitrone Protons

position	r^a	ρ^b
2	0.92	0.804
4	0.97	0.793
5	0.91	0.293
6	0.94	0.596
iminyl	0.90	0.244
tert-butyl	0.90	0.031

^{a} Correlation coefficient. ^{b} Reaction constant.

Table III. Hammett Analysis of Para-Substituted Nitrone Protons

position	σ	λ^a	r	ρ
tert-butyl	R^0	1.562	0.969	0.042
iminyl	R^0	0.737	0.989	0.437
ortho	R^0	0.683	0.888	0.346
meta	R$^-$	1.459	0.957	0.810

^{a} ρ_R/ρ_I, where ρ_R and ρ_I are polar and resonance reaction constants, respectively.
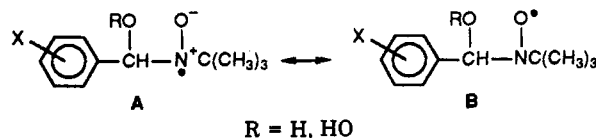
The oxidation/rearrangement synthesis was used only sparingly. While the cost of the reagents is lowest for this method, it suffers from the fact that it involves several reactions instead of only one. The added amount of time needed to carry out the synthesis is an additional consideration.

The ^{1}H-NMR data for the spin traps are listed in Table I. DMSO-d_6 was found to be the best choice of solvent. However, since the acyl group of 4-AcO-PBN was cleaved in this solvent, its NMR data were obtained in CDCl$_3$. In DMSO-d_6 the NMR spectrum of 4-AcO-PBN is identical to that of 4-HO-PBN.

Hammett analyses were carried out on the ^{1}H-NMR data from the 3- and 4-substituted nitrones. The 3-X nitrones could be correlated with σ_m and σ_p^+ using the standard Hammett equation: $\Delta\delta = \rho\sigma_m$ [or σ_p^+]. However, a dual substituent parameter equation gave the best results with the 4-X nitrones: $\Delta\delta = \rho(\sigma_I + \lambda\sigma_R)$. Correlation coefficients for the 3-X nitrone protons are shown in Table II. The values obtained for the protons of the 4-X nitrones are shown in Table III.

NMR spectra of several of the 4-X nitrones were obtained by Murray and Singh.[29] Although their data differ from ours due to a change in solvent and in concentration, the same general trend in the chemical shifts of the various protons is seen. For example, the chemical shift of the α-H changes from δ 7.75 for 4-MeO-PBN, to 7.85 for PBN itself, to 8.15 for 4-NO$_2$-PBN. This downfield shift with increasing electronegativity of the substituent groups is also seen with the meta and *tert*-butyl protons. The same trend was also seen with the ortho protons, although they did not correlate as well as the others.

We measured the hfsc's of both the hydroxyl and hydroperoxyl radical adducts of PBN and of several of its 3- and 4-substituted analogues in acetonitrile. Our results are given in Table IV. As expected a consistent decrease in measured hfsc with increasing electron-withdrawing capability of the substituent on the phenyl ring is seen.[1a] The two main resonance forms of the oxyl adducts are shown below. Electron-withdrawing substituents destabilize resonance structure A. This lowering of the spin

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A ⟷ B

R = H, HO

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Table IV. HFSC[a] and Decay Rate Data for Radical Adducts of Nitrones

compound	HO• adduct		HOO• adduct		
	a_β^H	a^N	a_β^H	a^N	k^b
4-CH$_3$O	2.83	14.86	2.34^c	13.96^c	13.88
4-CH$_3$	2.83	14.80	2.31	13.73	7.14
3-CH$_3$	2.74	14.79	2.41	13.69	5.50
H	2.75	14.76	2.29	13.69	7.15
3-CH$_3$O	2.73	14.75	2.25	13.66	8.39
4-Br	2.63	14.74	2.09	13.65	3.55
4-Cl	2.34	14.58	2.05	13.55	4.58
3-F	2.43	14.59	1.96	13.56	5.55
3-Cl	2.29	14.52	1.97	13.56	4.52
3-Br	2.43	14.68	2.04	13.52	2.53
4-CF$_3$^{d}					3.58
4-CN	2.06	14.45	1.84	13.42	2.09
3-NO$_2$	2.04	14.58	2.08^c	13.77^c	2.77
4-NO$_2$	2.06	14.41	1.79	13.41	2.25
r	0.96	0.91	0.96	0.97	0.88
ρ	−0.86	−0.39	−0.66	−0.36	1.47

^{a} In gauss. Obtained at room temperature in CH$_3$CN. ^{b} The rate constant ($\times 10^2$) for the first-order decay of the hydroxyl radical adduct of the given spin trap determined at room temperature. ^{c} These hfsc's were not included in calculations of r as they are based on fewer points than the other examples. ^{d} Hfsc's for this compound could not be determined due to the presence of di-*tert*-butylaminoxyl impurity.

density on the nitrogen atom with electron-withdrawing substituents has the effect of decreasing the observed N hfsc. The same effect is found on the magnitude of the β-H hfsc.

There are some deviations to linearity in the Hammett plot.[25] One of the causes of this result may be a counterbalancing change in the planarity, or s orbital character, of the aminoxyl function. As the molecule becomes less planar, taking on more s orbital character, the magnitude of the hfsc should increase.

A further analysis of the expected change in the relative contributions of the individual resonance forms also helped us determine which peaks in a given spectrum to assign to which adduct. The hydroperoxyl group is more electronegative than the hydroxyl group. Thus in the hydroperoxyl radical adducts, the aminoxyl spin is shifted more toward **B** relative to that in the hydroxyl radical adducts. Accordingly, the N and β-H hfsc's would be expected to be lower. The well-known relationship between the magnitude of the β-H hfsc's and the dihedral angle between the p orbital of the nitrogen and the C–H$_\beta$ bond supports the assignment of these hfsc's. It has been shown that as this angle increases the hfsc decreases. The larger hydroperoxyl group should increase this angle.

A comparison between our data and the hfsc's of the same adducts in other solvents shows a decrease in the magnitude of the hfsc's consistent with the effect of solvent polarity.[30] For example, the N hfsc for the hydroxyl radical adduct of PBN in various solvents is as follows: water, 15.46; acetonitrile, 14.76; and toluene, 14.35 G.

Experimental Section

General. Melting points are uncorrected. ^{1}H-NMR spectra were recorded at room temperature on a Varian XL-300 spectrometer using tetramethylsilane (TMS) as an internal standard. Either DMSO-d_6 or CDCl$_3$ was used as the solvent. A concentration of 0.25 M in DMSO-d_6 was used for all nitrones included in the Hammett analysis. EPR spectra were recorded at room temperature on either a Bruker ER 300 or EXP 300E instrument. Typical settings were receiver gain = 1 × 10^5, sweep time = 84 s, sweep width = 50 G, modulation amplitude = 0.2 G, modulation frequency = 100 kHz, and center field = 3475 G. Elemental

analyses were carried out by Galbraith Laboratories (Knoxville, TN).

Materials. Except as noted below all starting materials were purchased from Aldrich and used as received. *tert*-Butyl-*N*-hydroxylamine was obtained from its hydrochloride salt by treatment with NaHCO$_3$.

Determination of Hyperfine Splitting Constants and Decay Rates. A 0.04 M solution of the chosen spin trap was made up to 1% in H$_2$O$_2$. The sample was bubbled with N$_2$ for 10 min and introduced into the EPR sample cell (flat for H$_2$O and CH$_3$CN, round for C$_6$H$_6$). The cell was then placed in the cavity of the EPR spectrometer. A brief (∼1 s) UV irradiation resulted in the formation of both the HO• and HOO• adducts of the spin trap. It was not necessary to determine the absolute concentrations of these adducts.[25]

Once the positions of all of the EPR signal peaks were determined the adduct was given time to decay completely. The field was centered on a characteristic peak of the HO• adduct and the sweep width was set to 0 G. A few seconds after the sweep was begun the sample was reirradiated briefly. The EPR trace then showed the formation and decay of the adduct. At least two traces were obtained for each nitrone analyzed.[25]

Synthesis. All spin traps were prepared by condensation of the appropriate aldehyde with *tert*-butylhydroxylamine (I), by in situ reduction/condensation (II), or by oxidation of the appropriately substituted imine with 3-chloroperbenzoic acid (III). Reaction were carried out on a 0.1-mol scale. The method of synthesis is specified below for each compound. A typical procedure for each synthesis is given below.

General Procedures: Method I. The substituted benzaldehyde (10 mmol) and the free hydroxylamine (11 mmol, 0.98 g) were dissolved in 75 mL of benzene and a small amount of *p*-toluenesulfonic acid was added as a catalyst. This solution was then refluxed until none of the low-boiling 2-methyl-2-nitrosopropane was formed (3 h to several days). This compound and water were removed by means of a Dean–Stark trap. A second portion of the hydroxylamine was then added (4 mmol, 0.36 g) and the solution again refluxed to ensure complete reaction of the aldehyde. This could be followed by watching the disappearance of the characteristic blue color of 2-methyl-2-nitrosopropane.

The solution was concentrated on a Rotovap, leaving a clear or light-yellow solid or oil which was dissolved in ether (50 mL) and extracted with water, with 1 N NaHCO$_3$, and again with water (50 mL each). After drying the organic layer with Na$_2$SO$_4$ the ether was evaporated. The resulting solid was purified by sublimation.

An oil was occasionally obtained following final evaporation of the ether. This oil was solidified in one of two ways. Following addition of 1 mL of acetone, the oil was cooled with dry ice and then brought to room temperature while being stirred with a spatula. If this failed the oil was allowed to stand in a refrigerator until it solidified (e.g., after 2–4 weeks).

Method II. The desired substituted benzaldehyde (10 mmol), 2-methyl-2-nitropropane (20 mmol, 2.06 g), and zinc (30 mmol, 1.96 g) were placed in a round-bottomed flask along with 75 mL of 95% ethanol and cooled to 0 °C. Acetic acid (60 mmol, 3.79 g) was added slowly with stirring. The solution was allowed to come to room temperature, stirred for an additional 1–2 h, and stored in a refrigerator overnight. The Zn(OAc)$_2$ was filtered out and the solution concentrated on a Rotovap, leaving a clear solid. This solid was purified as described under method I.

Method III. *tert*-Butylamine (0.73 g, 1.05 mL, 10 mmol) was placed in a round-bottomed flask along with a magnetic stir bar and cooled to 0 °C with an ice bath. The desired substituted benzaldehyde (10 mmol) was added over the next 30 min. The solution was brought to room temperature and a pellet of KOH was added, followed by stirring for another hour. The solid mass was dissolved in CH$_2$Cl$_2$, dried with NaOH, filtered, and cooled in an ice bath. A solution of 3-chloroperbenzoic acid (12 mmol) in CH$_2$Cl$_2$ was added dropwise with stirring. The yellow solution turned green and then blue as 2-methyl-2-nitrosopropane formed. Once again the solution was allowed to come to room temperature and stirred overnight. The nitroso compound was distilled and the remaining solution diluted with ether and washed with water, with 15% NH$_4$OH, 10% HCl, and again with water. After drying

(30) See ref 1a, p 281.

Chart I
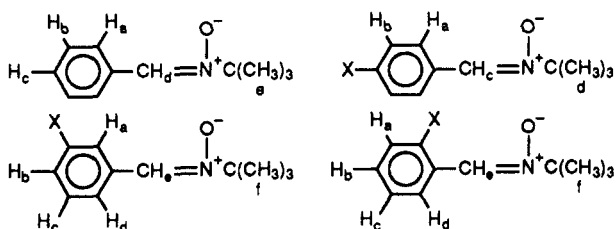
the organic layer with Na_2SO_4, the oxaziridine was recovered by rotoevaporating the solvent. The oxaziridine obtained was dissolved in acetonitrile and the solution was refluxed for several days. The solvent was rotoevaporated. The resulting orange mass was washed with ether, yielding a white powder which was recrystallized from an appropriate solvent.

Hydrogen labels given in the descriptions below are shown in Chart I.

C-Phenyl-N-tert-butylnitrone. Method II. Benzaldehyde was distilled prior to use. Yield: 61%; mp 73–74 °C (lit.[26i] mp 74–75 °C). ¹H NMR (DMSO-d_6): δ 8.36 (dd, 2 H, J_{ab} = 7.23 Hz, J_{ac} = 2.39 Hz, H$_a$), 7.85 (s, 1 H, H$_d$), 7.41 (m, 1 H, H$_c$), 7.40 (m, 2 H, H$_b$), 1.51 (s, 9 H, H$_e$). Anal. Calcd for C₁₁H₁₅NO: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.88, H, 8.64; N, 7.95.

C-(4-Methylphenyl)-N-tert-butylnitrone. Method II. Yield: 68%; mp 67–69 °C (lit.[26i] mp 68–70 °C). ¹H NMR (DMSO-d_6): δ 8.27 (d, 2 H, J_{ab} = 8.1 Hz, H$_a$), 7.79 (s, 1 H, H$_c$), 7.23 (d, 2 H, J_{ba} = 7.9 Hz, H$_b$), 2.33 (s, 3 H, CH₃), 1.50 (s, 9 H, H$_d$). Anal. Calcd for C₁₂H₁₇NO: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.16; H, 8.74; N, 7.38.

C-(3-Methylphenyl)-N-tert-butylnitrone. Method II. Yield: 76%; mp 69–70 °C. ¹H NMR (DMSO-d_6): δ 8.24 (s, 1 H, H$_a$), 8.13 (d, 1 H, J_{dc} = 7.8 Hz, H$_d$), 7.79 (s, 1 H, H$_c$), 7.30 (t, 1 H, J_{cb} = J_{cd} = 7.6 Hz, H$_c$), 7.22 (d, 1 H, J_{bc} = 7.6 Hz, H$_b$), 2.33 (s, 3 H, CH₃), 1.50 (s, 9 H, H$_f$). Anal. Calcd for C₁₂H₁₇NO: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.44; H, 8.98; N, 7.34.

C-(2-Methylphenyl)-N-tert-butylnitrone. Method II. Yield: 66%; mp 68–69.5 °C. ¹H NMR (DMSO-d_6): δ 9.03 (d, 1 H, J_{dc} = 7.2 Hz, H$_d$), 7.77 (s, 1 H, H$_e$), 7.25 (m, 3 H, Ar H), 2.38 (s, 3 H, CH₃), 1.53 (s, 9 H, H$_f$). Anal. Calcd for C₁₂H₁₇NO: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.59; H, 9.14; N, 7.38.

C-(4-Hydroxyphenyl)-N-tert-butylnitrone. Method I. Yield: 62%; mp 226 °C dec (lit.[31] mp 212–215 °C). ¹H NMR (DMSO-d_6): δ 8.26 (d, 2 H, J_{ab} = 8.8 Hz, H$_a$), 7.68 (s, 1 H, H$_c$), 6.79 (d, 2 H, J_{ba} = 8.8 Hz, H$_b$), 1.49 (s, 9 H, H$_d$). Anal. Calcd for C₁₁H₁₅NO₂: C, 68.37; H, 7.82; N. 7.25. Found: C, 68.44; H, 7.97; N, 7.31.

C-(3-Hydroxyphenyl)-N-tert-butylnitrone. Method I. Yield: 43%; mp 172 °C dec. ¹H NMR (DMSO-d_6): δ 8.07 (s, 1 H, H$_a$), 7.73 (s, 1 H, H$_e$), 7.55 (d, 1 H, J_{dc} = 7.4 Hz, H$_d$), 7.20 (t, 1 H, J_{cb} = J_{cd} = 7.9 Hz, H$_c$), 6.81 (d, 1 H, J_{bc} = 7.9 Hz, H$_b$), 3.39 (br s, 1 H, HO), 1.49 (s, 9 H, H$_f$). Anal. Calcd for C₁₁H₁₅NO₂: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.38; H, 7.97; N, 7.20.

C-(4-Fluorophenyl)-N-tert-butylnitrone. Method II. Yield: 67%; mp 82–83 °C (lit.[26a] mp 82–84 °C). ¹H NMR (DMSO-d_6): δ 8.48 (dd, 2 H, J_{ab} = 9.1 Hz, J_{aF} = 5.9 Hz, H$_a$), 7.89 (s, 1 H, H$_c$), 7.26 (t, 2 H, J_{ba} = 9.0 Hz, H$_b$), 1.51 (s, 9 H, H$_d$). Anal. Calcd for C₁₁H₁₄NOF: C, 67.68; H, 7.23; N, 7.17. Found: C, 67.44; H, 7.11; N, 7.19.

C-(3-Fluorophenyl)-N-tert-butylnitrone. Method II. Yield: 83%; mp 64–65 °C. ¹H NMR (DMSO-d_6): δ 8.48 (d, 1 H, J_{aF} = 11.3 Hz, H$_a$), 7.97 (d, 1 H, J_{dc} = 8.5 Hz, H$_d$), 7.96 (s, 1 H, H$_e$), 7.47 (dd, 1 H, J_{bc} = J_{bF} = 7.3 Hz, H$_b$), 7.25 (t, 1 H, J_{cd} = 8.5 Hz, H$_c$), 1.52 (s, 9 H, H$_f$). Anal. Calcd for C₁₁H₁₄NOF: C, 67.68; H, 7.23; N, 7.17. Found: C, 67.46; H, 7.38; N, 6.40.

C-(4-Cyanophenyl)-N-tert-butylnitrone. Method III. Yield: 27% (from aldehyde); mp 169–174 °C. ¹H NMR (DMSO-d_6): δ 8.52 (d, 2 H, J_{ab} = 8.5 Hz, H$_a$), 8.06 (s, 1 H, H$_c$), 7.88 (d, 2 H, J_{ba} = 8.6 Hz, H$_b$), 1.53 (s, 9 H, H$_d$). Anal. Calcd for C₁₂H₁₄N₂O: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.36; H, 7.12; N, 13.92.

C-(3-Cyanophenyl)-N-tert-butylnitrone. Method I. Yield: 3.1%; mp 43–51 °C. ¹H NMR (DMSO-d6): δ 8.38 (s, 1 H, H$_a$), 8.15 (s, 1 H, H$_e$), 8.10 (d, 1 H, J_{dc} = 7.8 Hz, H$_d$), 7.91 (d, 1 H, J_{bc} = 7.1 Hz, H$_b$), 7.66 (t, 1 H, J_{cb} = J_{cd} = 7.6 Hz, H$_c$), 1.26 (s, 9 H, H$_f$). Anal. Calcd for C₁₂H₁₄N₂O: C, 71.26; H, 6.98; N, 13.85. Found: C, 76.51; H, 7.17; N, 14.18.

C-(4-Methoxyphenyl)-N-tert-butylnitrone. Method II. Yield: 52%; mp 95–97 °C (lit.[32] mp 96.5–97 °C). ¹H NMR (DMSO-d_6): δ 8.36 (d, 2 H, J_{ab} = 9.0 Hz, H$_a$), 7.75 (s, 1 H, H$_c$), 6.98 (d, 2 H, J_{ba} = 9.0 Hz, H$_b$), 3.80 (s, 3 H, CH₃O), 1.49 (s, 9 H, H$_d$). Anal. Calcd for C₁₂H₁₇NO₂: C, 69.54; H, 8.27; N, 6.76. Found: C, 70.56; H, 8.64; N, 6.64.

C-(3-Methoxyphenyl)-N-tert-butylnitrone. Method II. Yield: 76%; mp 90–91 °C. ¹H NMR (DMSO-d_6): δ 8.21 (s, 1 H, H$_a$), 7.84 (s, 1 H, H$_e$), 7.79 (d, 1 H, J_{dc} = 7.8 Hz, H$_d$), 7.33 (t, 1 H, J_{cb} = J_{cd} = 7.9 Hz, H$_c$), 6.98 (dd, 1 H, J_{bc} = 8.2 Hz, J_{bd} = 2.8 Hz, H$_b$), 3.77 (s, 3 H, CH₃O), 1.51 (s, 9 H, H$_f$). Anal. Calcd for C₁₂H₁₇NO₂: C, 69.54; H, 8.27; N, 6.76. Found: C, 68.85; H, 8.12; N, 6.69.

C-(2-Methoxyphenyl)-N-tert-butylnitrone. Method II. Yield: 97%; mp 83–84 °C. ¹H NMR (DMSO-d_6): δ 9.26 (dd, 1 H, J_{dc} = 7.9 Hz, J_{db} = 1.6 Hz, H$_d$), 7.97 (s, 1 H, H$_e$), 7.39 (td, 1 H, J_{cd} = J_{cb} = 7.8 Hz, J_{ca} = 1.8 Hz, H$_c$), 7.06 (m, 1 H, H$_a$), 6.98 (t, 1 H, J_{bc} = J_{ba} = 7.6 Hz, H$_b$), 3.85 (s, 3 H, CH₃O), 1.50 (s, 9 H, H$_f$). Anal. Calcd for C₁₂H₁₇NO₂: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.04; H, 8.25; N, 6.88.

C-(4-Chlorophenyl)-N-tert-butylnitrone. Method II. Yield: 80%; mp 71–72 °C (lit.[32] mp 69–71 °C). ¹H NMR (DMSO-d_6): δ 8.42 (d, 2 H, J_{ab} = 8.7 Hz, H$_a$), 7.92 (s, 1 H, H$_c$), 7.49 (d, 2 H, J_{ba} = 8.6 Hz, H$_b$), 1.52 (s, 9 H, H$_d$). Anal. Calcd for C₁₁H₁₄NOCl: C, 62.41; H, 6.67; N, 6.62. Found: C, 62.40; H, 6.56; N, 6.60.

C-(3-Chlorophenyl)-N-tert-butylnitrone. Method II. Yield: 55%; mp 78–79 °C. ¹H NMR (DMSO-d_6): δ 8.68 (s, 1 H, H$_a$), 8.15 (t, 1 H, J_{cb} = J_{cd} = 8.0 Hz, H$_c$), 7.95 (s, 1 H, H$_e$), 7.46 (m, 2 H, H$_b$, H$_d$), 1.51 (s, 9 H, H$_f$). Anal. Calcd for C₁₁H₁₄NOCl: C, 62.41; H, 6.67; N, 6.62. Found: C, 62.18; H, 6.60; N, 6.62.

C-(2-Carboxylphenyl)-N-tert-butylnitrone. Method I. After the reaction was completed the benzene solution was extracted with 1 N NaOH. The aqueous layer was then neutralized with HCl, causing the nitrone to precipitate. This precipitate was filtered out, dried, and weighed. Yield: 25%; mp 139–141 °C. ¹H NMR (DMSO-d_6): δ 7.83 (s, 1 H, H$_e$), 7.75 (d, 1 H, J_{dc} = 7.43 Hz, H$_d$), 7.53 (t, 1 H, J_{cb} = J_{cd} = 7.4 Hz, H$_c$), 7.45 (t, 1 H, J_{ba} = J_{bc} = 7.4 Hz, H$_b$), 7.33 (d, 1 H, J_{ab} = 7.3 Hz, H$_a$), 1.33 (s, 9 H, H$_f$). Anal. Calcd for C₁₂H₁₅NO₃: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.06; H, 6.96; N, 6.32.

C-(4-Nitrophenyl)-N-tert-butylnitrone. Method I. Yield: 87%; mp 147–149 °C (lit.[26a] mp 147–148 °C). ¹H NMR (DMSO-d_6): δ 8.60 (d, 2 H, J_{ab} = 8.8 Hz, H$_a$), 8.28 (d, 2 H, J_{ba} = 8.8 Hz, H$_b$), 8.15 (s, 1 H, H$_c$), 1.55 (s, 9 H; H$_d$). Anal. Calcd for C₁₁H₁₄N₂O₃: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.48; H, 6.43; N, 12.41.

C-(3-Nitrophenyl)-N-tert-butylnitrone. Method I. Yield: 92%; mp 108–110 °C. ¹H NMR (DMSO-d_6): δ 9.52 (s, 1 H, H$_a$), 8.58 (d, 1 H, J_{dc} = 7.8 Hz, H$_d$), 8.24 (dd, 1 H, J_{bc} = 8.1 Hz, J_{bd} unclear, H$_b$), 8.18 (s, 1 H, H$_e$), 7.72 (t, 1 H, J_{cb} = J_{cd} = 8.1 Hz, H$_c$), 1.55 (s, 9 H, H$_f$). Anal. Calcd for C₁₁H₁₄N₂O₃: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.34; H, 6.37; N, 12.45.

C-(2-Nitrophenyl)-N-tert-butylnitrone. Method I. Yield: 78%; mp 50–58 °C. ¹H NMR (DMSO-d_6): δ 8.20 (d, 1 H, J_{dc} = 7.9 Hz, H$_d$), 8.17 (s, 1 H, H$_e$), 7.99 (d, 1 H, J_{ab} = 8.1 Hz, H$_a$), 7.78 (t, 1 H, J_{cb} = J_{cd} = 7.6 Hz, H$_c$), 7.62 (t, 1 H, J_{ba} = J_{bc} = 7.8 Hz, H$_b$), 1.48 (s, 9 H, H$_f$).

C-[4-(Methylthio)phenyl]-N-tert-butylnitrone. Method II. Yield: 68%; mp 93–95 °C. ¹H NMR (DMSO-d_6): δ 8.32 (d, 2 H, J_{ab} = 8.3 Hz, H$_a$), 7.80 (s, 1 H, H$_c$), 7.28 (d, 2 H, J_{ba} = 8.3 Hz, H$_b$), 2.51 (s, 3 H, CH₃S), 1.50 (s, 9 H, H$_d$). Anal. Calcd for C₁₂H₁₇NOS: C, 64.54; H, 7.67; N, 6.27. Found: C, 64.64; H, 7.83; N, 6.29.

C-(4-Acetamidophenyl)-N-tert-butylnitrone. Method I. Yield: 61%; mp 181–182 °C. ¹H NMR (DMSO-d_6): δ 8.31 (d,

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(32) Markowicz, T.; Skolimowski, J.; Skowronski, R. *Pol. J. Chem.* **1981**, *55*, 2505–2508.

2 H, J_{ab} = 8.8 Hz, H$_a$), 7.75 (s, 1 H, H$_c$), 7.63 (d, 2 H, J_{ba} = 8.8 Hz, H$_b$), 3.41 (s, 1 H, CONH), 2.07 (s, 3 H, CH$_3$C=O), 1.55 (s, 9 H, H$_d$). Anal. Calcd for C$_{13}$H$_{18}$N$_2$O$_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 62.06; H, 8.11; N, 11.11.

***C*-(4-Acetoxyphenyl)-*N*-*tert*-butylnitrone. Method I.** Yield: 60%; mp 211 °C dec. ^{1}H NMR (CDCl$_3$): δ 8.19 (d, 2 H, J_{ab} = 8.8 Hz, H$_a$), 7.51 (s, 1 H, H$_c$), 6.87 (d, 2 H, J_{ba} = 8.9 Hz, H$_b$), 2.09 (s, 3 H, CH$_3$CO$_2$), 1.61 (s, 9 H, H$_d$). Anal. Calcd for C$_{13}$H$_{17}$NO$_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 63.68; H, 7.61; N, 5.97.

***C*-[4-(α,α,α-Trifluoromethyl)phenyl]-*N*-*tert*-butylnitrone. Method II.** Yield: 86%; mp 79–83 °C (lit.[26a] mp 85–87 °C). ^{1}H NMR (DMSO-d_6): δ 8.58 (d, 2 H, J_{ab} = 7.9 Hz, H$_a$), 8.05 (s, 1 H, H$_c$), 7.78 (d, 2 H, J_{ba} = 8.2 Hz, H$_b$), 1.54 (s, 9 H, H$_d$). Anal. Calcd for C$_{12}$H$_{14}$NOF$_3$: C, 58.77; H, 5.75; N, 5.71. Found: C, 58.92; H, 5.66; N, 5.77.

***C*-[3-(α,α,α-Trifluoromethyl)phenyl]-*N*-*tert*-butylnitrone. Method II.** Yield: 93%; mp 55.5–57.5 °C. ^{1}H NMR (DMSO-d_6): δ 9.00 (s, 1 H, H$_a$), 8.51 (d, 1 H, J_{dc} = 7.8 Hz, H$_d$), 8.09 (s, 1 H, H$_e$), 7.76 (d, 1 H, J_{bc} = 7.8 Hz, H$_b$), 7.67 (t, 1 H, J_{cb} = J_{cd} = 7.8 Hz, H$_c$), 1.54 (s, 9 H, H$_f$). Anal. Calcd for C$_{12}$H$_{14}$NOF$_3$: C, 58.77; H, 5.75; N, 5.71. Found: C, 58.81; H, 5.95; N, 5.69.

***C*-(4-Bromophenyl)-*N*-*tert*-butylnitrone. Method II.** Yield: 80%; mp 61–62 °C (lit.[33] mp 61–62 °C). ^{1}H NMR (DMSO-d_6): δ 8.34 (dd, 2 H, J_{ab} = 8.7 Hz, $J_{ab'}$ = 1.84 Hz, H$_a$), 7.90 (s, 1 H, H$_c$), 7.62 (dd, 2 H, J_{ba} = 8.7 Hz, $J_{ba'}$ = 1.90 Hz, H$_b$), 1.51 (s, 9 H, H$_d$). Anal. Calcd for C$_{11}$H$_{14}$NOBr: C, 51.58; H, 5.51; N, 5.47. Found: C, 51.30; H, 5.44; N, 5.47.

***C*-(3-Bromophenyl)-*N*-*tert*-butylnitrone. Method II.** Yield: 31%; mp 78–79 °C. ^{1}H NMR (DMSO-d_6): δ 8.82 (s, 1 H, H$_a$), 8.20 (d, 1 H, J_{dc} = 7.8 Hz, H$_d$), 7.93 (s, 1 H, H$_e$), 7.60 (br d, 1 H, J_{bc} = 9.3 Hz, H$_b$), 7.39 (t, 1 H, J_{cb} = J_{cd} = 7.9 Hz, H$_c$), 1.51 (s, 9 H, H$_f$). Anal. Calcd for C$_{11}$H$_{14}$NOBr: C, 51.58; H, 5.51; N, 5.47. Found: C, 51.90; H, 5.77; N, 5.45.

***C*-(2-Bromophenyl)-*N*-*tert*-butylnitrone. Method II.** Yield: 79%; mp 78–81 °C. ^{1}H NMR (DMSO-d_6): δ 9.23 (dd, 1 H, J_{dc} = 8.0 Hz, J_{db} = 1.7 Hz, H$_d$), 8.01 (s, 1 H, H$_a$), 7.74 (dd, 1 H, J_{ab} = 8.0 Hz, J_{ac} = 1.3 Hz, H$_a$), 7.45 (t, 1 H, J_{cd} = J_{cb} = 7.2 Hz, H$_c$), 7.34 (td, 1 H, J_{ba} = J_{bc} = 7.6 Hz, J_{bd} = 1.8 Hz, H$_b$), 1.54 (s, 9 H, H$_f$). Anal. Calcd for C$_{11}$H$_{14}$NOBr: C, 51.58; H, 5.51; N, 5.47. Found: C, 51.36; H, 5.53; N, 5.39.

Registry No. Benzaldehyde, 100-52-7; 4-methylbenzaldehyde, 104-87-0; 3-methylbenzaldehyde, 620-23-5; 2-methylbenzaldehyde, 529-20-4; 4-hydroxybenzaldehyde, 123-08-0; 3-hydroxybenzaldehyde, 100-83-4; 4-fluorobenzaldehyde, 459-57-4; 3-fluorobenzaldehyde, 456-48-4; 4-cyanobenzaldehyde, 105-07-7; 3-cyanobenzaldehyde, 24964-64-5; 4-methoxybenzaldehyde, 123-11-5; 3-methoxybenzaldehyde, 591-31-1; 2-methoxybenzaldehyde, 135-02-4; 4-chlorobenzaldehyde, 104-88-1; 3-chlorobenzaldehyde, 587-04-2; 2-formylbenzoic acid, 119-67-5; 4-nitrobenzaldehyde, 555-16-8; 3-nitrobenzaldehyde, 99-61-6; 2-nitrobenzaldehyde, 552-89-6; 4-(methylthio)benzaldehyde, 3446-89-7; 4-acetamidobenzaldehyde, 122-85-0; 4-acetoxybenzaldehyde, 878-00-2; 4-(trifluoromethyl)benzaldehyde, 455-19-6; 3-(trifluoromethyl)benzaldehyde, 454-89-7; 4-bromobenzaldehyde, 1122-91-4; 3-bromobenzaldehyde, 3132-99-8; 2-bromobenzaldehyde, 6630-33-7; *C*-phenyl-*N*-*tert*-butylnitrone, 3376-24-7; *C*-(*p*-tolyl)-*N*-*tert*-butylnitrone, 40117-29-1; *C*-(*m*-tolyl)-*N*-*tert*-butylnitrone, 115995-19-2; *C*-(*o*-tolyl)-*N*-*tert*-butylnitrone, 135485-37-9; *C*-(4-hydroxyphenyl)-*N*-*tert*-butylnitrone, 93376-44-4; *C*-(3-hydroxyphenyl)-*N*-*tert*-butylnitrone, 104883-61-6; *C*-(4-fluorophenyl)-*N*-*tert*-butylnitrone, 85623-70-7; *C*-(3-fluorophenyl)-*N*-*tert*-butylnitrone, 139607-30-0; *C*-(4-cyanophenyl)-*N*-*tert*-butylnitrone, 67036-01-5; *C*-(3-cyanophenyl)-*N*-*tert*-butylnitrone, 135485-36-8; *C*-(4-methoxyphenyl)-*N*-*tert*-butylnitrone, 40117-28-0; *C*-(3-methoxyphenyl)-*N*-*tert*-butylnitrone, 115995-22-7; *C*-(2-methoxyphenyl)-*N*-*tert*-butylnitrone, 130995-65-2; *C*-(4-chlorophenyl)-*N*-*tert*-butylnitrone, 40117-30-4; *C*-(3-chlorophenyl)-*N*-*tert*-butylnitrone, 115995-24-9; *C*-(2-carboxyphenyl)-*N*-*tert*-butylnitrone, 137353-83-4; *C*-(4-nitrophenyl)-*N*-*tert*-butylnitrone, 3585-88-4; *C*-(3-nitrophenyl)-*N*-*tert*-butylnitrone, 115995-25-0; *C*-(2-nitrophenyl)-*N*-*tert*-butylnitrone, 139607-31-1; *C*-[4-(methylthio)phenyl]-*N*-*tert*-butylnitrone, 117458-02-3; *C*-(4-acetoxyphenyl)-*N*-*tert*-butylnitrone, 139607-32-2; *C*-[4-(trifluoromethyl)phenyl]-*N*-*tert*-butylnitrone, 122778-03-4; *C*-[3-(trifluoromethyl)phenyl]-*N*-*tert*-butylnitrone, 139607-33-3; *C*-(4-bromophenyl)-*N*-*tert*-butylnitrone, 76790-28-8; *C*-(3-bromophenyl)-*N*-*tert*-butylnitrone, 139069-93-5; *C*-(2-bromophenyl)-*N*-*tert*-butylnitrone, 139607-34-4; *C*-(2-hydroxyphenyl)-*N*-*tert*-butylnitrone, 104883-60-5; *C*-(2-fluorophenyl)-*N*-*tert*-butylnitrone, 122778-00-1; *C*-(4-*tert*-butylphenyl)-*N*-*tert*-butylnitrone, 88888-33-9; sodium 2-[(*tert*-butylimino)methyl]benzenesulfonate *N*-oxide, 73475-11-3; 4-[(*tert*-butylimino)methyl]-*N*,*N*,*N*-trimethylbenzenaminium *N*-oxide, 88888-34-0; hydroxyl, 3352-57-6; hydroperoxyl, 3170-83-0; *C*-(4-acetamidophenyl)-*N*-*tert*-butylnitrone, 139607-35-5.

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