25.20 MHz. All spectra were obtained with the use of Fourier transform techniques. The δ values portrayed on formulas **8**, **9**, **19**, **20**, and **21** refer to $Me_2SO\text{-}d_6$ solutions, those on formulas **6** and **7** to deuteriochloroform solutions, and those on formulas **10**, **11** and **12** imply chloroform [δ (Me_4Si) = $\delta(CHCl_3)$ + 77.2 ppm] as solvent.

Registry No.—**1**, 981-15-7; **2**, 22611-34-3; **3**, 1259-86-5; **3a**, 1448-23-3; **13a**, 25514-29-8; **13b**, 37746-38-6; **14a**, 25514-30-1; **14b**, 55606-57-0; **15**, 990-35-2; **16**, 990-33-0; **17a**, 55658-68-9; **17b**, 55606-58-1.

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Equilibrium in the Behrend Rearrangement of Nitrones

Peter A. S. Smith* and Stewart E. Gloyer[1]

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48104

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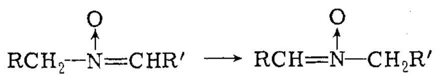
A group of α-phenyl-*N*-benzylnitrones bearing one of the substituents nitro (*o*-, *m*-, or *p*-), chloro (*o*- or *p*-), methyl (*p*-), methoxy (*o*-, *m*-, *p*-), as well as the *p*-methoxy-*p*-nitro derivative and α,α-diphenyl-*N*-benzylnitrone, were made to undergo Behrend rearrangement to the isomeric nitrone resulting from 1,3-prototropic shift by treatment with sodium methoxide in refluxing ethanol. It was demonstrated that an equilibrium mixture was obtained in each case by approaching the equilibrium from either side. Equilibrium compositions were determined by NMR spectroscopy. All para substituents favored the isomer with substituent on the α-phenyl group. *m*-Methoxy as a substituent was almost without effect on the equilibrium, and a *m*-nitro group slightly favored the isomer with the substituent on the *N*-benzyl group. The ortho substituents strongly favored the isomer with the substituent on the *N*-benzyl group, presumably for steric reasons. α-Phenyl-*N*-benzhydrylnitrone was favored over its isomer, α,α-diphenyl-*N*-benzylnitrone (K = 0.57). The results with the para substituents are consistent with an electronically amphoteric capability of the nitrone group for conjugation.

Isomerization of nitrones by a 1,3-prototropic shift has been called the Behrend rearrangement after its discoverer[2] (eq 1). The closely related isomerization of imines has

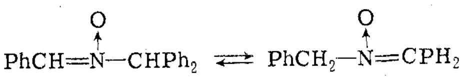


$$\mathrm{RCH_2{-}\overset{\overset{O}{\uparrow}}{N}{=}CHR' \longrightarrow RCH{=}\overset{\overset{O}{\uparrow}}{N}{-}CH_2R'} \qquad (1)$$

been extensively studied, owing to its importance in biological transamination,[3] but the Behrend rearrangement has received only casual attention.

The initial work on the Behrend rearrangement was essentially qualitative,[2,4–6] directed mainly to the question of whether or not a given nitrone would rearrange. Neubauer[4] investigated a number of substituted α-phenyl-*N*-benzylnitrones, examining the products by fractional crystallization. According to his work and that of Behrend, two such systems (*p*-chloro and *p*-nitro) underwent the 1,3-prototropic shift reversibly, one of them (α-*m*-nitrophenyl) underwent irreversible rearrangement, and many (*p*-methoxy, *p*-hydroxy, *o*-hydroxy, *o*-chloro, *o*-nitro) were inert to attempted rearrangement catalyzed by alcoholic sodium ethoxide. The confusing inconsistency of the observations was noted much later by Lamchen.[7]

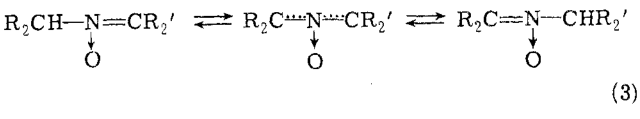
The Behrend rearrangement may occur during the preparation or isolation of nitrones, as first noticed by Behrend and König.[2] Cope and Haven prepared[8] α,α-diphenyl-*N*-benzylnitrone (**2**) successfully from benzophenone imine and *N*-benzylhydroxylamine hydrochloride when they used ammonia as the base, but use of sodium ethoxide brought about isomerization to α-phenyl-*N*-benzhydrylnitrone (**1**).



$$\mathrm{PhCH{=}\overset{\overset{O}{\uparrow}}{N}{-}CHPh_2 \rightleftarrows PhCH_2{-}\overset{\overset{O}{\uparrow}}{N}{=}CPH_2} \qquad (2)$$

1 2

Smith and Robertson[9] encountered rearrangement of certain nitrones during a study of the site of alkylation of oxime anions. The collected reports point to catalysis by strong base, an unelucidated dependence of both the ease and direction of rearrangement on structure, and a susceptibility to rearrangement equal to or greater than that of imines. The mechanism is presumed to involve abstraction of a proton to form a delocalized carbanion (eq 3).[7,9]



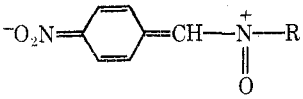
$$\mathrm{R_2CH{-}\underset{\underset{O}{\downarrow}}{N}{=}CR_2' \rightleftarrows \overset{-}{R_2C{\cdots}\underset{\underset{O}{\downarrow}}{N}{\cdots}CR_2'} \rightleftarrows R_2C{=}\underset{\underset{O}{\downarrow}}{N}{-}CHR_2'} \qquad (3)$$

Table I

					$R{-}C_6H_4CH_2{-}\overset{\overset{O}{\uparrow}}{N}{=}CHC_6H_4{-}R'$			
	α-Phenyl-*N*-benzylnitrones				Ir, cm^{-1}		NMR, ppm	
Nitrone	R	R′	Yield, %	Mp, °C	N→O	C=N	N=CH	NCH_2
5a	*p*-NO_2	H	71	112–113^a	1150	1615, 1605, 1590	(∼7.5)^b	5.06
5b	*p*-Cl	H	86	124–125^c	1175	1595	(∼7.3)^b	4.91
5c	*p*-CH_3	H	92	82–83	1160	1580	(∼7.3)^b	4.94
5d	*p*-CH_3O	H	99	108–109	1150	1615	(∼7.3)^b	4.92
5e	*o*-NO_2	H	58	104.5–105.5^d	1140	1615, 1580	>7.1^b	5.4
5f	*o*-Cl	H	96.5	73.5–75^e	1150	1600, 1590	>7.1^b	5.11
5g	*o*-CH_3O	H	30	90–92	1145	1605, 1595, 1580	>6.8^b	5.10
5h	*m*-NO_2	H	62	116–117^f		1590	>7.3^b	5.15
5i	*m*-CH_3O	H	58	95.5–97	1150	1590	>6.8^b	5.0
5j	*p*-CH_3O	*p*-NO_2	77.5	140–141	1160	1615, 1605	>7.35^b	5.05
6a	H	*p*-NO_2	75.5	118–119^g	1155	1600	7.44	4.97
6b	H	*p*-Cl	93	121–122^h	1150	1585	(∼7.3)^b	4.93
6c	H	*p*-CH_3	90	117–118^i	1150	1595	(∼7.3)^b	4.92
6d	H	*p*-CH_3O	89	108–109^j	1150	1605	(∼7.4)^b	4.94
6e	H	*o*-NO_2	79	127–128^k	1175	1615, 1695, 1585	>7.1^b	5.01
6f	H	*o*-Cl	81.5	87.5–88.5^l	1155	1575	>7.1^b	5.01
6g	H	*o*-CH_3O	69	83.5–85	1160	1600	>6.7^b	4.98
6h	H	*m*-NO_2	89.5	149–150^m	1160	1590	>7.25^b	5.08
6i	H	*m*-CH_3O	70	76–77	1155	1600, 1585	>6.8^b	5.02
6j	*p*-NO_2	*p*-CH_3O	45.5	151.5–152.5		1610, 1585	>7.3^b	5.11

[a] Lit. mp 113.5–114.5°: R. Behrend and E. König, *Ber.*, **23**, 2751 (1890). [b] Signal incorporated in phenyl multiplet. [c] Lit.[4] mp 125–126°. [d] Lit. mp 104–105°: C. Kjellin and K. G. Kuzlenstjena, *Ber.*, **30**, 1898 (1897). [e] Lit. mp 75–77°: F. Wegener, *Justus Liebigs Ann. Chem.*, **314**, 235 (1900). [f] Lit.[2] mp 114–115°. [g] Lit.[14] mp 118°. [h] Lit.[4] mp 121°. [i] Lit. mp 119°: P. Grammaticakis, *C. R. Acad. Sci.*, **224**, 1568 (1947). [j] Lit. mp 109°: E. Beckmann, *Ber.*, **23**, 1690 (1890). [k] Lit. mp 124°: E. Beckmann, *Justus Liebigs Ann. Chem.*, **367**, 273 (1909). [l] Lit.[4] mp 86°. [m] Lit. mp 148–150°: H. Goldschmidt, *Ber.*, **23**, 2174 (1890).

The present study was undertaken in order to obtain systematic data on the Behrend rearrangement. Apart from the lack of consistency of the previous reports with expectations based on accepted effects of substituents,[7] there is also the interesting aspect that the nitrone function should be electronically amphoteric in its interaction with attached aryl groups (cf. structures **3** and **4**). We also wished to have information on the position of equilibrium of pairs of nitrones for interpreting the results of oxidation of the corresponding hydroxylamines, which would form the same pairs of isomeric nitrones.[10]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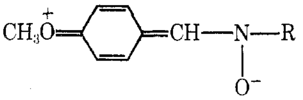
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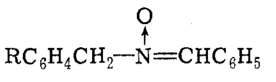
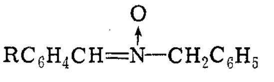
Results and Discussion

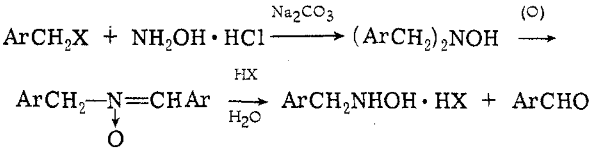
This study required a series of α-phenyl-*N*-benzylnitrones (*N*-benzylbenzaldimine *N*-oxides) of unambiguous structures (**5** and **6**). These were prepared by condensation of benzaldehydes with *N*-benzylhydroxylamines without added base, under which conditions it could be demonstrated spectroscopically that rearrangement did not occur. The required *N*-benzylhydroxylamines were obtained in either of two ways: benzaldoximes were reduced with diborane, or *N,N*-dibenzylhydroxylamines (obtained from benzyl halides and hydroxylamines) were oxidized to the corresponding nitrone and then hydrolyzed (eq 4). The nitrones prepared are listed in Table I. α-Phenyl-*N*-benzhydrylnitrone and α,α-diphenyl-*N*-benzylnitrone were prepared as reported by Cope and Haven.[9] Their infrared spectra showed one or more bands in the 1580–1615-cm^{-1} region, attributable to N → O stretching. The NMR signals of the benzylic hydrogens appeared in the range δ 4.91–5.40; the "aldehydic", N=CH signals fell in among the phenyl multiplets, in the region δ 6.8–7.8 ppm, and could not be unambiguously identified. The nitrones were presumed to have been obtained in the configurations with the phenyl and benzyl groups trans, which would be the more stable for steric reasons; in general, this assumption was supported by their spectra (the benzylic methylene group always showed a sharp NMR singlet, which was not altered by subjection to equilibrating conditions). The signals for ortho hydrogens of the α-phenyl groups appeared about 0.8 ppm downfield of the other hydrogens (generally about δ 8.0–8.2).


$RC_6H_4CH_2{-}\overset{\overset{O}{\uparrow}}{N}{=}CHC_6H_5$

5

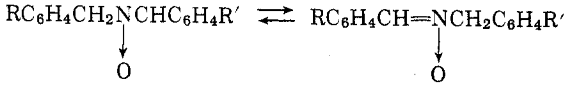

$RC_6H_4CH{=}\overset{\overset{O}{\uparrow}}{N}{-}CH_2C_6H_5$

6


$$ArCH_2X + NH_2OH\cdot HCl \xrightarrow{Na_2CO_3} (ArCH_2)_2NOH \xrightarrow{(O)} ArCH_2{-}\underset{\underset{O}{\downarrow}}{N}{=}CHAr \xrightarrow[H_2O]{HX} ArCH_2NHOH\cdot HX + ArCHO \quad (4)$$

The composition of the mixtures of isomeric nitrones obtained by the Behrend rearrangement was determined by NMR. The signals of the benzylic protons of the pairs of isomers **1–2**, **5a–6a** through **5h–6h**, and **5j–6j** were sufficiently differentiated to allow independent integration. For **5i–6i** mixtures, in which the benzylic proton signals were not clearly resolved, it was necessary to compare the strength of the total benzylic signal with that of the ortho protons furthest downfield, making use of the fact that **5i** has two ortho protons in the region δ 8.15–8.3 ppm, where-

Table II
Equilibrium Values



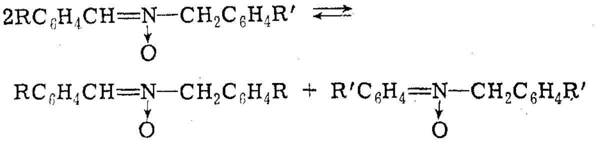
$$RC_6H_4CH_2\underset{\substack{\downarrow\\ O}}{N}CHC_6H_4R' \rightleftarrows RC_6H_4CH{=}\underset{\substack{\downarrow\\ O}}{N}CH_2C_6H_4R'$$

5 6

Substituents					
R	R′	Start	6, %	K, 5/6	Time, hr
p-NO_2	H	**5a**	54.9	0.82	1
			53.3	0.88	2
		6a	49.7	1.01	1
			50.5	0.98	3
p-Cl	H	**5b**	62.8	0.59	1
			63.3	0.58	6
		6b	62.2	0.61	1
			59.3	0.69	5
p-CH_3	H	**5c**	60.2	0.66	1
			61.9	0.62	3
		6c	61.4	0.63	1
			63.4	0.58	3
p-CH_3O	H	**5d**	75.3	0.33	2
			74.8	0.34	3
		6d	75.3	0.33	2
			74.5	0.34	5
o-NO_2	H	**6e**	8.2	11.2	3
			10.0	9.0	25
o-Cl	H	**5f**	19.3	4.18	1
			18.5	4.41	3
		6f	17.6	4.68	1
			18.5	4.41	3
o-CH_3O	H	**5g**	30.7	2.25	5
			32.8	2.04	7.5
		6g	33.6	1.98	1.5
			33.5	1.99	3
m-NO_2	H	**5h**	46.4	1.16	1
			46.9	1.13	3
		6h	44.8	1.23	1
			44.7	1.24	3
m-CH_3O	H	**5i**	53.8	0.86	3
		6i	51.5	0.94	1
			49.5	1.01	3
p-CH_3O	*p*-NO_2	**5j**	72.8	0.36	1
			72.3	0.37	3
		6j	75.0	0.33	1
			72.1	0.39	3

as **6i** has only one (the proton that is ortho to both the methoxy group and the azomethine group has its signal at higher field). For every pair of isomers, the reliability of the method was tested on mixtures of known composition. The percentage of each isomer in the known mixtures differed among separate determinations in most instances by less than one percent unit. Duplicate determinations were made for all unknown mixtures, and in many cases, duplicate experiments were performed.

The analytical spectra were taken in deuteriochloroform solution. We found that unanticipated signals sometimes appeared as a result of disproportionation of the nitrones (eq 5), apparently catalyzed by traces of HCl in the solvent.



$$2RC_6H_4CH{=}\underset{\substack{\downarrow\\ O}}{N}{-}CH_2C_6H_4R' \rightleftarrows$$
$$RC_6H_4CH{=}\underset{\substack{\downarrow\\ O}}{N}{-}CH_2C_6H_4R + R'C_6H_4{=}\underset{\substack{\downarrow\\ O}}{N}{-}CH_2C_6H_4R' \quad (5)$$

The addition of a small amount of triethylamine to the solvent before preparing the solutions for analysis completely suppressed disproportionation, even after standing for 24 hr. In untreated deuteriochloroform, mixtures of **5d** and **6d** rapidly developed four distinct peaks in the benzylic proton region, and solutions of Va and VIa developed three benzylic peaks and formed a precipitate of α-*p*-nitrophenyl-*N*-*p*-nitrobenzylnitrone.

Behrend rearrangement was brought about by means of sodium methoxide in refluxing ethanol. In every case, equilibrium was reached within 1 hr; determinations made after 3 hr did not differ significantly from the earlier ones. For every isomeric pair, equilibrium was approached from each side. Use of triethylamine in place of sodium methoxide did not bring about rearrangement. The results are recorded in Table II.

For one pair of nitrones only, equilibrium was not unambiguously achieved. The pair with *o*-nitro groups (**5e–6e**) formed a precipitate of a sodium salt when treated with alcoholic sodium methoxide; it was identical (spectrum and melting point) regardless of the isomer used. When a molar amount of the base was used instead of the usual catalytic amount, a ca. 60% yield of this product was isolated. The infrared band at 1355 cm^{-1}, characteristic of the nitro group, was absent. Acidification, even when carried out cautiously, produced only an intractable tar. Analysis for sodium gave variable results, but was qualitatively consistent with a monosodium salt; it seems most likely that a benzylic proton was lost, with the formation of a nitronate salt or a heterocyclic system. This substance was not further investigated.

Our results eliminate the inconsistencies in previous reports[2,4,7] and show that a straightforward thermodynamic equilibrium is reached with only a catalytic amount of strong base. Earlier reports that certain of the nitrones included in Table II did not rearrange must have resulted from inability to detect the minor isomer. The conditions required to bring about equilibration were similar to those that have been used for isomerization of the corresponding imines catalyzed by simple bases, although the time required may have been somewhat less.

All para substituents studied favored formation of the para-substituted benzylidene derivative (**6**), although the effect of the *p*-nitro group was very small. Such a situation may be explained if electron-donating substituents favor this isomer by combined inductive and mesomeric effects, but the effect of electron-withdrawing substituents is more than counterbalanced by enhanced conjugation, as in **3**. This interpretation is supported by the facts that a *m*-nitro group, in contrast, disfavors the substituted benzylidene isomer, and that the effect of a methoxy group drops sharply in going from the para to the meta position. The two ortho substituents for which results were obtained, chloro and methoxy, both strongly disfavored the substituted benzylidene isomer; presumably this fact is a result of steric interference by the ortho substituent with conjugation.

The system **1–2** had an equilibrium constant of 0.57, consistent with the report of Cope and Haven[8] that **2** easily isomerized to **1** in the presence of strong base. The fact that the α-monophenyl isomer is more stable than the α,α-diphenyl isomer is presumably a steric phenomenon.

Experimental Section

Infrared spectra were determined as Nujol mulls on a Perkin-Elmer Model 237B instrument, and NMR spectra were determined in deuteriochloroform solution with tetramethylsilane as internal reference, on a Varian A-60 instrument, unless otherwise indicated. Melting points are uncorrected. Elemental analyses were made by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Hydroxylamines. Benzylhydroxylamine was prepared from benzyl chloride according to the method of Sneed and Jones,[11] in which *N,N*-dibenzylhydroxylamine is first prepared by reaction with hydroxylamine, and is then oxidized to a nitrone by mercuric oxide and then hydrolyzed. *o*-Nitrobenzylhydroxylamine,[12] *o*-chlorobenzylhydroxylamine,[13] *m*-nitrobenzylhydroxylamine,[2] *m*-methoxybenzylhydroxylamine, and *p*-nitrobenzylhydroxylamine[14] were prepared analogously. *N,N*-Bis(*m*-Methoxybenzyl)hydroxylamine was obtained in 72.5% yield by refluxing a solution of 16.0 g (80 mmol) of *m*-methoxybenzyl bromide, 2.73 g (40 mmol) of hydroxylamine hydrochloride, and 13.3 g (120 mmol) of sodium carbonate in a mixture of 125 ml of 90% ethanol and 50 ml of water for 4 hr, and diluting the cooled reaction mixture with 300 ml of water to induce crystallization; mp 86–88° after recrystallization from cyclohexane; ir 3100–3350 (OH), 3040, 1605, 1600, 1590, 1260, 1170, 1040, 785, 745, and 695 cm^{-1}; NMR δ 3.67 and 3.74 (singlets, total 10 H, CH_3O and CH_2) and 6.64–7.35 ppm (m, 9 H, aryl CH plus OH).

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.49; H, 7.04; N, 5.03.

Oxidation with mercuric oxide produced an oil that could not be crystallized or distilled; its NMR spectrum, δ 3.78 (s, 6 H, CH_3O), 5.0 (s, 2 H, CH_2), 6.77–7.62 (m, 8 H, aryl CH plus N=CH), and 8.15–8.25 (m, 1 H, 6-H of α-*m*-methoxyphenyl), was consistent with the expected α-*m*-methoxyphenyl-*N*-*m*-methoxybenzylnitrone. Hydrolysis of the foregoing oil by steam distillation from 10 g of concentrated hydrochloric acid to remove the *m*-anisaldehyde formed, followed by basification of the residual solution with excess sodium carbonate solution and extraction with ether, drying ($MgSO_4$), and concentrating, produced *m*-methoxybenzylhydroxylamine as an oil which resisted attempts at crystallization. The entire amount was allowed to stand for 12 hr at ambient temperature with 0.715 g (6.75 mmol) of benzaldehyde in a small amount of ethanol. Concentration of the mixture gave 0.94 g (39%) of α-phenyl-*N*-*m*-methoxybenzylnitrone: mp 95.5–97°; ir 3040, 1590, 1485, 1295, 1260, 1150, 1045, 950, 875, 765, 755, and 695 cm^{-1}; NMR δ 3.77 (s, 3 H, CH_3O), 5.0 (s, 2 H, CH_2), 6.8–7.7 (m, 8 H, aryl CH plus N=CH), and 8.15–8.3 ppm (m, 2 H, *o*-H of α-phenyl).

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.53; H, 6.30; N, 5.65.

Bis(*m*-nitrobenzyl)hydroxylamine, required for preparing previously known *m*-nitrobenzylhydroxylamine,[2] was prepared in 38% yield from *m*-nitrobenzyl bromide in a manner analogous to that used for bis(*m*-methoxybenzyl)hydroxylamine. It had mp 106–108°; NMR δ 4.0 (s, 4 H, CH_2) and 7.3–8.34 ppm (m, 9 H).

Anal. Calcd for $C_{14}H_{13}N_3O_5$: C, 55.45; H, 4.32. Found: C, 55.62; H, 4.40.

p-Nitrobenzylhydroxylamine[14] (35% yield), *p*-chlorobenzylhydroxylamine[4] (29% yield), *p*-methylbenzylhydroxylamine (23% yield), *p*-methoxybenzylhydroxylamine[15] (24% yield), and *o*-methoxybenzylhydroxylamine[16] (38% yield) were prepared by reduction of the corresponding benzaldoxines with diborane in tetrahydrofuran by the method of Feuer, Vincent, and Barttell.[17] In several instances, a substantial amount of the corresponding benzylamine was also formed; it could be removed by preferential precipitation as the hydrochloride when dry HCl was passed into an ethereal solution of the reduction products, providing that the resulting mixture was filtered forthwith.

Nitrones. The required unsymmetrically substituted nitrones were prepared by dissolving equimolar amounts of a hydroxylamine and an aldehyde in a minimal volume of ethanol and allowing the mixture to stand at ambient temperature for about 12 hr. The precipitated products were then recrystallized from benzene or ethanol. The data are collected in Table I. Nitrones 1 and 2 were prepared as described by Cope and Haven.[8]

Isomerization of Nitrones. The instance of α-phenyl-*N*-*o*-chlorobenzylnitrone (**5f**) provides a representative example. To a solution of 0.3 g (1.22 mmol) of **5f** in 5 ml of absolute ethanol was added 2 drops of a stock solution prepared from 0.64 g (11.8 mmol) of sodium methoxide and 2 g of ethanol. The resulting solution was heated at reflux, and samples were removed after 1 and 3 hr. Each sample was evaporated to dryness in a stream of nitrogen. and the residue was dissolved in 50 ml of ether and washed with water. The ethereal solution was dried ($MgSO_4$), filtered, and then evaporated to dryness under aspirator vacuum; the residue was dissolved in deuteriochloroform to which sufficient triethylamine had been added to give a basic reaction, and the solution was examined by NMR spectroscopy. Comparison of the integrated intensities of the signals of the methylene groups of **5f** and its isomer **6f** gave the following values for the percent of **6f**: after 1 hr, 17.7 and 17.5; after 3 hr, 20.5 and 20.0. In a second experiment, the values were: after 1 hr, 16.4 and 18.7; after 3 hr, 16.7 and 16.9. The average of all values was 18.05% **6f** and 81.95% **5f**, corresponding to an equilibrium constant **5f**/**6f** of 4.54.

The averaged equilibrium data obtained from each of the nitrones are listed in Table II. Agreement of values within each series was similar to the example of **6f**, and in most cases better (the outside limit for variation of determined composition was 3.9 percent units), and not significantly different from the variation of determined compositions of known mixtures.

Reliability of the determinations was established by making up mixtures of pairs of nitrones of known composition by weight, and performing duplicate NMR analyses on them. For each pair, a known composition approximating the equilibrium composition was used; for several pairs, a range of different known compositions was used. The system **5f**–**6f** provides a representative example: mixture 1 (33.4% **5f**, 66.6% **6f**), found 33.0:67.0; mixture 2 (67.2% **5f**, 32.8% **6f**), found 66.6:33.4, 67.6:32.4.

Attempted Equilibration of the *o*-Nitro System (5f–6f). Treatment of α-phenyl-*N*-*o*-nitrobenzylnitrone (**5e**) in the normal manner resulted in formation of a small precipitate, which was collected after 3 hr of refluxing: ir 3150–3600, 3130, 3060, 1625, 1520, 1505, 1290, 1215, 1175, 1100, 770, 750, 740, 725, and 685 cm^{-1}. The filtrate was examined in the customary manner, and gave no evidence of rearrangement, even after the reaction mixture had been refluxed for 6 hr. Similar treatment of the isomer, **6e**, produced a precipitate with superimposable ir spectrum. Spectroscopic examination of the filtrate after 1 hr of refluxing showed no rearrangement. After 3 hr of refluxing, the following ratios of **5e**:**6e** were found: 6.8:93.2; 8.8:91.2; 9.0:91.0. After 25 hr of refluxing, ratios of 9.95:90.05 and 10.0:90.0 were obtained.

A solution of 1.024 g of **5e** and 0.208 g of sodium methoxide in 12 ml of absolute ethanol was refluxed for 15 min and then filtered while hot. The precipitate was washed with ether and dried: wt 0.70 g; mp 267° dec. It was insoluble in chloroform or ether, but dissolved in water with gas evolution. Contact with concentrated H_2SO_4 caused an explosion with a flash of fire. Extraction of a water solution of the salt with ether produced nothing; addition of tribenzylammonium bromide, in an attempt to liberate any weak acid from its salt, likewise produced nothing extractable. Acidification with sulfuric acid, however, allowed a yellow substance to be extracted into ether, but concentration of the dried ether solution produced only a dark tar with inconclusive ir and NMR spectra.

The initial precipitate had an ir spectrum superimposable on those of previous samples, but it could not be purified. Analysis for sodium by repeated evaporation to dryness with sulfuric acid produced residues of sodium sulfate that corresponded to values for sodium content of 4.0–11.0% among different preparations (calcd for a monosodium salt $C_{14}H_{11}N_2O_3Na$, 8.3%). The material was not further investigated.

Registry No.—**5a**, 22661-28-5; **5b**, 55606-33-2; **5c**, 55606-34-3; **5d**, 55606-35-4; **5e**, 22661-27-4; **5f**, 55606-36-5; **5g**, 55606-37-6; **5h**, 55606-38-7; **5i**, 55606-39-8; **5j**, 55606-40-1; **6a**, 22661-23-0; **6b**, 22687-09-8; **6c**, 55606-41-2; **6d**, 32114-41-3; **6e**, 22661-22-9; **6f**, 22687-07-6; **6g**, 55606-42-3; **6h**, 5367-21-5; **6i**, 55606-43-4; **6j**, 55606-44-5; *p*-nitrobenzylhydroxylamine, 2912-97-2; *p*-chlorobenzylhydroxylamine, 51307-68-7; *p*-methylbenzylhydroxylamine, 16814-17-8; *p*-methoxylbenzylhydroxylamine, 51307-59-6; *o*-nitrobenzylhydroxylamine, 37558-77-3; *o*-chlorobenzylhydroxylamine, 55606-45-6; *o*-methoxybenzylhydroxylamine, 55606-46-7; *m*-nitrobenzylhydroxylamine, 55606-47-8; *m*-methoxybenzylhydroxylamine, 55606-48-9; benzylhydroxylamine, 622-30-0; benzaldehyde, 100-52-7; *p*-methoxybenzaldehyde, 123-11-5; *p*-nitrobenzaldehyde, 555-16-8; *p*-chlorobenzaldehyde, 104-88-1; *p*-methylbenzaldehyde, 104-87-0; *m*-methoxybenzaldehyde, 591-31-1; *o*-nitrobenzaldehyde, 552-89-6; *o*-chlorobenzaldehyde, 89-98-5; *o*-methylbenzaldehyde, 135-02-4; *m*-nitrobenzaldehyde, 99-61-6; bis-(*m*-nitrobenzyl)hydroxylamine, 55606-49-0; *m*-nitrobenzyl bromide, 3958-57-4; *N,N*-bis-(*m*-methoxybenzyl)hydroxylamine, 55606-50-3; *m*-methoxybenzyl bromide, 874-98-6; α-*m*-methoxyphenyl-*N*-*m*-methoxybenzylnitrone, 55606-51-4.

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Oxidation of Dibenzylhydroxylamines to Nitrones. Effects of Structure and Oxidizing Agent on Composition of the Products

Peter A. S. Smith* and Stewart E. Gloyer[1]

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48104

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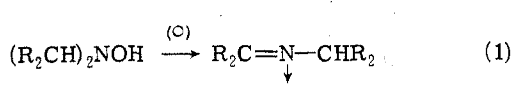
A group of dibenzylhydroxylamines bearing a para substituent (nitro, chloro, methyl, methoxy), a meta substituent (nitro, methoxy), or an ortho substituent (nitro, chloro, methoxy) as well as the *p*-methoxy-*p′*-nitro derivative, and the α-phenyl derivative, was treated with the oxidizing agents *N*-bromosuccinimide, (diacetoxyiodo)benzene, mercuric oxide, iodine, *tert*-butyl hydroperoxide, or ceric ammonium nitrate. The products were pairs of isomeric substituted *N*-benzyl-α-phenylnitrones; the compositions were determined by NMR. The isomer ratios differed from the known equilibrium ratios, in most cases only moderately, but markedly with the *p*-methoxy-*p′*-nitro and the α-phenyl examples; these facts imply kinetic control of product composition. Isomer ratios generally varied with the oxidizing agent used from slightly to moderately, a circumstance not altogether consistent with a common product-determining step, such as disproportionation of an intermediate nitroxide. Oxidations with mercuric oxide differed noticeably from those with the other oxidizing agents, especially in the cases with ortho substituents. Variation among oxidizing agents was marked with the α-phenyl derivative. Alternative product-determining steps, not involving nitroxide disproportionation, appear to be involved.

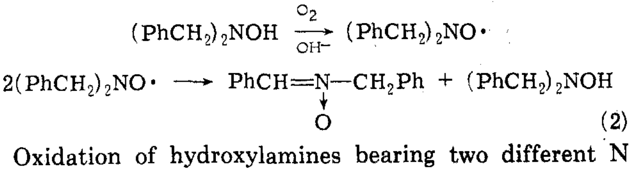
Oxidation of N,N-disubstituted hydroxylamines to nitrones (eq 1) has long been known, and occurs easily with a variety of oxidizing agents and in good yields. Although no



$$(R_2CH)_2NOH \xrightarrow{(O)} R_2C{=}\underset{\downarrow\atop O}{N}{-}CHR_2 \qquad (1)$$

general study of this reaction has been reported,[2] it has generally been presumed to proceed by a one-electron oxidation to an intermediate nitroxide radical. Support for this view is to be found in the work of Sheina and Gallai,[3] who observed a one-electron stage in the electrolytic oxidation of *N*-phenyl-*N*-benzylhydroxylamine, and that of Gutch and Waters,[4] who observed ESR signals corresponding to nitroxides during oxidation of several hydroxylamine derivatives with ceric ion or ferricyanide.

Oxidation of dibenzylhydroxylamine by oxygen in basic solution has been studied kinetically by Cowley and Waters,[5] who followed the appearance of the ESR signal of dibenzyl nitroxide. The second stage in the reaction was presumed to be disproportionation of the nitroxide into benzaldehyde *N*-phenylnitrone and dibenzylhydroxylamine (eq 2), but it was not specifically investigated.



$$(PhCH_2)_2NOH \xrightarrow[OH^-]{O_2} (PhCH_2)_2NO\cdot$$

$$2(PhCH_2)_2NO\cdot \longrightarrow PhCH{=}\underset{\downarrow\atop O}{N}{-}CH_2Ph + (PhCH_2)_2NOH \qquad (2)$$

Oxidation of hydroxylamines bearing two different N substituents appears not to have been studied, except for the work of Johnson, Rodgers, and Trappe[6] on the autoxidation of *N*-methyl-*N*-ethyl- and *N*-methyl-*N*-propylhydroxylamine, and certain cases where only one of the substituents bore an α hydrogen, and was thus oxidizable. If both substituents have α hydrogens, one would expect a pair of isomeric nitrones to be formed. If the ratio of isomers is thermodynamically determined, it would be identical with that determined from experiments on the equilibration of nitrones, modified slightly by any necessary differences in experimental conditions (i.e., temperature and solvent), but if the ratios are kinetically controlled, some differences from the equilibrium ratios might be found. If disproportionation of an intermediate nitroxide is the product-forming stage in the oxidation, the isomer ratios obtained would be the same, regardless of the oxidizing agent, even if kinetically determined. However, if the oxidizing agent is involved in the product-forming step, the isomer ratios might be sensitive to the nature of the oxidizing agent, presuming kinetic control.

We have undertaken a study of the ratios of isomeric nitrones produced from substituted dibenzylhydroxylamines, using a variety of oxidizing agents. We anticipated that the results would clarify some of the features of the mechanism, and would also have some practical value for the prediction of the major product to be expected where two are possible.

Results

A series of *N,N*-dibenzylhydroxylamines was prepared by treatment of monobenzylhydroxylamines[7] with benzyl halides in the presence of sodium carbonate. The yields and properties are reported in Table I. α-Phenyldibenzylhydroxylamine (*N*-benzyl-*N*-benzhydrylhydroxylamine) was prepared by the reaction of phenylmagnesium bromide with benzaldehyde-*N*-phenylnitrone.

Oxidations were carried out with *N*-bromosuccinimide in chloroform in the presence of pyridine or other amine, with (diacetoxyiodo)benzene (phenyliodoso acetate) in methylene chloride in the presence of cyclohexylamine, with