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N-NITROSOHYDROXYLAMINES I. ACETOLYSIS AND ACID-CATALYZED HYDROLYSIS OF N,O-DIBENZYL-N-NITROSOHYDROXYLAMINES. REACTION WITH POTASSIUM *t*-BUTOXIDE

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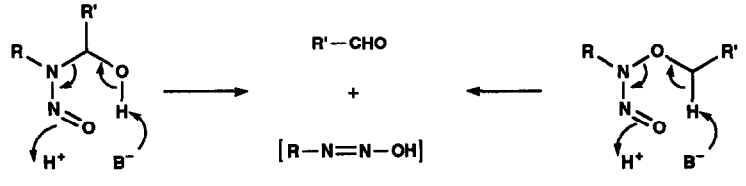
Abstract

The major products of the hydrolysis of N,O-dibenzyl-N-nitrosohydroxylamines (**3**) are the denitrosated parent hydroxylamines (**6**); under more forcing conditions, products of the further hydrolysis of **6** are obtained. Acetolysis in acetic acid gives the benzyl acetates derived from both N- and O-substituents. With potassium *tert*-butoxide, the major path is abstraction of an O-benzyl hydrogen followed by fragmentation to the aldehyde and the benzyldiazotate ion. Possible mechanisms for the formation of the products are discussed.

Introduction

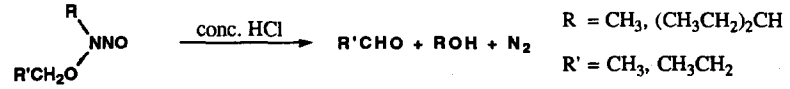
α-Hydroxy N-nitrosamines (**1**) resulting from the enzymatic hydroxylation of N-nitrosamines have been postulated as *precarcinogens*,[1] which could eventually be transformed into biologically active species such as diazonium or carbonium ions. The hemi-aminal nature of α-hydroxy N-nitrosamines makes their isolation and routine use difficult;



1 **2**

Scheme 1

derivatives such as α-acyloxy N-nitrosamines have been utilized for the study of α-hydroxy N-nitrosamines.[2] On the other hand, N,O-dialkyl-N-nitrosohydroxylamines (**2**) are stable and their *isosteric* relationship with α-hydroxy N-nitrosamines suggests that they might behave in a manner similar to α-hydroxy N-nitrosamines. Unfortunately there are very few reports on N,O-dialkyl-N-nitrosohydroxylamines[3-5] and to our knowledge the paper of Major *et al.*[3a] is the sole study of the acid-catalyzed hydrolysis of N,O-dialkyl-N-nitrosohydroxylamines (*Eq. 1*) which was reported to give



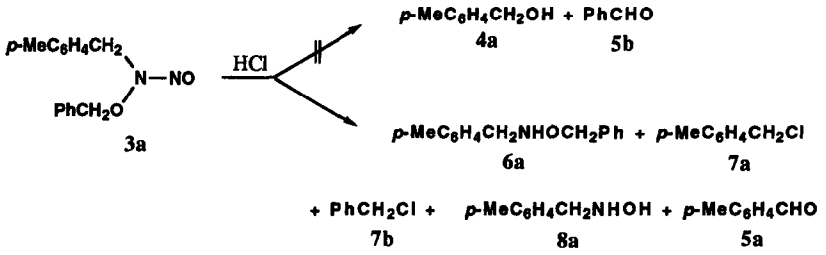
(1)

the products anticipated on the basis of the mechanistic path shown in *Scheme 1*. However, these procedures were less than clearly described, particularly with regard to reaction time, temperature and yield. In view of the paucity of available information, an investigation of the behavior of N,O-dibenzyl-N-nitrosohydroxylamines toward acids and alkoxides was undertaken.

Results and Discussion

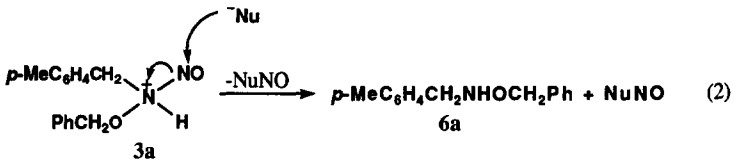
A. *Hydrolysis in concentrated Hydrochloric Acid*

The hydrolysis of N-(*p*-methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (**3a**) in conc. hydrochloric acid carried out *at 70-90°* gave the denitrosated product N-(*p*-methylbenzyl)-O-benzylhydroxylamine (**6a**) as the major product, in addition to *p*-methylbenzyl chloride (**7a**), benzyl chloride (**7b**), N-(*p*-methylbenzyl)hydroxylamine (**8a**) and *p*-tolualdehyde (**5a**) (*Scheme 2* and *Table 1*); neither the alcohol (**4a**) nor benzaldehyde (**5b**) expected on the basis of the



Scheme 2

results of Major[3a] were found. The formation of **6a** as the major product may be rationalized *via* initial protonation at the hydroxylamine nitrogen followed by loss of nitrosyl chloride (or nitrous acid) to afford hydroxylamine **6a** as with N-nitrosamines (*Eq. 2*).[2] On the other hand, when hydrolysis of **3a** in conc. hydrochloric acid was carried out *at reflux*,



(2)

not even traces of **6a** could be detected and the products were *p*-methylbenzyl chloride (**7a**), benzyl chloride (**7b**), *p*-tolualdehyde (**5a**) and N-(*p*-methylbenzyl)hydroxylamine (**8a**) in addition to trace amounts of benzaldehyde (**5b**); the yields of benzyl chloride (**7b**) and N-(*p*-methylbenzyl)hydroxylamine (**8a**) increased significantly (see Table). Similar results were also obtained from the hydrolysis of N-benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (**3b**).

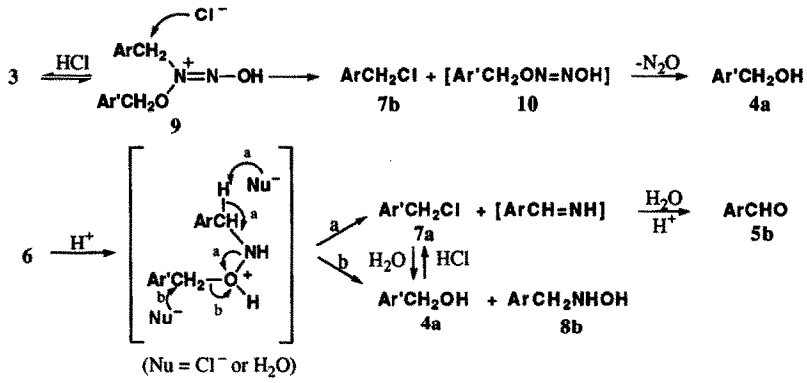
TABLE 1. Solvolysis of **3a** and **3b** in conc. Hydrochloric Acid[a]

Cmpd	Temp. (°C)	5a	5b	6a	6b	7a	7b	8a	8b
3a	70-90[b]	0.2	—	2.0	—	0.5	0.4	0.8	—
3a	80-110[b]	0.3	—	1.9	—	0.8	0.2	0.5	—
3a	reflux	0.1	traces	—	—	0.7	3.0	2.3	—
3b	reflux	—	0.5	—	—	3.8	0.7	—	2.0

a) Units are in mmol and four mmol of nitrosohydroxylamine were used. b) Temperature of oil bath.

The absence of N,O-dibenzylhydroxylamines (**6**), coupled with the increased yield of N-benzylhydroxylamines (**8**) and of the O-benzyl-derived chlorides (**7**) in the reactions *at reflux* suggested that **6** might be a source of **7** and **8**. It had been reported that N,O-dibenzylhydroxylamine in aqueous hydrochloric acid at 150° afforded benzyl

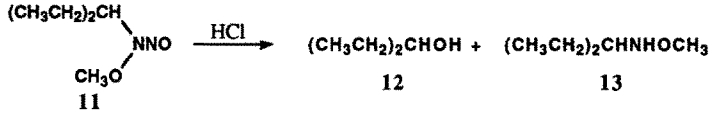
chloride and N-benzylhydroxylamine.[6] In order to confirm this possibility, N-benzyl-O-(*p*-methylbenzyl)hydroxylamine (**6b**) was heated in conc. hydrochloric acid at reflux and gave benzylaldehyde (**5b**), *p*-methylbenzyl chloride (**7a**) and N-benzylhydroxylamine (**8b**) in good yields. A possible rationalization for the formation of the products is



Scheme 3

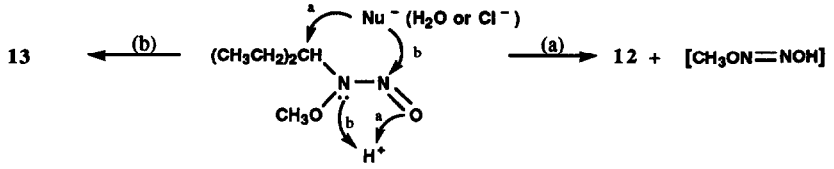
shown in *Scheme 3*. While protonation at the *amino* nitrogen of **3** leads to denitrosation as discussed earlier (*Eq. 2*), protonation at the *nitroso oxygen* followed by displacement by chloride ion (or water followed by reaction with HCl) could yield **7** and the benzyl hyponitrite **10**; extrusion of nitrous oxide from **10** would lead to the alcohol **4** as had been previously reported;[7] subsequent reaction with hydrochloric acid would account for the formation of **7**. Lamberton and Yusuf[3b] had described the formation of nitrous oxide from the hydrolysis of N-methyl-O-ethyl-N-nitrosohydroxylamine in 40% sulfuric acid. Alternatively, protonation of **6** at oxygen followed by either nucleophilic displacement at the O-benzyl carbon (*path b*) or removal of the α-hydrogen of the N-benzyl group (*path a*) would lead to the observed products as depicted in *Scheme 3*.

In view of the difference between our results of the hydrolysis in conc. hydrochloric acid and those of Major and his group,[3a] it was felt that this discrepancy might perhaps be caused by the benzylic substituents on the nitrosohydroxylamines studied. It was thus decided to reinvestigate the hydrolysis of N,O-dialkyl-N-nitrosohydroxylamines. Since the use of N-(*n*-butyl)-O-[(3-phenylpropyl)]-N-nitrosohydroxylamine as a substrate for this hydrolysis led to intractable tars, the hydrolysis of N-(3-pentyl)-O-methyl-N-nitrosohydroxylamine (**11**), one of the compounds used by Major, was carried out at room temperature. Even though 3-pentanol (**12**) was detected as a main product, there was no evidence of the formation of formaldehyde; N-(3-pentyl)-O-methylhydroxylamine (**13**) was isolated as the major product. Thus, 3-pentanol (**12**) could not have arisen *via* the path described by Major and his group (*Eq. 1*) but rather would



(3)

be generated by direct displacement as well as by subsequent hydrolysis of 3-chloropentane as shown in *Scheme 4*; no attempt was made to detect the by-product (methanol) from the aqueous reaction mixture. Secondly, Major and his group had reported the near quantitative formation of nitrogen (*Eq. 1*) which suggested the total loss of two nitrogens of **11**; however, N-(3-pentyl)-O-methylhydroxylamine (**13**) was obtained in approximately 50% yield in our experiment.

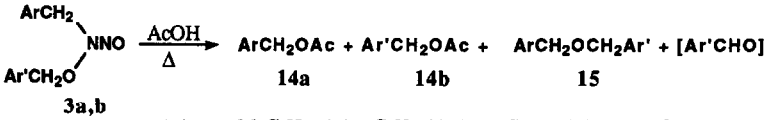


Scheme 4

Although the gas generated was not measured or characterized in our experiments, the results obtained in our study clearly cannot accommodate the possibility of quantitative formation of nitrogen. It is conceivable that hydroxylamine **13** could be further hydrolyzed in a manner similar to N,O-dibenzylhydroxylamine but it has been reported that N,O-dialkylhydroxylamines are nearly inert to boiling aqueous acids and neither N- nor O-substituents are easily removed by hydrolysis;[8a] this was confirmed in the present work by the nearly quantitative recovery of hydroxylamine **13** from its attempted hydrolysis in conc. hydrochloric acid at reflux. Finally, the reaction did not require heating for completion as previously described.[3a]

B. ***Acetolysis***

In order to gain further insight into the behavior of N-nitrosohydroxylamines, it was decided to study the solvolysis of N,O-dibenzyl-N-nitrosohydroxylamines (**3**) in glacial acetic acid. The reaction of **3b** in glacial acetic acid at reflux for 22 hrs gave benzyl acetate (**14b**), *p*-methylbenzyl acetate (**14a**) and benzyl *p*-methylbenzyl ether (**15**) as the



(4)

a) Ar = *p*-MeC_6H_4, Ar' = C_6H_5 b) Ar = C_6H_5, Ar' = *p*-MeC_6H_4

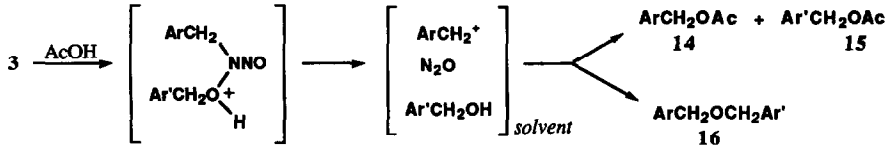
major products, in addition to a trace amounts of benzaldehyde; N-(*p*-methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (**3a**) afforded similar results (*Table 2*); coincidentally the *same* products were actually obtained in both cases. The acetolysis of **3a**, carried out for shorter periods of time under similar conditions afforded the same products in addition to benzyl alcohol originating from the O-benzyl substituent; however, the yield of benzyl acetate from the O-benzyl substituent decreased. These results clearly indicated that the alcohol had to be the precursor of the acetate and indeed, a control reaction of benzyl alcohol in acetic acid under similar conditions gave benzyl acetate in nearly quantitative yield. The fact that the denitrosated hydroxylamines (**6**) were *not* the intermediate in this reaction (*vide supra*) was demonstrated by a control reaction of **6** with acetic acid; under the same conditions, N-acetyl-N,O-dibenzylhydroxylamines were obtained in nearly quantitative yield and only trace amounts of the benzyl acetates could be detected.

TABLE 2. Acetolysis of **3a** and **3b** in Acetic Acid[a,b]

Cmpd	14a	14b	15
3a	3.7	3.8	1.0
3b	3.6	3.0	0.7

a) Units are in mmol and five mmol of nitrosohydroxylamine were used. b) At reflux.

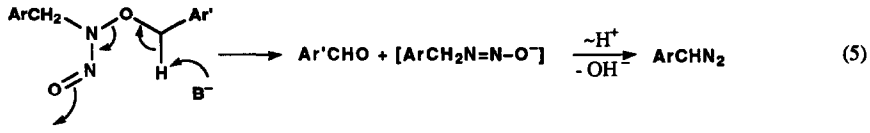
The benzyl acetates **14** and **16** might be generated *via* a mechanism related to that proposed by White and his group[8b] involving extrusion of nitrous oxide with concurrent generation of the N-derived benzyl carbocation and the O-derived benzyl alcohol, followed by reaction with acetic acid. Interaction of the carbocation with the alcohol within the solvent cage would account for the formation of the mixed dibenzyl ether as illustrated in *Scheme 5*.



Scheme 5

C. ***Base-catalyzed Decomposition***

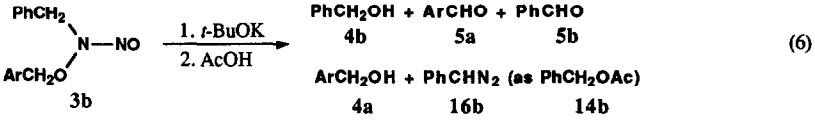
If N,O-dibenzyl-N-nitrosohydroxylamines decompose in a manner similar to α-hydroxy N-nitrosamines under



(5)

basic conditions,[1] the products would be the arylaldehyde and the benzyldiazotate ion which is known to be a precursor of the corresponding aryldiazomethanes.[9-11]

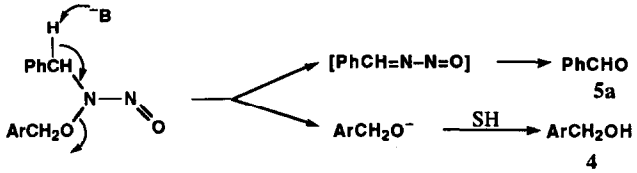
In order to minimize nucleophilic displacement observed with sodium methoxide and to avoid possible side-reactions, potassium *tert*-butoxide was used to react with N-benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (**3b**, 5 mmol) in glyme (dimethoxyethane) at ambient temperature for 24 hrs; after quenching with acetic acid, benzaldehyde (1.2 mmol), *p*-tolualdehyde (2.5 mmol), benzyl alcohol (0.5 mmol), *p*-methylbenzyl alcohol (2.2. mmol) and phenyldiazomethane (**16b**) (isolated as benzyl acetate, 2.3 mmol), were obtained. The formation of phenyldiazomethane could



(6)

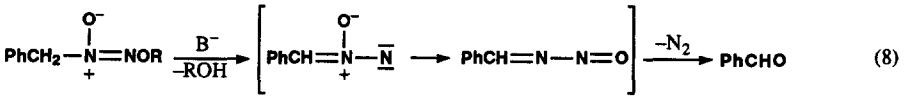
be observed by the change in the color of the initially yellow solution of the nitroso compound to pink upon addition of the base; the pink color disappeared after quenching with acetic acid. A possible rationalization for the formation of phenyldiazomethane illustrated in *Eq. 5* and *Scheme 1* involves abstraction of a benzylic hydrogen of the O-benzyl group followed by fragmentation to the benzyldiazotate ion and *p*-tolualdehyde (**5**, Ar = *p*-MeC_6H_4) which is one of the products characterized as shown in *Eq. 6*. It has been suggested by Gutsche and Johnson[9] that the mechanism for the formation of aryldiazomethanes from benzyldiazotate ions follows an E2 elimination process by a hydrogen transfer followed by loss of hydroxide ion to give the diazoalkanes. Therefore, electron-donating groups on the ring should retard the reaction while electron-withdrawing groups should favor this reaction. Indeed, when the reaction was carried out with N-(*p*-methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (**3a**), the yield of acetate **14a** was much lower than that of the N-benzyl case (**14b**); on the other hand, N-(*p*-chlorobenzyl)-O-benzyl-N-nitrosohydroxylamine (**3c**) afforded a much higher yield of *p*-chlorobenzyl acetate (**14c**).

The formation of benzaldehyde and *p*-methylbenzyl alcohol may be rationalized by abstraction of the N-benzylic hydrogen by the base; loss of the benzyl alkoxide - which of course leads to the benzyl alcohol - would



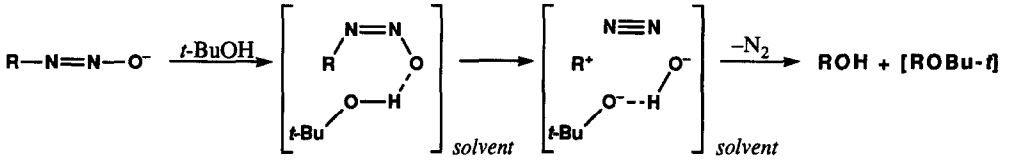
(7)

yield N-nitrosobenzaldimine, an intermediate previously postulated to lead to benzaldehyde (*Eq. 8*).[10]



(8)

Moss[11] has suggested that the formation of α-methylbenzyl alcohol from the diazotate ion proceeds *via* a "solvent cage" mechanism. Although the base-catalyzed decomposition was carried out in an aprotic solvent (glyme), proton abstraction by *tert*-butoxide could generate sufficient quantities of *tert*-butanol (or *tert*-butanol left over from the preparation of *tert*-butoxide) to serve as a proton source for the formation of the minor product, benzyl alcohol (*Scheme 6*).



Scheme 6

Meesters and his group[12] have studied the reaction of N,O-dialkyl-N-nitrosohydroxylamines with organolithium and Grignard reagents in order to prepare the corresponding azoxyalkanes. Although the expected products were obtained, albeit in relatively poor yields (0-50%), the by-products were unfortunately not reported; in view of our results, it is not unlikely the poor yields obtained by Meester might be rationalized in terms of abstraction of one of the α-hydrogens thus leading to products similar to those obtained in our case.

In conclusion, the acid hydrolysis of N,O-dialkyl-N-nitrosohydroxylamines resembles that of the corresponding nitrosamines rather than that of the isosteric α-hydroxy N-nitrosamines. On the other hand, N,O-dialkyl-N-nitrosohydroxylamines are solvolyzed by acetic acid at reflux, conditions which do not affect nitrosamines. While removal of the more acidic α-hydrogen of the N-benzyl substituent occurs to a substantial degree, it is interesting to note that the removal of the O-benzyl hydrogen is a major competing reaction.

EXPERIMENTAL SECTION

All mps and bps are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord Model 137B spectrophotometer (KBr pellets or NaCl plates). Unless otherwise noted, NMR spectra were determined on a Hitachi Perkin-Elmer R-24 (60 MHz) and Varian XL 300 in carbon tetrachloride for liquid samples or deuteriochloroform for solid samples using tetramethylsilane as the internal standard. Mass spectra were recorded on a Varian Mat 8200 Mass spectrometer. Elemental analyses were carried out by the Microanalysis Laboratories of the University of Massachusetts at Amherst. Gas liquid chromatographic analyses were performed on a GOW-MAC Instruments Co. Gas Chromatograph, Series 550 Thermal Conductivity Detector with DC-200 column, helium as a carrier gas (5 psi), the column, detector and injection temperatures were 110°, 135° and 120° respectively; the retention times (min.) of compounds were benzyl chloride (14), *p*-methylbenzyl chloride (27), benzyl alcohol (11), *p*-methylbenzyl alcohol (20), benzaldehyde (7), *p*-tolualdehyde (15), benzyl acetate (22) and *p*-methylbenzyl acetate (47). All solvents used for the reactions were dried and kept over molecular sieves (4Å). All products obtained from reactions were compared with authentic samples by spiking tlc, ir and nmr spectra. Physical constants for benzyl alcohol, *p*-methylbenzyl alcohol, *p*-chlorobenzyl alcohol, benzyl chloride, *p*-methylbenzyl chloride, benzaldehyde, *p*-tolualdehyde, *p*-chlorobenzaldehyde, benzyl acetate, *p*-methylbenzyl acetate and *p*-chlorobenzyl acetate and *p*-chlorobenzyl acetate were obtained from one of the following sources: "CRC Handbook of Chemistry and Physics", "Merck Index", "Dictionary of Organic Compounds" and Fieser's "Reagents for Organic Synthesis".

O-(*p*-Methylbenzyl)benzaldoxime.- A solution of O-(*p*-methylbenzyl)hydroxylamine (20 g, 0.15 mol), bp. 67°/0.3 mm Hg [prepared in 83% yield from N-(*p*-methylbenzyloxy)phthalimide (mp. 143-144.5°) obtained from the reaction of N-hydroxyphthalimide and *p*-methylbenzyl chloride according to the procedure of Fujii *et al.*[13]] and benzaldehyde (17 g, 0.16 mol) and one drop of conc. H_2SO_4 in ethanol (200 ml) was heated at reflux overnight. The ethanol was evaporated *in vacuo* to give an oil which was dissolved in ether (150 ml). The ethereal solution was washed with aq. $NaHSO_3$ and water, dried over $MgSO_4$ and the ether was evaporated to give 25 g (82%) of O-(*p*-methylbenzyl)benzaldoxime. An analytical sample was obtained by crystallization from pet. ether, mp. 45-45.5°; ^{1}H NMR: δ 8.05 (s, 1H, CH), 7.31 (br, 9H, ArH), 5.16 (s, 2H, CH_2), 2.22 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.01; H, 6.76; N, 6.15

O-Benzyl-(*p*-chloro)benzaldoxime.- A mixture of *p*-chlorobenzaldehyde (8.6 g, 70 mmol) and O-benzylhydroxylamine (9.8 g, 70 mmol)[13] in 100 ml of ethanol with 1 drop of conc. H_2SO_4 was heated to reflux overnight; the ethanol was then evaporated to give an oil which was dissolved in 150 ml of ether. The ethereal solution was washed with water, aq. $NaHSO_3$ and dried over $MgSO_4$. After filtration, the ether was evaporated to give an oil which was distilled to give 15.2 g (88%) of a colorless liquid, bp. 151°/0.3 mm Hg, which solidified upon standing. An analytical sample was prepared by recrystallization from hexane, mp. 47.5-48°; ^{1}H NMR: δ 7.84 (s, 1H, CH), 7.20 (br, 9H, ArH), 5.05 (s, 2H, CH_2).

Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68.43; H, 4.92; N, 5.70; Cl, 14.43. Found: C, 68.65; H, 4.89; N, 5.63; Cl, 14.74

N-(*p*-Methylbenzyl)-O-benzylhydroxylamine Hydrochloride.- To a solution of O-benzyl *p*-tolualdoxime (22.5 g, 0.39 mol) and borane-pyridine complex (36 g, 0.39 mmol) in ethanol (200 ml) was added dropwise ethanolic hydrogen chloride (47 g in 138 ml of EtOH) at 15-40° and the mixture was stirred at ambient temperature overnight. The white precipitate was collected, washed with water and air-dried to give 18.4 g (70%) of the hydrochloride, mp. 180-185°; ^{1}H NMR (as free hydroxylamine): δ 7.12 (s, 5H, PhH), 6.98 (br, 4H, ArH), 5.39 (s, 1H, NH), 4.47 (s, 2H, NCH_2), 3.79 (s, 2H, OCH_2), 2.24 (s, 3H, CH_3).

N-Benzyl-O-(*p*-methylbenzyl)hydroxylamine Hydrochloride.- To a solution of O-(*p*-methylbenzyl)benzaldoxime (22.5 g, 0.1 mmol) and borane-pyridine complex (36 g, 0.39 mol) in ethanol (200 ml) was added ethanolic hydrogen chloride (47 g in 138 ml) at 25-40° and the mixture was stirred at ambient temperature overnight. The white precipitate was collected and washed with water to give 21 g of the hydrochloride (80%), mp. 182-184°. It was used for the nitrosation step without purification; ^{1}H NMR (as free hydroxylamine): δ 7.01 (s, PhH) 6.89 (br, 4H, ArH), 5.10 (br, 1H, NH), 4.36 (s, 2H, NCH_2), 2.16 (s, 3H, CH_3).

N-(*p*-Chlorobenzyl)-O-benzylhydroxylamine Hydrochloride.- To a solution of O-benzyl *p*-chlorobenzaldoxime (11.4 g, 0.04 mol) and borane-pyridine complex (14.9 g, 0.16 mol) in ethanol (85 ml) was added dropwise ethanolic hydrogen chloride (19 g in 55 ml of ethanol) at 20-35° and the mixture was stirred at ambient temperature overnight. The white precipitate was collected and washed with water and dried to yield the hydrochloride, 9.8 g (88%), mp. 160-161°. It was used without further purification for the nitrosation step; ^{1}H NMR (as free hydroxylamine): δ 7.08 (s, 5H, PhH), 7.00 (br, 4H, ArH), 5.42 (s, 1H, NH), 4.37 (s, 2H, NCH_2), 3.29 (s, 2H, OCH_2).

N-(*n*-Butyl-O-[(3-phenylpropyl)]carbethoxyhydroxamate.- To a suspension of dry sodium hydride (0.9 g, 36 mmol) in THF (10 ml) in an ice-bath was added dropwise a solution of O-[(3-phenylpropyl)]carbethoxyhydroxamate (7.7 g, 35 mmol) in THF (60 ml) and then the mixture was heated to reflux for 30 min. Subsequent dropwise addition of a solution of *n*-butyl iodide (6.7 g, 36 mmol) in THF (30 ml) to the reaction mixture cooled in an ice-bath and heating of the resulting mixture to reflux for 3 days gave a precipitate upon cooling. The mixture was filtered and the filtrate was concentrated to give an oil which was dissolved in ether (50 ml). The ethereal solution was washed with water, dried over $MgSO_4$ and the ether was evaporated to afford an oil (9.1 g, 94%). The hydroxamate was utilized for the next step without purification.

N-(*n*-Butyl-O-[(3-phenylpropyl)]hydroxylamine.- A mixture of N-(*n*-butyl)-O-[(3-phenylpropyl)]carboethoxyhydroxamate (9.04 g, 32.4 mmol) and sodium hydroxide (3 g, 75 mmol) in water (35 ml) and ethenol (25 ml) was heated to reflux for 2 days, then was diluted with 100 ml of water. The product was extracted with ether and the ethereal layer was washed with water, dried over $MgSO_4$ followed by evaporation of the ether to give 6.1 g of an oil. It was distilled to give 5.58 g (84%) of a colorless oil, bp. 98°/0.035 mm Hg.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.50; H, 10.21; N, 6.69

N-(*p*-Methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (3a).- To a suspension of N-(*p*-methylbenzyl)-O-benzylhydroxylamine hydrochloride (18.4 g, 0.07 mol) in ethanol-water (150 ml, 80 ml) in an ice-bath was slowly added 4 ml of conc. hydrochloric acid. After a solution of sodium nitrite (10 g, 0.14 mol) in water (80 ml) was added dropwise to the mixture, the mixture was stirred at ambient temperature overnight. The pale yellow product which had precipitated was collected and washed with ether. Crystallization from methanol gave 15 g (84%) of pale yellow needles, mp. 83.5-84.5°; ^{1}H NMR: δ 7.13 (br, 9H, ArH), 5.03 (s, 2H, NCH_2), 4.68 (s, 2H, OCH_2), 2.25 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.08; H, 6.14; N, 10.92

N-Benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (3b).- To a suspension of N-benzyl-O-(*p*-methylbenzyl)hydroxylamine hydrochloride (21 g, 0.08 mol) in ethanol-water (160 ml, 80 ml) in an ice-bath was slowly added conc. hydrochloric acid (8 ml). After the mixture was stirred for 30 min. in an ice-bath, a solution of sodium nitrite (11 g, 0.16 mol) in water (80 ml) was added dropwise to the suspension cooled in an ice-bath and the resulting mixture was stirred at ambient temperature overnight. The precipitated product was collected, washed with water and recrystallized from methanol to give 16 g (78%) of N-benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine, mp. 88-89°; ^{1}H NMR: δ 7.32 (s, 5H, PhH), 7.11 (s, 4H, ArH), 5.05 (s, 2H, NCH_2), 4.79 (s, 2H, OCH_2), 2.32 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.06; H, 5.98; N, 10.91

N-(*p*-Chlorobenzyl)-O-benzyl-N-nitrosohydroxylamine (3c).- To a suspension of N-(*p*-chlorobenzyl)-O-benzylhydroxylamine hydrochloride (8.6 g, 30 mmol) in ethanol (30 ml) and water (20 ml) in an ice-bath was slowly added 2 ml of conc. hydrochloric acid followed by the dropwise addition of a solution of sodium nitrite (3.5 g, 50 mmol) in water (25 ml). The mixture was stirred at ambient temperature overnight and the pale yellow precipitate was collected and washed with water; recrystallization from methanol gave 7.52 g (90%) of pale yellow needles, mp. 56.5-57.5°; ^{1}H NMR: δ 7.16 (br, 9H, ArH), 4.97 (s, 2H, NCH_2), 4.79 (s, 2H, OCH_2).

Anal. Calcd. for $C_{14}H_{13}ClN_2O_2$: C, 60.76; H, 4.73; N, 10.13; Cl, 12.81. Found: C, 60.71; H, 4.80; N, 10.23; Cl, 12.60

N-(*n*-Butyl-O-[(3-phenylpropyl)]-N-nitrosohydroxylamine.- To a solution of 4.14 g (20 mmol) of N-(*n*-butyl)-O-[(3-phenylpropyl)]hydroxylamine in water (20 ml) and ethanol (10 ml) cooled in an ice-bath was added dropwise conc. hydrochloric acid and then a solution of sodium nitrite (2.75 g, 40 mmol) in water (20 ml). The mixture was stirred at ambient temperature and the oily product was extracted into ether. The ethereal layer was washed with water, dried over $MgSO_4$ and the ether was evaporated to give 4.5 g of an oily product, which was then purified by chromatography on 20 g of silica gel using chloroform as an eluent to yield 4.4 g (90%) of the pure product as a yellow oil.

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.35; H, 8.29; N, 11.78

Hydrolysis of N-(*p*-Methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (3a) in conc. Hydrochloric Acid

At 70-90°.- A suspension of **3a** (1.02 g, 4 mmol) in conc. hydrochloric acid (50 ml) was heated at 70-90° (oil bath) under N_2 for 5 hrs. The white precipitate which had formed upon cooling was collected and dried to give 0.5 g (2.0 mmol) of N-(*p*-methylbenzyl)-O-benzylhydroxylamine hydrochloride (mp. 180-185°); a portion was neutralized with aq. $NaHCO_3$ to give the corresponding free hydroxylamine for identification; its nmr and ir spectra were superimposable on authentic spectra. The filtrate was extracted with ether (50 ml x 2) and the ethereal layer was washed with water

until neutral, dried over $MgSO_4$ and the ether evaporated to give 0.13 g of an oil which was shown to contain benzyl chloride (0.4 mmol), *p*-methylbenzyl chloride (0.5 mmol) and *p*-tolualdehyde (0.2 mmol); the yields were estimated by integration of the NMR spectrum. The aqueous layer was made basic with Na_2CO_3 and then extracted with ether. The ethereal layer was dried and the ether was evaporated to give an oil which solidified upon standing to yield N-(*p*-methylbenzyl)hydroxylamine (0.11 g, 0.8 mmol) whose NMR spectrum was superimposable upon that of an authentic sample [^{1}H NMR: δ 6.98 (br, 4H, ArH), 6.39 (br, 2H, NH and OH), 3.71 (s, 2H, CH_2), 2.21 (s, 3H, CH_3)].

At 80-110°.- A suspension of **3a** (1.02 g, 4 mmol) in conc. hydrochloric acid (50 ml) was heated in an oil bath at 80-110° for 5 hrs. under nitrogen. After the same workup as described previously, N-(*p*-methylbenzyl)-O-benzylhydroxylamine hydrochloride (0.49 g, 1.9 mmol) and N-(*p*-methylbenzyl)hydroxylamine (0.07 g, 0.5 mmol) were isolated and characterized. A mixture of benzyl chloride, *p*-methylbenzyl chloride and *p*-tolualdehyde were obtained from the acid layer, and their yields were estimated by vpc to be 0.2 mmol, 0.8 mmol and 0.3 mmol respectively.

At Reflux.- A suspension of **3a** (1.02 g, 4 mmol) in conc. hydrochloric acid (50 ml) was heated at reflux for 5 hrs. under nitrogen. The cooled reaction mixture was extracted with ether (50 ml x 2) and the ethereal layer was washed with water until neutral and dried over $MgSO_4$. The ether was evaporated *in vacuo* to give an oil (0.49 g) consisting of *p*-methylbenzyl chloride (0.7 mmol), *p*-tolualdehyde (0.1 mmol), benzyl chloride (3.0 mmol) and a trace amount of benzaldehyde (vpc). The aqueous layer and the washes were combined and concentrated to give a solid which was then neutralized with saturated $NaHCO_3$ and extracted with ether.The ethereal layer was dried over $MgSO_4$ and the ether was evaporated *in vacuo* to yield a white solid (0.32 g, 2.3 mmol) whose nmr and IR spectra showed it to be N-(*p*-methylbenzyl)hydroxylamine.

Hydrolysis of N-Benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (3b) in conc. Hydrochloric Acid at Reflux.- A suspension of N-benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (1.02 g, 4 mmol) in conc. hydrochloric acid (50 ml) was heated to reflux under nitrogen for 5 hrs. The cooled mixture was extracted with ether (50 ml x 2) and the ethereal layer was washed with water until neutral, dried over $MgSO_4$ followed by evaporation of the ether to yield 0.68 g of an oil containing benzaldehyde (0.5 mmol), benzyl chloride (0.7 mmol) and *p*-methylbenzyl chloride (3.8 mmol), as determined by vpc. The aqueous layer and the washes were combined and concentrated *in vacuo* to give a white solid which was then neutralized with aqueous $NaHCO_3$ and then extracted with ether. The ethereal layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid (0.25 g, 2.0 mmol) whose nmr and IR spectra matched those of an authentic sample of N-benzylhydroxylamine [^{1}H NMR: δ 7.18 (s, 5H, PhH), 6.50 (br, 1H, OH), 3.79 (s, 2H, CH_2)].

Hydrolysis of N-Benzyl-O-(*p*-methylbenzyl)hydroxylamine (6b) in conc. Hydrochloric Acid at Reflux.- A suspension of N-benzyl-O-(*p*-methylbenzyl)hydroxylamine (0.53 g, 2.3 mmol) in conc. hydrochloric acid (25 ml) was heated at reflux for 5 hrs. under N_2. The cooled reaction mixture was extracted twice with ether (50 ml) and each ethereal layer was washed with water until neutral. The combined ethereal phase was dried over $MgSO_4$ and evaporated to give 0.24 g of an oily mixture containing *p*-methylbenzyl chloride (2.4 mmol) and benzaldehyde (0.3 mmol) (vpc). The aqueous layer and the washes were combined and concentrated *in vacuo* to give a white solid which was then neutralized with saturated $NaHCO_3$ and extracted with ether. The ethereal layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid (0.2 g, 1.6 mmol) whose nmr and IR spectra were identical to those of N-benzylhydroxylamine.

Hydrolysis of O-(*p*-Methylbenzyl)hydroxylamine in conc. Hydrochloric Acid at Reflux.- A mixture of 0.61 g (4.5 mmol) of O-(*p*-methylbenzyl)hydroxylamine in conc. hydrochloric acid (50 ml) was heated to reflux for 12 hrs. under nitrogen atmosphere and diluted with 100 ml of ice water. After extraction with ether (50 ml x 2), the ethereal layer was washed with water and aqueous $NaHCO_3$, dried over $MgSO_4$ and the ether was evaporated to give 0.43 g (3.0 mmol) of *p*-methylbenzyl chloride. However, neutralization of the aqueous layer followed by extraction with ether gave no product.

Hydrolysis of N-Benzylhydroxylamine in conc. Hydrochloric Acid at Reflux.- To cold conc. hydrochloric acid (50 ml) was added slowly 0.49 g (4 mmol) of N-benzylhydroxylamine and the mixture was heated to reflux for 5 hrs. under N_2 and then diluted with 30 g of ice. It was extracted with ether (50 ml x 2) and the ethereal layer was washed with water, dried and the ether was evaporated to give 0.01 g of a residue. The aqueous layer was made basic with solid $NaHCO_3$ and extracted with ether. The ethereal layer was dried and the ether was evaporated to give 0.39 g of N-benzylhydroxylamine (80% recovery).

Hydrolysis of N-(*n*-Butyl)-O-(3-phenylpropyl)-N-nitrosohydroxylamine.- An oil bath was preheated to 55°. A mixture of the nitrosohydroxylamine (4 mmol) in conc. hydrochloric acid (50 ml) was heated in the oil bath under N_2 atmosphere and the temperature of the mixture was kept at 45° for 24 hrs. The reaction mixture was diluted with 100 g of ice and extracted with ether (50 ml x 2). The ethereal solution was dried over $MgSO_4$ and the ether was distilled at atmospheric pressure to leave a black oil which was distilled and an unknown colorless liquid was collected, bp. 40-100° at atmospheric pressure. Neither *n*-butyl chloride nor butyraldehyde could be detected by vpc which exhibited many peaks.

Hydrolysis of N-(3-Pentyl)-O-methyl-N-nitrosohydroxylamine (11) in conc. Hydrochloric Acid.- To 1 g (6.8 mmol) of N-(3-pentyl)-O-methyl-N-nitrosohydroxylamine[3a] in an ice-bath was added dropwise 2 ml of conc. hydrochloric acid under N_2 atmosphere; gas evolution could subsequently be observed. After the vigorous reaction was over, the yellow color of the reaction mixture had disappeared. The reaction mixture was stirred at ambient temperature overnight and then neutralized with a saturated solution of sodium bicarbonate. The hydrolysis products were extracted with 20 ml of ether and the ethereal layer was washed with water. After drying over $MgSO_4$, the ether was carefully distilled to give 0.48 g of an oil whose vpc showed two products, 3-pentanol (1.5 mmol) and N-(3-pentyl)-O-methylhydroxylamine (3 mmol); their retention times were 13 min. and 8 min. respectively. The vpc was carried out on a carbowax column, at 80°, 120° and 95° (column, detector and injection port temperatures respectively).

In the *p*-nitrophenylhydrazine hydrochloride trap which was attached to the condenser, 10 mg of a solid had precipitated. However, it did not match authentic *p*-nitrophenylhydrazone of formaldehyde by ir and tlc.

Solvolysis of N-Benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (3b) in Acetic Acid at Reflux.- A solution of 1.23 g (5 mmol) of N-benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (**3b**) in 15 ml of acetic acid was degassed with nitrogen for 30 min. and heated to reflux for 22 hrs. The mixture was poured into 150 g of ice-water and extracted with ether (50 ml x 2). The ethereal layer was washed with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$ and the ether was evaporated to give 1.30 g of an oil, which was then chromatographed on 50 g of silica gel with benzene as eluent. Benzyl (*p*-methylbenzyl) ether 0.7 mmol) was collected in the earliest fraction. The next fraction contained, in addition to *p*-tolualdehyde (0.03 mmol), *p*-methylbenzyl acetate and benzyl acetate and the remaining fractions also contained the two acetates. The total yields of *p*-methylbenzyl acetate and benzyl acetate estimated by the nmr spectra of the acetate fractions were 3.6 mmol and 3.0 mmol respectively.

Solvolysis of N-(*p*-Methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (3a) in Acetic Acid At Reflux.- A solution of N-(*p*-methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (**3a**, 1.23 g, 5 mmol) in acetic acid (15 ml) degassed for 15 min. with nitrogen, was heated to reflux for 9 hrs. and stirred at ambient temperature for 14 hrs. The reaction mixture was poured into 150 ml of ice-water and extracted with ether (50 ml x 2). The ethereal layer was washed with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$ and the ether was evaporated to give 1.36 g of an oil containing benzyl (*p*-methylbenzyl) ether (1.0 mmol), *p*-methylbenzyl acetate (3.7 mmol) and benzyl acetate (3.8 mmol), whose identity and yields were estimated by nmr spectrum of the oil. The oil was chromatographed on silica gel (50 g), using benzene as eluent. Benzyl (*p*-methylbenzyl) ether (total 1.0 mmol) was eluted first, then a mixture of benzyl acetate and *p*-methylbenzyl acetate was obtained in several fractions. The yields of *p*-methylbenzyl and benzyl

acetates as estimated by the nmr spectra of the acetates fraction were 3.4 mmol and 3.6 mmol respectively.

At 100°.- A solution of 1.02 g (4 mmol) of **3a** in 20 ml of acetic acid was stirred at ambient temperature for 20 hrs under nitrogen; the color of the solution did not change. It was heated to about 100° for 5 hrs. then stirred at ambient temperature for 24 hrs. After work-up as described previously, 0.81 g of an oil was obtained. The yields were estimated from the nmr and vpc as follows: benzyl acetate (0.3 mmol), *p*-methylbenzyl acetate (3.1 mmol), benzyl alcohol (0.7 mmol) and benzyl (*p*-methylbenzyl) ether (0.9 mmol).

Reaction of Benzyl Alcohol in Acetic Acid.- A solution of benzyl alcohol (1.06 g, 10 mmol) in acetic acid (30 ml) was heated at reflux for 24 hrs. under nitrogen. The reaction mixture diluted with 100 g of ice was extracted with ether (50 ml x 2) and the ethereal layer was washed with water and aq. $NaHCO_3$. The dried ethereal layer was concentrated to give 1.32 g (88%) of an oil, which was primarily benzyl acetate; only trace amounts of benzyl alcohol (and benzaldehyde, present in the starting material) were detected.

Reaction of N-(*p*-Methylbenzyl)-O-benzylhydroxylamine in Acetic Acid.- A solution of N-(*p*-methylbenzyl)-O-benzylhydroxylamine (0.51 g, 2.3 mmol) in acetic acid (15 ml) was heated to reflux for 24 hrs. under nitrogen and the cooled reaction mixture was diluted with 100 ml of ice water. After extraction with ether (50 ml x 2), the ethereal solution was washed with water and aq. $NaHCO_3$, dried over $MgSO_4$ and the ether was evaporated to give 0.44 g (87%) of a colorless oil which contained N-acetyl-N-(*p*-methylbenzyl)-O-benzylhydroxylamine as the major product. The *p*-methylbenzyl and benzyl acetates were formed in trace amounts. The ir and nmr spectra of the N-acetylhydroxylamines were superimposable on those of an authentic sample prepared from the acetylation of the corresponding hydroxylamine according to the procedure of Ludwig *et al.*[14] A mixture of N-(*p*-methylbenzyl)-O-benzylhydroxylamine (0.114 g, 0.5 mmol), pyridine (0.039 g, 0.5 mmol) and acetyl chloride (0.39 g, 0.5 mmol) in benzene (5 ml) was heated to reflux overnight. The white solid which had precipitated was removed. The filtrate was washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to give an oil (0.13 g, 93%) which was triturated with ether-pet. ether to afford a white solid, mp. 66-66.5°.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.73; H, 7.05; N, 5.18

Reaction of N-Benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (3b) with Potassium *tert*-Butoxide in Glyme.- To a solution of N-benzyl-O-(*p*-methylbenzyl)-N-nitrosohydroxylamine (1.26 g, 4.9 mmol) in glyme (20 ml) was added 0.6 g (5 mmol) of potassium *tert*-butoxide and the mixture was stirred at ambient temperature for 24 hrs. under a nitrogen atmosphere. To the pink reaction mixture cooled in an ice bath was added acetic acid (1 ml) and the mixture was stirred for 30 min. After addition of 50 ml of water, the products were extracted into ether (50 ml x 2) and the ethereal layer was washed with saturated $NaHCO_3$ and dried over $MgSO_4$. The ether was evaporated to give an oil (1.09 g) which was shown to contain benzaldehyde (1.2 mmol), *p*-tolualdehyde (3.5 mmol), benzyl alcohol (0.5 mmol), *p*-methylbenzyl alcohol (2.2 mmol) and benzyl acetate (2.3 mmol) by nmr and vpc; the yields were estimated by vpc.

Reaction of N-(*p*-Methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (3a) with Potassium *tert*-Butoxide in Glyme.- To a solution of N-(*p*-methylbenzyl)-O-benzyl-N-nitrosohydroxylamine (1.26 g, 4.9 mmol) in glyme (20 ml) was added potassium *tert*-butoxide (0.6 g, 5 mmol) and the mixture was stirred at ambient temperature for 24 hrs. After work-up of the pink reaction mixture as described in the previous reaction, 1.06 g of an oil was obtained and chromatographed on silica gel (50 g) using benzene as first eluent to give *p*-tolualdehyde (1.9 mmol), benzaldehyde (0.4 mmol) and *p*-methylbenzyl acetate (1.2 mmol) characterized and estimated by nmr and vpc. Benzyl alcohol (3.0 mmol) and *p*-methylbenzyl alcohol (0.7 mmol) were obtained as a mixture in second and third fractions using chloroform and methanol respectively as eluents and their yields were estimated by vpc.

Reaction of N-(*p*-Chlorobenzyl)-O-benzyl-N-nitrosohydroxylamine (3c) with Potassium *tert*-Butoxide in Glyme.- To a solution of 1.38 g (5 mmol) of N-(*p*-chlorobenzyl)-O-benzyl-N-nitrosohydroxylamine in glyme (20 ml) was added

0.6 g of potassium *tert*-butoxide and the mixture was stirred at ambient temperature under a nitrogen atmosphere. Acetic acid (1.5 ml) was added to the pink reaction mixture cooled in an ice bath and stirring was continued for 2 hrs. Saturated $NaHCO_3$ (50 ml) was added and products were extracted with ether. The ethereal solution was washed with water, dried over $MgSO_4$ and the ether was evaporated to give an oil (1.88 g); 1.09 g of this mixture was chromatographed over SiO_2 (50 g) using benzene as an eluent; *p*-chlorobenzaldehyde (1.5 mmol), benzaldehyde (1.2 mmol), *p*-chlorobenzyl alcohol (0.3 mmol), benzyl alcohol (1.5mmol) and *p*-chlorobenzyl acetate (2.8 mmol) were characterized and the yields (based on the original weight) were estimated by nmr.

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