N-Nitrosohydroxylamines. 2. Thermal Decomposition of *N,O*-Dibenzyl-*N*-nitrosohydroxylamines

Kunio Kano[†] and Jean-Pierre Anselme[*]

Department of Chemistry, University of Massachusetts at Boston, Harbor Campus, Boston, Massachusetts 02125

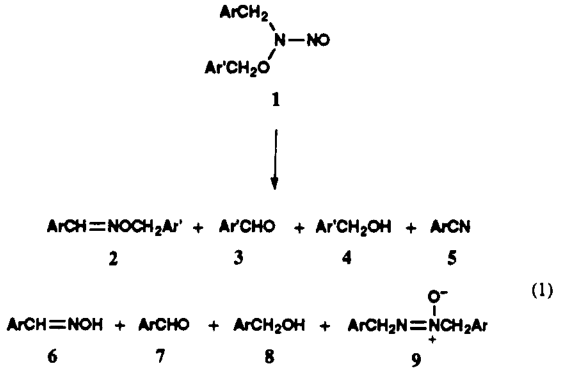
Received July 28, 1992

Introduction

As part of our interest[1] in the little-studied *N*-nitrosohydroxylamines,[2] we investigated the thermal decomposition of a series of *N,O*-dibenzyl-*N*-nitrosohydroxylamines. The *isosteric* relationship α-hydroxy *N*-nitrosamines (**B**) suggested that *N*-nitrosohydroxylamines (**A**) might also collapse by a similar path, albeit with greater difficulty (C–H vs O–H cleavage). However, the loss of nitric oxide could be a competing pathway in analogy with *N*-nitrosamines.[3]

Results

The thermal decomposition of *N,O*-dibenzyl-*N*-nitrosohydroxylamine (**1a**) was initially carried out in *benzene* and gave benzonitrile, *O*-benzylbenzaldoxime, benzaldehyde, and benzyl alcohol. In order to determine the origin of the benzyl groups (N or O) in each product, *N*-benzyl-*O*-(*p*-methylbenzyl)-*N*-nitrosohydroxylamine (**1b**) was synthesized and its thermal decomposition studied at reflux in *toluene* (12 h).[4] In this case, a more complex mixture was obtained (eq 1 and Table I); the presence of ω,ω′-azoxytoluene (**9a**) could be detected by NMR. 4,4′-Dimethyl-ω,ω′-azoxytoluene (**9c**) was isolated and its identity confirmed in the product mixture of a similar decomposition of *N*-(*p*-methylbenzyl)-*O*-benzyl-*N*-nitrosohydroxylamine (**1c**).



$$ArCH{=}NOCH_2Ar' + Ar'CHO + Ar'CH_2OH + ArCN$$

$$ArCH{=}NOH + ArCHO + ArCH_2OH + ArCH_2\overset{O^-}{\underset{+}{N}}{=}NCH_2Ar \quad (1)$$

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

Scheme I

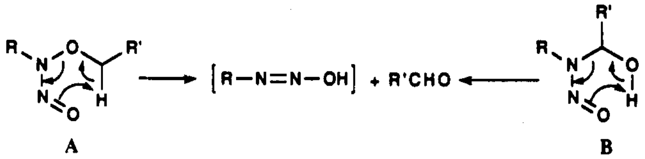


Table I. Products of Thermal Decomposition of *N*-Nitrosohydroxylamines (1)

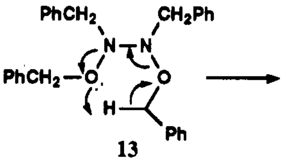
compd[a]	2	3	4	5	6	7	8	9
1a[b]	√	√	√	√	c	c	c	c
1b[d]	1.5	1.5	1.6	0.3	0.6	0.4	0.2	traces
1c[d]	1.0	0.2	1.3	0.8	0.1	0.2	0.4	0.3

[a] Yield of products are given in mmoles starting from 4.9 mmol of *N*-nitrosohydroxylamines. [b] Carried out in *benzene* at reflux. [c] Not determined. [d] Carried out in *toluene* at reflux.

Discussion

While the cyclic decomposition illustrated in Schemes I and V accounts for some of the products, it is likely that a radical mechanism is involved in the generation of the ω,ω′-azoxytoluenes. Addition of a benzyl radical (originating from the nitrogen) to **1** would lead to **10**. However, instead of loss of the benzyloxy radical to give the azoxytoluenes (**9**), intermediate **10** would be more likely to expel the more stabilized benzyl radical ($ArCH_2^\bullet$) to either revert to **1** or to yield the alkoxy diimide *N*-oxides (**11**)[5] as is illustrated in Scheme II.

Homolytic scission of the weak N–N bond of **1** to the *N*-(benzyloxy)-*N*-benzylamino radicals **12**,[6] followed by abstraction of the N-benzylic hydrogen, may account for the formation of the oxime ethers **2**; further radical promoted loss of the elements of $ArCH_2OH$ could account for the formation of the nitriles **5**. Dimerization of **12** would yield the bis(benzyloxy)hydrazine **13**;[7] bis(benzyloxy)hydrazine **13**, generated from the reaction of the hydroxylamine with silver oxide or *tert*-butoxy radical was shown to fragment ("Russel mechanism") to the corresponding azo compound, the aldehyde, the alcohol, and the oxime ether (eq 2).[6] However, ω,ω′-azotoluenes were not among the products isolated in our cases,[6] and indeed it is doubtful that they would have survived the conditions of the reaction. A more reasonable path initiated by radical abstraction of an *O*-benzyl hydrogen of **10** is depicted in



13

$$PhCH_2N{=}NCH_2Ph + PhCHO + PhCH_2OH + PhCH{=}NOCH_2Ph \quad (2)$$

[†] Taken from the Ph.D. Thesis of K. Kano, University of Massachusetts at Amherst, May 1986.

(1) This is the second in a series of papers dealing with the chemistry of *N,O*-dialkyl-*N*-nitrosamines. For the previous paper, see: Kano, K.; Anselme, J.-P. *Tetrahedron* **1992**, *48*, 10075.

(2) Challis, B. C.; Challis, J. A. *N*-Nitrosamines and *N*-Nitrosoimines. In *Supplement F: The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives, Part 2*; John Wiley and Sons: New York, 1982; p 1184. Anselme, J.-P. *N-Nitrosamines*; ACS Symposium Series, No. 101, American Chemical Society: Washington, D.C., 1979.

(3) Reference 2, p 1191.

(4) Complete decomposition required 7 days in benzene.

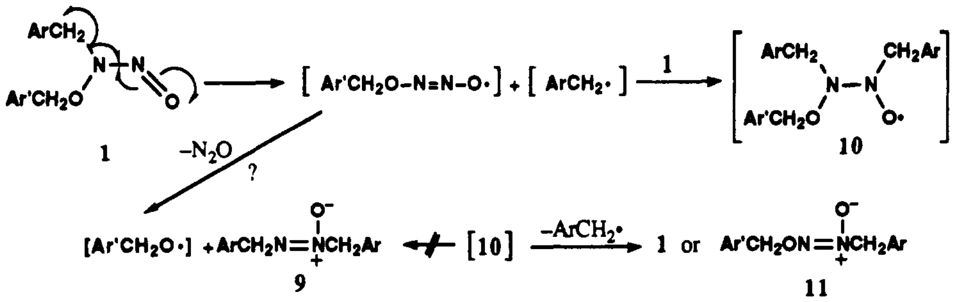
(5) (a) Freeman, J.-P. *J. Org. Chem.* **1963**, *28*, 2508. (b) Freeman, J.-P.; Lilliwitz, L. D. *Ibid.* **1970**, *35*, 3107 and references therein. (c) Stevens, T. E. *Ibid.* **1964**, *29*, 311.

(6) Kaba, R. A.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7375. ω,ω′-Azotoluene could be detected by NMR and TLC of the crude reaction mixture.

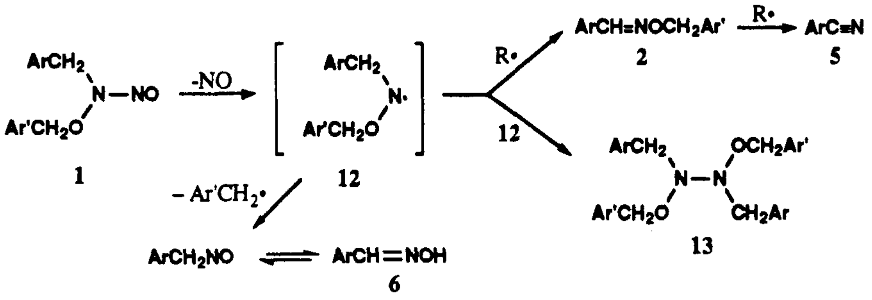
(7) Our attempts to prepare hydrazines of type **13** from the reaction of *N*-(*p*-methylbenzyl)-*N*-(benzyloxy)carbamoyl chloride with sodium peroxide [Kastoder, K. Ger. Pat. 1,072,627; *Chem. Abstr.* **1961**, *55*, 10386b] gave only the corresponding urea, mp 87–87.5 °C.

0022-3263/93/1958-1564$04.00/0

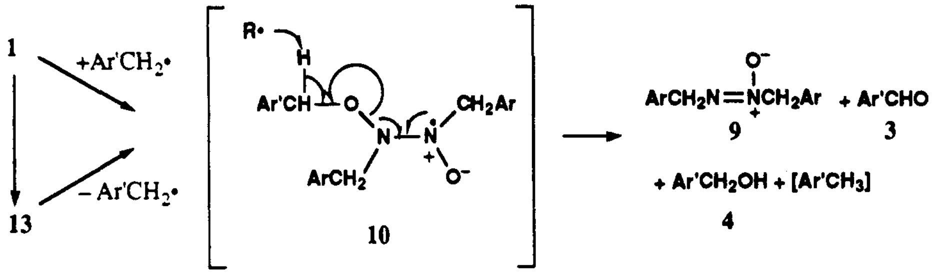
Scheme II



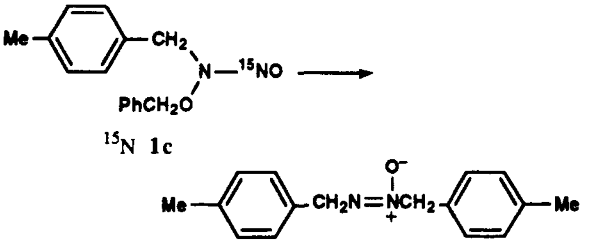
Scheme III



Scheme IV



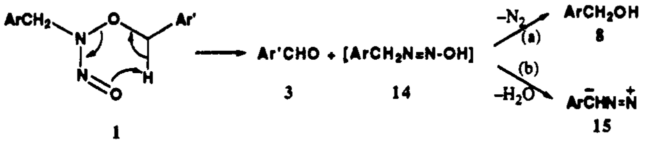
Scheme IV. The obvious critical difference between the two mechanisms depicted in Schemes II and III involves the mode of generation of intermediate **10**. If Scheme II is operative, then the two nitrogens of **10** (and of the azoxy compounds **9**) originate from the *two* intact nitrogens of the starting *N*,*O*-dibenzyl-*N*-nitrosohydroxylamines (**1**). On the other hand, the alternate mechanism illustrated in Scheme III *requires* that the two nitrogens arise from the combination of *two* hydroxylamino nitrogens. Conclusive evidence for this latter path was adduced from ^{15}N labeling studies; the thermal decomposition of *N*-[^{15}N]-nitroso-*N*-(*p*-methylbenzyl)-*O*-benzylhydroxylamine (^{15}N-**1c**) provided 4,4′-dimethyl-ω,ω′-azoxytoluene (**9c**) whose mass spectrum was in perfect agreement with that of an authentic *unlabeled* sample;[8] the benzaldehyde expected on the basis of this path (Scheme IV) was characterized, but *p*-xylene (from **1b**) could not be detected.



(3)

9c

Scheme V



Although the benzylic hydrogen of the *O*-benzyl group of the *N*-nitrosohydroxylamines (**A**) is evidently not as labile as the OH of α-hydroxy nitrosamines (**B**), the formation of benzaldehyde may be understood by the cyclic path illustrated in Scheme V. The accompanying fragment, the diazoic acid (**14**), then decomposes to give either the alcohols **8** or the aryldiazoalkanes.[2,5b,9] Evidence for this path was provided by the isolation of 2,2′-dimethylbenzalazine (**16d**, Ar = *o*-$CH_3C_6H_4$) from the decomposition of *N*-nitroso-*N*-(*o*-methylbenzyl)-*O*-benzylhydroxylamine (**1d**, Ar = *o*-$CH_3C_6H_4$). Loss of water from *o*-methylphenyl)methanediazohydroxide (**14d**, Ar = *o*-$CH_3C_6H_4$) would lead to the diazoalkane thence to the azine **16d** (eq 4). The yield of *o*-methylbenzyl alcohol (**8d**) was much lower than that of the accompanying benzaldehyde (**3a**) since the precursor diazohydroxide (**14d**) is consumed in two different subsequent reactions.

The benzylic hydrogen adjacent to the partially positive nitrogen in **1** should be relatively labile as well, based on the analogy with *N*-nitrosamines.[2] Thus, fragmentation

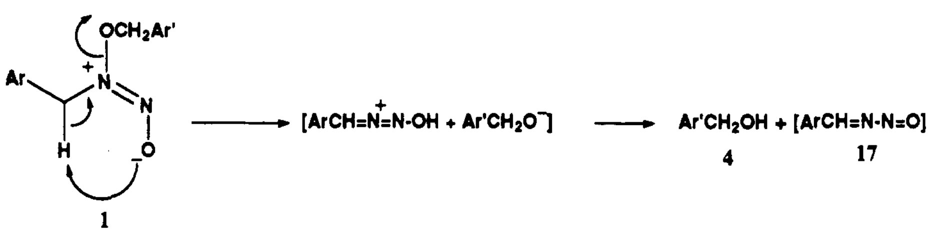
---

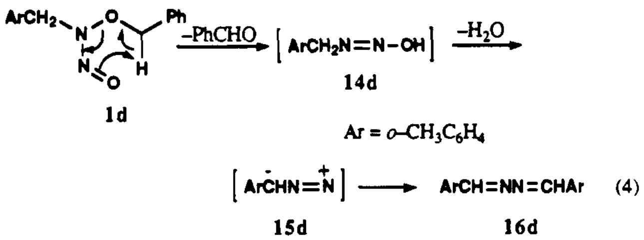
[8] Bukel, A. F.; Waters, W. A. *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 312.

[9] (a) Moss, R. A. *Acc. Chem. Res.* **1974**, *7*, 421. (b) Jappy, J.; Preston, P. N. *Tetrahedron Lett.* **1970**, 1157.

[10] Kano, K.; Anselme, J.-P. *Tetrahedron* **1992**, *48*, 10075.

Scheme VI





of 1 followed by rapid acid–base reaction would give the alcohol and the *N*-nitrosoimines (17) (Scheme VI), known to give benzaldehydes.[5b,11] Intermediate 17 should also eliminate HNO to yield the benzonitriles (5), one of the products characterized from the reaction mixtures.

$$\underset{5}{\mathrm{ArC{\equiv}N}} \xleftarrow{-\mathrm{HNO}} \underset{17}{[\mathrm{ArCH{=}N{-}N{=}O}]} \xrightarrow{-\mathrm{N_2}} \underset{7}{\mathrm{ArCHO}} \qquad (5)$$

In conclusion, the results herein described suggest that in contrast to aliphatic nitrosamines, the N–N bond of *N*,*O*-dibenzyl-*N*-nitrosohydroxylamines appears to undergo radical cleavage under rather mild conditions. This is perhaps due to the increased stabilization of the resulting hydroxylamino radical.[6]

Experimental Section

All mps and bps are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord Model 137B spectrophotometer (neat or as KBr pellets). Unless otherwise noted, NMR spectra were determined on a Hitachi Perkin-Elmer R-24 (60MHz) and Varian XL 300 instruments 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 analysis 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) (column, detector, and injection port temperatures 110, 135, and 120 °C, respectively); the retention times (min) of compounds at those conditions are benzyl alcohol (11), *p*-methylbenzyl alcohol (20), benzaldehyde (7), *p*-tolualdehyde (15), benzonitrile (12), and *p*-toluonitrile (23). All solvents used for the reaction were dried and kept over molecular sieves (4 Å). All products obtained from reactions were compared with authentic samples by TLC, IR, and NMR spectra. Physical constants for benzyl alcohol, *p*-methylbenzyl alcohol, *p*-chlorobenzyl alcohol, benzaldehyde, *p*-tolualdehyde, benzonitrile, *p*-toluonitrile 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*. The hydroxylamines and oximes obtained were characterized previously.[10]

Thermal Decomposition of *N*-Benzyl-*O*-(*p*-methylbenzyl)-*N*-nitrosohydroxylamine (1b). A solution of *N*-benzyl-*O*-(*p*-methylbenzyl)-*N*-nitrosohydroxylamine (**1b**, 1.26 g, 4.9 mmol) in toluene (10 mL) was heated at reflux for 48 h under a nitrogen atmosphere. The solution was then deposited on a column of SiO_2 (petroleum ether), and the toluene was eluted with petroleum ether. Then the products were separated using benzene and then chloroform as eluents to give *O*-(*p*-methylbenzyl)benzaldoxime (1.5 mmol), benzaldehyde (0.4 mmol), and *p*-tolualdehyde (1.5 mmol); ω,ω′-azoxytoluene was detected in the next fraction, and its presence was confirmed by addition of authentic ω,ω′-azoxytoluene[5a] to the NMR sample. Continued elution gave benzonitrile (0.3 mmol), benzaldoxime (0.6 mmol), benzyl alcohol (0.2 mmol), and *p*-methylbenzyl alcohol (1.6 mmol) whose yields were estimated by VPC and NMR.

Thermal Decomposition of *N*-(*p*-Methylbenzyl)-*O*-benzyl-*N*-nitrosohydroxylamine (1c). A solution of *N*-(*p*-methylbenzyl)-*O*-benzyl-*N*-nitrosohydroxylamine (**1c**, 1.26 g, 4.9 mmol) in toluene (10 mL) was heated to reflux for 48 h under nitrogen. The reaction mixture was worked up as previously described and in addition to *O*-benzyl-*p*-tolualdoxime (1.0 mmol), *p*-toluonitrile (0.8 mmol), *p*-tolualdehyde (0.2 mmol), benzaldehyde (0.9 mmol), *p*-methylbenzyl alcohol (0.4 mmol), benzyl alcohol (1.3 mmol), and *p*-tolualdoxime (0.1 mmol); 4,4′-dimethyl-ω,ω′-azoxytoluene (0.3 mmol) was isolated, mp 67–68 °C, M^+ 254, whose NMR spectrum was superimposable on that of an authentic sample prepared as described below.

4,4′-Dimethyl-ω,ω′-azoxytoluene (9c). To a solution of *m*-chloroperbenzoic acid (0.7 g, 4 mmol) in methylene chloride (10 mL) in an ice bath was added dropwise a solution of 4,4′-dimethyl-ω,ω′-azotoluene (0.74 g, 3 mmol)[12] in methylene chloride (5 mL), and the mixture was stirred at ambient temperature overnight. After filtration of the white precipitate, the methylene chloride filtrate was washed with a saturated solution of $NaHCO_3$ and water and dried over $MgSO_4$, and the methylene chloride was evaporated in vacuo to leave an oil which was crystallized from hexane to give a white solid (0.30 g, 30%): mp 74–75 °C, ^1H NMR δ 7.04 (br, 8 H, ArH), 5.08 (s, 2 H, CH_2), 4.37 (s, 2 H, CH_2), 2.21 (s, 6 H, CH_3).

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.76; H, 6.97; N, 11.28.

Thermal Decomposition of *N*-Benzyl-*O*-(*p*-methylbenzyl)-*N*-nitrosohydroxylamine (1b) in Benzene. After a solution of **1b** (1.28 g, 5.0 mmol) in benzene (10 mL) was heated to reflux for 24 h under nitrogen, the benzene was evaporated in vacuo to leave 1.01 g of an oil whose VPC and IR spectrum showed the absence of benzaldehyde and of benzonitrile; the products were *p*-tolualdehyde (1.6 mmol), *O*-(*p*-methylbenzyl)benzaldoxime (0.82 mmol), ω,ω′-azoxytoluene (1.2 mmol), *N*-benzyl-*O*-(*p*-methylbenzyl)hydroxylamine (0.82 mmol), and *p*-methylbenzyl alcohol (1.6 mmol) estimated by NMR.

***N*-[^{15}N]Nitroso-*N*-(*p*-methylbenzyl)-*O*-benzylhydroxylamine (^{15}N-1c)**, mp 83–83.5 °C, was prepared by the procedure described earlier.[10] *N*-(*p*-Methylbenzyl)-*O*-benzylhydroxylamine hydrochloride (5.27 g, 20 mmol) and sodium nitrite (^{15}N, 95% enrichment, 2.24 g, 30 mmol) gave 4.26 g (88%) of the product. Its mass spectrum did not give M^+; this result was also observed with unlabeled *N*-(*p*-methylbenzyl)-*O*-benzyl-*N*-nitrosohydroxylamine. Thus, the presence of the label was confirmed by its ^{15}N NMR spectrum which exhibited a strong peak at 518 (+5) ppm, using $^{15}NH_4Cl$ as the external standard. The ^{15}N spectra of *N*-nitrosodimethylamine and *N*-nitrosodiphenylamine exhibited the nitroso nitrogen at 534.8 and 554.4 ppm, respectively.[13]

Thermal Decomposition of *N*-[^{15}N]Nitroso-*N*-(*p*-methylbenzyl)-*O*-benzylhydroxylamine (^{15}N-1c) in Benzene. A

---

[11] Thoman, C. J.; Hunsberger, I. M. *J. Org. Chem.* **1968**, *33*, 2852.

[12] Bandish, B. K.; Garner, H. W.; Hodges, M. L.; Timberlake, J. W. *J. Am. Chem. Soc.* **1975**, *97*, 5856.

[13] Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*; John Wiley and Sons: New York, 1979; p 90.

solution of **1d** (0.8 g, 3.1 mmol) in benzene (15 mL) was heated reflux for 24 h under nitrogen. 4,4′-Dimethyl-ω,ω′-azoxytoluene was isolated from the mixture by column chromatography (SiO_2, hexane, twice), 0.25 g (1.1 mmol), and the sample for mass spectroscopy was prepared by recrystallization from methanol, mp 64–65 °C (lit.[12] mp 63–65 °C); M^+ 238.

***N*-Nitroso-*N*-(*o*-methylbenzyl)-*O*-benzylhydroxylamine (1d).** To a solution of *N*-(*o*-methylbenzyl)-*O*-benzylhydroxylamine (20.3 g, 90 mmol) in ethanol (150 mL) cooled in an ice bath was slowly added concd hydrochloric acid (10 mL) followed by the dropwise addition of a solution of sodium nitrite (9.3 g, 140 mmol) in water (10 mL). Then an additional 60 mL of water was added, and the mixture was stirred at ambient temperature overnight. The precipitated product was collected, washed with water, and air-dried. Crystallization from methanol–petroleum ether afforded 19.0 g (82%) of pale yellow needles: mp 60.5–61.5 °C; ^1H NMR δ 7.15 (br, 9 H, ArH), 5.02 (s, 2 H, CH_2), 4.70 (s, 2 H, CH_2), 2.30 (s, 3 H, CH_3).

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.47; H, 6.18, N, 10.93.

Acknowledgment. The authors thank the University of Massachusetts at Boston, the Polaroid Corporation, and Merck Sharp and Dohme for the support of this work. The generous help of Dr. B. H. Arison of Merck Sharp and Dohme is hereby gratefully acknowledged.