1560 *J. Org. Chem.* **1993,** *58,* 1560–1563

Notes

On the Thermal Deoxygenation of 1-(Dimethylamino)adamantane *N*-Oxide

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Received September 14, 1992

Introduction

Tertiary amine *N*-oxides, $R_1R_2R_3N^+O^-$, are readily reduced to the corresponding amines by numerous reagents.[2] Although small amounts of deoxygenation product frequently accompany the better known Cope elimination[3,5] and Meisenheimer rearrangement products,[4,6–8] spontaneous deoxygenation has rarely been observed as a *major* pathway of thermal decomposition.

Exceptions are Laughlin's finding of a 51% yield of tertiary amine when he attempted a Cope elimination in a sealed tube,[9] Quin and Shelburne's observation of the tertiary amine as the only product from heating 1-methyl-2-arylpiperidine *N*-oxides neat,[10] and a report by Kohrman and co-workers of deoxygenation of 2-(alkylthio)pyridine *N*-oxides.[11] Laughlin explained his observations in terms of reduction of the *N*-oxide by *N,N*-dimethylhydroxylamine. Apart from this example, studies of the mechanism of spontaneous reduction of *N*-oxides appear to be lacking.

We have attempted a Meisenheimer rearrangement of 1-(dimethylamino)adamantane *N*-oxide. We wish to report that heating this *N*-oxide neat at and above 145 °C causes loss of oxygen *as the main reaction.* A smaller amount of demethylation, forming 1-(methylamino)-adamantane, also occurs. Dioxygen is not formed, but CO_2 is formed. The Meisenheimer rearrangement product has not as yet been detected.

A polar mechanism can be written for this deoxygenation, cf. Scheme I, giving initially 1-(methylamino)-adamantane and formaldehyde. All the known reaction products can be explained by postulating that formaldehyde reduces the *N*-oxide to the tertiary amine and that the formic acid produced can reduce a second molecule of *N*-oxide to the amine, thus forming CO_2. This mechanism is analogous to that proposed by Laughlin (vide infra). The reaction of formaldehyde with tertiary amine *N*-oxides has been reported only once, together with the reactions of acetaldehyde and acrolein, but only the yields of acids were given.[12] We have therefore investigated the N-containing products of reduction of the *N*-oxides of *N,N*-dimethylaniline and 1-(dimethylamino)adamantane with formaldehyde and of the former with formic acid.

Scheme I. Proposed Mechanism of Amine *N*-Oxide Reduction in Absence of Cope Elimination

$$RMe_2N^+O^- + H_2O \rightarrow RMe_2N^+OH,\ OH^- \rightarrow RMeN^+{=}CH_2 + H_2O + OH^-$$

$$RMeN^+{=}CH_2 + OH^- \rightarrow RMeNCH_2OH \rightarrow RMeNH + HCHO$$

$$RMe_2N^+O^- + HCHO \rightarrow RMe_2N^+OCH_2O^-$$

$$RMe_2N^+OCH_2O^- + H_2O \rightarrow RNMe_2 + HCO_2^- + H_3O^+$$

$$HCO_2^- + H_3O^+ \rightarrow HCO_2H + H_2O$$

$$RMe_2N^+O^- + HCO_2H \rightarrow RMe_2N^+OCHO + OH^-$$

$$RMe_2N^+OCHO + OH^- \rightarrow RNMe_2 + CO_2 + H_2O$$

Briefly, the reason for attempting the Meisenheimer rearrangement of 1-(dimethylamino)adamantane *N*-oxide was as follows. Several reports[13–18] had described generation of the bridgehead radical 1-adamantyl by several methods for the purpose of investigating the stereochemistry of aliphatic radicals. Major discrepancies existed among these methods as to rate of radical formation, usually relative to *tert*-butyl. The Meisenheimer rearrangement had not as yet been included in such a study,

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0022-3263/93/1958-1560$04.00/0

although Adams and Kovacic have observed a 25% yield of Meisenheimer product from pyrolysis of *N,N*-dimethyl-3-aminohomoadamantane *N*-oxide.[19]

We originally wished to study *N*-(1-adamantyl)-*N*-methylaniline *N*-oxide, since *N*-benzyl-*N*-methylaniline *N*-oxide rearranges readily at 70 °C in aqueous 80% ethanol.[6,7] We did not succeed in preparing the required amine. Instead we have studied 1-(dimethylamino)adamantane *N*-oxide, **IIa**, preparation of which has been reported by Aldrich and co-workers.[20] We have also studied for comparison the rate and products of decomposition of *N,N*-dimethylbenzylamine *N*-oxide, previously reported by Schulman and co-workers.[21]

Results

Preparation of Amines and Amine *N*-Oxides. The *N,N*-dimethyl tertiary amine **Ia** was prepared, as previously reported, from 1-adamantanamine by treatment with formaldehyde and formic acid,[20] eq 1; amines **Ia–c** were

$$\mathrm{RNH_2} \xrightarrow[\mathrm{HCO_2H}]{\mathrm{HCHO}} \mathrm{RNMe_2} \xrightarrow{\mathrm{H_2O_2}} \underset{\textbf{IIa–c}}{\mathrm{RMe_2N^+O^-}} \xrightarrow{\Delta} \underset{\textbf{IIIb}}{\mathrm{Me_2NOR}} \quad (1)$$

a: R = 1-adamantyl
b: R = benzyl
c: R = phenyl

oxidized to the oxides, **IIa–c**, with 30% H_2O_2. All oxides were isolated as their hydrates, assumed to be trihydrates. **IIa** was also isolated as its hydrochloride; finally, nearly anhydrous **IIa** was prepared by treating chloroform solutions with molecular sieves; the anhydrous material was, however, extremely hygroscopic.

Condensed Products of Thermal Decomposition of *N*-Oxide (IIa) Hydrate. Heating **IIa** hydrate for several hours at 145–165 °C led to a dark mixture containing only reduction products; heating at 130 °C had led to recovery of **IIa**. The rearrangement product was expected to absorb in ^{1}HNMR at ca. 2.6 ppm (*N*-methyl H's), by analogy with IIIb. The product mixture, however, showed a sharp peak at 2.3 ppm, enhanced by addition of **Ia**, in addition to broad absorption at 1.55 and 2.0 ppm, characteristic of 1-adamantyl protons.

The mixture from **IIa** hydrate also showed a weaker sharp singlet at 2.4 ppm, and a second product showing this peak, a white solid, was isolated by preparative GLPC. This product was expected to be 1-(methylamino)adamantane, **Va**, since significant amounts of CO_2 and small amounts of CH_4 were also observed. Amine **Va**, a white solid, was synthesized from 1-bromoadamantane and formamide,[22] followed by reduction of the resulting *N*-(1-adamantyl)formamide, **IVa**, with $LiAlH_4$. The product from IIa was identical in all respects with Va, and addition of synthetic Va to reaction mixtures enhanced both ^{1}HNMR and GLPC peaks. Demethylation had clearly accompanied simple deoxygenation. This process appears to be the key to the deoxygenation mechanism.

Table I. Products of Thermal Decomposition of IIa at ca. 160 °C

glass	additive	% Ia	% Va	% (Ia + Va)	% Ia/ % Va
Pyrex[a]	none	46[a]	18[a]	64[a]	2.6[a]
Pyrex[a]	none	42[b]	22[b]	64[b]	2.0[b]
Pyrex[a]	KOH, 0.1 equiv	39[b]	32[b]	71[b]	1.2[b]
Pyrex[a]	benzoic acid, 1 equiv	24[b]	15[b]	39[b]	1.6[b]
soft	none	51[b]	21[b]	72[b]	2.4[b]
quartz	none	49[a]	24[a]	73[a]	2.0[a]

[a] Mean of four runs. [b] Mean of two runs.

Table II. Gaseous Products of Pyrolysis of IIa at 165 °C

additive	product	mol/mol *N*-oxide
KOH, 0.2 mol/mol oxide[a]	H_2	0.049
	CO_2	0.205[b]
	CH_3OH	0.006
	$CH_3CO_2CH_3$	0.002
none[c]	CH_4	0.005
	CO_2	0.152
	CH_3OH	0.0003
	$CH_3CO_2CH_3$	0.0007
benzoic acid, 0.1 mol/mol oxide[d]	H_2	0.0014
	CH_4	0.023
	CO_2	0.289

[a] Heated for 48 h. [b] Total yield; 0.193 mol/mol oxide liberated via acetic acid. [c] Heated for 6 h. [d] Heated for 3 h.

Products of the thermal decomposition in Pyrex vessels of **IIa**, both pure and in the presence of either added KOH or added benzoic acid, were determined by GLPC. The results are shown in Table I. The total yields of **Ia** and **Va** averaged 64–71% either with or without added KOH, but seemed to decrease in the presence of benzoic acid. The ratio of **Ia/Va** from pure **IIa** hydrate was 2.0 or more, but fell to 1.2 with added KOH. With benzoic acid the ratio **Ia/Va** was significantly less than 2.0. Control experiments showed that 72–85% of the tertiary amine could be recovered after heating with or without KOH or benzoic acid. The corrected total yield with or without KOH would then be more nearly 80–90%.

Thermal decomposition of pure **IIa** in soft glass and in quartz gave total yields of **Ia** and **Va** and **Ia/Va** ratios essentially the same as those in Pyrex.

Gaseous Products of Thermal Decomposition of IIa. Heating samples of **IIa** in vacuo resulted in mixtures of gases, detailed in Table II, in which CO_2 predominated, but which never contained O_2. Small amounts of CH_4 and H_2 were found under certain conditions, along with traces of methanol and methyl acetate. With added KOH, the bulk of the CO_2 appeared after distilling acetic acid in vacuo into the product mixture; it was identified by strong IR bands at 2325 and 610–710 cm^{-1}. The yields of CO_2 with and without KOH are similar to those of **Va**, but that with 1 equiv of benzoic acid is about twice that of **Va**.

Products of Thermal Decomposition of IIb. Amine oxide **IIb**, heated at 120–127 °C, gave mixtures of rearrangement product **IIIb** and amine **Ib** in which the former predominated greatly; the two were distinguished by their *N*-methyl proton signals at 2.5 and 2.2 ppm, respectively. Formation of **Ib** was not reported by Schulman and co-workers.[21]

Kinetics of Decomposition of IIa and IIb. Kinetics of disappearance of these two amine *N*-oxides, measured

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Table III. Rate of Pyrolysis of IIa[a]

additive	temp, ±1 °C	time, min	% **IIa** conv[b]
none	155	30	6
none	160	24	13
none	159	47	35
none	158	70	48
none	157	>315	>90
benzoic acid	162	41	95
KOH	159	125	17
KOH	155	337	46
KOH	155	457	58
KOH	158	200	58

[a] In open Pyrex test tubes. [b] By integration of **IIa** methyl H signal (3.0 ppm) vs CH_3NO_2 (4.3 ppm).

by monitoring their *N*-methyl ^{1}HNMR signals, were first order. The rate constants (cf. supplementary material, Table 2S) show that oxide **IIa** is much more stable than **IIb**. Oxide **IIa** had $k_1 = 1.7 \times 10^{-5}$ s^{-1} at 145.0°, while **IIb** had $k_1 = 3.6 \times 10^{-4}$ s^{-1} at 127.0 °C, the latter in good agreement with the value of Schulman and co-workers.[21]

"One-point" rates were also measured for decomposition of **IIa** in the presence of KOH or benzoic acid and their absence; the results appear in Table III. KOH retarded the reaction, while benzoic acid accelerated it; the ratios were several-fold in both cases.

Reactions of Amine *N*-Oxides with Formaldehyde and with Formic Acid. Aqueous 37% formaldehyde reduced *N,N*-dimethylaniline *N*-oxide, **IIc**, to **Ic** in high yield in 24 h *at room temperature*. Reaction with formic acid, however, was much slower, requiring 105 °C to give a comparable yield in 22 h. These two reactions are represented in Scheme I.

Reaction of **IIa** with formaldehyde was very slow, as expected, giving only about a 20% yield of **Ia** after 72 h at 105 °C in a glass-stoppered flask. Attempts to conduct the reaction in sealed tubes, even thick-walled ones, resulted in failure of the tubes. However, one experiment with added concd HCl in a glass-stoppered flask gave **Ia** quantitatively in 72 h at 100 °C. Considering the slowness of reaction of **IIa** with formaldehyde and of **IIc** with formic acid, the reaction of **IIa** with formic acid could require a temperature of 150 °C or more, in the range for "spontaneous" thermal deoxygenation of **IIa**. (Formic acid decomposes very slowly to CO and H_2O at 150–160 °C.[23]) We therefore have not attempted to observe a reaction of **IIa** and formic acid.

Discussion

Mechanisms of Thermal Reduction. Although amine *N*-oxide pyrolyses frequently form some reduction product,[2] it is highly unusual to find reduction as the major pathway. The mechanism proposed by Laughlin[9] invokes the reduction of the *N*-oxide by the Cope elimination intermediate, *N,N*-dimethylhydroxylamine, which is oxidized to *N*-methylnitrone and H_2O. The nitrone then undergoes 1,3-dipolar cycloaddition to the olefin to form the observed isoxazolidine. Cope and LeBel[24] had observed isoxazolidine formation from *N*,2-dimethylpiperidine *N*-oxide, but did not suggest what reagent oxidized the hydroxylamine to the nitrone.

For 1-adamantyl *N*-oxide **IIa**, we propose the analogous mechanism shown in Scheme I: the amine oxide is postulated to rearrange to the hydroxymethylamine, which should decompose to formaldehyde and secondary amine; formaldehyde reduces amine *N*-oxide; and the formic acid produced is expected to reduce additional amine *N*-oxide, leading to CO_2. This mechanism explains the following observations: (1) secondary amine (**Va**) and CO_2 are products; (2) their yields are similar; (3) the ratio of **Ia**/**Va** is in the vicinity of 2.0. Observations 1–3 are reflected in eq 2. Furthermore, the postulated reduction of 1-(dimethylamino)adamantane *N*-oxide by formaldehyde (cf. Scheme I) in fact occurs, and at a lower temperature than does the decomposition of **IIa**. Although the reduction of **IIa** by formic acid has not yet been demonstrated, that of **IIc** has been, and formic acid has a considerable lifetime at 150–160 °C.[23]

$$\underset{\textbf{IIa}}{3\,\mathrm{RMe_2N^+O^-}} \rightarrow \underset{\textbf{Ia}}{2\,\mathrm{RMe_2N}} + \underset{\textbf{Va}}{\mathrm{RMeNH}} + \mathrm{CO_2} + \mathrm{H_2O} \quad (2)$$

The slow step in the decomposition of **IIa** is no doubt the formation of secondary amine, since the reduction of *N*-oxide by formaldehyde is relatively fast. It follows that the formation of secondary amine is acid catalyzed, a function probably served by the water of the amine *N*-oxide hydrate. In the absence of added acid or base, formic acid resulting from the reduction step probably reduces additional *N*-oxide, affording ca. 2 mol of tertiary amine, **Ia**, per mol of both secondary amine, **Va**, and CO_2.

The reduction steps are closely analogous to the reported reduction of amine *N*-oxides by acetic formic anhydride,[25] eq 3. Reaction with formic acid may involve the common intermediate R_3N^+OCHO, which reacts with an available base to form $R_3N + CO_2$ (cf. Scheme I).

$$\mathrm{CH_3COOCHO} + {}^{-}\mathrm{O^+NR_3} \rightarrow \mathrm{CH_3CO_2H} + \mathrm{CO_2} + \mathrm{NR_3} \quad (3)$$

With added base, as compared to neutral conditions, the rate was less, the ratio of **Ia**/**Va** was less, and the yield of **Va** was *greater*; the yield of CO_2 was *less* than that of **Va**, rather than the same. The yield of CO_2 reflects the extent of reduction of **IIa** by formaldehyde and either formic acid or formate ion. Base must cause Cannizzaro disproportionation of formaldehyde to methanol and formate. Indeed, cf. Table II, basic conditions produced some 20 times as much methanol as did neutral conditions, while acidic conditions produced none; since the methanol was detected in the vapor phase, the true yield may have been even higher. Thus, less of the *N*-oxide is reduced by formaldehyde than under neutral conditions, and the ratio **Ia**/**V** is smaller.

With 0.1 equiv of added acid the decomposition of **IIa** was accelerated, and the yield of CO_2 was greater than under basic or neutral conditions. The CO_2 yield was not determined with 1.0 equiv of acid, but the yield of **Ia** decreased sharply. This decrease may have resulted from protonation of the amine *N*-oxide, decreasing its rate of reduction.

Quin and Shelburne's,[10] as well as Cope and LeBel's,[24] results can be explained in terms of the mechanism proposed here for the 1-adamantyl case. Quin and Shelburne's reduction was suppressed by most solvents because reactions of formaldehyde and formic acid with *N*-oxides must follow *second*-order kinetics, while their

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(23) Engler, C.; Grimm, J. *Ber.* **1897**, *30*, 2921. A sample of formic acid heated 8 h in a sealed tube at 150–160 °C gave CO in less than 5% yield.

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desired Meisenheimer rearrangement is *first* order. Quin and Shelburne's findings cannot be explained in the same way as the Cope–LeBel and Laughlin[9] results, with a Cope step opening the ring and the amine *N*-oxide oxidizing the hydroxylamine: Cope and LeBel showed clearly that the parent *N*-methylpiperidine *N*-oxide did not undergo Cope elimination ring opening, but decomposed at 200–240 °C to both *N*-methylpiperidine and piperidine.[24]

The mechanism by which we have explained our results appears to possess some generality, and may be applicable to many cases of thermal deoxygenation of amine *N*-oxides.

Experimental Section

General. 1-Adamantanamine was purchased from the Aldrich Chemical Co.; *N*,*N*-dimethylbenzylamine was obtained from Eastman Organic Chemical Co. Melting points are uncorrected. Most ^{1}HNMR spectra were recorded and integrated at 60 MHz; for later work (C. M. U.; reactions with formaldehyde and formic acid) a GE QE-300 spectrometer was used. Mass spectra of liquid products were obtained on a Hewlett-Packard 5995A GC/MS instrument, while those of gaseous products were obtained on a Consolidated 21-103C spectrometer. GC analyses were performed on Hewlett-Packard 5750 and Varian Aerograph instruments equipped with thermal conductivity detectors and 2-m aluminum columns packed with 17% Apiezon N on 80–100 mesh Chromosorb W washed with 2% KOH solution; column temperature was 185 °C; chromatograms were quantitated using *p*-dimethoxybenzene or nitromethane as internal standard.

N-(1-Adamantyl)formamide (**IVa**) was prepared in 86% yield by the method of Haaf; mp 135–137 °C (lit.[22] mp 140 °C). 1-(Methylamino)adamantane (**V**) was prepared in 66% yield by $LiAlH_4$ reduction of **IVa**; mp 41–45 °C (lit.[26] mp 46 °C); MS base peak, *m*/*e* 108; mol. ion, *m*/*e* 165. 1-(Dimethylamino)adamantane was prepared in 63% yield by the method of Aldrich et al.[20] bp 55–60 °C/0.05 Torr (lit.[20,27] bp 80 °C/2 Torr); ms base peak, *m*/*e* 122; mol. ion, *m*/*e* 179. Amine *N*-oxides **IIb** and **IIc** were prepared from the amines and H_2O_2 as described for **IIa** (vide infra); **IIb** (60% yield) was sticky white crystals, while **IIc** (87% yield) was a viscous rust-colored oil; their ^{1}HNMR spectra ($CDCl_3$) showed methyl signals at 3.0 and 3.6 ppm, respectively.

Isolation of Gaseous Products of *N*-Oxide Decomposition. The vacuum line was attached to a mercury manometer. The decomposition flask was a Claisen flask with a vacuum stopcock and ground glass joint sealed onto the sidearm. A weighed sample of **IIa** (and acid or base if required) was added through the main neck of the flask, and the neck was sealed. The flask was attached to the vacuum line, evacuated, and heated at 125 °C to drive off much of the water, and the stopcock was closed. After decomposition, the cooled flask was again attached to the vacuum line, the gases were expanded into the evacuated manifold, and the pressure of gases was measured. The gases were condensed into a sampling bulb with liquid nitrogen and analyzed later. The volume of the bulb was measured by filling with water; that of the vacuum line plus decomposition flask was determined by expanding air from the sampling bulb into the line.

1-(Dimethylamino)adamantane *N*-Oxide Hydrate, IIa. The method was similar to that of Aldrich and co-workers.[20] From **Ia** (18 g, 0.10 mol) and 30% hydrogen peroxide (11.3 g, 0.10 mol peroxide) in 20 mL of methanol were obtained white crystals, 14.2 g, 0.057 mol, 57% (based on trihydrate): mp 120–130 °C (lit.[20] mp 130–132 °C). Picrate: mp 238–240 °C (lit.[20] mp 240 °C); ^{1}HNMR ($CHCl_3$; ppm) 1.7, 2.15 (adamantyl), 3.0 (methyl), 4.6 (H_2O). The **IIa** hydrate was hygroscopic and was stored in a desiccator. Use of a 2-fold excess of hydrogen peroxide gave higher yields.

1-(Dimethylamino)adamantane *N*-Oxide Hydrochloride, IIa·HCl. The **IIa** hydrate was dissolved in warm acetone, and dry HCl was bubbled through the solution for 40 min, whereupon the solution became deep red and turbid. The acetone was stripped off, and the residue was recrystallized from acetone, white crystals, mp 188–189 °C dec.

Decomposition of 1-(Dimethylamino)adamantane *N*-Oxide, IIa, in Pyrex. A Pyrex tube fitted with a 12/30 male joint was charged with a sample of **IIa** (100.3 mg, 0.403 mmol), evacuated on the vacuum line, and sealed. The lower end was heated in a silicone oil bath at 160 °C for 5 h. The tube was cooled and opened, and the white residue was dissolved in 1.0 mL of spectroscopic-grade methanol with *p*-dimethoxybenzene (12.5 mg, 9.9×10^{-2} mmol). GC analysis showed **Va**, 23.4%, at 12.7 min, and **Ia**, 52.0%, at 18.4 min.

Reaction of *N*,*N*-Dimethylaniline *N*-Oxide and Formaldehyde. The *N*-oxide (**IIc**) (2.00 g, 0.0105 mol) and 37% formaldehyde solution (4.0 g, 0.050 mol) were mixed in a 25-mL Erlenmeyer flask with ground glass neck, and the flask was stoppered and let stand 24 h. The dark rust colored solution was basified with 25 mL of 1 M NaOH and extracted with three 30-mL portions of dichloromethane. The extracts were stripped, leaving 2.95 g of dark brown oil smelling strongly of *N*,*N*-dimethylaniline. The product was shown by IR, ^{1}HNMR, and GC to contain primarily *N*,*N*-dimethylaniline (**Ic**), but no *N*-methylaniline (**IVc**). Control experiments using 2–4 mL of deionized water in place of formaldehyde solution at 95–105 °C for 2.5–22 h led to residues of no more than 0.078 g.

Similar techniques were employed to investigate the reactions of **IIc** with formic acid and **IIa** with formaldehyde; cf. supplementary material.

Acknowledgment. The authors are grateful for financial assistance through a grant from the U. S. Army Research Office–Durham, to the NSF for partial support of the purchase of the GE QE-300 NMR spectrometer used in the later stages of this work (NSF/ILI Grant No. USE-8852049), and Mr Eugene Camehl (since retired) and Dr. L. Shadoff of the Dow Chemical Company for providing mass spectra of gas samples.

Registry numbers supplied by author: *N*-(1-adamantyl)formamide, 3405-48-9; 1-aminoadamantane, 768-94-5; aniline, 62-53-3; 1-(dimethylamino)adamantane, 3717-40-6; 1-(dimethylamino)adamantane *N*-oxide, 3717-41-7; *N*,*N*-dimethylaniline, 121-69-7; *N*,*N*-dimethylaniline *N*-oxide, 874-52-2; *N*-benzyl-*N*,*N*-dimethylamine, 103-83-3; *N*-benzyl-*N*,*N*-dimethylamine *N*-oxide, 5400-82-8; 1-(methylamino)adamantane, 3717-38-2.

Supplementary Material Available: Table of ^{1}H chemical shifts of **Ia**,**b**, **IIa–c**, **IIIb**, and **Va**, table of rate constants of decomposition of two amine oxides, and descriptions of preparations of compounds and reactions of amine oxides with formaldehyde and with formic acid (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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