Aliphatic Azoxy Compounds. III. Reduction of Nitrosoalkane Dimers as an Approach to Symmetrical Azoxyalkane Synthesis[1]

K. Grant Taylor,* Min-Shong Chi, and Melvin S. Clark, Jr.

Department of Chemistry, University of Louisville, Louisville, Kentucky 40208

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Catalytic hydrogenation of nitrosoalkane dimers **3a–d** using Pd/charcoal catalyst was tested as a synthetic approach to low molecular weight, symmetrically substituted azoxyalkanes. The method appears to be useful for making *Z* azoxyalkanes of carbon content not smaller than C_4, at which point overreduction becomes a deleterious side reaction. The requisite nitrosoalkane dimers **3a–d** were preparable by peracetic acid oxidation of *E* benzaldimines (**3a–c**) or by direct oxidation of the amine (**3d**). An anhydrous work-up allowed the synthesis, by this approach, of (*E*)-nitrosomethane dimer, a more convenient procedure than those previously published. Further, mixtures of *Z* and *E* oxaziridines were obtained from the oxidation of *E* imines, a result, it is argued, which is inconsistent with a concerted, olefin-epoxidation-like mechanism. Some aspects of the NMR spectrum of azoxycyclohexane are discussed.

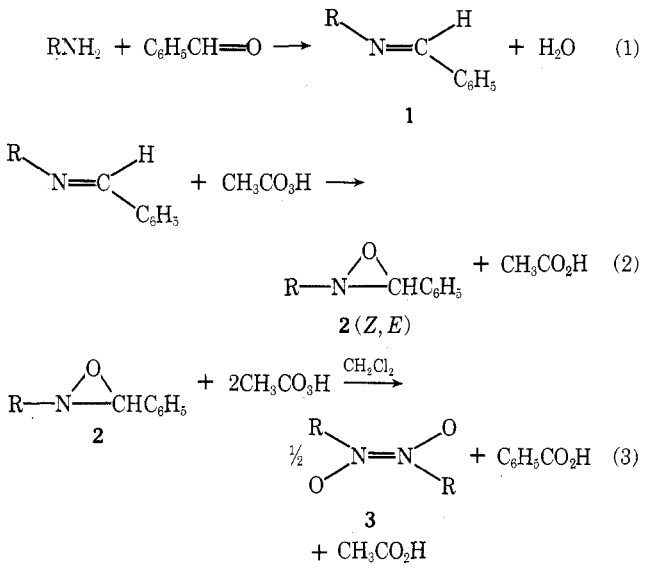
As part of a program of investigation of the chemistry of azoxyalkanes we began investigating methods of synthesis which might complement (or replace) existing synthetic approaches. A survey of the literature at the time this present project was begun indicated that the major approach to symmetrically substituted azoxyalkanes was (and still is) via oxidation of the corresponding azoalkane,[2] with the most commonly employed oxidizing agents being organic peroxy acids.[2] To complement the oxidative approach, a small selection of chemical reduction reactions was available; but these, most often involving the reduction of an aromatic nitro compound, were applicable only to the synthesis of aromatic azoxy compounds.[2] It should be noted that Snyder[3a] and Greene[3b] have recently reported the reduction of cyclic (hence, cis) azo dioxides to azoxyalkanes using hexachlorodisilane, a reagent previously employed by Mislow and co-workers in the deoxygenation of phosphine and amine oxides.[3c] The reagent will also effect the deoxygenation of cis and trans azoxyalkanes,[3a,d,e] but apparently has not been tested with acyclic nitrosoalkane dimers.[2,3f] However, Meister[4] had reported the high-yield catalytic reduction of nitrosocyclododecane and nitrosocyclohexane dimers to their respective azoxy derivatives, and this, together with Emmons' facile synthesis of nitrosoalkane dimers,[5] prompted us to test Meister's hydrogenation approach for the synthesis of lower molecular weight symmetrically substituted azoxyalkanes.[6,7] Also involved was a possible modification of Emmons' method to enable the preparation of low molecular weight nitrosoalkane dimers.

As the results below will show, atmospheric catalytic hydrogenation of nitrosoalkane dimers with palladium on charcoal catalysts is a useful method for preparation of higher molecular weight azoxyalkanes[8] but does not appear to be a worthwhile approach for the preparation of azoxyalkanes of carbon content C_4 or smaller. However, the project did yield an improved synthesis of (*E*)-nitrosomethane dimer and also afforded a key mechanistic insight into the formation of oxaziridines by the oxidation of imines with organic peroxy acids. The details are outlined below.

Results

The synthetic approach and the results are summarized below in Scheme I, reaction 4, and Table I. Regarding Scheme I, benzaldimine formation is rapid, usually exothermic, and more convenient than ketimine formation,[5] especially for low molecular weight amines. For example, for the preparation of **1a** a 40% solution of methylamine in water can be used. Only the *E* diasteromers of 1 were obtained. In reaction 2, Emmons' oxaziridine preparation, both *Z* and *E* diastereomers were obtained,[3,4] a result inconsistent with a concerted mechanism of oxidation (see below). For the preparation of nitrosoalkane dimers **3a** and **3b** it was necessary to isolate and purify (distillation) the corresponding oxaziridine. For best yields in reaction 3 some care had to be taken to keep the reagents near the stoichiometric ratio of 1 mol of **2** to 2 mol of peracetic acid. This approach resulted in the recovery of some 10–15% of unreacted oxaziridine[9] (the yields in Table I are *not* corrected for this), but employing a substantial excess of oxidizing agent gave poorer yields of nitrosoalkane dimer. The second mole of peroxy acid was required for oxidation of the benzaldehyde which is generated in the oxidation of **2**, and which competed with **2** in the consumption of peracetic acid. For the preparation of dimers **3a** and **3b** a nonaqueous modification of Emmons' work-up procedure was devised with neutralization of the acidic reaction mixture being accomplished by stirring the solution with excess powdered sodium carbonate. After solvent evaporation the (*E*)-nitrosomethane dimer present in the mixture crystallized. Washing with pentane separated it from the pentane-

Scheme I. Reaction Scheme for the Preparation of *E* Nitrosoalkane Dimers



a, R = CH_3
b, R = C_2H_5
c, R = *i*-C_3H_7
d, R = C_6H_{11}
e, R = 1-adamantyl (**3e** = 1-nitroadamantane)

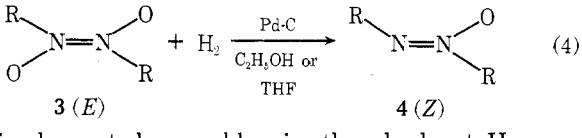
Table I. Yields (%) of Products Obtained in Scheme I and from Catalytic Hydrogenation (Reaction 4)

R	Compd: Imine, 1	Oxaziridine, 2	E nitroso dimer, 3	Z azoxyalkane, 4
CH_3	92[a]	76[b]	36	10[c]
C_2H_5	95	83[b]	50	22
i-C_3H_7	90	*d*	48	57
C_6H_{11}			36[e]	83
1-Adamantyl	90	70	*f*	

[a] Yields are of isolated products of 95–100% purity unless otherwise noted. [b] Mixture of cis and trans isomers. [c] Yield estimated from VPC. [d] Oxaziridine not isolated. [e] Dimer prepared directly from cyclohexylamine.[5] [f] 1-Nitroadamantane is the oxidation product.

soluble, unreacted (*E*)-oxaziridine. The 36% (unoptimized) yield is modest compared with the >80% obtained by periodic acid oxidation of methylhydroxylamine[10] but that procedure requires a tedious ion exchange chromatography plus lyophilization of the resulting large quantity of water. [The isolation of **3b** (R = C_2H_5) is discribed in the Experimental Section.] Not unexpectedly[5] the method failed to produce 1-nitrosoadamantane, producing, instead, the "overoxidized" product, 1-nitroadamantane (**3e**). The nitrosoalkane dimers prepared were the *E* diastereomers.

The hydrogenation reaction (4) proceeded smoothly in the case of **3d** nitrosocyclohexane dimer, in ethanol with hydrogen uptake stopping after 1.15 mol. With **3c** overre-



(4)

3 (*E*) 4 (*Z*)

duction began to be a problem in ethanol solvent. However, with tetrahydrofuran solvent, hydrogen uptake stopped after 1.12 mol. We believe that the modest isolated yield of azoxyisopropane (**4c**) is principally a result of small-scale isolation of the liquid product (VPC yield ~80%). For nitrosoethane dimer (**3b**), overreduction was a principal cause for the low yield. Hydrogen uptake never completely stopped during the hydrogenation reaction, and the reaction was stopped after 1.3 mol uptake (6 h). For nitrosomethane dimer (**3a**), its insolubility in ethanol and THF (and other solvents) added to the problem of overreduction and a satisfactory preparation of azoxymethane was never achieved. The formation of **4a** as a reduction product was evidenced by VPC analysis.

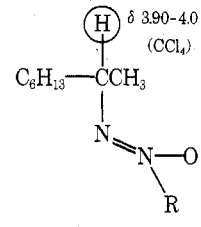
The azoxyalkanes, **4**, that were produced in reaction 4 were the known *Z* (or trans) diastereomers. For example, the azoxyisopropane produced in reaction 4 was identical with that prepared by peracid oxidation of *trans*-asoisopropane and different from that prepared by oxidation of *cis*-azoisopropane.[11] Interestingly, as indicated in Table II, in azoxycyclohexane the proximal and distal H's display an accidental magnetic equivalence, an NMR pattern strongly reminiscent of H_α's of the cyclic *E* azoxyalkanes (cis) reported by Greene[12] and Snyder.[13] In addition, the 1300-cm^{-1} ir band of the NNO function, normally a strong absorption in *Z* azoxyalkanes, was much reduced in intensity in **4d**, again reminiscent of the ir data reported for cyclic *E* azoxyalkanes.[12,13] Thus, a chemical confirmation of the geometry of azoxycyclohexane was required, and the azoxycyclohexane produced in reaction 4 was found to be identical with that produced by peroxy acid oxidation of (*E*)-azocyclohexane. Further, while the chemical shift differences for the proximal and distal H_α's ($\Delta\delta$p–d in Table II) of azoxy-

Table II. Proton NMR Chemical Shifts (δ) of Azoxyalkanes in CCl_4 Solvent

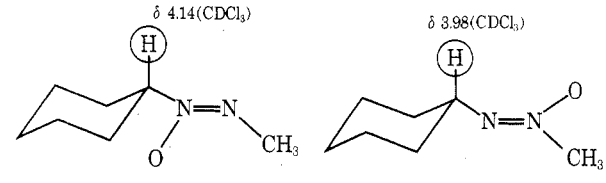
Compd	Proximal[a] H_α	Proximal[a] H_β	Distal[a] H_α	Distal[a] H_β	$\Delta\delta$ p–d for H_α
Azoxyethane	4.14 (q)[b]	1.47 (t)	3.37 (q)	1.23 (t)	0.77
Azoxyisopropane	4.38 (sp)	1.42 (d)	4.12 (sp)	1.11 (d)	0.26
Azoxycyclohexane	3.93 (m)	1.6 (bm)	3.93 (m)	1.6 (bm)	0

[a] Defined as follows: (proximal) HC_β–HC_α–N(O)=N-CH_α–CH_β (distal). [b] Multiplicities as follows: q = quartet (J = 6–7 Hz): t = triplet (J = 6–7 Hz); sp = septet (J = 6–7 Hz); m = multiplet (unresolved); bm = broad multiplet.

ethane and azoxyisopropane follow the predictions of Snyder's[14] calculations and analysis, the analogous H's of azoxycyclohexane do not fit the pattern. While the chemical shift of the distal H of azoxycyclohexane appears to be "normal" if we compare it with the chemical shifts of the analogous protons of structures **5**,[15] **7**,[16] and **4c**, the chemi-



5a. R = CH_3
b. R = allyl
c. R = n-C_3H_7



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cal shift of the proximal H_α of azoxycyclohexane appears to be unusually shielded if azoxyisopropane is used as a model. However, consideration of the more appropriate model compound **6**[16] reveals that the chemical shift of the proximal H_α of azoxycyclohexane is not too far from "normal" for a cyclohexyl methine hydrogen. Further comment must await conformational analysis of acyclic azoxyalkanes.

Observations. As mentioned above, *Z* and *E* oxaziridines, **2**, were obtained from the peracetic acid oxidation of certain *E* benzaldimines, **1**. The observed *Z*:*E* ratios and chemical shifts of the benzylic hydrogen atoms of **2** are collected in Table III. The data of Table III are consistent with those reported by Boyd[17] and co-workers for the *m*-chloroperbenzoic acid oxidation of (*E*)-*N*-alkyl-*p*-nitrobenzaldimines. Clapp and Mandan,[18] from a kinetic study of the *m*-chloroperbenzoic acid oxidation of benzaldimines, proposed a mechanism involving concerted nucleophilic displacement at peracid (dimer) oxygen by the imine CN double bond (the "olefin epoxidation" mechanism[5]). Conversely, Ogata and Sawaki,[19] from a kinetic study of the perbenzoic acid oxidation of *N*-(para-substituted benzylidene)-*tert*-butylamines, concluded that the oxidation involves two steps, proceeding, initially, by addition of peracid across the imine CN double bond, followed by ring closure to oxaziridine (the "Baeyer–Villiger type" mechanism[5]).

Table III. Relative *Z*–*E* Ratios of Oxaziridines and NMR Chemical Shifts (δ) of H_{C_3} of Oxaziridine Diastereomers in CCl_4 Solvent

R of compd 2	$\delta_{H_{C_3}}$		Ratio	
	Z	*E*	*Z*	*E*
CH_3	5.14[a]	4.37[b]	47[c]	53[c]
C_2H_5	5.12	4.35	22	78
n-C_4H_9[d]	5.06	4.28	18	82
i-C_3H_7		4.38		100
1-Adamantyl		4.90		100

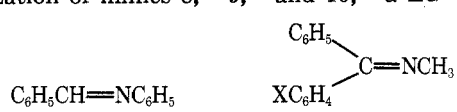
[a] δ_{CH_3} 2.22. [b] δ_{CH_3} 2.58. [c] Ratio of integration values of H_{C_3}'s. [d] Consistent elemental analysis obtained on mixture.

Table IV. Estimation of $\Delta G^{\ddagger}$ at 0°C for *Z*, *E* Isomerization of Imines

Imine	Reaction	Exp E_a, kcal	$\Delta S^{\ddagger}$, eu	Approximate $\Delta G^{\ddagger}$, 0°C, kcal mol^{-1}
8	*Z* → *E*	16.5	*a*	18
9	*Z* → *E*	25.0	−4.7	26
10	*E* → *Z*	27.1	+2.7	26
1 (R = CH_3)	*Z* → *E*			22–23[b]

[a] A $\Delta S^{\ddagger}$ range of −5 to −10 eu was used for calculation of $\Delta G^{\ddagger}$ at 0°; from k = 1.46 sec^{-1} at 30.0°,[20] $\Delta G^{\ddagger}$ = 17.5 kcal mol^{-1}. [b] Sum of $\Delta G^{\ddagger}$ at 0° for 8 plus a $\Delta\Delta G^{\ddagger}$ = 4–5 kcal; $\Delta\Delta G^{\ddagger}$ is based on a (conservative) 10^3 reduction in k for isomerization of *N*-alkylketimines compared with *N*-arylketimines.[8]

For the Clapp mechanism to be consistent with the present work two conditions must apply: (1) the rate of *E* to *Z* imine isomerization should be faster than the rate of oxidation, and (2) the rate of oxidation of *Z* imine must be faster than that of *E* imine. Regarding condition 1, from kinetic data and activation parameters published for the isomerization of imines **8**,[20] **9**,[21] and **10**,[21] a $\Delta G^{\ddagger}$ = 22–23



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9, X = *p*-Cl
10, X = *p*-NO_2

kcal mol^{-1} for *Z* to *E* isomerization of aldimines 1 can be estimated (see Table IV). To estimate $\Delta G^{\ddagger}$ for *E* to *Z* isomerization of **1**, the free-energy difference between the *Z* and *E* ($\Delta G_{Z,E}$) isomers of 1 must, again, be estimated. The value of $\Delta G_{Z,E}$ for 1 must lie between the $\Delta G_{Z,E}$ for stilbene[21] (2.3–2.9 kcal mol^{-1}, $r_{C=C}$ 1.35 Å) and the $\Delta G_{Z,E}$ for azobenzene[21] (9.9 kcal mol^{-1}, $r_{N=N}$ 1.23 Å). Using $r_{C=N}$ 1.24–1.30 Å, we estimate a $\Delta G_{Z,E}$ for 1 of 5.5–9.5 kcal mol^{-1}. This would indicate that the $\Delta G^{\ddagger}$ for *E* to *Z* isomerization of 1 at ~0°, the temperature of our oxidation conditions, could range from 27 to 31 kcal mol^{-1} (or, at the least, about 23 kcal mol^{-1}: $\Delta G^{\ddagger}$ of 8 + $\Delta G_{Z,E}$ = 5.5 kcal mol^{-1}). The activation parameters found by Clapp[18a] for the oxidation of *N*-(*p*-nitrobenzylidene)-*tert*-butylamine at 25.5° (E_a = 5.0 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −47 eu) allow an estimation of $\Delta G^{\ddagger}$ at 0°C = 18 kcal mol^{-1}. From the substantial difference between the $\Delta G^{\ddagger}$ for the *E* to *Z* isomerization of 1 and the $\Delta G^{\ddagger}$ for the oxidation reaction, one would conclude that, under usual oxidation conditions, *E* to *Z* isomerization of aldimines is decidedly slower than their oxidation to oxaziridines.[20,22] Regarding condition 2, we conservatively estimate that imine **1a** contains less than 1% of the *Z* diastereomer.[23] Given 0.1% of (*Z*)-**1a** *at equilibrium*, it would have to be oxidized 870 times faster than (*E*)-**1a** to give the ratio of isomers shown in Table III. Given the generous event of as much as 1% (*Z*)-**1a** *at equilibrium*, then (*Z*)-**1a** would have to be oxidized 87 times faster than the *E* isomer. Both of these figures seem improbably high in view of the fact that *Z* olefins are epoxidized faster than *E* olefins by a factor of only 2 or 3[25] (e.g., oleic acid:elaidic acid, 1.6; *Z*, *E* stilbenes, 1.93; (*Z*,*E*)-1,2-dineopentylethylenes, 2.6; recenoleic acid, 1.6). Thus, the fulfilling of *both* conditions required for accommodation of the present data to the "olefin epoxidation mechanism"[18] is not met. We conclude that the present stereochemical results are more consistent with, and support, the "Baeyer–Villiger mechanism" advanced by Ogata and Sawaki[19] for the oxidation of imines to oxaziridines.

Experimental Section

General. Melting points (uncorrected) were taken on a Thomas-Hoover melting point apparatus. NMR spectra were obtained on a Varian Associates A-60A spectrometer using tetramethylsilane as internal standard, and CCl_4 as solvent, unless noted otherwise. Ir spectra were obtained on a Perkin-Elmer 337 (grating) spectrometer and uv spectra with a Cary 14 spectrophotometer. Midwest Microlab, Inc., Indianapolis, Ind., performed the elemental analyses. Analyses by VPC were performed on Hewlett-Packard instruments: Model 5750 with flame ionization detector or Model 700 with a thermal conductivity detector. The following columns were used: column A, 15% Carbowax 20M on Anakrom; column B, 10% Hewlett-Packard silicone rubber UCW 98 on Chromosorb G (NAW); column C, 2% silicone rubber UCW-98 on Diatoport S.

Preparation of Imines. Two procedures were used. (A) For water-soluble amines, e.g., methylamine, equal volumes of ether and 40% aqueous methylamine were stirred and cooled to 0°. Benzaldehyde (limiting reagent) was then added dropwise to the stirred mixture, and, after addition was complete, the cooling bath was removed and stirring continued for 2 h. Solid NaOH was then added, the organic layer separated and dried (Na_2CO_3 or NaOH), and the product isolated by distillation in vacuo from a few KOH pellets. (B) For water-insoluble amines, the amine was cooled to 0° and, with stirring, an equivalent amount of benzaldehyde was added dropwise. After completion of the addition, cooling was discontinued and stirring continued for 1 h. Solid NaOH was then added, at which point the procedures became identical.

***N*-(Benzylidene)methylamine (1a),**[26] procedure A: bp 89° (30 mm); ir (neat) 1650 cm^{-1} (C=N); NMR δ 8.15 (methine H).

***N*-(Benzylidene)ethylamine (1b),**[26] procedure A: bp 109° (47 mm); ir (neat) 1650 cm^{-1} (C=N); NMR δ 8.17 (methine H).

***N*-(Benzylidene)-2-propylamine (1c),**[26] procedure B: bp 116° (24 mm); ir (neat) 1650 cm^{-1} (C=N); NMR δ 8.34 (methine H).

***N*-(Benzylidene)-1-butylamine,** procedure B: bp 56–57° (0.03 mm); ir (neat) 1650 cm^{-1} (C=N); NMR δ 8.32 (methine H).

Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.39; N, 8.69. Found: C, 81.93; H, 9.53; N, 8.93.

***N*-(Benzylidene)-1-adamantylamine (1e),** procedure B (inverse addition): mp 58–61°; ir (neat) 1650 cm^{-1} (C=N); NMR δ 8.20 (methine H).

Anal. Calcd for $C_{17}H_{21}N$: C, 85.31; H, 8.84; N, 5.85. Found: C, 85.24; H, 8.91; N, 5.83.

Preparation of Oxaziridines. The method of Emmons[5] was used.

2-Methyl-3-phenyloxaziridine (2a):[26] bp 64° (0.27 mm); NMR δ 6.97 (s, phenyl H).

2-Ethyl-3-phenyloxaziridine (2b):[26] bp 42° (0.1 mm); NMR δ 7.3 (two singlets with 0.8-Hz separation, *Z*, *E* phenyls), 2.81 (q, J = 7 Hz, *E*-CH_2), 2.58 (q, J = 7 Hz, *Z*-CH_2), 1.17 (t, J = 7 Hz, *E*-CH_3), 0.99 (t, J = 7 Hz, *Z*-CH_3).

(*E*)-2-(2-Propyl)-3-phenyloxaziridine:[26] bp 52° (0.05 mm); NMR δ 7.31 (d, phenyl H), 2.21 [septet, J = 6.5 Hz, $HC(Me)_2$], 1.21, 1.04 (two doublets, J = 6.5 Hz, nonequivalent isopropyl group CH_3's).

(*Z*,*E*)-2-(1-Butyl)-3-phenyloxaziridine: bp 72–76° (0.09 mm); NMR, see Table III; complex patterns seen for butyl group signals.

Anal of mixture. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.71; H, 8.76; N, 8.09.

(*E*)-2-(1-Adamantyl)-3-phenyloxaziridine (2e): mp 69–72°; NMR, see Table III.

Anal. Cacld for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.20; H, 8.38; N, 5.41.

(*E*)-Nitrosomethane Dimer (3a). Anhydrous peracetic acid[5,27]

(1.02 mol) in 120 ml of methylene chloride was added dropwise to an ice-cooled solution of 61.6 g (0.45 mol) of **2a** in 120 ml of methylene chloride. The mixture was allowed to gradually warm to room temperature (with stirring) over a 12-h period. After further dilution with methylene chloride the solution was stirred with excess powdered anhydrous sodium carbonate until carbon dioxide evolution ceased. After filtration, the solvent was evaporated in vacuo at room temperature, affording a pale yellow solid plus a pale yellow liquid. Dissolution of the liquid in pentane yielded (as residue) 7.31 g (36%) of white, crystalline **3a**, mp 120–122° (lit.[28] mp 122°), NMR ($CDCl_3$) δ 3.89 (s) [lit.[29] δ 4.0 (s)]. Distillation of the pentane wash afforded recovery of 8.25 g (13%) of (*E*)-**2a**.

(*E*)-Nitrosoethane Dimer (3b). Anhydrous peracetic[27] acid (0.86 mol) in 120 ml of methylene chloride was used to oxidize 52.6 g (0.35 mol) of **2b** using the procedure successful for the preparation of **3a**. After filtration of the sodium carbonate (neutralizing and drying agent), evaporation of the solvent failed to produce a crystalline residue. Thus the liquid residue was distilled at room temperature in vacuo. The distillate, bp 22° (0.15 mm, collected in a receiver cooled to −78°), was further purified by recrystallization from ether at −78°. Siphoning of the ether solvent [from which 4.5 g (8.5%) of (*E*)-**2b** was recovered] gave 10.6 g (50%) of (*E*)-nitrosoethane dimer, a liquid at room temperature: uv (H_2O) λ_{max} 277 nm (lit.[28,30] λ_{max} 277 nm); NMR δ 4.00 (q, J = 7 Hz, CH_2), 1.30 (t, J = 7 Hz, CH_3); mass spectrum m/e (rel intensity) 118 $M^{\cdot+}$ dimer (~1), 117 $M^{\cdot+}$ dimer − H (~1), 71 (5), 59 $M^{\cdot+}$ nitrosoethane monomer (65), 41 m/e 71 − NO (74), 30 $M^{\cdot+}$ monomer − C_2H_5 (35), 29 $M^{\cdot+}$ monomer − NO (56), 27 HCN (100); metastables at 23.7 and 14.25 support the m/e 71 − NO and 59 − NO fragmentations, respectively.

Anal. Calcd for $C_4H_{10}N_2O_2$: C, 40.66; H, 8.53; N, 23.72. Found: C, 40.92; H, 9.19; N, 23.74.

(*E*)-2-Nitrosopropane Dimer (3c). Anhydrous peracetic acid[27] (1.2 mol) in 150 ml of methylene chloride was added dropwise to an ice-cooled solution of 53.3 g (0.36 mol) of imine **1c** in 100 ml of methylene chloride. After addition, the stirred mixture was allowed to warm to room temperature and remain as such overnight. The mixture was then washed successively with dilute aqueous sodium sulfite solution, water, and dilute aqueous sodium bicarbonate solution. The organic layer was then dried (sodium carbonate) and evaporated in vacuo. The resulting oily residue was dissolved in 60 ml of ether and cooled at −78° for 0.5 h. Filtration gave 12.8 g (48%) of colorless, crystalline **3c:** mp 51–52° (lit.[5] mp 53°); NMR δ 5.43 [septet, J = 6.5 Hz, $HC(Me)_2$], 1.35 (d, J = 6.5 Hz, *gem*-dimethyl groups). From the filtrate 5.5 g (~9%) of (*E*)-**2c** was recovered by distillation in vacuo.

(*E*)-Nitrosocyclohexane Dimer (3d). Cyclohexylamine was oxidized as previously described[5] to give **3d** in 36% yield: mp 118° (lit.[5] mp 119–120°); NMR δ 5.17 (broad m, HCNO), 1.9 (broad m, ring CH_2).

(*Z*)-Dicyclohexyldiazene Oxide (4d). A solution of 1.0 g (0.004 mol) of **3d** in 10 ml of ethanol was hydrogenated at 1 atm using 50 mg of 5% or 10% palladium on charcoal. Hydrogen uptake ceased after 3.5 h and 1.15 mol consumption. Filtration and evaporation of the solvent gave a residue which, on short-path distillation (in vacuo), gave 0.77 g (83%) of colorless **4d:** mp 20–22° (lit.[4] mp 22°); ir (neat) 1493 (s), 1290 cm^{-1} (w) (lit.[31] ir 1495 and 1285 cm^{-1}); VPC (column B, 6 ft × 0.125 in.) indicated 98% purity; *m*-chloroperbenzoic acid oxidation of azocyclohexane[31] gave **4d,** identical with that obtained by hydrogeneration of **3d.**

(*Z*)-Bis(1-methylethyl)diazene Oxide (4c). In a manner similar to that for **3d,** 1.16 g (0.008 mol) of **3c** in 5.3 ml of THF was hydrogenated using 43 mg of palladium on charcoal. Hydrogen consumption was 1.12 mol in 9.5 h. Filtration and evaporation of the solvent gave a residue which was dissolved in methylene chloride and passed over a 15-g column of alumina. The first 15 ml of eluent was collected and distilled (1 atm) to give 0.60 g (57%) of colorless **4c:** VPC (column C, 6 ft × 0.125 in.) indicated 96% purity; bp 134–135° [lit.[31] bp 38° (14 mm)]; ir (neat) 1500 (s) and 1297 cm^{-1} (s) (lit.[31] ir 1500 and 1295 cm^{-1}).

(*Z*)-Diethyldiazene Oxide[8b] (4b). A tetrahydrofuran solution of **3b** (1.38 g, 0.012 mol) was hydrogenated using 67 mg of Pd/charcoal. The reaction was discontinued after 1.3 mol of hydrogen was consumed. The THF solvent was distilled at atmospheric pressure and the product, **4b,** was isolated by preparative VPC (column A, 6 ft × 0.25 in.) of the distillation residue. The yield of pure **4b** was 0.265 g (22%): ir (neat) 1510 (s) and 1318 cm^{-1} (s); NMR, see Table II.

Caution. Azoxyethane is a demonstrated carcinogen in experimental animals.[7] Isolation procedures should be conducted with appropriate ventilation and trapping of contaminated effluents.

Hydrogenation of (*E*)-Nitrosomethane Dimer. Attempts to prepare **4a** were made using both Pd/charcoal and PtO_2 catalysts in methanol, ethanol, and THF. Overreduction was a problem in all three solvents, and azoxymethane was observed to codistill with all three solvents. Azoxymethane was seen to be a reduction product by VPC identification using an authentic sample.[32] With Lindlar catalyst, no hydrogen uptake was observed.

Oxidation of Adamantyl Derivatives. Peracetic acid oxidation of both 1-adamantylamine and oxaziridine **2e** gave 1-nitroadamantane as the major product (40–60%), mp 155° (lit.[33] mp 158°).

Registry No.—**1a,** 25521-74-8; **1b,** 27845-47-2; **1c,** 27845-51-8; **1e,** 57527-54-5; **1** (R = *n*-C_4H_9), 57527-55-6; *cis*-**2a,** 39245-63-1; *trans*-**2a,** 40264-03-7; *cis*-**2b,** 57527-56-7; *trans*-**2b,** 57527-57-8; *trans*-**2c,** 57527-58-9; *trans*-**2e,** 57527-59-0; *cis*-**2** (R = *n*-C_4H_9), 57527-60-3; *trans*-**2** (R = *n*-C_4H_9), 57527-61-4; **3a,** 37765-15-4; **3b,** 57527-62-5; **3c,** 57527-63-6; **3d,** 26049-06-9; **4b,** 57527-64-7; **4c,** 35216-94-5; **4d,** 57497-40-2; benzaldehyde, 100-52-7; methylamine, 74-89-5; ethylamine, 75-04-7; isopropylamine, 75-31-0; *n*-butylamine, 109-73-9; 1-adamantylamine, 768-94-5; cyclohexylamine, 108-91-8.

References and Notes

(1) (a) Partial support for this work by the National Institutes of Health, Grant NS07119, is acknowledged with thanks. (b) Part II: K. G. Taylor and T. Riehl, *J. Am. Chem. Soc.*, **94,** 250 (1972).

(2) For a general review of methods see S. R. Sandler and W. Karo, "Organic Functional Group Preparations", Vol. 12-II, Academic Press, New York, N.Y., 1971, Chapters 14 and 15.

(3) (a) J. P. Snyder, M. L. Heyman, and E. N. Suciu, *J. Org. Chem.*, **40,** 1395 (1975); (b) F. D. Greene and K. E. Gilbert, *ibid.*, **40,** 1409 (1975); (c) K. Naumann, G. Zon, and K. Mislow, *J. Am. Chem. Soc.*, **91,** 7012 (1969); (d) J. P. Snyder, L. Lee, and V. T. Bandurco, *ibid.*, **94,** 3260 (1972); (e) J. L. Swigert and K. G. Taylor, unpublished observations; (f) J. W. Timberlake and J. C. Stowell in "The Chemistry of the Hydrazo, Azo, and Azoxy Groups", S. Patai, Ed., Wiley, New York, N.Y., 1975, Chapter 4.

(4) H. Meister, *Justus Liebigs Ann. Chem.*, **679,** 83 (1964).

(5) W. D. Emmons, *J. Am. Chem. Soc.*, **79,** 6522 (1957).

(6) The development of a synthesis of low molecular weight azoxyalkanes using intermediates of relatively low vapor pressure was an inducement to investigate this approach as a safer alternate to existing methods. For example, *trans*-nitrosomethane dimer melts at 122° while the carcinogenic azomethane, the necessary intermediate in the oxidative approach, has P_{vapor} ~750 mm at 0°.

(7) For a recent comprehensive review of the carcinogenic properties of azoxyalkanes and related compounds, see J. H. Weisburger, *Cancer,* **28,** 60 (1971).

(8) (a) These results agree with those of Biela, Höring, and Pritzkow.[8b] The hydrogenation investigations were terminated at the presently indicated stage when this work became known. (b) Von R. Biela, R. Höring, and W. Pritzkow, *J. Prakt. Chem.*, **36,** 197 (1967); *Chem. Abstr.*, **67,** 99555c (1967).

(9) While the starting oxaziridinine was often a mixture of *Z* and *E* isomers, the recovered oxaziridine was the *E* isomer. Thus, the *Z* oxaziridines (which were configurationally stable under preparation and reaction conditions) were oxidized more rapidly than the corresponding *E* isomers.

(10) T. Emery and J. B. Neilands, *J. Am. Chem. Soc.*, **82,** 4903 (1960).

(11) K. G. Taylor and J. S. Swigert, *J. Am. Chem. Soc.*, **93,** 7337 (1971).

(12) F. D. Greene and S. S. Hecht, *Tetrahedron Lett.*, 575 (1969).

(13) J. P. Snyder and V. T. Bandurco, *Tetrahedron Lett.*, 4643 (1969).

(14) J. P. Snyder, V. T. Bandurco, F. Darack, and H. Olsen, *J. Am. Chem. Soc.*, **96,** 5158 (1974).

(15) R. A. Moss and G. M. Love, *Tetrahedron Lett.*, 4701 (1973).

(16) K. G. Taylor, S. R. Isaac, and M. S. Clark, Jr., *J. Org. Chem.*, following paper in this issue.

(17) D. R. Boyd, W. B. Jennings, and R. Spratt, *J. Chem. Soc., Chem. Commun.*, 745 (1970).

(18) (a) V. Madan and L. B. Clapp, *J. Am. Chem. Soc.*, **91,** 6078 (1969); (b) V. Madan and L. B. Clapp, *ibid.*, **92,** 4902 (1970).

(19) (a) Y. Ogata and Y. Sawaki, *J. Am. Chem. Soc.*, **95,** 4687 (1973); (b) Y. Ogata and Y. Sawaki, *ibid.*, **95,** 4692 (1973).

(20) (a) D. G. Anderson and G. G. Wettermark, *J. Am. Chem. Soc.*, **87,** 1433 (1965). Under anhydrous conditions, the rate of *Z* to *E* isomerization of 10^{-4} M **8** was the same in ethanol as in 10^{-3} M ethanolic acetic acid–sodium acetate (1.4:1 and 7:1) buffer. Thus, the *Z* to *E* isomerization of this aldimine is, apparently, not catalyzed by excess acetic acid.[20b] (b) The "rotational" barrier of the C=N bond of $[(CH_3)_2N]_2C{=}N^+HAr$ is modestly lowered or raised, relative to the unprotonated molecule, depending on the substituent in the Ar group: H. Kessler and D. Leibfritz, *Tetrahedron*, **25,** 5127 (1969).

(21) D. Y. Curtin and J. W. Hausser, *J. Am. Chem. Soc.*, **83,** 3474 (1961).

(22) For oxidation,[18] ψk_1 = 10^{-2}–10^{-4} at 25°; for isomerization[8,20] of C=NR, k_1 = 10^{-5}–10^{-6} at 60°.

(23) (a) We examined the NMR of **1a** in detail, especially the region upfield from NCH_3,[24] in "normal" NMR solvents and also under conditions mimicking our oxidation conditions (acetic acid added, trace H_2SO_4, peracid omitted). By spiking with a known quantity of a CH_3 standard we concluded that 1% of (*Z*)-**1a** would have been readily detected in the NCH_3 region. (b) Karabatsos and Lande list the *E*/*Z* ratio of 14 aldi-

mines as 100/0, and that "neither heat nor acid or dimsyl sodium produced detectable amounts of the Z isomer": G. J. Karabatsos and S. Lande, *Tetrahedron*, **24**, 3907 (1968).
(24) Interestingly, Olah claims to have prepared a mixture of the *Z* and *E* isomers of *N*-(benzylidene)methylamine. In liquid SO_2, he assigned the upfield NCH_3 signal as that due to the *Z* isomer. The isomers were reportedly stable to distillation (in vacuo, temperature unspecified). G. A. Olah and P. Kreienbuhl, *J. Am. Chem. Soc.*, **89**, 4756 (1967).
(25) (a) M. S. Newman, N. Gill, and D. W. Thompson, *J. Am. Chem. Soc.*, **89**, 2059 (1967); (b) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).
(26) R. G. Pews, *J. Org. Chem.*, **32**, 1628 (1967).
(27) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957).
(28) B. G. Gowenlock and J. Trotman, *J. Chem. Soc.*, 1670 (1956).
(29) J. P. Freeman, *J. Org. Chem.*, **28**, 2508 (1963).
(30) Gowenlock and Trotman report mp 84° and λ_{max} (H_2O) 266 for (*Z*)-nitrosoethane dimer which isomerized to the *E* isomer in various solvents. They were unable to isolate a crystalline *E* isomer but report a decrease in melting point of 10–40° upon cis to trans isomerization of two other nitrosoalkane dimers (nitrosomethane excepted). The present data[16] support a nitrosoethane dimer structure and we feel that it is the *E* diastereomer.
(31) B. W. Langley, B. Lythgoe, and L. S. Rayner, *J. Chem. Soc.*, 4191 (1952).
(32) Available from Ash Stevens Inc., Detroit, Mich.
(33) G. W. Smith and H. D. Williams, *J. Org. Chem.*, **26**, 2207 (1961).
(34) In ring compounds **2** the *E* and *Z* designations, which are traditionally used to show steric relations around one or more double bonds, are used nonsystematically here for the sake of consistency within the paper.

Aliphatic Azoxy Compounds. IV. Reaction of Nitrosoalkanes with Hydroxylamines. Synthesis of Unsymmetrical Primary and Secondary Azoxyalkanes by N–N Bond Formation[1]

K. Grant Taylor,* S. Ramdas Isaac, and Melvin S. Clark, Jr.

Department of Chemistry, University of Louisville, Louisville, Kentucky 40208

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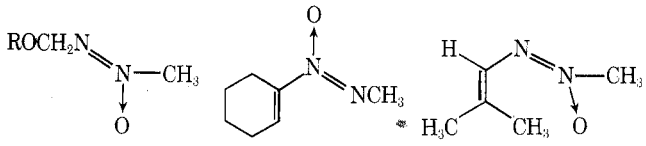
The condensation of *N*-alkylhydroxylamines with photolytically monomerized nitrosoalkanes yields mixtures of O-position isomers of *Z* azoxyalkanes **5a–g** and **6c–g** in ~30–95% yields. The major isomer is that one with the less bulky N substituent syn to the oxygen atom of the azoxy group. This isomer predominates regardless of whether the less bulky group is on the hydroxylamine or nitrosoalkane reactant. Use of *N*-alkyl-*O*-methylhydroxylamines in the condensation gives a single azoxyalkane product, that isomer wherein the azoxy oxygen atom is derived from the nitrosoalkane; however, the yields are low in these reactions. Aspects of the uv and NMR spectra of the azoxyalkanes are discussed.

Aliphatic[2] and aromatic[3] azoxy compounds exist in nature and, without exception, are unsymmetrically substituted compounds with potent physiological activity. An example of recent interest is cycasin (**1a**), known to be carcinogenic in experimental animals.[2d] The aglycone of cycasin, **1b**, the synthetic acetate, **1c**, and synthetic low molecular weight azoxyalkanes are among the most potent of chemical carcinogens.[2d,4] There has been a sustained interest in the chemistry of azoxyalkanes, but, as Moss[5] has pointed out, until 1972 there existed no general, directed method for the synthesis of unsymmetrically substituted azoxyalkanes. The major approach to the synthesis of such compounds has been the oxidation of unsymmetrical azoalkanes,[6] and, to date, no clear mechanistic picture has emerged to permit a prediction of which NO-position isomer can be expected as the major product of oxidation. For example, **2** and **3** are the azoxy compounds isolated from oxidations of the respective azoalkenes.[7] In the aromatic series, all nonortho substituents on monosubstituted diaryldiazenes seem to mildly direct the oxidation toward the more remote N atom of the azo linkage.[8] Moss and co-workers' alkylation of alkane diazotates[5] of structure R′–N=N–O⁻ by alkyl iodides, RI, gives *Z* azoxyalkanes **4** in 32–64% yields. The reaction, a C–N bond synthesis via SN2 displacement,[5b] is best suited for the preparation of **4** when R is a primary alkyl group and R′ is either a primary or secondary alkyl group. When R is a secondary alkyl group the yield of azoxyalkane is decreased (competing E2?), as it also is when R′ is a tertiary alkyl group of an alkane diazotate (competing O-alkylation?).[5] Kovacic and co-workers[9] have also developed a directed synthesis of azoxyalkanes. Based on N–N bond formation between nitroso compounds and *N,N*-dichloroamines, the approach is applicable to the synthesis of unsymmetrical tertiary dialkyldiazene monoxides.



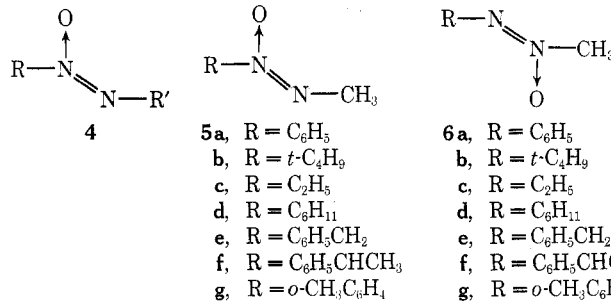
1a, R = D-glucosyl
b, R = H
c, R = $COCH_3$

2

3

Our attention was drawn to the N–N bond formation approach by the work of Freeman,[10] who, in extending Aston's[11] work, reported the formation of (for practical purposes) only **5a** and **5b** from the condensation of *N*-methylhydroxylamine with nitrosobenzene and 2-methyl-2-nitrosopropane, respectively. These results stood in sharp contrast to the results of such condensations in the aromatic series. For example, the condensation of *p*-chloronitrosobenzene with phenylhydroxylamine gives azoxybenzene and 4,4′-dichloroazoxybenzene in addition to an unsymmetrical azoxyarene.[12] Work by Russell and Geels[13] substantiated an oxidation–reduction pathway (eq 1) for the for-

$$ArNO + ArNHOH \longrightarrow [ArNHO\cdot] \longrightarrow ArN(O){=}NAr \quad (1)$$



4

5a, R = C_6H_5
b, R = t-C_4H_9
c, R = C_2H_5
d, R = C_6H_{11}
e, R = $C_6H_5CH_2$
f, R = $C_6H_5CHCH_3$
g, R = o-$CH_3C_6H_4$

6a, R = C_6H_5
b, R = t-C_4H_9
c, R = C_2H_5
d, R = C_6H_{11}
e, R = $C_6H_5CH_2$
f, R = $C_6H_5CHCH_3$
g, R = o-$CH_3C_6H_4$