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(3) Recently the synthesis of 7-β-phenoxyacetylpenicillanic acid was reported, which showed some antibiotic activity: J. C. Sheehan and Y. S. Lo, *J. Org. Chem.*, **38**, 3227 (1973).

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(5) J. Hooz and S. Linke, *J. Am. Chem. Soc.*, **90**, 6891 (1968). We have no ready explanation for the role which water plays in this reaction, since the reaction proceeds well under anhydrous condition on substrates used by Hooz. The presence of sulfur and the formation of the sulfoxide (**8**) need to be considered in this respect.

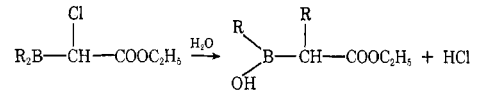
(6) Hydroboration of terminal simple alkenes gives rise to 6% addition of the boron to the 2 and 94% addition to the 1 position.[7] However, we could not detect any 1-(α-methylnonanoyl)piperidine using GLC and NMR techniques.

(7) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972, Part 5.

(8) The synthesis of benzhydryl 7-diazocephalosporanate has been reported via diazotation of the amine. However, no yield and experimental details were given: L. D. Cama, R. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Am. Chem. Soc.*, **94**, 1408 (1972).

(9) H. C. Brown, M. H. Midland, and A. B. Levy, *J. Am. Chem. Soc.*, **94**, 3662 (1972).

(10) Nucleophilic induced substitution of the chloro substituent, occurring in more simple systems, is apparently not the case here (ref 9).



(11) H. C. Brown and M. K. Unni, *J. Am. Chem. Soc.*, **90**, 2902 (1968).

(12) H. C. Brown and R. L. Sharp, *J. Am. Chem. Soc.*, **90**, 2915 (1968).

(13) H. C. Brown and R. M. Gallivan, Jr., *J. Am. Chem. Soc.*, **90**, 2906 (1968).

(14) The two alcohols *N*-(4-hydroxybutyl)benzamide and *N*-(3-hydroxybutyl)-benzamide were formed in the ratio 89:11, which implied that 11% of the boron had been added to the 2 position of the alkene moiety of **19**.

(15) D. J. Pasto and P. W. Wojtkowski, *Tetrahedron Lett.*, 215 (1970).

(16) R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, **39**, 437 (1974).

(17) D. A. Johnson and D. Mania, *Tetrahedron Lett.*, 267 (1969).

(18) R. A. Firestone, N. Schelechow, D. H. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972).

(19) D. M. Brunwin, G. Love, and J. Parker, *J. Chem. Soc. C*, 3756 (1971).

(20) H. C. Brown and G. Zweifel, *Org. React.*, **13**, 1 (1963).

(21) The yield of **5** strongly depends on the purity of the precursor **4** and the rate of addition of the *p*-toluenesulfinic acid to **4**.

Nitrosation of 1-Substituted Aziridines

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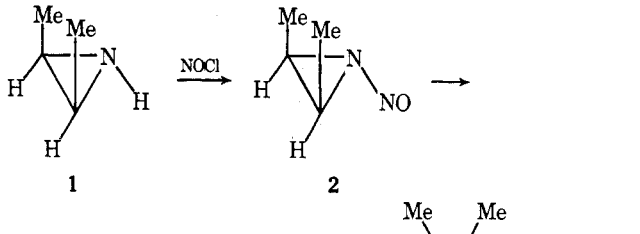
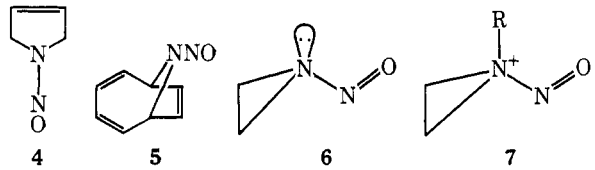
Three aziridines, (*Z*)-1-butyl-, (*Z*)-1-benzyl-, and (*Z*)-1-(4-chlorophenyl)-2,3-diphenylaziridine, have been prepared and their reaction with nitrous acid in acetic acid studied. The principal product of the *N*-alkylaziridine nitrosation has been assigned the structure of an *N*-alkylnitrosenamine, a new type of compound, on the basis of its chemical and spectroscopic behavior (including high-resolution MS and ^1H and ^{13}C NMR). Acid-catalyzed hydrolysis of (*E*)-1,2-diphenyl-1-(*N*-butyl)nitrosaminoethene gave benzoin in addition to the expected benzyl phenyl ketone. Other products from the nitrosation were benzaldehyde and *threo*-1,2-diphenyl-2-(*N*-butyl)nitrosaminoethyl acetate. The reaction of the *N*-arylaziridine with nitrous acid gave these latter two types of products, and *N*-4-chlorophenylbenzamide among others. Mechanisms which accommodate these findings are discussed.

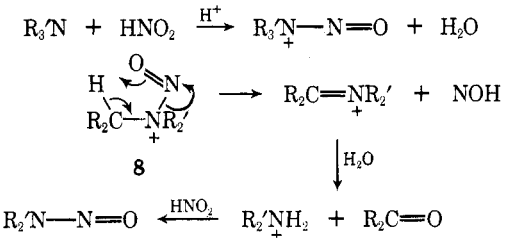
Since the discovery of the facile nitrous oxide extrusion reaction of *N*-nitroso aziridines[1] this transformation (eq 1)



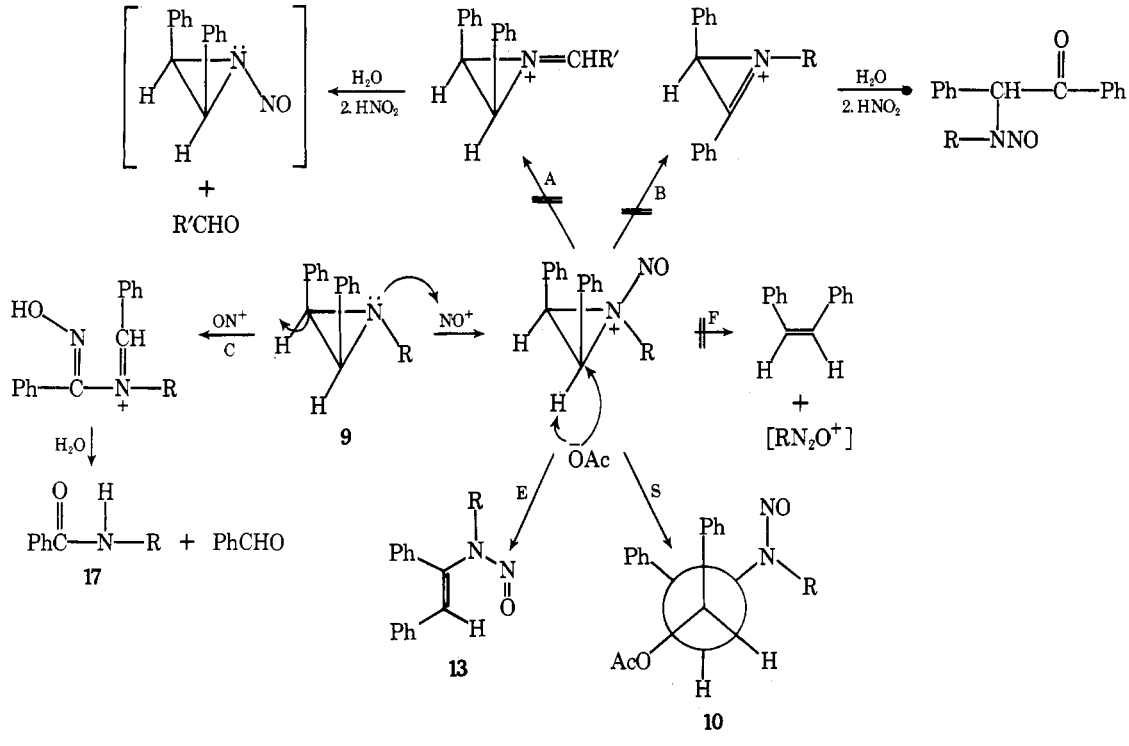
has been of considerable synthetic and theoretical interest.[2-7] Woodward and Hoffmann presented the reaction as an example of a nonlinear cheletropic cycloreversion in explaining the observation of both facile extrusion and retention of stereochemistry.[8] In principle two modes of decomposition are open to the *N*-nitroso aziridines, a linear conrotatory process and the observed disrotatory transformation, although geometric factors allow only this latter mode of decomposition. In order to explain the stability of *N*-nitroso-3-pyrroline **4** and the nitrous oxide adduct of cyclooctatetraene **5** Mock and Isaac[9] have postulated that unlike other nitrosamines the amino nitrogen of *N*-nitroso aziridine exists in a tetrahedral array **6** which uniquely predisposes it to cheletropic fragmentation. Examination of the correlation diagram of Mock and Isaac has led us to consider the fate of the related species **7** where the unshared pair is coordinated with an alkyl or aryl cation. It appears that such a species is capable of facile decomposition to an olefin and [R—N⋯N⋯O$^+$]. A species akin to **7**, the trialkylnitrosammonium ion **8**, has been shown by Smith and Loeppky[10] to lie on the pathway for the nitrosative cleavage of alkyl tertiary amines. This reaction, which has been periodically rediscovered over the past 100 years,[11] proceeds by the mechanism depicted in Scheme I. In this paper we



Scheme I



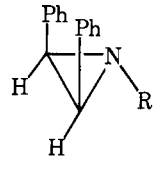
Scheme II

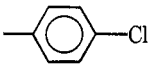


present our studies of the nitrosation of certain 1-alkyl- and 1-aryl-2,3-diphenylaziridines which we presupposed might decompose through a species such as **7** (Scheme II, path F) to give either olefin via RN_2O^+ extrusion or alkyl nitrogen cleavage as depicted in Scheme II, paths A and B. Added impetus to this research has come fron concern over the carcinogenic properties of some nitrosamines which can be produced in the stomach from nitrite and secondary or tertiary amines present in foodstuffs or drugs.[12]

Results

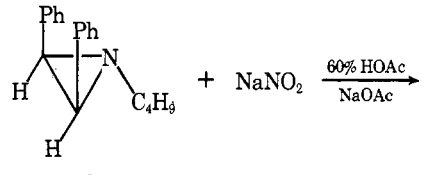
Because of advantages in their handling and purification we chose to utilize 1-substituted 2,3-diphenylaziridines in this study and their synthesis by well-established methods is outlined in the Experimental Section. The general mode of aziridine ring construction utilized in this work involved the ring closure of the appropriate β-chloro secondary amines. This method produced only the *Z*-1-substituted 2,3-diphenylaziridines **9a–c** since the precursors to the cor-



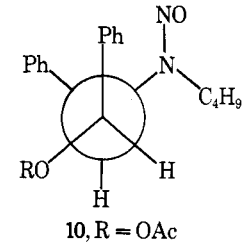
9a, R = *n*-C_4H_9
b, R = CH_2Ph
c, R = 

responding trans aziridines, the erythro β-chloro amines, could not be produced from either of the diastereomeric amino alcohols. A variety of reagents and reaction conditions produced only the threo β-chloro amines.

Although 1-unsubstituted aziridines have been nitrosated with NOCl, we initiated our studies with an investigation of the reaction of **9a** with nitrous acid in 60% acetic acid buffered to pH 4 with sodium acetate at 90 °C because these are the conditions which have been employed in the nitrosation of other tertiary amines.[10] The products of this transformation, which were separated and purified by chromatography on alumina, were determined to be *threo*-1,2-diphenyl-2-(*N*-*n*-butyl)nitrosaminoethyl acetate (**10a**) and *threo*-1,2-diphenyl-2-(*N*-*n*-butyl)nitrosaminoethanol (**11**) in 97% combined yield (eq 2). The alcohol **11** was



9a

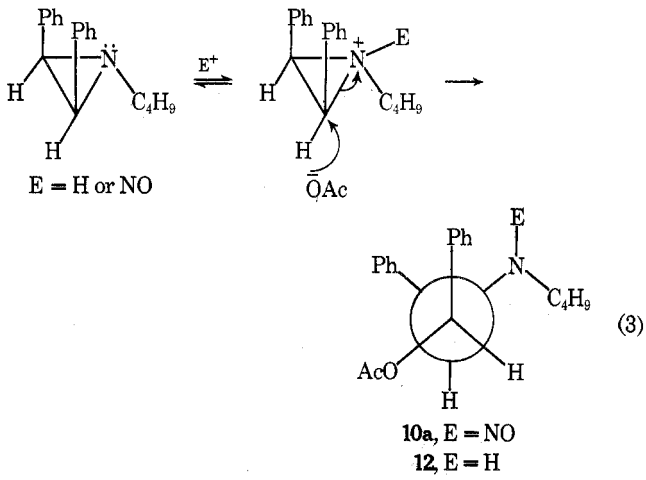


(2)

10, R = OAc
11, R = H

found to arise from the ester **10a** in the course of the work-up procedure. The key to the identity of these products was given by their analyses, spectral data, and independent synthesis, which are given in the Experimental Section.

Since the products of this transformation are similar to those expected from the solvolytic ring opening of the aziridine in acetic acid we chose to examine the fate of **9a** in the reaction media in the absence of sodium nitrite. Treatment of **9a** with 60% acetic acid and sodium acetate at pH 4 and 90 °C resulted in its complete conversion to the threo amino acetate **12** (E = H) in 2.5 h as monitored by NMR. This result is not unexpected,[13] and as has been observed for similar cases is found to occur with inversion of configuration at carbon as is depicted in eq 3 where $E^+ = H^+$. The ring opening under nitrosating conditions proceeded slightly more rapidly than it did in the absence of $NaNO_2$. It is therefore possible that the opening is induced by nitrosammonium formation (eq 3, $E^+ = NO^+$) as well as by protona-



(3)

tion. It is just as likely, however, that nitrosation occurred after acid-catalyzed ring opening and for this reason we sought conditions which would permit the unambiguous study of aziridine nitrosation.

Our attention was next directed at glacial acetic acid as a suitable solvent for the aziridine and the generation of nitrous acid. We found that **9a** could be recovered quantitatively after dissolution in glacial acetic acid for 2.25 h at 25 °C. While such conditions do not induce aziridine ring opening, the "end of reaction" conditions from the addition of aqueous sodium nitrite are not expected to be as hospitable to the aziridine for they begin to approximate the buffered aqueous acetic acid used previously (eq 4).

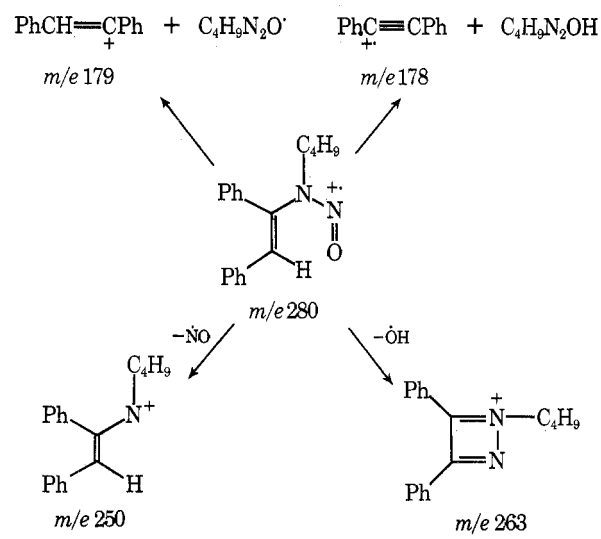
$$2HOAc + 2NaNO_2 \xrightarrow[\Delta]{} H_2O + 2NaOAc + NO_2 + NO \quad (4)$$

By making the extravagant assumption that all of the nitrite added to glacial acetic acid is consumed as shown in eq 4 we prepared a solution of the aziridine in this "end of the reaction" media by adding the appropriate amount of water and sodium acetate and followed the fate of the aziridine by NMR. The half-life of the aziridine under these conditions was 12.75 h and the product isolated after 24 days of reaction was the threo amino acetate **12.**

Since the degradation of the aziridine under these conditions was not rapid we undertook the study of the nitrosation of 3.5% (wt) solution of **9a** in glacial acetic acid. After a reaction time of 2.5 h three products were separated from the reaction mixture (Scheme II, paths C, E, and S). The minor components of this mixture were benzaldehyde (19% yield based on GLC) and the threo nitrosamino acetate **10a** (yield 20%). The major product (yield 62%) of this transformation proved to be a substance of novel structure and unusual properties to which we have assigned the structure of (*E*)-1,2-diphenyl-1-(*N*-butyl)nitrosaminoethene (**13a**). To the extent of our knowledge this is the first nitrosenamine to be reported although allusions to them have been made in the literature.[14,15] Its structure is based on the spectroscopic and chemical data presented below.

The compound **13a** is a white, crystalline solid (mp 91–92 °C), insoluble in acid and base and analyzing for $C_{18}H_{20}N_2O$. The fact that the two phenyl groups and the *n*-butyl group have traversed the reaction course intact was indicated by both the ^1H and ^{13}C NMR spectra of **13a,** the details of which are given in the Experimental Section. The enamine functionality of **13a** was indicated by the ir spectrum (1650 cm^{-1}, w), the uv spectrum (227 nm, ϵ 1.3 × 10^4, and 285 nm, ϵ 1.5 × 10^4) in comparison with spectra of known enamines and enamides[16–20] (223–222 and 278–312 nm), and its ^1H and ^{13}C NMR spectra. The ^1H NMR of **13a** exhibited a nonexchangeable singlet at δ 7.9 which was assigned to the vinyl hydrogen in **13a.** This signal is a full 1

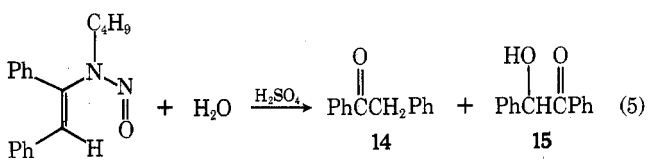
Scheme III



ppm downfield from the vinyl hydrogen of structurally similar enamides[18,19] and this effect is thought to be produced by the deshielding of the nitroso function (vide infra). The ^{13}C NMR of **13a** exhibited eight peaks in the region δ 128.78–148.27 and the lowest field peak was assigned to the nitrogen bearing carbon on the basis of decoupling experiments which showed it to be a quaternary carbon and upon comparison with the spectrum of 1-pyrrolidino-1,2-diphenylethene (C-1, δ 148.64). The nitrosamino functionality was suggested by the intense ir absorption in the region 1300–1500 cm^{-1}, the mass spectrum, which showed peaks due to parent minus OH and parent minus NO, and the ^{13}C spectrum. The nitrogen-bound carbon of **13a** resonates at δ 53.05 which compares favorably with values of δ 59.9 and 50.4 observed for dibutylnitrosamine.[25]

The cis arrangement of the phenyl groups in **13a** is based on its mode of formation (vide infra), the extreme deshielding of its vinyl hydrogen, its uv spectrum in comparison with those of similar compounds,[16–20] and particularly its mass spectrum. High-resolution mass spectrometry of **13a** confirmed the empirical formula and gave as the most significant spectral feature a base peak *m/e* 178 having the formula $C_{14}H_{10}$ assigned the radical cation of diphenylacetylene. This fragment and the second most abundant ion, the stilbene cation (*m/e* 179), are envisioned to arise by the processes shown in Scheme III.[27] All of the peaks found in the mass spectrum of stilbene and diphenylacetylene were found in the mass spectrum of **13a.**[28] The facile McLafferty-type rearrangement of the parent ion to give the diphenylacetylene radical cation is strongly suggestive of the cis ene geometry.

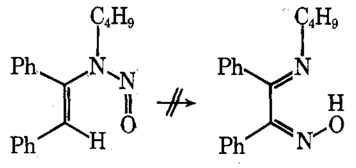
While the extensive spectroscopic data convincingly support the structure assigned to **13a** its reactivity was surprising but none the less corroborative and our cursory investigation of its most interesting chemistry has demonstrated the lack of extensive skeletal rearrangements such as phe-



(5)

nyl migrations. The acid-catalyzed hydrolysis of **13a** gave, in addition to the expected product, benzyl phenyl ketone (**14**), a good yield of benzoin **15.** The chemistry of **13a** dif-

fered from that of other enamides and enamines in other ways as well, since it did not react with Br_2/CCl_4 or H_2/Pt. Furthermore, **13a** failed to give a positive Liebermann's *N*-nitroso test and does not give any indication of isomerizing under acidic or basic conditions to the iminooxime **16** as



13a **16** (6)

does its trans isomer.[15,29] Numerous attempts to synthesize **13a** by independent routes have not yet met with success.[29] Our synthetic efforts have been frustrated by our inability to obtain the precursor erythro β-chloronitrosamine (vide supra).

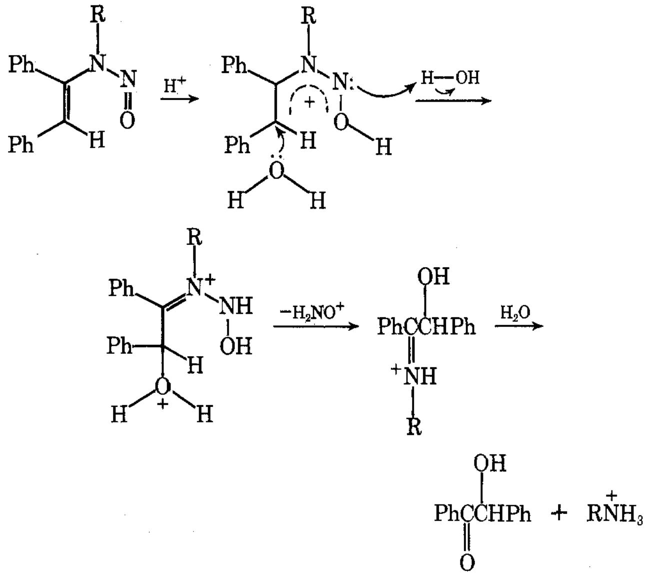
In addition to our investigation of the nitrosation of the *N*-butylaziridine **9a** we also examined the reaction of (*Z*)-1-benzyl-2,3-diphenylaziridine (**9b**) with sodium nitrite in glacial acetic acid. This transformation proceeded in much the same manner as we have described for **14a** to give benzaldehyde (18%), (*E*)-1-*N*-benzylnitrosamino-1,2-diphenylethane (**13b,** 49%), *threo*-1,2-diphenyl-2-*N*-benzylnitrosaminoethyl acetate (**10b,** 18%), and an additional compound characterized as *N*-benzyl-*N*-(1,2-diphenyl-2-acetoxyethyl)ethanamide (**19,** 4%). We have also made a cursory, preliminary investigation of the nitrosation reaction of (*Z*)-1-(4-chlorophenyl)-2,3-diphenylaziridine (**9c**) in glacial acetic acid. Even though our study of this transformation is not completed, it is worth mentioning because it appears to take a course different from the nitrosation of the *N*-alkylaziridines. From a mixture of seven compounds produced in this transformation we have isolated and characterized benzaldehyde, *threo*-1,2-diphenyl-2-*N*-(4-chlorophenyl)nitrosaminoethyl acetate (**10c**), and *N*-4-chlorophenylbenzamide (**17**, R = 4-ClC_6H_4). A preliminary investigation of the reaction of **9a** with nitrosyl chloride has revealed the existence of numerous products and the reaction is under further study.

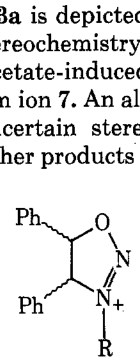
Discussion

Perhaps the most striking feature to arise from our examination of the nitrosation of 1-substituted aziridines is the finding that the reaction proceeds neither by the path (F, Scheme II) taken by their 1-unsubstituted counterparts nor by the route elucidated for the nitrosation of tertiary amines (A and B, Scheme IV). A new mode of tertiary amine nitrosation has been uncovered, and we will now consider the probable origin of the various products. The product whose mode of formation is most easily dealt with is the threo nitrosamino acetate **10.** The production of only the threo diastereomer dictates that this compound be formed from the aziridine with inversion of one of the carbons as is indicated in Scheme II (path S). Even though we found conditions under which the aziridine was nitrosated much more rapidly than it underwent acid-catalyzed ring opening, the observation that this latter process occurs with the same stereochemical result will not permit the conclusion that **10** is formed solely by N-nitrosation followed by nucleophilic ring opening by acetate. The addition of aqueous sodium nitrite to glacial acetic acid produces an environment toward the end of reaction which is more favorable to acid-catalyzed ring opening. We are unable without kinetic data to determine if **10** was formed by nitrosation before or after ring opening.

The elimination of acetic acid from the nitrosamino acetate **10** provides an appealing path for the formation of the *N*-nitrosoenamine **13.** We must argue against this route for the formation of **13,** however, because the subjection of **10a** to the reaction and work-up conditions for the formation of **13a** did not produce **13a.** Furthermore, we were unable to induce the formation of **13a** from **10a** by either pyrolysis or elimination catalyzed by sodium acetate or stronger bases. Indeed, the anti elimination of acetic acid from **10a** would produce the trans nitrosenamine. A more reasonable path for the formation of **13a** is depicted in Scheme II, path E. The nitrosenamine stereochemistry is indicative of its formation by a simple, acetate-induced E-2 type ring opening of the nitrosammonium ion **7.** An alternate route involves a ring expansion of uncertain stereochemistry to **18** and would surely lead to other products as well.

Scheme IV





18

The details of the origin of the benzaldehyde in these reactions is a subject of current research in our laboratories but we will make few observations here. We presume that each aziridine taking the aldehyde cleavage route produces a single molecule of benzaldehyde. With this assumption our material balance is 96% for the reaction of **9a.** There may be more than one nitrogenous product from this pathway. The only clue we have to the origin of benzaldehyde comes from the nitrosation of **9c** which gave the benzamide **17** as well. A possible path to these products is given in Scheme II, path C. Nitrosation is envisioned to occur at the aziridine C–C bond assisted by the nitrogen unshared pair. The resulting α-nitroso iminium salt isomerizes and hydrolyzes in the media to the observed products. There are, of course, alternative routes.

Our data and the preceding analysis of the 2,3-diphenylaziridine nitrosation lead us to conclude that less than 20% of the reaction proceeds via C-nitrosation and 82% of the aziridine is consumed by N-nitrosation. The nitrosammonium ion so produced is destroyed stereospecifically in a classical elimination (76%)–substitution (24%) competition. Although we have not followed the relative product yields

Table I. Physical Properties of Aziridines and Their Precursors

Series		Mp or bp, °C	Yield, %	Registry no.
		Amino Ketones		
a	*n*-Butyl HCl[a]	226–228	90	7253-85-2
c	*p*-Chloro-phenyl	164–165.5	91	58268-09-0
		Amino Alcohols (Erythro)		
a	*n*-Butyl	131–133	78, 86	58268-10-3
c	*p*-Chloro-phenyl	109–110	96	58268-11-4
b	Benzyl	154–156	92	58268-12-5
a	*n*-Butyl (threo)	60.5–61.5	85	58268-13-6
		Amino Chlorides (Threo)		
a	*n*-Butyl HCl[b]	214–215	69	58268-14-7
c	*p*-Chloro-phenyl HCl	140	53	58268-15-8
b	Benzyl HCl	175–177	35	58268-16-9
		Aziridines (Cis)		
9a	*n*-Butyl[c,e]	126–127 (0.1 mm)	90	58268-17-0
9c	*p*-Chloro-phenyl	89–90.5	73	58268-18-1
9b	Benzyl[d]	52.5–53.5	76	42136-65-2

[a] Free base is an oil. [b] Anal. Calcd: C, 66.67; H, 7.15; N, 4.32. Found: C, 66.75; H, 7.13; N, 4.23. [c] Anal. Calcd: C, 86.00; H, 8.42; N, 5.57. Found: C, 86.21; H, 8.40; N, 5.59. [d] Anal. Calcd: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.50; H, 6.82; N, 4.86. [e] n^{20}D 1.5510.

(**10** and **13**) of this competition as a function of time it is well known that where elimination and substitution reactions are in competition elimination can be favored by the employment of stronger base. As acetic acid is diluted with water the acetate ion becomes a weaker base and this may explain why nitrosenamine formation is favored in the medium having the higher acetic acid content.

Our study of 1-substituted aziridine nitrosation is not far enough advanced to determine why the reaction did not take paths A, B, or F of Scheme II. Phenyl substitution on the aziridine ring certainly aids the processes observed whereas intramolecular elimination (Scheme II, paths A or B) is not expected to be facile in small rings and is particularly impeded if NO and H are not syn to one another.

Finally we must comment on the unusual chemical properties of the nitrosenamine. Although our work on these substances is far from complete the hydrolysis of **13a** reveals a mode of reaction which has not previously been reported for enamines or enamides. The formation of benzoin upon acidic hydrolysis requires that this oxidation be accompanied by the reduction of the nitrogen-containing fragment. Although we have not isolated a nitrogen-bearing fragment from the hydrolysis mixture as yet a plausible mode of benzoin formation is depicted below. The reaction is perceived to occur by nucleophilic attack of water on the alkenyl carbon which is assisted by protonation on the nitroso oxygen and fission of the N–N bond (Scheme IV). It has been demonstrated that the most nucleophilic site (and presumably the most basic site as well) in nitrosamines is the nitroso oxygen[30] and this fact accompanied by the well-known resistance of nitrosamines to hydrolysis and the elimination of NO as NO^- or NOH accounts for the predominance of the benzoin-forming reaction path. The formation of benzyl phenyl ketone by the more usual mode of enamine hydrolysis requires protonation on carbon and acceptance of the positive charge by the amino (amide) nitrogen and must be preceded in enamide hydrolysis by the amide hydrolysis to generate the secondary enamine which then hydrolyzes. The specific nature of this hydrolysis is being further explored.

In conclusion our initial studies of aziridine nitrosation have demonstrated a new mode of tertiary amine nitrosation which warrants further investigation. We have discovered an enamine with unusual properties and further exploration will allow us to evaluate its synthetic utility and provide us with an understanding of its reactivity.

Experimental Section

Boiling points and melting points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken on a Perkin-Elmer 237B grating infrared spectrometer and NMR spectra were taken on a Varian A-60 or a Bruker HX90 spectrometer. ^{13}C NMR spectra were measured by pulse FT spectroscopy utilizing a Nicolet 1083 computer, and all chemical shifts are referenced to internal Me_4Si. GLC was performed on a Microtek 2000 GCR using a 20% SE column on Chromosorb W with anisole as an internal standard. TLC was performed with Eastman silica gel plates with fluorescent indicator and developed with a solution of 5% ethyl acetate in petroleum ether "F", unless otherwise noted. Uv spectra were taken of cyclohexane solutions on a Cary 15 uv–visible spectrometer. Mass spectra were recorded on a CEC 21-110 mass spectrometer at 70 eV utilizing perfluorokerosene in the peak matching.

Synthesis of Aziridines. Aziridines were prepared by the methods given below for *n*-butyl series. Their physical properties and those of their precursors are given in Table I.

Method A. *erythro*-1,2-Diphenyl-2-(*N*-*n*-butylamino)ethanol. *erythro*-1,2-Diphenyl-2-(*N*-*n*-butylamino)ethanol was prepared from *trans*-stilbene oxide according to the method of Lutz, Freek, and Murphey[31] to give a 78% yield: mp 131–133 °C (lit.[13] 134–135 °C); NMR ($CDCl_3$) δ 7.15 (s, 10, phenyl), 4.82 (d, 1, –NC**H**Ph, J = 5.5 Hz), 3.88 (d, 1, PhC**H**OH, J = 5.5 Hz), 2.48 (t, 1.6, $-NCH_2-$, J = 6.5 Hz), 0.62–1.70 (m, 7.4, $-CH_2CH_2CH_3$).

Method B. To 41.17 g (0.136 mol) of α-(*N*-*n*-butylamino)benzyl phenyl ketone hydrochloride in 300 ml of ethanol was added dropwise 4.6 g (0.121 mol, 0.484 equiv) of sodium borohydride in 125 ml of ethanol. The mixture was refluxed for 2 h, cooled, and poured into an excess of water. The crystals were collected and recrystallized from ethanol to give 31.14 g (82%) of *erythro*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethanol: mp 132.5–134 °C (lit.[31] 134–135 °C); NMR identical with that of the *erythro*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethanol prepared by method A.

α-(*N*-*n*-Butylamino)benzyl Phenyl Ketone. α-(*N*-*n*-Butylamino)benzyl phenyl ketone was prepared according to the literature method and collected as the hydrochloride (56%), a white solid: mp 226–228 °C (lit.[31] 184–186 °C); ir (Nujol) (as the hydrochloride) 2375 (NH) and 1690 cm^{-1} (ketone); NMR ($CDCl_3$) (as the free base) δ 6.9–8.3 (m, 10, phenyl), 5.39 (s, 0.6, NH, exchangeable in D_2O), 4.15 (s, 1.1, PhC**H**C=O), 2.3–3.8 (m, 1.8, $-NHCH_2-$), 0.6–2.0 (m, 7.3, $-CH_2CH_2CH_3$).

***threo*-1,2-Diphenyl-2-(*N*-*n*-butylamino)ethanol.** *threo*-1,2-Diphenyl-2-(*N*-*n*-butylamino)ethanol was prepared by the literature method[31] and collected in 58% yield as the hydrochloride, mp 184–185 °C (lit.[31] 181–182 °C). Shaking a portion of the hydrochloride with 10% sodium carbonate solution followed by extraction with ether, concentration, and recrystallization from 30–60 °C petroleum ether gave the free base, mp 60.5–61.5 °C (lit.[31] 63–64 °C).

***threo*-1,2-Diphenyl-2-(*N*-*n*-butylamino)ethyl Chloride.** This amino chloride was prepared by a method following that of Taylor, Owen, and Whittaker.[32] A 300-ml single-neck round-bottom flask fitted with a magnetic stirrer was charged with 31.1 g (0.116 mol) of *erythro*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethanol in 104 ml of dry chloroform. Phosphorus pentachloride (28 g, 0.13 mol) was added slowly to the stirred mixture. A strongly exothermic reaction ensued. The resulting mixture was cooled and the precipitate was collected. Recrystallization of the crude product from ethanol gave 32.7 g (87.5%) of a white solid as the hydrochloride: mp 214–215 °C; ir 3400 cm^{-1} (weak, –NH); NMR ($CDCl_3$) δ 7.08 (s, 10, phenyl), 4.95 (d, 1, PhC**H**N–, J = 9.5 Hz), 4.03 (d, 1,

Table II. Nitrosation of Aziridines. Experimental Details

Expt. no.	Compd	Wt, g (mol)	Solvent (ml)	Wt., g $NaNO_2$ (H_2O, ml)	Temp, °C	Reaction time, h	% yield of **10**	% yield of **13**	% yield of PhCHO	Other products (% yield)
1	**9a**	27 (0.11)	60% HOAc[a] (500)	69 (100)	90	2.5	10	10		**12** (88)
2	**9a**	8 (0.032)	HOAc (216)	22 (30)	25	2.5	20.2	62.1	19.2	
3	**9b**	2.54 (8.9×10^{-3})	HOAc (61)	6.15 (8)	25	2	18%	49	18	**19** (4)
4[b]	**9c**	5 (0.0164)	HOAc (120)	12 (20)	25	2	Undetd		19	**17** (?)

[a] 68 g of sodium acetate added. [b] 31% starting material recovered.

PhCHCl, J = 9.5 Hz), 2.3–3.1 (m, 2, $-NCH_2-$), 0.7–1.7 (m, 7.5, $-CH_2CH_2CH_3$).

Anal. Calcd for $C_{18}H_{23}NCl_2$: C, 66.67; H, 7.15; N, 4.32. Found: C, 66.75; H, 7.13; N, 4.23.

Hydrolysis of *threo*-1,2-Diphenyl-2-(*N*-*n*-butylamino)ethyl Chloride. The hydrolysis of the chloride was undertaken in order to establish unequivocally its stereochemistry and that of the aziridine **9a**. The hydrochloride (5.2 g, 0.016 mol) was placed in a 500-ml single-neck round-bottom flask fitted with a condenser, and 350 ml of a saturated sodium hydrogen carbonate solution was added. The mixture was refluxed for 16 h, cooled, and washed four times with ether. The ethereal extracts were combined, dried, and concentrated. The resulting solid was recrystallized from ethanol to give a white solid in good yield, mp 131–134 °C, undepressed by addition of an authentic sample of *erythro*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethanol.

(*Z*)-1-*n*-Butyl-2,3-diphenylaziridine (9a). Following the method of Taylor, Owen, and Whittaker,[32] a 3-l. three-neck round-bottom flask was fitted with a reflux condenser and a mechanical stirrer and 129 g (0.40 mol) of *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl chloride hydrochloride was placed therein. After the addition of 2.12 l. of 22% alcoholic potassium hydroxide, the stirred reaction mixture was heated at reflux for 1.5 h, then cooled and poured into 3 l. of water. The resulting mixture was extracted with ether and concentrated and the resulting wet oil taken up in benzene and dried. The benzene solution was filtered, concentrated, and distilled in vacuo, giving 86.5 g (86.6%) of a colorless liquid: bp 114–116 °C (0.1 mm); mp 32.0–35.5 °C; n^{25}D 1.5510; ir (neat) 3040, 2945, 1615, 1505, 1460, 1420, 1380, 1030, 760, 700 cm^{-1}; NMR δ 7.05 (s, 10, phenyl), 2.78 (s, 2, PhCH–), 2.6 (t, 1.6, $-NCH_2-$, J = 6.5 Hz), 0.65–2.00 (m, 7.4, $-CH_2CH_2CH_3$). The NMR spectrum was not temperature dependent down to −50 °C.

Nitrosation of Aziridines. The general procedure for the nitrosation of the aziridine involved its dissolution in the acidic solvent and stirring while a 10 M excess of saturated sodium nitrite solution was added dropwise and the solution stirred at the prescribed temperature for the time noted along with quantities in Table II.

Work-up involved pouring the reaction mixture into twice the volume of water followed by extraction with five portions of $CHCl_3$, drying, and removal of the $CHCl_3$ after analysis for benzaldehyde. GC analysis for benzaldehyde was performed by adding a known quantity of anisole to a known volume of the reaction mixture and the determination of the benzaldehyde yield was made from the corresponding peak areas via a calibration curve. The reaction mixture or a weighed portion thereof was chromatographed on silica gel by eluting with 20% ethyl acetate–petroleum ether. The details of product characterization are given below for each experiment.

Experiment 1. Nitrosation of 9a. The $CHCl_3$ solution was subjected to GC analysis and the presence of a trace of butanal found, which was confirmed by its conversion to its 2,4-dinitrophenylhydrazone, mp 118–122 °C (lit.[33] 123 °C). Column chromatography gave *threo*-1,2-diphenyl-2-(*N*-*n*-butylnitrosoamino)ethyl acetate (**10a**, 10%): mp 135–136.5 °C; Liebermann nitroso test[34] positive; ir (CCl_4) no –OH, or –NH, 1750 cm^{-1} (ester carbonyl), 1470, 1439, 1280, and 1030 (weak, possibly associated with N–NO);[35] NMR ($CDCl_3$) δ 7.30 (s, 10, phenyl), 6.70 (d, 1, PhCHN–NO, J = 10.5 Hz), 5.80 (d, 1, AcOCHPh, J = 10.5 Hz), 2.90–4.10 (broad m, 2, $-CH_2N-NO$), 1.94 (s, 3, acetate), and 0.65–1.70 (m, 7, $-CH_2CH_2CH_3$).

Synthesis of 10a. A 100-ml single-neck round-bottom flask fitted with a magnetic stirrer and drying tube was charged with 3.7 g (0.012 mol) of *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethanol and 22.4 ml of freshly distilled acetyl chloride. The mixture was allowed to stir for 24 h at room temperature. The resulting crystals were filtered off and recrystallized from acetonitrile to give 3.15 g (74.5%) of product as the hydrochloride: mp 190.5–191.5 °C; ir (Nujol) 2700 (NH·HCl), 1750 cm^{-1} (ester carbonyl); NMR ($CDCl_3$) δ 7.40 (m, 10, phenyl), 6.45 (d, 1, PhCHOAc, J = 10 Hz), 4.30–4.80 (d, 1, PhCHNH·HCl, J = 10 Hz), 2.92 (m, 1.6, $-CH_2NH\cdot HCl$), 2.39 (s, 3, acetate), 0.65–2.30 (m, 7.4, $-CH_2CH_2CH_3$).

A 50-ml test tube equipped with a magnetic stirrer was charged with 0.153 g (0.00044 mol) of *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl acetate hydrochloride and 1.3 ml of water. Sodium nitrite (0.4 g) in 1.3 ml of water was added in portions while stirring continued.[36] The mixture was stirred at room temperature for 1.5 h, then diluted with water and extracted with ether. The ethereal solution was dried overnight (sodium sulfate), then filtered and stripped of solvent at room temperature to give 0.14 g (30%) of *threo*-1,2-diphenyl-2-(*N*-*n*-butylnitrosamino)ethyl acetate as white crystals: mp 136.5–137.5 °C; mmp with **10a** (expt 1) 135–136 °C; Liebermann nitroso test positive.

Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.65; H, 7.12; N, 8.14. Found: C, 70.36; H, 7.34; N, 8.09.

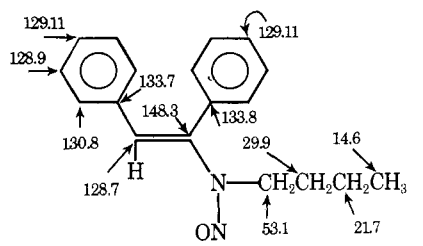
threo-1,2-Diphenyl-2-(*N*-*n*-butylnitrosamino)ethanol (**12**): 7.27 g; mp 79.0–79.2 °C; Liebermann nitroso test positive; ir (CCl_4) 3400 (–OH), no carbonyl, 1480, 1440, 1285, and 1030 cm^{-1} (weak, possibly associated with N–NO); NMR ($CDCl_3$) δ 7.21 (s, 10, phenyl), 5.64 (d, 0.94, PhCHN–NO, J = 9 Hz), 5.11 (d, 0.94, PhCHOH, J = 9 Hz), 2.77–4.11 (m, 2.98, $-CH_2N-NO$), 0.50–1.56 (m, 7.1, $-CH_2CH_2CH_3$).

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.54; H, 7.51; N, 9.36. Found: C, 72.70; H, 7.44; N, 9.40.

Conversion of 12 to 10a. *threo*-1,2-Diphenyl-2-(*N*-*n*-butylnitrosamino)ethanol (**12**), isolated from the reaction of **9a** with nitrous acid, was converted to *threo*-1,2-diphenyl-2-(*N*-*n*-butylnitrosamino)ethyl acetate (**10a**) as follows:[37] 1.0 g of the nitrosamino alcohol was added to 10 ml of dry pyridine in a 50-ml one-neck round-bottom flask fitted with a reflux condenser. Four grams of freshly distilled acetic anhydride was added through the condenser and the solution was refluxed for 5 min. The mixture was cooled and poured into 30 ml of ice water. The solid was filtered off, washed with 2% hydrochloric acid solution, and recrystallized from ethanol to give a white solid, mp 139–140 °C, mixture melting point with **10a** 139–140 °C.

Experiment 2. Nitrosation of 9a in Glacial Acetic Acid. Chromatography of 9.44 g of reaction mixture provided the following compounds.

13a: 5.79 g (62.1% of crude product mixture); mp 91.5–92.5 °C; ir (CCl_4) no –NH, –OH, carbonyl, 1479, 1439, 1290, 1041 cm^{-1} (weak, may be associated with N–NO); NMR ($CDCl_3$) δ 7.90 [s, 0.965, HC=C(Ph)N–NO], 6.82–7.55 (m, 10, phenyl, 3.60 (t, 1.93, $-CH_2N-NO$, J = 7 Hz), 0.70–1.95 (m, 7.21, $-CH_2CH_2CH_3$); ^{13}C NMR assignments are given below in parts per million relative to



Me_4Si = 0; uv 227 nm (ϵ 1.3 × 10^4), 285 (1.5 × 10^4); Br_2/CCl_4, no color loss; $KMnO_4$, slow reaction; Liebermann nitroso test, negative. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.97; H, 7.10; N, 9.83.

Mass spectrum *m/e* (rel intensity): 281 (9), 280 (40), 279 (4.6), 264 (5), 263 (3), 262 (3), 250 (3), 237 (7), 224 (2), 221 (3), 208 (2), 207 (2), 206 (2), 196 (4), 195 (8), 194 (8), 193 (9), 180 (12), 179 (73), 178 (100), 177 (18), 176 (15), 175 (5), 174 (13), 169 (6), 167 (37), 166 (5), 165 (10), 159 (5), 153 (5), 152 (19), 151 (9), 132 (10), 131 (53), 126 (3), 119 (5), 118 (13), 115 (13), 105 (11), 104 (25), 103 (7), 102 (3), 91 (9), 89 (6), 77 (14), 76 (6), 63 (3), 57 (5), 51 (10), 39 (5). Precise mass data (formula, observed mass, calculated mass): $C_{18}N_{20}N_2O$, 280.1565, 280.1576; $C_{13}H_{11}$, 167.085658, 167.086071; $C_{12}H_8$, 152.061113, 152.062597; $C_8H_7N_2$, 131.060125, 131.060920; C_7H_6N, 104.049648, 104.050022.

10a: 1.91 g (20.2%); mp 136–137 °C; mixture melting point with *threo*-1,2-diphenyl-2-(*N*-*n*-butylnitrosamino)ethyl acetate undepressed.

Benzaldehyde. An aliquot of the original chloroform extract was examined by GC for volatile compounds and benzaldehyde was found in 19.2% yield, based on the starting aziridine using the method previously given. Treatment of the extract with 2,4-dinitrophenylhydrazine gave benzaldehyde 2,4-dinitrophenylhydrazone, mp 235–236 °C (lit.[38] 237 °C).

Experiment 3. Nitrosation of 9b in Acetic Acid. Chromatography gave *threo*-1,2-diphenyl-2-(*N*-benzylnitrosamino)ethyl acetate (**10b**): mp 121.5–121.9 °C; ir (Nujol) no –OH, –NH, 1723, 1733 cm^{-1} (ester carbonyl); NMR ($CDCl_3$) δ 6.88–7.45 (m, 15, phenyl), 6.70 (d, 1.08, PhC**H**N–NO, J = 10.5 Hz), 5.40 (d, 1.08, PhC**H**OAc, J = 10.5 Hz), 5.31 (d, 0.75, PhCH_2N–NO, J = 15 Hz), 1.92 (s, 2.66, acetate).

Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.57; H, 6.05; N, 7.33.

(*E*)-1,2-Diphenyl-1-(*N*-benzylnitrosamino)ethene (**13b**): 1.38 g (4.4 × 10^{-3} mol, 49%); mp 97.5–98 °C; ir (Nujol) no –NH, –OH, or carbonyl, 1474, 1440, 1305 cm^{-1} (possibly associated with N=O); NMR ($CDCl_3$) δ 7.95 [s, 0.78, **H**C(Ph)=C(Ph)N(R)NO], 6.78–7.47 (m, 15, phenyl), 4.80 (s, 1.69, PhCH_2N–NO).

Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.41; H, 5.91; N, 8.83.

Benzaldehyde assayed by the previous method, yield 18%.

19: tentatively identified by its spectra as *N*-benzyl-*N*-(1,2-diphenyl-2-acetoxyethyl)ethanamide: 0.15 g; ir (neat oil) 3375 (weak, broad), 1730, 1685 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 7.07–8.19 (m, phenyl), 6.94 (s), 6.91 (d, J = 10.5 Hz), 5.22 (d, J = 10.5 Hz), 5.08 (d, J = 15 Hz), 3.90 (d, J = 15 Hz), 2.20 (s), 1.71 (s).

Experiment 4. Nitrosation of 9c in Acetic Acid. 1-(*4*-Chloro)phenyl-2,3-diphenylaziridine (5.0 g, 0.0164 mol) was nitrosated in glacial acetic acid in the usual manner. A solid was filtered from the reaction mixture and the supernatant liquid extracted in chloroform as before. The odor of benzaldehyde was noted as is the usual case in these reactions. The solid filtered off proved to be unreacted starting material (1.55 g, 31%) (NMR identical, mixture melting point undepressed, 86.5–88.5 °C, mp of starting material 87–88 °C). GC assay for benzaldehyde showed the yield of this compound to be 19.1%.

threo-1,2-Diphenyl-2-(*N*-4-chlorophenylnitrosamino)ethyl acetate (**10c**) was observed (same R_f as the authentic compound).

N-4-Chlorophenylbenzamide (**34**) was isolated: mp 183.5–184 °C; ir (Nujol) 3330 (–NH), 1645 cm^{-1} (amide); mixture melting point 184–187 °C (lit.[39] 192 °C); TLC R_f identical.

Control Reaction of (*Z*)-1-*n*-Butyl-2,3-diphenylaziridine with Hot Buffered 60% Aqueous Acetic Acid. A solution of 1.5 g of the aziridine **9a** in 29 ml of 60% aqueous acetic acid buffered to pH 4–5 with sodium acetate was heated to 90 °C on a steam bath in a 100-ml three-neck round-bottomed flask fitted with a condenser, mechanical stirrer, and dropping funnel. At 90 °C, 5.6 ml of water was added slowly through the dropping funnel. At the end of 1 h, all of the aziridine had disappeared (TLC). Heating was continued for a total of 2.5 h. Work-up was performed as in the nitrosation reaction. The product was an oil, *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl acetate: 1.88 g; ir (neat) 3325 (–OH or –NH), 1750 (ester carbonyl, weak), and 1630 cm^{-1}, identical with the spectrum for *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl acetate; NMR δ 7.29 (d, 10, phenyl), 5.45 (d, 0.46, J = 7.5 Hz), 5.00 (d, 0.46, J = 7.5 Hz), 4.58 (d, 0.40, J = 8.5 Hz), 3.61 (d, 0.40, J = 8.5 Hz), 2.81–3.22 (m, 1.03), 2.26–2.70 (m, 0.91), 2.03 (s, 1.84, acetate), 0.48–1.92 (m, 7.75, $-CH_2CH_2CH_3$).

Reaction of (*Z*)-1-*n*-Butyl-2,3-diphenylaziridine with Glacial Acetic Acid. The fate of the aziridine **9a** in glacial acetic acid at room temperature was monitored by following the changes in the aziridine ring protons in the NMR. The peak corresponding to the ring protons was unchanged and undiminished after a 1-h period.

In a separate experiment, 1.0 g of the aziridine **9a** was dissolved in 25 ml of glacial acetic acid and stirred for 2.5 h at room temperature. Following the standard work-up, ir and TLC demonstrated the product to be unchanged starting material. No ring-opening products were observed and 1.0 g of the aziridine was recovered.

Lifetime Study of (*Z*)-1-*n*-Butyl-2,3-diphenylaziridine under Conditions Corresponding to the End of the Nitrosation Reaction in Glacial Acetic Acid. A solution corresponding to that obtained after the total decomposition and loss of nitrous acid under the glacial acetic acid nitrosating conditions was prepared by mixing 2.61 g of sodium acetate, 3.24 g of water, and 20.8 g of glacial acetic acid. Under the conditions of the reaction 0.8 g of the aziridine should be added but this is too little to allow the ring protons to be seen conveniently in the NMR spectrum. Instead, 1.25 g of the aziridine was added to give a satisfactory NMR signal. The aziridine dissolved slowly. The ^1H NMR was followed for 13 h and the ratio of the integrated intensities of the phenyl to aziridine ring protons obtained.

Table III. Kinetics of Solvolysis of 9a under "End of the Reaction Conditions"

Time, min	Ratio[b]	Time, min	Ratio[b]
10	10:1.68	125	10:1.27
20	10:1.52	150	10:1.17
50	10:1.62	765	10:1.02
75	10:1.34		

[a] As followed by ^1H NMR at 35 °C. [b] Aromatic to aziridine ring hydrogens.

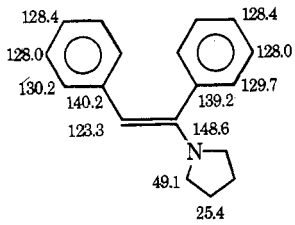
The portion of the reaction mixture that was not used for the NMR study was allowed to stand for 24 days, at which time the now lavender solution was neutralized with 10% sodium carbonate solution and subjected to the standard work-up. The oily product possessed the following spectral properties: ir (neat) 3370 (–OH or –NH), 1735 (ester), 1620 cm^{-1} (amine); NMR ($CDCl_3$) δ 6.83–7.50 (m, 10, phenyl), 5.42 (d, 0.75, PhC**H**N, J = 7.5 Hz), 5.02 (d, 0.75, PhC**H**OAc, J = 7.5 Hz), 3.00 (m, 1.27 NCH_2–), 2.01 (s, 2.2, acetate), 0.45–1.58 (m, 7.3, $-CH_2CH_2CH_3$).

Stability of 13a and 10a under the Reaction Conditions. (*E*)-1,2-Diphenyl-1-(*N*-*n*-butylnitrosamino)ethene (**13a,** 0.5 g) was placed in 13.5 ml of glacial acetic acid and treated with 2.37 g of sodium nitrite in 1.87 g of water, added all at once. The solution was stirred for 2 h, then given the standard work-up to yield 0.5 g of unchanged starting material, mp 88–89 °C.

Similarly, 0.5 g of *threo*-1,2-diphenyl-2-(*N*-*n*-butylnitrosamino)ethyl acetate (**10a**) was treated to the reaction conditions above with 0.47 g of unchanged starting material isolated at the end of 2 h, mp 133–135 °C.

Hydrolysis of (*E*)-1,2-Diphenyl-1-(*N*-*n*-butylnitrosamino)ethene (13a) in Acidic Dioxane. The *N*-nitrosenamine **13a** (1.0 g, 0.0036 mol) was taken up in a solution of 45.5 ml of dioxane, 22.5 ml of water, and 3.0 ml of concentrated sulfuric acid and refluxed for 47 h. The reaction mixture was poured into excess water and extracted into ether. The ether extract was spotted on freshly prepared silica gel TLC plates and run against starting material, benzoin, and benzyl phenyl ketone in 5% ethyl acetate–petroleum ether F. The TLC showed no spots due to **13a** and only those of benzoin (R_f 0.065), benzyl phenyl ketone (R_f 0.325), and **13a** (R_f 0.45). After drying the ether was stripped to give a solid–oil mixture. Removal of the solid and recrystallization from ethanol gave benzoin (0.25 g, 37%), mp 129–130 °C (lit.[40] 129.5–130.5 °C). The oil and the stripped filtrate from the crystallization were chromatographed on silica gel to give benzyl phenyl ketone which was identified as its 2,4 dinitrophenylhydrazone, mp 198–199 °C (lit.[41] 204 °C).

Synthesis of 1,2,Diphenyl-1-pyrrolidinoethene. This enamine was prepared from benzyl phenyl ketone and pyrrolidine by the method of Dulou et al.[17] and its properties agreed with those reported for it: ir C=C, 1610 cm^{-1}; uv 227 nm (ϵ 1.25 × 10^4), 312 (1.98 × 10^4); ^1H NMR >C=CH– δ 5.32; ^{13}C NMR assignments given below.



Registry No.—**10a,** 58268-19-2; **10b,** 58268-20-5; **10c,** 58268-21-6; **12,** 58268-22-7; **13a,** 58268-23-8; **13b,** 58268-24-9; **19,** 58268-25-0; **34,** 2866-82-2; *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl acetate HCl, 58268-26-1; *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl acetate, 58268-27-2; 1,2-diphenyl-1-pyrrolidinoethane, 58268-28-3.

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The Configuration[1] of Nicotine. A Nuclear Magnetic Resonance Study

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Radiofrequency irradiation of the *N*-methyl group in nicotine at pD values of 11.0, 5.0, and 0.8 caused nuclear Overhauser enhancements (NOE) of the pyridyl protons and the C-2′ and C-5′ protons on the pyrrolidine ring. However, irradiation of the *N*-methyl group at 3.13 ppm of nicotine in trifluoroacetic acid solution (TFA) did not cause an NOE on the pyridyl protons but rather on the C-2′ and C-5′*β* protons. In TFA, the rate of deprotonation of nicotinium diacid salts is slow compared to the NMR time scale, and the peak at 3.13 ppm is attributed to the nicotinium salt in which the *N*-methyl group is trans to the pyridine ring. A second singlet at 2.82 ppm is attributed to the nicotinium salt in which the *N*-methyl group is cis to the pyridine ring. These assignments were established by NMR studies in mixtures of TFA–TFA-*d*. These results are interpreted in terms of nitrogen protonation–deprotonation–pyramidal inversion equilibria and the complexities of NOE studies on configurationally mobile systems. The rates of inversion and proton relaxation are considered. It is estimated that nicotine-free base exists with its *N*-methyl group preferentially (90.9 ± 0.9%) trans to the pyridine ring by gas-phase kinetic quenching experiments.

The configuration[1] of nicotine and nicotine acid salts has been a topic of concern for many years.[2-9] Nicotine structural analysis indicates two unknown features: the orientation of the *N*-methyl group and the relative position of the pyridine and pyrrolidine rings. Experimental determination of these two structural parameters is complicated by the likelihood of low energy barriers to change.[10] We now report the results of our studies which show that the preferred (>90%) configuration of the *N*-methyl group in nicotine is 1′ (*R*) (i.e., trans to the pyridine ring) under a variety of experimental conditions.

Recently, Chynoweth, Ternai, Simeral, and Maciel[8] concluded on the basis of their NMR studies of nicotine in $CDCl_3$ and D_2O "that the N-methyl group is preferentially on the same side of the pyrrolidine ring as the pyridine ring". That conclusion[8] contrasted with perturbative configuration interaction calculations performed by Pullman, Courriere, and Coubeils,[7a] which indicated that 1 (see Scheme I) was approximately 4 kcal/mol more stable than **2**.[11] Other investigators[2-4] based their configurational assignments on (1) steric evaluations using space-filling models or (2) demethylation studies of nicotine *N*′-oxide. Any conclusion based on these latter two criteria meets with severe criticism.[12] Finally, Koo and Kim[5] have reported the x-ray analysis of a crystal of nicotine dihydriodide in which the *N*-methyl group was in a trans configuration with respect to the pyridine ring (cf. **3**). However, the crystalline sample was undoubtedly prepared under conditions in which the equilibria shown in Scheme I were operative, and it is theoretically possible that a minor component, or one of a number of components, crystallized. In addition, conclusions based on x-ray data of a solid cannot necessarily be applied to the conformation or configuration of the same molecule in solution, especially if protonation–deprotonation reactions are occurring in solution.[14]