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Methamphetamine from Ephedrine: I. Chloroephedrines and Aziridines

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ABSTRACT: Illicit methamphetamine clandestinely synthesized from ephedrine via reduction of chloroephedrine is discussed. The stereochemistry, mechanism, synthetic impurities, and analysis of clandestine methamphetamine samples is addressed. Stereochemical relation of (+)methamphetamine to its initial precursor (−)ephedrine or (+)pseudoephedrine is achieved by detection of (+)chloropseudoephedrine or *cis*-1,2-dimethyl-3-phenylaziridine, in the case of the first, and (−)chloroephedrine or *trans*-1,2-dimethyl-3-phenylaziridine in the case of the latter.

KEYWORDS: toxicology, methamphetamine, chemical analysis

In clandestine methamphetamine laboratories seized by the Drug Enforcement Administration (DEA) in recent years (1983 to 1985), the second most frequently encountered synthesis is the ephedrine to chloropseudoephedrine followed by reduction. In this paper we address the stereochemistry of the ephedrines, the ephedrine to methamphetamine conversion procedure, the mechanisms involved in the conversion, the impurities or by-products which arise during the conversion procedure, and the identification of starting materials based on final product analysis. Impurities addressed in this study have been detected by us in varying levels from clandestine (+)methamphetamine samples utilizing the techniques of gas chromatography/mass spectrometry (GC/MS) and ^{1}H nuclear magnetic resonance (NMR).

Experimental Procedure

Standards of (−)ephedrine and (+)pseudoephedrine were obtained commercially from Sigma Chemical Co. The respective chloro analogs were prepared as described by Emde [*1*]. The respective aziridines were prepared from the chloro analogs by addition of concentrated sodium hydroxide (NaOH), with gentle warming, allowing the aziridine to volatilize into a hanging drop of dilute hydrochloric acid.

Nuclear magnetic resonance spectra were obtained with a Nicolet NT-200WB Fourier transform spectrometer equipped with a model 293a programmable pulser. Spectra were obtained on the free bases in deuterochloroform with tetramethylsilane as reference. Sam-

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ples were processed by extraction from deuterated water, sodium carbonate added, into deuterchloroform contained within the NMR tube. Inspection of the lower ($CDCl_3$) layer via ^1H NMR produced spectra illustrated in Figs. 1, 2, and 3. Infrared spectra were recorded in potassium bromide with a Beckman model 4240 spectrometer.

Gas chromatography/mass spectrometry was performed on a Hewlett-Packard 5987a GC/MS system, interfaced with a 5880a series GC. The gas chromatograph was operated in the split mode (50:1) and was equipped with a 12-m by 0.20-mm inside diameter fused silica capillary column with a bonded methyl silicon liquid phase. Injector temperature was maintained at 260°C. Oven temperature was programmed as follows: initial temperature 100°C; initial hold 2 min; temperature program rate 15°C/min; final temperature 275°C; final hold 2 min. Ion source was maintained at 200°C and the electron impact conditions at 70 eV. Nitrogen was used as carrier gas at a flow rate of 50 cm/s.

Clandestine (+)methamphetamine samples were analyzed for trace or major impurities via extracting the equivalent of 300-mg (+)methamphetamine from 1-mL deuterated water, sodium carbonate added, into 1-mL deuterochloroform. Inspection of the $CDCl_3$ layer via ^1H NMR was followed by dilution of the $CDCl_3$ with 200 mL CH_2Cl_2. Introduction of 1 μL into the GC/MS allowed detection of impurities.

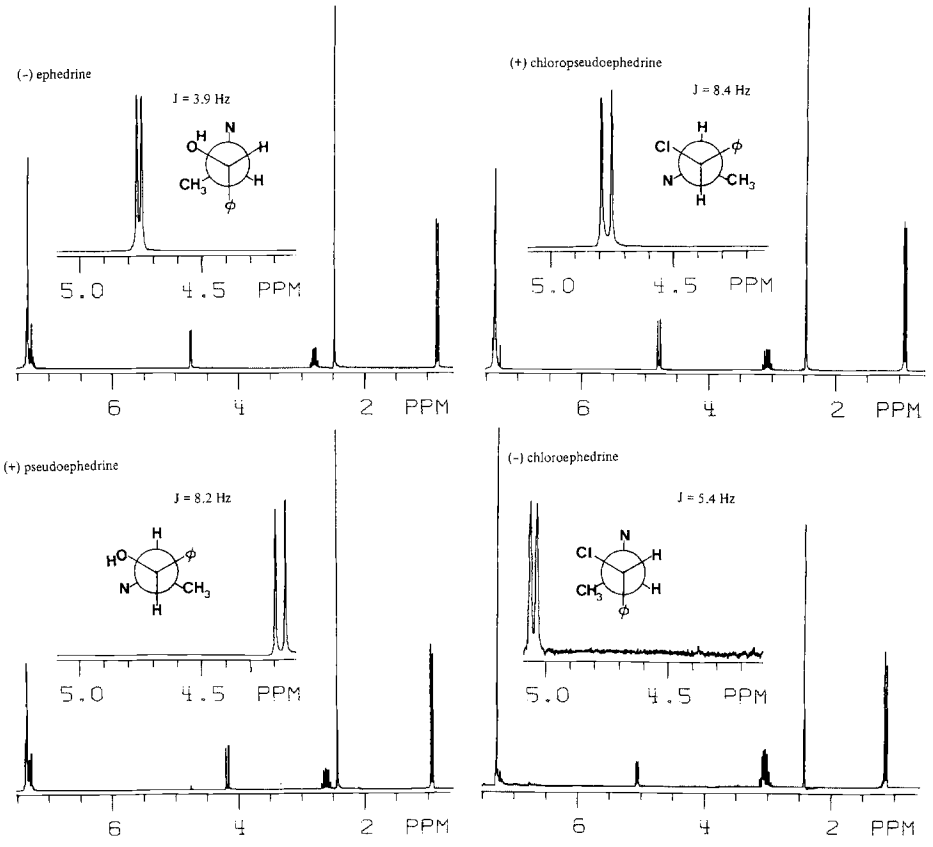


FIG. 1—*^1H NMR spectra of (−)ephedrine* (top left), *(+)chloropseudoephedrine* (top right), *(+)pseudoephedrine* (bottom left), *and (−)chloroephedrine* (bottom right), *obtained in $CDCl_3$ after extraction from D_2O/Na_2CO_3 at 200 MHz.*

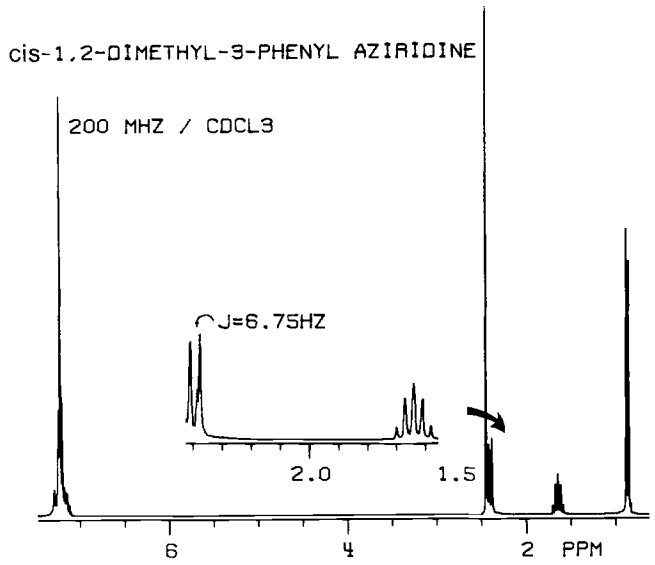


FIG. 2—*^1H NMR spectra of* cis-*1,2-dimethyl-3-phenyl aziridine prepared from (+)chloro-pseudoephedrine (a product of (−)ephedrine), obtained in $CDCl_3$ after extraction from D_2O/Na_2CO_3 at 200 MHz.*

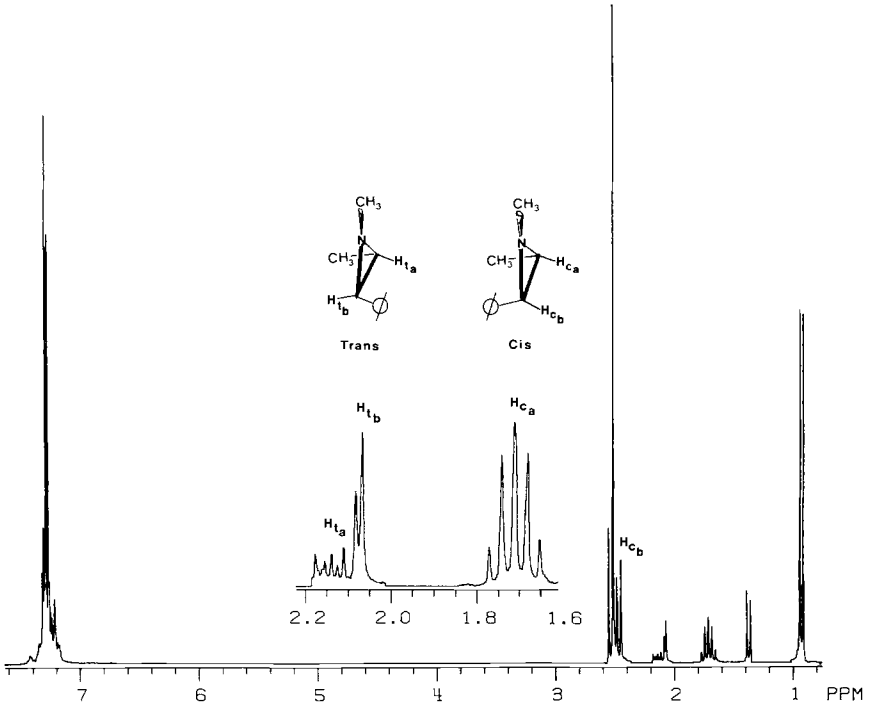


FIG. 3—*^1H NMR spectra of a mixture of* cis- *and* trans-*1,2-dimethyl-3-phenyl aziridines prepared from the chloro analogs which result from (+)pseudoephedrine, obtained in $CDCl_3$ after extraction from D_2O/Na_2CO_3 at 200 MHz.*

Stereochemistry

Stereochemical refinements are best approached by a brief review of ephedrine and pseudoephedrine stereochemistry. Fisher projections of enantiomers and diastereomers of ephedrine and methamphetamine demonstrate their structural relationships (Fig. 4) [*2*]. Comparison of these structures shows that stereochemistry about the carbon alpha to the benzene ring is immaterial in methamphetamine production, this carbon becomes achiral (a methylene). Although all ephedrine enantiomers and diastereomers may be converted to methamphetamine, stereochemistry about the beta carbon to the benzene ring shows that only (−)ephedrine and (+)pseudoephedrine yield *d*-methamphetamine [*1,3,4*]. This stereospecificity is one of the appealing features of this synthesis, since *d*-methamphetamine is physiologically more active than *l*-methamphetamine.

Ephedrine/Methamphetamine Conversion

The most commonly applied clandestine laboratory conversions of ephedrine to methamphetamine (1983 to 1985) involve first converting the ephedrine to its chloro analog by reaction with $SOCl_2$, PCl_5, $POCl_3$, or PCl_3, secondly, the chloro analog is reduced by catalytic hydrogenation (Fig. 5). Reaction of ephedrine with $SOCl_2$ yields the chloro analog in near complete *inversion* of configuration around the carbon alpha(to the benzene ring), yielding chloropseudoephedrine to the extent of 99% [*3*].

Reaction of pseudoephedrine with this reagent, in our hands as prescribed by Ref *1*, resulted in a 60:40 mixture (quantitation via ^1H NMR) of chloropseudoephedrine (retention) and chloroephedrine (inversion). These results suggest that a simplistic interpretation of the overall mechanisms governing these diastereomeric conversions is dangerous. The usual reaction of alcohols with thionyl chloride to produce alkyl chlorides proceeds via a substitution nucleophilic internal (SN_i) mechanism [*5*]. The SN_i reaction proceeds in two steps: dissociation of the chlorosulfite into an ion pair, then immediate attack on the carbocation by the

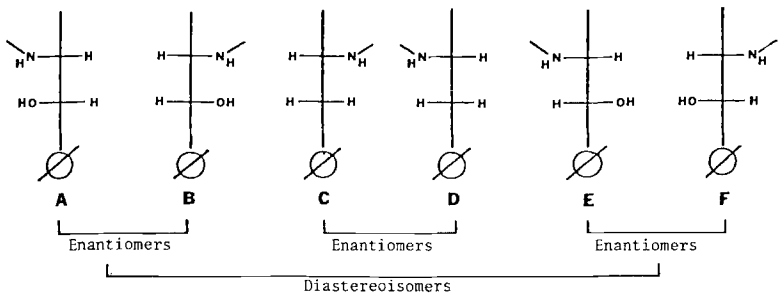


FIG. 4—*Fisher projections of enantiomers and diastereoisomers of ephedrine and methamphetamine:* A = *(+)ephedrine;* B = *(−)ephedrine;* C = d-*methamphetamine;* D = l-*methamphetamine;* E = *(−)pseudoephedrine;* F = *(+)pseudoephedrine.*

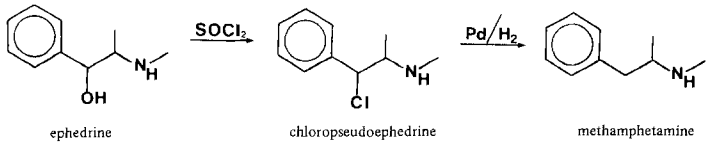


FIG. 5—*Synthetic conversion of ephedrine to methamphetamine via chloropseudoephedrine.*

chloride. Attack occurs from the front side; thus, SN_i reactions result in end products which *retain* configuration of starting materials (Fig. 6).

A second mechanism which yields products which retain configuration of starting materials is the neighboring group mechanism. In this mechanism, nitrogen functions as a nucleophile, attacking and forcing out the leaving group without giving up its own position in the molecule. This results in inversion of configuration at the carbon alpha to the benzene ring (Step 1, Fig. 7). Chlorine then attacks, negating nitrogen's effect and once again inverting configuration around the alpha carbon (Step 2, Fig. 7). This path amounts essentially to two serial SN_2 substitutions, each with inversion of configuration; the net result is *retention* of configuration. In this sequence the neighboring nitrogen group is said to lend anchimeric assistance.

The third mechanism is another two-step reaction. First $SOCl_2$ attacks nitrogen and oxygen, forming a bridged species and freeing chloride ion into solution (Step 1, Fig. 8). Free

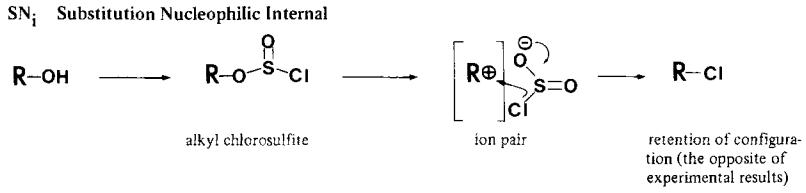


FIG. 6—*Reaction of a chiral alcohol (R-OH) with thionyl chloride proceeds via a substitution nucleophilic internal mechanism to yield an alkyl chloride with* retention *of configuration.*

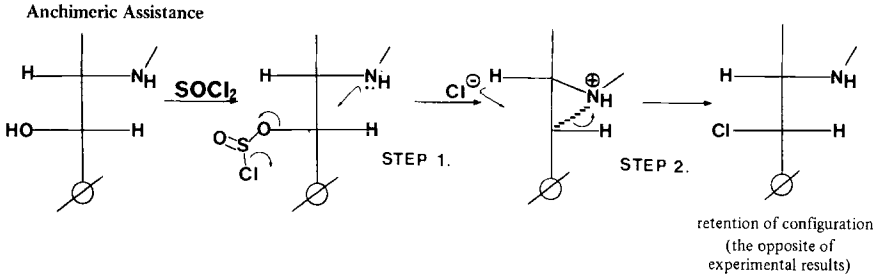


FIG. 7—*Mechanism in which ephedrine is converted to the alkyl chloride with anchimeric assistance from nitrogen, resulting in* retention *of configuration.*

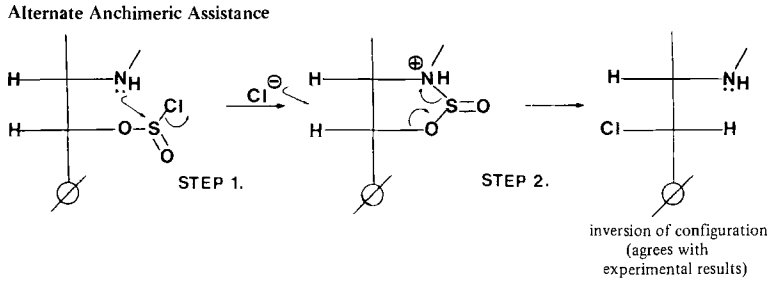


FIG. 8—*Proposed mechanism of ephedrine's conversion to chloropseudoephedrine, which relies on alternate anchimeric assistance, yields* inversion *of configuration.*

chloride ion may then attack from the back side, resulting in an *inverted* configuration at the alpha carbon (Step 2, Fig. 8). Support for this mechanism is found in the reaction of chiral alcohols, thionyl chloride with pyridine added [5]. Unlike SN_i reactions, wherein the pyridine is absent, this reaction results in inversion of configuration around the chiral center. This is due to the immediate reaction of SO_2+ with both pyridine and the alcohol, leaving Cl^- ion free to attack from the rear in an SN_2 reaction.

Neuman projections for (−)ephedrine and (+)pseudoephedrine are shown in Fig. 9. Evidence that these are the correct Neuman projections rotamers for (−)ephedrine and (+)pseudoephedrine is furnished by their respective proton NMR spectra (see Fig. 1). Vicinal proton coupling (J) for (−)ephedrine is 3.9 Hz, reflective of a dihedral angle near 80 to 90°. Similarly, the J-value for the vicinal protons on (+)pseudoephedrine is 8.2 Hz, indicative of a dihedral angle near 150 to 190° [6]. Thus, in carrying these Neuman projections forward in the reaction sequence, for (−)ephedrine the alkyl sulfite is sterically hindered from front side attack and is unhindered from back side attack. The final chloro-product shows *inversion* of configuration. Conversely, the front and back side approaches to the intermediate sulfite of (+)pseudoephedrine are equally hindered. Both *retention* and *inversion* of configuration is in the final chloro product. Note that the inversion product has the larger number of gauche interactions, therefore the product with retention of configuration will predominate.

This last rationalization, that of alternate anchimeric assistance, is consistent with experimental facts. We feel justified in identifying alternate anchimeric assistance as the parable mechanism involved in the synthetic conversion of ephedrine to chloropseudoephedrine with thionyl chloride.

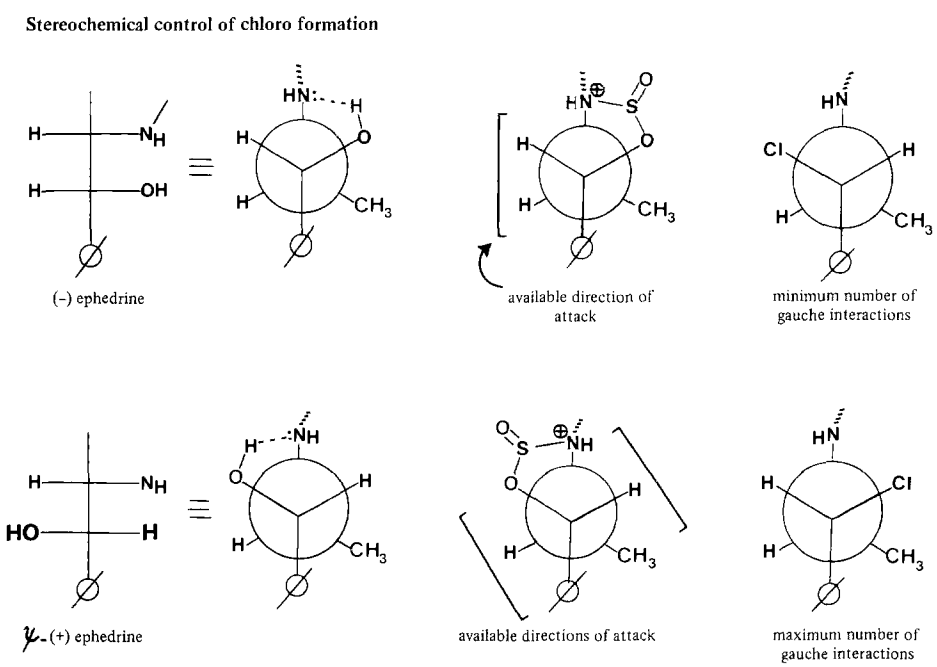


FIG. 9—*Stereochemical control of chloro formation for (−)ephedrine* (top) *and (+)pseudoephedrine* (bottom) *with Fisher projections* (far left) *translated into Neuman projections* (right), *justified by ^1H NMR coupling constants and alternate anchimeric assistance.*

Impurities

The principal impurities in the conversion of ephedrine to methamphetamine which we have analyzed from clandestine samples are the unreduced chloro analog of ephedrine and 1,2-dimethyl-3-phenyl aziridine (Fig. 10).

Aziridines result from internal substitution of chloro ephedrines. This rearrangement can be catalyzed by alkali or by heat. These aziridines have stereospecific qualifiers since internal substitution of nitrogen for chlorine is via backside attack. Shown in Fig. 11 are geometric and stereospecific consequences of HCl elimination from (+)chloropseudoephedrine (derived from (−)ephedrine) leading to *cis*-1,2-dimethyl-3-phenyl aziridine. Similarly, (−)chloroephedrine (derived from (+)pseudoephedrine) rearranges to *trans*-1,2-dimethyl-3-phenyl aziridine [7]. Unfortunately, results of analysis are not unambiguous. This is due to the fact that the *trans*-1,2-dimethyl-3-phenyl aziridine is unstable and easily polymerizes, a feature not equally shared by the more stable *cis* isomer [7,8].

Simple rationalization of experimental results based on steric repulsion would draw the opposite conclusion, that is, *cis* would be rationalized to be less stable that *trans*. The explanation for experimental fact, *trans* is less stable that *cis*, comes from the symmetry rules

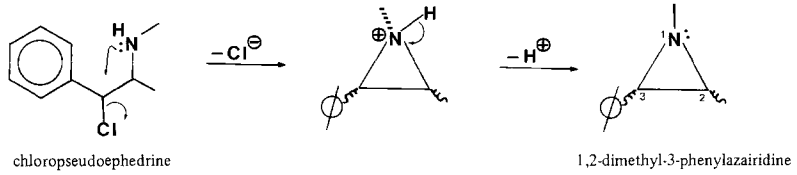


FIG. 10—*Internal rearrangement of chloropseudoephedrine with the net loss of HCl to yield an aziridine (a three-membered ring containing nitrogen).*

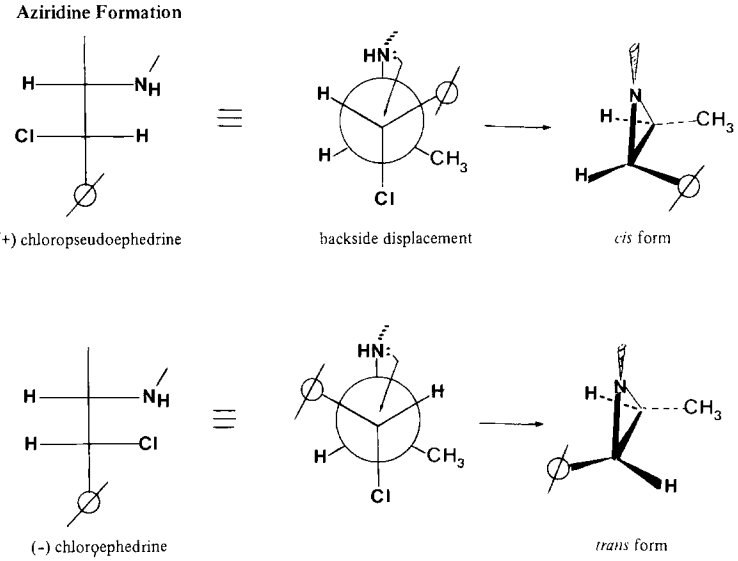


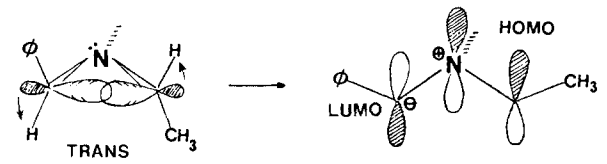
FIG. 11—*Stereochemical control of aziridine formation for (+)chloropseudoephedrine* (top) *and (−)chloroephedrine* (bottom) *which yield, respectively,* cis *and* trans *substituted aziridines.*

governing molecular orbital theory. In this concept, ring opening of the aziridine system is viewed as a four-electron conrotatory process (Fig. 12). The sterics involved in the *cis* structure would tend to favor a disrotatory opening, which is *not* allowed by these symmetry rules. Stated another way, one might consider the vicinal steric repulsion in the *cis* isomer to be, in effect, holding the molecule together. This steric repulsion is not present in the *trans* aziridine, and the symmetry-allowed conrotatory ring opening may proceed. Furthermore, a close look at the ring-opened products show the *trans* isomer to be more linear than the *cis* product and consequently the more favored ring opening [*9*].

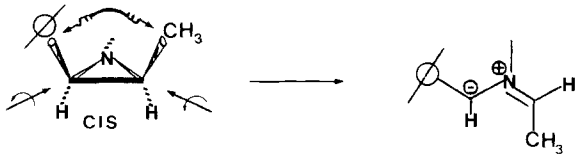
Analysis

From the discussion in the previous section one may conclude that clandestine samples of (+)methamphetamine synthesized from ephedrines may contain complex mixture of components. Less numerous in components and thus easier to analyze are samples prepared from (−)ephedrine. Impurity components prominent from this precursor route are (+)chloropseudoephedrine and *cis*-1,2-dimethyl-3-phenyl aziridine. On the other hand, samples of (+)methamphetamine which had as their origin (+)pseudoephedrine pose more of an analytical problem. Components to be expected from (+)pseudoephedrine route are (−)chloroephedrine, (+)chloropseudoephedrine, *trans*/*cis*-1,2-dimethyl-3-phenyl aziridine, and retro-ring openings of aziridines, that is, dimers and polymers of aziridines and the hydrolysis product phenyl-2-propanone [*10*].

Analytical techniques which qualitatively address these impurities or rearrangements may introduce problems in themselves. Attempts to chromatograph the chloro analogs of ephedrine via gas chromatography result in thermal elimination to aziridines. Similarly, strong base conditions often employed in extraction schemes for isolating components in clandestine samples will effect the same transformation. Our analytical approach to these samples relies heavily on ^{1}H NMR. Proton resonance spectroscopy offers the advantage of ambient temperature, neutral conditions, and the ability to distinguish diastereoisomers—indispensible if the precursor's stereochemistry is to be determined. Fortunately, critical resonances of the impurities in question do not overlap to the extent of interference with the analysis (Figs. 1, 2, and 3). Enlarged ^{1}H NMR windows (5.1 to 4.1 ppm), illustrated in Fig. 1, reveal that these diastereoisomers may be distinguished. Chemical shifts and coupling constants of



Stability of *cis* versus *trans* aziridine: Sterics are working against a conrotatory opening in the *cis* isomer but not in the *trans* isomer



4e conrotatory symmetry allowed

cis product is less linear (less favored) than the *trans*

FIG. 12—*Molecular orbital theory interpretation of aziridine ring opening which justifies the increased stability of* cis *versus* trans.

the beta (to nitrogen) methine hydrogen may be used to identify the particular ephedrine precursor or the chloro-intermediates present from clandestine mixtures or both. Similarly, the proton resonance region between 2.2 and 1.6 ppm, which is normally clear of resonances, is inspected for impurities of *cis* or *trans* aziridines or both. Illustrated in Fig. 2 is the proton resonance spectrum of *cis*-1,2-dimethyl-3-phenyl aziridine, a product of internal substitution from (+)chloropseudoephedrine initially produced from (−)ephedrine. Similarly, Fig. 3 illustrates the proton resonance spectrum of the mixture resulting from the chloro analogs produced from (+)pseudoephedrine.

Mass spectrometry via gas chromatography may be utilized for analysis of these complex mixtures provided standards and caution is exercised. Standards should be available in order to chromatographically distinguish the aziridines. Shown in Fig. 13 is a reconstructed gas chromatogram illustrating the separation, and thus discrimination, possible for the aziridines. Because of the high-energy nature of the three-membered ring aziridines, their mass spectra are virtually identical (Fig. 14). One should exercise caution in relating quantitative estimations of aziridine or their actual presence in samples. This is to say that GC/MS detection of these aziridines may or may not represent their actual presence in samples, since internal substitution/ring closure leading to aziridines may be an artifact of the GC injection port, that is, thermal rearrangement of chloroephedrine.

Conclusion

The mechanism of conversion for ephedrine(s) via $SOCl_2$ to its alkyl chloride has been rationalized as proceeding by alternate anchimeric assistance. Clandestine *d*-methamphetamine samples which are prepared by way of these alkyl chloride(s) have been analyzed to determine the stereo-identity of the precursor. Spectral data via ^1H NMR spectroscopy and GC/MS spectrometry have been presented to aid in the analysis of these precursors, intermediates and rearrangements.

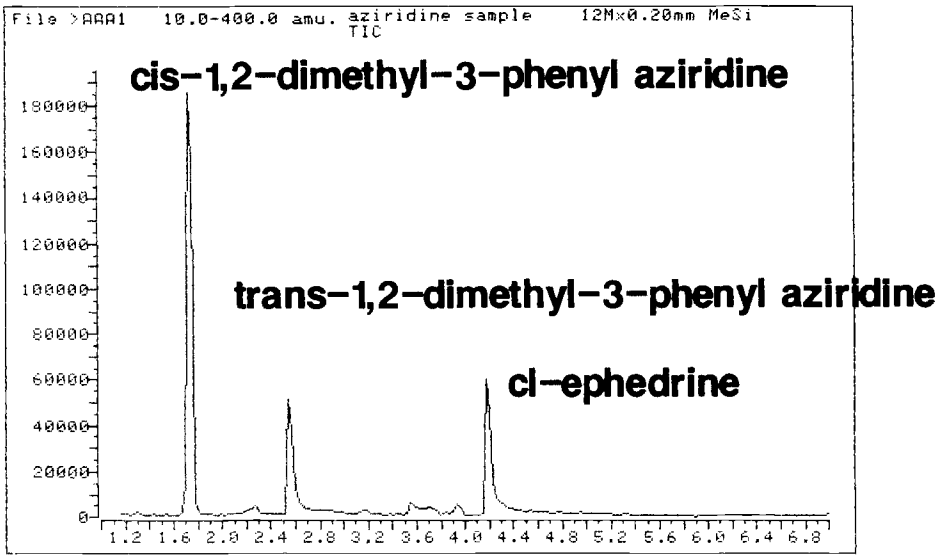


FIG. 13—*Reconstructed Gas Chromatography illustrating separation achieved between* cis- *(1.76 min) and* trans- *(2.54 min) 1,2-dimethyl-3-phenyl aziridine utilizing a 12-m by 0.20-mm bonded methyl silicone column. Other clandestine components, phenyl-2-propanone and methamphetamine, have retention times 1.67 min and 2.38 min respectively.*

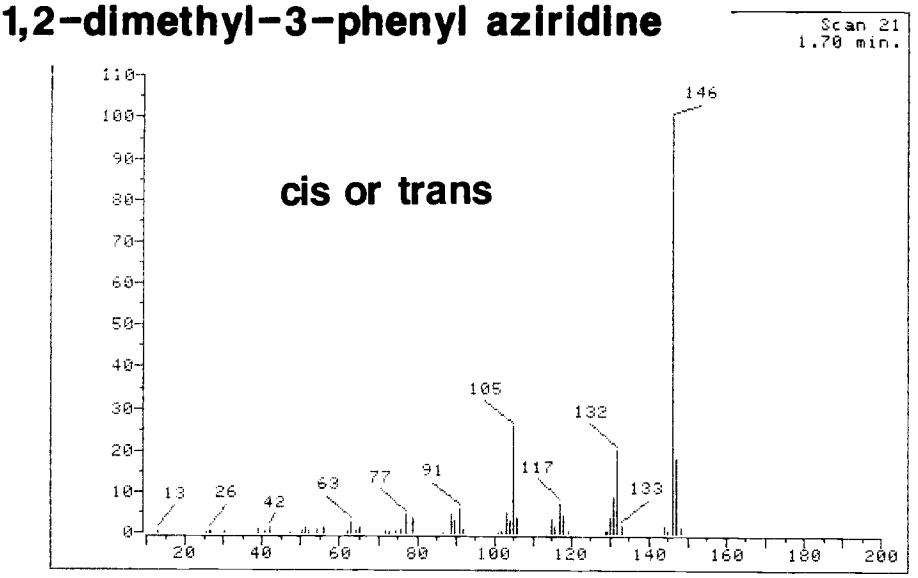


FIG. 14—*Mass spectrum via electron impact of* cis *or* trans-*1,2-dimethyl-3-phenyl aziridine.*

Acknowledgments

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