

Preparation of Epiminostearates. Comparison of Methods

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Abstract

The addition of N,N-dichlorourethan (DCU) to internal olefins has been found to be an acceptable reaction leading to the preparation of internal fatty acid aziridines. The yields of isolated epimino derivatives are in the 50–60% range, only slightly lower than those obtained by the iodine isocyanate (INCO) method. In order to compare the stereochemistry of the two methods, an IR spectroscopic procedure was developed which permits an estimation of the relative amounts of *cis*- and *trans*-aziridines in mixtures of the two. In agreement with literature reports, the INCO method is stereospecific, the *cis*-olefins giving rise to *cis*-aziridines and the *trans*-olefins forming *trans*-aziridines. On the other hand, DCU addition to olefins results in mixtures of *cis*- and *trans*-aziridines in which the latter isomers predominate. This finding is compatible with the reported free-radical nature of the DCU reaction.

Introduction

Of the available synthetic procedures for the introduction of the aziridine ring structure into organic substrates the Gabriel and Wenker methods have been the most widely employed (1,2). These procedures, however, are generally not applicable to the preparation of fatty acid epimino derivatives, because of the inaccessibility of the required starting materials. Only very recently have the first examples of long chain fatty acid derivatives containing an internal aziridine group been reported (3,4). The procedure utilized for the preparation of these compounds was the addition of iodine isocyanate (INCO), prepared in situ from silver cyanate and iodine, to an olefin, followed by methanolysis and basic ring closure to the aziridine ring structure.

We have been interested in finding alternate and more direct procedures for the preparation of fat-derived aziridines. As part of this work we have investigated the addition of N,N-dichlorourethan (DCU) to internal olefins as a means of preparing the desired compounds. Previous studies have been concerned mainly with the addition of this reagent to terminal and cyclic olefins, while its reaction with internal olefins has been limited to highly substituted ethylenes and to *trans*-3-hexene (5–7).

The purpose of the present investigation was to compare the yields and the stereochemistry of the fatty aziridines prepared by the DCU procedure with those obtained by the INCO method.

Experimental Procedures

Materials and Equipment

cis- and *trans*-9-Octadecene were prepared by the lithium aluminum hydride reduction of the tosylates of oleyl and elaidyl alcohol (8). Their purity as determined by gas liquid and thin layer chromatography exceeded 98%.

Methyl Oleate 99% and Methyl Elaidate 99% were purchased from Applied Science Lab. and were used as received.

N,N-Dichlorourethan (DCU) was prepared by the chlorination of urethan utilizing the procedure of Foglia and Swern (5). Its purity by iodometric titration was >99%.

All other reagents were used as received from commercial suppliers except for boron trifluoride etherate, which was distilled prior to use.

Analytical Procedures

Titration of aziridines was carried out by a procedure developed in this laboratory (9). A sample containing 0.2 to 0.4 meq of epimino compound is weighed into a stoppered flask, dissolved in 10 ml of acetic anhydride, and allowed to stand for 15 min. To the solution is added 5 ml of 10% tetra-*n*-butylammonium iodide solution and one drop of crystal violet indicator solution, and the mixture is titrated rapidly with standard 0.02 N HClO₄ to the first true blue endpoint.

IR spectra were obtained on a Perkin Elmer Model 237-B spectrophotometer with sodium chloride optics. The spectra were taken at 5% concentration in potassium bromide pellets. The disks were rotated through 360 deg and several scans were recorded to compensate for variance in cell thickness. The absorbance values were then calculated as an average of these values.

Procedures

cis-9,10-Epiminooctadecane Prepared with INCO. Pure *cis*-9-octadecene (6.0 g, 0.024 mole) was converted to *threo*-9-iodo-10-isocyanatooctadecane by reaction with iodine (6.0 g, 0.024 mole) and silver cyanate (4.3 g, 0.029 mole) in tetrahydrofuran (150 ml) by the method of Rosen and Swern (10), and then converted to *threo*-9-iodo-10-(methylcarbamoyl)octadecane by refluxing for 1.5 hr with methanol (100 ml). Potassium hydroxide (6.0 g, 0.107 mole) in water (20 ml) was added, and the solution was refluxed overnight. The resulting mixture was poured into water (400 ml) and extracted with ether (4 × 100 ml). The combined organic layers were washed with water (2 × 25 ml), dried over anhydrous sodium sulfate and the solvents removed in vacuo to leave 6.2 g of white solid, purity by titration 80%, 77% yield. The solid was recrystallized from acetone (5 ml/g) at -20 C to give 4.0 g of epimino compound, mp 63.5–64 C (lit mp = 65–66 C (3)), purity 98.4%, 62% yield.

trans-9,10-Epiminooctadecane. Reaction of *trans*-9-octadecene (6.0 g, 0.024 mole) with iodine isocyanate as above followed by methanolysis and basic ring closure gave 5.5 g (purity 48.9%, 42% yield) of crude *trans*,9,10-epiminooctadecane. After three recrystallizations from hexane 1.40 g (purity 95.7%, 22% yield) of white solid was obtained, mp 45–48 C (lit mp 48–50 C (3)). Chromatography on alumina (pH 7) (1 g/30 g) gave the pure material, mp = 48–49 C, purity 99.6%.

9,10-Epiminooctadecane prepared with DCU. A solution of N,N-dichlorourethan (8.8 g, 0.055 mole) in benzene (25 ml) was placed in a 100 ml flask and the solution was purged with and kept under an atmosphere of nitrogen. *cis*-9-Octadecene (12.6 g, 0.050 mole) was then added dropwise at a suitable

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rate to maintain the reaction temperature at 30–35 C. When addition was complete the reaction mixture was refluxed until disappearance of olefin was complete as noted by glpc. A 20% aqueous solution of sodium bisulfite (50 ml) was added at 5–10 C. The organic layer was separated, and the aqueous phase was extracted with ether (2 × 25 ml). The organic layers were combined, washed with water (2 × 25 ml), dried over anhydrous sodium sulfate, and the solvent was removed in vacuo to leave 16.6 g of 9-chloro-10-(ethylcarbamoyl)-octadecane. Potassium hydroxide (11.2 g, 0.20 mole) in ethanol (100 ml) was added, and the solution was refluxed for 4 hr. The mixture was poured into water (400 ml) and extracted with ether (4 × 100 ml). The organic layers were washed with water (2 × 25 ml), dried over anhydrous sodium sulfate and the solvent removed in vacuo to leave 11.8 g of residue (purity 74%, yield 65%). The residue was recrystallized from acetone (5 ml/g) at –20 C to yield 6.4 g of epiminooctadecane, mp = 44–46 C, yield 48%, purity 97.8%.

Potassium *cis*-9,10-Epiminooctadecanoate (INCO Method). Methyl oleate (29.6 g, 0.10 mole) was converted to the *threo*-9(10),10(9)-iodoisoocyanate by reaction with iodine (25.4 g, 0.10 mole) and silver cyanate (18.0 g, 0.12 mole) in tetrahydrofuran (250 ml) by the method of Rosen and Swern (10), and then converted to methyl *threo*-9(10)-iodo-10(9)-(methylcarbamoyl)octadecanoate by refluxing for 1.5 hr with methanol (200 ml). Potassium hydroxide (33.6 g, 0.60 mole) in methanol (300 ml) was added and the mixture refluxed overnight. The hot reaction mixture was filtered, and the collected precipitate was washed with hot methanol (100 ml) and discarded (8.3 g). The combined filtrates (600 ml) were concentrated to 400 ml, cooled to 0 C, and the precipitate was collected by vacuum filtration. The filtrate was concentrated to 200 ml, cooled to 0 C and the precipitate was collected. The solids were combined to give 42.1 g of crude potassium 9,10-epiminooctadecanoate. The potassium salts (33.7 g) were taken up in hot 95% ethanol (550 ml) and the precipitate filtered. The solid residue was washed with hot ethanol (100 ml) and discarded (3.7 g). The filtrates were combined (650 ml) and one-fifth was set aside. The remainder of the filtrate was cooled to 0 C, and the precipitated solid collected (14.2 g), mp = 246–248 C (lit mp = 242–245 C) (3), purity 98.6%, yield 66%.

Analysis: Calculated for $C_{18}H_{34}NO_2K$: C, 64.4; H, 10.2; N, 4.17; K, 11.7. Found: C, 64.5; H, 10.2; N, 4.11; K, 11.5.

Methyl *cis*-9,10-Epiminooctadecanoate. To a solution of boron trifluoride etherate (4.3 g, 0.030 mole) in methanol (50 ml) was added potassium *cis*-9,10-epiminooctadecane (2 g, 6 mmole). The mixture was refluxed for 5 min, and the solution was concentrated in vacuo to about 10 ml. This slurry was shaken with 5% aqueous sodium hydroxide (60 ml), and the mixture was extracted with ether (4 × 25 ml). The combined organic layers were washed with water (2 × 25 ml), dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. The residue (1.6 g, purity 95.0%, yield 83%) was recrystallized from hexane to give the analytical sample, mp = 50–51 C.

Analysis: Calculated for $C_{19}H_{37}NO_2$: C, 73.3; H, 12.0; N, 4.50. Found: C, 73.2; H, 11.9; N, 4.52.

Potassium *trans*-9,10-Epiminooctadecanoate. Methyl elaidate (12.0 g, 0.040 mole) was converted to potassium *trans*-9,10-epiminooctadecanoate by the procedure

described for the *cis*-isomer. The crude salt (13.5 g) was recrystallized three times from 95% ethanol to yield 4.9 g of epimino compound with mp 240–243 C, purity 92.4%, yield 36%. The pure salt was obtained by basic hydrolysis of the pure methyl ester (see below) followed by recrystallization from ethanol, mp = 243–245 C.

Analysis: Calculated for $C_{18}H_{34}NO_2K$: C, 64.4; H, 10.2; N, 4.17; K, 11.7. Found: C, 64.5; H, 10.1; N, 4.22; K, 11.6.

Methyl *trans*-9,10-Epiminooctadecanoate. Potassium *trans*-9,10-epiminooctadecanoate (2.0 g, 6 mmole) was methylated by the procedure described for the *cis*-isomer. The crude product was recrystallized from hexane at –20 C to give 1.2 g of white solid, mp = 37–39 C, yield 63%. The pure sample was obtained by chromatography on silica gel (1 g/45 g). This material had mp = 40–41 C, purity by titration 99.3% and by glpc 99.1% (6 ft × ¼ in. 10% SE-30 on Diatoport S, column temperature of 230 C).

Analysis: Calculated for $C_{19}H_{37}NO_2$: C, 73.3; H, 12.0; N, 4.50. Found: C, 73.2; H, 11.9; N, 4.52.

Potassium 9,10-Epiminooctadecanoate (DCU Method). Methyl oleate (14.8 g, 0.050 mole) was converted to methyl 9(10)-chloro-10(9)-(ethylcarbamoyl)octadecanoate by reaction with DCU (8.8 g, 0.055 mole) in benzene (25 ml) utilizing the above procedure for *cis*-9-octadecene. The crude β -chlorocarbamate (21.6 g) in methanol (50 ml) was added to a solution of potassium hydroxide (16.8 g, 0.30 mole) in methanol (200 ml), and the mixture was refluxed overnight.

The reaction was worked up in the same fashion as for the INCO method product to give 9.6 g of potassium 9,10-epiminooctadecanoate, mp = 242–248 C, purity 100.3%, yield 57%.

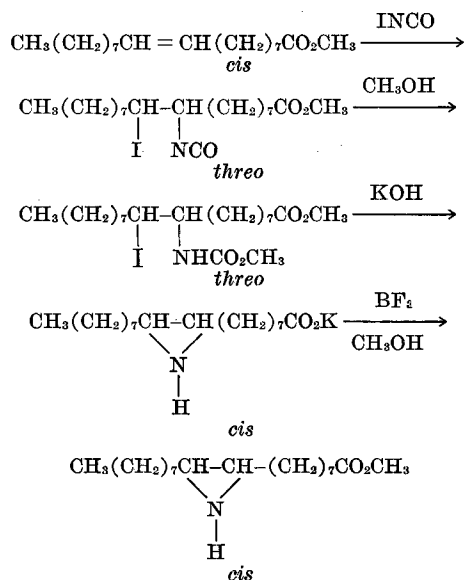
Methylation of the potassium salt was carried out by the procedure described above. The pure methyl ester had a mp = 39–42 C after recrystallization from hexane at –15 C.

Results and Discussion

The model unsaturated compounds selected for this investigation were *cis*- and *trans*-9-octadecene, methyl oleate and methyl elaidate. The general procedure employed for the preparation of their epimino derivatives by the iodine isocyanate (INCO) method is illustrated in Scheme I for the conversion of methyl oleate to methyl *cis*-9,10-epiminooctadecanoate. The esterification reaction shown in Scheme I has not been reported previously.

Attempts to prepare aziridine compounds bearing a free carboxylic acid substituent have been unsuccessful owing to the lability of the aziridine ring system towards carboxylic acids (3,4,15). However, we have been able to obtain the methyl ester of these derivatives by the controlled reaction of the carboxylic salts, e.g., potassium 9,10-epiminooctadecanoate, with boron trifluoride etherate in methanol. Excessive reaction times with this methylating reagent must be avoided to prevent the Lewis acid catalyzed ring opening of the aziridine ring with methanol. The crude esterification product, a Lewis acid-base complex of boron trifluoride and aziridine, must be decomposed with strong base, such as sodium hydroxide, in order to obtain the free methyl epimino derivative.

In general the procedure utilized in the DCU method is similar to that of the INCO addition, but is more direct. DCU, a readily available reagent, adds to the olefin to give the β -chlorocarbamate



Scheme I

directly after reduction, while in the INCO addition the corresponding β -iodocarbamate is formed from the olefin in two steps. Subsequent preparation of the aziridine requires cyclization in basic medium for both methods. Comparison of the results (Table I) shows that for the conversion of *cis*-9-octadecene to its 9,10-epimino derivative the yield is only 12% lower by the DCU procedure than by the iodine isocyanate method of preparation. This yield differential, calculated from ring titration data, is the average of several runs and is reproducible to within $\pm 5\%$. Similar results were obtained for the reaction of methyl oleate with iodine isocyanate and *N,N*-dichlorourethan. The difference in the yields of methyl 9,10-epimino-octadecanoate was found to be less than 10%, with the iodine isocyanate route giving the higher yield, whereas the difference in the crude yields of

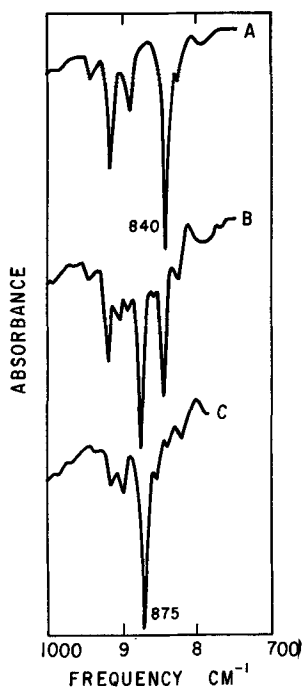
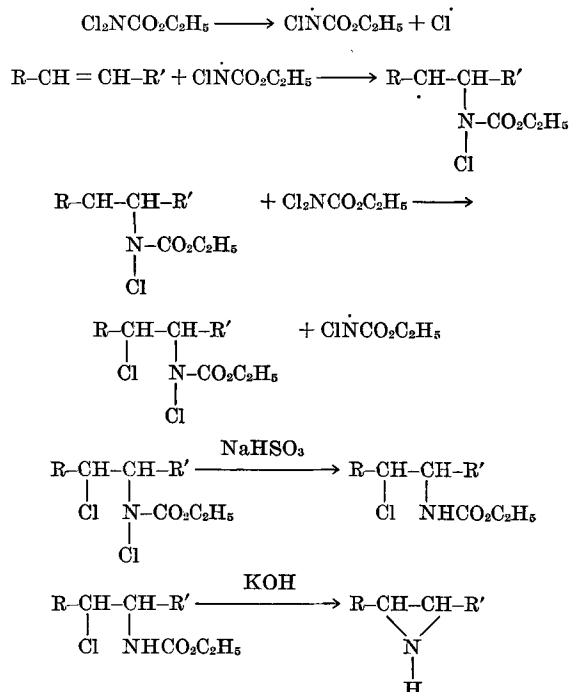


FIG. 1. IR spectra of potassium 9,10-epimino-octadecanoate A, *cis* isomer; B, *cis-trans* mixture from DCU procedure; C, *trans* isomer.



R, C_8H_{17} ; R', C_8H_{17} or $\text{C}_7\text{H}_{15}\text{CO}_2\text{CH}_3$

Scheme II

aziridines was determined to be about 6% from titration data.

It has been noted previously (3) that the yield of *trans*-9,10-epimino-octadecane is poor when prepared via the INCO method. In contrast, the DCU procedure leads to identical yields of aziridines from *cis*- and *trans*-9-octadecene (see Table I).

Previous work (7) has shown that in the reaction of *N,N*-dichlorourethan with some internal aliphatic olefins, allylic hydrogen atom abstraction is the major side reaction. This alternate pathway can compete with the addition reaction and may result in lower yields of β -halocarbamate addition products compared with those obtained via the iodine isocyanate route. This diminution of β -halocarbamate would subsequently lead to lower overall yields of the desired epimino compounds. No such byproducts were observed, and in view of the yields obtained, it is doubtful that this side reaction is important in this series.

The stereochemical course of the INCO addition to olefins has been studied extensively, and has been found to be *trans* (11-13). The ring closure of the derived vicinal iodocarbamates to aziridines has been shown to proceed with inversion of configuration (14) at the carbon atom bearing iodine. Accordingly a *cis*-aziridine is obtained from a *cis*-olefin and a *trans*-aziridine is obtained from a *trans*-olefin.

On the other hand, the addition of *N,N*-dichlorourethan to olefins has been shown (5,7) to proceed

TABLE I
Yields of 9,10-Epimino-octadecane and Methyl 9,10-Epimino-octadecanoate

Starting olefin	Aziridine isomer	Method ^a	Aziridine yield %
<i>cis</i> -9-Octadecene	<i>cis</i>	INCO	77
<i>cis</i> -9-Octadecene	<i>cis</i> and <i>trans</i>	DCU	65
<i>trans</i> -9-Octadecene	<i>trans</i>	INCO	42
<i>trans</i> -9-Octadecene	<i>cis</i> and <i>trans</i>	DCU	67
Methyl oleate	<i>cis</i>	INCO	54
Methyl oleate	<i>cis</i> and <i>trans</i>	DCU	46
Methyl elaidate	<i>trans</i>	INCO	36

^a INCO = iodine isocyanate; DCU = *N,N*-dichlorourethan.

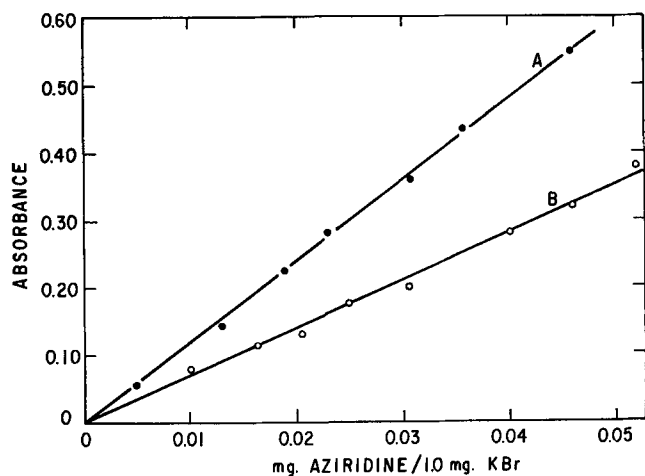


FIG. 2. Lambert-Beer plot of 840 cm^{-1} absorbance for A, *cis*-9,10-epiminooctadecane; B, potassium *cis*-9,10-epiminooctadecanoate.

via a free radical chain propagation sequence. An application of this mechanism to the present study is shown in Scheme II. Accordingly, addition of this reagent to *cis*- or *trans*-9-octadecene or to methyl oleate and methyl elaidate produces a diastereomeric mixture of *erythro* and *threo*- β -chlorocarbamates after reduction with aqueous sodium bisulfite. Subsequent ring closure of the β -chlorocarbamates with alkali gives a mixture of *cis*- and *trans*-9,10-epimino derivatives.

Since the epimino derivatives obtained from the N,N-dichlorourethan procedure were expected to be mixtures of *cis*- and *trans*-aziridines, it was deemed necessary to determine the isomer distribution. This necessitated the development of a physical technique to distinguish between the two geometric isomers. It was found that a semi-quantitative correlation of isomer distribution could be achieved by the use of IR spectroscopy. The spectra of the pure *cis*-isomers of 9,10-epiminooctadecane and potassium 9,10-epiminooctadecanoate, were found to have strong IR absorption bands at 3150 and 840 cm^{-1} (Fig. 1). The spectra of the *trans*-isomers were characterized by strong absorption bands at 3150 and 875 cm^{-1} . The bands in the 800 – 900 cm^{-1} region are characteristic for each of the isomers and are found only when the spectra are run as solid films or in potassium bromide pellets. When the spectra are recorded in the liquid state or in solution all the absorption bands characteristic of the aziridine function are no longer present and the spectra of the *cis* and *trans*-epimino compounds become indistinguishable by IR. Upon cooling, or evaporation of the solvent, a solid film of the epimino compound is obtained and the individual bands reappear in the spectra. These bands have been ascribed to a deformation or vibration of the aziridine ring (3,16), while a reviewer has suggested that the absorption may be due to crystalline effects. Although the exact origin of these bands is not known with certainty, their use as a means of determining the relative amounts of *cis* and *trans*-epimino compounds in reaction mixtures is not precluded. For the *cis*-isomers the absorbance at 840 cm^{-1} was found to obey the Lambert-Beer relationship. This is shown in Figure 2. In contrast, the 875 cm^{-1} absorbance for the *trans*-isomers was found not to be linear with concentration.

The *cis-trans*-isomer distribution for the aziridines obtained from the reaction of N,N-dichlorourethan

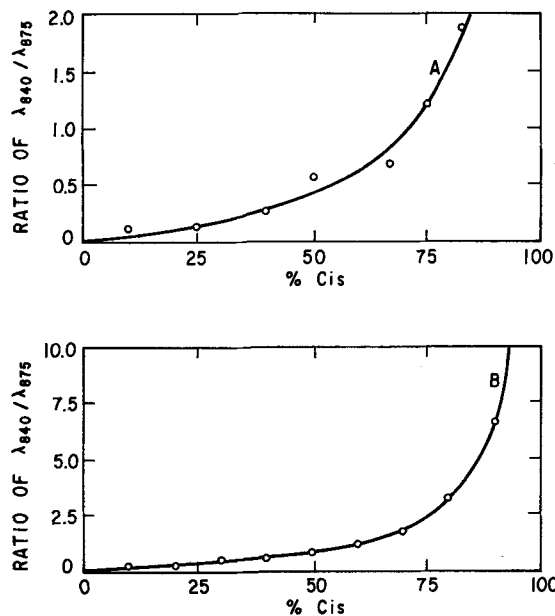


FIG. 3. Percent *cis*-component vs. absorbance ratio of 840 cm^{-1} to 875 cm^{-1} bands for A, 9,10-epiminooctadecane; B, potassium 9,10-epiminooctadecanoate.

with *cis*-9-octadecene and methyl oleate was determined by the use of a calibration curve. This curve was obtained by plotting the ratio of the 840 to 875 cm^{-1} band vs. percent *cis*-isomer on synthetic mixtures prepared from the pure *cis*- and *trans*-isomers. The curves obtained by this procedure are given in Figure 3. Absorbance ratios determined from experimental DCU products were found, by this method, to represent 60/40 *trans/cis* mixtures for both 9,10-epiminooctadecane and potassium 9,10-epiminooctadecanoate. These values are considered to be accurate to within $\pm 5\%$. As anticipated, reaction of a *trans*-olefin with N,N-dichlorourethan gives an isomer distribution identical with that obtained from a *cis*-olefin.

Previous workers have found (3) that the ring closure of *threo*-iodocarbamates to *cis*-aziridines occurs readily with methanolic potassium hydroxide while the *erythro*-isomers do not cyclize nearly as well to the corresponding *trans*-aziridines. This difference in behavior has been ascribed to a preference for dehydrohalogenation in *erythro*-iodocarbamates because of assumed steric requirements in the transition state leading to aziridine formation. However, the results obtained in the present investigation would seem to indicate that this steric inhibition toward ring closure to *trans*-aziridines is not the major factor in determining the yields of aziridine compounds. It has been demonstrated above that the DCU method gives predominately the *trans*-aziridine isomer from both *cis*-9-octadecene and methyl oleate. The present data would seem to indicate that the ring closure of *erythro*- β -chlorocarbamates to aziridines occurs more readily than the ring closure of the corresponding *erythro*- β -iodocarbamates. Since the transition state in going from β -halocarbamate to aziridine is essentially the same for both derivatives, the poor yields obtained from the iodocarbamate precursors cannot be solely attributed to a steric effect as previously suggested (3).

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