Synthesis of Fatty Acid Derivatives Containing an Internal Aziridine Group[1]

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Fatty acid derivatives containing an internal aziridine group were prepared by reaction of base with methyl iodocarbamates obtained by addition of iodine isocyanate to a fatty acid derivative followed by reaction with methanol. Aziridines prepared were potassium *cis*-9,10-aziridinooctadecanoate, *cis*- and *trans*-9,10-aziridinooctadecan-1-ol, and *cis*- and *trans*-9,10-aziridinooctadecane. The *cis*-aziridines have melting points 10–17° higher than the corresponding *trans* isomers and both isomers melt higher than the corresponding oxiranes. Infrared spectra of *cis*-aziridines show a strong band at about 850–855 cm^{-1}, while the *trans* isomers have a similar band at about 880–890 cm^{-1}. *threo*-Iodocarbamates (from *cis*-unsaturated compounds) undergo ring closure with base more readily than the corresponding *erythro*-iodocarbamates (from *trans*-unsaturated compounds) and yield *cis*-aziridines. Little, if any, azirdine can be obtained by reaction of base with *erythro*-iodocarbamates unless water is present. These are the first reported examples of fatty acid derivatives containing an internal aziridine group.

The use of the iodine isocyanate addition reaction to olefins to prepare aziridines was first demonstrated by Drefahl and Ponsold[4] who prepared an aziridine from tetralin. Hassner and Heathcock,[5-9] who studied this reaction extensively, added iodine isocyanate to 2-cholestene, cyclohexene, 1,2-dihydronaphthalene, indene, and styrene, converted the resulting *trans* adducts to the corresponding methyl iodocarbamates, and then effected ring closure to the corresponding aziridines with alcoholic potassium hydroxide. Ring closure was shown[8] to proceed with inversion *via* a N-carbalkoxy aziridine intermediate. Since initial addition of iodine isocyanate proceeds in a *trans* manner,[4,6] the final aziridine has the same geometry as that of the starting unsaturated compound. Since all the compounds studied by earlier investigators were either *cis* or terminal olefins, the sequence would be *cis* olefin → *threo*-iodoisocyanate → *threo*-iodocarbamate → *cis*-aziridine.

We have now extended these studies to the *erythro*-iodocarbamates derived from *trans* olefins and have also prepared the first examples of long-chain fatty acid derivatives containing an internal aziridine group.

Experimental Section

Methyl oleate (methyl *cis*-9-octadecenoate) was prepared by vacuum distillation of the methyl ester of a commercial oleic acid (Emery 3528-R); glpc anslysis showed the fractions used to be over 99% pure methyl oleate. A sample of pure (99.9+%) methyl oleate was purchased from Applied Science Labs, State College, Pa.

Elaidic acid (*trans*-9-octadecenoic acid) was prepared by isomerizing oleic acid with selenium[10] or nitrogen oxides.[11] Conversion to the methyl ester was effected in the usual manner; glpc analysis showed the methyl ester to be over 99% pure. Pure oleyl alcohol (9-octadecen-1-ol) was prepared by vacuum distillation of a commercial material (Adol 90, Archer, Daniels, Midland Corp.). This was shown to be pure by glpc analysis. Pure elaidyl alcohol (9-octadecen-1-ol) was prepared by isomerization of oleyl alcohol[11] followed by recrystallization from acetone. Purity was assayed by glpc. *cis*- and *trans*-9-octadecene were prepared from oleyl and elaidyl alcohol, respectively, by reduction of the corresponding tosylates with lithium aluminum hydride.[12] After recrystallization from petroleum ether (bp 30–60°), these were shown to be pure by glpc analysis. All other olefins studied were obtained from Phillips Petroleum Co. or Columbia Organic Chemicals. The silver cyanate was obtained from Eastman Organic Chemicals. Iodine (triply sublimed) was obtained from Fisher or Baker. All other chemicals were of reagent grade or better.

Infrared spectra were obtained on Nujol mulls using a Perkin-Elmer Infracord 137 with NaCl optics. Glpc analyses were run on a F & M Model 500 chromatograph using a thermal conductivity cell. The columns used included Carbowax 20 M, ethylene glycol succinate, and butanediol succinate. Elemental analyses were obtained from Microanalysis, Inc., Wilmington, Del.

A. Potassium *cis*-9,10-Aziridinooctadecanoate.—Pure methyl oleate (Applied Science Labs) (0.337 mole, 100.0 g) was converted to the *threo*-9(10),10(9)-iodoisocyanate by treatment with iodine (0.370 mole, 93.0 g) and silver cyanate (0.493 mole, 73.9 g) in ether (500 ml) at −5° for several hours (occasionally overnight) and then converted to methyl 9(10)-iodo-10(9)-(methylcarbamoyl) octadecanoate by refluxing for 1 hr with methanol (300 ml), after filtering off the silver salts. Potassium hydroxide (2.17 moles, 121.8 g) was added; the solution was refluxed overnight, filtered to remove an inorganic precipitate (probably potassium carbonate and potassium iodide), was cooled to 2°, and the product was collected by vacuum filtration. Crude yield was 110 g (97% of theory) of potassium *cis*-9,10-aziridinooctadecanoate. This material was recrystallized twice from methanol to give a pure product, mp 242–245°. In another preparation, the crude product was isolated by salting out of an aqueous solution with potassium chloride.

Anal. Calcd for $C_{18}H_{34}NO_2K$: C, 64.43; H, 10.21; N, 4.17. Found: C, 64.53; H, 10.34; N, 4.37.

The infrared spectrum of potassium *cis*-9,10-aziridinooctadecanoate showed bands at 1580 (COO^-), 3200 (NH), and 855 cm^{-1} (about as intense as the band at 3200 cm^{-1}). This latter band is tentatively assigned to the *cis*-aziridine ring. Neutralization of this salt to pH 7.5 with hydrochloric acid shifted the NH band to 3450 cm^{-1} and the 855-cm^1 band vanished completely. There was also a band at 1710 cm^{-1} (–COOH) in the neutralized sample. A sample of this aziridine was analyzed by Dr. G. Maerker (Eastern Regional Research Labs, U. S. D. A., Wyndmoor, Pa.) using a titration procedure which is to be published. The compound was reported to be 100.3% pure. The methyl iodocarbamate prepared from methyl oleate could not be ring closed to the aziridine using sodium bicarbonate as the base.

B. *cis*-9,10-Aziridinooctadecan-1-ol.—Oleyl alcohol (0.10 mole, 26.8 g) in ether (500 ml) was treated as previously described with iodine isocyanate (from iodine (0.103 mole, 26.0 g)

(1) Pseudohalogens. IV. For part III, see S. Rosen and D. Swern, *Anal. Chem.*, **38**, 1392 (1966). Presented in part at the Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1966. The authors are grateful to the U. S. Public Health Service for partial support of this work under Research Grants CA-07803 and CA-07174 of the National Cancer Institute.

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(4) G. Drefahl and K. Ponsold, *Chem. Ber.*, **93**, 519 (1960); G. Drefahl, K. Ponsold, and G. Köllner, *J. Prakt. Chem.*, **23**, 136 (1964).

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(6) A. Hassner and C. C. Heathcock, *ibid.*, 1125 (1964).

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(8) A. Hassner and C. C. Heathcock, *J. Org. Chem.*, **29**, 3640 (1964).

(9) A. Hassner and C. C. Heathcock, *ibid.*, **30**, 1748 (1965); A. Hassner, M. E. Lorber, and C. Heathcock, *ibid.*, **32**, 540 (1967).

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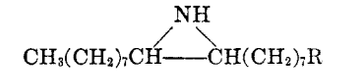
(12) M. E. Dyen, H. C. Hamann, and D. Swern, *ibid.*, **43**, 431 (1966).

TABLE I

SUMMARY OF AZIRIDINES PREPARED IN THIS STUDY



Isomer	R	Starting material	Yields,[a] %	Mp, °C	Infrared absorpn, aziridine ring,[b] cm^{-1}
cis	COOK	Methyl oleate	51–97[c]	242–245	855
cis	CH_2OH	Oleyl alcohol	70[c]	71.5–72.5	849
trans	CH_2OH	Elaidyl alcohol	53–58[d]	61.0–62.0	885
cis	CH_3	*cis*-9-Octadecene	47[e]	65–66	850
trans	CH_3	*trans*-9-Octadecene	19[e]	48–50	885

[a] Based on iodocarbamate. [b] Tentative assignment. For additional examples see G. Swift and D. Swern, *J. Org. Chem.*, **32**, 511 (1967). [c] Ring closure in essentially anhydrous methanol. [d] Ring closure in 80% methanol, 20% water. [e] Ring closure in 92% methanol, 8% water.

and silver cyanate (0.133 mole, 20.0 g)) to form the 9,10-vicinal iodoisocyanate which was then converted to the corresponding methyl iodocarbamate by refluxing for 2 hr with 200 ml of methanol. After removal of the silver salts and solvent and washing with aqueous sodium sulfite to remove traces of iodine, 35.9 g (77% of theory) of crude *threo*-9(10)-iodo-10(9)-(methylcarbamoyl)octadecan-1-ol was isolated as a pale yellow oil. The infrared spectrum showed bands at 3350 and 1520 (NH), 3480 (OH), and 1720 cm^{-1} (C=O). Ring closure was effected without further purification by treating it (0.037 mole, 17.3 g) with potassum hydroxide (0.260 mole, 14.6 g) in methanol (260 ml) and refluxing overnight. The solvent was then concentrated to about 50 ml and cooled to 2°. The resulting precipitate was filtered, transferred to a beaker, and washed with warm (75°) water to remove any inorganic salts. After vacuum drying, 9.5 g (91% of theory) of crude, yellow aziridine, mp 60.5–62.5°, was obtained. This was recrystallized three times from acetone to give pure *cis*-9,10-aziridinooctadecan-1-ol, a white solid, mp 71.5–72.5°.

Anal. Calcd for $C_{18}H_{37}NO$: C, 76.26; H, 13.16; N, 4.94. Found: C, 76.79; H, 13.09; N, 4.93.

The infrared spectrum of this new aziridine showed bands at 3400 (OH), 3200 (NH), and 849 cm^{-1}. This latter band is assigned to the *cis*-aziridine ring. Attempts to ring close *threo*-9(10)-iodo-10(9)-(methylcarbamoyl)octadecan-1-ol with triethyl amine were unsuccessful and apparently led to dehydrohalogenation.

C. *trans*-9,10-Aziridinooctadecan-1-ol.—*erythro*-9(10)-Iodo-10(9)-(methylcarbamoyl)-octadecan-1-ol was prepared from elaidyl alcohol in a manner similar to that described above for the *threo* isomer. In this case, conversion to the carbamate was best effected by stirring the iodoisocyanate overnight at room temperature with methanol. (With the *erythro* isomer, refluxing with methanol was avoided owing to side reactions which led, partially, to oxazolidone formation. These side reactions are being investigated further.) The infrared spectrum showed bands at 3450 (OH), 3350 and 1530 (NH), and 1750 cm^{-1} (C=O).

The aziridine was prepared by refluxing *erythro*-9(10)-iodo-10(9)-(methylcarbamoyl)octadecan-1-ol (0.023 mole, 10.8 g) with potassium hydroxide (0.160 mole, 9.0 g) in a solvent consisting of methanol (260 ml) and water (20 ml) for 2 hr. The solution was then evaporated to dryness and extracted with petroleum ether which was then cooled to 2°. A pale yellow solid (3.8 g, 58% yield) was isolated and recrystallized from petroleum ether to give a white solid, mp 57–59°. Further recrystallization from methanol and petroleum ether gave an analytically pure, white product, mp 61.0–62.0°.

Anal. Calcd for $C_{18}H_{36}NO$: C, 76.26; H, 13.16; N, 4.94. Found: C, 76.22; H, 12.98; N, 5.02.

The infrared spectrum of *trans*-9,10-aziridinooctadecan-1-ol showed bands at 3250 (OH), 3150 (NH), and 885 cm^{-1}. This latter band is tentatively assigned to the *trans*-aziridine group.

The yield of this reaction could be increased to over 95 (crude) or 55% (once recrystallized) by conducting the ring-closure step in a solvent system of 80:20 methanol–water. When less than 1% water was present, however, no aziridine could be isolated. Similarly, attempts to effect ring closure with potassium *t*-butoxide in *t*-butyl alcohol failed to produce any aziridine. In this case, infrared spectra indicated that dehydrohalogenation had occurred.

D. *cis*-9,10-Aziridinooctadecane.—*cis*-9-Octadecene (0.024 mole, 6.0 g) was converted to the *threo*-iodoisocyanate in the manner described above using iodine (6.0 g) and silver cyanate (4.3 g) in ether solution (150 ml). After 5 hr at 0°, the solution was warmed to room temperature, filtered, and the ether evaporated. The sample was dissolved in methanol (300 ml) and refluxed 2 hr. Potassium hydroxide (0.107 mole, 6.0 g) dissolved in water (20 ml) was then added and refluxing was continued for 4 hr. The entire sample was then poured into an excess of water and the insoluble solid extracted with ether. After evaporation of the ether and recrystallization of the residue two times from petroleum ether, a white solid (3.0 g, 47% of theory) was obtained, mp 65–66°.

Anal. Calcd for $C_{18}H_{37}N$: C, 80.82; H, 13.94; N, 5.24. Found: C, 80.66; H, 13.90; N, 5.14.

The infrared spectrum of *cis*-9,10-aziridinooctadecane showed bands at 3150 (NH) and 850 cm^{-1}. This latter band is assigned to the *cis*-aziridine ring.

E. *trans*-9,10-Aziridinooctadecane.—The *erythro*-9-iodo-10-(methylcarbamoyl)octadecane was prepared from *trans*-9-octadecene (0.050 mole, 12.6 g) in the same manner as described for the *threo* isomer. In this case, ring closure was effected using potassium hydroxide (11.2 g, 0.20 mole) in a solvent system of 92:8 methanol–water. After 5-day refluxing, the solution was poured into an excess of water and the solid was extracted with ether. Recrystallization from petroleum ether gave an analytically pure, white solid, mp 48–50° (2.5 g, 18% of theory), of *trans*-9,10-aziridinooctadecane.

Anal. Calcd for $C_{18}H_{37}N$: C, 80.82; H, 13.94; N, 5.24. Found: C, 80.82; H, 13.94; N, 5.24.

The infrared spectrum of this aziridine showed bands at 3140 (NH) and 885 cm^{-1}. This latter band is assigned to the *trans*-aziridine ring.

Results

The properties of the five new aziridines prepared in this study are summarized in Table I. In all cases, the melting point of the *cis*-aziridine is 10–17° higher than of the corresponding *trans* isomer. A similar but smaller effect has been noted in the structurally similar oxiranes.[13]

Aziridines also melt higher than corresponding oxiranes.

The infrared spectra of *cis*- and *trans*-aziridines show one major difference. The *cis* isomers have a strong band at 850–860 cm^{-1} while the *trans* isomers show a band at 880–890 cm^{-1}. These bands, which are absent in the iodocarbamates, iodoisocyanates, and starting materials, may be due to a deformation[14] or vibration of the aziridine ring.

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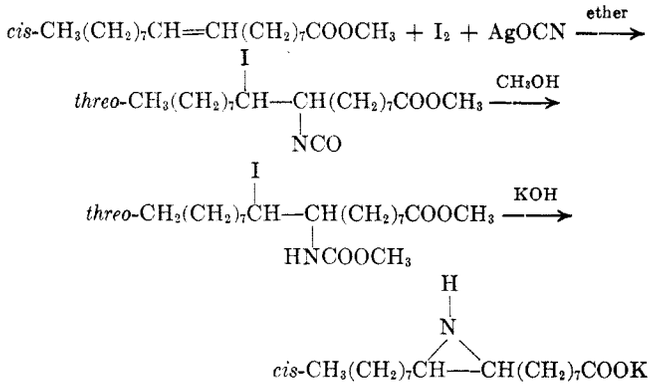
(14) W. J. Rabourn and W. L. Howard, *J. Org. Chem.*, **27**, 1039 (1962).

Discussion

The general procedure used in this study is illustrated in Scheme I for the conversion of methyl oleate to potassium *cis*-9,10-aziridinooctadecanoate.

SCHEME I



The addition of iodine isocyanate to olefins is known to proceed in a *trans* manner. Thus, a *threo* adduct is obtained from a *cis* olefin and an *erythro* adduct from a *trans* olefin. Conversion to the carbamate does not affect the stereochemistry.

The mechanism of the ring closure of vicinal iodocarbamate derivatives has been studied extensively by Hassner and Heathcock.[8] As noted earlier, all the compounds studied by these workers were prepared from terminal or cyclic olefins. Iodocarbamates prepared from cyclic olefins were all of the *trans* configuration.

Prior to this study, no studies had been made on the ring closure of the *threo* isomers of internally located, aliphatic, vicinal iodocarbamates, or on *erythro* isomers of any type. The difference in behavior of these two isomers is quite striking.

The *threo*-iodocarbamates from methyl oleate, oleyl alcohol, and *cis*-9-octadecene all ring close readily to the aziridine on treatment with methanolic potassium hydroxide. The ring closure occurred readily in essentially anhydrous methanol (less than 1% water) or even in systems containing appreciable amounts of water. When the water content was low, a precipitate, presumably potassium carbonate, formed almost immediately upon adding the base to the solution of the iodocarbamate.

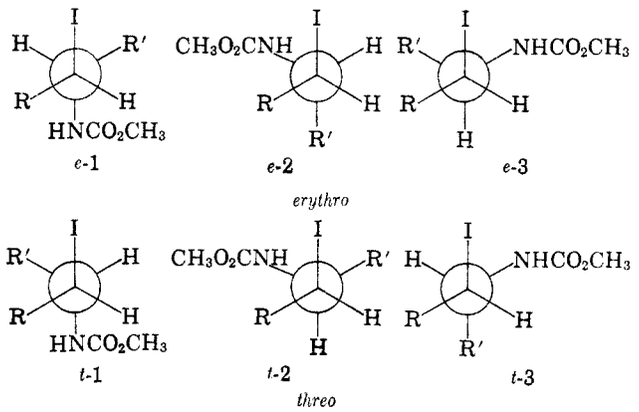
Ring closure could not be effected using sodium bicarbonate or triethylamine. Similar results have been reported by Hassner and Heathcock.[8] Spectra of the products of the reaction with triethylamine were consistent with the occurrence of a *trans* dehydrohalogenation, but this reaction was not investigated further.

The *erythro* isomer did not ring close nearly so well as the *threo* isomer. In essentially anhydrous methanolic systems (less than 1% water), no aziridine could be isolated from the reaction mixture. A similar effect occurred in anhydrous isopropyl alcohol (less than 1% water). When the system contained as little as 6% water (balance methanol), the yield of aziridine rose to about 20%. When 80% methanol–20% water systems were used, the yield was around 50%. The *erythro* isomer from elaidyl alcohol did not ring close on treatment with potassium *t*-butoxide. Again, infrared spectra suggested that *trans* dehydrohalogenation had occurred.

An attempt has been made to explain the difference between *threo*- and *erythro*-iodocarbamates on treatment with base, using conformational analysis and examining models of *threo* and *erythro* isomers.

Three staggered conformations can be written for each isomer (Chart I). With each isomer, the most

CHART I



stable conformer should be the one in which the larger groups are farthest apart. In our cases, the R groups contain at least eight carbon atoms and are quite bulky. Although it does not contain many atoms, the methyl carbamoyl group is also bulky. This is due, to a great extent, to the to the carbonyl group. Iodine is larger than the hydrogens but considerably smaller than the carbamoyl or R groups.

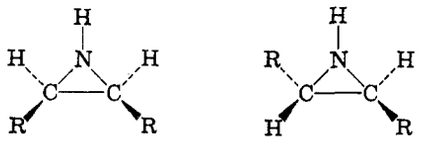
The most stable conformation in the *erythro* case would be *e*-1, the staggered conformation. From models, structure *e*-2 appears to be the least stable since the carbamoyl group interacts readily with both alkyl groups in this conformation. In *e*-3, the carbamoyl group interacts with one alkyl group and iodine, but models show that the molecule is slightly less crowded.

In the *threo* configuration, all three conformers are more crowded than in the *erythro* case and no conformation appears nearly as uncrowded as *e*-2. Conformer *t*-2, with R and R′ as far apart as possible, is slightly less crowded than *t*-3, while *t*-1 appears more crowded than the others.

The choice of conformers *e*-1 and *t*-2 as the most stable *erythro*- and *threo*-iodocarbamate isomers corresponds exactly to the conclusion reached by Hassner and Heathcock[6] for the *erythro*- and *threo*-iodoisocyanate isomers obtained from the 2-butenes.

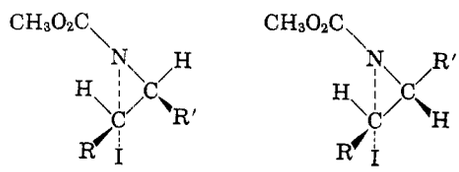
Ring closure of iodocarbamates to aziridines proceeds in a *trans* manner. This reaction must then occur with conformers *e*-1 and *t*-1. Since conformer *e*-1 is the most stable *erythro* isomer and conformer *t*-1 is the least stable *threo* isomer, we might expect the *erythro* isomer to ring close much better than the *threo*. In actual fact, the opposite situation prevails; the *threo* isomer ring closes to the aziridine much more readily. Clearly, the explanation for this phenomenon cannot lie only in considerations of the ground states.

Aziridines from ring closure of *threo* isomers would have the *cis* configuration and those from the *erythro* isomers the *trans* configuration.



cis (from *threo*) *trans* (from *erythro*)

According to the mechanism proposed by Hassner and Heathcock,[8] ring closure involves an internal nucleophilic displacement of the iodine by the negatively charged nitrogen atom (the proton is removed by the base). The transition state that should arise in this displacement is not the same for each isomer.



TS-*t* (from *threo*) TS-*e* (from *erythro*)

The transition state from the *threo* isomer (TS-*t*) is less crowded than the transition state from the *erythro* isomer (TS-*e*). It is immediately obvious from models that the carbamate group will interact with both alkyl groups in the TS-*e* state and there is no way to avoid these interactions. The TS-*t* state can readily avoid these interactions and should, therefore, have a lower energy content.

The more reasonable side reactions that can be envisioned for *erythro*-iodocarbamates on reaction with base (SN2 displacement of iodine, elimination of HI, and ring closure to an oxazolidone) are inconsistent with the observed results. One major possibility remains, however; namely, the aziridine actually forms and isomerizes to another compound. Most aziridines are completely stable under basic conditions, but Heine, Kenyon, and Johnson[15] have observed that certain types of aziridines can undergo isomerization with nucleophiles, such as iodide or thiocyanate ion. These aziridines contain a carbonyl on the nitrogen atom. The reaction product is the 2-oxazoline.

Heine, *et al.*,[15a] reported infrared bands at 1081, 1073, 1019, 964, 954, 908, 877, and 858 cm^{-1} for 2-nitrophenyl-4-ethyl-2-oxazoline. They reported no bands in the 1640–1690-cm^{-1} region where C=N might be expected to absorb. The side products encountered in the present study showed bands at 1080, 1020, 958, 890, and 868 cm^{-1}. Elemental analysis did not agree with that required for the 2-oxazoline, but were consistent with calculated values for a mixture of 2-oxazoline and aziridine. Thus, a reasonable side reaction appears to be the isomerization of the N-carbomethoxyaziridine to a 2-methoxy-2-oxazoline derivative, although we have not yet demonstrated this reaction.[16]

Recently, Heine, King, and Portland[17] observed that *threo*-N-1,2-diphenyl-2-chloroethyl-*p*-nitrobenzamide undergoes ring closure to the *cis*-aroylaziridine on treatment with alcoholic sodium ethoxide, but the corresponding *erythro*-N-1,2,-diphenyl-2-chloroethyl-*p*-nitrobenzamide undergoes ring closure to the oxazoline under these conditions.

These considerations suggest that the *erythro*-iodocarbamates ring close to the N-carbomethoxyaziridines but then decarboxylate with great difficulty. The fact that the yield of aziridine increases markedly in systems containing appreciable amounts of water is also consistent with this hypothesis. In anhydrous methanolic potassium hydroxide solutions, the basic species is primarily methoxide ion. When an appreciable amount of water is present, the main basic species is hydroxide. Since hydroxide is a much smaller species than methoxide, it can more readily penetrate the hindering alkyl groups and effect decarboxylation. In the competing reaction, the iodide ion probably attacks at the aziridine carbon causing ring opening.

Experimentally, decarboxylation can be favored by increasing the hydroxide concentration; the iodide concentration is limited since it arises solely from the initial ring closure to the N-carbomethoxyaziridine. The evidence is consistent with the conclusion that *erythro* isomers form N-carbomethoxyaziridines even in anhydrous media. The initial ring closure gives an intermediate which must be decarboxylated. The *cis*- and *trans*-N-carbomethoxyaziridines, derived from *threo*- and *erythro*-iodocarbamates, respectively, do not undergo this step with equal ease. This difference is due mainly to steric factors.

Registry No.—Potassium *cis*-9,10-aziridinooctadecanoate, 13865-83-3; *cis*-9,10-aziridinooctadecan-1-ol, 13865-82-2; *trans*-9,10-aziridinooctadecan-1-ol, 13866-33-6; *cis*-9,10-aziridinooctadecane, 13866-34-7; *trans*-9,10-aziridinooctadecane, 13864-72-7; *erythro*-9(10)-iodo-10(9)-(methylcarbamoyl)octadecan-1-ol, 13864-73-8; *threo*-9(10)-iodo-10(9)-(methylcarbamoyl)octadecan-1-ol, 13865-17-3.

(15) (a) H. W. Heine, W. G. Kenyon, and E. M. Johnson, *J. Am. Chem. Soc.*, **83**, 2570 (1961); (b) H. W. Heine, *Angew. Chem. Intern. Ed. Engl.*, **1**, 528 (1962).

(16) G. E. Ham, Abstracts of 147th National Meeting of the American Chemical Society, Philadelphia, Pa., 1964, p 16N.

(17) H. W. Heine, D. C. King, and L. A. Portland, *J. Org. Chem.*, **31**, 2662 (1966).