p-Nitrocarbobenzoxy-L-allylglycyl-L-leucine Benzyl Ester.—To a solution of 1.176 g. (4 mmoles) of *p*-nitrocarbobenzoxy-L-allylglycine, 1.892 g. of L-leucine benzyl ester *p*-tosylate,[8] and 0.35 ml. of triethylamine in 40 ml. methylene chloride was added 0.940 g. of dicyclohexylcarbodiimide. The mixture was shaken overnight at room temperature; 0.5 ml. of acetic acid was added. The solvent was evaporated from the filtered solutions and the residue taken up in 100 ml. of ethyl acetate. The extract was washed with 0.5 *N* hydrochloric acid, water, saturated sodium hydrogen carbonate, and water. Concentration to 20 ml. yielded 1.57 g. (79%) of crude product, m.p. 140–142°. Recrystallization from methylene chloride and ligroin yielded 1.34 g., m.p. 146–148°.

Anal. Calcd. for $C_{26}H_{31}N_3O_7$: C, 62.76; H, 6.28; N, 8.45. Found: C, 62.84; H, 6.43; N, 8.98.

p-Nitrocarbobenzoxy-L-allylglycyl-L-leucine.—This compound could be prepared either by saponification of the benzyl ester (74% yield, m.p. 70–73°) or by direct coupling. To a solution of 1.176 g. of *p*-nitrocarbobenzoxy-L-allylglycine and 0.55 ml. of triethylamine in 12 ml. of tetrahydrofuran at −5° was added 0.38 ml. of ethylchloroformate. After 25 min., 576 mg. of L-leucine in 2.2 ml. of 2 *N* sodium hydroxide was added; the mixture was held at room temperature overnight. After evaporation of the solvent and addition of 15 ml. of water, the solution was extracted with ethyl acetate and the extract was discarded. The aqueous portion was acidified and extracted with ethyl acetate, the extract was washed with water and dried over magnesium sulfate, and the solvent was evaporated. After two crystallizations from toluene, 0.96 g. (59%) of product was obtained, m.p. 69–73°.

Anal. Calcd. for $C_{19}H_{25}N_3O_7$: C, 56.01; H, 6.19; N, 10.31; neut. equiv., 407. Found: C, 56.28; H, 6.21; N, 10.55; neut. equiv., 410.

Oxidation Procedure.—To 18 ml. of 0.115 *M* sodium metaperiodate at 20° was added 0.5 mmole of olefin; the pH was adjusted to 7.5 with 0.5 *M* sodium carbonate. The addition of 2 ml. of 0.01 *M* potassium permanganate initiates the oxidation. Usually, the reaction was stopped after 1 hr. by acidification to pH 2. In some experiments, the pH of the mixture was readjusted to pH 7.5 after the first hour and a second increment of 0.01 *M* potassium permanganate was added. However, the effect of this treatment on the yields of oxidation products was slight.

The aspartic acid derivatives have been isolated either by extraction with ethyl acetate or by crystallization from the concentrated reaction mixture. For the latter procedure, the cooled reaction mixture was titrated with 1 *M* sodium metabisulfite until a colorless solution was obtained, excess acid was destroyed with solid sodium hydrogen carbonate, the solution was concentrated under reduced pressure, and the pH was readjusted to pH 2. Storage of the mixture overnight at 4° yielded crystalline product.

Oxidation of 0.5 mmole of carbobenzoxy-L-allylglycine[6] gave carbobenzoxy-L-aspartic acid in 78% yield when extracted into ethyl acetate while *p*-nitrocarbobenzoxy-L-allylglycine was converted to *p*-nitrocarbobenzoxy-L-aspartic acid in 95% yield when isolated from the aqueous phase after sodium metabisulfite treatment.

Conversion of *p*-Nitrocarbobenzoxy-L-allylglycyl-L-leucine to α-L-Aspartyl-L-leucine.—The acidified oxidation mixture from 407 mg. of *p*-nitrocarbobenzoxy-L-allylglycyl-L-leucine was extracted twice with 30-ml. portions of ethyl acetate. The combined extracts were washed with water and dried over magnesium sulfate; the solvent was evaporated at reduced pressure. The residue, which was noncrystalline, was dissolved in 5 ml. of acetic acid and hydrogenated at room temperature and 1 atm. in the presence of 50 mg. of palladium black for 2 hr. Filtration, evaporation of most of the acetic acid, and addition of ether yielded 158 mg. (64%) of crystalline α-L-aspartyl-L-leucine, recrystallized from aqueous acetone for analysis.

Anal. Calcd. for $C_{10}H_{18}N_2O_5$: N, 11.38; neut. equiv., 246. Found: N, 11.44; neut. equiv. (titrated to pH 6.5), 251.

The material prepared by the above procedure and α-L-aspartyl-L-leucine prepared by the method of Bryant, *et al.*,[3] were indistinguishable; their infrared spectra as potassium bromide pellets were completely superimposable; each gave only one ninhydrin-positive spot after chromatography on Whatman No. I paper in *n*-butanol–acetic acid–water, 4:1:5 (v./v.), R_f 0.59 (Bryant, *et al.*,[3] reported R_f 0.60); $[\alpha]^{25}D$ −9.8° (*c* 3.3, 0.1 *N* hydrochloric acid) [Bryant, *et al.*,[3] reported $[\alpha]^{26}D$ −9.7° (*c* 3.42, 0.1 *N* hydrochloric acid)].

Quaternization of Aziridines. Evidence for the Monomeric State of Products[1]

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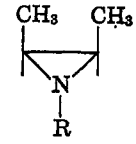
In the synthesis of a series of β-substituted amines, quaternary aziridinium salts were considered as potentially convenient alkylating agents. Protonated aziridines of varying stability have been isolated and described,[3–5] but there is no comparable description of exhaustively alkylated species prepared directly from aziridines. The exceptional reactivity of the quaternary salts toward nucleophiles has virtually restricted salt preparation to those exceptional instances in which the anion and solvent have low nucleophilicity,[6] the carbon skeleton has special steric features,[7,8] or (in one instance) a stable complex forms.[9] Quite recently, however, Bottini and VanEtten investigated the quaternization of *cis*- and *trans*-1,2-dimethyl-3-isopropylaziridine and demonstrated the formation of stable monomeric iodides.[10]

When *cis*- or *trans*-1,2,3-trimethylaziridine (**1a**) was treated with methyl iodide, a white crystalline solid formed rapidly. The product was found to de-



1a, R = CH_3
b, R = CH_3CH_2

compose readily on attempted recrystallization. Similar observations were made with isomers of 1-ethyl-2,3-dimethylaziridine (**1b**). If an analogy were made with the hydrochlorides of aziridines, it could not be assumed that the materials were monomeric species, for these protonated compounds polymerized vigorously at room temperature.[3,5] The instability of the quaternary salts to procedures used for crystallization, however, indicated a structural feature other than an unstrained, quaternized nitrogen atom of the piperazine type **4**. Such piperazinium salt formation has been observed[4,11] in the spontaneous dimerization of nitrogen mustards.

(1) Supported in part by Cancer Research Funds of the University of California and Grant GM 8185 from the National Institutes of Health, U. S. Public Health Service.

(2) Taken in part from the Ph.D. Thesis of R. D. Clark.

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(6) N. J. Leonard and K. Jann, *J. Am. Chem. Soc.*, **82**, 6418 (1960).

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(10) A. T. Bottini and R. L. VanEtten, *J. Org. Chem.*, **30**, 575 (1965). We are grateful to Professor Bottini for informing us of these results prior to publication and for extensive discussion on the monomeric *vs.* dimeric nature of the products.

(11) P. D. Bartlett, S. D. Ross, and C. G. Swain, *J. Am. Chem. Soc.*, **69**, 2971 (1947).

When the methiodides of 1 were treated with silver 2,4,6-trinitrobenzenesulfonate, stable salts were obtained. In an attempt to ascertain the state of the compounds, molecular weights were determined by vapor pressure osmometry. With acetonitrile as solvent and benzil as a standard, the compounds appeared to be dimeric. In ethanol, with biphenyl as a standard, the results were equivocal. Table I presents a summary of data observed for species as related to the two considered states of association.

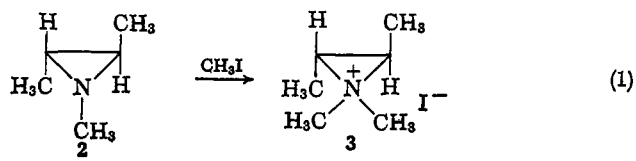
TABLE I

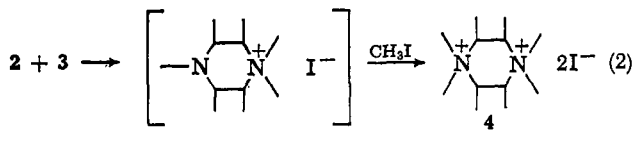
EQUIVALENT WEIGHTS OF QUATERNARY AZIRIDINIUM SALTS DETERMINED BY OSMOMETRY[a]

	Equiv. wt., calcd. for		Equiv. wt., found in	
Aziridinium salt; anion	Dimer	Monomer	Acetonitrile	Ethanol
trans-1,1,2,3-Tetramethyl; iodide	141	106	157[b] 145[c]	138[c]
trans-1,1,2,3-Tetramethyl; TNBS[d]	252	189	251[b] 233[c]	...
trans-1-Ethyl-1,2,3-trimethyl; iodide	153	114	153[b] 142[c]	137[c]
trans-1-Ethyl-1,2,3-trimethyl; TNBS[d]	261	196	264[b] 245[c]	...

[a] Determined with a Mechrolab Model 301A osmometer, values based on assumption of complete ion dissociation. [b] Benzil as reference standard. [c] Biphenyl as reference standard. [d] 2,4,6-Trinitrobenzenesulfonate anion.

In the absence of definitive data concerning the monomeric or dimeric states of the quaternized aziridines, the use of optically active 1,2,3-trimethylaziridine (2) was considered. The alkylation of the active compound, eq. 1, would lead to an optically active monomer 3 in the absence of racemization. If the reaction proceeded beyond the monomeric state in the presence of excess alkylating agent, eq. 2, the dimeric material should have the *meso* structure shown by structure 4. If the configuration were other than that of 4, it would have to have resulted from racemization or *cis*-opening of the immonium ring. Only in the latter instance could it be possible to obtain an optically active dimeric product. By analogy with other ring-opening reactions such as acid-catalyzed reactions of epoxides, there is evidence for retention of configuration as a specific process only in those instances in which substituents are arranged for neighboring group participation.[12]





(12) R. E. Parker and N. S. Isaacs, *Chem Rev.*, **59**, 737 (1959).

When the optically active aziridine was used, it was found to form an iodide with a moderately high specific rotation: $[\alpha]^{22}D$ +31.55° (0.445 *F* in ethanol). The assigned structure then must be that of the monomer 3. In order to provide further confirmation, the reaction of 3 with excess ammonia or dimethylamine was followed polarimetrically. Each reaction was first order in aziridinium salt (Table II) through at least three half-lives of material.

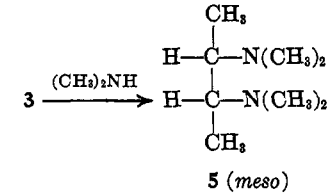
TABLE II

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE REACTION OF 1,1,2,3-TETRAMETHYLAZIRIDINIUM IODIDE WITH AMINES[a]

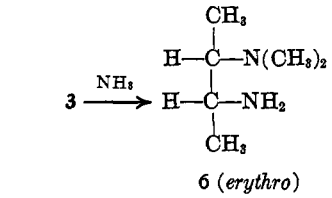
Reactant amine	Amine concn., *F*	Rate constant, min.$^{-1}$	Half-life, min.
NH_3	4.74	0.0237	29.2
		0.0232	29.8
$(CH_3)_2NH$	3.32	0.0679	10.1
		0.0668	10.3

[a] Followed polarimetrically at 400 mμ and 25°.

The reaction with dimethylamine, eq. 3, yielded an optically inactive product, the bisdimethylaminobutane (5) with a specific rotation of $[\alpha]^{25}_{400}$ 0.00 ± 0.01°. The ammonia reaction, on the other hand, yielded an optically active product (6, eq. 4) with a specific rotation of $[\alpha]^{25}_{400}$ 16 ± 2°.



5 (*meso*)



6 (*erythro*)

The mere fact that the alkylation product of an aziridine reacted readily with a nucleophile verifies the conclusion that the three-membered ring remained intact, for the dimeric product, a derivative of piperazine, should not have been as easily susceptible to attack by a nucleophilic species. The retention of optical activity in the formation of 6 excluded racemization as a principal feature of the process, and the formation of the inactive compound would characterize it as predominantly *meso*.

Experimental[13]

N-Alkyl-2,3-Dimethylaziridines.—The aziridines were prepared from the corresponding epoxides by the Wenker method[14] as applied by Ghirardelli and Lucas in the butene series.[15] Yields of products varied from 30 to 50%.

trans-**1,2,3-Trimethylaziridine.**—The compound was prepared from 25.8 g. (0.36 mole) of *trans*-2,3-epoxybutane: yield, 10.0 g., 33%; b.p. 71.0–71.2° (735 mm.); $n^{20}D$ 1.4045.

Anal. Calcd. for $C_5H_{11}N$: C, 70.53; H, 13.02. Found: C, 70.26; H, 13.20.

(13) Microanalyses were by C. F. Geiger, Ontario, Calif.
(14) H. Wenker, *J. Am. Chem. Soc.*, **57**, 2329 (1935).
(15) R. Ghirardelli and H. J. Lucas, *ibid.*, **79**, 734 (1957).

trans-**1-Isopropyl-2,3-dimethylaziridine.**—The compound was prepared from 12 g. (0.17 mole) of *trans*-2,3-epoxybutane: yield, 6 g., 31%; b.p. 102–102.5° (735 mm.); $n^{23.5}D$ 1.4019.

Anal. Calcd. for $C_7H_{15}N$: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.23; H, 13.22; N, 12.12.

trans-**1-Isopropyl-2,3-dimethylaziridinium 2,4,6-Trinitrobenzenesulfonate.**—The salt was prepared as a derivative of the aziridine by adding a 10% solution of the aziridine in acetonitrile to a solution of 2,4,6-trinitrobenzenesulfonic acid in the same solvent until a distinct red coloration appeared. The red color was discharged by the addition of a small amount of the acid. After the product was precipitated by the addition of ether, it was recrystallized twice from absolute ethanol; m.p. 211.5–212.5°.

Anal. Calcd. for $C_{13}H_{18}N_4O_9S$: C, 38.42; H, 4.46; N, 13.79. Found: C, 38.41; H, 4.26; N, 14.09.

trans-**1,1,2,3-Tetramethylaziridinium Iodide.**—The salt was prepared by adding 2.1 g. (0.025 mole) of *trans*-1,2,3-trimethylaziridine to 25 ml. of methyl iodide which had been cooled to about −50°. White crystals began to form immediately. After about 10 min., when the mixture had reached room temperature, the crystalline solid was removed by filtration and air dried; yield, 5.4 g., 96%. The compound melted with decomposition in the region of 135–150°.

Since the methiodide could not be recrystallized without excessive decomposition, it was converted to the 2,4,6-trinitrobenzenesulfonate salt. To 0.050 g. (0.00125 mole) of silver trinitrobenzenesulfonate in 15 ml. of acetonitrile was added 0.301 g. (0.00125 mole) of the aziridinium iodide. Silver iodide (0.27 g.) precipitated immediately. The product was precipitated by the addition of about 500 ml. of anhydrous ether and recrystallized from acetonitrile–ether. The product melted at 205–206° dec.

Anal. Calcd. for $C_{12}H_{16}N_4O_9S$: C, 36.73; H, 4.11; N, 14.28. Found: C, 36.88; H, 4.44; N, 13.98.

trans-**1,1,2,3-Tetramethylaziridinium 2,4,6-Trinitrobenzenesulfonate.**—In an alternate procedure for the preparation of the trinitrobenzenesulfonate, 1.0 g. (0.0025 mole) of trimethyloxonium trinitrobenzenesulfonate[16] in 15 ml. of acetonitrile was added to 0.21 g. (0.0025 mole) of *trans*-1,2,3-trimethylaziridine in 15 ml. of acetonitrile. The solution was allowed to stand for 15 min. before precipitation of the product by the addition of about 500 ml. of anhydrous ether. The yields in this and subsequent analogous reactions were nearly quantitative. The infrared spectrum and melting point of the salt were identical with those of the product formed from the quaternary iodide. A mixture melting point showed no depression.

cis-**1-Ethyl-1,2,3-trimethylaziridinium Iodide.**—The compound was prepared by a method analogous to that described for the *trans*-tetramethylaziridine. Methyl iodide was used as the alkylating agent for the N-ethylaziridine. The iodide salt again was unstable and could not be recrystallized; m.p. 116–128° dec.

cis-**1-Ethyl-1,2,3-trimethylaziridinium Bromide.**—The bromide was prepared from the reaction between *cis*-1-ethyl-2,3-dimethylaziridine and methyl bromide in which the latter was the solvent. The highly hygroscopic product was purified by sublimation; m.p. 134–138° dec.

Anal. Calcd. for $C_7H_{16}BrN$: C, 43.31; H, 8.33; Br, 41.17. Found: C, 43.31; H, 8.68; Br, 40.73.

trans-**1-Ethyl-1,2,3-trimethylaziridinium Iodide.**—The compound was prepared directly from the aziridine and methyl iodide. The product decomposed on attempted recrystallization. Nitrogen analysis (calcd., 5.81%; found, 5.74%) was satisfactory, but the compound was converted to the trinitrobenzenesulfonate for further characterization.

trans-**1-Ethyl-1,2,3-trimethylaziridinium 2,4,6-Trinitrobenzenesulfonate.**—The compound was prepared by the alternative routes described for the corresponding N,N-dimethyl derivative. Both routes yielded identical products; m.p. 212–214° dec.

Anal. Calcd. for $C_{13}H_{18}N_4O_9S$: C, 38.42; H, 4.46; N, 13.79. Found: C, 38.71; H, 4.78; N, 14.08.

Equivalent Weight Determination.—Measurements were carried out with a Mechrolab Model 301A vapor pressure osmometer. The solutions were between 0.04 and 0.06 *F*, assuming the molecular weight of the monomer. Standard curves were determined with benzil and biphenyl as the solute in acetonitrile or ethanol.

D(+)-**1,1,2,3-Tetramethylaziridinium Iodide.**—The optically active iodide was prepared in the manner described for the inactive salt. It was used directly for kinetic measurements because of its instability on attempted recrystallization. The corresponding trinitrobenzenesulfonate could not be utilized because it also reacted with the ammonia or dimethylamine to be used for ring opening. The specific rotation of the iodide, $[\alpha]^{22}D$ +31.55°, was determined in ethanol. There was no change of rotation with time in solution, so no reaction with solvent was apparent. Even so, it was impossible to reisolate the compound in purer form.

meso-**Bis-2,3-dimethylaminobutane.**—The compound was isolated from the reaction mixture used for kinetic measurements. The reaction solution consisted of 0.050 g. of D(+)-1,1,2,3-tetramethylaziridinium iodide dissolved in 2.00 ml. of 3.32 *M* aqueous dimethylamine. After the solution had stood for 2 hr. at 25°, it was saturated with potassium hydroxide and extracted with ether. The ether solution was dried over potassium hydroxide pellets. The introduction of hydrogen chloride to the supernatant ether solution precipitated a white solid which was crystallized successively from ethanol and 1-propanol and sublimed. Because of inconsistent melting point characteristics and long melting point range, the hydrochloride was converted to the trinitrobenzenesulfonate by the addition of 2,4,6-trinitrobenzenesulfonic acid to an ethanolic solution and precipitation with ether. The product was recrystallized from acetonitrile containing a small amount of water; m.p. 263–264° dec.

Anal. Calcd. for $C_{20}H_{26}N_8O_{18}S_2$: C, 32.88; H, 3.59; N, 15.34. Found: C, 32.85; H, 3.62; N, 15.09.

(2*S*:3*R*)-**2-Dimethylamino-3-aminobutane.**—The compound was isolated as the hydrochloride from the solution used for kinetic measurements. The technique was that described for the bisdimethylamino product. The hydrochloride was very hygroscopic, but it was converted to a stable, easily handled compound by the addition of 2,4,6-trinitrobenzenesulfonic acid to an ethanolic solution. The trinitrobenzenesulfonate was crystallized from nitromethane–ether; m.p. 255–258° dec.

Anal. Calcd. for $C_{18}H_{22}N_8O_{18}S_2$: C, 30.77; H, 3.16; N, 15.95. Found: C, 30.50; H, 3.39; N, 15.70.

Kinetic Measurements.—The reactions of ammonia and dimethylamine with the optically active aziridinium iodide were followed polarimetrically at 400 mμ, using a J. C. Rudolph and Sons manual spectropolarimeter with an oscilloscope for readout. The temperature of all runs was kept at 25.0°. The reaction mixtures were prepared at the operating temperature and placed into a thermostated, 10-cm. polarimeter tube of all glass construction except for quartz windows. Measurements were made to ±0.003° rotation through at least three half-lives of the optically active reactant. The optical activity of the reactant and its concentration in solution were used to estimate the optical activity of products. In the case of the bisdimethylaminobutane, the lack of optical activity was verified by noting the lack of optical rotation of its dihydrochloride.

(16) D. J. Pettitt and G. K. Helmkamp, *J. Org. Chem.*, **28**, 2932 (1963).

Preparation of Oxamide from Hydrogen Cyanide and Hydrogen Peroxide

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Attfield[1] in 1863 and Radziszewski[2] in 1885 reported that hydrogen cyanide and hydrogen peroxide react to form oxamide, $(CONH_2)_2$, but Rupp and Pfennig[3] found that carbon dioxide and ammonia also are produced. The reaction to produce oxamide may be written

$$2HCN + H_2O_2 \longrightarrow (CONH_2)_2$$

(1) Attfield, *J. Chem. Soc.*, **16**, 94 (1863).
(2) B. Radziszewski, *Ber.*, **18**, 355 (1885).
(3) E. Rupp and F. Pfennig, *Chem. Ztg.*, **34**, 322 (1910).