The second method of preparation proceeded *via* 1-chloro-2,2,3,3-tetramethylcyclopropane. This compound has been prepared in 67% yield from chlorocarbene and 2,3-dimethyl-2-butene.[33] In our hands, the yield was 43%.

The chlorotetramethylcyclopropane was converted to the lithium derivative in a manner identical with the preparation of cyclopropyllithium. This lithium derivative was treated with an excess of dicyclopropyl ketone. By this method, 2,2,3,3-tetramethyltricyclopropylmethanol was prepared in a 24% yield based on the chlorotetramethylcyclopropane.

2,3-cis-Dimethyltricyclopropylmethanol. The lithium derivative of 1-chloro-2,3-*cis*-dimethylcyclopropane[32] was prepared in the same manner as cyclopropyllithium. Treatment with excess dicyclopropyl ketone produced (after hydrolysis) the title alcohol in 50% yield based on the chloride, b.p. 72–74° (3.5 mm.).

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.9; H, 11.2. Found: C, 79.8; H, 11.7.

Attempts to observe the carbonium ion derived from this alcohol failed at 25°. In view of recent work,[12,14] it would probably be easily observable at −50°.

α,α′-Dideuteriotricyclopropylmethanol. 1,7-Dichloro-4-heptanone was prepared as described.[34] A mixture of 66 g. of the ketone, 80 g. of D_2O, and 10 g. of PCl_5 was heated and stirred for 20 hr. at 40–50°. The organic layer was separated and washed with water and aqueous Na_2CO_3. The n.m.r. spectrum indicated that the α-hydrogens were 86% deuterated. The process was repeated to increase the deuteration to 93%.

A mixture of 150 ml. of 20% aqueous NaOH and 40 g. of 3,3,5,5-tetradeuterio-1,7-dichloro-4-heptanone was refluxed for 30 min. with vigorous stirring. An additional 100 ml. of water was added and the ketone was separated by steam distillation. Despite this treatment, little deuterium was lost. After ether extraction and Na_2SO_4 drying, dicyclopropyl ketone was obtained in 86% yield and it was 75% deuterated as calculated from n.m.r. band areas.

The addition of α,α′-dideuteriodicyclopropyl ketone to excess cyclopropyllithium produced α,α′-dideuteriotricyclopropylmethanol. The n.m.r. spectrum showed the expected reduction of the band areas of the α-hydrogen to about 50% of their normal value.

Acknowledgment. We are grateful to the National Science Foundation for funds to support fellowships for J. L. and J. T., a cooperative fellowship for D. L., and funds to aid in the purchase of a Varian A-60 spectrometer. We are also grateful to the Petroleum Research Fund of the American Chemical Society for funds to support a fellowship for J. L.

(33) G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **82**, 5723 (1960).
(34) H. Hart and O. E. Curtis, Jr., *ibid.*, **78**, 112 (1956).

Nucleophilic Displacements on Three-Membered Rings

James A. Deyrup[1] and Richard B. Greenwald

Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. *Received May 27, 1965*

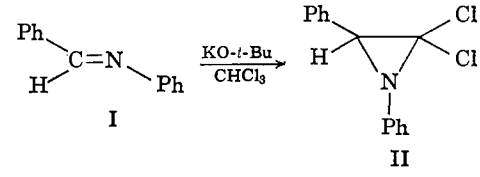
Two routes to monochloroaziridines have been discovered and the stereochemistry of these compounds has been determined by spectroscopic methods. The chemistry of these monohaloaziridines has been investigated and found to have little analogy with similar cyclopropyl systems. The chloro group is easily displaced from these monochloroaziridines and the displacement products are formed with inversion of stereochemistry. These displacements constitute the first facile displacements on three-membered rings of any kind. Evidence is presented for the intermediacy of the aziridinyl cation, and the reasons for its stereospecific attack are discussed.

Introduction

Displacements of leaving groups from carbocyclic three-membered rings are notoriously difficult. This difficulty has been ascribed to various factors including the relatively high electronegativity of cyclopropyl carbon atoms and the introduction of "*I*" strain in the developing transition state.[2] Furthermore, exothermic generation of cationic centers on three-membered rings leads to noncyclic products except in those cases where steric constraint inhibits ring opening.[3] This paper deals with the dramatic enhancement in reactivity caused by the presence of a nitrogen atom in a three-membered ring and the accompanying facile displacements on these heterocyclic compounds without loss of ring integrity. The particular systems in which these results have been observed are the monochloroaziridines.

Synthesis and Stereochemistry

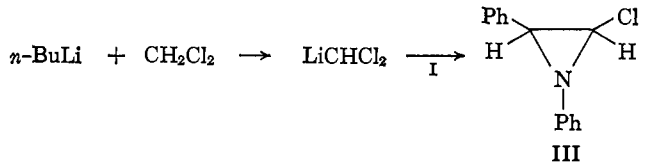
Dichloroaziridines are readily available from the addition of dichlorocarbene to Schiff bases.[4] Prior



I II

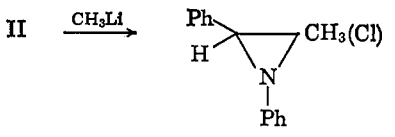
(1) Department of Chemistry, The University of Florida, Gainesville, Fla.
(2) J. Hine, "Physical Organic Chemistry," 2d Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 165.
(3) E. J. Corey and R. F. Atkinson, *J. Org. Chem.*, **29**, 3703 (1964), and references given therein.
(4) (a) E. K. Fields and S. M. Sandri, *Chem. Ind.* (London), 1216 (1959); (b) P. K. Kadaba and J. O. Edwards, *J. Org. Chem.*, **25**, 1431 (1960); (c) A. G. Cook and E. K. Fields, *ibid.*, **27**, 3686 (1962).

to this study, however, no monochloroaziridines had been reported. Extension of the carbenoid route to the preparation of monochloroaziridines required modification of existing procedures and even then was of limited scope. This modification and its use in the stereospecific preparation of III have already been described in a preliminary communication.[5]



III

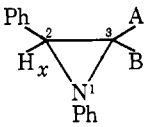
Another successful source of monochloroaziridines which complements the carbenoid route was found in the coupling of methyllithium with dichloroaziridines to give, in the case of II, a single product in 66% yield. Assignment of stereochemistry to IV was made by a



IV

careful study of the n.m.r. spectra of IV and related 1,2-diphenylaziridines. The data which were used in this assignment are presented in Table I.

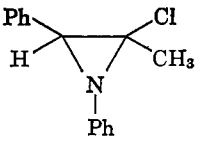
Table I. N.m.r. Spectra of 1,2-Diphenylaziridines



1,2-Diphenylaziridines	Entry	A	B	δ_{H_x}[a]
Unsubstituted[b]	1	H	H	170
cis-3-Chloro- (III)	2	Cl	H	192
3,3-Dichloro- (II)	3	Cl	Cl	212
trans-3-Chloro-	4	H	Cl	190[c]
cis-3-Methyl- (XIII)	5	CH_3	H	186
trans-3-Methyl- (XVI)	6	H	CH_3	165
cis-3-Chloro-3-methyl- (V)	7	Cl	CH_3	186[d]
cis-3-Chloro-3-methyl-	8	Cl	CH_3	187[c]
trans-3-Chloro-3-methyl-	9	CH_3	Cl	206[c]

[a] All n.m.r. chemical shifts reported in this article are expressed in c.p.s downfield from internal tetramethylsilane and measured in CCl_4 solutions on a Varian A-60 spectrometer at 60 Mc.p.s. [b] E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965). [c] Calculated. [d] Observed.

The differences between entries 3 and 2 (20 c.p.s.) and entries 2 and 1 (22 c.p.s.) represent the deshielding of H_x caused by the introduction of chloro groups *cis* and *trans* to H_x, respectively.[6] Addition of these deshielding values to *cis*-3-methyl-1,2-diphenylaziridines (20 + 186 = 206) and *trans*-3-methyl-1,2-diphenylaziridine (22 + 165 = 186) allowed the calculation of the expected values of H_x for the two isomers of IV (entries 8 and 9). These calculations thus identify the coupling product as V (*cis*-3-chloro-3-methyl-1,2-diphenylaziridine).



V

Before proceeding with the discussion of the chemistry of V (and III), it is necessary to consider the accuracy of the above spectral analysis of the 1,2-diphenylaziridine system. The initial assumption of the analysis concerns the additivity of substituent effects. The additivity of substituents has been considered by Shoolery and applied to substituted methylenes and methines.[9] Although the agreement between observed and calculated values was reasonably good, two potentially serious sources of error in these calculations have been pointed out.

The first arises from the possibility that the "electron withdrawal from a carbon atom becomes more difficult as the number of electron-withdrawing substituents is increased."[9] To the extent that this effect is important in II, the deshielding by a *trans* chloro group would be underestimated. Thus, the calculated value of H_x for the stereoisomeric form of V (entry 9) would be even more divergent from the observed value of the coupling product. That this effect is probably not significant is shown in Table II.

Table II. Deshielding of the Methyl Group by β-Chloro Substituents

Compound	δ_{CH_3}	$\Delta\delta_{CH_3}$	Ref.
CH_3-satd. hydrocarbon	53		*a*
		36	
CH_3CH_2Cl	89		*b*
		35	
CH_3CHCl_2	124		*c*
		40	
CH_3CCl_3	164		*c*
XVI	65		
		33	
V	98		

[a] Reference 9, p. 52 (average value, ±1 c.p.s). [b] "High-Resolution N.m.r. Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 11. [c] N. Sheppard and J. J. Turner, *Proc. Roy. Soc.* (London), **A252**, 506 (1959).

The second source of potential error arises from the long-range anisotropic shielding which is a function of the distance and angle between the proton and the group in question. As a consequence of this, in some of the series of compounds which Shoolery studied, hindered rotation caused varying conformation populations and resulted in deviations from substituent additivity.[10] In the case of 1,2-diphenylaziridines, rotation about single bonds is, of course, impossible. The anisotropic effect of the chloro groups *cis* to H_x should be, therefore, the same in II as in V.

(5) J. A. Deyrup and R. B. Greenwald, *Tetrahedron Letters*, **321** (1965).

(6) Similar small differences between the effect of chloro groups *cis* and *trans* to H_x have been observed in chloro epoxides (5 c.p.s.)[7] and chlorocyclopropanes (8 c.p.s.).[8] These shifts are the summation of deshielding due to the electronegativity of the chloro group and the anisotropic effect of the C–Cl bond on H_x.

(7) K. L. Williamson, C. A. Lanford, and C. R. Nicholson, *J. Am. Chem. Soc.*, **86**, 762 (1964).

(8) H. M. Hutton and T. Schaefer, *Can. J. Chem.*, **41**, 1623 (1963).

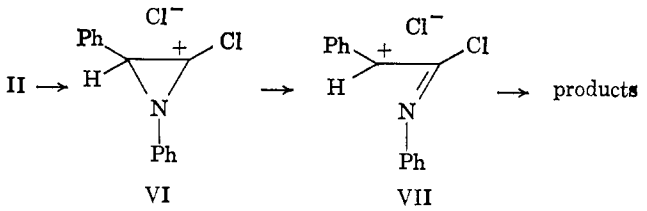
(9) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 59.

(10) Reference 9, p. 130.

In the case of aziridines, a third potential source of error must be considered. This source of error arises from the fact that the position of the N-phenyl group (and the unshared electron pair) is not fixed but free to take up conformations *cis* and *trans* to H_x. If variations in the size of the C-3 substituent alter the population of these two conformations, consequent variations in the anisotropic shielding of H_x will cause deviations from additivity. The two phenyl groups, however, are considerably larger than the C-3 substituents under consideration (CH_3, Cl, H). From an inspection of molecular models, it seems reasonable to conclude that the introduction of chloro groups into XIII and XVI does not significantly alter the *trans* conformation of the phenyl groups. In support of this conclusion, it is interesting to compare the isomeric 3-methyl-1,2-diphenylaziridines in which the steric variation at C-3 is greater than in the isomeric 3-chloro-3-methyl-1,2-diphenylaziridines. The methyl groups absorb at 63 and 65 c.p.s. in *cis*- and *trans*-3-methyl-1,2-diphenylaziridine, respectively, and the C-3 protons absorb at 140 c.p.s. in both compounds.

Nucleophilic Displacements

In contrast to their carbocyclic analogs, dichloroaziridines undergo facile hydrolysis and alcoholysis.[4a] The mechanism of the hydrolysis has been studied in detail and evidence presented for the following mechanism.[11] Although the intermediacy of aziridinyl



VI VII

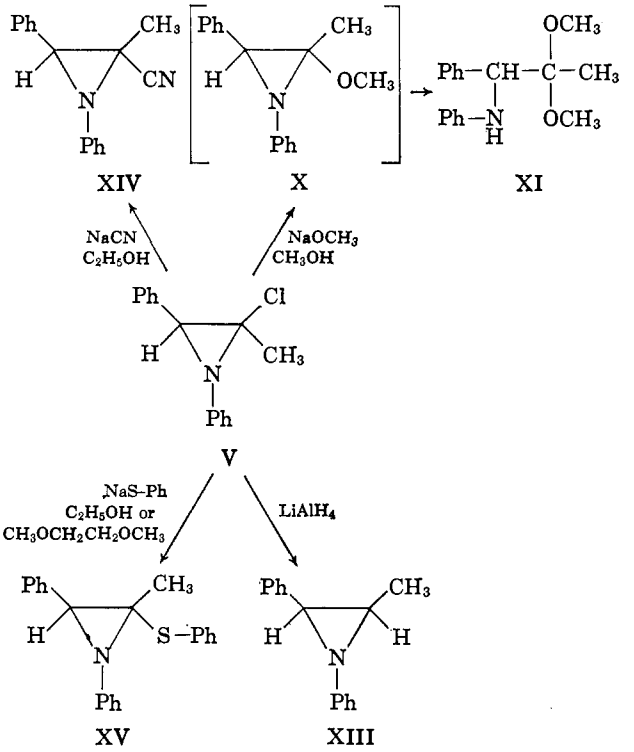
cation VI could be inferred from kinetic data, it was not possible to intercept it or detect reversibility in its formation. The reaction of methoxide in methanol with II, while not studied in kinetic detail, yielded products VIII and IX which supplied additional support for the above scheme.

VIII IX

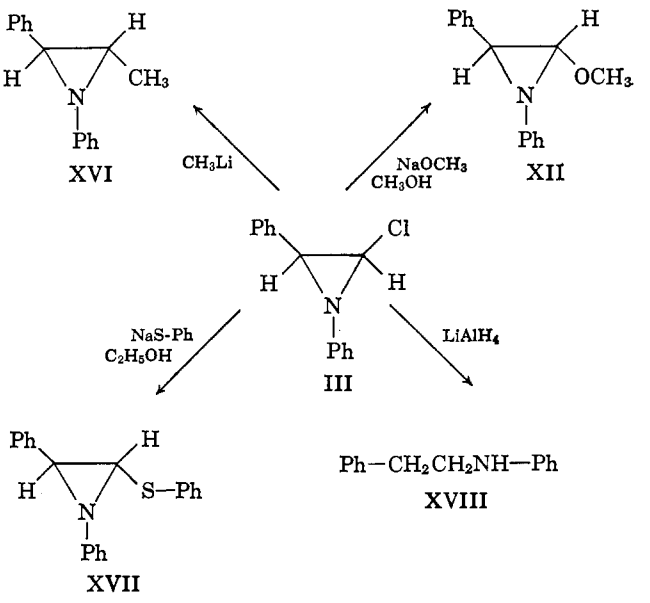
The first indication of radically differing behavior between the mono- and dichloroaziridines was found in the reaction of V with methoxide in methanol. The sole product of this reaction was the ketal XI. Ring opening had thus involved rupture of the C-3–N bond instead of the C-2–N bond. Formation of a ketal under basic conditions precluded carbonyl precursors and thereby indicated the intermediacy of X. Similar treatment of III with sodium methoxide in methanol yielded an isolable methoxyaziridine XII. The stereochemistry assigned to XII was derived from the observation of J_{ax} = 2.0 c.p.s. The stability of XII towards methoxide implies that the ring opening of X does not occur *via* bimolecular attack. It is possible that the methyl group lends sufficient additional stability to developing positive charge on C-3 to allow unimolecular rupture of the N–C-3 bond followed by capture of the resultant carbonium ion by methanol or methoxide.

As a result of these preliminary indications that certain aziridines underwent nucleophilic substitution reactions without ring opening, an investigation of the scope of these reactions was initiated. Some of these results are summarized in Schemes I and II.

Scheme I



Scheme II



The stereochemical assignments indicated in Scheme II for compounds XII, XVI, and XVII were made from an inspection of the coupling constants between adjacent ring protons. Similar arguments could be extended for the stereochemistry of XIII (Table III).

(11) R. E. Brooks, J. O. Edwards, G. Levey, and F. Smyth, in preparation. We wish to thank these authors for allowing us to see their manuscript.

Table III. Coupling Constants between Aziridine Ring Protons

cis		trans	
Compound	J, c.p.s.	Compound	J, c.p.s.
2-Phenylaziridine[a]	7.9	2-Phenylaziridine[a]	5.3
XIII	6.0	XVI	2.7
III[b]	5.0	XVII	2.5
		XII	2.0

[a] S. J. Brois, *J. Org. Chem.*, **27**, 3532 (1962); A. Hassner and C. C. Heathcock, *Tetrahedron Letters*, 1125 (1964). [b] Williamson has studied the effect of electronegative groups on J_{vic} in epoxides and cyclopropanes.[7] He has observed an inverse relationship between J_{vic} and the electronegativity of adjacent atoms. Since his results predict that the methoxy and chloro groups will have approximately the same effect on the coupling constant, the stereoisomer of III should have a coupling constant of approximately 2 c.p.s.

Some support for the stereochemistry assigned to XV was obtained from using the shift (22 c.p.s.) between XVII and 1,2-diphenylaziridine as a measure of the effect of an S-phenyl group *cis* to H_x. Addition of this value to *cis*-3-methyl-1,2-diphenylaziridine (XIII) gives a calculated shift for XV of 208 c.p.s. This is quite close to the observed value of 212 c.p.s. Unfortunately, the lack of other model compounds makes it impossible to calculate the effect on H_x of a *trans* S-phenyl group. Additional considerations concerning the stereochemistry of XIV and XV will be discussed below in connection with the over-all picture of aziridine displacement reactions.

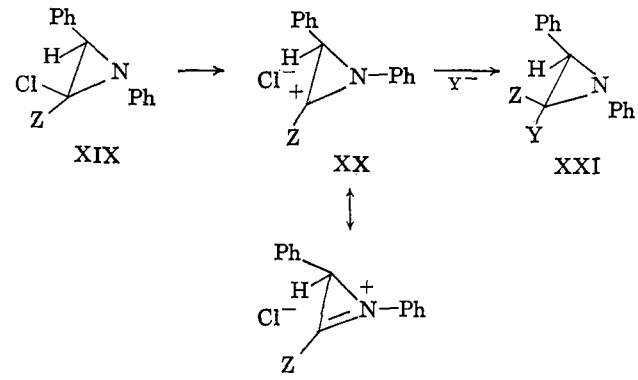
A number of the products described in Schemes I and II could not be isolated in pure, analytical form owing to their instability. It was possible, however, to obtain adequate spectral evidence for their structures and for their stereochemical homogeneity as well as to effect their conversion to suitable derivatives. Even those products which were stable enough to be purified could not be purified without loss due to decomposition. This instability of the products necessitated that they be formed under extremely mild conditions. That this was indeed the case is best exemplified by the completion of the reaction between V and NaS–Ph in 10 min. at 25° in ethanol. In spite of the associated experimental difficulties, the reactivity of the chloroaziridines and their displacement products appeared to merit further study in hopes that it might be possible to harness this reactivity into synthetically useful chemistry.

For this reason, our efforts were directed towards an understanding of the mechanism of these displacements. In view of the stereochemical results, both mono- and bimolecular pathways had to be considered. Preliminary qualitative evidence in favor of the former came from an examination of the conditions required for preparation of the phenyl thioethers XV and XVII from V and III, respectively. Although V reacted readily in dimethoxyethane, III was essentially inert towards sodium thiophenolate in this solvent under the same conditions. In a better ion-solvating medium, ethanol, XVII could be formed without difficulty. The fact that the methyl group, which would be expected to hinder bimolecular attack, was actually enhancing the reactivity suggested a two-step mechanism involving a cationic intermediate.

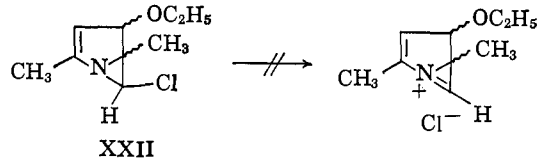
This suggestion was clearly supported by the titrimetrically measured rate of thiophenolate consumption by III and V in ethanol. Both compounds obeyed a first-order (in haloaziridine) rate law. The half-lives were again indicative of the great reactivity of these compounds. The less reactive of the two, III, had a half-life of 73 sec. at 72° in ethanol. In agreement with the above-mentioned qualitative results, the half-life of the methyl-substituted derivative V was 58 sec. at 25° in ethanol. Finally, further confirmation of the ionic character of the transition state was found in the rate increase observed in the presence of added salt.[12]

Based on these results, the over-all reaction can be represented by Scheme III. This scheme also serves to explain the greatly enhanced reactivity of haloaziridines over halocyclopropanes. This reactivity must be due to the stabilization of the cationic center by the adjacent electron pair on nitrogen. Subsequent to the completion of this work, a report appeared concerning a monochloroaziridine XXII which was clearly

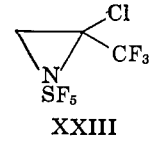
Scheme III



extremely stable in comparison to the aziridines which have been described in this communication.[14] Ap-



parently, it is necessary, in spite of "*I*" strain considerations, for both the cationic center and the nitrogen to become coplanar for effective overlap. A second monochloroaziridine (XXIII) was also reported during this work which possesses a stability due, at least in part, to the inability of the nitrogen to donate its electron pair to the incipient carbonium ion.[15]



XXIII

The products of the displacement reactions on V are all formed with inversion of configuration at C-3. This is also true of the displacement product on III where the stereochemistry is readily available from in-

(12) $Bu_4N^+ Br^-$ was considerably more effective in increasing the rate of the reaction of V with NaS–Ph in spite of the fact that the latter is nearly 10^4 as good a nucleophile as Br^- in ethanol.[13] Adherence to the first-order rate law was observed in all cases.

(13) A Streitwieser, Jr., *Chem. Rev.*, **56**, 583 (1956).

(14) R. Nicoletti and M. L. Forcellese, *Tetrahedron Letters*, 153 (1965).

(15) A. L. Logothetis, *J. Org. Chem.*, **29**, 3049 (1964).

spection of coupling constants. Two explanations for this steric course can be presented and the currently available data do not allow a selection between them. The first explanation is that the intermediate XX is a tight ion pair in which the chloride ion shields the carbonium ion and thus promotes backside attack.[16] The second explanation suggests that the intermediate XX is symmetrically solvated and that nucleophilic attack takes place stereoselectively from the side *trans* to the C-2 phenyl group. In addition to the n.m.r. arguments for the stereochemistry of XV and analogy to the formation of XIII, the stereochemistry assigned to XV and XIV is also supported by the fact that neither explanation for the stereochemical course of the displacements makes it seem likely that alteration of Z from H to CH_3 in the planar intermediate XX would completely reverse the side of attack.

Additional functionally substituted aziridines are under investigation and further examples of their novel chemistry have been observed. Efforts are also in progress to identify the source of the observed stereospecificity of these nucleophilic displacements.

Experimental Section[17]

cis-3-Chloro-3-methyl-1,2-diphenylaziridine (V). A solution of 0.50 g. (1.9 mmoles) of 3,3-dichloro-1,2-diphenylaziridine[4] in 10 ml. of absolute ether (under nitrogen) was cooled in an ice bath. A second solution of 6.3 ml. of 0.43 *N* methyllithium (2.7 mmoles total base)[19] was added dropwise to the well-stirred aziridine solution over a 5-min. period. When the addition was complete, the ice bath was removed and stirring continued for 20 min. at room temperature. Water was then cautiously added to the reaction mixture, the ether layer separated, and the ether removed *in vacuo*. The resultant solid residue was recrystallized from petroleum ether to give 0.29 g. (66%), m.p. 110–111°.[20] The analytical sample was prepared by recrystallization from hexane until a constant melting point of 114–115° was reached; n.m.r. (CCl_4): 98 (singlet, methyl), 186 (singlet, C-2 proton).

Anal. Calcd. for $C_{15}H_{14}NCl$: C, 73.93; H, 5.79; N, 5.74. Found: C, 74.08; H, 5.96; N, 5.77.

cis-3-Chloro-1,2-diphenylaziridine (III). A solution of 35 ml. of dry tetrahydrofuran, 25 ml. of anhydrous ether, and 6.20 g. (0.08 mole) of methylene chloride was cooled in an ether–liquid nitrogen bath under nitrogen. A hexane solution of *n*-butyllithium[21] (0.04 mole in 16.7 ml.) was added dropwise with good stirring to the above cooled solution. The reaction temperature was maintained below −90° at all times. The resulting opaque solution was stirred for *ca.* 2 min. at −100° and 1.81 g. (0.01 mole) of benzalaniline[22] in 8 ml. of ether was added dropwise. After the addition (during which the temperature was maintained below −90°) was complete, the reaction temperature was allowed to rise to −75°. The resulting homogeneous orange-yellow solution was stirred at −75° for 5–10 min. and then allowed to warm up slowly. At *ca.* −50° the solution began to turn darker. As soon as room temperature was reached, the reaction mixture was poured into water and the organic layer separated and washed well with three portions of water. The resulting solution, which varied in color from orange to dark red-brown, was dried over potassium carbonate and evaporated *in vacuo* to leave 2.3 g. (96%) of crude III which could be used directly. A partial purification, which appeared to remove polymeric and some colored impurities, could be effected by rapid filtration of a benzene solution through deactivated alumina. The great instability and reactivity of this compound prohibited further purification or preparation of an analytical sample; n.m.r. (CCl_4): 192 (doublet [J = 5 c.p.s.], C-2 proton), 259 (doublet [J = 5 c.p.s.], C-3 proton), 433 (broad complex multiplet, aromatic protons); area: 1:1:10.[23]

Reaction of Dichloroaziridine II with Sodium Methoxide. A solution of 2.64 g. (0.01 mole) of II and 0.02 mole of freshly prepared sodium methoxide in 50 ml. of methanol was refluxed for 21 hr. The mixture was poured into water and extracted with ether. After drying the ethereal solution, the solvent was removed *in vacuo* to leave 2.65 g. of a colorless oil; infrared (film): 6.02 μ (C=N, intense); n.m.r. (CCl_4): 195, 225, 228 (singlets, OCH_3), 293 ($CHOCH_3$ of VIII, singlet, 62%), 331 (CHCl of IX, singlet, 38%).

This oil was refluxed for an additional 17 hr. with 0.02 mole of sodium methoxide in methanol. Isolation of the product in the above manner yielded a product which was unchanged except for an increase in the percentage of VIII to 66%.

Two drops of concentrated sulfuric acid was added to a homogeneous solution of 0.40 g. of the mixture (62% VIII, 38% IX) in aqueous methanol. The reaction mixture was refluxed for 10 hr., cooled, diluted with water, and extracted with ether. The ether solution was washed well with water and dried over sodium sulfate. Evaporation of the solvent left 0.31 g. of an oil. The infrared and n.m.r. spectra of this oil were superimposable on those of a mixture of methyl 2-methoxy-2-phenylacetate[24] and methyl 2-chloro-2-phenylacetate.[25]

Solvolysis of II in methanol at 25° produced the above two esters directly (in addition to aniline hydrochloride). It is interesting and probably significant that the halo to

(16) *Cf.* H. Weiner and R. A. Sneen, *J. Am. Chem. Soc.*, **87**, 292 (1965).

(17) All melting points are uncorrected. Liquids were molecularly distilled in "Kugelrohrs"[18] and boiling points refer to the temperature of the hot air bath heater. All n.m.r. spectra were recorded on a Varian A-60 and the values reported are in c.p.s. downfield from tetramethylsilane.[7] All haloaziridines must be stored *in vacuo* at 0° to prevent decomposition. They also must be handled with care, since one person became seriously allergic to them. Microanalyses were performed by H. Frohofer (University of Zürich) and S. Nagy (M.I.T.).

(18) *Cf.* R. Graeve and G. H. Wahl, Jr., *J. Chem. Educ.*, **41**, 279 (1964).

(19) H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, **55**, 1252 (1933).

(20) This procedure can be performed on a larger scale if slower addition and lower temperatures are used.

(21) Lithium Corp. of America.

(22) L. A. Bigelow and H. Eatough, "Organic Synthesis," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1931, p. 80.

(23) In addition, there was a broad peak centered between 40 and 100 c.p.s. This material could not be removed without destruction of the aziridine and apparently was derived from reaction between the *n*-butyllithium and the methylene chloride. It did not interfere with further reactions. Both the "crude" and the "purified" product lacked n.m.r. absorption which could be attributed to isomeric aziridine. This was also true of V and the displacement products from III and V. A conservative estimate of the amount of impurity spectrally detectable in V and its displacement products is 3%. A value of 2–5% can be estimated for III and its displacement products except VIII in which competing reactions made the spectrum less suitable for the detection of isomers.

(24) R. Meyer, *Ann.*, 220, 1 (1883).

(25) P. Walden, *Z. physik. Chem.*, 17, 715 (1894).

methoxy ester ratio is identical in both their direct and indirect formation from II.

Reaction of V with Sodium Methoxide. A mixture of 0.48 g. (2.0 mmoles) of V and 2.2 mmoles of freshly prepared sodium methoxide in 20 ml. of methanol was warmed briefly until homogeneous and then allowed to stand at room temperature for 6 hr. The precipitated clusters of colorless crystals were removed by filtration and recrystallized from methanol to give 0.35 g. (65%) of 1-phenyl-1-anilino-2,2-dimethoxypropane (XI), m.p. 132–134°.[26] An analytical sample was prepared by several recrystallizations from methanol, m.p. 135.5–136.0°; n.m.r. (CCl_4): 65 (singlet, methyl), 191 (singlet, two methoxy groups), 269 (singlet, C-2 proton), 420 (broad complex multiplet, aromatic protons).

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.17. Found: C, 75.00; H, 7.98; N, 5.10.

Hydrolysis of XI with 10% hydrochloric acid gave 1-phenyl-1-anilino-2-propanone as shown by comparison of spectra (infrared and n.m.r.) with an authentic sample.[27]

trans-3-Ethoxy-1,2-diphenylaziridine (XIIa). A solution of 2.0 g. (8.7 mmoles) of *cis*-3-chloro-1,2-diphenylaziridine and 2.2 mmoles of sodium ethoxide in 25 ml. of ethanol was stirred at 65° for 16 hr. The dark reaction mixture was cooled, poured into water, and extracted twice with ether. The ethereal solution was washed well with three portions of water. The dried ether extracts were removed *in vacuo* to leave 1.6 g. (82%) of *trans*-3-ethoxy-1,2-diphenylaziridine (XIIa). This material could not survive chromatography. Molecular distillation, b.p. 125–135° (0.05 mm.), resulted in considerable residual polymer (even from previously distilled material). This instability prohibited preparation of an analytical sample; n.m.r. (CCl_4): 66 (triplet [J = 7 c.p.s.], methyl), 217 (quartet[28] [J = 7 c.p.s.], O–CH_2), 200 (doublet [J = 2.5 c.p.s.], C-2 proton), 250 (doublet [J = 2.5 c.p.s.], C-3 proton).

In a similar manner, it was possible to prepare *trans*-3-methoxy-1,2-diphenylaziridine (XIIb); n.m.r. (CCl_4): 205 (singlet, methoxy), 200 (doublet [J = 2 c.p.s.], C-2 proton), 249 (doublet [J = 2 c.p.s.], C-3 proton).

Additional support for the structures of these alkoxyaziridines was obtained by passing a stream of anhydrous HCl through a solution of 0.71 g. (3.0 mmoles) of the ethoxyaziridines XIIa in ethanol. After 3 min., the stream of HCl was stopped and the solution allowed to stand for 19 hr. at room temperature. The ethanol was removed *in vacuo* to leave a dark brown viscous oil which solidified on standing. The solid was washed with ether and then recrystallized from acetone–petroleum ether, m.p. 135–136° dec. The product, 0.41 g. (42%), was identified as 2-anilino-2-phenylacetaldehyde diethyl acetal hydrochloride by its n.m.r. spectrum ($CDCl_3$): 55 and 72 (triplets [J = 7 c.p.s.], OCH_2CH_3), 201 and 222 (quartets [J = 7 c.p.s.], OCH_2CH_3),[29] 269 and 325 (doublets [J = 6 c.p.s.], C-1 and C-2 protons).

Anal. Calcd. for $C_{18}H_{24}ClNO_2$: C, 67.17; H, 7.51; N, 4.35. Found: C, 67.26; H, 7.71; N, 4.27.

Reaction of V with Sodium Cyanide. A mixture of 0.40 g. (1.6 mmoles) of *cis*-3-chloro-3-methyl-1,2-diphenylaziridine, 0.43 g. (10 mmoles) of sodium cyanide, and 50 ml. of ethanol was heated with stirring at 70°. After 2 hr., the mixture was cooled, poured into water, and extracted with ether. The ether solution was washed three times with water, dried, and evaporated *in vacuo*. The product, XIV (0.40 g.), was chromatographed on alumina. Elution with benzene and molecular distillation (b.p. 120–125° at 0.03–0.05 mm.) gave an analytical sample as a colorless oil; infrared (film): 4.42 μ (C≡N); n.m.r. (CCl_4): 75 (singlet, methyl), 219 (singlet, C-2 proton), 432 (broad multiplet, aromatic protons).

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.79; H, 6.15; N, 12.09.

Reaction of V with Sodium Thiophenolate. A solution of 0.66 g. (5.0 mmoles) of sodium thiophenolate[30] and 0.24 g. (1.0 mmole) of *cis*-3-chloro-3-methyl-1,2-diphenylaziridine in 15 ml. of dry dimethoxyethane was stirred at 55–65° for 1 hr. (a precipitate was noticed after a few minutes). The reaction mixture was then cooled, poured into water, and extracted with ether. After washing and drying the ether layer, the solvent was evaporated *in vacuo* to leave 0.30 g. (95%) of crude XV as an orange oil; n.m.r. (CCl_4): 87 (singlet, methyl), 212 (singlet, C-2 proton).[31]

This compound was also very unstable and could neither be chromatographed or distilled. Characterization was thus attempted *via* oxidation to a sulfoxide or sulfone.

A twofold molar excess of sodium periodate in the minimum amount of water was added to a stirred solution of 0.50 g. (6.3 mmoles) of XV in methanol. The proportions of solvent were adjusted to produce a homogeneous solution. After stirring at room temperature for 2 hr., the solution was filtered to remove the sodium iodate, poured into water, and extracted with chloroform. The solvent, after drying, was evaporated *in vacuo* and the 0.26 g. of the residual oil crystallized on standing. This solid was recrystallized from chloroform–ether to give 0.12 g. (57%) of colorless plates, m.p. 158–159°. An analytical sample was prepared by further recrystallization, m.p. 160–160.5°.

Anal. Calcd. for $C_{21}H_{19}NSO$: C, 75.65; H, 5.74; N, 4.20; S, 9.62; mol. wt., 333. Found: C, 75.43; H, 5.88; N, 4.00; S, 9.78; mol. wt. (mass spectral), 333.

Although this derivative served the purpose of providing analytical confirmation for the structure of XV, spectral data clearly demonstrated that an isomerization had taken place during or after the oxidation; n.m.r. ($CDCl_3$): 262 and 286 (doublets [J = 7 c.p.s.]), 324 (singlet), 420 (complex aromatic proton multiplet), area: 1:1:1:15; infrared ($CHCl_3$): 2.92 (N–H), 5.90 (weak, C=C), 9.65 μ (S=O). Further investigation of this product, its structure, and the mechanism

(26) The same product was obtained when 1.1 mmoles of sodium methoxide was employed.

(27) P. E. Verkade and E. F. J. Janetzky, *Rec. trav. chim.*, **62**, 775 (1943).

(28) This quartet was, in turn, split into four doublets (J = 2 c.p.s.), presumably owing to hindered rotation.

(29) The different chemical shift of the two ethyl groups in this relatively nonpolar solvent probably arises from hydrogen bonding between the $>NH_2^+$ group and one ethoxy group.

(30) J. C. Sheehan and G. D. Daves, Jr., *J. Org. Chem.*, **29**, 2006 (1964).

(31) Although the product was slightly purer from dimethoxyethane, similar results were obtained in ethanol.

of its formation is under investigation. Tentatively, the structure can be assigned as 3-phenyl-3-anilino-2-phenylsulfinylpropene-1.

Reaction of III with Sodium Thiophenolate. This reaction was carried out in ethanol using the same conditions and isolation procedure described for the corresponding reaction between V and sodium thiophenolate. Only limited reaction was observed when dimethoxyethane was used as a solvent. The product of this reaction, XVII, was also quite unstable and could not be purified. Attempts to oxidize XVII to similar solid sulfoxide derivatives were unsuccessful; n.m.r. (CCl_4): 192 (doublet [J = 2.5 c.p.s.], C-2 proton), 229 (doublet [J = 2.5 c.p.s.], C-3 proton), 432 (broad multiplet, aromatic protons). Additional peaks between 275 and 300, although not attributable to a stereoisomer of XVII, indicated that a small amount of concurrent solvolysis and/or further reaction had occurred.

1-Phenyl-1-anilino-2-chloropropane. Sodium borohydride (3.02 g., 0.08 mole) was added in portions with good stirring to a suspension of 18 g. (0.08 mole) of 1-phenyl-1-anilino-2-propanone[27] in 100 ml. of methanol. After the addition was complete, the homogeneous solution was stirred at room temperature for 30 min. Water (*ca.* 150 ml.) was added and the resulting yellow oil was dissolved in ether and dried over sodium sulfate. Removal of the ether left 18.2 g. of 1-phenyl-1-anilino-2-propanol as a viscous, pale yellow oil; infrared (neat): 2.90 μ (strong, O–H).

Phosphorus pentachloride (9.1 g., 0.088 equiv.) was added in portions to a well-stirred solution of 11 g. (0.048 mole) of the above crude amino alcohol in 50 ml. of chloroform cooled to 0° in an ice bath. When the addition was complete, the dark brown mixture was stirred at room temperature for 15 min. and then evaporated to a small volume *in vacuo*. The reaction mixture was shaken with a 10% sodium hydroxide solution until the aqueous phase remained basic. Ether was then added and the deep red organic layer, after separation from the aqueous phase, was dried over sodium sulfate. The ether was evaporated *in vacuo* to leave the product, 1-phenyl-1-anilino-2-chloropropane, as a greenish red oil; infrared (neat): 3.0 μ (N–H).

cis- and trans-3-Methyl-1,2-diphenylaziridine. The above crude chloroamine was dissolved in 75 ml. of 95% ethanol, and 5.0 g. of potassium hydroxide was added to the solution. The solution was refluxed for 30 min., poured into a large volume of water, and extracted with ether. The ether extracts were dried, and the solvent was removed to give 7.3 g. of a red oil. From a molecular distillation (b.p. 95–115°, at 0.2 mm.) of this crude product, 2.5 g. (25% over-all yield from 1-phenyl-1-anilino-2-propanone) of the isomeric aziridines was obtained. Filtration of this product in benzene through alumina followed by a second distillation provided an analytical sample.

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.00; H, 7.39; N, 6.67.

The n.m.r. spectrum of the original, unchromatographed distillate consisted of 75 ± 5% *trans* and 25 ± 5% *cis* isomers. The two isomers could be separated from each other by multiple careful chromatography with considerable sacrifice of material and time. Much more efficient routes to the pure isomers from the appropriate monochloroaziridines are described below.

trans-3-Methyl-1,2-diphenylaziridine from III. A solution of 0.50 g. (0.22 mmole) of III in 10 ml. of ether (under a nitrogen atmosphere) was cooled to 0°, and 10 ml. of 0.72 M (7.2 mmoles) methyllithium[19] was added dropwise with good stirring. The solution was allowed to warm to room temperature at the end of the addition and stirring was continued for an additional 30 min. Water was added very cautiously to decompose excess methyllithium. The ether layer was separated and dried over potassium carbonate; the solvent was removed to leave 0.40 g. (88%) of crude product. Purification was accomplished by filtration through alumina with benzene and molecular distillation to give a colorless oil which was identical on thin sheet chromatography with the slower moving component in the above isomeric mixture; n.m.r. (CCl_4): 65 (doublet [J = 6.0 c.p.s.], CH-CH_3), 140 (complex multiplet, C-3 proton), 165 (doublet [J = 2.7 c.p.s.], C-2 proton), 427 (broad multiplet, aromatic protons).

cis-3-Methyl-1,2-diphenylaziridine from V. A stirred suspension of 34 mg. of lithium aluminum hydride, 244 mg. (1.0 mmole) of V, and 10 ml. of ether was refluxed for 6 hr. The reaction mixture was then stirred for 14 hr. at room temperature. The excess lithium aluminum hydride was decomposed with ethyl acetate followed by addition of a 10% Rochelle salt solution. The ether layer was separated and washed with water. The dried ether extracts were evaporated to leave 185 mg. (89%) of *cis*-3-methyl-1,2-diphenylaziridine. This material was identical on thin sheet chromatography with the faster moving component in the isomeric mixture. Further purification was achieved by filtration through alumina with benzene followed by molecular distillation (b.p. 90–95°, 0.06 mm.); n.m.r. (CCl_4): 62 (doublet [J = 6.0 c.p.s.], CH-CH_3), 140 (quintet [J = 6.0 c.p.s.], C-3 proton), 186 (doublet [J = 6.0 c.p.s.], C-2 proton), 427 (broad multiplet, aromatic protons).

Lithium Aluminum Hydride Reduction of III. A stirred mixture of 0.40 g. (1.6 mmoles) of III, 0.37 g. (0.01 mole) of lithium aluminum hydride, and 25 ml. of ether was refluxed for 16 hr. The excess lithium aluminum hydride was decomposed and the product isolated according to the procedure of Micovic.[32] In this manner 0.25 g. of pale yellow oil was obtained whose infrared and n.m.r. spectra were identical with those of 2-phenyl-N-phenylethylamine (XIX). The hydrochloride, m.p. 128–130°, showed no melting point depression when mixed with an authentic sample.[33] This same compound could be obtained from dichloroaziridine II. In this case, however, prolonged reflux in tetrahydrofuran was necessary.

Procedure for Measurement of Reaction Rates.[34] An absolute ethanol solution (volume *ca.* 20 ml.) of sodium thiophenolate was thermostated to the desired temperature in a constant-temperature bath. Solutions of the chloroaziridine in 1 ml. of dry tetrahydrofuran were then added. Aliquots of 1-ml. were periodically re-

(32) V. M. Micovic and M. L. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).
(33) R. Wegler and G. Pieper, *Chem. Ber.*, **83**, 1 (1950).
(34) *Cf.* J. Hine and W. H. Brader, Jr., *J. Am. Chem. Soc.*, **75**, 3964 (1953).

Table IV. Rates of Reaction of Chloroaziridines with Thiophenolate

Aziridine—	Wt., g.	NaS–Ph, g.	$Bu_4N^+Br^-$, g.	Temp., °C.	Rate × 10^2, sec.$^{-1}$
V	0.24	0.53	...	24.8	1.19 ± 0.05
V	0.23	0.23	...	24.8	0.92 ± 0.06
V	0.23	0.25	0.88	24.8	1.77 ± 0.08
III	0.26	0.54	...	71.9	0.94 ± 0.07

moved and quenched in *ca.* 25 ml. of glacial acetic acid. A standard iodine solution was used to titrate the unconsumed thiophenol. Typical results are shown in Table IV.

Acknowledgment. We wish to thank Professor John O. Edwards for his helpful discussions and information concerning his results prior to publication.

Kinetics and Mechanism of the Hydroxide Ion and Morpholine-Catalyzed Hydrolysis of Methyl *o*-Formylbenzoate. Participation by the Neighboring Aldehyde Group[1]

Myron L. Bender, Jerome A. Reinstein,[2] Marc S. Silver,[3] and Robert Mikulak[4]

Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois. *Received May 17, 1965*

The hydroxide ion, hydronium ion, and morpholine-catalyzed hydrolyses of methyl o-formylbenzoate have been investigated. The hydroxide ion and morpholine catalyses lead to exceedingly rapid hydrolysis of this methyl ester around neutrality. In the morpholine-catalyzed hydrolysis the formation and decomposition of an unstable intermediate could be observed spectrophotometrically. With 0.085 M morpholine, the maximal concentration of the intermediate occurred after 2 sec. and the decomposition was virtually complete in another 8 sec. The intermediate was isolated from the reaction mixture at low temperature after a short time and identified as 3-morpholinophthalide. The intermediacy of this compound was proven by demonstrating that it was converted to product at exactly the same rate that the intermediate was converted to product, and that morpholine affected the rate of these conversions in exactly the same manner. Morpholine affected the rate of hydrolysis of the intermediate since this hydrolysis is reversible under the conditions employed. The pH–rate profiles of the hydrolysis of 3-morpholinophthalide and of 3-methoxyphthalide were determined. Both hydrolyses show a reaction independent of pH near neutrality and a reaction dependent on hydroxide ion at higher pH. The hydrolysis of 3-morpholinophthalide is faster than that of 3-methoxyphthalide by 10^3–10^4 in both regions. Mechanisms of these processes are discussed as is the relationship of these catalyses to enzymatic catalysis.

Introduction

Intramolecular catalysis by neighboring carboxylate ion, carboxylic acid, imidazole, carboxamide, and aromatic and aliphatic hydroxyl groups constitutes an effective avenue of ester hydrolysis.[5-12] Interest in these intramolecular catalyses has been high because of their application as possible models for the intracomplex and intramolecular catalyses in enzymatic reactions, since each of these groups is present as a substituent in enzymes.

Other functional groups may also participate as intramolecular catalysts in ester hydrolysis. Recently Newman and Hishida[13] explained the exceptional hydrolytic reactivity of certain methyl-substituted *o*-benzoylbenzoates in terms of the initial attack of hydroxide ion on the keto group of the substrate. We report here the hydrolytic reactions of the similar compound, methyl *o*-formylbenzoate, using hydroxide ion and morpholine as catalysts.[14]

Experimental Section

Materials. Methyl *o*-formylbenzoate was prepared from phthalaldehydic acid (Eastman Kodak Co.) and diazomethane in ether. The ether was evaporated *in vacuo*, leaving methyl *o*-formylbenzoate, which was placed in the freezer. One such preparation gave material which was not contaminated by the corresponding pseudo-ester, as determined by the different characteristic spectra of these two compounds, while another preparation was contaminated with about 10% of pseudo-methyl ester (3-methoxyphthalide) as shown by the lactone carbonyl absorption at 5.63 μ.

(1) Supported by grants from the National Science Foundation.
(2) National Institutes of Health Postdoctoral Research Fellow.
(3) National Science Foundation Postdoctoral Research Fellow on leave from Amherst College.
(4) Participant in National Science Foundation Summer Research Program.

(5) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).
(6) T. C. Bruice, *Brookhaven Symp. Biol.*, **15**, 52 (1962).
(7) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Am. Chem. Soc.*, **84**, 2421 (1962).
(8) T. C. Bruice and S. J. Benkovic, *ibid.*, **85**, 1 (1963).
(9) E. J. Fuller, *ibid.*, **85**, 1777 (1963).
(10) M. L. Bender, F. J. Kézdy, and B. Zerner, *ibid.*, **85**, 3017 (1963).
(11) S. M. Kupchan, S. P. Eriksen, and Y.-T. Shen, *ibid.*, **85**, 350 (1963).
(12) T. C. Bruice and T. H. Fife, *ibid.*, **84**, 1973 (1962).
(13) M. S. Newman and S. Hishida, *ibid.*, **84**, 3582 (1962).
(14) A portion of this work was communicated previously: M. L. Bender, and M. S. Silver, *ibid.*, **84**, 4589 (1962).