tion of a higher activation energy for epoxide formation (reaction 4) in competition with absorption of oxygen (reaction 2) and the difficulty in maintaining saturation of the solution with oxygen leads to the formation of increasing proportions of both α-methylstyrene oxide and distillation residue and less acetophenone. Slowing the oxidation (and presumably increasing the oxygen concentration) by dilution with *o*-dichlorobenzene increases the yield of acetophenone at the expense of epoxide and residue. Residues are associated with epoxide formation and the formation of ether links, reactions 4 and 6. Residues made at low oxygen concentrations have H:C ratios that seem also to require incorporation of $-OCH_2O-$ groups,[1] particularly in residues that have not been strongly heated. At higher conversions, residues also contain condensation products of acetophenone, formaldehyde, and α-methylstyrene oxide, the major primary products of oxidation.

Detailed investigations of some residues confirm the presence of ether groups and $-OCH_2O-$ units but they bring out the great complexity of the residue and, with the exception of 6% of α-methylstyrene glycol, the absence of important proportions of any single component. This work shows that the hydrocarbon units between the ether links contain seven, eight, and ten carbon atoms as well as two kinds of C_9 units. Some of the cuts in this investigation contained many more than 50 individual components.

This work is consistent with, and extends, our findings that oxidations of isobutylene[4,5] and cyclopentene[5,6] also give high-boiling residues. Those residues also consist of monomer units, or fragments of them, joined together with ether links (and some peroxide links in oxidations below 100°), some with additional oxygen-containing groups on the chains.

Acknowledgment. This research was part of a basic study of reactions of organic compounds with oxygen, supported by a group of oil and chemical companies in the United States, Europe, and Japan.

Registry No.—α-Methylstyrene, 98-83-9.

Supplementary Material Available. Details of investigations of residues 18, 39, 45, and 53 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N. W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-889.

References and Notes

(1) F. R. Mayo and A. A. Miller, *J. Amer. Chem. Soc.*, **80**, 2480, 6701 (1958).
(2) (a) J. K. Castleman and T. Mill; (b) R. M. Silverstein and O. Rodin.
(3) D. E. Van Sickle, F. R. Mayo, E. S. Gould, and R. M. Arluck, *J. Amer. Chem. Soc.*, **89**, 977 (1967).
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α-Methylenelactam Rearrangement

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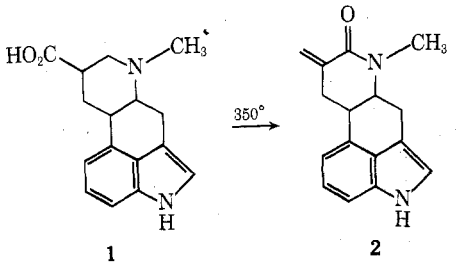
The acetic anhydride promoted rearrangement of cyclic β-amino acids to α-methylenelactams has been investigated. In particular, the effect of ring size, N substitution, and α substitution on the yield of the rearranged product was determined. When applicable, the stereochemistry of the rearrangement was also examined. These observations have led to elucidation of the mechanism of the α-methylenelactam rearrangement which is initiated by a cyclic β-amino acid reacting in its zwitterionic form with acetic anhydride to yield the protonated amino mixed anhydride. β elimination then readily occurs, and recyclization takes place by nucleophilic attack of the amino group on the mixed anhydride function.

The rearrangement of a cyclic β-amino acid to an α-methylenelactam was first observed[1] in an attempt to purify dihydrolysergic acid (1). Sublimation of acid 1 led to a substantial portion of rearranged product, dihydrolysergic lactam (2). Subsequently, this rearrangement was utilized in the transformation of lysergic acid (3) to 6,8-dimethylergoline (4).[2]



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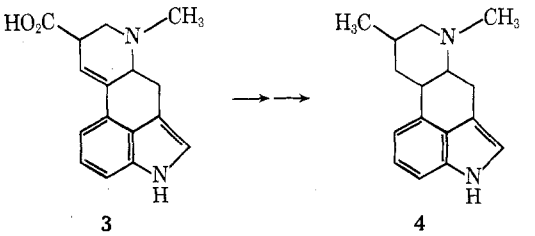
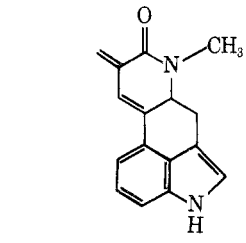


3 4

In addition to the above pyrolytic route, the rearrangement of cyclic β-amino acids to α-methylenelactams has been effected through the use of acetic anhydride. In seeking to racemize the C-8 asymmetric center of lysergic acid (3), it was treated[3] with acetic anhydride in the expectation of preparing lysergic acetic anhydride. The product obtained was lactam 5. Similarly, the rearrangement of

N-methylnipecotic acid (6) to 1-methyl-3-methylene-2-piperidone (7) has been reported.[4]



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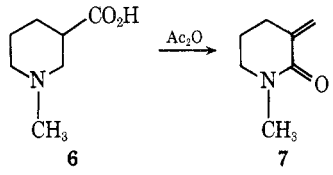
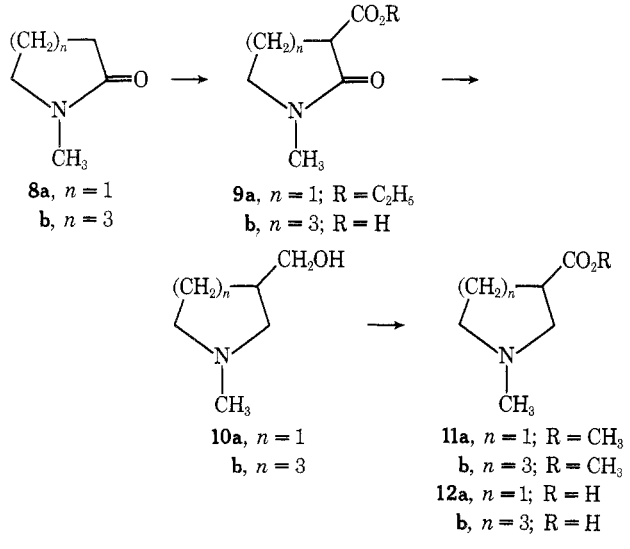


6 7

Since then, this reaction appears to have gone unnoticed until the recent[5] utilization of this rearrangement for nicotinic acid degradation. Recognition of the reaction's synthetic potential was achieved when the rearrangement was employed as a key step in the synthesis of camptothecin and camptothecin analogs.[6,7] The multitude of possible subsequent transformations of the product lactams, for which the synthesis of camptothecin is a good example, makes these lactams very versatile synthons. With this in mind, we have explored the mechanism and some aspects of the scope of this rearrangement. In particular, the yield of rearranged product as a function of ring size, N substitution, and α substitution was of prime interest. The stereochemistry of the rearrangement of α-substituted derivatives was also examined.

Syntheses. The five- and seven-membered ring β-amino acids **12a** and **12b** were prepared as outlined in Scheme I.

Scheme I



8a, $n = 1$
b, $n = 3$

9a, $n = 1$; R = C_2H_5
b, $n = 3$; R = H

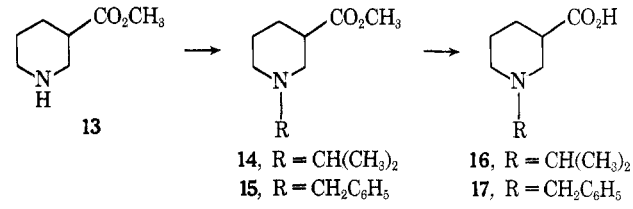
10a, $n = 1$
b, $n = 3$

11a, $n = 1$; R = CH_3
b, $n = 3$; R = CH_3
12a, $n = 1$; R = H
b, $n = 3$; R = H

Treatment of the corresponding amides **8a** and **8b** with lithium diisopropylamide followed by the addition of diethyl carbonate or carbon dioxide yielded the carboxyl derivatives **9a** and **9b**, respectively. Lithium aluminum hydride reduction of the carboxyl and amide functions afforded the aminols **10a** and **10b**, and chromium trioxide–sulfuric acid oxidation of the alcohols gave acids **12a** and **12b**, purified *via* their respective methyl esters, **11a** and **11b**.

Preparation of the N-substituted acid derivatives **16** and **17** was accomplished as outlined in Scheme II. Methyl nipecotate (**13**) was treated with either isopropyl iodide or benzyl bromide to yield the N-alkyl derivatives **14** or **15**. Acid hydrolysis of the esters then afforded the desired acids **16** and **17** as the hydrochloride salts.

Scheme II

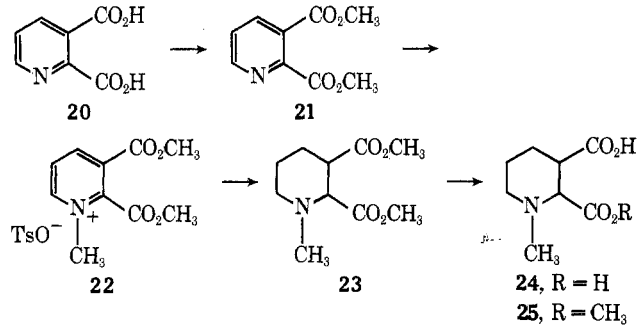


13

14, R = $CH(CH_3)_2$
15, R = $CH_2C_6H_5$

16, R = $CH(CH_3)_2$
17, R = $CH_2C_6H_5$

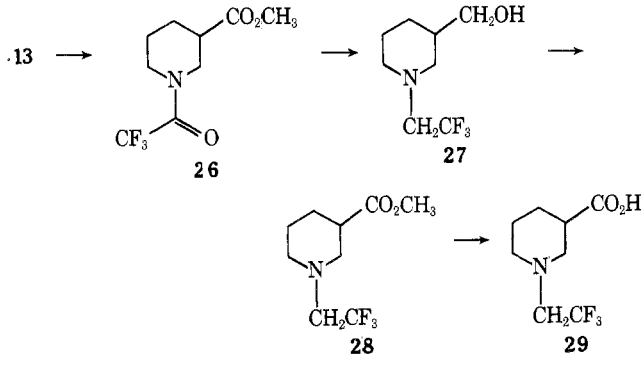
Scheme III



20 **21** **22** **23**

24, R = H
25, R = CH_3

Scheme IV



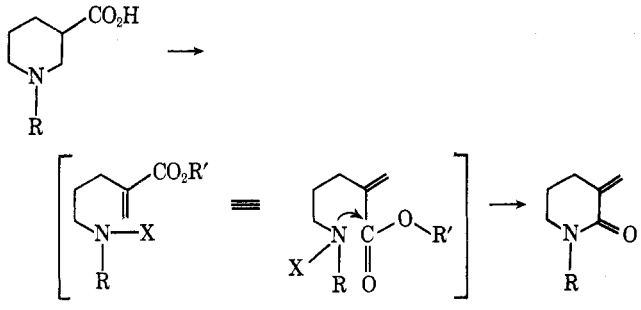
26 **27** **28** **29**

Three 1-methyl 2-substituted nipecotic acids were examined. The 2-methyl- and 2-phenyl-1-methylnipecotic acids (**18** and **19**, respectively) were made from the known ethyl esters.[8] Scheme III delineates the preparation of the 2-carboxynipecotic acid derivatives **24** and **25**. 2,3-Pyridinedicarboxylic acid (**20**) was esterified with methanol–HCl to yield pyridine diester **21**. Subsequent treatment of **21** with methyl *p*-toluenesulfonate afforded the *N*-methylpyridinium carboxylic ester salt **22**, which was hydrogenated employing platinum as the catalyst to yield the piperidine **23**. Hydrolysis of diester **23** was effected in 6 *N* HCl, selectively to monoester **25** at room temperature overnight and totally to diacid **24** on refluxing for 20 hr.

1-(2,2,2-Trifluoroethyl)nipecotic acid (**29**) was prepared as shown in Scheme IV. Methyl nipecotate **13** was treated with excess trifluoroacetic anhydride to yield the amido ester **26**. Selective reduction of the amide function in **26** could not be accomplished with diborane,[9] which converted **26** to the aminol **27**. Oxidation of **27** with chromium trioxide–sulfuric acid followed by esterification with methanol–HCl yielded the amino ester **28**, which was hydrolyzed in 6 *N* HCl to produce acid **29**.

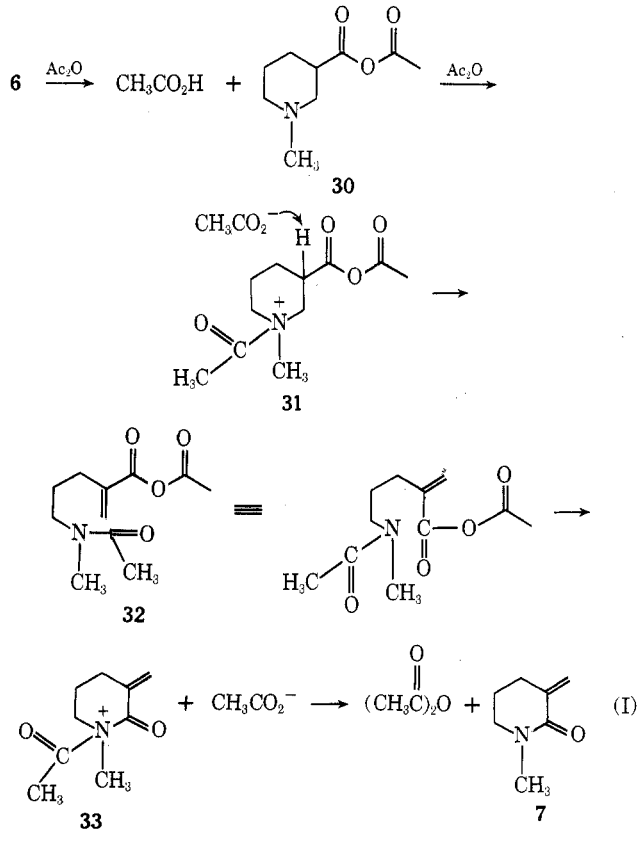
Mechanism. Experiments using a carbon-14 label established[5] that the carboxyl carbon of *N*-methylnipecotic acid (**6**) becomes C-2 of lactam **7** after rearrangement in refluxing acetic anhydride. This fact, coupled with the fact that β-amino acids are known to undergo elimination to α,β-unsaturated acids, allows the following mechanism

to be postulated initially. In the simplest view, a cyclic β-amino acid undergoes β elimination to yield an open-



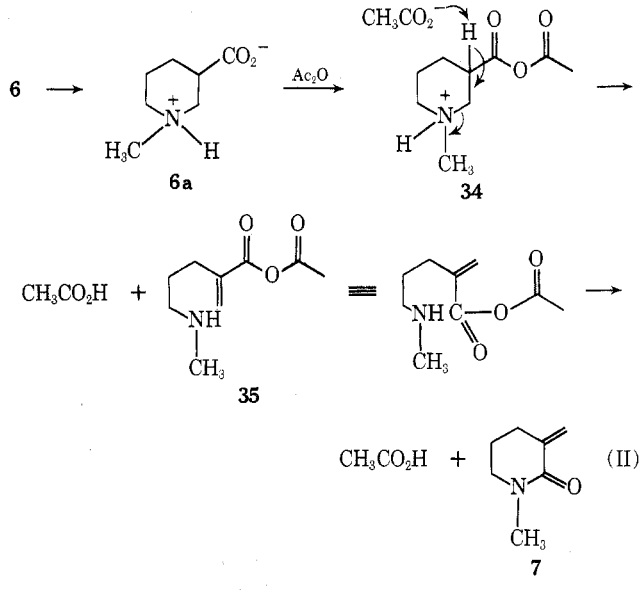
chain intermediate. Subsequent ring closure of the intermediate then occurs through attack of the nitrogen atom on the carboxyl carbonyl group. Conceivably, the amine in the open-chain intermediate can exist either as its *N*-acetyl derivative or as the free amine. Also, the carboxyl function in the open-chain intermediate may exist either as the acid or as the mixed anhydride. The fact that cyclic β-amino acids do not rearrange at 140° in the absence of acetic anhydride, *i.e.*, in refluxing xylene or in refluxing xylene containing acetic acid, indicates that mixed anhydride formation is a prerequisite for rearrangement. Thus, mixed anhydride formation increases the acidity of the α hydrogen, facilitating β elimination. Additional evidence in support of this postulate is the fact that the ester derivatives also do not rearrange or undergo β elimination under these conditions. Therefore, the mechanism is limited to one of the two possibilities, I or II.

According to mechanism I, mixed anhydride formation followed by acetylation of the tertiary amine would yield the intermediate **31**. The quaternary nitrogen, now being

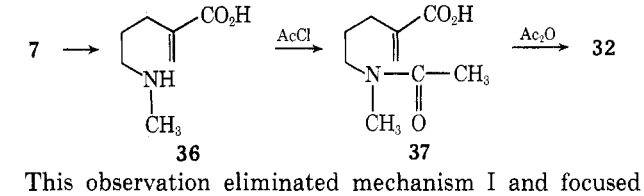


a better leaving group, promotes β elimination, possibly by an E1 mechanism; however, owing to the increased acidity of the hydrogen α to the mixed anhydride moiety, elimination can also be of the E2 or E1cB nature. Ring opening would yield the *N*-acetyl derivative **32**, followed by ring closure to the ionic imidium intermediate **33**. Attack of the imidium ion intermediate by acetate ion would then yield lactam **7**, regenerating acetic anhydride.

The alternative mechanism II again starts with mixed anhydride formation but from the zwitterionic ion form of **6, 6a**. Acetate ion, formed concurrently, is the base which promotes elimination readily in the protonated amine **34** to give the open-chain intermediate **35**. Intramolecular nucleophilic attack by the free secondary amine then leads to ring closure, forming lactam **7**.



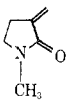
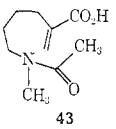
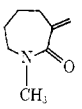
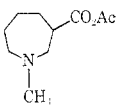
To differentiate between these mechanisms, the open-chain derivative **32** was prepared by acid hydrolysis of lactam **7** to the open-chain amino acid **36** hydrochloride, followed by treatment with acetyl chloride in the presence of K_2CO_3 to form the *N*-acetyl derivative **37**. Heating the acid **37** in acetic anhydride at reflux for 3 hr gave only mixed anhydride **32**; no ring closure occurred.



This observation eliminated mechanism I and focused attention on mechanism II. Evidence for this latter hypothesis was obtained when the acid **36** was refluxed in acetic anhydride and yielded, after an aqueous isolation, the lactam **7** and the open-chain *N*-acetyl derivative **37**. Since it had been established that *N*-acetyl derivatives **37** and **32** did not ring close to **7** in refluxing acetic anhydride and that the acid **37** did not close to **7** simply by heating at 140°, it could be inferred that production of **7** must be derived from the amine mixed anhydride intermediate **35**.

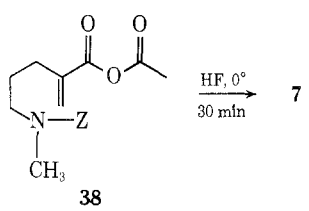
The formation of both lactam **7** and *N*-acetyl mixed anhydride **32** (isolated after hydrolysis as **37**) on heating the amino acid **36** in acetic anhydride can be rationalized as the result of competition between two reactions. One is N-acetylation, which then prevents ring closure and results in formation of **32**. The other is O-acetylation (mixed anhydride formation) followed by internal N-acylation forming lactam **7**. When one begins with the cyclic amino acid **6**, none of the *N*-acetyl derivatives **37** and **32** are formed. Since the mixed anhydride **34** is the primary product, the initial ring-opened product is amine mixed anhydride **35**. None of the open-chain amino acid **36** is formed, and ring closure by internal N-acylation completely excludes bimolecular N-acetylation.

Table I
α-Methylenelactam Rearrangement of 3-Carboxy-1-methylpyrrolidine, -piperidine, and -hexahydroazepine

Compd	Reaction conditions[a]	Products: Lactam	Yield, %	Other	Yield, %
12a	Ac_2O, K_2CO_3	 40	95		
12b	Ac_2O, K_2CO_3			 43	93
12b	150 mol % Ac_2O in xylene, K_2CO_3	 42	40	**43**	40
 41	100 mol % AcOH in xylene	**42**	40	**43**	10
6	Ac_2O	**7**	93		

[a] All reactions were conducted for 3 hr at reflux.

Further evidence for the plausibility of amine mixed anhydride intermediate **35** ring closing to lactam **7** was sought by treating the benzyloxycarbonyl derivative **38** with anhydrous hydrogen fluoride at 0° in an attempt to isolate **35** hydrofluoride under these mild reaction conditions. However, only lactam **7** was produced. Since mixed anhydrides can form acyl fluorides in the presence of hydrogen fluoride,[10] the integrity of the mixed anhydride function is in doubt in this experiment, and it cannot be claimed as definitive evidence for the intermediacy of **35**.



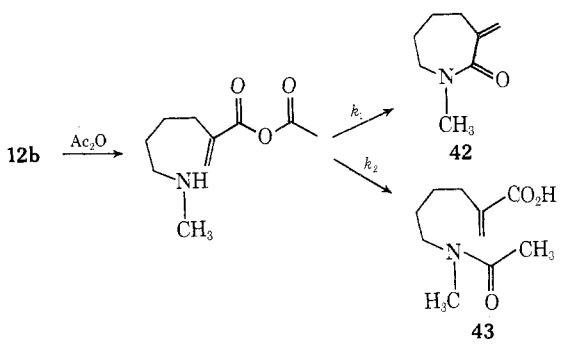
Similarly, lactam **7** was obtained when anhydride **38** was treated with *p*-toluenesulfonic acid in ether at room temperature for 15 min. Mixed sulfonic-carboxylic anhydride formation was not anticipated as a possible complication, since formation of such mixed anhydrides normally requires heating the anhydride with *p*-toluenesulfonic acid at temperatures ≥120° for at least 30 min.[11] However, a control experiment at room temperature for 15 min using acetic anhydride and *p*-toluenesulfonic acid gave mixed sulfonic carboxylic anhydride almost quantitatively.

To circumvent the possible problem of mixed anhydride exchange in the mechanism proof, sulfuric acid was employed as the acid for benzyloxycarbonyl removal. Thus, when the anhydride **38** was treated with sulfuric acid in ether at room temperature, the lactam **7** was obtained. Since mixed sulfate-carboxylic anhydride formation does not occur under these conditions, amine anhydride **35** as a viable intermediate is strongly indicated.

Scope. Rearrangement of β-Amino Acid Salts. Both the hydrochloride and the sodium salts of the β-amino acids can be employed in the rearrangement. Though solution of the sodium salt in acetic anhydride is slow, the reaction time is comparable to that required for the free amino acid. The rate of reaction of the hydrochloride is considerably slower than that of the free amino acid; however, the reaction of the hydrochloride can be considerably accelerated if 1 equiv of base (50 mol % potassium carbonate) is added. Since considerable difficulties in the purification of the zwitterionic intermediates frequently are encountered, the acids are normally used as the hydrochlorides, which are obtained directly from acid hydrolysis of the purified methyl esters.

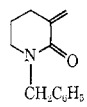
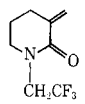
Variations in Reaction Conditions. Normally the reaction is conducted at the temperature of refluxing acetic anhydride; however, it has been found that the lower temperature limit to effect rearrangement is around 100°, with increased reaction time to obtain comparable yields. Although potassium carbonate was the base most commonly employed in the rearrangement of the hydrochloride salts of the acids, triethylamine can be substituted and might be advantageous when a homogeneous solution is desired.

Effect of Ring Size. As can be seen from Table I, the α-methylenelactam rearrangement is quite facile in the five- and six-membered ring systems. However, when the seven-membered ring acid **12b** was treated under the usual reaction conditions with excess acetic anhydride, no lactam **42** was obtained, and the sole product was the *N*-acetyl derivative, isolated as acid **43** after an aqueous treatment. Apparently, intermolecular acylation (k_2) with acetic anhydride was occurring faster than intramolecular acylation (k_1) in the open-chain intermediate.



Examination of the stoichiometry of the proposed reaction mechanism shows that only 1 mol of acetic anhydride

Table II
Effect of the N Substituent on the α-Methylenelactam Rearrangement of Nipecotic Acids

Compd	Reaction time,[a] hr	Product: Lactam	Product: Yield, %
16	3	 44	90
17	3	 45	92
29	3	 46	17
29	24	**46**	93

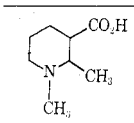
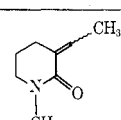
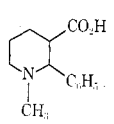
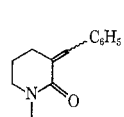
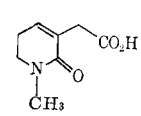
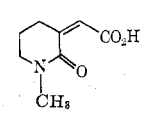
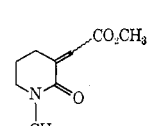
[a] All reactions were conducted at reflux in acetic anhydride containing potassium carbonate.

is required to effect the rearrangement. Therefore the acid **12b** was refluxed in xylene in the presence of 1.5 mol of acetic anhydride. Under these conditions a substantial amount of the lactam **42** was formed as well as *N*-acetyl derivative **43**. In an attempt to minimize the amount of free acetic anhydride present in the reaction mixture so as to diminish the formation of *N*-acetyl compound **43**, two further modifications of the normal experimental procedure were tried. In the first, the acetic anhydride was added to a mixture of the acid **12b** in xylene at reflux over a period of 4 hr. No improvement in the yield of the lactam **42** or attenuation of the amount of *N*-acetyl derivative **43** was noticed *via* this dilution technique. The second modification consisted of preforming the mixed anhydride of the acid **12b** prior to heating it to effect rearrangement. One equivalent of acetic acid was added as a source of base (acetate ion). No improvement in lactam formation was noted, though the amount of the *N*-acetyl derivative **43** was diminished. Evidently mixed anhydride disproportionation[12] was occurring.

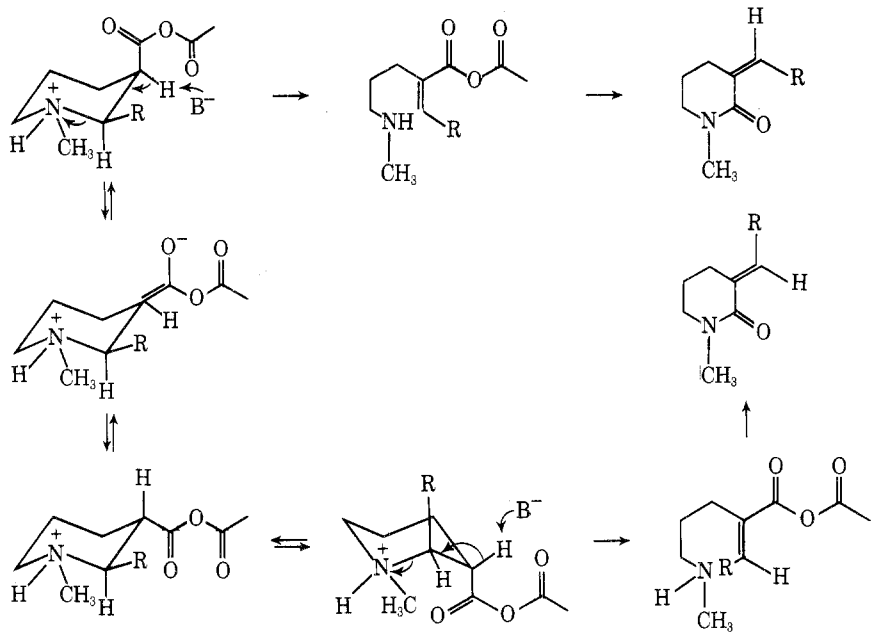
Effect of N Substitution. Examination of the effect of N substitution on the yield and rate of the rearrangement was confined to the six-membered ring systems. The N substituents employed were methyl, isopropyl, benzyl, and 2,2,2-trifluoroethyl. The *N*-isopropyl group illustrates the fact that steric hindrance about nitrogen does not affect the rearrangement, and the *N*-benzyl group indicates the further utility of the lactams as synthons since the benzyl group is potentially easily removable. The *N*-trifluoroethyl derivative was chosen to determine the effects of a strong electron-withdrawing substituent situated on nitrogen. As seen from Table II, the *N*-2,2,2-trifluoroethyl derivative **29** required a substantially longer reaction time to give an acceptable yield. This observation is in agreement with the proposal that β elimination must occur through the protonated amine. Owing to the decreased basicity of amine **29** ($pK_a \cong 5$),[13] a smaller fraction of the amine would be protonated in the reaction mixture, and therefore, a slower rate of reaction would be expected.

Effect of α Substitution. In the rearrangement of the 2-substituted nipecotic acid derivatives, shown in Table III, a mixture of lactam isomers was obtained with the trans isomer (trans to the carbonyl group) generally predominating. Assignments of cis and trans are based on the chemical shift of the olefinic proton, which is farther

Table III
α-Methylenelactam Rearrangement of 2-Substituted 1-Methylnipecotic Acids

Compd	Reaction conditions[a]: Reagents	Reaction conditions[a]: Time, hr	Products: Lactam	Products: Trans:cis ratio	Products: Yield, %	Products: Other	Products: Yield, %
 18	Ac_2O, K_2CO_3	3	 47	50:50	93		
 19	Ac_2O, K_2CO_3	3	 48	70:30	90		
24	Ac_2O, K_2CO_3	3				 50	93
24	Xylene[b]	24	 49	0	75	**50**	15
25	Ac_2O, K_2CO_3	3	 51	77:23	94		

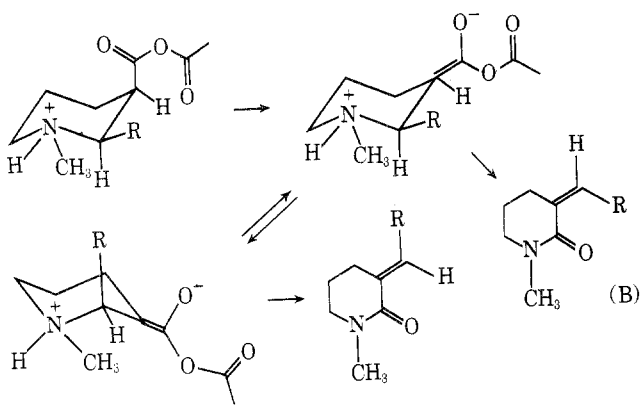
[a] All reactions were conducted at reflux. [b] Condensate was returned through Soxhlet thimble containing anhydrous $MgSO_4$.



(A)

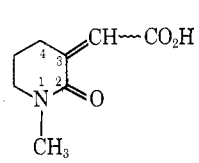
downfield (δ 6.6–7.6) in the trans isomer (proton cis to amide carbonyl) as compared to the cis (olefinic proton, δ 5.6–6.3, trans to amide carbonyl). Since (1) the starting acids were of one specific stereochemical configuration, presumably cis based on the nmr coupling constants of the C-2 protons ($J_{2,3}$ = 4 Hz), and (2) the product lactams did not isomerize under the reaction conditions, the fact that both lactam isomers were obtained indicated a loss of the stereospecificity of the starting acid prior to β elimination. Several possible explanations for this observation can be envisaged. One possibility, path A, which is schematically illustrated, assumes that β elimination is primarily E2 in nature with elimination occurring antiperiplanar. Moreover, equilibration at the C-3 center prior to β elimination is assumed.

Another possibility, path B shown below, assumes that β elimination is of the E1cB nature with cis elimination occurring. Of course, it is possible that elimination is also antiperiplanar, but, in either case, demonstration of the loss of stereospecificity from the starting acids is clear. In either case, there appears to be no obvious explanation for the predominant formation of the trans lactams. Clearly more studies with various α-substituted derivatives are required for a definitive elucidation of the stereochemical course of the rearrangement.

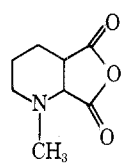


(B)

In the rearrangement of the 2-carboxynipecotic acid derivative **24**, neither of the exocyclic olefinic lactams **49** was obtained; instead, the endocyclic olefinic lactam **50** was the exclusive product. The assignment of the double bond as endo is based on the appearance of a two-proton doublet downfield at δ 3.1 as compared to the higher field multiplets for the allylic methylene group when the double bond is exo. The olefinic proton appears at δ 6.10 in the endocyclic isomer whereas in the two exo isomers it is at δ 5.66 in the cis and δ 6.66 in the trans.



49



52

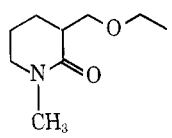
Unlike most of the other lactam products, where the C-4 hydrogens were only allylic, the C-4 hydrogens of the anticipated exocyclic olefinic lactam **49** would also be γ to an α,β-unsaturated carboxyl system, and in the reaction mixture they would be γ to an α,β-unsaturated mixed anhydride. Thus, one would expect a greater acidity for the C-4 hydrogens, and, when the C-4 hydrogens are sufficiently acidic, isomerization of the exocyclic olefin to the endocyclic olefin occurs and is favored. The C-4 hydrogens of the lactam **51** are also γ to an α,β-unsaturated carbonyl system, but no isomerization of the olefin to the endocyclic position was observed with this ester. As was previously discussed in relation to the mechanism, the mixed anhydride function increases the acidity of its α hydrogens sufficiently for anion formation and isomerization with the base present under the reaction conditions; when the conjugating group is an ester, anion formation and isomerization do not occur.

As was pointed out, mixed anhydride formation is a prerequisite for arrangement, and this activation has been accomplished conveniently with acetic anhydride. The 2-carboxynipecotic acid derivative also lends itself to internal anhydride formation, and rearrangement of internal anhydride **52** to lactam should proceed merely through the addition of base (acetate or triethylamine) and heat. Moreover, owing to the internal constraints of the system, the only exocyclic olefinic lactam produced should be the cis. In an attempt to obtain the internal anhydride **52**, diacid **24** was refluxed in xylene in the presence of magnesium sulfate. The product obtained was not **52** but the lactams **49** and **50**. Again some exo to endo double bond isomerization had occurred; however the lactam **49** produced in this reaction was all cis, as predicted.

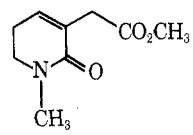
Exo-Endo Double Bond Stability. Since rearrangement of the diacid **24** in acetic anhydride–K_2CO_3 yielded

only the endocyclic olefinic lactam **50**, the question arose whether the other exocyclic olefinic lactams could be isomerized to the endocyclic form through the use of stronger base. Treatment of the lactam **7** with sodium ethoxide yielded the Michael-like product **53**. Lithium diisopropylamide, potassium *tert*-butoxide, or lithium cyclohexylisopropylamide also apparently resulted in 1,4-addition products, as indicated by the loss of olefinic absorption in the nmr, while use of lithium 2,2,6,6-tetramethylpiperidide[14] as a means of minimizing 1,4 addition to the lactam **7** yielded only unidentified products lacking any olefinic absorptions.

Treatment of the cis methoxycarbonyl substituted lactam **51a** with sodium methoxide in refluxing methanol for 4 days resulted in a 90% conversion to the endocyclic lactam **54**. Aliquots of the reaction mixture were monitored periodically, and at no time was any of the trans exocyclic olefin **51b** detected. This indicates, at least in the methoxycarbonylmethylene-substituted lactams, that the endocyclic olefin is more stable.



53



54

Treatment of the benzylidene lactam **48** with lithium 2,2,6,6-tetramethylpiperidide resulted only in the recovery of starting material. To determine if anion formation was occurring, the reaction was quenched with deuterated acetic acid and the resulting lactam showed incorporation of deuterium at C-4. Thus, the double bond is more stable exocyclic in this case.

Summary

The rearrangement of cyclic β-amino acids to α-methylenelactams by heating with acetic anhydride appears to be quite general with yields mostly exceeding 90%. The rearrangement occurs with facility to a single product in the five- and six-membered ring systems, while with the seven-membered ring a competing side reaction gives the open-chain *N*-acetyl compound as well as the α-methylenelactam. Substituents on nitrogen may vary with no adverse effect on the yield of rearranged product, and the rearrangement is compatible with a variety of substituents α and α′ to the nitrogen.[6,7]

The rearrangement has been shown to proceed *via* the zwitterion of the amino acid through the protonated amine–mixed anhydride which then undergoes β elimination followed by recyclization. We are now directing our efforts to further applications of this reaction to other heterocyclic systems and to the synthesis of more complex molecules.

Experimental Section

Solvent evaporations were carried out *in vacuo* using a Berkeley rotary evaporator. All melting points are uncorrected. Infrared (ir) spectra were measured in Nujol (unless otherwise noted) for solids and as thin films for liquids on a Perkin-Elmer 137 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained in CCl_4 (unless otherwise noted) with a Varian T-60 spectrometer; peak positions are given as δ values downfield from tetramethylsilane as internal standard, except that sodium trimethylsilylpropanesulfonate was used as internal standard in aqueous solutions. Gas chromatography (gc) was performed on a 5% QF-1 on Chromosorb W column, 10 ft × 0.25 in., at 125–200°. All elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

Rearrangement of Acids to Lactams. General Procedure. A. To 10 mmol of the cyclic β-amino acid was added 100 ml of acetic anhydride. The solution was then heated at reflux for 3 hr under nitrogen, cooled, poured into an aqueous solution of potassium carbonate (100 g in 200 ml of H_2O), and stirred for 4 hr at 0°. At the end of this time additional potassium carbonate was added, if necessary, to adjust to pH 8. The aqueous solution was then extracted with chloroform (3 × 100 ml), and the chloroform extracts were combined, dried over magnesium sulfate, filtered, and evaporated to yield the lactam. Analytical samples were obtained through preparative gc. Isomer ratios were also determined by gc.

B. To 10 mmol of the cyclic β-amino acid hydrochloride was added 100 ml of acetic anhydride and 0.69 g (5 mmol) of potassium carbonate. The mixture was then treated as above.

3-Carboxyl-1-methyl-2-oxohexahydroazepine (9b). To an acetone–Dry Ice bath cooled solution of 11.3 g (0.11 mol) of diisopropylamine and 150 ml of ether was added 64 ml of a 1.5 *M* solution of butyllithium in hexane. Stirring for 15 min was followed by addition of 10.1 g (80 mmol) of *N*-methylcaprolactam (**8b**)[15] in 50 ml of ether over a period of 5 min. After an additional 10 min, the cooling bath was removed, carbon dioxide was bubbled in for 10 min, the reaction mixture was poured into 300 ml of ice–water, and the layers were separated. The aqueous phase was adjusted to pH 2 with 2 *N* HCl and extracted with chcloroform (4 × 200 ml) and the combined chloroform extracts were evaporated to yield 12.0 g (87%) of the crude acid. Recrystallization from methylene chloride–ethyl ether afforded analytically pure acid **9b:** mp 118–119°; ir (KBr) 1640, 1750, 3000–3400 cm^{-1}; nmr ($CDCl_3$) δ 1.41–2.57 (m, 6 H), 3.06 (s, 3 H), 3.29, 3.99 (m, 3 H), 14.3 (s, 1 H).

Anal. Calcd for $C_8H_{13}NO_3$: C, 56.1; H, 7.7; N, 8.2. Found: C, 56.2; H, 7.7; N, 8.1.

3-Hydroxymethyl-1-methylhexahydroazepine (10b). To a mixture of 2.28 g (60 mmol) of lithium aluminum hydride and 100 ml of tetrahydrofuran (THF) was added 3.42 g (20 mmol) of the acid **9b** in 100 ml of THF over a period of 30 min. After being stirred overnight at room temperature, the mixture was refluxed for 5 hr and cooled, and the excess $LiAlH_4$ was destroyed with water and 15% NaOH. The mixture was filtered, and the dried filtrate was evaporated to yield 2.8 g (98%) of the aminol **10b:** ir 3400 cm^{-1}; nmr δ 1.10–1.98 (m, 6 H), 2.35 (s, 3 H), 2.39–3.00 (m, 3 H), 3.34–3.71 (m, 2 H), 4.78 (s, 1 H).

Anal. Calcd for $C_8H_{17}NO$: C, 67.1; H, 12.0; N, 9.8. Found: C, 67.2; H, 11.8; N, 9.6.

3-Methoxycarbonyl-1-methylhexahydroazepine (11b). A solution of 2.1 g (15 mmol) of the aminol **10b,** 0.35 ml of concentrated sulfuric acid, and 17 ml of water was treated at 0° with a solution of 1.25 g (12 mmol) of chromium trioxide, 0.85 ml of concentrated sulfuric acid, and 20 ml of water. The reaction mixture was stirred for an additional 5 min at 0°, heated at 100° for 2 min, and cooled to 0°, after which another solution of 1.25 g of chromium trioxide, 0.85 ml of concentrated acid, and 20 ml of water was added. Heating at 100° for 30 min was followed by cooling and adding sodium bisulfite to destroy excess oxidant. The pH was adjusted to 10 with 6 *N* NaOH, the mixture was filtered, and the filtrate was acidified (pH 2) with 6 *N* HCl and evaporated to dryness. Methanol (100 ml, previously saturated with HCl gas) was added to the dry residue and the mixture was stirred overnight at room temperature. The methanol was evaporated, 100 ml of water was added, and the pH was adjusted to 8 with potassium carbonate. After extraction of the aqueous solution with chloroform, the combined chloroform extracts were dried and evaporated to yield 1.1 g (41%) of the ester **11b:** ir 1750 cm^{-1}; nmr δ 1.50–1.97 (m, 6 H), 2.31 (s, 3 H), 2.39–3.0 (m, 5 H), 3.53 (s, 3 H).

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.1; H, 10.0; N, 8.2. Found: C, 63.0; H, 10.0; N, 8.1.

3-Hydroxymethyl-1-methylpyrrolidine (10a). 3-Ethoxycarbonyl-1-methyl-2-pyrrolidinone (**9a**)[16] was reduced as described for the reduction of **9b** to **10b,** to yield the aminol **10a:**[17] nmr δ 1.1–2.2 (m, 3 H), 2.23 (s, 3 H), 2.45 (m, 4 H), 3.37 (d, 2 H), 4.75 (s, 1 H).

3-Methoxycarbonyl-1-methylpyrrolidine (11a). The aminol **10a** was oxidized as described for the oxidation of **10b** to **11b** to yield the acid followed by esterification to **11a:** bp 45–46° (3 mm); ir 1750 cm^{-1}; nmr δ 1.74–2.11 (m, 2 H), 2.15 (s, 3 H), 2.35–3.16 (m, 5 H), 3.59 (s, 3 H),

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.7; H, 9.2; N, 9.8. Found: C, 58.5; H, 9.0; N, 9.6.

3-Carboxyl-1-methylpyrrolidine Hydrochloride (12a). The ester **11a** was stirred overnight at room temperature in 6 *N* HCl and the solution was evaporated to yield quantitatively the acid **12a:** nmr (D_2O) δ 2.40 (m, 2 H), 2.9–4.0 (m, 5 H), 2.95 (s, 3 H); high-resolution mass spectrum, calcd for $C_6H_{11}NO_2$ (M^+ − HCl), 129.0790; found, 129.0805.

Methyl *N*-Isopropylnipecotate (14). To a mixture of 7.5 g (53 mmol) of methyl nipecotate (**13**),[18] 7 g (50 mmol) of potassium carbonate, and 100 ml of benzene was added 10.5 g (63 mmol) of isopropyl idiode over a period of 45 min. The mixture was heated at reflux for 20 hr, cooled, and poured into 50 ml of water. The layers were separated, and the benzene was evaporated to a residue which on distillation yielded 5.27 g (58.5%) of the ***N*-isopropyl derivative 14:** bp 80–82° (5 mm); ir 1750 cm^{-1}; nmr ($CDCl_3$) δ 1.02 (d, J = 3 Hz, 6 H), 1.35–3.10 (m, 10 H), 4.65 (s, 3 H).

Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.3; N, 7.6. Found: C, 64.7; H, 10.4; N, 7.4.

Methyl *N*-Benzylnipecotate (15). The ester **15** was prepared from methyl nipecotate (**13**)[18] and benzyl bromide in a manner analogous to the alkylation of **13** to **14.** Distillation afforded an analytically pure sample of the ester **15:** bp 108–109° (1 mm); ir 1750 cm^{-1}; nmr δ 1.3–3.1 (m, 9 H), 3.49 (s, 2 H), 3.61 (s, 3 H), 7.22 (s, 5 H).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 71.9; H, 8.0; N, 6.1.

***N*-Isopropylnipecotic Acid Hydrochloride (16).** The methyl ester **14** was stirred overnight in 6 *N* HCl at room temperature. Evaporation quantitatively yielded the acid **16:** nmr (D_2O) δ 1.27 (d, J = 3 Hz, 6 H), 1.6–2.0 (m, 4 H), 2.4–2.8 (m, 1 H), 2.9–3.65 (m, 5 H).

1,2-Dimethylnipecotic Acid Hydrochloride (18). A solution of 1.0 g (5.4 mmol) of the ethyl 1,2-dimethylnipecotate[8] and 50 ml of 6 *N* HCl was stirred overnight at room temperature. Evaporation to dryness and recrystallization of the residue from isopropyl alcohol yielded the hydrochloride **18:** mp 184–186°; nmr (D_2O) δ 1.23 (d, J = 6 Hz, 1.5 H), 1.44 (d, J = 6 Hz, 1.5 H), 1.6–2.2 (m, 4 H), 2.82, (s, 1.5 H), 2.86 (s, 1.5 H), 2.88–4.27 (m, 4 H). Based on the nmr, this material appears to be a mixture of two compounds, and a nmr–temperature study indicates that they are isomers; however, repeated recrystallization does not affect the isomer ratio or melting point.

1-Methyl-2-phenylnipecotic Acid Hydrochloride (19). A mixture of 2.0 g (8.1 mmol) of ethyl 1-methyl-2-phenylnipecotate[8] and 50 ml of 6 *N* HCl was heated at reflux overnight, followed by evaporation to yield the acid **19:** nmr (D_2O) δ 2.05–2.35 (m, 4 H), 2.74 (s, 3 H). 2.95–3.90 (m, 3 H), 4.50 (d, 1 H, $J_{2,3}$ = 4 Hz), 7.46 (s, 5 H).

Dimethyl 1-Methylpiperidine-2,3-dicarboxylate (23). A mixture of 5.48 g (28 mmol) of the diester **21**[19] and 5.25 g (28 mmol) of methyl *p*-toluenesulfonate was heated under nitrogen at 100° for 1 hr. The resultant **22** as a viscous oil was dissolved in 50 ml of methanol, the solution was hydrogenated utilizing a platinum catalyst for 20 hr at 38 psi, the solution was poured into 100 ml of aqueous potassium carbonate, and the aqueous solution was extracted with chloroform (3 × 75 ml). The chloroform extracts were dried, filtered, and evaporated to an oily residue, which was distilled to yield 1.2 g (20%) of the piperidine **23:** bp 72–75° (1 mm); nmr δ 1.5–1.85 (m, 4 H), 2.1–2.95 (m, 4 H), 2.29 (s, 3 H), 3.55 (s, 6 H).

Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.8; H, 8.0; N, 6.5. Found: C, 55.6; H, 7.8; N, 6.6.

1-Methyl-2,3-piperidinedicarboxylic Acid Hydrochloride (24). A mixture of 0.50 g (2.3 mmol) of the diester **23** and 25 ml of 6 *N* HCl was heated at reflux overnight. Evaporation to dryness quantitatively yielded the diacid hydrochloride **24:** nmr (D_2O) δ 1.44–2.12 (m, 4 H), 2.83 (s, 3 H), 2.78–3.49 (m, 3 H), 3.90–4.14 (m, 1 H).

2-Methoxycarbonyl-3-carboxy-1-methylpiperidine Hydrochloride (25). A mixture of 0.50 g (2.34 mmol) of the diester **23** and 25 ml of 6 *N* HCl was stirred overnight at room temperature. When the dimethyl ester **23** was added to 6 *N* HCl, the OCH_3 absorption at δ 3.55 (6 H) was split into two, one at δ 3.71 (3 H) and the other at δ 3.77. The course of this selective hydrolysis was followed by the disappearance of the δ 3.71 absorption, and the reaction mixture was then poured into 100 ml of aqueous potassium carbonate and extracted with chloroform. The aqueous solution was acidified with HCl and applied to a cation exchange column (250 ml, AG-50W-X-1, H^+ form, 20–50 mesh). The column was washed with water until neutral, and then with 300 ml of *N* ammonium hydroxide, collecting and evaporating the first 250 ml of alkaline eluent to yield the free amino acid ester: nmr (D_2O) δ 1.5–2.0 (m, 4 H), 2.83 (s, 3 H), 2.7–3.37 (m, 3 H), 3.60 (s, 3 H), 3.91 (d, 1 H, $J_{2,3}$ = 4 Hz). To the dry residue was added 10 ml of 1 *N* HCl, and the resultant solution was again evaporated to dryness to yield 0.45 g (82%) of the acid **25:** nmr (D_2O) δ 1.60–2.17 (m, 4 H), 2.80–3.6 (m, 3 H), 3.08 [s, 3 H), 3.77 (s, 3 H), 4.22–4.45 (m, 1 H).

Methyl *N*-Trifluoroacetylnipecotate (26). To a solution of 3.9 g (27 mmol) of methyl nipecotate (**13**) and 50 ml of ether at 0° was added 20 g (0.1 mol) of trifluoroacetic anhydride. The reaction mixture was stirred for 1 hr at room temperature and poured into 100 ml of ice–water, the aqueous layer was separated and extracted with chloroform (3 × 75 ml), and the combined organic extracts were dried, filtered, and evaporated, yielding 5.9 g (91%) of the ester **26:** ir 1680, 1730 cm^{-1}; nmr δ 1.35–2.18 (m, 4 H), 2.20–2.78 (m, 1 H), 2.88–3.47 (m, 2 H), 3.64 (s, 3 H), 3.77–4.49 (m, 2 H).

Anal. Calcd for $C_9H_{12}NO_3F_3$: C, 45.2; H, 5.1. Found: C, 45.2; H, 5.0.

1-(2,2,2-Trifluoroethyl)-3-hydroxymethylpiperidine (27). To a solution of 3.0 g (12 mmol) of the ester **26** and 25 ml of tetrahydrofuran (THF) at 0° was added 35 ml of a 1 *M* THF solution of borane over a period of 15 min. The reaction mixture was heated at reflux for 2 hr and cooled to 0°, methanol (25 ml) was added, and the mixture was again heated at reflux for 1 hr. After cooling, the mixture was poured into 100 ml of saturated sodium bicarbonate solution which was then extracted with chloroform (3 × 75 ml). The organic extracts were combined, dried, and evaporated to yield 2.28 g (93%) of the aminol **27:** ir 3500 cm^{-1}; nmr δ 0.72–2.53 (m, 8 H), 2.54–3.15 (m, 4 H), 3.38 (d, 2 H, J = 5 Hz).

Anal. Calcd for $C_8H_{14}NOF_3$: C, 48.7; H, 7.2; N, 7.1. Found: C, 48.8; H, 7.1; N, 7.0.

Methyl *N*-(2,2,2-Trifluoroethyl)nipecotate (28). The alcohol **27** was oxidized to the acid followed by esterification to **28** in 41% yield as previously described for the conversion of **10b** to **11b.** Gc yielded an analytically pure sample of the ester **28:** ir 1730 cm^{-1}; nmr δ 1.37–2.03 (m, 4 H), 2.17–3.27 (m, 7 H), 3.57 (s, 3 H).

Anal. Calcd for $C_9H_{14}NO_2F_3$: C, 48.0; H, 6.3; N, 6.2. Found: C, 47.9; H, 6.2; N, 6.3.

2-Methylene-5-(*N*-methylamino)pentanoic Acid Hydrochloride (35). A solution of 1.25 g (10 mmol) of the lactam **7** and 50 ml of 6 *N* HCl was heated at reflux for 20 hr. The cooled solution was extracted with chloroform to remove starting lactam, and the aqueous phase was then evaporated to dryness to yield 1.5 g (82%) of the acid hydrochloride **36:** mp 94–98°; nmr (D_2O) δ 1.69–2.16 (m, 2 H), 2.24–2.60 (m, 2 H), 2.67 (s, 3 H), 2.90–3.24 (m, 3 H), 5.64 (br s, 1 H), 6.14 (s, 1 H).

Anal. Calcd for $C_7H_{14}NO_2Cl$: C, 46.8; H, 7.9; N, 7.8. Found: C, 46.7; H, 7.9; N, 7.8.

5-(*N*-Acetyl-*N*-methylamino)-2-methylenepentanoic Acid (37). To a mixture of 0.950 g (5.3 mmol) of the acid hydrochloride **36,** 1.46 g (10.6 mmol) of potassium carbonate, and 40 ml of glyme at 0° was added 2.1 g (27 mmol) of acetyl chloride. The reaction mixture was stirred overnight at room temperature and then poured into 100 ml of ice–water. Extraction with chloroform and evaporation of the combined, dried chloroform extracts yielded 0.5 g (52%) of the acid **37:** mp 79–80°; nmr ($CDCl_3$) δ 1.50–2.10 (m, 3 H), 2.11 (s, 3 H), 2.12–2.53 (m, 2 H), 2.95 (d, 3 H, J = 2 Hz), 3.10–3.55 (m, 2 H), 5.57 (s, 1 H), 6.19 (s, 1 H).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.4; H, 8.2; N, 7.6. Found: C, 58.2; H, 8.0; N, 7.6.

Reaction of 36 with Acetic Anhydride. A mixture of 1.8 g (10 mmol) of the acid **36** and 25 ml of acetic anhydride was stirred overnight at room temperature. The reaction mixture was then poured into 100 ml of saturated aqueous sodium carbonate and stirred for 3 hr. Additional sodium carbonate was added to pH 8, and the aqueous solution was extracted with chloroform. The chloroform extracts were dried, filtered, and evaporated to yield 0.69 g (55%) of the lactam **7.** Acidification of the aqueous layer and extraction with chloroform yielded after evaporation of the chloroform 0.83 g (45%) of the acid **37.**

5-(*N*-Benzyloxycarbonyl-*N*-methylamino)-2-methylenepentanoic Acid (39). To a solution of 0.81 g (5.7 mmol) of the amino acid **36** and 3 ml of 2 *N* sodium hydroxide at 0° were simultaneously added 0.96 g (5.7 mmol) of benzyl chloroformate and 3 ml of 2 *N* sodium hydroxide over a period of 10 min. After stirring for 20 min more, the aqueous solution was washed once with ether, and the aqueous phase was acidified to pH 2 with 10% HCl. The aqueous solution was extracted with chloroform, and the dried chloroform extracts were evaporated to yield 1.01 g (64%) of the acid **39:** nmr ($CDCl_3$) δ 1.36–1.89 (m, 2 H), 2.01–2.35 (m, 2 H), 2.76 (s, 3 H), 3.13 (t, 2 H, J = 6 Hz), 4.95 (s, 2 H), 5.41 (s, 1 H), 6.08 (s, 1 H), 7.07 (s, 5 H), 11.2 (s, 1 H).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.1. Found: C, 64.8; H, 6.8; N, 5.2.

5-(*N*-Benzyloxycarbonyl-*N*-methylamino)-2-methylenepentanoic Acetic Anhydride (38). A mixture of 1.0 g (3.6 mmol) of the acid **39** and 40 ml of acetic anhydride was stirred overnight at

room temperature. Evaporation of the acetic acid and excess acetic anhydride afforded a quantitative yield of the mixed anhydride **38**: ir 1725, 1750, 1848 cm^{-1}; nmr δ 1.62–2.14 (m, 2 H), 2.34 (s, 3 H), 2.35–2.60 (m, 2 H), 2.99 (s, 3 H), 3.30–3.50 (t, 2 H), 5.09 (s, 2 H), 5.82 (s, 1 H), 6.19 (s, 1 H), 7.10 (s, 5 H).

Reaction of 38 with p-Toluenesulfonic and Sulfuric Acid. A solution of 1.1 g (3.5 mmol) of the anhydride **38** in 20 ml of ether at room temperature was treated with 3.5 mmol of *p*-toluenesulfonic acid or 2 mmol of concentrated sulfuric acid. Conversion to lactam **7** was immediate and dramatic (by gc) in both instances.

1-Methyl-3-methylene-2-pyrrolidinone (40). The acid **12a** was rearranged as described in the general procedure to yield the lactam **40**: ir 1680 cm^{-1}; nmr δ 2.78 (m, 2 H), 2.83 (s, 3 H), 3.35 (t, 2 H), 5.10 (m, 1 H), 5.66 (m, 1 H).

Anal. Calcd for C_6H_9NO: C, 64.8; H, 8.2; N, 12.6. Found: C, 64.8; H, 8.3; N, 12.5.

1-Methyl-3-methylene-2-oxohexahydroazepine (42) and 6-(*N*-Methyl-*N*-acetylamino)-2-methylenehexanoic Acid (43). The methyl ester **11b** was stirred overnight in 6 *N* HCl at room temperature. Evaporation of the solution gave a quantitative yield of the acid hydrochloride **12b** which was used for the following experiments without further purification: nmr (D_2O) δ 1.42–1.98 (m, 6 H), 2.74 (s, 3 H), 2.76–3.64 (m, 5 H).

A. When the acid **12b** was submitted to the general procedure for rearrangement, none of the lactam **42** was obtained. Reacidification of the aqueous solution, followed by extraction with chloroform and subsequent evaporation of the chloroform and acetic acid, afforded the open-chain derivative **43** in 93% yield. Recrystallization from ethyl acetate gave analytically pure acid **43**: mp 94–95°; ir ($CHCl_3$) 1650, 1725, 3000–3500 cm^{-1}; nmr ($CDCl_3$) δ 1.38–1.80 (m, 4 H), 2.15 (s, 3 H), 2.20–2.57 (m, 2 H), 2.98 (d, *J* = 2 Hz, 3 H), 3.16–3.58 (m, 2 H), 5.60 (m, 1 H), 5.25 (m, 1 H), 11.3 (s, 1 H).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.6; N, 7.0. Found: C, 60.5; H, 8.5 N, 7.1.

B. A mixture of 0.43 g (2.7 mmol) of the acid **12b**, 0.42 g (4.1 mmol) of acetic anhydride, 0.2 g (1.4 mmol) of potassium carbonate, and 30 ml of xylene was heated at reflux for 5 hr. The product was isolated as described in the general procedure to yield 0.22 g (40%) of the *N*-acetyl derivative **43** and 0.15 g (40%) of the lactam **42**: ir 1650 cm^{-1}; nmr δ 1.54–1.81 (m, 4 H), 2.14–2.42 (m, 2 H), 2.88 (s, 3 H), 3.12–3.36 (m, 2 H), 5.05 (m, 1 H), 5.30 (m, 1 H).

Anal. Calcd for $C_8H_{13}NO$: C, 69.0; H, 9.4; N, 10.1. Found: C, 68.8; H, 9.4; N, 10.3.

C. A mixture of 2.5 g (11 mmol) of the mixed anhydride **41** (prepared by stirring the acid **12b** overnight at room temperature in acetic anhydride), 0.7 g (5 mmol) of potassium carbonate, 0.60 g (10 mmol) of acetic acid, and 70 ml of xylene was heated at reflux for 4 hr. Isolation as before yielded 0.63 g (42%) of the lactam **42** and 0.5 g of the *N*-acetyl derivative **43**.

1-Isopropyl-3-methylene-2-piperidone (44). The acid **16** was rearranged as described in the general procedure to yield lactam **44**: **ir 1680 cm^{-1}**; nmr ($CDCl_3$) δ 1.10 (d, *J* = 3 Hz, 6 H), 1.6–2.5 (m, 2 H), 2.37–2.72 (m, 2 H), 3.15 (t, 2 H), 4.90 (heptet, 1 H), 5.19 (s, 1 H), 6.12 (s, 1 H).

Anal. Calcd for $C_9H_{15}NO$: C, 70.6; H, 9.9; N, 9.1. Found: C, 70.5; H, 10.0; N, 9.3.

1-Benzyl-3-methylene-2-piperidone (45). The methyl ester **15** was stirred overnight in 6 *N* HCl at room temperature. Evaporation of the solution afforded a quantitative yield of the acid hydrochloride **17** [nmr δ 1.5–2.4 (m, 4 H), 2.8–3.3 (m, 3 H), 3.35–3.85 (m, 2 H), 4.38 (s, 2 H), 7.50 (s, 5 H)] which was rearranged as described in the general procedure to yield the lactam **45**: ir 1680 cm^{-1}; nmr δ 1.23–1.74 (m, 2 H), 2.12–2.40 (m, 2 H), 2.98 (t, *J* = 6 Hz, 2 H), 4.38 (s, 2 H), 5.00 (m, 1 H), 6.00 (m, 1 H), 7.04 (s, 5 H).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.6; H, 7.5; N, 7.0. Found: C, 77.4; H, 7.4; N, 6.9.

3-Methylene-2-oxo-1-(2,2,2-trifluoroethyl)piperidine (46). A solution of the ester **28** and 6 *N* HCl was stirred overnight at room temperature. Evaporation of the solution afforded a quantitative yield of the acid hydrochloride **29** [nmr (D_2O) δ 1.68–2.15 (m, 4 H), 2.7–3.9 (m, 5 H), 4.20 (q, 2 H, *J* = 9 Hz)] which was rearranged as described in the general procedure with the exception that the reaction time was increased from 3 hr to 24 hr. A 93% yield of the lactam **46** was obtained: ir 1630, 1680 cm^{-1}; nmr δ 1.67–2.22 (m, 2 H), 2.41–2.80 (m, 2 H), 3.40–3.66 (t, 2 H, *J* = 6 Hz), 3.83–4.38 (q, 2 H, *J* = 10 Hz), 5.22–5.35 (m, 1 H), 6.05–6.18 (m, 1 H).

Anal. Calcd for $C_8H_{10}NOF_3$: C, 49.7; H, 5.2; N, 7.3. Found: C, 49.9; H, 5.1; N, 7.3.

3-Ethylidene-1-methyl-2-piperidone (47). The acid **18** was rearranged as described in the general procedure to yield a 50:50 mixture of cis and trans lactams **47a** and **47b**, respectively. Chromatography using ethyl ether as the eluent separated the isomers and gc yielded a pure sample of the cis lactam **47a**: nmr δ 1.68–2.14 (m, 5 H), 2.19–2.55 (m, 2 H), 2.93 (s, 3 H), 3.15 (t, 2 H), 5.65 (q of t, 1 H, *J* = 7, 1 Hz).

Anal. Calcd for $C_8H_{13}NO$: C, 69.0; H, 9.4; N, 10.1. Found: C, 68.8; H, 9.2; N, 10.0.

Similarly, gc afforded an analytically pure sample of the trans lactam **47b**: nmr δ 1.57–2.08 (m, 5 H), 2.22–2.60 (m, 2 H), 2.90 (s, 3 H), 3.30 (t, 2 H), 6.67 (q of t, 1 H, *J* = 7, 1 Hz).

Anal. Calcd for $C_8H_{13}NO$: C, 69.0; H, 9.4; N, 10.1. Found: C, 68.9; H, 9.2; N, 9.9.

3-Benzylidene-1-methyl-2-piperidone (48). The acid **19** was rearranged as described in the general procedure to yield a 30:70 mixture of the cis and trans lactams **48a** and **48b**, respectively, separated by chromatography employing ethyl ether as the eluent. Gc yielded a pure sample of the oily cis lactam **48a**: nmr δ 1.70–2.18 (m, 2 H), 2.37–2.64 (m, 2 H), 2.84 (s, 3 H), 3.24 (t, 2 H, *J* = 6 Hz), 6.32 (br s, 1 H), 6.95–7.45 (m, 5 H).

Anal. Calcd for $C_{13}H_{15}NO$: C. 77.6; H, 7.5; N, 7.0. Found: C, 77.4; H, 7.3; N, 7.0.

Recrystallization from petroleum ether (bp 30–60°)–ether afforded a pure sample of the trans lactam **48b**: mp 70–72°; nmr δ 1.57–2.04 (quintet, 2 H), 2.57–2.85 (m, 2 H), 2.94 (s, 3 H), 3.33 (t, 2 H), *J* = 5 Hz), 7.18 (s, 5 H), 7.55 (br s, 1 H).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.6; H, 7.5; N, 7.0. Found: C, 77.6; H, 7.3; N, 6.9.

Rearrangement of 1-Methyl-2,3-piperidinedicarboxylic Acid Hydrochloride (24). A. A mixture of 0.33 g (1.5 mmol) of the diacid **24**, 20 ml of acetic anhydride, and 0.21 g (1.5 mmol) of potassium carbonate was heated at reflux under nitrogen for 3 hr. The reaction mixture was cooled, poured into 100 ml of ice–water, stirred for 4 hr, and extracted with chloroform (3 × 75 ml). The chloroform extracts were dried, filtered, and evaporated to yield 0.22 g (88%) of the endocyclic α,β-unsaturated lactam acid **50**: nmr ($CDCl_3$) δ 2.32–2.63 (m, 2 H), 3.00 (s, 3 H), 3.24–3.75 (m, 4 H), 6.50 (t, 1 H, *J* = 4 Hz).

The lactam acid **50** was then treated with diazomethane to yield the ester **54**, and gc afforded a pure sample of **54**: ir 1626, 1681, 1739 cm^{-1}; nmr δ 2.20–2.55 (m, 2 H), 2.93 (s, 3 H), 3.10 (d, 2 H, *J* = 1 Hz), 3.33 (t, 2 H, *J* = 5 Hz), 3.60 (s, 3 H), 6.10 (t, 1 H, *J* = 3 Hz).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59,0; H, 7.2; N, 7.7. Found: C, 58.8; H, 7.3; N, 7.7.

B. A mixture of 0.40 g (1.8 mmol) of the diacid **24**, 1.0 g of magnesium sulfate, and 50 ml of xylene was heated at reflux under nitrogen for 20 hr. The reaction mixture was cooled, filtered, and evaporated to yield 0.28 g (91%) of a 17:83 mixture of the lactams **50** and **49**, respectively. The lactams were also further characterized as their respective methyl ester derivatives **54** and **51a**.

Lactam 51. The acid **25** was rearranged as described in the general procedure to yield a 23:77 mixture of the cis and trans lactams **51a** and **51b**, respectively. Gc afforded analytically pure samples. Cis lactam **51a** had nmr δ 1.78–2.2 (m, 2 H), 2.42–2.76 (m, 2 H), 2.95 (s, 3 H), 3.37 (t, 2 H, *J* = 5 Hz), 3.6 (s, 3 H), 5.66 (t, 1 H, *J* = 1 Hz).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.0; H, 7.2; N, 7.7. Found: C, 58.8; H, 7.2; N, 7.8.

Trans lactam **51b** had ir 1610, 1650, 1710 cm^{-1}; nmr δ 1.6–2.1 (m, 2 H), 2.8–3.18 (m, 2 H), 2.98 (s, 3 H), 3.2–3.55 (m, 2 H), 3.65 (s, 3 H), 6.66 (t, 1 H, *J* = 1 Hz).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.0; H, 7.2; N, 7.7. Found: C, 58.9; H, 7.2; N, 7.6.

Isomerization of Lactam 51a to Lactam 54. A solution of 0.030 g (0.16 mmol) of the lactam **51a**, 0.010 g (0.16 mmol) of sodium methoxide, and 10 ml of anhydrous methanol was heated at reflux under nitrogen for 96 hr. The cooled reaction mixture was poured into 50 ml of water, the aqueous phase was acidified (pH 2) and extracted with chloroform (3 × 50 ml), and the chloroform extracts were dried, filtered, and evaporated to yield an oil whose nmr spectrum was commensurate with a 90:10 ratio of the lactams **54** and **51a**, respectively, as confirmed by gc analysis.

1-Methyl-3-ethoxymethyl-2-piperidone (53). To 25 ml of absolute ethanol was added 0.46 g (20 mmol) of sodium. After the sodium had dissolved, 2.5 g (20 mmol) of 1-methyl-3-methylene-2-piperidone (**7**) was added and the reaction mixture was boiled for 7 days, cooled, poured into 100 ml of water, and extracted with chloroform. The dried extracts were evaporated and the residue

was analyzed by gc, indicating a 40% conversion of **7** to **53**. A pure sample of **53** was obtained as an oil by gc: ir 1650 cm^{-1}; nmr (CCl_4) δ 1.19 (t, 3 H, J = 6 Hz), 1.5–2.5 (m, 5 H), 2.95 (s, 3 H), 2.73–3.14 (m, 6 H).

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.1; H, 10.0; N, 8.2. Found: C, 63.0; H, 9.9; N, 8.3.

Reaction of 1-Methyl-3-benzylidene-2-piperidone (48b) with Lithium 2,2,6,6-Tetramethylpiperide. To 0.28 g (2 mmol) of 2,2,6,6-tetramethylpiperidine in 10 ml of ether was added 1.3 ml of a 1.5 M solution of butyllithium in hexane. After stirring for 10 min, 0.4 g (2 mmol) of lactam **48b** was added, and the reaction mixture was refluxed for 20 hr, cooled, and quenched with 5 ml of CH_3COOD. The ethereal solution was washed with 2 N hydrochloric acid and saturated bicarbonate solution, dried, and evaporated to yield lactam **48b** partially deuterated at C-4: nmr δ 1.57–2.04 (q, 2 H), 2.57–2.85 (m, 1.2 H), 2.94 (s, 3 H), 3.33 (t, 2 H, J = 5 Hz), 7.18 (s, 5 H), 7.55 (br s, 1 H).

Registry No.—7, 1690-73-9; **8b**, 2556-73-2; **9a**, 30932-85-5; **9b**, 50585-84-7; **10a**, 5021-33-0; **10b**, 50585-85-8; **11a**, 34616-29-0; **11b**, 50585-86-9; **12a**, 50585-87-0; **12b**, 50585-88-1; **13**, 50585-89-2; **14**, 50585-90-5; **15**, 50585-91-6; **16**, 50678-87-0; **17**, 50585-92-7; *cis*-**18**, 50585-51-8; *trans*-**18**, 50585-52-9; **19**, 50585-93-8; **21**, 605-38-9; **23**, 50585-94-9; **24**, 50585-95-0; **25**, 50585-96-1; **26**, 50585-97-2; **27**, 50585-98-3; **28**, 50585-99-4; **29**, 50586-00-0; **36**, 50586-01-1; **37**, 50586-02-2; **38**, 50586-03-3; **39**, 50586-04-4; **40**, 50586-05-5; **41**, 50586-06-6; **42**, 50586-07-7; **43**, 50586-08-8; **44**, 50586-09-9; **45**, 50586-10-2; **46**, 50586-11-3; **47a**, 50585-53-0; **47b**, 50586-54-1; **48a**, 50586-55-2; **48b**, 50586-56-3; **50**, 50586-12-4; **51a**, 50585-57-4; **51b**, 50585-58-5; **53**, 50586-13-5; **54**, 50586-14-6; diisopropylamine, 108-18-9; isopropyl iodide, 75-30-9; benzyl bromide, 100-39-0; ethyl 1,2-dimethylnipecotate, 14997-01-4; ethvl 1-methyl-2-phenylnipecotate, 50586-15-7; methyl *p*-toluenesulfonate, 80-48-8; benzyl chloroformate, 501-53-1.

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Interconversions of Aziridine Carboxylates and β-Lactams[1]

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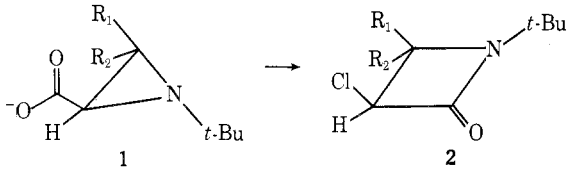
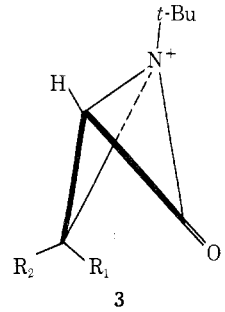
A variety of carboxylate activitating groups convert aziridine carboxylates to 3-halo-2-azetidinones. Yields are in the 20–80% range. The reaction is stereospecific and believed to proceed *via* a 1-azabicyclo[1.1.0]butan-2-one cation. Confirmation for this postulate is found by nmr spectral studies in liquid sulfur dioxide of aziridinecarboxylic anhydrides. In this solvent, equilibrium appears to exist between the anhydride on one hand and the cation and aziridine carboxylate on the other. This equilibrium is displaced toward the cation with arylsulfonyl halides. Attempts to generate the same intermediate from the halolactams were not successful. Ring contraction of the 3-halo-2-azetidinones has also been observed.

In a previous communication, we reported the stereospecific conversion of certain aziridine carboxylates (**1**) to γ-halo-β-lactams (**2**).[1a] In this original communication we



1 **2**

sketched some evidence for product structures and suggested that the ring expansion might proceed *via* the novel and strained bicyclic intermediate **3**. In this paper, we present an elaboration on the previous publication



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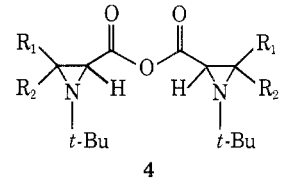
with experimental details and give additional evidence for intermediate **3**.

Preparation of Starting Materials and Structure Proof of Products. The aziridine carboxylates were prepared *via* hydrolysis of the appropriate aziridine ester. The nmr spectrum of each salt in D_2O was in agreement with the assigned structure. The aziridine anhydrides (**4**)



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were prepared by reaction of the aziridine carboxylates with 1 equiv of arenesulfonyl chloride. Although the resultant anhydrides were not crystalline and were too reactive for further purification, their spectral and chemical properties were in full agreement with the assigned structure. The infrared spectra of these substances showed characteristic anhydride carbonyl peaks at 1820 and 1760 cm^{-1}. Their nmr spectra revealed typical monosubstituted aziridine splitting patterns with chemical shifts which were almost identical with those of the ring protons of corresponding aziridine esters.[2] In addition, **4a** reacted with