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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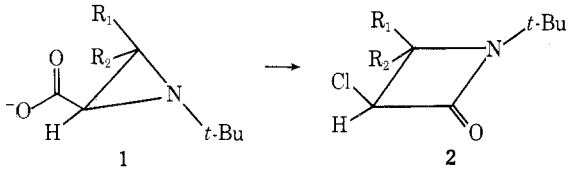
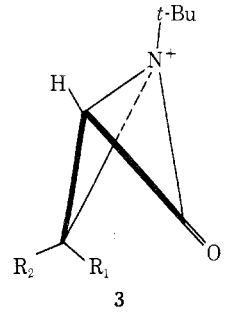
A variety of carboxylate activitating groups convert aziridine carboxylates to 3-halo-2-azetidinones. Yields are in the 20–80% range. The reaction is stereospecific and believed to proceed *via* a 1-azabicyclo[1.1.0]butan-2-one cation. Confirmation for this postulate is found by nmr spectral studies 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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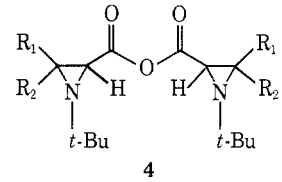
with experimental details and give additional evidence for intermediate **3**.

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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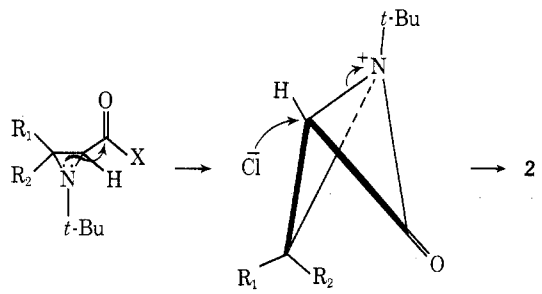
were prepared by reaction of the aziridine carboxylates with 1 equiv of arenesulfonyl chloride. Although the resultant anhydrides were not crystalline and were too reactive for further purification, their spectral and chemical properties were in full agreement with the assigned structure. The infrared 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

Table I
Aziridine Ring Expansions

Starting material[b]	Product[b]	Conditions	Yield, %
1a	**2a**	$C_2O_2Cl_2$–C_6H_6	26
1a	**2a**	$C_2O_2Cl_2$–Et_3N–C_6H_6	29
1a	**2a**	$SOCl_2$–THF–NaH	33
4a	**2a**	Et_4NCl–CH_3CN[a]	14
1b	**2b**	$C_2O_2Cl_2$–C_6H_6	79
4b	**2b**	Et_4NCl–CH_3CN[a]	75
1c	**2c**	$C_2O_2Cl_2$–C_6H_6	63

[a] In the absence of Et_4NCl, β-lactam products apparently formed from the reaction of **2** with TsO^- and CH_3CN. These products were unstable and difficult to purify, and were not characterized further. [b] **a**, $R_1 = R_2 = H$; **b**, $R_1 = CH_3$; $R_2 = H$ (cis); **c**, $R_1 = H$; $R_2 = CH_3$ (trans).

Scheme I



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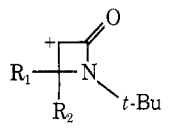
sodium methoxide in methanol to give **1a** and methyl 1-*tert*-butyl-2-aziridinecarboxylate.

Empirical formulae were assigned to the halolactams on the basis of analytical and mass spectral data. The infrared spectra of these compounds showed carbonyl absorption at 1760 cm^{-1} as would be expected for the 2-azetidinone structure. Hydrogenolysis of **2a** yielded 1-*tert*-butyl-2-azetidinone, which was identical with an authentic sample prepared by an alternative procedure. The nmr spectra of the products was also in agreement with the proposed structure. Extraction of the coupling constants from these spectra allowed assignment of the cis-trans stereochemistry based on the expectation that J_{cis} is greater than J_{trans}.[3]

Ring Expansion and Mechanism. The conditions for ring expansion of **1** and **4** are described in Table I. All reactions were carried out at ambient temperature. Although sensitive to structural change, it is significant that changes in the carboxylate activating reagent and proton scavenger had relatively little effect on the yield. We thus conclude that the mechanism for ring expansion does not involve acid-catalyzed nucleophilic ring opening of the aziridine ring and that the activating reagent plays no role other than to foster acyl-oxygen cleavage. Within limits of nmr spectral detection (approximately 1% in this case) formations of **2b** and **2c** were totally stereospecific. It is unlikely, therefore, that "free" carbonium ions (*e.g.*, **5**)



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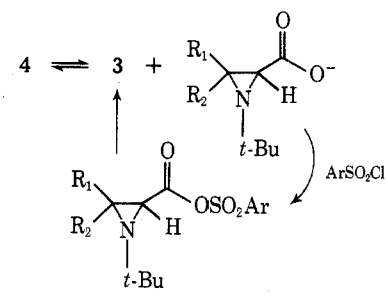
intervene in the expansion process. In view of these considerations; there appears to be only one mechanism which fits the experimental data. This mechanism is shown in Scheme I. Among other things, this mechanism is in agreement with the observed stereochemistry of products **2a** and **2b** by virtue of expected back-side attack on the C_3–N_1 bond.

Table II
Sulfur Dioxide Nmr Spectra of Cis Aziridine Derivatives[a]

	Compd			
Group	Methyl *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate	**4b**	**3b**	Δδ, ppm[b]
t-Bu	0.40	0.39	0.76,[c] 0.78[d]	0.38
CHCH	1.72	1.78	2.76,[c] 2.80[d]	1.00
CH_3	0.58	0.62	0.93,[c] 0.95[d]	0.32

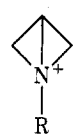
[a] Chemical shifts (δ) relative to external tetramethylsilane in carbon tetrachloride. [b] Difference in chemical shifts of **4b** and average of ions **3b**.[c,d] [c] Counterion was tosylate. [d] Counterion was nosylate.

Scheme II



7

Participation by nitrogen has considerable precedent and recent work in several laboratories has provided convincing evidence for the intermediacy of **6** and its derivatives.[4] The added strain imposed by the C=O group in a three-membered ring and the relationship of **3** to β-lactam chemistry caused us to seek more information concerning the properties of **3** and additional support for its intermediacy.



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Spectral Studies. Strong evidence for the bicyclic cation **3** was obtained from the nmr spectra of the aziridine anhydrides **4a** and **4b** in sulfur dioxide. A dilute sulfur dioxide solution of **4b**, after standing at room temperature for a short time in an nmr tube, gave two sets of nmr spectral signals with similar splitting patterns. One set had chemical shifts comparable to those of the corresponding aziridine ester and was attributed to the anhydride itself. The second set was displaced downfield by 0.3–1.0 ppm (Table II). We assign this latter set to the bicyclic ion **3b**. Addition of nosyl chloride or tosyl chloride to these solutions resulted in the disappearance of the upfield sets of signals and enhancement of the downfield set of signals. This result is readily explainable in terms of the equilibria depicted in Scheme II. Similar results were obtained with the trans anhydride **4c**. A sulfur dioxide solution of this anhydride in the presence of excess nosyl chloride showed both upfield and downfield sets of signals (Table III). If this solution was maintained at −20° for a short period of time, a clean spectrum of bicyclic ion **3c** was obtained. On warming to room temperature, peaks assigned to **3c** disappeared and were replaced by peaks identical with those of authentic β-lactam **2c** in sulfur dioxide.

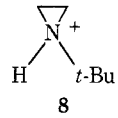
The downfield protons described in Tables II and III are reminiscent of previously observed aziridinium species. Olah has obtained the nmr spectra of 1-*tert*-butylaziridinium ion (**8**) in both antimony pentafluoride-

Table III
Sulfur Dioxide Nmr Spectra of Trans Aziridine Derivatives[a]

Group	Compd: Methyl *trans-tert*-butyl-3-methyl-2-aziridinecarboxylate	Compd: **3c**[b]	Δδ, ppm[c]
t-Bu	0.62	0.88	0.26
CHCH	2.04	2.80	0.76
CH_3	0.83	1.15	0.32

[a] Chemical shifts (δ) relative to external tetramethylsilane in carbon tetrachloride. [b] Counterion was nosylate. [c] Difference in chemical shifts between the trans methyl ester and **4c**.

sulfur dioxide and acidic sulfur dioxide.[5] The values of Δδ (1.20) for the ring hydrogens and for the *tert*-butyl group (1.26) are in reasonable agreement with corresponding Δδ values found in this work. Discrepancies between the monocyclic aziridinium ion and our bicyclic aziridinium ion are readily attributable to such factors as differences in counterion, the anisotropic effect of the carbonyl group, etc.



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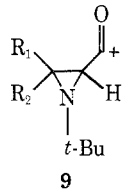
In view of the lack of precedent for structure **3**, it is necessary to consider other species which could give the downfield nmr spectral signals which we attribute to **3**. One such structure is the acylium ion **9**. Acylium ions



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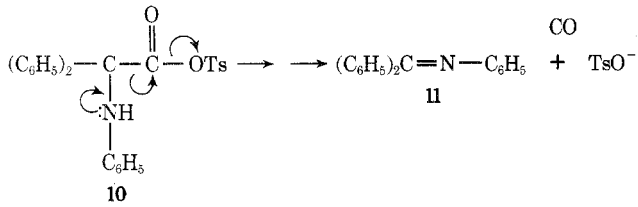
have been observed by Olah, who obtained them from the reaction of acyl halides with Lewis acids.[6] Once formed, these acylium ions were effective acylating agents when quenched by a variety of nucleophiles. In the absence of Lewis acids, these acyl halides were apparently inert toward ionization in SO_2. In contrast to these normal acyl halides, precursors of **3** apparently produced ionized species rapidly in SO_2 without Lewis acid catalysis. It is difficult, therefore, to account for the reactivity of these precursors without invoking participation by nitrogen. When solutions of **3b** were quenched with tetraethylammonium chloride in acetonitrile, **2b** was the only isolated product.

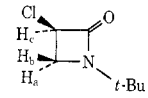
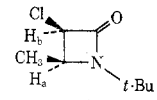
In this connection, it is interesting to contrast the behavior of the mixed anhydride **7** with that of **10**.[7] The latter compound undergoes rapid fragmentation to produce iminium ion **11**. The difference between the two systems is readily explainable in terms of expected and previously observed strain inhibition to ionization in small-ring heterocycles.[3,6]

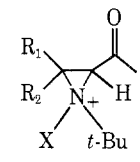


10 **11**

Other obvious sources of the observed spectra may be readily discounted. Nmr spectra in liquid SO_2 of both **2** and its coordinated derivatives have been obtained (*vide infra*) and are distinctly different from the spectra of **3**. Our careful attempts to exclude proton sources and the nature of the product of quenching would appear to convincingly rule out any monocyclic aziridinium species **12**.

Table IV
Sulfur Dioxide Spectra of β-Lactams

Compd	R	SO_2	SO_2–SbF_5	Δδ, ppm
 **2a**	*t*-Bu	0.75	1.15	0.40
	H_c	4.08	4.89	0.81
	H_b	3.18	4.02	0.84
	H_a	2.70	3.59	0.89
 **2b**	*t*-Bu	0.76	1.08	0.32
	H_b	4.22	4.95	0.73
	H_a	3.56	4.37	0.81
	CH_3	0.80	1.25	0.45



12 (X = H, RCO, etc.)

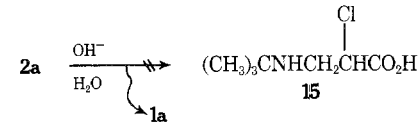
Chemistry of the β-Lactams. The chlorolactams could also potentially serve as precursors to bicyclic ion **3**. Based on the extensive precedents of Olah, antimony pentafluoride was chosen to assist in removing the chloride group. Thus the 3-chloro-2-azetidinones **2a** and **2b** were dissolved in a saturated solution of antimony pentafluoride in sulfur dioxide. The nmr spectrum of the resulting solution was compared to that of the azetidinones in sulfur dioxide (relative to external TMS in CCl_4). Considerable downfield shifts were observed (Δδ, Table IV) for the antimony pentafluoride solutions, but little change in the splitting pattern was noted.

The spectra of the antimony pentafluoride solutions are quite different from the sulfur dioxide spectra of the same supposed ions generated from the anhydride precursors.

However, when attempts were made to quench these supposed ions with methanol, only the original chloroazetidinones could be recovered. These results are interpreted as indicating donor–acceptor complex formation, probably either with oxygen and/or nitrogen and antimony pentafluoride, but not ionization.[8]

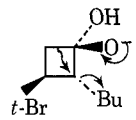
The reluctance of the 3-substituted 2-azetidinones to ionize to the bicyclic cations can be rationalized on stereochemical grounds. An examination of models shows that the unshared pair of electrons on nitrogen is not oriented favorably for overlap at the incipient cation center. Considerable bond deformation, and hence strain, is required for participation and thus ionization to occur. Furthermore, the planar amide linkage would presumably inhibit such a deformation.

One other aspect of the chemistry of these halo-β-lactams proved to be of particular interest. Attempts to selectively convert β-lactam **2a** to amino acid **15** instead reformed the original aziridine carboxylate **1a** in nearly quantitative yield. Reaction with methoxide in methanol



produced the corresponding methyl ester. This ring contraction apparently is stereospecific, since both **2b** and **2c** formed **1b** and **1c**, respectively, stereospecifically. This stereospecific ring contraction has precedent in the carbocyclic case, where the reaction is thought to involve con-

certed (Favorskii type) rearrangement of tetrahedral intermediate **16**.[9] Although a similar Favorskii-type path is



16

possible in the contraction of **2**, an alternate route is possible. This route involves a nucleophilic attack on the C=O, formation of **1b**, and subsequent ring closure to **15**. Since both routes would be stereospecific, we have no basis at the present time for selecting between these two mechanisms. In either case, this and similar ring contraction may have general utility in interconversion of small-ring heterocycles.

Experimental Section

The melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are recorded as the temperature at which the material distils, are at atmospheric pressure unless otherwise noted, and are uncorrected. Evaporative distillations were performed on small samples of material following the (Kugelrohr) procedure of Graeve and Wahl.[10] The infrared spectra were recorded on a Perkin-Elmer Model 137 instrument. The routine nmr spectra were recorded on a Varian Associates A-60A 60-MHz recording spectrometer. The nmr data are presented as follows: chemical shift (splitting pattern, number of hydrogens, coupling constant, assignment). Chemical shifts are expressed in parts per million and, in carbon tetrachloride and chloroform, are relative to internal tetramethylsilane. In deuterium oxide chemical shifts are relative to a position 4.99 ppm upfield from the DOH signal. In sulfur dioxide chemical shifts are relative to external tetramethylsilane in carbon tetrachloride. Molecular weights were determined by mass spectrometry. The mass spectra were recorded on a RMU 6E mass spectrometer at 70 eV. The fragments are reported as *m/e* (rel intensity). Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by PCR, Inc., Gainesville, Fla.

Methyl *cis*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate. Methyl 2,3-dibromobutyrate[11] (100 g, 0.38 mol), triethylamine (100 g, 0.96 mol), and methanol (400 ml) were stirred at room temperature for 3 hr. *tert*-Butylamine (70 g, 0.96 mol) was added, and the mixture was allowed to stand at room temperature for 2 days. Water was added, and the solution was extracted two times with benzene, dried ($MgSO_4$), and evaporated to an oil which on distillation gave 51 g (78%) of a mixture of methyl *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (85%) and methyl *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (15%). The pure cis isomer was obtained by spinning band distillation: bp 65° (3.0 mm); ir (liquid film) 2900 (CH) and 1750 cm^{-1} (C=O); nmr (CCl_4) δ 0.95 (s, 9, *tert*-butyl), 1.17 (d, 3, J = 5.3 Hz, CH_3), 2.05 (m, 2, J = 6.3 Hz, CHCH), and 3.65 (s, 3, OCH_3); mol wt 171.

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.03; H, 9.99; N, 7.95.

Methyl *trans*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate. Methyl 2,3-dibromobutyrate (26 g, 0.10 mol) and triethylamine (39 g, 0.015 mol) were dissolved in benzene (50 ml) and left at room temperature overnight. The amine hydrobromides were removed by filtration, and the filtrate was evaporated to an oil. The oil was dissolved in *tert*-butylamine (18.2 g, 0.25 mol) and left at room temperature for 4 days. The amine hydrobromides were removed by filtration, and the filtrate was evaporated to an oil which on distillation gave 12.4 g (72%) of a mixture of *cis*- (33%) and *trans*- (67%) methyl 1-*tert*-butyl-3-methyl-2-aziridinecarboxylate. The trans isomer, after washing with aqueous sodium carbonate, was completely separated from the cis isomer by spinning band distillation: bp 65° (0.2 mm); ir (liquid film) 2950 (CH) and 1730 cm^{-1} (C=O); nmr (CCl_4) δ 1.10 (s, 9, *tert*-butyl), 1.26 (d, 3, J = 5.5 Hz, CH_3), 2.13 (d, 1, J = 2.4 Hz, C_2H), 2.46 (m, 1, C_3H), 3.63 (s, 3, OCH_3); mol wt 171.

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.44; H, 10.14; N, 8.31.

Sodium *cis*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate (1b). Methyl *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (7.35 g, 0.043 mol) was stirred overnight at room temperature with sodium hydroxide (1.68 g, 0.042 mol) in water (50 ml). The resulting solution was washed with chloroform and evaporated to 7.44 g (99%) of the sodium salt: ir (Nujol) 1600 cm^{-1} (CO_2^-); nmr (D_2O) δ 1.30 (s, 9, *tert*-butyl), 1.44 (d, 3, CH_3), 2.48 (m, 1, C_3H), and 2.74 (d, 1, J = 6.3 Hz, C_2H).

Sodium *trans*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate (1c). Methyl *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (1.20 g, 7.0 mmol) and sodium hydroxide (0.28 g, 7.0 mmol) were stirred together in water (15 ml) at room temperature overnight. The resulting solution was evaporated to 1.19 g (96%) of the sodium salt: ir (Nujol) 1615 and 1590 cm^{-1} (CO_2^-); nmr (D_2O) δ 1.45 (s, 9, *tert*-butyl), 1.58 (d, 3, J = 6 Hz, CH_3), and 2.61 (m, 2, ring protons).

Reaction of Lithium 1-*tert*-Butyl-2-aziridinecarboxylate with Thionyl Chloride. A sodium hydride suspension (0.96 g, 20.0 mmol), washed three times with cyclohexane, was added to tetrahydrofuran (25 ml) under nitrogen to form a slurry. Lithium 1-*tert*-butyl-2-aziridinecarboxylate[2] (1.0 g, 6.7 mmol) was added to the slurry followed by dropwise addition of thionyl chloride (1.19 g, 0.01 mol). The resulting mixture was stirred at room temperature for 1.25 hr. Solvent was removed by evaporation and cyclohexane (35 ml) was added followed by careful addition of water to destroy the sodium hydride present. The organic layer was separated and washed with water, dried ($MgSO_4$), and, after evaporation of the solvent, distilled to give 0.25 g (23%) of 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**): bp 70° (0.2 mm); ir (liquid film) 1760 (C=O), 814, 745, and 695 cm^{-1} (CCl); nmr (CCl_4) δ 1.31 (s, 9, *tert*-butyl), 3.18 (dd, 1, CH), 3.78 (dd, 1, CH), and 4.57 (dd, 1, CH); mol wt 161.

Anal. Calcd for $C_{17}H_{12}NOCl$: C, 52.01; H, 7.43; N, 8.67. Found: C, 52.27; H, 7.65; N, 8.46.

Slightly improved yields could be obtained by removing excess sodium hydride and salts by filtration followed by distillation of the residual oil (33%).

Reaction of Sodium 1-*tert*-Butyl-2-aziridinecarboxylate with Oxalyl Chloride. Solid sodium 1-*tert*-butyl-2-aziridinecarboxylate (1.05 g, 6.3 mmol) was added to a solution of oxalyl chloride (0.95 g, 7.5 mmol) in benzene (10 ml) at room temperature. Both heat and gas were evolved. The resulting slurry was refluxed for 15 min. Benzene (20 ml) was added, and the slurry was washed with aqueous sodium carbonate and water and dried ($MgSO_4$). Distillation of the residual oil left after evaporation of the solvent gave 0.266 g (26%) of 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**). This was identified by spectral comparison to an authentic sample, bp 90° (0.7 mm).

Reaction of Sodium 1-*tert*-Butyl-2-aziridinecarboxylate with Oxalyl Chloride in the Presence of Triethylamine. The sodium salt (1.05 g, 6.3 mmol) was slowly added to a mixture of oxalyl chloride (0.95 g, 7.5 mmol) and triethylamine (0.76 g, 0.0075 mol) in benzene (50 ml). The dark brown slurry was stirred at room temperature for 45 min, washed with 5% HCl, sodium carbonate, and water, dried ($MgSO_4$), and evaporated to 0.30 g (29%) of 1-*tert*-butyl-3-chloro-2-azetidinone. This was identified by comparison to an authentic sample.

Reaction of Sodium *cis*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate (1b) with Oxalyl Chloride. The sodium salt (**1b**, 3.4 g, 0.019 mol) was added slowly to a solution of oxalyl chloride (3.0 g, 0.0238 mol) in benzene (20 ml). The resulting slurry was stirred at ambient temperature for 1 hour, and then a few chips of ice were added. Benzene (20 ml) was added, and the reaction mixture was washed with sodium carbonate and water, dried ($MgSO_4$), and evaporated to 3.2 g (98%) of a clean oil which was distilled to give 2.6 g (79%) of *cis*-1-*tert*-butyl-3-chloro-4-methyl-2-azetidinone (**2b**): bp 65° (0.1 mm); ir (liquid film) 2930 (CH), 1750 cm^{-1} (C=O); nmr CCl_4) δ 1.35 (s, 9, *tert*-butyl), 1.40 (d, 3, J = 6.4 Hz, CH_3), 4.01 (m, 1, CHN), and 4.70 (d, 1, J = 5.1 Hz, CHCO); mol wt 175.

The oil was redistilled for an analytical sample, but even when stored under vacuum it was unstable at room temperature. Thus it is not surprising that the analytical sample did not check.

Anal. Calcd for $C_8H_{14}NOCl$: C, 54.66; H, 8.03; N, 7.98. Found: C, 53.83; H, 7.93; N, 8.02.

Reaction of Sodium *trans*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate (1c) with Oxalyl Chloride. A mixture composed of sodium *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (**1c**, 1.3 g, 3.0 mmol) and an inert salt was added slowly to a solution of oxalyl chloride (1.09 g, 8.7 mmol) in benzene (25 ml). The resulting slurry was stirred at room temperature for 1 hr, washed with 5% HCl, aqueous sodium carbonate, and water, and dried ($MgSO_4$). The solution was evaporated to 0.33 g (63%) of *trans*-1-*tert*-butyl-3-chloro-4-methyl-2-azetidinone (**2c**). The oil was distilled for an analytical sample: bp 65° (0.1 mm); ir (liquid film)

2900 (CH) and 1751 cm^{-1} (C=O); nmr (CCl_4) δ 1.34 (s, 9, *tert*-butyl), 1.45 (d, 3, J = 6.1 Hz, CH_3), 3.68 (m, 1, CHN), and 4.09 (d, 1, J = 1.7 Hz, CHCO); mol wt 177.

Anal. Calcd for $C_8H_{14}NOCl$: C, 54.66; H, 8.03; N, 7.98. Found: C, 54.79; H, 7.91; N, 7.87.

Ring Expansion of Sodium 1-*tert*-Butyl-2-aziridinecarboxylate (1a) with Nosyl Chloride in Acetonitrile. The sodium salt (**1a**, 1.29 g, 6.0 mmol) and nosyl chloride (1.34 g, 6.0 mmol) were stirred together in benzene (50 ml) for 4 hr at room temperature. The slurry was washed with water, dried ($MgSO_4$), and evaporated to an oil which consisted of a mixture of nosyl chloride and 1-*tert*-butyl-2-aziridinecarboxylic acid anhydride (**4a**). The oil was taken up in a solution of tetraethylammonium chloride (2.68 g, 16.0 mmol) in acetonitrile and left at room temperature overnight. The resulting orange solution was evaporated to an oil, taken up in petroleum ether (bp 37–46°), washed with water, dried ($MgSO_4$), and evaporated to a pale yellow oil (0.202 g) which was shown by nmr spectroscopy to consist of 0.13 g (14%) of 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**) together wtih some impurities.

Ring Expansion of Sodium *cis*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate (1b) with Nosyl Chloride in Acetonitrile. The sodium salt (**1b**, 0.37 g, 2.0 mmol) and nosyl chloride (0.44 g, 2.0 mmol) were stirred together in benzene (50 ml) for 4 hr at room temperature. The slurry was washed with water, dried ($MgSO_4$), and evaporated to an oil. The oil was dissolved in a solution of tetraethylammonium chloride (0.33 g, 2.0 mmol) and left at room temperature overnight. Acetonitrile was removed by evaporation and the residual oil was taken up in petroleum ether, washed with water, dried ($MgSO_4$), and evaporated to 0.274 g (75%) of an oil identified as *cis*-1-*tert*-butyl-3-chloro-4-methyl-2-azetidinone (**2b**). Distillation (65°, 0.1 mm) gave 0.17 g.

***cis*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylic Anhydride (4b).** Sodium *cis*-1-ert-butyl-3-methyl-2-aziridinecarboxylate (1.0 g, 5.8 mmol) and nosyl chloride (0.62 g, 2.8 mmol) were stirred together in benzene at room temperature for 4.5 hr. The resulting slurry was washed with water, aqueous sodium carbonate, and again with water, dried ($MgSO_4$), and evaporated to 0.633 g (76%) of an oil identified as *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylic anhydride (**4b**). The oil was taken up in petroleum ether and filtered to remove a fine, insoluble suspension. Evaporation of the filtrate gave 0.574 g (69%) of the anhydride **4b** as an oily solid: ir (liquid film) 2920 (CH), 1820, 1800, and 1760 cm^{-1} (C=O); nmr (CCl_4) δ 1.0 (s, 9, *tert*-butyl), 1.26 (broad d, 3, CH_3), and 2.15 (m, 2, ring protons).

Reaction of *cis*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylic Anhydride with Sodium Methoxide in Methanol. Sodium *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (**1b**, 0.34 g, 2.0 mmol) and nosyl chloride (0.44 g, 2.0 mmol) were stirred at room temperature in benzene, washed with water, dried ($MgSO_4$), and evaporated in an oil composed of the anhydride **4c** and nosyl chloride. The oil was dissolved in a solution of sodium methoxide (0.10 g, 1.8 mmol) in methanol and left at room temperature overnight. The resulting solution was poured into benzene and washed with water. The benzene layer was dried ($MgSO_4$) and evaporated to an oily solid. The residue was taken up in chloroform and the solids were removed by filtration. The chloroform solution was evaporated to 0.118 g (35%) of an oil identified as methyl *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate by nmr spectroscopy.

The water layer was evaporated to a solid which was identified as a mixture of sodium nosylate and sodium *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (**1b**) by nmr spectroscopy.

Reaction of Sodium *trans*-1-*tert*-Butyl-3-methyl-2-aziridinecarboxylate (1c) with Nosyl Chloride. Sodium *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (0.3 g, 1.7 mmol) and nosyl chloride (0.388 g, 1.7 mmol) were stirred in benzene at room temperature for 4 hr. The resulting slurry was washed with aqueous sodium carbonate and water, dried ($MgSO_4$), and evaporated to an oil (0.38 g) consisting of a mixture of *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylic anhydride (**4c**) and unreacted nosyl chloride: nmr (CCl_4) δ 1.17 (s, 9, *tert*-butyl), 1.42 (m, 3, CH_3), 2.30 (d, 1, C_2H), and 2.60 (m, 1, C_3H).

Nmr Spectra of the Anhydrides in Sulfur Dioxide. The anhydrides were dissolved in liquid sulfur dioxide at −10° and transferred in a laboratory atmosphere to nmr sample tubes, which were sealed. Samples of the anhydrides with nosyl or tosyl chloride present were compared by treating the appropriate sodium salts with equimolar amounts of the arylsulfonyl chlorides and dissolving the residual oil left after the usual work-up in sulfur dioxide as above. The same spectra could be obtained by adding the arylsulfonyl chlorides to solutions of the anhydride in sulfur dioxide, but this was found to be less convenient.

The chemical shifts for the ionized and un-ionized anhydrides are reported with reference to external tetramethylsilane in carbon tetrachloride and are tabulated in Tables II and III.

The solution of the cis anhydride in the presence of nosyl chloride or tosyl chloride (after ionization had occurred) was quenched by pouring the sulfur dioxide solution into a solution of tetraethylammonium chloride in acetonitrile. After the usual work-up *cis*-1-*tert*-butyl-3-chloro-4-methyl-2-azetidinone was recovered in yields of 13 and 14%, respectively.

Nmr Spectra of 3-Chloro-2-azetidinones in Antimony Pentafluoride–Sulfur Dioxide. Sulfur dioxide (2 ml) at −10° was saturated with antimony pentafluoride and cooled to −70°. Approximately 300 mg of 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**) was dissolved in the resultant solution, and an aliquot was sealed in an nmr sample tube. The spectrum of the solution was compared to a spectrum of the same azetidinone in sulfur dioxide and both are reported in Table IV. The antimony pentafluoride–sulfur dioxide solution was poured into a solution of sodium methoxide in methanol (−70°). This solution was then warmed to room temperature, poured into water, and extracted with benzene. The benzene layer was dried ($MgSO_4$) and evaporated to a colorless oil identified as extremely clean 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**).

In a similarly fashion *cis*-1-*tert*-butyl-3-chloro-4-methyl-2-azetidinone (**2b**) was treated with antimony pentafluoride–sulfur dioxide. The nmr spectra was recorded as above, and work-up of the solution with sodium methoxide in methanol yielded only extremely clean *cis*-1-*tert*-butyl-3-chloro-4-methyl-2-azetidinone (**2b**).

Reduction of 1-*tert*-Butyl-3-chloro-2-azetidinone (2a) with Zinc. Zinc dust (2.5 g, 30 mmol), activated by stirring for 2 min in concentrated hydrochloric acid, washing four times with distilled water and four times with acetone (reagent grade), and drying *in vacuo* for 15 min, was added to a solution of 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**, 0.40 g, 2.49 mmol) in ethanol. The heterogeneous mixture was then refluxed for 10 days, cooled, filtered, and evaporated to an oil. The oil was distilled to give 0.13 g (41%) of 1-*tert*-butyl-2-azetidinone, bp 90–100° (25 mm).

1-*tert*-Butyl-2-azetidinone. Triethylamine (3.55 g, 35.0 mmol) was added to a slurry of 3-*tert*-butylaminopropionic acid (**11**, 1.3 g, 9.0 mmol) in dry tetrahydrofuran (10 ml). A solution of thionyl chloride (1.4 g, 12 mmol) in tetrahydrofuran (10 ml) was slowly added to the stirred slurry. The resulting yellow mixture was stirred at room temperature for 14 hr, then filtered through a filter cell, and the filtrate was evaporated to a dark brown sludge. The sludge was washed through 5% alumina with chloroform, and the eluent was evaporated to 0.085 g (7%) of a yellow oil identical with the 1-*tert*-butyl-2-azetidinone prepared by reduction of 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**): ir (liquid film) 2900 (CH) and 1740 cm^{-1} (C=O); nmr (CCl_4) δ 1.28 (s, 9, *tert*-butyl), 2.68 (m, 2, CH_2), and 3.12 (m, 2, CH_2); mol wt 127.

Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.02; H, 10.46; N, 10.92.

Reaction of 1-*tert*-Butyl-3-chloro-2-azetidinone (2a) with Sodium Methoxide. In a drybox 1-*tert*-butyl-3-chloro-2-azetidinone 1.2 mmol) was stirred with a solution of sodium hydroxide (0.06 g, 1.5 mmol) in water (5 ml) for 2 hr. The mixture was then refluxed for 3 hr. The resulting solution was cooled, and solvent was removed by evaporation to give 0.245 g (94%) of a pale yellow powder in which the sole organic species present was identified as sodium 1-*tert*-butyl-2-aziridinecarboxylate (**1a**) by comparison of the ir and nmr spectra with spectra of an authentic sample.

Reaction of 1-*tert*-Butyl-3-chloro-2-azetidinone (2a) with Sodium Methoxide. In a dry box 1-*tert*-butyl-3-chloro-2-azetidinone (**2a**, 0.31 g, 1.8 mmol) was added to a solution of sodium methoxide (0.16 g, 3.0 mmol) in methanol (2.5 ml) and left at room temperature for 2 days. The reaction mixture was poured into benzene (15 ml), washed with water, dried ($MgSO_4$), and evaporated to 0.14 g (48%) of an oil identified as methyl 1-*tert*-butyl-2-aziridinecarboxylate by comparison of ir and nmr spectra with the spectra of an authentic sample.

Reaction of *cis*-1-*tert*-Butyl-3-chloro-4-methyl-2-azetidinone (2b) with Sodium Hydroxide. The azetidinone (**2b**, 0.30 g, 1.7 mmol) was dissolved in dioxane (1 ml), and the resulting solution was added to a solution of sodium hydroxide (0.16 g, 40.0 mmol) in water (2 ml). More water was added until the mixture became clear, and the solution was left at room temperature for 30 days. It was then washed with ether and evaporated to 0.38 g (83%) of a white powder identified as sodium *cis*-1-*tert*-butyl-3-methyl-2-az-

iridinecarboxylate (**1b**) by comparison of the ir and nmr spectra with the spectra of a known sample.

Reaction of *trans*-1-*tert*-Butyl-3-chloro-4-methyl-2-azetidinone (2c) with Sodium Hydroxide. The azetidinone (**2c**, 0.30 g, 1.7 mmol) was dissolved in dioxane (1 ml), and the resulting solution was added to a solution of sodium hydroxide (0.18 g, 45.0 mmol) in water (2 ml). Water was added until the mixture became clear, and the resulting solution was left at room temperature for 21 days. It was washed with chloroform and evaporated to a white solid. Nmr observation showed that about 30% of the solid consisted of sodium *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (**1c**). The other components of the mixture were not characterized.

Registry No.—**1a**, 24719-64-0; **1b**, 50562-57-7; **1c**, 50562-58-8; **2a**, 23120-47-0; **2b**, 50562-60-2; **2c**, 50562-61-3; **3b**, 50562-62-4; **3c**, 50562-63-5; **4b**, 50562-64-6; **4c**, 50562-65-7; **11**, 574-45-8; methyl *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate, 34863-28-0; methyl *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate, 34856-93-4.

Supplementary Material Available. Nmr spectra of representative key compounds described in this paper (*e.g.*, **2a, 2b, 2c, 3b, 3c,** and **4a**) 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-74-902.

References and Notes

(1) (a) A portion of these results was presented as a Communication: J. A. Deyrup and S. C. Clough, *J. Amer. Chem. Soc.*, **91**, 4590 (1969). (b) Support of the National Science Foundation (Grant GP 17642) is gratefully acknowledged.
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The Reaction of 6-Amino- and 6-Hydrazinopyrimidines with Diethyl Azodicarboxylate. A New Method for Carbon-5 Functionalization of Pyrimidines[1]

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6-Amino- and 6-hydrazinopyrimidines are shown to react with diethyl azodicarboxylate to give 5-(1,2-dicarbethoxyhydrazino) derivatives. The synthetic potential of this simple method for the direct introduction of nitrogen into the 5 position of the pyrimidine ring is illustrated by a synthesis of 1,3-dimethyluric acid from 1,3-dimethyl-6-aminouracil by reaction with diethyl azodicarboxylate, reduction to 1,3-dimethyl-5-carbethoxyamino-6-aminouracil, and thermal ring closure.

6-Aminopyrimidines unsubstituted at position 5 react with a wide variety of electrophiles (NO^+, NO_2^+, X^+, $RC{=}O^+$, etc.) to give 5-substituted derivatives which number among the most versatile and useful of pyrimidine intermediates.[2] We have now examined the reaction of a number of 6-amino- and 6-hydrazinopyrimidines with diethyl azodicarboxylate and have found that the products are 5-(1,2-dicarbethoxyhydrazino)pyrimidines.[3] These Michael adducts, which possess a reduced nitrogen substituent at position 5, have proved to be versatile synthetic intermediates. The present paper describes this new procedure for C-5 functionalization of pyrimidines;[4] subsequent papers will report the conversion of these adducts to 6- and 7-azapteridines, including the antibiotics fervenulin[4] and 2-methylfervenulone (MSD-92).[5]

Our results are summarized in Tables I and II. The reaction proceeds with remarkable ease when run in suspension in hot dichlorobenzene. Under these conditions the reactants slowly dissolve, and the product then generally crystallizes directly from the hot reaction solution. Electron-withdrawing substituents which reduce the nucleophilicity of the pyrimidine ring towards electrophilic reagents (*e.g.*, **5**), not surprisingly, retard the reaction. Furthermore, the reaction is either retarded or inhibited with 6-hydrazinopyrimidines if the proton adjacent to the ring is substituted by an alkyl group (*e.g.*, **13** and **15**). This observation suggests that the diethyl azodicarboxylate–6-amino- (or 6-hydrazino-) pyrimidine reaction may involve a cyclic transition state similar to that proposed for the reaction of diethyl azodicarboxylate with olefins,[6] where a concerted mechanism with little or no charge development is involved. Proton abstraction from the allylic position of the olefin would thus have its counterpart in the present case in N–H abstraction from the 6 substituent. When such a cyclic transition state is not feasible