The Chemistry of Azocines. Intermediates for the Synthesis of Pyrrolizidines[1]

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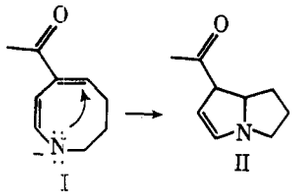
Received February 28, 1977

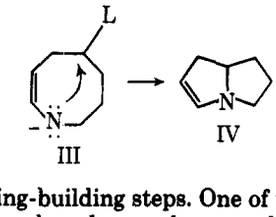
Investigations concerned with the preparation of 1,8-dihydro- and 1,6,7,8-tetrahydroazocines and the utilization of transannular reactions of $\Delta^{4,5}$-epoxyhexahydroazocines for the generation of highly functionalized pyrrolizidines are described. Methods to synthesize 3,4-dicarbomethoxy-1,8-dihydro- and 1,6,7,8-tetrahydroazocines, **19** and **21**, starting with 1,2-dihydropyridines, **22** and **16**, having the *N*-β-styryl and *N*-bromomethyldioxolylethyl substituents as nitrogen protecting groups, are discussed and compared to unsuccessful attempts using a variety of common nitrogen blocking groups. In addition, procedures to convert azocines to functionalized pyrrolizidines using transannular cyclization reactions have been explored. A high yielding sequence starting with the $\Delta^{4,5}$-epoxyhexahydroazocine **33** and proceeding through the intermediate bicyclic amino ether **34** has been developed. The synthetic and mechanistic details of the chemistry regarding the preparation and reactions of azocines are discussed.

A moderate amount of attention has been given recently to the development of general methods to prepare highly functionalized pyrrolizidines which comprise the basic skeletal unit in members of the Senecio alkaloid class[3] and the BC ring system of the potent antitumor and antibacterial agent, mitomycin C.[4] Investigations in this area have led to several novel approaches to the synthesis of these compounds. Synthetic designs followed to date include cycloadditions of γ-substituted crotonic acid esters to 1-pyrroline 1-oxides,[5] intramolecular cyclizations of perhydroazocinones,[6] additions of acetylenes to Munchnone intermediates,[7] photo-Fries rearrangements of lactones,[8] and intramolecular nucleophilic additions to cyclopropane-1,1-dicarboxylic acid derivatives[9] as well as a variety of more classical methodologies.[10]

As part of recent studies targeted at the synthesis of the mitomycins, we have investigated several, potentially novel approaches for the preparation of highly functionalized pyrrolizidines. The strategy of one of these approaches is to employ transannular Michael addition (I → II) and displacement (III → IV) reactions of appropriately substituted azocinyl



I II

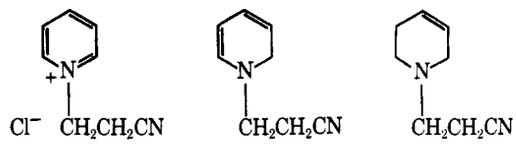


III IV

anions in key ring-building steps. One of the attractive features of sequences based upon these synthetic designs is the demonstrated availability of substituted 1,8-dihydroazocines from cycloaddition reactions of acetylenic esters to 1,2-dihydropyridines[11,12] which in turn are easily prepared by sodium borohydride reduction of corresponding pyridinium salts.[13] Therefore, the plan of the present studies was to investigate methods for generation of appropriately substituted azocines which contain nitrogen protecting groups and for effecting transannular cyclization to pyrrolizidines.

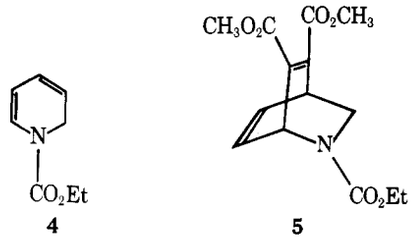
Preparation of N-Protected Azocines. The 1,2-dihydropyridine–acetylene cycloaddition route has been used previously to prepare a variety of 1,8-dihydro- and 1,6,7,8-tetrahydroazocines having alkyl and aryl substitution on nitrogen.[11,12] As a result of our desire to investigate transannular cyclization reactions of azocinyl anions, initial efforts were directed at the development of methods to obtain hydroazocines which lack substitution on nitrogen. Our design was to use nitrogen protecting groups which could be introduced at the pyridinium salt stage and removed at later points in the synthetic sequences after the azocine ring systems are constructed. A variety of typical nitrogen blocking groups, including the carbomethoxy, β-cyanoethyl, and diphenylmethyl, were explored without success. It is instructive to discuss these unsuccessful attempts since the results obtained aid in an evaluation of the types of restrictions that need to be placed on satisfactory blocking groups required for this specific application.

The β-cyanoethyl protecting group appeared applicable for the purpose outlined owing to both its projected ease of removal under base-catalyzed β-elimination conditions and the availability of the starting β-cyanoethylpyridinium salt **1**.[14] Attempts to prepare the intermediate 1-(2-cyanoethyl)-1,2-dihydropyridine (**2**) by borohydride reduction of **1** were futile, however, as a result of the need to conduct these reactions at elevated pH (aqueous sodium carbonate or sodium hydroxide).[13] Thus, from reactions of **1** in aqueous sodium borohydride solutions at varying pH only the cyanoethyltetrahydropyridine **3** (pH 7) or acrylonitrile and pyridine (pH > 7) could be isolated. It appears that at elevated pH reduction is not significantly competitive with β-elimination.



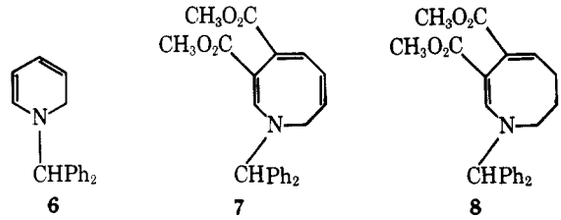
1 2 3

An alternate approach investigated takes advantage of the convenient blocking group properties of alkoxycarbonyl substituents which allows them to be easily removed using a variety of acidic and basic conditions. 1-Carboethoxy-1,2-dihydropyridine (**4**), prepared in a 73% yield by a procedure similar to that described earlier by Fowler,[15] smoothly adds dimethyl acetylenedicarboxylate (neat, room temperature, 71%) via a Diels–Alder [4 + 2] reaction pathway rather than by the typical [2 + 2] mode followed when alkyl- or aryl-substituted 1,2-dihydropyridines are employed. It is evident from the efficiency of the Diels–Alder process, leading to the isoquinuclidiene **5**, that the carbonyl grouping on nitrogen causes significant deactivation of the enamine function required for [2 + 2] cycloaddition to the acetylenic diester.[16]



4 5

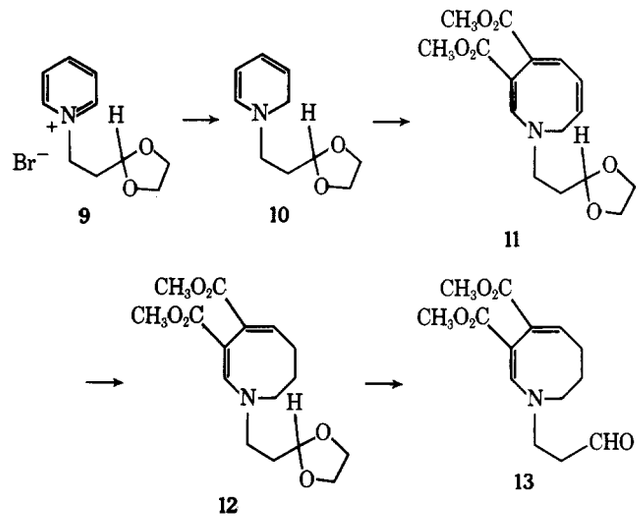
Our attention next turned to the employment of arylmethyl blocking groups since problems associated with the preparation of the corresponding N-substituted 1,2-dihydropyridines and reactions with dimethyl acetylenedicarboxylate should be minimal. Indeed, 1-diphenylmethyl-1,2-dihydropyridine (6), prepared from the reported pyridinium salt[17] using borohydride reduction (10% Na_2CO_3, room temperature, ca. 60%), reacts cleanly with the acetylene (C_6H_6, room temperature, 62%) to produce the benzhydryl substituted dihydroazocine 7 in high yield. However, one further limitation on the type



6 7 8

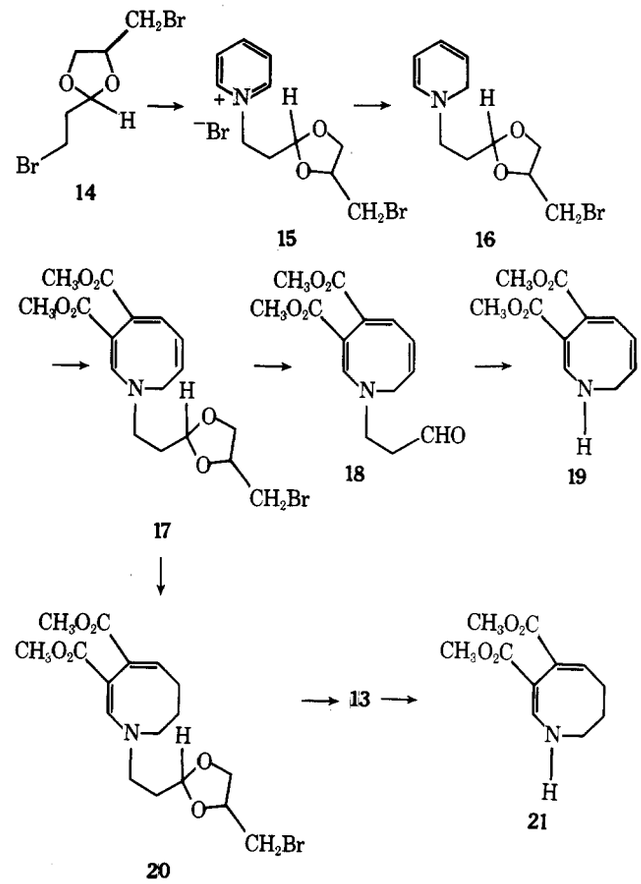
of blocking group required for the preparation of nitrogen unsubstituted azocines is pointed out by the behavior of 7 under reaction conditions normally employed for removal of the diphenylmethyl group. Exhaustive catalytic hydrogenation of 7 at 50 psi using a Pd/C catalyst led only to quantitative formation of the 1,6,7,8-tetrahydroazocine 8 retaining the diphenylmethyl substituent. Additionally, mild acid treatment of 7 or 8 led to rapid decomposition generating a host of unidentifiable products.

As documented by these findings, several of the more typical procedures for nitrogen protection appear incompatible with the general methods used to prepare azocines and the acid sensitivity of these heterocyclic compounds. It is clear that unique types of nitrogen blocking are required in applications of the routes proposed for preparation of pyrrolizidines. As a result, an alternate method to generate dihydroazocines which utilizes base-catalyzed eliminative deblocking of intermediate β-azocinylpropionaldehydes was explored. The strategy used to gain entry into this series of azocine precursors took into account the requirement for utilization of masked carbonyl functions which would survive conditions needed to produce appropriate 1,2-dihydropyridines and which could be removed using methods compatible with the extreme acid lability of dihydro- and tetrahydroazocines. Initial difficulties were encountered with the dioxolane masked propionaldehyde blocking group. Although the dihydroazocine ethylene acetal 11 can be easily prepared in an overall yield of 47% from the known 2-(2-bromoethyl)-1,3-dioxolane,[18] via the pyridinium salt 9 and dihydropyridine 10, unmasking of the aldehyde function under a variety of acid-catalyzed conditions failed to produce detectable quantities of the desired azocinyl aldehyde 18. Similarly, the tetrahydroazocine acetal 12, derived by reduction of 11, can be converted in only poor yield (17%) to the corresponding aldehyde 13 using aqueous hydrochloric acid in tetrahydrofuran at room temperature. Significant improvement was noted when masked propionaldehyde groups which require nonacidic conditions for liberation of the aldehyde function were used. Accordingly, the bromoethylbromomethyldioxolane 14 was generated from 1-bromopropane-2,3-diol[19] and



9 10 11 12 13

acrolein in the presence of hydrogen bromide and converted to the corresponding pyridinium salt 15. Reduction of 15 under the normal conditions led to the dihydropyridine 16 which added dimethyl acetylenedicarboxylate to furnish the dihydroazocinylbromomethyldioxolane 17 in an overall yield of 45% from the bromopropanediol. Aldehyde deprotection was carried out of this stage, using the reported activated zinc fragmentation conditions (MeOH, reflux) developed by Corey,[20] to yield quantitatively the desired aldehyde 18.

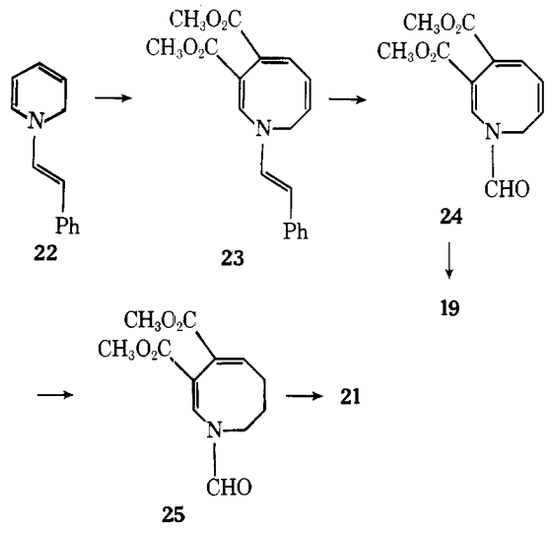


14 15 16 17 18 19 20 21

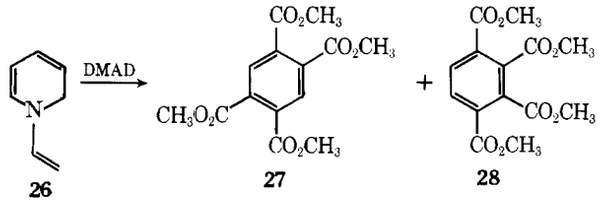
Similarly, the tetrahydroazocinyl aldehyde 13 can be derived from 17 by catalytic hydrogenation (10% Pd/C, MeOH, quantitative) to form 20 followed by zinc deblocking (94%). The final steps in routes to azocines which employ the masked propionaldehyde protecting group employ conditions which affect β-elimination. The most efficient procedure found for this purpose is exemplified by the reactions of 13 and 18 with potassium *tert*-butoxide in dilute *tert*-butyl alcohol solutions

at room temperature. Under these conditions the dihydro- and tetrahydroazocines, **19** and **21**, can be obtained in respective yields of 33 and 43%.

With the goal of providing an alternate and more efficient route to the nitrogen-unsubstituted azocines, the less obvious *N*-β-styryl protecting group was investigated. Several of the attractive features of this group are indicated by observations[12] which show that 1-*trans*-β-styryl-1,2-dihydropyridine (**22**)[21] is an easily prepared, stable solid, its reaction with dimethyl acetylenedicarboxylate proceeds in high yield to furnish the 1-β-styryl-1,8-dihydroazocine **23**, and electrophilic addition reactions of **23** are selective for the exocyclic π bond. Advantage can be taken of this latter property in developing procedures for removal of the β-styryl moiety. Accordingly, we have found that controlled ozonolysis of **23** in methanol followed by reductive decomposition of the intermediate ozonide using dimethyl sulfide leads to cleavage of the styryl π bond and liberation of the 1-formyldihydroazocine **24** (60%). Final deprotection is accomplished in a 72% yield by room temperature treatment of benzene solutions of **24** with sodium methoxide. The tetrahydroazocine **21** can be derived in an analogous fashion by catalytic hydrogenation of **24** (Pd/C, MeOH, 50 psi, quantitative) to yield the formamide **25** followed by deformylation (90%) using sodium methoxide.

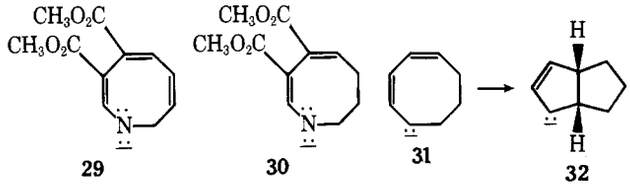


As a consequence of this tailored, stepwise deblocking method it is possible to obtain both the dihydro- and tetrahydroazocines in reasonably high yield. We have attempted, without success, to circumvent the only major limitation held by this last method which derives from the moderately lengthy procedure required to prepare the starting 1-β-styrylpyridinium salt.[21] It was our thought that simple *N*-vinyl groups might serve equally as well in these sequences. However, dramatic differences between the reactivity of 1-vinyl-1,2-dihydropyridine (**26**), prepared by borohydride reduction of the pyridinium bromide salt,[22] and **22** have been observed. Reaction of **26** with dimethyl acetylenedicarboxylate appears to take place exclusively at the exocyclic enamine function and leads to a complex mixture of products containing the tetramethyl esters of 1,2,4,5- and 1,2,3,4-benzenetetracarboxylic acid, **27** and **28**. Thus it appears that the



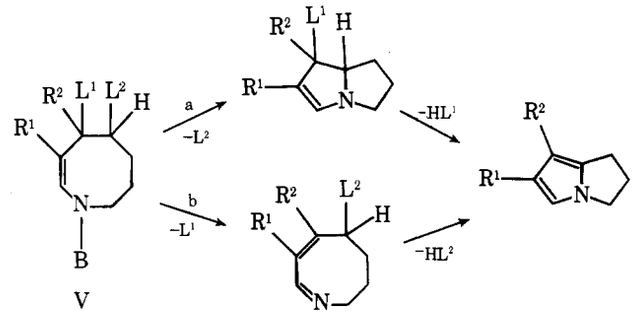
phenyl substituent in **22** is required for selective deactivation of the exocyclic vinyl moiety toward reaction with the acetylenic diester.

Transannular Cyclization. With these initial efforts as background attention was next directed at the development of methods for internal cyclization of the azocines to generate the pyrrolizidine ring systems. The azocinyl anions, **29** and **30**, appeared attractive for this purpose since both possess nucleophilic nitrogen centers correctly located for Michael addition to C-5 of the α,β-unsaturated ester moiety. From an alternate view, both anions contain the heteropentadienyl anion chromophore analogous to those in hydrocarbon systems which undergo $[{}_{\pi}4_s + {}_{\pi}2_s]$ electrocyclizations to produce cyclopentenyl anions.[23] Of particular relevance is the observation that the 1,3-cyclooctadien-5-yl anion (**31**) is efficiently transformed to the bicyclic allyl ion **32**.[23a] Despite this prec-



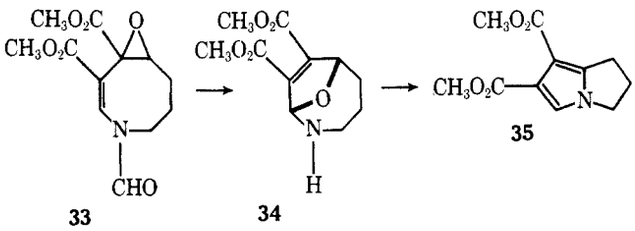
edent, both **29** and **30**, generated using sodium hydride in dimethoxyethane or dimsyl sodium in dimethyl sulfoxide, fail to produce detectable quantities of the corresponding pyrrolizidines. Specifically, the tetrahydroazocinyl anion **30** [^{1}H NMR (Me_2SO-d_6) δ 7.84 (s, H-2), 5.24 (t, H-5); ^{13}C NMR, see Table I] is remarkably stable at room temperature for extended periods, and is transformed back to its amine progenitor upon quenching with water or methanol. The remarkable stability of **30** in contrast to the behavior of **31** appears temporarily rationalized on the basis of an equilibrium between cyclic and bicyclic forms which heavily favors the open anion in the base and solvent systems explored. The thermodynamic stability of the azocinyl anion **30** due to extended conjugation and the low C–N bond dissociation energy may be such as to disfavor the less conjugated cyclized anion. Thus, in the base and solvent systems chosen, reaction would go undetected. Alternatively, steric constraints placed on the tetrahydroazocinyl anion by the medium-sized ring may prevent proper orientation of nitrogen for approach to the α,β-unsaturated ester moiety.[24] However, in light of the observations with **31**, this seems to be a less likely rationale.

In contrast to this, a successful procedure for conversion of hydroazocines to pyrrolizidines resulted from studies of an $\Delta^{4,5}$-epoxyazocine. Consideration was given to the possibility that hydroazocines, having leaving groups at C-4 and C-5 (V), might be useful starting materials for cyclization reactions since generation of the amide anion could be followed by transannular substitution at C-5 followed by elimination of the group at C-4 (pathway a) or by internal elimination followed by cyclization (pathway b). In order to test this hypothesis, the epoxyazocine **33** was prepared by high-temperature oxidation of the formamide **25** with *m*-chloroperbenzoic acid ($ClCH_2CH_2Cl$, Na_2PO_4, reflux, 75%). As can be seen, the



oxirane functionality of **33** can serve as the leaving group at both the C-4 and C-5 azocine positions. Interestingly, deformylation of **33** using sodium methoxide (C_6H_6, 0 °C, 95%) generates in high yield a product which has been characterized as the bicyclic amino ether **34** on the basis of its spectroscopic properties and by single-crystal x-ray diffraction of its tosylamide derivative **36** (*p*-TsCl, pyridine, reflux, 65%).

Crystals of **36** (0.46 × 0.33 × 0.16 mm) suitable for analysis



33 **34** **35**

were grown from ethanol. Diffraction data indicated that the system was monoclinic with unit cell dimensions a = 10.069 (4), b = 11.214 (4), c = 16.668 (7) Å, and β = 97.12 (2)°. The space group is $P2_1/c$ with Z = 4, ρ(calcd) = 1.33 g cm^{-3}, mol wt 374.3 ($C_{20}H_{21}NO_5S$), and V = 1867.5 (1.3) Å^3. Intensity data were collected with a manual General Electric diffractometer using Mo Kα radiation (λ = 0.71069 Å) and balanced zirconium/yttrium filters. The stationary counter–stationary crystal method was employed with 10-s counts recorded for each filter. A total of 2368 independent reflections was measured with 1461 classified as statistically above background. The structure was solved by means of the MULTAN system[26] and then refined by full-matrix least-squares calculations. Reasonable positions for 14 of the 21 hydrogen atoms were located in a subsequent difference Fourier map. These together with the calculated positions for the remaining seven hydrogen atoms were used in the final structure factor calculations, but the hydrogen parameters were not allowed to refine. All of the nonhydrogen atoms were refined with anisotropic temperature factors. The final agreement index is 0.059 where $R = \Sigma||F_o| - |F_c||/\Sigma F_o$ and the weighted agreement index is 0.084 where $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w F_o^2]^{1/2}$. Figure 1 shows an ORTEP[27] plot of the molecular structure with 30% probability ellipsoids for the nonhydrogen atoms.[28]

Although seemingly unusual, the bicyclic amino ether **34** is one of the more likely products expected if the internal elimination pathway is followed in reactions of the anion produced by deformylation of **33**. Accordingly, assisted heterolytic cleavage of the C_4–O epoxide bond would furnish the intermediate **37** having the alkoxy anionic and imine centers correctly disposed for transannular addition to form the bicyclic structure. In this way, the conversion of **33** to **34** can be thought of as the first step in a sequence which is modeled after pathway b for transformation of azocines of general structure V to pyrrolizidines. This feature is demonstrated by the observation that the bicyclic amino ether **34** can be efficiently converted to the pyrrolizidine diester **35** under acid-catalyzed dehydrative conditions using pyridinium hydrochloride (pyridine, reflux, 70%). The structural assignment to **35** rests on firm spectroscopic grounds [^{1}H NMR δ 7.18 (s, 1 H, H-2), 3.98 and 3.07 (t, CH_2), and 2.56 (q, CH_2)].

Although the origin of pyrrolizidine **35** under these reaction conditions can be explained using several mechanisms, it appears quite reasonable that the intermediate iminium ion **38** resulting from acid-catalyzed opening of **34** would undergo a facile hydride shift to furnish the β-keto ester **39**. This substance now possesses the correct functionality and structure for precedented cyclodehydration[6] to the dicarbomethoxy substituted pyrrolizidine.

It is clear from these initial observations that synthetic designs for the preparation of highly functionalized pyrrolizidines which utilize transannular cyclization of hydroazocines hold promise.

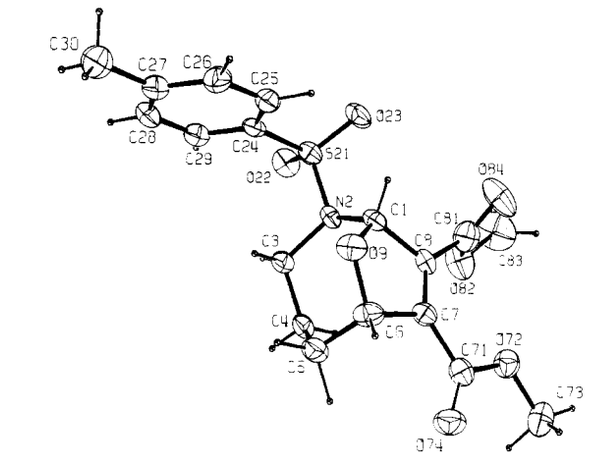
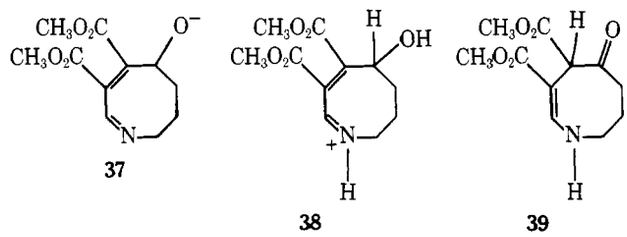


Figure 1. ORTEP perspective drawing of **36** with thermal ellipsoids scaled to 30% probability for nonhydrogen atoms.



37 **38** **39**

Experimental Section

General. ^{1}H NMR spectra were taken on a Varian EM-360, T-60, or HA-100 spectrometer using tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained from a JEOL PS-100 NMR with dedicated probe using a Nic pulsed FT data collection system at an operating frequency of 25.0345 MHz with Me_4Si as an internal standard. Mass spectra were taken on a Du Pont CEC21-110B high-resolution mass spectrometer. UV data were obtained from a Beckman spectrophotometer, Model ACTA III. Infrared spectra were recorded on a Perkin-Elmer 237B, Beckman IR8, or Beckman IR12 spectrophotometer.

Melting points were taken on a Griffin Mel-Temp 110-V capillary melting point apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Preparative chromatographic work was done with either Baker "TLC" silica gel 7GF, Baker "TLC" aluminum oxide 9F, Grace silica gel, Davison grade 923, or MCB Type F-20 activated alumina. Hydrogenations were carried out on a Parr low-pressure hydrogenation apparatus. Ozonolyses were performed using a Welsbach T-408 laboratory ozonator. Unless otherwise mentioned Na_2SO_4 was used as drying agent in workup of reaction mixtures.

1-(2-Cyanoethyl)-1,2,5,6-tetrahydropyridine (3). To a solution of 0.225 g (5.95 mmol) of $NaBH_4$ in 20 mL of 10% aqueous Na_2CO_3 at 0 °C was added a solution of 1.00 g (5.90 mmol) of 1(2-cyanoethyl)pyridinium chloride[14] in 2 mL of water. After stirring at room temperature under N_2 for 15 min, the solution was extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated in vacuo giving an air-unstable, colorless liquid, 0.571 g (71%), characterized as the substituted tetrahydropyridine: IR (CCl_4) 3010, 2235, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.70 (m, 2 H), 3.02 (m, 2 H), 2.64 (m, 6 H), 218 (m, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 136 (12, M$^+$), 96 (100), 83 (7), 54 (44); high-resolution mass spectrum *m/e* 136.099640 ($C_8H_{12}N_2$ requires 136.100040).

1-Carboethoxy-1,2-dihydropyridine (4). A procedure similar to that reported by Fowler[15] for preparation of 1-carbomethoxy-1,2-dihydropyridine was used. A solution of 3.46 mL (44 mmol) of ethyl chloroformate in 6 mL of ether was added to a mixture containing 1.78 g (47 mmol) of sodium borohydride in 3.58 mL (44 mmol) of dry pyridine and 17 mL of ethanol at −78 °C under N_2. After stirring at −78 °C for an additional 1.5 h the mixture was poured into 200

mL of ice water and the resulting solution extracted with ether. The ethereal extracts were washed with water, dried, and concentrated in vacuo, giving a pale yellow oil consisting of pure (>95%) 1-carboethoxy-1,2-dihydropyridine (5.05 g, 73%). Spectra characteristics of this compound follow: IR ($CHCl_3$) 1700, 1645, and 1588 cm^{-1}; UV max ($CHCl_3$) 304 nm; ^1H NMR ($CDCl_3$) δ 6.76 (d, 1 H, J = 8 Hz, H-6), 5.54 (m, 1 H, H-4), 5.16 (t, 1 H, J = 8 Hz, H-5), 5.84 (m, 1 H, H3), 4.38 (q, 2 H, J = 1 Hz, NCH_2), 4.24 (q, 2 H, OCH_2), 1.30 (t, 3 H, CH_3).

2-Carboethoxy-5,6-dicarbomethoxy-2-azabicyclo[2.2.2]-octa-5,7-diene (5). To 0.294 g (1.92 mmol) of freshly prepared 1-carboethoxy-1,2-dihydropyridine at 0 °C under Ar was added 0.734 mL (5.98 mmol) of dimethyl acetylenedicarboxylate. The solution was warmed to room temperature, stirred for 7 days, and chromatographed on a Florisil column. Elution with ether–hexane (0–25%) gave 0.402 g (71%) of the tricarboalkoxyisoquinuclidiene as a yellow oil. Attempts at further purification of this material by distillation at reduced pressure and at temperatures as low as 50 °C cause fragmentation to dimethyl phthalate. Spectral properties of this compound follow: IR (CCl_4) 3030, 1724, and 1699 cm^{-1}; UV max (CH_3CN) 207 nm (log ϵ 3.89); ^1H NMR ($CDCl_3$) δ 8.72 (m, 2 H, vinyl), 5.90 (m, 1 H, bridghead NCH), 4.14 (m, 1 H, bridgehead CH), 4.14 (q, 2 H, J = 7 Hz, OCH_2), 3.14 (m, 2 H, NCH_2), 1.25 (t, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 165.7 (s, co), 163.8 (s, CO), 155.5 (s, CO), 144.7 (s, vinyl C), 140.8 (s, vinyl C), 135.8 (d, vinyl CH), 133.9 (d, vinyl CH), 61.4 (t, NCH_2), 52.3 (q, OCH_3's), 50.6 (d, NCH), 44.3 (t, OCH_2), 40.1 (d, bridgehead CH), 14.7 (q, CH_3); mass spectrum (70 eV) m/e (rel intensity) 295 (7), 263 (1), 236 (3), 194 (4), 163 (100); high-resolution mass spectrum m/e 295.106229 ($C_{14}H_{17}NO_6$ requires 295.106555).

1-Benzhydryl-1,2-dihydropyridine (6). A solution containing 5.00 g (17 mmol) of 1-benzhydrylpyridinium chloride[17] and 0.151 g (4.0 mmol) of $NaBH_4$ in 30 mL of 10% aqueous Na_2CO_3 was stirred at room temperature under Ar. After 15 min a yellow solid had separated from the reaction mixture. This substance was rapidly filtered, washed with water, and dried under an Ar stream. This procedure gave 2.50 g (60%) of the desired dihydropyridine as an exceptionally unstable solid: ^1H NMR ($CDCl_3$) δ 7.28 (s, 10 H, aromatic), 6.05 (d, 1 H, H-6), 5.14 (s, 1 H, Ph_2CH), 5.10 (m, 1 H, H-4), 4.68 (td, 1 H, H-5), 4.36 (m, 1 H, H-3), 3.81 (dd, 2 H, NCH_2). NMR indicated that this material was contaminated with ca. 20% of the tetrahydropyridine and ca. 5% with the 1,4-dihydro isomer.

1-Benzhydryl-3,4-dicarbomethoxy-1,8-dihydroazocine (7). A mixture of 2.00 g (8.00 mmol) of 1-benzhydryl-1,2-dihydropyridine and 4.50 g (32.0 mmol) of dimethyl acetylenedicarboxylate in 30 mL of C_6H_6 was stirred at room temperature for 10 h under Ar. Concentration of the reaction mixture in vacuo gave a red oil which was subjected to column chromatography on silica gel. Elution with hexane followed by 40% Et_2O–hexane gave the pure azocine, 1.90 g (62%), as orange flakes (from EtOH): mp 73–77 °C; IR (CCl_4) 2910, 3010, 1715, 1675, 1690, 1235, 1450, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (t, 2 H, J = 4.0 Hz, $-CH_2-$), 5.61 (dt, 1 H, J = 4.0 and 10.0 Hz), 6.35 (dd, 1 H, J = 3.0 and 10.0 Hz), 6.70 (d, 1 H, J = 3.0 Hz), 7.61 (s, 1 H, H-2), 3.50 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 5.67 (s, 1 H, methine), 7–7.4 (m, 10 H, aromatic); mass spectrum (70 eV) m/e (rel intensity) 389 (2.5, M^+), 358 (2), 349 (s), 300 (1), 167 (100), 152 (5), 77 (1), 59 (1), 165 (7.5); UV max (EtOH) 288 nm (log ϵ 4.02); ^{13}C NMR ($CDCl_3$) 149.2 (d), 95.7 (s, C-3), 131.3 (s, C-4), 128.1 (d, C-5), 126.9 (d, C-6), 127.9 (d, C-7), 56.1 (t, $-CH_2-$), 169.0 (s, CO), 169.4 (s, CO), 51.1 (q, OCH_3), 52.0 (q, OCH_3), 74.1 (d, methine), 128–135 (aromatic); high-resolution mass spectrum m/e 389.161825 ($C_{24}H_{23}NO_4$ requires 389.162685).

1-Benzhydryl-3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine (8). Catalytic hydrogen of 1.00 g (2.60 mmol) of 1-benzhydryl-3,4-dicarbomethoxy-1,8-dihydroazocine in 300 mL of MeOH containing 0.5 g of 10% Pd/C was conducted in a Parr apparatus at room temperature and 55 psi for extended time periods. The calculated H_2 uptake was 1 equiv. The crude reaction mixture was filtered and concentrated in vacuo giving 1.02 g (100%) of the benzhydryltetrahydroazocine: IR (CCl_4) 3010, 2930, 1700, 1580, 1440, 1250, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (s, 1 H, H-1), 6.32 (dd, 1 H, J = 8.0 and 1.0 Hz), 2.2–3.8 (m, 6 H, methylenes), 3.52 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 5.56 (s, 1 H, methine), 7.0–7.4 (m, 10 H, aromatic); mass spectrum (70 eV) m/e (rel intensity) 391 (16, M^+), 360 (s), 224 (4), 192 (6), 167 (100), 152 (10); UV max (EtOH) 310 nm (log ϵ 3.83), 281 (4.03); ^{13}C NMR ($CDCl_3$) 149.5 (d), 92.8 (s, C-3), 133.8 (s, C-4), 134.9 (d, C-5), 25.1 (t, C-6), 17.7 (t, C-7), 45.6 (t, C-8), 169.5 (s, CO's), 51.1 (q, OCH_3), 51.8 (q, OCH_3), 73.6 (d, methine), 128.7–138.7 (aromatic); high-resolution mass spectrum m/e 391.179313 ($C_{24}H_{25}NO_4$ requires 391.178335).

1-(2-Dioxol-2-ylethyl)pyridinium Bromide (9). A mixture of 3.86 g (47.9 mmol) of pyridine and 8.67 g (47.9 mmol) of 2-(3-bromopropyl)-1,3-dioxolane[18] in 10 mL of C_6H_6 was refluxed under Ar for 3 days. Concentration of this mixture in vacuo gave a pale yellow oil, 12.49 g (ca. 100%), which crystallized at 0 °C. A reasonably pure sample, mp 74–82 °C, was prepared by Et_2O trituration followed by rigorous drying over P_2O_5. ^1H NMR ($CDCl_3$) δ 9.36 (d, 2 H), 8.26 (t, 2 H), 8.74 (t, 1 H), 5.04 (t, 1 H), 4.90 (t, 2 H), 3.82 (m, 4 H), 2.40 (sextet, 2 H); UV max (H_2O) 260 nm (log ϵ 3.66), 234 (2.95). Attempts to obtain samples pure enough for elemental analysis failed owing to the extreme hydroscopic nature of this compound.

1-(2-Dioxol-2-ylethyl)-1,2-dihydropyridine (10). To 0.502 g (1.932 mmol) of 1-(2-dioxol-2-ylethyl)pyridinium bromide in 4 mL of 2 N aqueous NaOH at 0 °C under N_2 was added 73.1 mg (1.932 mmol) of $NaBH_4$. $CHCl_3$ (6 mL) was quickly added to this solution and after 30 min the $CHCl_3$ layer was separated, dried, and concentrated in vacuo giving 0.256 g (73%) of a labile oil characterized as the dihydropyridine which was used immediately in ensuing reactions: UV max ($CHCl_3$) 339 nm; ^1H NMR ($CDCl_3$) δ 6.01 (d, 1 H, J = 7 Hz), 58.2 (m, 1 H), 5.08 (m, 1 H), 4.94 (t, 1 H), 4.66 (t, 1 H), 3.91 (m, 6 H), 3.02 (t, 2 H), and 1.88 (m, 2 H).

1-(2-Dioxol-2-ylethyl)-3,4-dicarbomethoxy-1,8-dihydroazocine (11). A solution prepared by adding 15.78 mL (0.129 mol) of dimethyl acetylenedicarboxylate to 15.63 g (85.6 mmol) of freshly prepared 1-(2-dioxol-2-ylethyl)-1,2-dihydropyridine in 50 mL of C_6H_6 at 0 °C under Ar was stirred at room temperature for 4 h. The mixture obtained by solvent removal in vacuo was subjected to column chromatography on silica gel. Elution with Et_2O–hexane mixtures ranging from 10 to 100% Et_2O gave a red oil, 17.69 g (64%), characterized as pure dihydroazocine: IR (CCl_4) 2995, 1729, 1705, 1617, and 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (s, 1 H, H-2), 6.68 (t, 1 H, H-5), 6.54 (d, 1 H), 6.34 (dt, 1 H), 4.89 (t, 1 H), 3.92 (m, 6 H), 3.74 (s, 3 H), 3.60 (s, 3 H), 3.27 (m, 2 H), 1.92 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 323 (52, M^+), 292 (17), 264 (8), 237 (81), 202 (100); UV max (MeOH) 286 nm (log ϵ 4.08), 229 (4.07); ^{13}C NMR ($CDCl_3$) 169.3 (s, CO), 168.7 (s, CO), 149.9 (d), 131.3 (d), 133.4 (d), 135.0 (d), 132.5 (s), 101.7 (d), 94.9 (s), 64.9 (t), 53.5 (t), 51.9 (q, OCH_3), 50.9 (q, OCH_3), 46.6 (t), 32.9 (t); high-resolution mass spectrum m/e 323.136042 ($C_{16}H_{21}NO_6$ requires 323.136855).

1-(2-Dioxol-2-ylethyl)-3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine (12). Catalytic hydrogenation of 15.50 g (48 mmol) of 1-(2-dioxol-2-ylethyl)-2,3-dicarbomethoxy-1,8-dihydroazocine in 150 mL of MeOH containing 20 mg of 5% Pd/C at 53 psi was conducted in a Parr apparatus until 1 equiv of H_2 was consumed. Preparative TLC on silica gel (Et_2O) of the crude mixture obtained after filtration and concentration in vacuo gave 15.68 g (quantitative) of pure tetrahydroazocine: IR ($CHCl_3$) 1713, 1680, 1658, 1605, and 1587 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (s, 1 H, H-2), 6.31 (t, J = 9 Hz, H-5), 4.92 (t, 1 H, J = 4 Hz, OCHO), 3.93 (m, 6 H, OCH_2 and H-8), 3.74 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 3.29 (dt, 2 H, NCH_2), 2.87 (m, 2 H, H-6), 2.48 (m, 2 H, H-7), 1.97 (m, 2 H, CH_2); mass spectrum (70 eV) m/e (rel intensity) 325 (68, M^+), 294 (62), 266 (23), 239 (45), 204 (70), 73 (100); UV max (MeOH) 281 nm (log ϵ 3.89), 211 (3.92); ^{13}C NMR ($CDCl_3$) 169.4 (s, CO), 169.3 (s, CO), 150.5 (d), 134.5 (d), 133.7 (s), 101.8 (d), 92.2 (s), 64.9 (t), 52.9 (t), 51.8 (q, OCH_3), 51.0 (q, OCH_3), 44.9 (t), 32.8 (t), 25.1 (t), 17.6 (t); high-resolution mass spectrum m/e 325.151190 ($C_{16}H_{23}NO_6$ requires 325.152505).

2-(2-Bromoethyl)-4-bromomethyl-1,3-dioxolane (14). To a solution of 96.50 g (0.68 mol) of 1-bromopropane-2,3-diol[19] in 125 mL of $CHCl_3$ containing 63.00 g (0.77 mol) of dissolved HBr at 0 °C was added 37 mL (0.57 mol) of acrolein. The resulting mixture was stirred at room temperature for 3 h and concentrated in vacuo. A pentane solution of the remaining viscous oil was washed with H_2O and 5% $NaHCO_3$, dried, and concentrated in vacuo giving 166.0 g (quantitative) of pure dioxolane. Analytically pure samples of this material were obtained by vacuum distillation: bp 70–71 °C (0.05 mm); ^1H NMR ($CDCl_3$) δ 5.08 (m, 1 H), 4.26 (m, 1 H), 3.50 (m, 6 H), 2.18 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 275, 273, 271 (2, 4, 2, M^+), 165 (100), 167 (95), 57 (29), 137 (9). Anal. Calcd for $C_6H_{10}O_2Br_2$: C, 26.31; H, 3.68; Br, 58.33. Found: C, 26.16; H, 3.62; Br, 58.02.

1-[2-(4-Bromomethyl)dioxol-2-ylethyl]pyridinium Bromide (15). A solution containing 1.10 g (4.01 mmol) of the bromomethyldioxolane of 3-bromopropionaldehyde and 0.33 mL (4.1 mmol) of pyridine in 5 mL of C_6H_6 was refluxed under Ar for 3 days. Concentration of this mixture gave 1.58 g of an extremely viscous oil characterized as the desired pyridinium bromide: ^1H NMR (Me_2SO-d_6) δ 9.23 (d, 2 H), 8.65 (t, 1 H), 8.17 (t, 2 H), 5.18 (dt, 1 H), 4.83 (dt, 2 H), 4.24 (m, 1 H), 3.54 (m, 4 H), 2.42 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 193, 195 (0.6, $C_6H_{10}O_2Br$), 167 (4), 165 (4), 129 (1), 125 (3), 99 (5), 79 (100); UV max (H_2O) 260 nm (log ϵ 3.69) and 204 (3.91).

1-[2-(4-Bromomethyl)dioxol-2-ylethyl]-1,2-dihydropyridine (16). To a solution of 25.1 g (70.8 mmol) of 1-[2-(4-bromometh-

yl)dioxol-2-ylethyl]pyridinium bromide in 80 mL of 2 N NaOH was added 2.68 g (70.9 mmol) of $NaBH_4$ in 20 mL of 2 N NaOH under N_2 at 0 °C. Stirring of this reaction mixture for 30 min was followed by $CHCl_3$ extraction. The $CHCl_3$ extracts were dried and concentrated in vacuo to give 15.5 g (80%) of a labile yellow oil characterized as the desired dihydropyridine. This material was used immediately after its formation: UV ($CHCl_3$) max 339 nm; ^1H NMR ($CDCl_3$) δ 6.00 (d, 1 H, J = 7.0 Hz), 5.84 (m, 1 H), 5.08 (m, 1 H), 4.66 (t, 1 H), 4.32 (m, 3 H), 3.92 (m, 2 H), 3.38 (m, 2 H), 3.00 (dt, 2 H), 1.92 (m, 2 H).

1-[2-(4-Bromomethyl)dioxol-2-ylethyl]-3,4-dicarbomethoxy-1,8-dihydroazocine (17). A solution of 10.32 mL (84 mmol) of dimethyl acetylenedicarboxylate and 15.50 g (56.0 mmol) of 1-[2-(4-bromomethyl)dioxol-2-ylethyl]-1,2-dihydropyridine in 50 mL of C_6H_6 was stirred at room temperature under Ar for 1 h. The crude mixture obtained by removal of the solvent in vacuo was subjected to column chromatography on silica gel. Elution with Et_2O–hexane ranging from 10 to 100% Et_2O gave 13.05 g (56%) of a maroon oil characterized as the pure dihydroazocine: IR (CCl_4) 2985, 1717, 1695, 1605, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (s, 1 H), 6.68 (t, 1 H), 6.54 (d, 1 H), 6.32 (dt, 1 H), 5.06 (dt, 1 H), 4.10 (m, 4 H), 3.75 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.36 (m, 4 H), 1.93 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 417 (M^+), 415 (12), 384 (6), 358 (5), 356 (5), 237 (69), 202 (100); UV max (MeOH) 287 nm (log ϵ 4.14), 229 (4.07); ^{13}C NMR ($CDCl_3$) δ 168.7 (s, CO), 149.8 (d), 135.1 (d), 133.5 (d), 132.5 (s), 131.2 (d), 102.8 (d), 102.2 (d), 95.0 (s), 77.5 (d), 75.3 (d), 74.8 (d), 69.8 (t), 68.8 (t), 53.3 (t), 52.0 (q), 51.0 (q), 46.6 (t), 32.8 (t); high-resolution mass spectrum m/e 417.059689 ($C_{17}H_{22}NO_6Br$ requires 417.06110).

1-[2-(4-Bromomethyl)dioxol-2-ylethyl]-3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine (20). Catalytic hydrogenation of 0.21 g (0.52 mmol) of 1-[2-(4-bromomethyl)dioxol-2-ylethyl]-3,4-dicarbomethoxy-1,8-dihydroazocine in 150 mL of CH_3OH containing 20 mg of 10% Pd/C was conducted in a Parr apparatus at 53 psi until 1 equiv of hydrogen was consumed. The material obtained after concentration in vacuo of the crude reaction mixture was purified by TLC on silica gel (Et_2O) giving 0.21 g (96%) of the pure tetrahydroazocine as a light yellow oil: IR ($CHCl_3$) 3000, 1713, 1687, 1605, and 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (s, 1 H), 6.33 (t, 1 H, J = 8.0 Hz), 5.05 (dt, 1 H), 4.10 (m, 6 H), 3.73 (s, 3 H), 3.61 (s, 3 H), 2.85 (2 H), 2.46 (m, 2 H), 1.97 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 419, 417 (45, M^+), 388, 386 (28), 360 (31), 338 (60), 192 (100); UV max (MeOH) 281 nm (log ϵ 4.09), 211 (4.02); ^{13}C NMR ($CDCl_3$) 169.5 (s, CO), 150.5 (d), 134.6 (d), 133.7 (s), 102.9 (d), 120.4 (d), 92.4 (s), 77.1 (d), 75.3 (t), 69.8 (t), 68.9 (t), 52.7 (t), 51.8 (q, OCH_3), 51.1 (q, OCH_3), 44.9 (t), 32.5 (t), 25.1 (t), 17.6 (t); high-resolution mass spectrum m/e 417.076491 ($C_{17}H_{24}NO_6Br$ requires 417.078720).

3-(3,4-Dicarbomethoxy-1,8-dihydroazocin-1-yl)propionaldehyde (18). A solution of 6.67 g (16.0 mmol) of 1-[2-(4-bromomethyl)dioxol-2-ylethyl]-3,4-dicarbomethoxy-1,8-dihydroazocine in 365 mL of MeOH containing 16.0 g (0.245 g-atom) of activated Zn was refluxed under Ar for 15 h. The resulting mixture was filtered and added to a sufficient quantity of $CHCl_3$ to cause precipitation of ZnBr. The filtrate obtained by filtration of this $CHCl_3$ solution was washed with H_2O, dried, and concentrated in vacuo giving 4.46 g (100%) of a yellow oil characterized as the desired propionaldehyde derivative: IR (CCl_4) 3000, 2810, 2690, 1724, 1703, 1685, 1610, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.82 (s, 1 H), 7.58 (s, 1 H), 6.70 (t, 1 H), 6.53 (d, 1 H), 6.32 (dt, 1 H), 3.75 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.50 (m, 4 H), 2.80 (t, 2 H); mass spectrum (70 eV) m/e (rel intensity) 279 (86, M^+), 248 (31), 220 (100), 202 (33); UV max (MeOH) 286 nm (log ϵ 4.01), 229 (3.99); ^{13}C NMR ($CDCl_3$) 199.6 (d, aldehydic), 169.2 (s, CO), 149.5 (d), 135.2 (d), 133.9 (d), 132.3 (s), 131.0 (d), 94.7 (s), 54.6 (t), 52.1 (q, OCH_3), 51.3 (q, OCH_3), 47.0 (t), 43.4 (t); high-resolution mass spectrum m/e 279.109852 ($C_{14}H_{17}NO_5$ requires 279.110645).

3-(3,4-Dicarbomethoxy-1,6,7,8-tetrahydroazocin-1-yl)propionaldehyde (13). A method similar to that described above was employed using 2.38 g (5.68 mmol) of 1-[2-(4-bromomethyl)dioxol-2-ylethyl]-3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine and 5.66 g (0.16 g-atom) of activated Zn in 70 mL of CH_3OH. This procedure gave 1.50 g (94%) of the pure propionaldehyde derivative as a yellow oil: IR ($CHCl_3$) 2970, 2825, 2680, 1712, 1680, 1600, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.80 (s, 1 H), 7.53 (s, 1 H), 6.32 (t, 1 H), 3.90 (m, 2 H), 3.73 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.44 (m, 2 H), 2.86 (m, 4 H), 2.46 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 281 (31, M^+), 250 (21), 222 (55), 117 (100); UV max (MeOH) 281 nm (log ϵ 4.09), 211 (4.01); ^{13}C NMR ($CDCl_3$) 199.8 (d, aldehydic), 169.3 (s, CO), 150.2 (d), 134.8 (d), 133.7 (s), 92.8 (s), 51.8 (q, OCH_3), 51.0 (q, OCH_3), 50.8 (t), 45.0 (t), 43.1 (t), 25.1 (t), 17.4 (t); high-resolution mass spectrum m/e 281.125139 ($C_{14}H_{19}NO_5$ requires 281.126295).

3,4-Dicarbomethoxy-1,8-dihydroazocine (19). Acrolein Elimination Method. A solution containing 4.32 g (3.87 mmol) of potassium *tert*-butoxide in 175 mL of *tert*-butyl alcohol was mixed with a solution containing 0.360 g (1.29 mmol) of 3-(3,4-dicarbomethoxy-1,8-dihydroazocin-1-yl)propionaldehyde in 25 mL of *tert*-butyl alcohol was stirred at room temperature for 1 h under Ar. The mixture was then neutralized with concentrated HCl and poured into an ice–H_2O mixture. The aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ extract was dried and concentrated in vacuo giving an oil which was purified by TLC on silica gel (Et_2O) giving 0.096 g (33%) of the pure dihydroazocine. The physical and spectroscopic properties were identical with those given below.

3,4-Dicarbomethoxy-1,6,7,8-tetrahydroazocine (21). Acrolein Elimination Method. A procedure similar to the one given above was used employing 0.386 g (3.45 mmol) of potassium *tert*-butoxide and 0.323 g (1.15 mmol) of 3-(3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocin-1-yl)propionaldehyde in 200 mL of *tert*-butyl alcohol. Reaction time was 2 h at room temperature under Ar. The procedure gave after TLC purification 0.110 g (43%) of pure tetrahydroazocine having identical spectroscopic and physical properties with those given below.

1-Formyl-3,4-dicarbomethoxy-1,8-dihydroazocine (24). Ozone in an oxygen stream was bubbled through a vigorously stirred solution of 3.5 g (11 mmol) of 1-*trans*-β-styryl-3,4-dicarbomethoxy-1,8-dihydroazocine[12] in dry MeOH at −50 °C. After 1 equiv of O_3 had passed through the sample, 25 mL of DMS in 25 mL of MeOH was added. The reaction mixture was warmed to room temperature and concentrated in vacuo. The odor of benzaldehyde was prevalent. This material was subjected to column chromatography on silica gel. Elution with 70% Et_2O–hexane gave 1.60 g (60%) of the desired 1-formyl-3,4-dicarbomethoxy-1,8-dihydroazocine: IR ($CHCl_3$) 3100, 2850, 1720, 1640, 1250, 1060, and 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.6 (s, 1 H, formyl), 7.9 (s, 1 H, H-2), 7.2 (d, 1 H, J = 3.2 Hz, H-5), 6.6 (dd, 1 H, J = 3.2 and 10 Hz, H-6), 6.3 (dt, 1 H, J = 7.5 and 10 Hz, H-7), 4.50 (d, 2 H, J = 7.5 Hz, $-CH_2-$), 3.75 (s, 3 H, OCH_3), 3.59 (s, 3 H, OCH_3); mass spectrum (70 eV) m/e (rel intensity) 251 (50, M^+), 220 (18), 192 (81), 163 (31), 132 (81), 104 (100), 77 (56); UV max (MeOH) 337 nm (log ϵ 4.02), 262 (3.84); ^{13}C NMR ($CDCl_3$) 163.5 (d, formyl), 140.4 (d, C-2), 108.1 (s, C-3), 130.5 (s, C-4), 136.6 (d, C-5), 134.6 (d, C-6), 128.3 (d, C-7), 37.8 (t, C-8), 167.4 (s, CO), 52.9 (q, OCH_3), 167.2 (s, CO), 52.1 (q, OCH_3).

Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.44; H, 5.51; N, 5.14.

1-Formyl-3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine (25). Hydrogenation of 1-formyl-2,3-dicarbomethoxy-1,8-dihydroazocine (1.00 g, 4.0 mmol) was conducted on a methanolic solution (124 mL) containing 0.5 g of Pd/C at 55 psi in a Parr apparatus. After uptake of 1 equiv of H_2, the catalyst was separated by filtration. Concentration of the filtrate in vacuo gave 0.99 g (quantitative) of the desired tetrahydroazocine: IR (CCl_4) 3010, 2990, 1730, 1690, 1610, 1440, 1270, and 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.50 (s, 1 H, formyl), 7.82 (s, 1 H, H-2), 3.76 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 6.79 (t, J = 8.2 Hz), 1.5–3.5 (m, 4 H), ~4.0 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 253 (40, M^+), 238 (48), 224 (60), 222 (24), 194 (16), 192 (100), 180 (16), 165 (16), 134 (40), 105 (24); UV max (MeOH) 280 nm (log ϵ 3.95); ^{13}C NMR ($CDCl_3$) 38.1 (t, C-8), 19.6 (t, C-7), 25.1 (t, C-6), 139.8 (d, C-5), 128.6 (s, C-4), 106.0 (s, C-3), 140.9 (d, C-2), 164.2 (d, formyl), 167.2 (s, CO), 167.7 (s, CO), 52.1 (q, OCH_3's); high-resolution mass spectrum m/e 253.095483 ($C_{12}H_{15}NO_5$ requires 253.094995).

3,4-Dicarbomethoxy-1,8-dihydroazocine (19). Deformylation Route. To a solution of sodium methoxide in MeOH [from 0.125 g (5.4 mg-atoms) of Na in 3 mL of MeOH] was added 0.425 g (1.7 mmol) of 1-formyl-3,4-dicarbomethoxy-1,8-dihydroazocine in 7 mL of C_6H_6 at room temperature under N_2. The mixture was then refluxed for 45 min. Extraction with $CHCl_3$ followed by concentration of the organic layer in vacuo gave a solid which was crystallized from CCl_4 to give 0.273 g (72%) of pure dihydroazocine: mp 146–149 °C; IR (CCl_4) 3420, 3030, 2995, 1735, 1610, 1445, and 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.65 (d, 1 H, J = 7.5 Hz), 7.65 (d, 1 H, J = 7.5 Hz), 3.75 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 6.76 (d, 1 H, J = 3.0 Hz), 6.58 (dd, 1 H, J = 10.0 and 3.0 Hz, H-6), 6.26 (dt, 1 H, H-7); mass spectrum (70 eV) m/e (rel intensity) 223 (30, M^+), 192 (15), 164 (75), 132 (30), 104 (100), 77 (25), 59 (10), 51 (25); UV max (MeOH) 226 nm (log ϵ 3.97), 276 (3.94); ^{13}C NMR ($CDCl_3$) 40.9 (t), 132.5 (d), 134.5 (d, C-6), 134.3 (d, C-5), 128.6 (s, C-4), 95.6 (s, C-3), 147.2 (d, C-2), 169.2 (s, CO), 169.5 (s, CO), 52.0 (q, OCH_3), 51.0 (q, OCH_3); high-resolution mass spectrum m/e 223.084791 ($C_{11}H_{13}NO_4$ requires 223.084435).

3,4-Dicarbomethoxy-1,6,7,8-tetrahydroazocine (21). Deformylation Route. A procedure similar to the one used for preparation of the dihydroazocine from the *N*-formyl precursor was used employing 6.0 g (23.7 mmol) of 1-formyl-3,4-dicarbomethoxy-

Table I. ^{13}C NMR Resonances for the Tetrahydroazocine 21 and Tetrahydroazocinyl Anion 30

Carbon[a]	Chemical shift, ppm rel to Me_4Si[b] Tetrahydroazocine 21	Tetrahydroazocinyl anion 30[c]
C-2	147.9	161.8
C-3	90.8	81.8
C-4	133.8	139.8
C-5	134.7	124.2
C-6	24.8	24.4
C-7	19.9	19.8
C-8		45.4
C=O	168.4	172.0
	168.4	168.9
C-O	50.3	48.4
	51.3	50.5

[a] Assignments were based upon multiplicities obtained from coupled spectra. [b] Spectra were recorded on Me_2SO-d_6 solutions. [c] The anion is generated from dimsyl-d_6 sodium in Me_2SO-d_6.

1,6,7,8-tetrahydroazocine, sodium methoxide [from 1.59 g (69 mg-atoms) of sodium in 50 mL of MeOH], and 55 mL of C_6H_6. Workup in a similar manner after 35 min at reflux gave 5.01 g (94%) of the pure tetrahydroazocine: mp 144–145 °C (from CCl_4); IR (CCl_4) 3420, 2990, 3020, 1720, 1600, 1450, 1265, and 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.69 (d, 1 H, J = 7.0 Hz, NH), 7.60 (d, 1 H, J = 7.0 Hz, H-2), 3.68 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3), 6.36 (dd, 1 H, J = 5.0 and 9.0 Hz), 2.3–3.4 (m, 4 H, CH_2's), ~3.8 (2 H); mass spectrum (70 eV) m/e (rel intensity) 225 (29, M^+), 194 (19), 166 (100), 138 (23), 134 (21), 106 (19), 77 (10), 59 (8); UV max (MeOH) 272 nm (log ϵ 4.31), 300 (3.88), 209 (4.12); ^{13}C NMR ($CDCl_3$) 39.3 (t), 19.6 (t), 24.9 (t), 135.5 (d), 133.6 (s), 92.1 (s), 147.8 (d), 169.3 (s), 169.1 (s), 50.7 (q), 51.4 (q).

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.36; H, 6.64; N, 6.04.

1-Vinyl-2,3-dihydropyridine (26). A mixture of 0.133 g (3.52 mmol) of $NaBH_4$ in 6 mL of cold 20% Na_2CO_3 was added to a solution of 1.308 g (7.03 mmol) of 1-vinylpyridinium bromide[22] in 4 mL of H_2O at −4 °C under N_2. $CHCl_3$ (11 mL) was quickly added and after 20 min the $CHCl_3$ layer was separated. The $CHCl_3$ solution was dried and concentrated in vacuo giving 0.338 g (45%) of a light-colored, labile oil characterized as the 1-vinyl-1,2-dihydropyridine: UV max ($CHCl_3$) 344 nm; ^1H NMR ($CDCl_3$) δ 6.47 (AB q, 1 H), 6.09 (d, 1 H), 5.80 (m, 1 H), 5.34 (m, 1 H), 4.56 (m, 1 H), 4.19 (m, 1 H), 3.90 (d, 1 H, J = 13 Hz), 3.75 (d, 1 H, J =16 Hz).

Generation and NMR Spectra of 3,4-Dicarbomethoxy-1,6,7,8-tetrahydroazocinyl Anion (30). Method A. To a suspension of 216 mg (8.90 mmol) of NaH (washed repeatedly with DME to remove dispersion oil) in 30 mL of DME under Ar at room temperature was added 0.30 g (0.34 mmol) of 3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine in 20 mL of DME. A bright red color appeared immediately. After a short period of time, ca. 3 h, the mixture was poured into ice–water and immediately extracted with $CHCl_3$. Concentration of the $CHCl_3$ layer after drying gave quantitative recovery of the starting tetrahydroazocine. It should be mentioned that prolonged standing of the aqueous solution obtained by quenching the tetrahydroazocinyl anion leads to complete destruction of the azocine skeleton.

Method B. A solution containing dimsyl-d_5 sodium in Me_2SO-d_6 [prepared from CaH_2 purified and dried Me_2SO-d_6 and 0.094 g (2.00 mmol) of NaH] and 0.30 g (0.34 mmol) of 3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine was prepared under N_2 at room temperature. Again the characteristic red color of the azocinyl anion was present. ^1H NMR and ^{13}C NMR spectra were recorded for this anion solution: ^1H NMR δ 7.84 (s, 1 H, H-2), 1.21 (m, 2 H, H-7), 3.26 (s, 3 H, OCH_3), 3.52 (s, 3 H, OCH_3), 5.22 (t, 1 H, H-5); ^{13}C NMR (see Table I).

1-Formyl-3,4-dicarbomethoxy-4,5-epoxy-1,4,5,6,7,8-hexahydroazocine (33). To a solution of 0.300 g (1.20 mmol) of 1-formyl-3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine in 30 mL of 1,2-dichloroethane containing finely powdered dry Na_2HPO_4 (0.382 g, 2.40 mmol) at reflux was added 0.479 g (2.40 mmol) of m-chloroperbenzoic acid in 20 mL of 1,2-dichloroethane over a 45-min period. The pH of the reaction medium was constantly monitored and Na_2HPO_4 was added to ensure neutrality. The reaction mixture was refluxed until KI/starch tests indicated the absence of unreacted MCPBA. The reaction mixture was then washed with 10% Na_2SO_3, added to water, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated $NaHCO_3$, dried, and concentrated in vacuo, giving an oil which was purified by TLC on silica gel (Et_2O). The procedure gave pure epoxyazocine, 0.230 g (73%), as a clear oil: IR ($CHCl_3$) 2990, 1740, 1635, 1445, 1260, 1143, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (s, 1 H, H-2), 3.40 (dd, 1 H), 1.80–2.48 (m, 4 H), 4.40 (dd, 2 H), 8.56 (s, 1 H), 3.80 (s, 6 H, OCH_3's); mass spectrum (70 eV) m/e (rel intensity) 269 (14, M^+), 240 (100), 238 (13), 210 (11), 209 (13), 182 (39), 153 (33), 150 (36), 122 (22), 94 (22), 77 (12), 59 (39); UV max (acetonitrile) 261 nm (log ϵ 4.24); ^{13}C NMR ($CDCl_3$) 142.4 (d), 104.1 (s), 56.7 (s), 62.3 (d), 25.0 (t), 24.6 (t), 39.5 (t), 163.7 (d), 170.2 (s), 167.2 (s), 53.1 (q), 52.4 (q).

Anal. Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.28; H, 5.53; N, 5.09.

7,8-Dicarbomethoxy-9-oxa-2-azabicyclo[4.2.1]non-7-ene (34). To a solution of 0.100 g (0.360 mmol) of 1-formyl-3,4-dicarbomethoxy-4,5-epoxy-1,4,5,6,7,8-hexahydroazocine in 10 mL of C_6H_6 at 0 °C under N_2 was added rapidly a mixture of $NaOCH_3$ in CH_3OH (from 0.72 g-atom of Na in 10 mL of CH_3OH). The reaction mixture was stirred at 0 °C for 10 min and poured into water. The $CHCl_3$ layer obtained by extraction was dried and concentrated in vacuo to give the bicyclic amino ether, 0.84 g (94%), which was purified further by TLC on silica gel (Et_2O): IR (CCl_4) 2980, 1740, 3400, 1450, 1270, 1670, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.88 (s, 1 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 2.50 (s, 1 H), 5.14 (dd, 1 H, J = 1.5 and 6.0 Hz), 1.88–2.20 (m, 4 H), 2.94 (dd, 2 H); mass spectrum (70 eV) m/e (rel intensity) 241 (8, M^+), 223 (8), 210 (15), 200 (17.5), 192 (15), 184 (50), 182 (95), 153 (100), 122 (35), 98 (13), 58 (80); UV max (EtOH) 210 nm (log ϵ 3.85), 270 (3.44); ^{13}C NMR ($CDCl_3$) 142.7 (s, olefinic), 134.5 (s, olefinic), 94.6 (d, bridgehead), 82.4 (d, bridgehead), 31.3 (t, $-CH_2-$), 28.6 (t, $-CH_2-$), 42.8 (t, $-CH_2-$), 163.2 (s, CO), 163.0 (s, CO), 52.4 (q, OCH_3's); high-resolution mass spectrum m/e 241.094216 ($C_{11}H_{15}NO_5$ requires 241.094995).

7,8-Dicarbomethoxy-9-oxa-2-azabicyclo[4.2.1]non-7-ene 2-*p*-Toluenesulfonamide (36). A solution containing 0.189 g (0.780 mmol) of 7,8-dicarbomethoxy-9-oxa-2-azabicyclo[4.2.1]non-7-ene and 0.165 g (0.860 mmol) of p-toluenesulfonyl chloride in 10 mL of pyridine was refluxed under N_2 for 1 h. The cooled reaction mixture was poured into H_2O and the resulting solution extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated in vacuo giving material which was purified by TLC on silica gel (Et_2O). This procedure afforded 0.199 g (65%) of the crystalline tosylamide derivative: mp 136–137 °C (from EtOH); IR ($CHCl_3$) 3050, 2980, 1730, 1750, 1475, 1450, 1350, 1170 $c6^{-1}$; ^1H NMR ($CDCl_3$) δ 6.72 (s, 1 H, H-1), 3.83 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 5.13 (t, 1 H, J = 4.0 Hz, H-6), 2.4 (s, 3 H), 1.70–3.40 (m, 6 H, methylenes), 7.75 (d, 2 H, J = 8.0 Hz, aromatic), 7.31 (d, 2 H, J = 8.0 Hz, aromatic); mass spectrum (70 eV) m/e (rel intensity) 395 (2, M^+), 364 (9.5), 326 (76.4), 305 (3), 240 (43.7), 208 (47), 179 (100), 153 (32); UV max (EtOH) 230 nm (log ϵ 4.22); ^{13}C NMR ($CDCl_3$) 92.4 (d), 143.6 (s, C-8), 140.6 (s, C-7), 84.3 (d, C-6), 32.6 (t, C-5), 23.2 (t, C-4), 45.3 (t, C-3), 52.5 (s, CO's), 127.4–136.5 (aromatics), 21.6 (q, methyl); high-resolution mass spectrum m/e 395.102393 ($C_{18}H_{21}NO_7S$ requires 395.103837).

3,4-Dicarbomethoxy-1-azabicyclo[3.3.0]octa-2,4-diene (35). A saturated solution of pyridinium hydrochloride in pyridine (40 mL) containing 0.490 g (2.00 mmol) of 7,8-dicarbomethoxy-9-oxa-2-azabicyclo[4.2.1]non-7-ene was refluxed under N_2 for 30 min. The crude reaction mixture was poured into ice–water and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated NaCl, dried, and concentrated in vacuo giving an oil which was purified by Tlc on silica gel (Et_2O) giving 0.310 g (70%) of the desired pyrrolizidine as a clear, light yellow glass: IR (CCl_4) 2990, 1730, 1445, 1540, 1270, 1105, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (s, 1 H, H-2), 2.56 (quintet, 2 H, methylene), 3.07 (t, 2 H, J = 8.0 Hz, methylene), 3.98 (t, 2 H, J = 8.0 Hz, methylene), 3.81 (s, 6 H, OCH_3's); mass spectrum (70 eV) m/e (rel intensity) 223 (42, M^+), 192 (100), 162 (18), 133 (21), 105 (24), 77 (18); UV max (EtOH) 260 nm (log ϵ 3.77); ^{13}C NMR ($CDCl_3$) 164.3 (s, C=O), 146.1 (s, C-3 and C-4), 121.5 (d, C-2), 119.3 (s, C-5), 51.3 (q, OCH_3), 47.2 (t, C-8), 26.8 (t, C-6), 25.4 (t, C-7); high-resolution mass spectrum m/e 223.083697 ($C_{11}H_{13}NO_4$ requires 223.084435).

Acknowledgments. Financial support for this research from the National Cancer Institute (CA-16695) and the Robert A. Welch Foundation is acknowledged. The JEOL PFT-100 spectrometer used in this research was purchased with grant support from the National Science Foundation. We would like to thank Ms. H. Mireles, Mr. M. Peters, and Dr. E. Krochmal for technical assistance.

Registry No.—1, 15201-08-8; 3, 62562-86-1; 4, 57956-33-9; 5, 62587-48-8; 6, 62562-87-2; 7, 62562-88-3; 8, 62562-89-4; 9, 62587-49-9; 10, 62562-90-7; 11, 62562-91-8; 12, 62562-92-9; 13, 62562-93-0; 14,

62562-94-1; **15**, 62562-95-2; **16**, 62562-96-3; **17**, 62562-97-4; **18**, 62562-98-5; **19**, 62562-99-6; **20**, 62587-50-2; **21**, 62563-00-2; **24**, 62563-01-3; **25**, 62563-02-4; **26**, 62563-03-5; **30**, 62587-52-4; **33**, 62563-04-6; **34**, 62563-05-7; **35**, 62563-05-8; **36**, 62587-51-3; ethyl chloroformate, 541-41-3; pyridine, 110-86-1; dimethyl acetylenedicarboxylate, 762-42-5; 1-benzhydrylpyridinium chloride, 26156-88-7; 2-(3-bromopropyl)-1,3-dioxolane, 62563-07-9; 1-bromopropane-2,3-diol, 4704-77-2; acrolein, 107-02-8; 1-*trans*-β-styryl-3,4-dicarbomethoxy-1,8-dihydroazocine, 62563-08-0; 1-vinylpyridinium bromide, 45590-50-9; *p*-toluenesulfonyl chloride, 98-59-9.

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Bis(methylsulfonoxymethyl) Ether

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Received December 23, 1976

Reaction of acetyl mesylate (**3**) with trioxane and certain other polyoxymethylene derivatives gives the previously unknown title compound in yields as high as 70%. This extremely active compound undergoes the expected dialkylation reactions with mercaptides and with pyridine, but in a few other reactions cleavage occurs leading to derivatives of formaldehyde. Reaction of **3** with paraformaldehyde gives good yields of methylene dimesylate which is the main product from trioxane when a substantial amount of free methanesulfonic acid is present.

Restrictions on the use of bis(chloromethyl) ether (BCME) because of its high level of carcinogenicity to man[1] have produced a need for a suitable substitute for this useful intermediate. Obviously, the bromo- or iodomethyl ethers would serve this purpose, but because of their close relationship to BCME they also are suspect. Utilization of a sulfonate ester, such as bis(methylsulfonoxymethyl) ether (**1**), appeared

$$RSO_3CH_2OCH_2OSO_2R$$

$$1, R = CH_3$$

$$2, R = p\text{-}CH_3C_6H_4$$

to offer the advantages of easier containment, due to a very low vapor pressure, and quite different physiological activity because of its high chemical reactivity as exemplified by a monofunctional analogue, methoxymethyl methanesulfonate.[2] [This compound was found to be 10^4 times more reactive with pure benzene (no catalyst) than is the corresponding chloromethyl ether (in acetic acid).] In fact, recent tests of **1** for mutagenic activity by microbial assay, with and without mammalian metabolic activation (Ames test[3]), gave negative results,[4] in contrast to BCME. (A positive test is suggestive that a chemical may be carcinogenic; on the other hand, a negative result cannot be taken as conclusive evidence to the contrary.[5])

A search of the literature produced no reference to a sulfonate analogue of BCME.[6] An early attempt to prepare for study bis(tosyloxymethyl) ether (**2**) by the direct reaction of silver tosylate with BCME led only to the isolation of *p*-toluenesulfonic anhydride in fair yield. A possible reaction path is shown in Chart I. This result might explain the absence in the literature of any reference to either **1** or **2**. Other examples of failures of double displacements on BCME have been noted elsewhere.[7]

Chart I