the *Clostridium* enzyme catalyzes a direct displacement of triphosphate by vitamin B_{12s}. Peterkofsky[7] has reported that the *Clostridium* enzyme will catalyze the exchange of inorganic [^{32}P]triphosphate with ATP in the absence of B_{12s}. This result was interpreted as evidence for initial formation of an adenosyl-enzyme intermediate. However, Mudd[14] has pointed out a number of potential flaws in Peterkofsky's interpretation. Since our results appear to be incompatible with the formation of an adenosyl-enzyme intermediate,[15] they reinforce Mudd's concerns and suggest that the exchange observed by Peterkofsky is due to processes other than the formation of an adenosyl-enzyme.

Acknowledgment. We thank Professor Frederick Rudolph for helpful advice concerning enzyme purification, the N.I.H. (GM-26166) and The Robert A. Welch Foundation (C-729) for support, and Dr. Robert Gampe of the University of Texas Medical Center, Houston, for NMR spectra.

Supplementary Material Available: Procedures for enzyme purification and for the enzymatic preparation of coenzyme B_{12} from labeled ATP's plus NMR spectra of unlabeled coenzyme B_{12} and of coenzyme B_{12} derived from (5′-$^2H_2$)ATP (5 pages). Ordering information is given on any current masthead page.

(14) Mudd, S. H. "The Adenosyltransferases" "The Enzymes VIIIA", 3rd ed.; Boyer, P. D., Ed.; Academic Press: New York, 1973; pp 121–152.
(15) Formation of coenzyme B_{12} via the two-step mechanism would require that one step take place retention of configuration and the other with inversion. Displacement with retention of configuration is mechanistically unlikely.

Mechanistic and Synthetic Studies of the Cyclopropyl Iminium Ion Rearrangement: An Efficient Route to Enammonium Salts and Related Enamines and Dienamines

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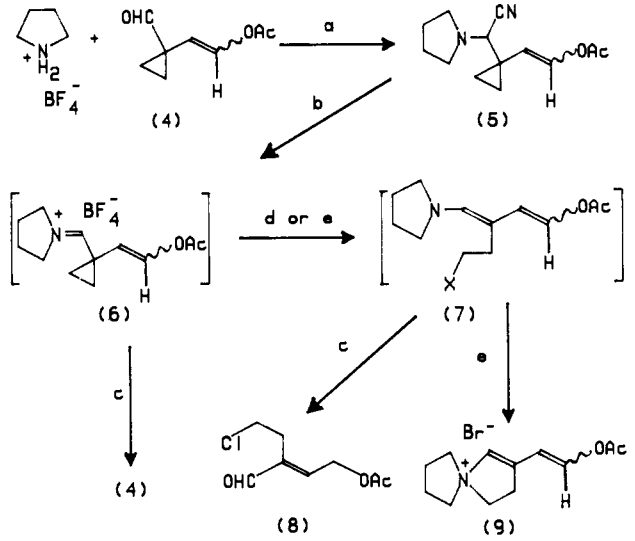
The extensive and systematic studies of Professor R. V. Stevens and co-workers established the generality and synthetic utility of the rearrangement of cyclopropyl imines under acidic catalysis at temperatures of 110 to 150 °C to provide Δ^2-pyrrolines.[1] Some evidence was accumulated which suggested that the rearrangement proceeded by a stepwise mechanism, however, no intermediates were detected to substantiate this reasonable and generally accepted hypothesis.[2,3] A number of syntheses of members of the mesembrine, amaryllidaceae, and pyrrolizidine alkaloid families have been completed by several groups utilizing this protocol.[1,3]

However, the method suffers from several limitations, the major one being the requirement for relatively vigorous acidic reaction conditions. In many instances, the success of the process depends upon the ability to remove the reactive endocyclic enamine from the reaction mixture as it is formed. Thus, there are inherent factors that reduce significantly the scope of the process, especially for applications involving relatively complex and sensitive multifunctional molecules. Therefore, we chose to investigate a process that might circumvent these difficulties and permit access to highly functionalized dienamines which were of interest as intermediates

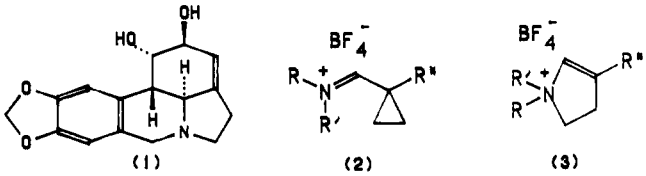
(1) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193.
(2) Stevens, R. V. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1977; Vol. III, p 439.
(3) A related transformation was recently reported by Wasserman and co-workers and its mechanism (also stepwise) defined: (a) Wasserman, H. H.; Dion, R. P. *Tetrahedron Lett.* **1982**, 1413. (b) Wasserman, H. H.; Dion, R. P. *Tetrahedron Lett.* **1983**, 3409.

Scheme I[a]



[a] Reagents: (a) KCN, $MgSO_4$/THF/40 °C/36 h; (b) $AgBF_4$ (1.5 equiv)/DME/room temperature; (c) H_2O; (d) LiCl (1.5 equiv)/DME/room temperature (1.5 h) then 82 °C/1 h; (e) LiBr (1.5 equiv)/CH_3CN/room temperature (4 h).

toward the amaryllidaceae alkaloid lycorine (**1**). We hypothesized that the more highly stabilized iminium ion **2**, which could conceivably be generated under mild, nonacidic conditions, would undergo more facile rearrangement to the stable cyclic enammonium salt **3**. The iminium ion rearrangement appeared to offer



the further advantages of (1) applicability to both 1° and 2° amines, (2) protection of the labile endocyclic enamine or dienamine as the readily isolable enammonium salt **3**, from which the related enamine could be regenerated upon choice of an appropriate alkyl group removable from nitrogen, and (3) substantial flexibility in the nature of the precursors to the iminium salts **2** as well as the conditions under which the intermediates **2** would be generated and the subsequent rearrangement conducted. This hypothesis proved to be correct as described below.

First, with regard to mechanism, we have been able to substantiate the stepwise nature of the transformation. Condensation of aldehyde **4** (cis/trans mixture)[4] with pyrrolidinium fluoroborate (KCN/$MgSO_4$/THF/40 °C/36 h) provided the cyanoamine **5**.[5] Treatment of **5** with $AgBF_4$ in DME (room temperature/0.75 h), as expected,[6] afforded the derived iminium ion **6** which upon addition of water regenerated **4** (Scheme I). Treatment of the solution of **6** in DME with LiCl at room temperature (1.5 h) followed by heating at reflux (1 h) resulted in generation of the intermediate enamine **7**, whose structure was established by hydrolysis to aldehyde **8**.[7] *When LiBr is utilized and the solvent*

(4) Compound **4** was prepared by the following six-step sequence. Alkylation of cyclopropyl cyanide with 3,3-dimethylallyl bromide (LDA) followed by reduction (DIBAL) and treatment of the resulting aldehyde with trimethyl orthoformate yielded the corresponding acetal. Subsequent ozonolysis, formation of the enol acetate (Et_3N/Ac_2O/DMAP), and acidic hydrolysis affords compound **4**.
(5) Direct condensation of the perchlorate salt and aldehyde by the method of Leonard and Paukstelis (Leonard, N. J.; Paukstelis, J. V. *J. Org. Chem.* **1963**, *28*, 3021) is unsuccessful.
(6) Reiber, H. G.; Stewart, T. D. *J. Am. Chem. Soc.* **1940**, *62*, 3026. Grierson, D. S.; Harris, M.; Husson, H. P. *J. Am. Chem. Soc.* **1980**, *102*, 1064.

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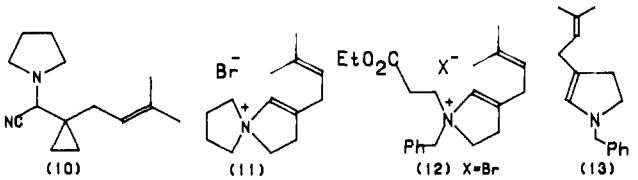
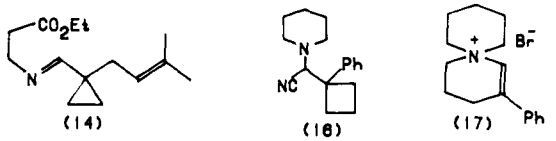
exchanged for acetonitrile, the enammonium salt 9 was obtained after stirring 4 h at room temperature (60%), extraordinarily mild conditions for this conversion.[1] A variety of functional groups are compatible with the rearrangement conditions, for example, cyanoamine **10** (prepared from the cyanohydrin and pyrrolidine, 75%), upon conversion to the iminium salt ($AgBF_4$ (1.55 equiv)/DME) and treatment with LiBr (1.55 equiv) and triethanolamine (1 equiv) (CH_3CN/room temperature (1.5 h) then reflux (2 h)) affords the spirocyclic enammonium salt **11** in 60%



(10) (11) (12) X=Br (13)
(15) X=I

yield.[8] Overall these reactions proceed rapidly under relatively mild, essentially neutral conditions. In the case of the acid sensitive system **5**, none of the desired salt **9** was obtained under acid catalysis. Similarly, attempted rearrangement of the related benzylimine also was unsuccessful using acid catalysis. It is particularly significant that the highly reactive endocyclic enamine functionality is conveniently masked in the easily handled enammonium salts. When it becomes desirable to liberate the masked enamine or dienamine to do further chemistry, one can accomplish this operation by employing the β-carbalkoxyethyl group[9] as the nitrogen protecting group from whose salts the enamine can be liberated upon mild base treatment. For example, exposure of ester salt **12** (prepared in the manner of **9**,[10] 54%) to DBU (1.1 equiv) and diethylamine (1.1 equiv) at 0 °C smoothly affords the sensitive enamine **13** (96%).

Considerable flexiblity exists for the generation of the iminium ions as well. For example, treatment of cyclopropyl imine **14**,



(14) (16) (17)

prepared by condensation of the aldehyde with β-alanine ethyl ester hydrochloride ($MgSO_4$/Et_3N/room temperature/18 h), with benzyl chloride (3 equiv)/NaI (3.8 equiv) in refluxing acetonitrile (4 h) affords directly the rearranged enammonium salt **15** in 66% yield.[11] The imine alkylation procedure is preferred where applicable owing to its generality and experimental simplicity.

The process also appears feasible for cyclobutyl systems, although only one case has been examined thus far.[12] Cyanoamine **16** (prepared as described for **10**) afforded spiro enammonium salt **17** in fair yield under somewhat more vigorous conditions ($AgBF_4$/LiBr/DMF/154 °C).[7] Further studies optimizing the rearrangement in cyclobutyl systems and establishing its scope, as well as evaluating preparation of stable precursors of the endocyclic enamines bearing no β substituent are in progress.

The significantly greater facility with which the above described iminium ions undergo rearrangement (generally mild and neutral conditions) provides an entry into previously unavailable enamine and dienamine systems via their stable enammonium salt precursors. Applications of this methodology to lycorine (**1**) and other more complex systems are under way and will be reported in due course.

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(7) All new compounds possessed satisfactory spectral data (IR, NMR, MS), and combustion analytical or high-resolution mass spectral data. Partial spectral data (NMR (δ) in $CDCl_3$): **5** (90 MHz) (trans isomer) 7.47 (d, J = 12 Hz, 1 H), 5.63 (d, J = 12 Hz, 1 H), 3.77 (s, 1 H), 2.62 (m, 2 H), 2.11 (s, 3 H), 1.79 (m, 2 H), 0.97–0.73 (m, 4 H); **8** (90 MHz) 9.44 (s, 1 H), 6.63 (t, J = 6 Hz, 1 H), 4.95 (d, J = 6 Hz, 2 H), 3.61 (t, J = 7 Hz, 2 H), 2.77 (t, J = 7 Hz, 2 H), 2.14 (s, 3 H); **9** (400 MHz) (trans isomer) 7.58 (d, J = 13 Hz, 1 H), 6.57 (s, 1 H), 6.22 (d, J = 13 Hz, 1 H), 4.03 (t, J = 7 Hz, 2 H), 3.92 (m, 2 H), 3.82 (m, 2 H), 3.08 (br t, 2 H) 2.37 (m, 4 H), 2.23 (s, 3 H), (cis isomer) 7.46 (d, J = 6 Hz, 1 H), 6.49 (s, 1 H), 5.48 (d, J = 6 Hz, 1 H), 3.60 (t, J = 7 Hz, 2 H), 3.49 (m, 4 H), 2.78 (br t, 2 H), 2.45 (m, 4 H), 2.17 (s, 3 H); **15** (300 MHz) 7.41 (m, 5 H), 6.15 (s, 1 H), 5.08 (AB q, 2 H), 4.93 (m, 1 H), 4.22 (m, 6 H), 2.89 (m, 2 H), 2.71 (d, 2 H), 2.43 (m, 1 H), 1.92 (m, 1 H), 1.68 (s, 3 H), 1.56 (s, 3 H), 1.23 (t, 3 H); **16** (300 MHz), 7.33 (m, 5 H), 3.74 (s, 1 H), 2.46 (dt, J_1 = J_2 = 7 Hz, 4 H), 2.25 (m, 4 H), 2.00 (m, 2 H), 1.38 (m, 6 H); **17** (400 MHz) 7.40 (m, 5 H), 6.78 (s, 1 H), 3.90 (m, 6 H), 2.73 (t, 2 H), 2.28 (app t, 2 H), 1.92 (m, 6 H).

(8) The presence of at least 1 equiv of a nonquaternizable tertiary amine base greatly facilitates the production of clean products in some instances. A variety of tertiary amines including diisopropylethylamine function well; however, triethanolamine offers the additional practical advantage of affording water-soluble salts easily separable from the enammonium salt products. The mechanistic ramifications of this observation are currently under investigation.

(9) The product in this case is a mixture of bromide and tetrafluorobrate salts.

(10) Protection of activated olefins by amines has been widely utilized in the Robinson annulation: Jung, M. E. *Tetrahedron* **1976**, *32*, 3. Protection of oxygen by the *p*-toluenesulfonyl ethyl group has also been reported: Miller, A. W.; Stirling, C. J. M. *J. Chem. Soc. C* **1968**, 2612.

(11) A single case of alkylation of an NH imine with methyl iodide was described by Stevens and co-workers: Stevens R. V.; Ellis, M. C.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5576.

(12) A brief study of the cyclobutyl analogue of the cyclopropyl imine rearrangement was conducted by Stevens and co-workers, and it was found to proceed even more sluggishly (temperature required was ≥170 °C): Stevens, R. V.; Shev, J. T. *J. Chem. Soc., Chem. Commun.* **1975**, 682. The greater facility of the iminium ion rearrangement proves particularly advantageous in these cases.

Intramolecular [2 + 2] Cycloadditions of Ketenes and Keteniminium Salts to Olefins

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Cyclobutanones are versatile synthetic intermediates[1] used in processes such as geminal[2] or vicinal[3] alkylation. They are readily prepared by the reaction of activated ketenes[4] or keteniminium salts[5] with olefins. The intramolecular version of these cycloadditions could offer promising routes for the regio- and stereocontrolled synthesis of polycyclic compounds. Isolated examples of intramolecular thermal[6] or photochemical[7] cycloadditions in-

(1) For selected examples, see: (a) Martin, P.; Greuter, H.; Bellus, D.; *Helv. Chim. Acta* **1981**, *64*, 64. (b) Brady, W. T. *Tetrahedron* **1981**, *37*, 2949. (c) Newton, R. F.; Roberts, S. M. *Tetrahedron* **1980**, 2163. (d) Goldstein, S.; Vannes, P.; Houge, C.; Frisque-Hesbain, A. M.; Wiaux-Zamar, C.; Ghosez, L. *J. Am. Chem. Soc.* **1981**, *103* 4616.

(2) Trost, B. M.; Preckel, M.; Leichter, L. M. *J. Am. Chem. Soc.* **1975**, *97*, 2224.

(3) (a) Ghosez, L. "Stereoselective Synthesis of Natural Products"; Bartmann, W., Winterfeldt, E., Eds.; Excerpta Medica: Amsterdam–Oxford, 1979; pp 93–105. (b) Michel, P.; O'Donnell, M. J.; Hesbain-Frisque, A. M.; Ghosez, L.; Declercq, J. P.; Germain, G.; Van Meerssche, M.; *Tetrahedron Lett.* **1980**, 2577.

(4) Recent review: Ghosez, L.; O'Donnell, M. J. "Pericyclic Reactions"; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. II, pp 79–140.

(5) (a) Ghosez, L.; Marchand-Brynaert, J. "Iminium Salts in Organic Chemistry Part 1; Böhme, J., Viehe, H. G., Eds., Wiley: New York, 1976; pp 421–532. (b) Falmagne, J. B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 879.

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