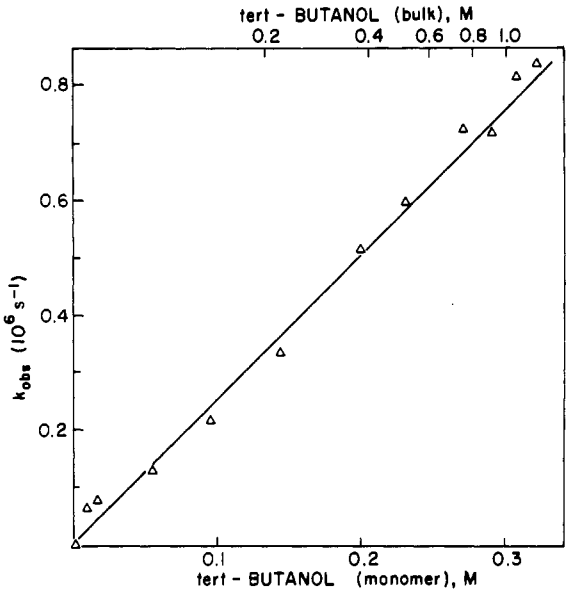

Figure 3. Quenching of AnĊCl by *tert*-butyl alcohol in isooctane at 300 K, plotted as a function of the monomer concentration.

The corresponding rate constant for the reaction of *tert*-butyl alcohol monomer was $(2.5 \pm 0.2) \times 10^6$ M^{-1} s^{-1}.[32]

The temperature dependence of the reaction of AnĊCl with methanol was in accord with this model since the observed rate constant increased as the temperature decreased. This observation is consistent with the increased formation of dimer and higher oligomers at the lower temperatures. Indeed, the observed activation energy of -4.7 ± 0.3 kcal mol^{-1} is similar to the enthalpy change associated with hydrogen bond formation.[33]

Interestingly, similar effects were not observed in the reactions of the same arylchlorocarbenes with acetic and other acids, e.g., reaction 13. In these cases dimers of

$$\text{PhĊCl} + \text{MeCO}_2\text{H} \rightarrow \text{PhCH(OCOMe)Cl} \rightarrow \text{PhCHO} + \text{MeCOCl} \quad (13)$$

the acids are the highest oligomers that form and the rate constants for these reactions were found to be close to the diffusion-controlled limit ($k_{13} = (3.1 \pm 0.6) \times 10^9$ M^{-1} s^{-1} in isooctane solvent at 298 K).[34]

Concluding Remarks

Laser flash photolysis studies of carbene reactions have provided insights into their mechanisms beyond those which could have been gained by product or competitive kinetic studies. Examples are the reversible formation of intermediates in cyclopropanation by phenylchlorocarbenes, discrimination by those carbenes toward alcohol monomers and oligomers. Measurements of absolute rate constants for carbene reactions have shown that electronic and steric factors can have an enormous effect on carbene lability. At one extreme, fluorenylidene reacts rapidly and relatively indiscriminately with almost all substrates while at the other extreme dimesitylcarbene is highly selective in its behavior and is relatively persistent. We expect that the experiments described in this Account are modest forerunners of those yet to come, in which the laser techniques are extensively applied in carbene chemistry.

(33) Joesten, M. D.; Schaad, L. J. "Hydrogen Bonding"; Marcel Dekker: New York, 1974; Chapter 5.
(34) Griller, D.; Liu, M. T. H.; Montgomery, C. R.; Scaiano, J. C.; Wong, P. C. *J. Org. Chem.* **1983**, *48*, 1359.
(35) **Note Added in Proof.** A recent report indicates that k_{ST} in acetonitrile is ca. one-third of the value originally reported[17] and that k_{ST} is solvent dependent. Sitzmann, E. V.; Langan, J.; Eisenthal, K. B. *J. Am. Chem. Soc.* **1984**, *106*, 1868.

Nucleophilic Additions to Tetrahydropyridinium Salts. Applications to Alkaloid Syntheses

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A previous *Account* from these laboratories[1] dealt with the development of two new and quite general methods for the stereospecific total synthesis of structurally diverse alkaloids. In that *Account*, a high premium was placed on efficiency of bond construction and stereochemical control. For example, the acid-catalyzed rearrangement of various cyclopropylimines to the corresponding 4,5-dihydropyrroles (cf. 1 to 2) provides an illustration wherein two new bonds are produced, as does the subsequent annulation of these and other endocyclic enamines (e.g., 4) to afford exclusively cis-fused hydroindolones (3) or hydroquinolones (5) (Scheme I). It is the goal of this *Account* to outline the genesis of a powerful heuristic[2] principle and to retrace the course of events from its inception to the present time.

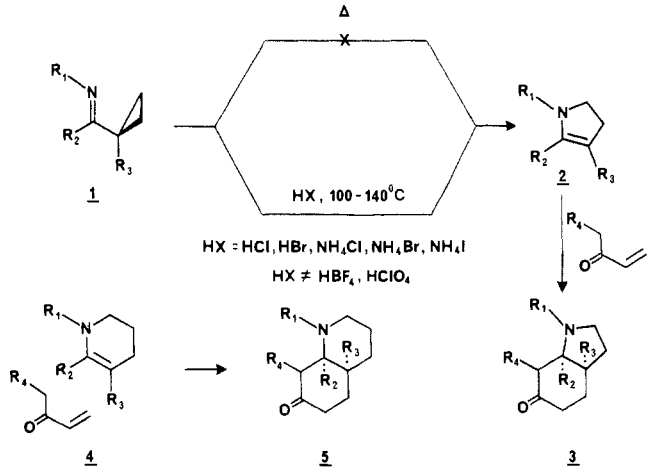
Professor Robert Velman Stevens was born on March 24, 1941, in Mason City, Iowa, and studied at Iowa State University for his B.S. degree, which he completed in 1963. In 1966, immediately following his graduate studies at Indiana University with Professor Ernest Wenkert, he was appointed to the faculty at Rice University, where he served for 11 years before joining the Department of Chemistry at the University of California, Los Angeles, as Professor of Chemistry. He earned for himself an international reputation as a master in the art of synthesis of complex organic structures and will be well remembered for his impressive synthetic approach to Vitamin B-12. In addition, his research interests focused on the development of new methodologies and strategies for the total synthesis of natural products including vitamins, steroids, terpenoids, and antibiotics, as well as alkaloids.

* Deceased March 9, 1984. Due to his untimely death, revision of Professor Stevens' original manuscript was conducted by his research group under the supervision of Professor Michael E. Jung. Please address correspondence to Dr. Jung, Department of Chemistry and Biochemistry, UCLA.

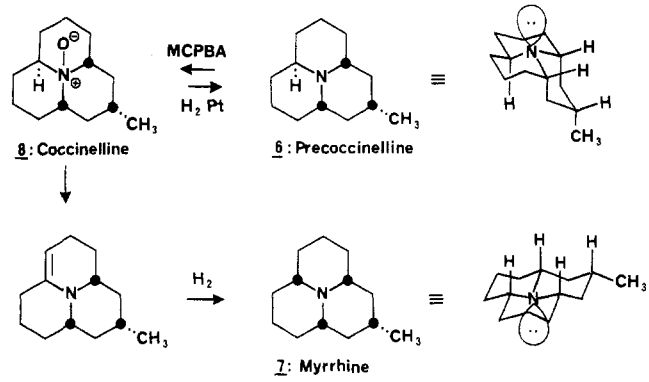
(1) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193.
(2) Webster defines heuristic as "serving to discover or to stimulate investigation; of methods of demonstration which tend to lead a person to investigate further".

0001-4842/84/0117-0289$01.50/0

Scheme I

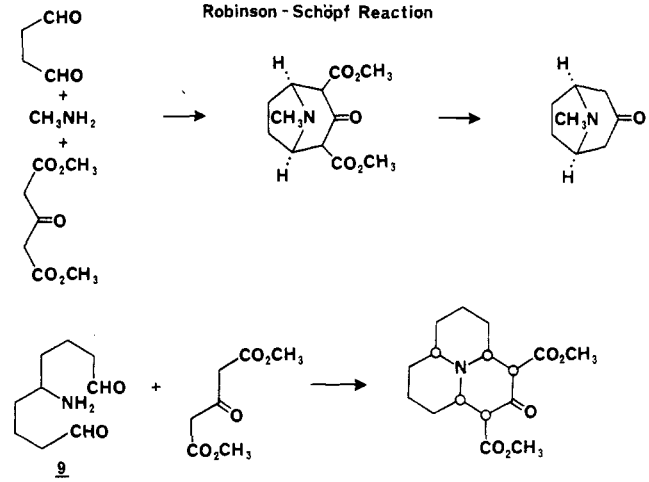


Scheme II

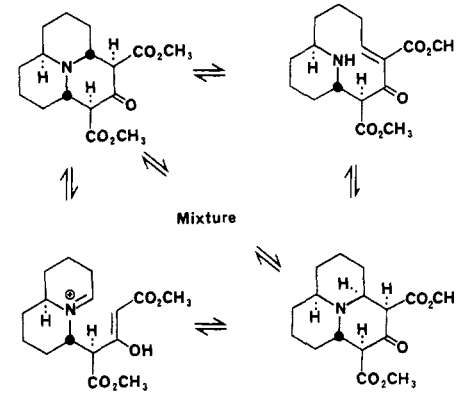


Scheme III

Robinson-Schöpf Reaction



Scheme IV



Applications

Additions. This story began when the structures of a family of novel tricyclic alkaloids first appeared. Small amounts of these substances were isolated from the defensive secretions of various species of ladybugs (*Coccinellidae*) in pioneering investigations headed by Professors B. Tursch at l'Université Libre Bruxelle and W. A. Ayer at the University of Alberta.[3] In contemplating the synthesis of these conformationally rigid systems, we noted that myrrhine (**7**), with its all-trans ensemble of quinolizidine rings, is clearly thermodynamically more stable than precoccinelline (**6**) (Scheme II).[4] It was therefore apparent at the outset that one could take advantage of the thermodynamic stability of myrrhine in synthetic planning but that any such plans for precoccinelline would probably have to rely on a kinetically controlled process. In less time than it took to write this paragraph we had developed an attractive approach that relies on one of the oldest reactions known in alkaloid synthesis, the classic Robinson–Schöpf condensation.[5] Clearly, if one can mix together the three reagents shown in Scheme III and obtain the tropane alkaloid skeleton, one could then predict that a mechanistically similar condensation between the amine dialdehyde **9** and acetone dicarboxylic ester should afford the parent ring system found in this new class of alkaloids. This idea was very nearly *not* pursued insofar as there superficially appeared to be little in the way of new chemistry involved. In contemplating other possible routes, however, we quickly became aware of the fact that, from the standpoint of efficiency of bond construction, this classic reaction is truly remarkable (and difficult to beat). Note that a total of *four* new bonds and *five* chiral centers are formed in a single vessel! The question then arose—what is the stereochemistry of this remarkable old reaction? The literature precedent sheds no light on this issue insofar as the tropane skeleton can only arise in the manner indicated. It was to clarify these stereochemical questions that we decided to initiate the research outlined below. It should be noted that at the time, we had no idea that the results of this investigation would provide us with a new and powerful heuristic principle upon which much of our subsequent research has been based. What *was* clear at the outset was the fact that selection of the proper conditions for the condensation reaction would be crucial insofar as all of the chiral centers could, in principle, be scrambled via either retro-Mannich and/or retro-Michael processes as illustrated in Scheme IV. These thoughts, then, set the stage for the following laboratory experiments.[6]

Once we had the requisite amino dialdehyde in hand as its dimethyl acetal **10**, we turned our attention to the

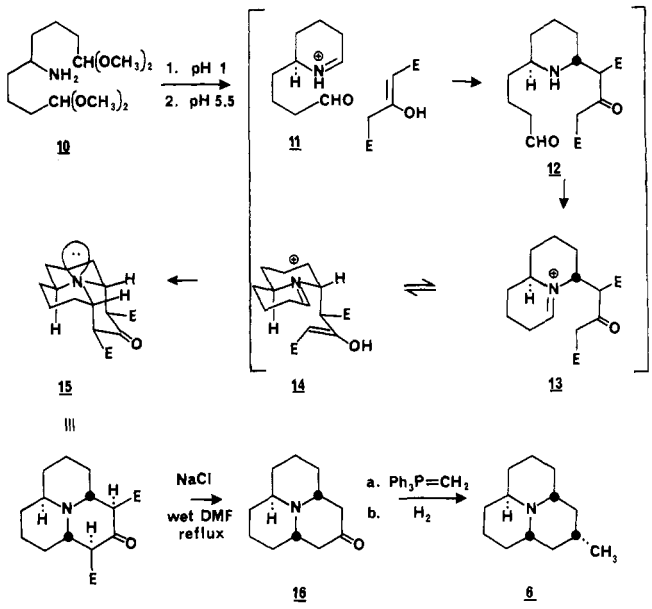
(3) For a stimulating earlier overview see: Ayer, W. A.; Browne, L. M. *Heterocycles* **1977**, *7*, 685.

(4) For previous syntheses of these compounds see: Ayer, W. A.; Furuichi, K. *Can. J. Chem.* **1976**, *54*, 1494. Mueller, R. H.; Thompson, M. E. *Tetrahedron Lett.* **1979**, 1991. Ayer, W. A.; Dawe, R.; Eisner, R. A.; Furuichi, K. *Can. J. Chem.* **1976**, *54*, 473.

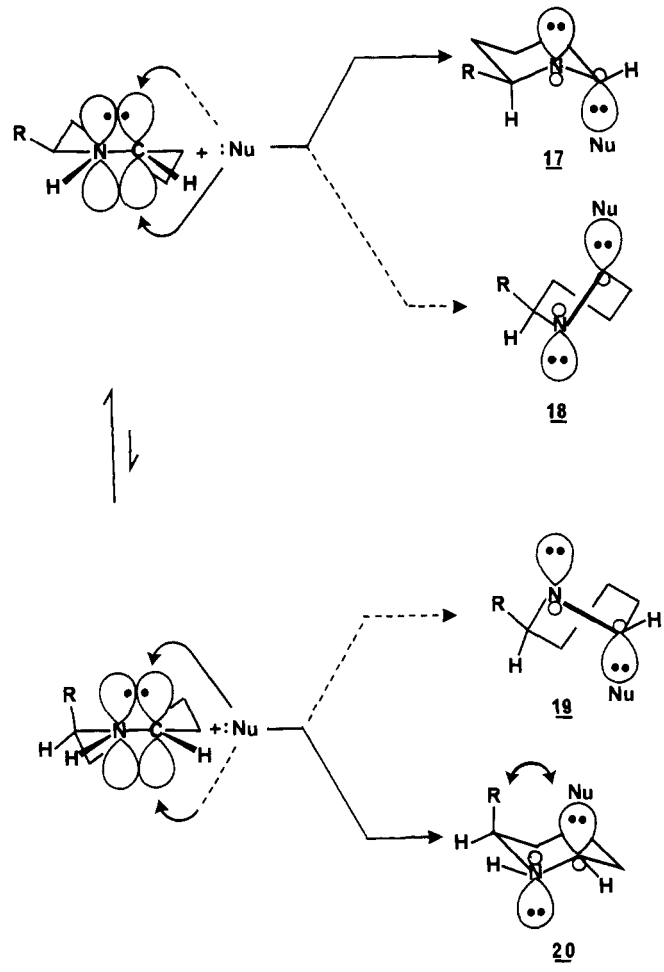
(5) Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762, 876. Schöpf, C. *Angew. Chem.* **1937**, *50*, 779, 797. For an interesting discussion of the reaction and synthesis, see: Fleming, I. "Selected Organic Syntheses"; John Wiley and Sons: London, 1973; p 17.

(6) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032.

Scheme V



Scheme VI



crucial condensation with the acetonedicarboxylic ester. The presence of the basic nitrogen dictated the employment of strong mineral acid to effect hydrolysis of the two acetal functions. Accordingly, hydrochloric acid at pH 1 was employed. The pH of the solution was then adjusted to about 5.5 by the careful addition of base followed by a citrate–phosphate buffer. A solution of acetonedicarboxylic ester in the same buffer was then added dropwise at room temperature to the stirred solution. Much to our delight, a *single* isomer crystallized directly from the reaction mixture in good yield. The structural and stereochemical assignments followed from the physical data. Decarbomethoxylation under neutral conditions afforded ketone **16**, which was transformed into precoccinelline (**6**) by Wittig methylenation followed by catalytic hydrogenation (Scheme V). This was subsequently carried on to coccinelline (**8**) via oxidation using *m*-chloroperoxybenzoic acid.

The remarkable stereochemistry observed in the condensation reaction (**10** to **15**) appeared to be in accordance with previously noted principles of stereoelectronic control.[7] Although there were no intermediates actually isolated in this reaction, we made the reasonable assumption that the first step in which relative stereochemistry is introduced involves the tetrahydropyridinium salt **11** and the enol of acetonedicarboxylic ester. Since we know the stereochemistry of these two kinetically controlled centers in the final tricyclic product, we can be reasonably certain that the **11** to **12** transformation proceeds stereochemically as indicated, but why? Intermediate **11** can exist in either of the two conformations shown in Scheme VI. There are four possible transition states wherein maximum orbital overlap is maintained between the approaching nucleophile and the developing lone-electron pair on nitrogen, resulting in products where the sp^3-hybridized orbitals generated are anti-coplanar. Two of these, **18** and **19**, require boatlike transition states and are kinetically disfavored. The remaining two possibilities involve chairlike transition states, but **20** clearly suffers from an unfavorable 1,3-diaxial interaction between the ring side chain (R) and the incoming nucleophile. Therefore, of the four possibilities in which maximum orbital overlap is maintained, **17** is the least objectionable and explains the observed product. After these two centers are established, the fate of the remaining centers is also determined. A second cyclization to afford the annulated tetrahydropyridinium salt **13** followed by enolization provides an intermediate **14**, whose ring closure is also stereoelectronically favorable and can proceed via a transition state wherein all three rings adopt chairlike conformations.

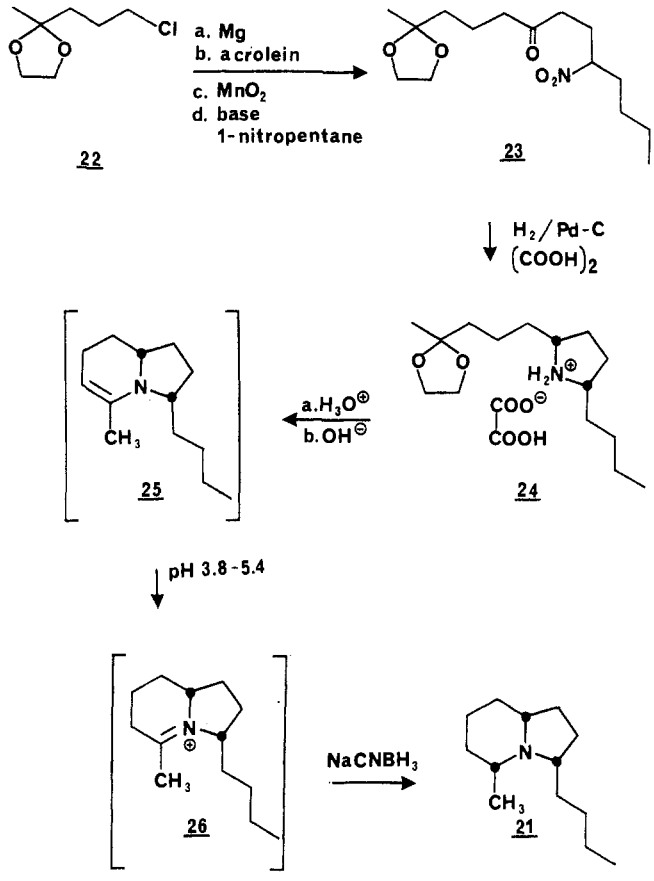
As pleasing as the above experimental results were, we were painfully aware of the fact that the mechanistic considerations advanced had little experimental support. Perusal of the literature uncovered a few more examples which were consistent with our hypothesis and inspired some degree of confidence.[8] At this stage we began to search for synthetic targets of chemical and/or biological interest which would provide further tests of these mechanistic considerations.

Once again, the insect domain served as a point of departure for this study. The Pharoah ant (*Monomorium pharaonis* L.) can be a serious pest in heated buildings, especially hospitals, in Great Britain and the Netherlands. F. J. Ritter et al.[9] were able to isolate and

(7) For a valuable discussion of many aspects of stereoelectronic control see: Deslongchamps, P. In "Organic Chemistry Series"; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1983; Vol. 1, p 211 and references cited therein. Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146. Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831.

(8) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstad, R. W. *Tetrahedron* **1958**, *2*, 1. Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109. See also ref 7.

Scheme VII



Scheme VIII

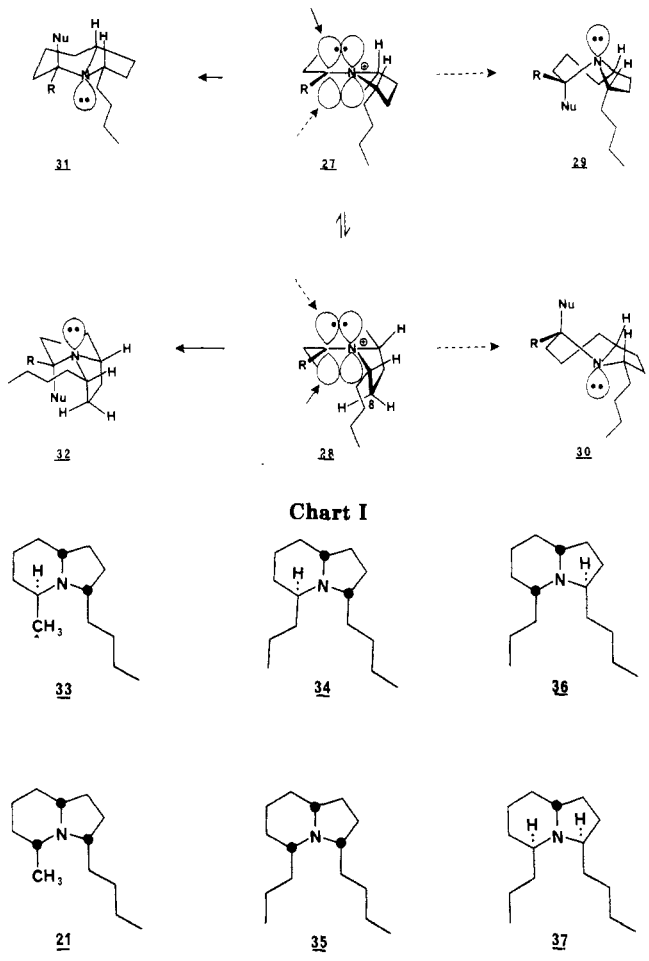


Chart I

determine the structure of one of the trail pheromones of these insects which was named monomorine I (**21**).[10] Our approach[11] to this substance began with the known chloro ketal **22**,[12] which was converted to nitro ketone **23** (Scheme VII). Although no systematic study on the stereochemistry of reduction of nitroketones to 2,5-disubstituted pyrrolidines had been made, we noted that such reductions previously reported[13] proceeded in a syn fashion to provide the cis product. After isolating the pyrrolidine as the oxalate salt **24**, we were now in a position to explore the key reaction—stereochemically speaking. Hydrolysis of the ketal in acid followed by a basic workup afforded the rather unstable endocyclic enamine **25** which was immediately treated with sodium cyanoborohydride under acidic conditions. Racemic monomorine I was the only volatile product produced in this sequence of reactions (68% overall yield from the salt **24**).

The stereochemical outcome observed in the **26** to **21** transformation parallels our earlier hypothesis. There are once again four possible transition states for this reduction wherein maximal orbital overlap can be maintained with respect to the developing lone-electron pair on nitrogen and the attacking hydride reagent. Two of these (cf. dotted arrows in **27** and **28**) require boat-like transition states leading to **29** and **30** and are disfavored kinetically. Of the two chairlike transition states shown in Scheme VIII (**31** and **32**), the latter suffers from a strong peri interaction with the proton at C-8 and is likewise disfavored, leaving **31** as the preferred product, which is consistent with our experimental observations.

The synthesis depicted in Scheme VII not only shed light on stereoelectronic control in nucleophilic additions to tetrahydropyridinium salts but also served as a vehicle for the synthesis of a closely related alkaloid, gephyrotoxin 223. This substance occurs in the skins of certain frogs (family *Dendrobatidae*) of neotropic distribution. Extracts from these frogs have been used by the natives of that region to poison the tips of darts and arrows, and in recent years these frogs have proved to be a rich source of neurotoxic alkaloids. A GC/MS analysis of a crude extract performed by Dr. John W. Daly at the National Institutes of Health revealed a minor alkaloid with a molecular weight of 223 (hence gephyrotoxin 223) and fragmentation pattern consistent with the gross structure shown (Chart I).[14] Of course, the issue of stereochemistry remained unresolved and provided us with a unique opportunity to test further the stereoelectronic principles discussed above and to produce material for biological evaluation. It should be noted that in the structure elucidation, no material was actually isolated. The structures of monomorine

(9) Ritter, F. J.; Rotgans, I. E.; Talman, E.; Vierwiel, P. E. J.; Stein, F. *Experientia* **1973**, *29*, 530. Ritter, F. J.; Persoons, C. J. *Neth. J. Zool.* **1975**, *25*, 261. Ritter, F. J.; Bruggeman-Rotgans, I. E. M.; Vierwiel, P. E. J.; Persoons, C. J.; Talman, E. *Tetrahedron Lett.* **1977**, 2617.

(10) Oliver, J. E.; Sonnet, P. E. *J. Org. Chem.* **1974**, *39*, 2662. Sonnet, P. E.; Oliver, J. E. *J. Heterocycl. Chem.* **1975**, *12*, 289.

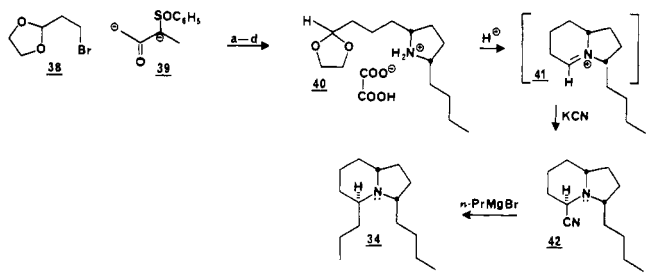
(11) Stevens, R. V.; Lee, A. M. W. *J. Chem. Soc., Chem. Commun.* **1982**, 102.

(12) Cannon, G. W.; Ellis, R. C.; Leal, J. R. *Org. Synth.* **1951**, *31*, 74.

(13) Benezva, L. L.; DePablo, S.; Osgood, E. R. Ger. Offen. 2 344 509, March 21, 1974; *Chem. Abstr.* **1974**, *80*, P146009*h*. Sonnet, P. E.; Netzel, D. A.; Mendoza, R. *J. Heterocycl. Chem.* **1979**, *16*, 1041.

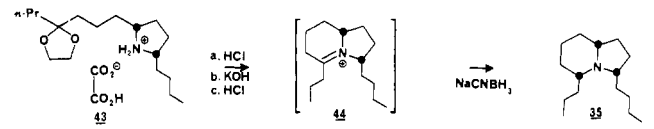
(14) Daly, J. W. *Fortsch. Chem. Org. Naturs.* **1982**, *41*, 205.

Scheme IX[a]



[a] a, condensation; b, elimination; c, 1-nitropentane and base; d, H_2.

Scheme X



I (21) and its C-1 epimer (33) are also shown in Chart I for comparison with the four possible diastereomers of gephyrotoxin 223. One of the diastereomers, 36, had already been synthesized and submitted to the NIH group for comparison with the crude extract.[15] It was initially reported that the fragmentation pattern in the mass spectrum was virtually identical with natural material—thus confirming the structural assignment.[15] However, the retention time on the gas chromatograph appeared different, leaving the important issue of stereochemistry in doubt. With this in mind, we initiated the syntheses of two of the other isomers, 34 and 35, in hopes of resolving this question. After our work was complete, it was reported that the retention times of 36 and the natural compound were the same,[16] suggesting that the relative stereochemistry of gephyrotoxin 223 is indeed that shown in formula 36.

The syntheses of 34 and 35 are outlined in Schemes IX[17] and X.[18] Hydrolysis of 40 and cyclization afforded the tetrahydropyridinium salt 41, which was isolated as a single stereoisomer of the cyanoamine 42 upon treatment with potassium cyanide. The cyanoamine served as a latent synthon for iminium salt 41,[19] and when treated with excess *n*-propylmagnesium bromide, led stereospecifically to gephyrotoxin 223 stereoisomer 34. In a similar fashion, hydride addition to the propyl-substituted iminium ion 44 afforded only stereoisomer 35.

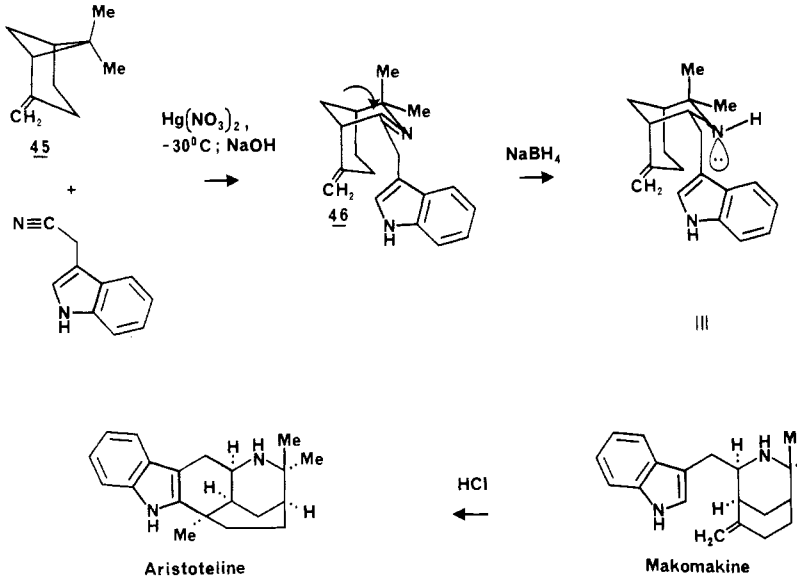
The extraordinarily high degree of stereoselectivity observed in all of the above nucleophilic additions is in agreement with the stereoelectronic arguments previously discussed. When one also considers the wide range of nucleophiles employed in these studies (enols, hydrides, cyanides, Grignard reagents) and the corresponding spectrum of transition states, these results are all the more remarkable.

With these results in hand let me now focus attention on how these considerations have come to influence our synthetic planning. Scheme XI shows the structures of aristoteline, makomakine, and hobartine. From the isolation studies[20] it was known that when exposed to acid, makomakine cyclizes, as expected, to aristoteline. Inspection of the preferred conformation of makomakine reveals that the α-hydrogen is anti-coplanar to the lone electron pair on nitrogen. From a stereoelectronic argument, one would expect hydride reduction of the corresponding imine 46 to proceed stereospecifically to provide makomakine. However, nucleophilic attack at this position is clearly obstructed by the axial methyl group. Which factor is more important—stereoelectronic control or steric hindrance? A short synthesis of makomakine[21] modeled after experiments performed by Delpech[22] confirms the importance of stereoelectronic control.[23] (+)-β-pinene (45) was added to a dichloromethane solution of 3-indolylacetonitrile and mercuric acetate at −30 °C. Isolation of the resultant imine 46 followed by reduction led to (−)-makomakine—no other stereoisomer was detected. Treatment of makomakine with concentrated hydrochloric acid afforded (+)-aristoteline. In a similar fashion, racemic hobartine was prepared from (+)-α-pinene (47). Delpech has postulated a mechanism which accounts for these remarkable cyclization reactions.[22]

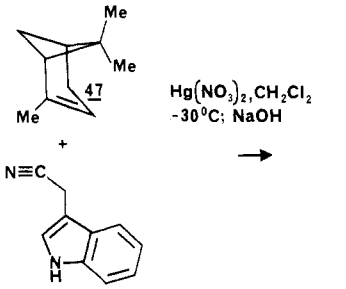
Annulations. As noted earlier, annulation of 4,5-dihydropyrroles or 1,4,5,6-tetrahydropyridines with methyl vinyl ketone or its derivatives has found widespread application in the total synthesis of alkaloids. Invariably, annulation of these endocyclic enamines affords exclusively cis-fused hydroindolones or hydroquinolones.[24] The conversion of 48 to 49 illustrated in Scheme XII is particularly intriguing. Since it is well established that hydroquinolones have a thermodynamic preference to exist as the corresponding trans isomer,[25] it is clear that the annulation must be kinetically controlled. We did not realize at the time that the cis stereochemistry can be rationalized stereoelectronically and that failure to appreciate this concept can have a deleterious impact on the outcome of an otherwise reasonable synthetic plan. We were to learn this in a most brutal fashion in connection with a projected synthesis of *N*-methyllycodine (Scheme XIII).[26] By analogy with successful annulations such as the 48 to 49 transformation,[27] it was anticipated that 1,4,5,6-tetrahydropyridine 50 would react with enone 51 to

(15) Macdonald, T. L. J. *J. Org. Chem.* **1980**, *45*, 193.
(16) Spande, Th. F.; Daly, J. W.; Hart, D. J.; Tsui, Y.-M.; Macdonald, T. L. *Experientia* **1981**, *37*, 1242.
(17) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 103.
(18) Stevens, R. V.; Nakagawa, Y., unpublished results, University of California, Los Angeles.
(19) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H. P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.
(20) Isolation of aristoteline: Anderson, B. F.; Robertson, G. B.; Avey, H. P.; Donovan, W. F.; Bick, I. R. C.; Bremmer, J. B.; Finney, A. J. T.; Preston, N. W.; Gallagher, R. T.; Russell, G. B. *J. Chem. Soc., Chem. Commun.* **1975**, 511. Kyburz, R.; Schopp, E.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta* **1981**, *64*, 2555. Isolation of makomakine: Bick, I. R. C.; Hai, M. A. *Heterocycles* **1981**, *16*, 1301. Isolation of hobartine: Kyburz, R.; Schopp, E.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta* **1979**, *62*, 2539.
(21) Stevens, R. V.; Kenney, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 384. For another synthesis of makomakine see: Mirand, C.; Massiot, G.; Levy, J. *J. Org. Chem.* **1982**, *47*, 4169.
(22) Delpech, B.; Khuong-Huu, Q. *J. Org. Chem.* **1978**, *43*, 4898.
(23) For other examples of additions to the more sterically hindered face see: Riediker, M.; Graf, W. *Helv. Chim. Acta* **1979**, *62*, 2053. Mueller, R. H.; Dipardo, R. M. *J. Chem. Soc., Chem. Commun.* **1975**, 565. Overman, L. E.; Freerks, R. L. *J. Org. Chem.* **1981**, *46*, 2833.
(24) See ref 1 and references cited therein.
(25) Grob, C. A.; Wilkens, H. J. *Helv. Chim. Acta* **1965**, *48*, 808. Takefumi, M.; Uchida, S.; Yamaashi, N.; Imanishi, T. *Heterocycles* **1975**, *3*, 713. Takefumi, M.; Uchida, S.; Hosoya, E.; Kinoshita, M.; Imanishi, T. *Chem. Pharm. Bull.* **1978**, *26*, 620.
(26) Stevens, R. V.; Hrib, N. *J. Chem. Soc., Chem. Commun.* **1983**, 1422.
(27) Stevens, R. V.; Mehra, R. K.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1969**, 877.

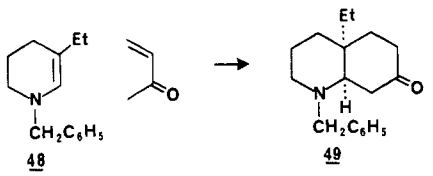
Scheme XI

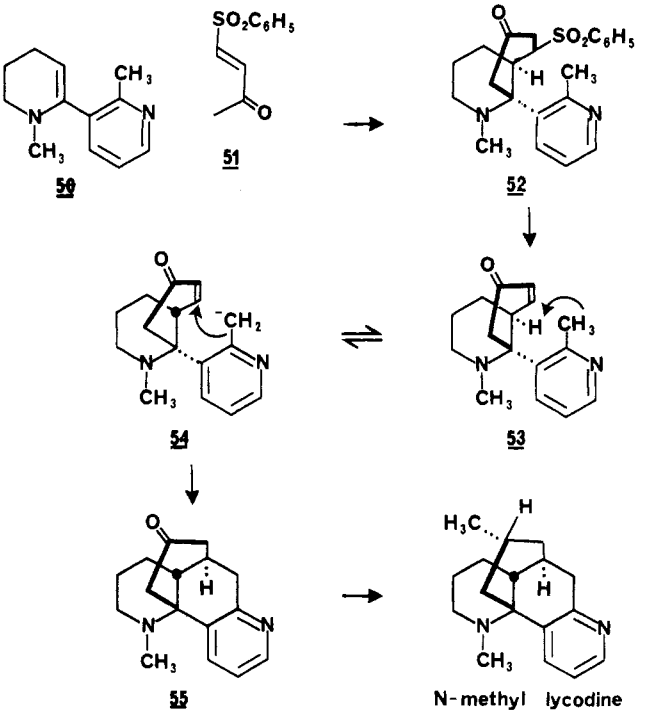


Scheme XII



Scheme XIII





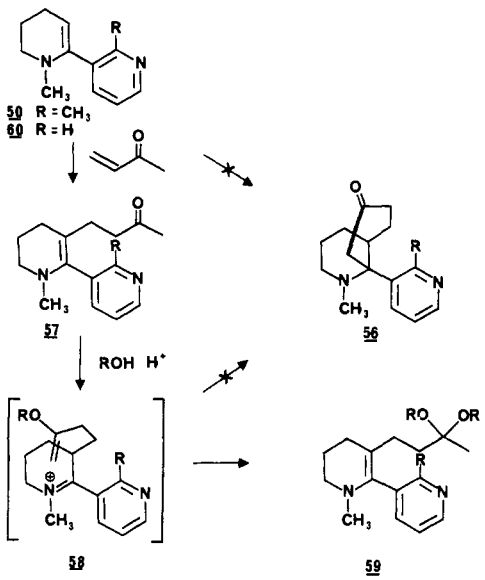
afford the cis-fused hydroquinolone **52**. Elimination of benzenesulfinic acid from the latter intermediate would then provide enone **53**, which could be epimerized and cyclized in the presence of a suitable base to provide the tetracyclic skeleton **55**.

The desired endocyclic enamine **50** was obtained via a very efficient route[28] and we were pleased to observe a smooth reaction with methyl vinyl ketone (and derivatives). However, we were surprised to learn that the product of this reaction was *not* the desired hydroquinolone **56**, but rather the alkylated but uncyclized enamine **57** (Scheme XIV). This unexpected result was followed by a series of unsuccessful experiments aimed at forcing the cyclization to occur under acidic conditions via enol–ether intermediates such as **58**. At first we attributed these failures to the methyl group on the pyridine ring which would provide steric hindrance to the nucleophilic addition. However, this possibility was ruled out when the corresponding desmethyl derivative **60** was prepared and underwent identical and disheartening behavior.

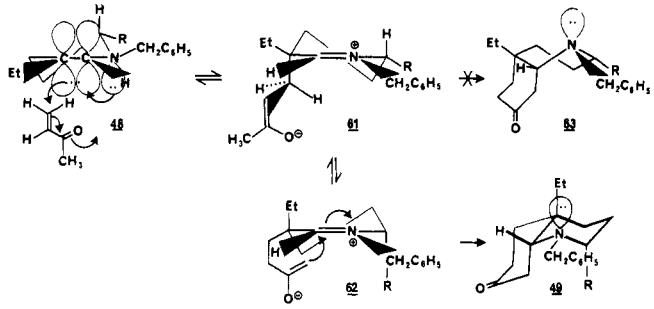
(28) Spath, E.; Bretschneider, H. *Chem. Ber.* **1928**, *61*, 327. Brandange, S.; Lindblom, L. *Acta Chem. Scand., Ser. B* **1976**, *30*, 93. Lecte, E.; Leete, S. A. S. *J. Org. Chem.* **1978**, *43*, 2122.

As attempt after attempt to bring about these annulations failed, we recognized that a serious flaw existed in our synthetic strategy. We now believe there are fundamental reasons for these observations and that an understanding of these principles can lead to stereorational design. Consider first the successful annu-

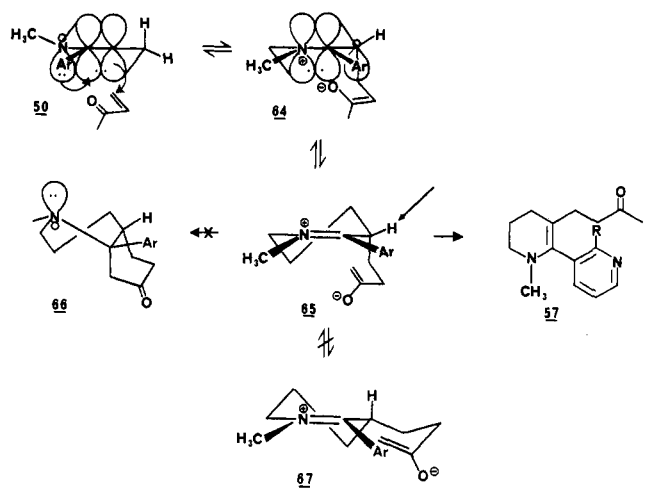
Scheme XIV



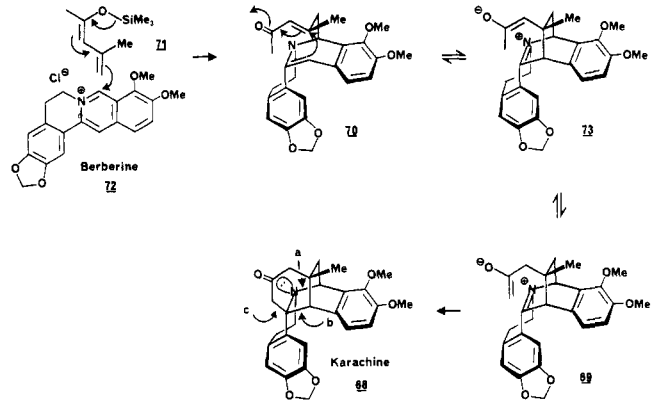
Scheme XV



Scheme XVI



Scheme XVII



lation sequence **48** to **49**. When analyzed closely, subtle yet decisive factors unfold. Data on other enamine systems suggest that the hybridization of nitrogen is between sp^3 and sp^2.[29] The important point here is that if the lone electron pair on nitrogen is anything other than sp^2 hybridized, it can only overlap with the adjacent π-cloud if it adopts a quasi-axial conformation.[30] By analogy with axial attack of electrophiles to cyclohexene systems,[31] one would expect electrophilic additions to endocyclic enamines to occur on the same face of the molecule as the lone electron pair on nitrogen. The full implications of these considerations on other systems which are conformationally rigid or biased (i.e., R $\neq$ H) are presently being investigated.

Let us turn our attention to Scheme XV, which illustrates the initial Michael adduct (R = H) proceeding on to cyclized product. After isomerization of the enolate to the terminal position, this closure can occur either from the conformation in which the enolate moiety is axial as in **61** or by conformational inversion, to one in which it is equatorial (**62**). The latter pathway is preferred because maximum orbital overlap can be achieved via a chairlike transition state with respect to *both* rings (cf. **62** to **49**). Maximum orbital overlap in the alternate conformation (**61** to **63**) can be achieved only at the expense of a boatlike transition state with respect to *both* rings and accordingly is disfavored.

These considerations provide an explanation for our inability to effect annulation of **50** to **56**. As shown in Scheme XVI, the initially formed zwitterion **65** cannot cyclize readily since it would require a double boatlike transition state, leading to **66**. Therefore, in order to complete the annulation process, **65** must first undergo conformational inversion to **67**. In this case, however, there is a substituent of substantial size at C-2 (Ar = 2-picolyl or 3-pyridyl). This conformation would suffer severe 1,2-allylic strain[32] between the aryl group and the equatorial enolate side chain.[33] In the face of these high-energy requirements for ring closure, the intermediate zwitterion **65** simply deprotonates at the site indicated to afford alkylated but uncyclized enamine **57**. Thus, these results provide a new perspective on, and respect for, the potential importance of stereoelectronic control in determining the fate of reactions of this type.

I would like to conclude this section with one such study just completed which illustrates the type of analysis now possible. The problem was to design an efficient synthesis of karachine (**68**), a recently isolated alkaloid of a new structural type (Scheme XVII).[34] At first we were discouraged by the fact that the ketone moiety is *not* anti and coplanar to the lone electron pair on nitrogen and therefore would require a boatlike

(29) Cook, A. G. "Enamines"; Marcel Dekker, Inc.: New York, 1969; pp 1–51. Brown, K. L.; Damm, L.; Dunitz, J. D.; Eschenmoser, A.; Hobi, R.; Kratky, C. *Helv. Chim. Acta* **1978**, *61*, 3108. Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975.
(30) Beeken, P.; Fowler, W. *J. Org. Chem.* **1980**, *45*, 1336.
(31) Valls, J.; Toromanoff, E. *Bull. Soc. Chim. Fr.* **1961**, 758.
(32) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
(33) Overman, L. E.; Freerks, R. L. *J. Org. Chem.* **1981**, *46*, 2833.
(34) Blasko, G.; Murugesan, N.; Freyer, A. J.; Shamma, M.; Ansari, A. A.; Rahman, A. V. *J. Am. Chem. Soc.* **1982**, *104*, 2039.

transition state for its formation from zwitterion **69**. However, closer inspection revealed that this bond and the lone electron pair are precisely syn to one another, and although anti additions are normally favored, examples of syn additions to olefins are known.[35] We were disturbed by the energy requirements for a boatlike transition state until we realized with some degree of embarrassment that zwitterion **69** is already in a boat conformation! Thus, the downpayment in terms of energy would have been made in advance during the formation of the bicyclic system. Retrosynthetically, we quickly realized that this bicyclic system could, in principle, be assembled from an intramolecular annulation of endocyclic enamine **70** which in turn could be derived, in situ, from γ-alkylation[36] of the known siloxydiene **71**[37] with commercially available berberine (**72**). The only other potential problem envisaged concerned the stereochemistry of the Michael addition step (**70** to **73**), but we soon realized that the stereoisomeric transition state would require much greater charge separation and accordingly, should not be favored. It was with these thoughts in mind that we reduced to practice this simple two step synthesis with most gratifying results.[38]

(35) Truce, W. E.; Levy, A. J. *J. Org. Chem.* **1963**, *28*, 679.
(36) Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, 3209. Fleming, I.; Lee, T. V. *Tetrahedron Lett.* **1981**, 705. Paterson, I.; Price, L. G. *Tetrahedron Lett.* **1981**, 2833.
(37) Wan, G. S. K.; Weedon, A. C. *J. Chem. Soc., Chem. Commun.* **1981**, 1235.

Conclusion

This *Account* has illustrated the gradual development of our approach to alkaloid synthesis. The exceptionally high stereoselectivity demonstrated in the examples presented lends support to our belief in the importance of the stereoelectronic arguments we have discussed. Nucleophilic additions to tetrahydropyridinium salts occur in such a manner as to preserve maximum orbital overlap between the nitrogen lone electron pair and the incoming nucleophile. This stereoelectronic requirement necessitates the formation of either chair- or boatlike transition states. The former are preferred even in the presence of unfavorable steric factors, except in special cases where the molecule is already constrained in a boat conformation. From our observations we contend that these stereoelectronic and geometric constraints are of such importance that the inability to achieve a chairlike transition state (e.g., due to allylic strain) will prevent the desired reaction from occurring. Consideration of these arguments has allowed us to design a number of stereorational syntheses, several of which are now under active investigation.

I would like to take this opportunity to express my gratitude to those graduate students cited whose efforts have borne so much fruit. The support of the National Science Foundation (NSF CHE 81-15444) and the National Institutes of Health (NIH GM 28122) is also gratefully acknowledged.

(38) Stevens, R. V.; Pruitt, J. R. *J. Chem. Soc., Chem. Commun.* **1983**, 1425.