occupy adjacent binding sites.[39]

We demonstrated in the previous section that netropsin alters the nucleic acid conformation at its binding site on poly(dA-dT) and that the structural perturbation (changes in the glycosidic torsion angles) is propagated to adjacent antibiotic-free base-pair regions.[37] Recent examples demonstrate that a second drug may exhibit enhanced binding to such an altered nucleic acid structure,[40] so that an understanding at the molecular level of such synergistic effects could lead to the successful design of classes of antibiotics to be used in combination chemotherapy. We predict that NMR spectroscopy will contribute to our understanding of this challenging problem.

(39) R. M. Wartell, J. E. Larson, and R. D. Wells, *J. Biol. Chem.*, **250**, 2698–2702 (1975).

(40) (a) W. E. G. Muller and R. K. Zahn, *Prog. Nucleic Acid Res. Mol. Biol.*, **20**, 32–33 (1977); (b) T. R. Krugh and M. A. Young, *Nature (London)*, **269**, 627–628 (1977); (c) K. Umezawa, A. Shirai, T. Matsushima, and T. Sugimura, *Proc. Natl. Acad. Sci. U.S.A.*, **75**, 928–930 (1978).

Zwittazido Cleavage

HAROLD W. MOORE

Department of Chemistry, University of California, Irvine, California 92717

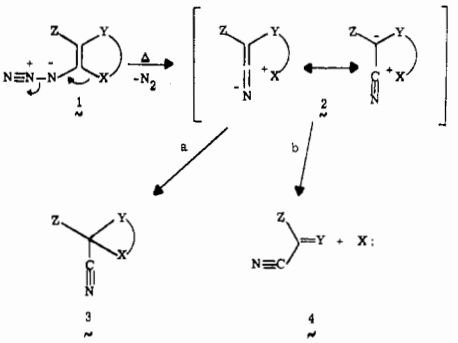
Received August 11, 1978

The idea of generating reactive intermediates or inducing concerted molecular rearrangements by the extrusion of a stable gaseous molecule from an organic compound has been the subject of extensive research effort. This is particularly true as it applies to the thermolysis and photolysis of organic azides.[1] Although a number of very interesting transformations have been discovered, the well-known Curtius rearrangement of acyl azides is one of the few that has found its place in the arsenal of the synthetic chemist. The prime objective of this Account is to add to this arsenal by defining and illustrating a new reaction of certain organic azides which has both synthetic and mechanistic significance. This reaction, which we call the *zwittazido cleavage*, constitutes the foundation of a research effort encompassing a number of intimately related topics, several of which will be discussed here.

First of all, let me define the zwittazido cleavage reaction. The definition stems from a generalized mechanistic model which can be used to predict the products from the thermolysis of appropriately substituted vinyl azides.[2] Specifically, we proposed that vinyl azides of general structure **1** (Scheme I) cleave to the zwitterions **2** when X is a substituent capable of cation stabilization and Y and/or Z are anion stabilizing groups. The zwitterionic intermediate **2** can then ring-close to **3** (ring contraction, path a) or cleave to **4** (fragmentation, path b). Henceforth, we wish to refer to reactions of this type as examples of the zwittazido cleavage, a name aptly describing the fact that cyclic vinyl azides of the structural type mentioned are thought to cleave to zwitterionic intermediates which proceed to products by pathways a or b.

This generalized mechanism is the fundamental "take home" message of this Account since it relates to the other objectives to be discussed. For example: (1) it defines the zwittazido cleavage reaction and illustrates the mechanism of this reaction; (2) it predicts a synthetic route to cyanoketenes by pathway b provided Y is a carbonyl and X is an appropriate leaving group; (3) it provides a powerful mechanistic probe for studying dipolar cycloadditions of cyanoketenes since one can independently generate the same zwitterionic intermediates from appropriately substituted vinyl azides, **1**, as are formed when cyanoketenes react with imidates, other ketenes, or aldehydes; (4) it illustrates a strategy for a new β-lactam synthesis from appropriately substituted 4-azido-Δ^3-2-pyrrolinones. Such compounds undergo ring contraction (pathway a) to 3-cyano-2-azetidinones via a zwitterionic intermediate analogous to **2**.

Scheme I



Synthesis of Cyanoketenes

A particularly suitable class of cyclic vinyl azides which are examples of structure **1** (Scheme I) are 2,5-diazido-1,4-benzoquinones. The thermal chemistry of such compounds has now been explored in moderate depth, and we have observed that they are ideal precursors to alkyl- and arylcyanoketenes.[3] A particularly

Harold W. Moore has been a member of the faculty at the University of California, Irvine, where he now is Professor of Chemistry, since its foundation in 1965. He was born in Fort Collins, Colorado, in 1936, and received undergraduate training at Colorado State University. His graduate studies were done at the University of Illinois with H. R. Snyder, and he received further training with Karl Folkers at Stanford Research Institute before joining the faculty of UC Irvine. His research concerns the chemistry of organoazides, ketenes, and quinones and the synthesis and biological evaluation of bioreductive alkylating agents.

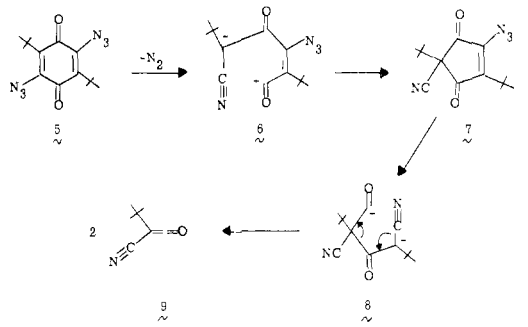
(1) S. Patai, Ed., "The Chemistry of the Azido Group", Interscience Publishers, New York, 1971.

(2) H. W. Moore, L. Hernandez, and A. Sing, *J. Am. Chem. Soc.*, **98**, 3728 (1976).

(3) W. Weyler, Jr., W. G. Duncan, and H. W. Moore, *J. Am. Chem. Soc.*, **97**, 6187 (1975).

0001-4842/79/0112-0125$01.00/0

Scheme II

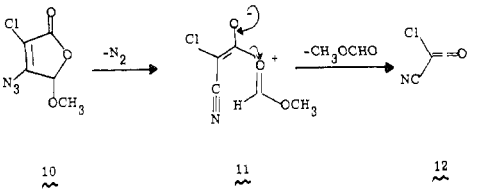


interesting example in this series is 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone (**5**) which cleaves to give 2 equiv of *tert*-butylcyanoketene (**9**) in nearly quantitative yield upon thermolysis in refluxing benzene. This is a most interesting electron-deficient ketene in that it is reasonably stable to self-condensation when kept in solution. However, it is very susceptible to cycloaddition reactions when treated with a variety of ketenophiles, e.g., alkenes, alkynes, enol ethers, imines, and imidates.[4] *tert*-Pentylcyanoketene can be prepared in a like manner and behaves analogously. Less bulky examples such as methyl-, isopropyl-, and phenylcyanoketene are also easily prepared by this route, but rapidly polymerize unless they are generated in the presence of ketene traps. Likewise, dicyanoketene can be generated in situ from 2,5-diazido-3,6-dicyano-1,4-benzoquinone.[5]

The mechanism for the formation of *tert*-butylcyanoketene from its diazide precursor is an example of the zwittazido cleavage and is outlined in Scheme II. The conversion of the diazide, **5**, to the cyclopentenedione, **7**, represents the ring contraction mode (pathway a, Scheme I), and cleavage of **7** to *tert*-butylcyanoketene (**9**) is an example of the fragmentation (pathway b, Scheme I). Consistent with this mechanism are the facts that the cyclopentenedione, **7**, has been shown to be formed under the reaction conditions and that it functions as a precursor to the ketene.[3] The zwitterions **6** and **8** are reasonably assumed to be intermediates in this reaction based upon unambiguous data for analogous transformations to be presented subsequently.

Attempts to extend the scope of cyanoketene syntheses from diazidoquinones to include the synthetically more versatile halocyanoketenes met with failure. However, this was circumvented by utilizing an azido-2(5*H*)-furanone precursor. It was observed that 4-azido-3-halo-5-methoxy-2(5*H*)-furanones, e.g., **10**, in refluxing benzene smoothly cleave to halocyanoketenes and methyl formate.[2,6] Again, we view this as an example of the zwittazido cleavage in which the products arise from fragmentation of the zwitterion, **11**,

Scheme III



as illustrated in Scheme III for the synthesis of chlorocyanoketene (**12**). In addition, the bromo and iodo analogues were prepared analogously, starting with the correspondingly substituted 2(5*H*)-furanones.

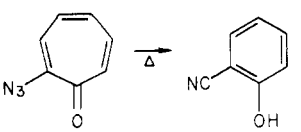
The methodologies described in Schemes II and III provide simple synthetic routes to a wide variety of substituted cyanoketenes. These thermolyses have the distinct advantage that the ketenes are generated in the absence of amine bases or metals, a situation that would not be so if classical dehydrohalogenation or dehalogenations of acid halide derivatives were employed. We have observed the presence of such reagents to have a deleterious effect upon cyanoketenes, as illustrated by the observation that attempts to prepare *tert*-butylcyanoketene by treatment of 2-cyano-3,3-dimethylbutanoyl chloride with triethylamine gave only 1,3-dicyano-1,3-di-*tert*-butylallene. The same product was also formed immediately upon treatment of a benzene solution of *tert*-butylcyanoketene with triethylamine.[7]

With a variety of cyanoketenes now at hand we next systematically explored their cycloaddition reactions. However, before presenting some of the results obtained, a brief mention of other reactions which can be formally outlined as further examples of the zwittazido cleavage is in order.

Other Examples of Zwittazido Cleavage Reactions

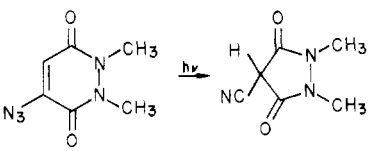
A number of reactions which can be catalogued according to Scheme I have appeared in the literature. They are mentioned in this Account to illustrate the potential generality of this reaction and to demonstrate the predictive power of the mechanistic formalism presented earlier (Scheme I). No attempt will be made to discuss the scope of these reactions. Rather, only selected examples in equation form are given (eq 1–10).

2-Azidotropone[8]



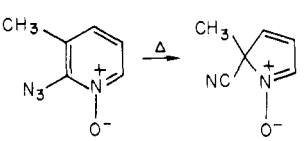
(1)

4-Azido-1,2-dimethylpyridazine-3,6-dione[9]



(2)

2-Azidopyridine 1-oxides[10]



(3)

(4) See, for example: (a) W. Weyler, Jr., L. R. Byrd, M. C. Caserio, and H. W. Moore, *J. Am. Chem. Soc.*, **94**, 1027 (1972); (b) M. D. Gheorghiu, C. Draghici, L. Stanescu, and M. Avram, *Tetrahedron Lett.*, 9 (1973); (c) H. A. Bampfield, P. R. Brook, and W. S. McDonald, *J. Chem. Soc., Chem. Commun.*, 132 (1975); (d) D. Becker and N. C. Brodsky, *ibid.*, 237 (1978); (e) Z. Lysenko, M. M. Jouillié, I. Miura, and R. Rodebaugh, *Tetrahedron Lett.*, 1705 (1977); (f) D. H. Aue and D. Thomas, *J. Org. Chem.*, **38**, 156 (1973); (g) M. D. Gheorghiu, *Rev. Roum. Chem.*, **22**, 1069 (1977); (h) M. D. Gheorghiu, F. Kerek, and M. Auram, *ibid.*, 2075 (1975).

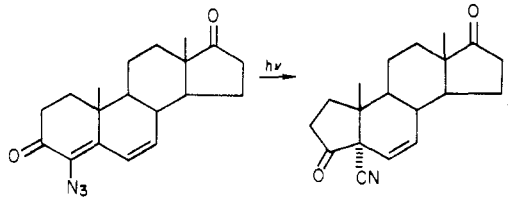
(5) R. Neidlein and E. Bernhard, *Angew. Chem., Int. Ed. Engl.*, **17**, 369 (1978).

(6) D. M. Kunert, R. Chambers, F. Mercer, L. Hernandez, Jr., and H. W. Moore, *Tetrahedron Lett.*, 929 (1978).

(7) H. W. Moore and W. G. Duncan, *J. Org. Chem.*, **38**, 156 (1973).

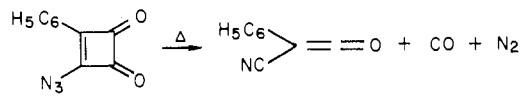
(8) J. D. Hobson and J. R. Malpass, *J. Chem. Soc. C*, 1645 (1967).

4-Azido-3-keto-$\Delta^{4,6}$-steroids[11]



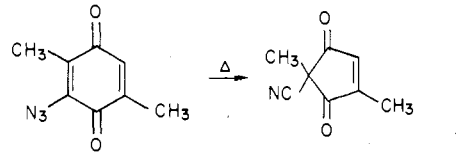
(4)

3-Azido-4-phenylcyclobutenedione[12]



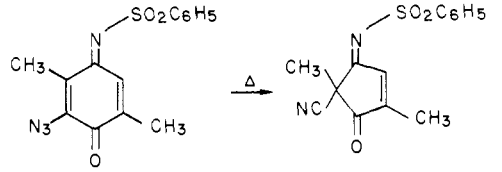
(5)

2-Azido-1,4-quinones[13]



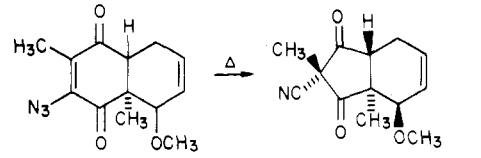
(6)

2-Azido-1,4-benzoquinone monobenzenesulfonimide[14]



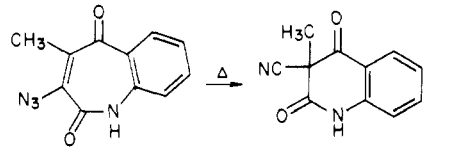
(7)

2-Azido-3,8aα-dimethyl-8β-methoxy-1,4-(4aβ,5,8,8a-tetrahydro)naphthoquinone[14]



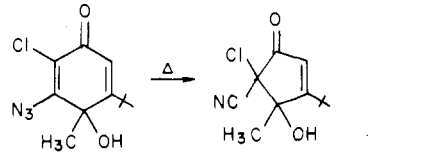
(8)

Azidoazepinediones[14]



(9)

Azidoquinols[14]

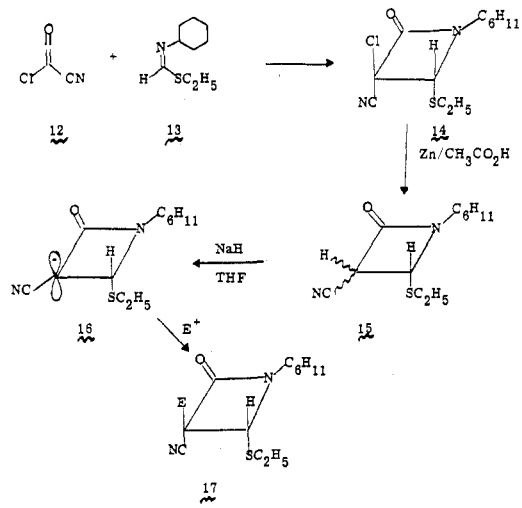


(10)

Cycloadditions of Cyanoketenes to Formimidates

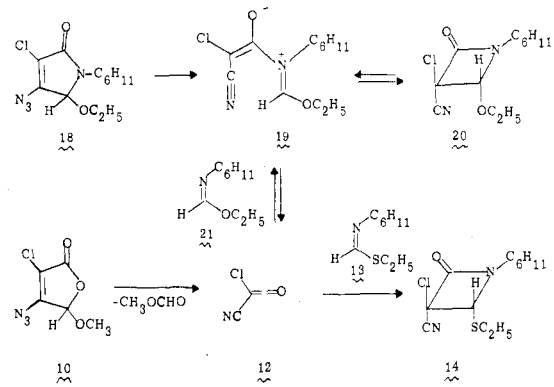
Within the general area of ketene chemistry one aspect which particularly attracted our attention was the cycloaddition reactions of cyanoketenes with formimidates and thioformimidates to give β-lactams. *tert*-Butyl-, methyl-, chloro-, bromo-, and iodocyanoketenes were found to cycloadd readily to a variety of formimidates to give 3-cyano-2-azetidinones in isolated yields ranging from 46 to 95%.[6] The fact that β-lactams are the products was not surprising since ketene cycloaddition to imines and imidates is one of the oldest synthetic routes to such compounds.[15] What was surprising is that all of the cyanoketene cycloadditions proceed in a stereospecific manner to give only those azetidinones in which the 3-cyano and the 4-protio groups reside in a trans relationship. The stereochemistry of the 60 examples thus far prepared is based upon chemical interconversions, carbon and proton NMR, and NOE data,[16] and in one case upon a complete X-ray crystal structure.[17] One example is sufficient to illustrate the cycloaddition, and this is provided in Scheme IV for the synthesis of the β-lactam **14**. Also briefly outlined in this scheme is the reductive dechlorination of **14** to give the dihydro derivative **15**

Scheme IV



E^+	E	Yield
CH_3I	CH_3-	91
CH_3OCOCl	CH_3OCO-	90
C_6H_5CHO	C_6H_5-CH- (OH)	60
$CH_2=CH-COCH_3$	$CH_3OC-CH_2-CH_2-$	92

Scheme V



(9) T. Sasaki, K. Kanematsu, and M. Murata, *Tetrahedron*, **29**, 529 (1973).
(10) R. A. Abramovitch and B. W. Cue, Jr., *J. Org. Chem.*, **38**, 173 (1973).
(11) E. M. Smith, E. L. Shapiro, G. Teutsch, L. Weber, H. L. Herzog, A. T. McPhail, P. W. Tschang, and J. Meinwald, *Tetrahedron Lett.*, 3519 (1974).
(12) R. D. DeSelms, *Tetrahedron Lett.*, 1179 (1969).
(13) W. Weyler, Jr., D. Pearce, and H. W. Moore, *J. Am. Chem. Soc.*, **95**, 2603 (1973).
(14) D. Rutolo, D. Stevens, H. R. Sheldon, G. Landen, R. Chambers, and H. W. Moore, unpublished results.
(15) For a recent review see: N. S. Isaacs, *Chem. Soc. Rev.*, 181 (1976).
(16) R. Chambers, D. Kunert, L. Hernandez, Jr., F. Mercer, and H. W. Moore, *Tetrahedron Lett.*, 933 (1978).
(17) R. J. Doedens, R. Chambers, and H. W. Moore, unpublished results.

as a mixture of diastereomers. This, in turn, can be converted to the enolate anion **16** which smoothly undergoes stereospecific alkylations, acylations, aldol condensations, and Michael additions from the side opposite the more bulky thioethyl group.[6] The synthetic significance of this discussion is that cyanoketene cycloadditions to formimidates, complemented by the anion chemistry of 3-cyano-2-azetidinones and further complemented by a new β-lactam synthesis yet to be discussed, constitute one of the most versatile synthetic routes known to highly substituted monocyclic β-lactams. The development of such synthetic methodology is of some practical importance since we have found many of these 3-cyano-2-azetidinones to show antibiotic and antifungal activity.

A mechanistic mystery, however, still remains. Why are these cycloadditions stereospecific? Does this mean that the reaction is concerted, or it is a rather rare example of a stereospecific stepwise process?[18]

Mechanism of Cyanoketene/Formimidate Cycloadditions

Answers to the above questions can now be provided. The mechanistic conflict has been resolved by a series of experiments which clearly establish that cyanoketenes cycloadd to formimidates by a dipolar nonconcerted pathway.[19] The pivotal experiment was to independently generate and trap the zwitterionic intermediate proposed in a cyanoketene/imidate cycloaddition and to show that it gave the same product and stereochemistry as obtained in the cycloaddition itself.

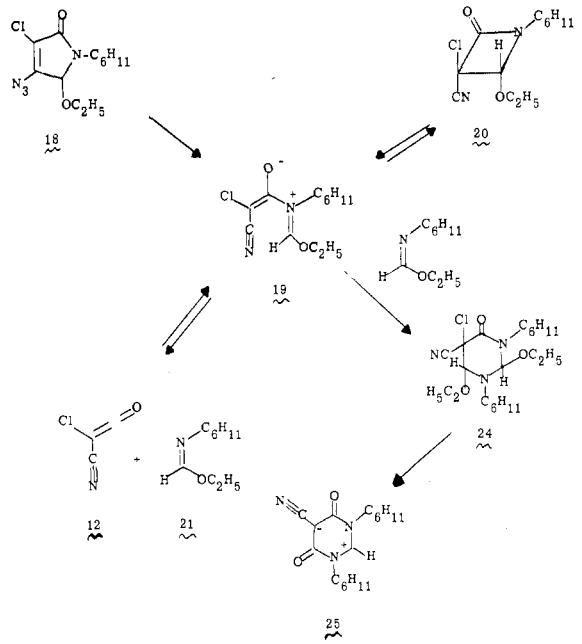
The genesis of this mechanistic probe relates again to the scheme for the zwittazido cleavage reaction (Scheme I). That is, this mechanism predicts that appropriately substituted 4-azido-2-pyrrolinones would give β-lactams upon thermolysis and that this transformation would involve the same zwitterionic intermediate as possibly being formed in the cycloaddition of a cyanoketene to an imidate. Thus, our initial study was to compare the products obtained from the thermolysis of 4-azido-3-chloro-1-cyclohexyl-5-ethoxy-Δ^3-2-pyrrolinone (**18**) with those resulting from the cycloaddition of chlorocyanoketene (**12**) to *O*-ethyl *N*-cyclohexylformimidate (**21**) (Scheme V). Thermolysis of **18** in refluxing benzene ($k = 0.24\ h^{-1}$)[7] gave only the β-lactam, **20** (94%). The same product was obtained in similar yield when **10** was decomposed in refluxing benzene containing a 10% molar excess of the imidate **21**. In this latter experiment it was also shown that the rate of the decomposition of the chlorocyanoketene precursor, **10**, was independent of the imidate concentration; thus any mechanism in which the imidate **21** interacts directly with the butenolide **10** prior to ketene formation is unlikely. These results alone clearly do not establish that the same intermediate is involved in both the azidopyrrolinone thermolysis and the cyanoketene/formimidate cycloaddition. Indeed, the conversion of **18** to **20** could arise by at least three possible pathways, i.e., (1) a concerted ring contraction, (2) fragmentation of **18** to chlorocyanoketene **12** and the imidate **21** followed by their subsequent cycloaddition to give **20**, and (3) cleavage of **18** to the zwitterion **19** and its subsequent ring closure to **20**.

In order to investigate the above possibilities the decomposition of **18** was accomplished as described above except that a 1.0 molar equiv of *S*-ethyl *N*-cyclohexylthioformimidate (**13**) was added. Here, both β-lactams, **14** and **20**, were found, and after 24% conversion (30 min) of the starting azide, **18**, the respective ratio of these products was 1.3:1.0. This ratio increased to 1.9:1.0 after 96% conversion (5.0 h). Next, the thermolysis (refluxing benzene) of **10** in the presence of 1.0 molar equiv of each of the imidates **13** and **21** was investigated in order to obtain an estimate of the relative rates of the reaction of chlorocyanoketene with the respective imidates. Here again, both β-lactams **14** and **20** were formed, and after approximately 25% conversion of **10** (15 min), their ratio was 2.4:1.0, which increased to 3.3:1.0 after complete reaction (ca. 4.5 h). The observed time dependence of the **14** to **20** product ratio in the above experiments is due to the fact that the β-lactams slowly revert to chlorocyanoketene and imidate in refluxing benzene. For example, when a benzene solution containing equivalent amounts of the β-lactam **20** and the thioformimidate **13** was refluxed for 48 h, an equilibrium mixture of the two β-lactams **14** (82%) and **20** (18%) was obtained. During the early stages of this equilibration experiment the rate of disappearance of **20** follows pseudo-first-order kinetics, and a rate constant of $k = 0.045\ h^{-1}$ can be estimated. This is 5.3 times slower than the rate of decomposition of the pyrrolinone **18** ($k = 0.24\ h^{-1}$). The salient points of these data are the following: (1) thermolysis of **18** in the presence of **13** gives both **20** and **14**; (2) chlorocyanoketene reacts with **13** faster than it does with **21**; (3) the β-lactam **20** reverts to chlorocyanoketene in refluxing benzene, but at a slower rate than the decomposition of **18**.

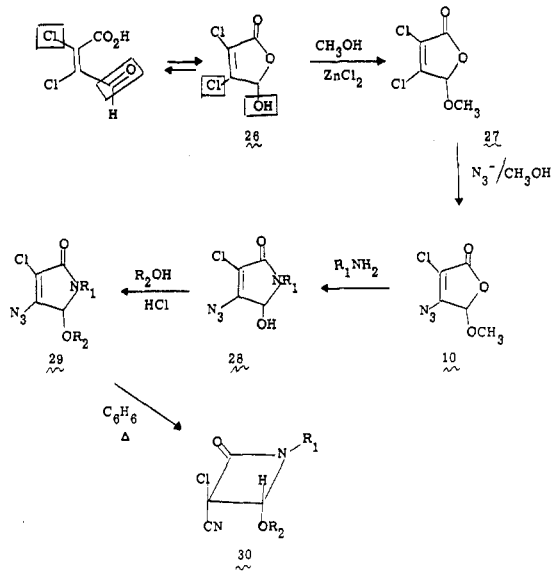
The most consistent interpretation of these results is as follows. A concerted ring contraction of **18** to **20** can be ruled out. This is so because of the facts that both β-lactams **20** and **14** were formed when **18** is decomposed in the presence of the thioimidate and that very little of **14** could arise from the cleavage of **20** to chlorocyanoketene after only 30 min of reaction time. Also, a pure ketene mechanism is unreasonable since, if this were so, one would expect the ratio of **14** to **20** to be much greater than the observed 1.3:1.0 after 30 min. That is, since chlorocyanoketene reacts faster with the thioformimidate **13** than with its oxygen analogue **21** and since the concentration of **21** would be very much smaller relative to that of **13** during the early stages of the reaction, one can reasonably assume that all ketene formed during the early stages of the decomposition of **18** would be trapped by **13** to give **14**. After 30 min 43% of the product mixture is the β-lactam **20** and 57% is the β-lactam **14**; therefore, a mechanism in which **18** exclusively fragments to chlorocyanoketene and *O*-ethyl *N*-cyclohexylformimidate and these then cycloadd to give **20** must be rejected. That leaves as the most reasonable alternative a mechanism in which the pyrrolinone **18** cleaves to the zwitterion **19**; this then partitions between ring closure (43%) to β-lactam **20** and cleavage (57%) to chlorocyanoketene and imidate. As a result, since stereospecific formation of the β-lactam **20** is observed from both the pyrrolinone thermolysis and the ketene cy-

(18) R. W. Hoffmann, U. Bressel, J. Gehlhaus, and H. Hauser, *Chem. Ber.*, **104**, 873 (1971).
(19) H. W. Moore, L. Hernandez, Jr., and R. Chambers, *J. Am. Chem. Soc.*, **100**, 2245 (1978).

Scheme VI



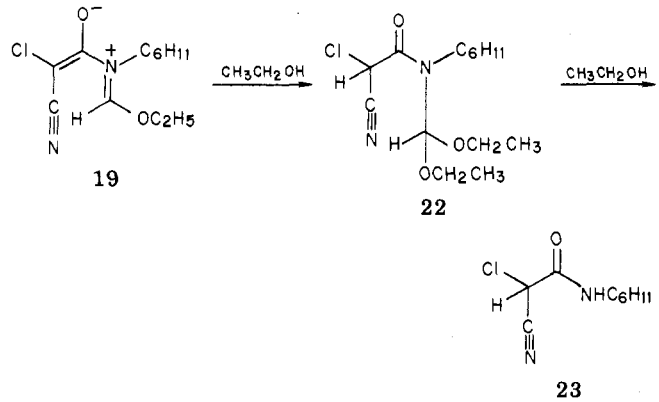
Scheme VII



	R_1	R_2	Yield
30a	CH_3	CH_3	55
30b	CH_3	CH_2CH_3	60
30c	CH_2CH_3	CH_2CH_3	88
30d	$CH_2CH_2CH_3$	CH_2-C_6H_5	90

cloaddition modes, one can now logically assume that both pathways involve the same zwitterionic intermediate, **19**.

Additional and more direct evidence for the existence of the zwitterion **19** comes from trapping experiments. We anticipated that **19** could be intercepted if the thermolysis of **18** were carried out in a protic solvent.[20] Thus, the decomposition of **18** was accomplished in refluxing anhydrous ethanol (11 h). This resulted in a mixture of products which has not yet been completely resolved. However, the results are exceptional in some regards. The four major products, as revealed by ^1H and ^{13}C NMR analysis of the crude reaction mixture, are ethyl chlorocyanoacetate, *N*-cyclohexyl-1-chloro-1-cyanoacetamide (**23**), *N*-cyclohexyl-*N*-(1,1-diethoxymethyl)-1-chloro-1-cyanoacetamide (**22**), and β-lactam **20**, and these are formed in a respective ratio of 4.0:3.0:2.3:1.0. The critical observation is that the amides **22** and **23** are formed in reasonable yields and that these are products that one would anticipate as arising from ethanolysis of the zwitterion **19**.



Still another series of trapping experiments which directly establish the zwitterion **19** are outlined in Scheme VI.[21] Here, we observed that when the pyrrolinone **18** or the β-lactam **20** was thermolyzed in refluxing benzene for 96 h in the presence of excess (ca. 10 equiv) formimidate **21**, a >70% yield of the unique mesoionic pyrimidine **25** was realized. In addition, this same product was formed in comparable yields when chlorocyanoketene **12** was generated in the presence of excess formimidate **21**. Thus, the pyrimidine results from three independent starting materials, all of which must be interrelated by a common intermediate, i.e., the zwitterion **19**. In the presence of excess formimidate the zwitterion is trapped by a cycloaddition to give **24**. This then suffers loss of the equivalent of diethyl ether and hydrogen chloride to give the mesoionic pyrimidine **25**.[22]

A New β-Lactam Synthesis

The facile conversion of the 4-azido-Δ^3-2-pyrrolinone **18** to the β-lactam **20** represents a new route to such compounds. The potential synthetic utility of this reaction as a general route to β-lactams is obvious when one considers the simple and versatile syntheses of the starting azidopyrrolinones. The readily available starting material is mucochloric acid (**26**) which is converted to the azidopyrrolinone by classical methodology as outlined in Scheme VII. The versatility of this procedure is further exemplified when one recognizes that a vast methodology exists for the modification of mucohalic acids. This has been adequately reviewed;[23] thus only the highlights will be mentioned here. Depending upon the pH and solvent, mucochloric acid can exist in either the ring-closed butenolide or ring-opened aldehyde form. In the aldehyde form the

(20) Such trapping experiments are analogous to the elegant work of R. Huisgen and his co-workers concerning the cycloaddition of TCNE to enol ethers. See R. Huisgen, *Acc. Chem. Res.*, **10**, 117 (1977).

(21) F. Mercer, L. Hernandez, and H. W. Moore, *Heterocycles*, in press.

(22) Such compounds are members of a very rare class of heterocycles. See, for example, Y. Maki, S. Sako, and M. Suzuku, *J. Chem. Soc., Chem. Commun.*, 999 (1972); T. Kappe and W. Lube, *Monatsh. Chem.*, **102**, 781 (1971); M. Prystas, *Collect. Czech. Chem. Commun.*, **32**, 4241 (1967); K. Potts and M. Sorm, *J. Org. Chem.*, **37**, 1422 (1972); T. Kappe and W. Lube, *Angew. Chem., Int. Ed. Engl.*, **10**, 925 (1971).

(23) For a review, see: Y. S. Rao, *Chem. Rev.*, **76**, 625 (1976).

boxed chlorine which is β to the aldehyde group can be replaced by nucleophiles; also, the aldehyde moiety is susceptible to attack by Grignard reagents, organolithium reagents, and enolate anions. Such additions, followed by relactonization, allow extensive modification at the γ position of the butenolide. In the ring-closed form, the chlorine β to the lactone carbonyl can be replaced by nucleophiles. The γ-hydroxy group can also be replaced by aryl substituents upon treatment of mucochloric acid with strong acid in the presence of aromatic hydrocarbons. The salient point of this discussion is that nearly every position of mucohalic acids is open to synthetic manipulation by known methodology. This, in conjunction with our observed ring contractions of azidopyrrolinones, suggests an exceptionally powerful synthetic route to highly functionalized β-lactams. A few selected examples of this ring contraction are also provided in Scheme VII. When one complements this methodology with the previously described cyanoketene/imidate cycloaddition route, the generality of 3-cyano-2-azetidinone syntheses is further magnified. The availability of such β-lactams is of more than academic interest since, as previously mentioned, we have recently observed that many of these simple compounds show biological activity.[24]

Biological Activity of 3-Cyano-2-azetidinones

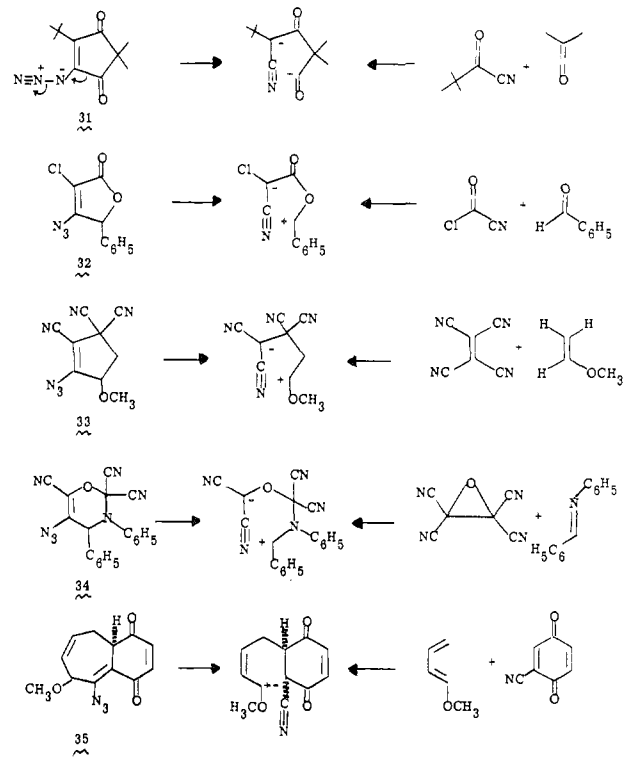
The open literature contains very few reports of biological activity for monocyclic β-lactams.[25] As a result, we were most surprised to find that a number of the cyano-substituted examples prepared as outlined here do show antimicrobial as well as antifungal activity. Such dual activity alone suggests that their mode of action differs from that of penicillin or cephalosporin since these and their related analogues are not generally active against fungi.

Twenty-six β-lactams were studied. Of these, seven were active against at least one of the Gram-positive bacteria, *Staphylococcus aureus*, *Bacillus subtilis*, or *Sarcina lutea*. Eleven examples, including all of those which were active against the bacteria, also showed antifungal properties against *Neurospora crassa*, *Mucor racemosus*, *Sacharomyces cerevisiae*, or *Candida albicans*. In fact, the antifungal activity was generally greater than the antibiotic activity. One of the most active examples was 3-chloro-3-cyano-1-phenyl-4-thiomethyl-2-azetidinone which showed minimum inhibitory concentration (MIC) values for the above-mentioned organisms of, respectively, 10, 100, 100, 10, 5, 5, and 5 μg/mL.

General Mechanistic Probe

The results presented earlier for the mechanism of chlorocyanoketene/imidate cycloadditions provide precedent that suggests a general mechanistic probe for the cycloadditions of cyanoketenes as well as other cyano-substituted compounds—that is, independent generation of reaction intermediates. One can envisage a large variety of cyclic vinyl azides which could undergo the zwittazido cleavage to give the same zwitterionic intermediates as could be formed in certain (2 + 2), (3 + 2), and (4 + 2) cycloadditions (Scheme VIII). For example, the azidocyclopentenedione **31** can be viewed as the masked zwitterion that could result when *tert*-butylcyanoketene cycloadds to another ketene. Likewise, **32** would be the precursor of the possible zwitterion resulting when chlorocyanoketene reacts with benzaldehyde. The azide **33** could be the forerunner of the zwitterion which Huisgen[20] has elegantly shown to be the intermediate in the cycloaddition of tetracyanoethylene to an enol ether. Analogously, **34** is the latent zwitterion that has been proposed as an intermediate in the 1,3-dipolar cycloaddition of tetracyanoethylene oxide to benzylideneaniline.[26] Finally, **35** could possibly function as a precursor to the same zwitterion that could be initially formed in a Diels–Alder reaction of cyano-1,4-benzoquinone with 1-methoxy-1,3-butadiene.

Scheme VIII



In order to investigate the utility of this mechanistic probe in more depth, we chose to study the cycloaddition of the electron-deficient *tert*-butylcyanoketene with electron-rich aldo- and ketoketenes, respectively, methyl- and dimethylketene. Also, the cycloaddition of chlorocyanoketene with a series of benzaldehydes was studied. The results here were then complemented with those obtained from the thermolysis of the appropriately substituted azides corresponding, respectively, to **31** and **32**. The results, which are outlined in Schemes IX and XI, again show these cycloadditions to proceed by zwitterionic intermediates.[27]

Methylketene cycloadds to *tert*-butylcyanoketene to give only the 2-oxetanone **35** in 49% purified yield (Scheme IX). Analogously, dimethylketene upon treatment with *tert*-butylcyanoketene gives only the 1,3-cyclobutanedione **36** in 37% purified yield. It was

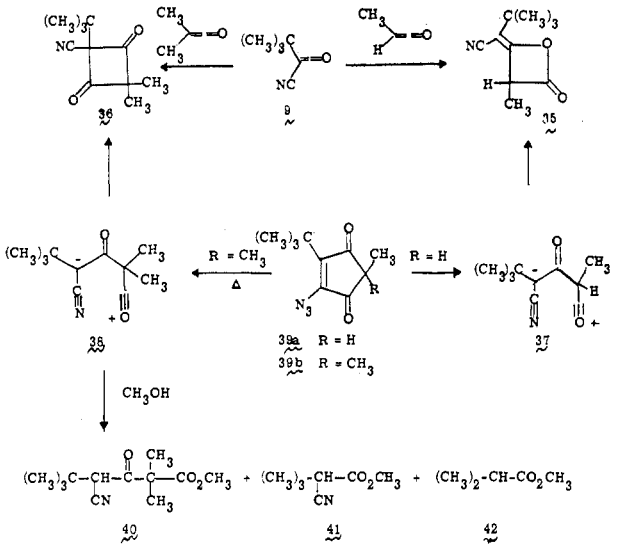
(24) C. Inderlied, P. Sypherd, R. Chambers, D. Kunert, L. Hernandez, Jr., F. Mercer, and H. W. Moore, *Antimicrob. Agents Chemother.*, submitted.

(25) R. F. Abdulla and K. H. Fuhr, *J. Med. Chem.*, **17**, 625 (1975); A. K. Bose, M. S. Manhas, J. C. Kapur, S. D. Sharma, and S. G. Amin, *ibid.*, **17**, 541 (1974).

(26) W. J. Linn and E. Ciganek, *J. Org. Chem.*, **34**, 2146 (1969).

(27) H. W. Moore and D. Scott Wilbur, *J. Am. Chem. Soc.*, **100**, 6523 (1978); H. W. Moore, F. Mercer, D. Kunert, and P. Albaugh, unpublished results.

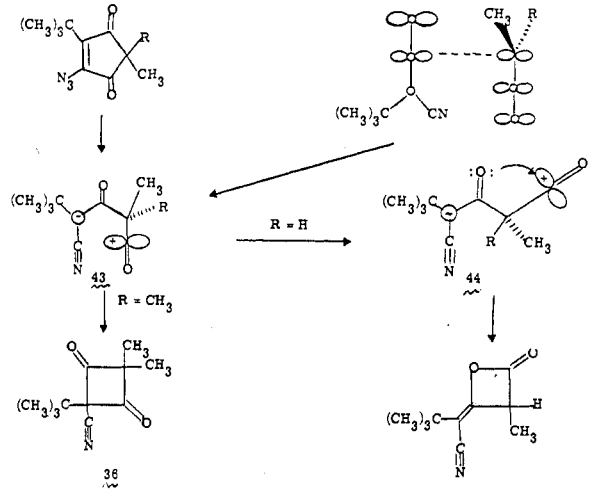
Scheme IX



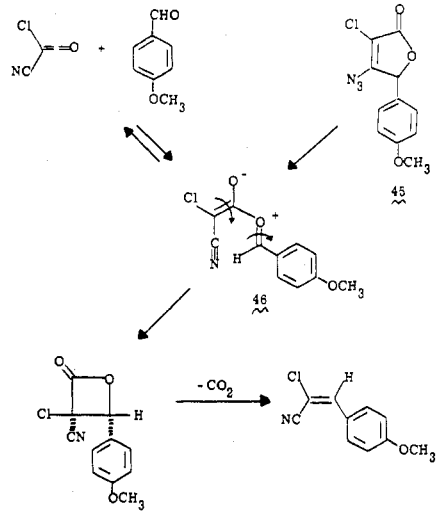
anticipated that if these cycloadditions proceed via the respective zwitterions, **37** and **38**, such intermediates could be independently generated upon thermolysis of the corresponding 4-azido-5-*tert*-butylcyclopentene-1,3-diones, **39a,b**. Thus, these were synthesized and subjected to thermolysis in refluxing benzene. Remarkably, thermolysis of **39a** gave only the 2-oxetanone **35** (82% purified yield) and **39b** gave only the cyclobutane-1,3-dione **36** (90% purified yield). In order to establish that these azidocyclopentenediones give zwitterions upon thermolysis, a trapping experiment was accomplished. Specifically, thermolysis of **39b** in refluxing methanol gave methyl 2-cyano-3,3-dimethylbutanoate (**41**) and methyl 2-methylpropanoate (**42**) in roughly equal amounts and, significantly, the β-keto ester **40** in 41% yield. In a control experiment the cyclobutane-1,3-dione **36** was subjected to methanolysis under the same conditions as above, and the exclusive product was the β-keto ester **40**. However, the rate of methanolysis of **36** is appreciably slower than that of **39b**. Thus, in the methanolysis of **39b**, some, if not all, of the β-keto ester **40** must be coming from methanol addition to the zwitterion **38**. Therefore, a concerted mechanism for the conversion of **39b** to **36** lacks credence. Also, a pure ketene mechanism is unreasonable, since if this were so, one would certainly expect the methanolysis of **39b** to give only the esters **41** and **42**. Yet, the major product is the β-keto ester **40**. That leaves as the most reasonable alternative a mechanism in which the azidocyclopentene-1,3-dione **39b** cleaves to the zwitterion **38** and this partitions between ring closure to **36** and equilibration with *tert*-butylcyanoketene and dimethylketene. When the decomposition of **39b** is accomplished in methanol, the zwitterion is trapped to give **40** and the respective ketenes give **41** and **42**. Finally, since the cycloadditions of *tert*-butylcyanoketene to dimethyl- and methylketene give exactly the same products as the thermolyses of **39b** and **39a**, both processes must involve common zwitterionic intermediates.

These data suggest still a further significant feature of the cycloaddition mechanism, namely that the two ketenes undergo initial bond formation from a head-to-tail orientation to give the zwitterion represented by conformer **43** (Scheme X). Such an interpretation is

Scheme X



Scheme XI

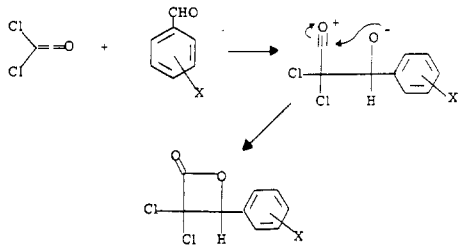


possible since **43** would be the expected conformer to arise directly when the zwitterion is independently generated from the cyclopentenedione precursors. Direct ring closure of **43** (R = CH_3) to **36** would involve the orthogonal enolate anion and acyl cation orbitals. In the less sterically hindered example **43** (R = H), rapid rotation to **44** is allowed and subsequent ring closure to the β-lactone, **35**, may be the most facile since it could involve a carbonyl nonbonding e^- pair in an orbital which is now not orthogonal to the acyl cation orbitals.

Based entirely upon analogy with the previously described results, we have recently shown that chlorocyanoketene cycloadds to benzaldehydes to give β-lactones via a zwitterionic mechanism. The β-lactones decarboxylate stereospecifically under the reaction conditions (80 °C) to give exclusively (*E*)-1-chloro-1-cyano-2-arylethenes (8–92%) as the isolatable products. That a zwitterion is the penultimate precursor to the β-lactones was evidenced by its independent generation from a 4-azido-3-chloro-5-aryl-2(5*H*)-furanone. This is schematically represented with the specific example outlined in Scheme XI.

The significant data of this study as they relate to the given mechanism are the following. (1) Both the rates of chlorocyanoketene cycloadditions to a series of

Scheme XII



substituted benzaldehydes and the product yields increase as the benzaldehyde substituent becomes more electron releasing. (2) The reaction appears to be completely stereospecific. (3) The same product and stereochemistry are observed from the azidofuranone decomposition as from the cycloadditions themselves. (4) Generation of chlorocyanoketene in the presence of a 1:10 ratio of *p*-methoxybenzaldehyde and benzaldehyde gave a 0.8:1.0 mixture of, respectively, the *p*-methoxyphenyl- and phenylethene products. On the other hand, when the *p*-methoxyphenylfuranone **45** was decomposed in the presence of 10 molar equiv of benzaldehyde, this ratio increased to 1.4:1.0. Thus the zwitterion **46** is reasonably assumed to partition between alkene product formation and cleavage to chlorocyanoketene and *p*-methoxybenzaldehyde.

These results are of particular interest when they are compared to other reported ketene/aldehyde cycloadditions. For example, dichloro-, methyl-, chloro-, isopropoxy-, and phenoxyketene do cycloadd to aldehydes, but unlike chlorocyanoketene, they react rapidly with electron-deficient aldehydes and slowly or not at all with electron-rich analogues.[28] As mentioned, the opposite is true for chlorocyanoketene. One such study of particular note was recently reported by Krabbenhoft[28e] who reported an investigation of the cycloaddition of dichloroketene with a series of substituted benzaldehydes, including many of the same derivatives we used in the analogous chlorocyanoketene study. Here it was observed that the reaction is most facile with the more electropositive benzaldehyde derivatives. Although the mechanism of these cycloadditions was not established, an extreme dipolar process which reflects the nucleophilic character of dichloroketene is outlined in Scheme XII. Thus, one comes to the rather startling conclusion that dichloroketene functions as a nucleophile in its reactions with benzaldehydes while chlorocyanoketene functions as an electrophile.

A final few brief comments regarding cyanoketene chemistry should be made in order that one is not left with the conclusion that all of their cycloadditions are nonconcerted. Results outlined here clearly show their reactions with imidates, ketenes, and benzaldehydes to be nonconcerted. The same is undoubtedly true for the reactions of *tert*-butylcyanoketene with enol ethers.[4d] Allenes, on the other hand, readily cycloadd to *tert*-butylcyanoketene, but the mechanism appears to vary between a concerted and dipolar process depending upon the allene substituents.[4a,c,i] Alkynes are proposed to react with this ketene by a concerted process,[4g] and alkenes have been documented to react by a ($_{\pi}2_s + {}_{\pi}2_a$) concerted mechanism.[4a,h]

Conclusions

In conclusion, I wish to summarize some significant points resulting from the studies outlined here. (1) For the first time the zwitterions resulting from the interaction of a ketene with an imidate or another ketene or an aldehyde have been independently generated and shown to give the same products as the cycloadditions themselves. (2) The fact that zwitterions are formed in the thermolyses of **18**, **39**, and **45** establishes the mechanism of the zwittazido cleavage, and thus a powerful predictive model is at hand. (3) A new β-lactam synthesis has been discovered, and many of the new cyano-substituted β-lactams show antimicrobial as well as antifungal activity. (4) Finally, a potentially generally mechanistic probe for the investigation of the cycloadditions of a variety of cyano-substituted substrates results from these investigations.

I wish to extend a special thanks to my graduate students and postdoctoral associates whose names appear in the literature cited. They, along with the generous financial support of the National Science Foundation and the National Institutes of Health, have made this research possible.

(28) (a) W. T. Brady and L. Smith, *J. Org. Chem.*, **36**, 1637 (1971); (b) D. Borrman and R. Wegler, *Chem. Ber.*, **99**, 1245 (1966); (c) D. Borrman and R. Wegler, *ibid.*, **102**, 64 (1969); (d) D. Borrman and R. Wegler, *ibid.*, **100**, 1575 (1967); (e) H. O. Krabbenhoft, *J. Org. Chem.*, **43**, 1305 (1978).

Revival of Troponoid Chemistry

FRANCESCO PIETRA

Laboratorio di Chimica Organica, Facoltà di Scienze, Libera Università di Trento, 38050 Povo, Trento, Italy

Received January 4, 1978

The chemistry of tropone (cycloheptatrienone) and its derivatives began as natural product chemistry.[1] In 1945, the tropolone (2-hydroxytropone) structure was first suggested for stipitatic acid (**1**), a mould metabolite of the Penicillium family, and colchicine (**2**), an alkaloid of the Liliaceae,[2] was recognized as a tropone derivative.

Francesco Pietra is Professor of Organic Chemistry at the University of Trento, Trento, Italy. He was born in Carrara and did his university study at the University of Padua, where he also did postdoctoral research with Antonino Fava. He was for several years at the University of Pisa, where he carried out most of his work on aromatic substitution, catalytic phenomena, bridged polycyclics, and troponoids, as well as at the University of Catania. He was also at the Gorlaeus Laboratoria, Leiden, and at Imperial College, London.

The author wishes to dedicate this work to Professor E. Havinga on the occasion of his 70th birthday.

(1) (a) T. Nozoe, *Fortschr. Chem. Org. Naturst.*, **13**, 232 (1956); J. G. Buta, J. L. Flippen, and W. R. Lubsy, *J. Org. Chem.*, **43**, 1002 (1978); (b) T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds", Academic Press, New York: Vol. I, 1975, p 398; Vol. II, 1972, pp 43–44.

(2) M. J. S. Dewar, *Nature (London)*, **155**, 50, 141, 479 (1945).

0001-4842/79/0112-0132$01.00/0