A New Synthetic Route to 2-Azetidinones. Ring Contraction of 4-Azido-2-pyrrolinones to 3-Cyano-2-azetidinones

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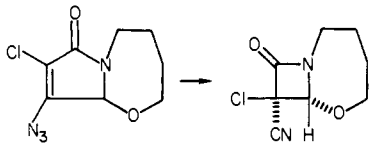
Abstract: Thermolysis or photolysis of 4-azido-2-pyrrolinones results in their ring contraction to 3-cyano-2-azetidinones. The mechanism of this rearrangement is discussed, and evidence is presented to establish zwitterionic intermediates as the penultimate precursors to the 2-azetidinones.

In preliminary reports, synthetic routes to halocyanoketenes and 3-cyano-2-azetidinones (β-lactams) were described; these products come respectively from the thermolysis of 4-azido-3-halo-5-methoxy-2(5*H*)-furanones and 4-azido-2-pyrrolinones.[1,2] The experimental details of the β-lactam synthesis as well as mechanistic discussions of this ring contraction are now reported.

The foundation of the synthetic applications as well as the mechanistic details of the work described here rests on a generalized rationale which is outlined in Scheme I.[3] Specifically, vinyl azides which are amenable to this reaction have the general structure **1**. The cleavage of **1** to the zwitterion **2** is facile when X can easily carry a positive charge and Y and/or Z are anion-stabilizing substituents. The zwitterionic intermediate **2** can then ring close to **3** (path a), cleave to **4** (path b) or, in cases where X carries an acidic proton, undergo proton transfer to **5** (path c). Inspection of this scheme allows one to envisage the predictive significance of this mechanism as it relates to the prime objectives of the research outlined here. For example, (1) it defines a potentially general reaction of certain vinyl azides and illustrates a mechanism which will be substantiated subsequently; (2) it depicts a strategy for cyanoketene syntheses starting from precursors where Y is a carbonyl group and X is an appropriate leaving group; (3) it provides a rationale for ring contraction of 4-azido-2-pyrrolinones to 3-cyano-2-azetidinones; (4) finally, it suggests an independent route to zwitterionic intermediates which could be the same as those formed in the dipolar cycloadditions of cyanoketenes to other substrates. Thus, a potentially powerful mechanistic probe for studying such cycloadditions is at hand.

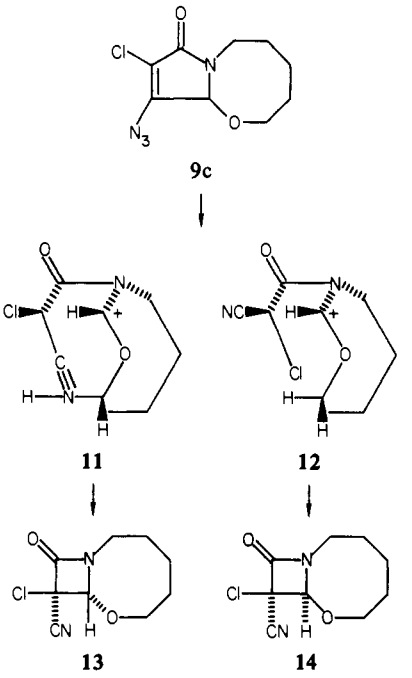
New β-Lactam Synthesis. As mentioned, appropriately substituted 4-azido-2-pyrrolinones, **6**, are predicted to thermally cleave to zwitterions **7** and these, in turn, could ring close to 3-cyano-2-azetidinones (β-lactams), **8**. Indeed, when the pyrrolinones **6a–f** were subjected to thermolysis in refluxing benzene, the corresponding *E* isomers of the β-lactams **8a–f**, were obtained in isolated yields ranging from 55–90% (Scheme II). This ring contraction could also be accomplished by photolytic means as shown by the conversion of **6e** to **8e** (72%) upon irradiation of a dichloromethane solution with a 200-W medium-pressure lamp.

The scope of this ring contraction was further studied to include bicyclic examples of β-lactams. Thus, the pyrrolinones **9a–c** were subjected to both pyrolysis (90 °C, toluene) and photolysis (450-W Hanovia lamp, 10 °C, carbon tetrachloride). Ring contraction was encountered for both **9b** and **9c**. The former gave only the *E* isomer **10** in excellent yield (90%, Δ; 91%, *hν*). The latter, **9c**,



9b **10**

gave both the *E* isomer **13** (36%, Δ; 38%, *hν*) and a small amount of its diastereomer **14** (6%, Δ; 7%, *hν*). This is unusual since



9c **11** **12** **13** **14**

it is the only case observed to give both *E* and *Z* stereoisomers. Models reveal an endo cyano group as in **11** to result in some steric congestion between the linear cyano group and one of the methylene groups of the eight-membered ring. Less obvious interactions are present in zwitterion **12** in which the chlorine is in the endo orientation. On the basis of electronic effects zwitterions such as **11** are suggested to be preferred due to electrostatic interactions between the cyano group, which bears some negative charge, and the cationic center of the zwitterion.[3] Thus, only *E* isomers of the 3-chloro-4-alkoxy-2-azetidinones are generally formed, and these presumably result from a conrotatory ring closure of the zwitterionic intermediates. However, in the above-mentioned thermolysis of **9c** the subtle steric effect allows some products to arise from the electronically less favored zwitterion **12**. Such an interpretation further assumes the equilibration between zwitterions **11** and **12** to be slow and that

(1) H. W. Moore, L. Hernandez, Jr., and A. Sing, *J. Am. Chem. Soc.*, **98**, 3728 (1976).
(2) D. M. Kunert, R. Chambers, F. Mercer, L. Hernandez, and H. W. Moore, *Tetrahedron Lett.*, 929 (1978).
(3) H. W. Moore, *Acc. Chem. Res.*, **12**, 125 (1979).
(4) E. Schaumann, H. Mrotzek, and F. A.βmann, *Liebigs Ann. Chem.*, **334** (1979).

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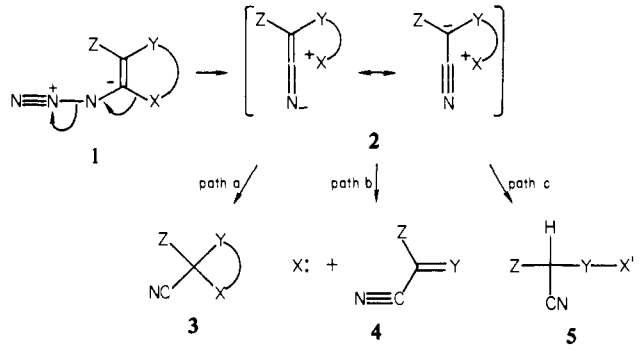
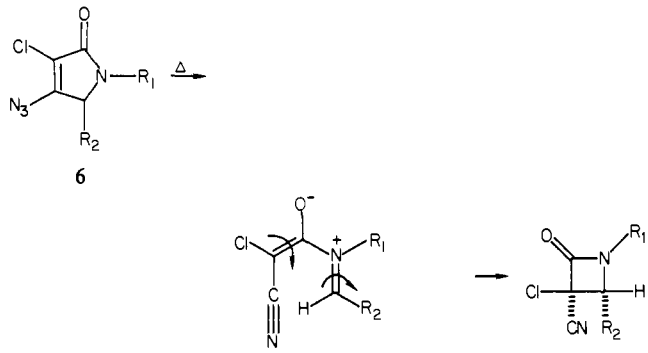
Scheme I



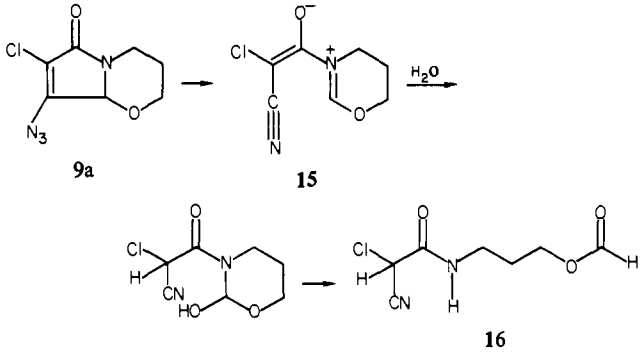
Scheme II



	% yield
a, $R_1 = CH_3$, $R_2 = OCH_3$	55
b, $R_1 = CH_3$, $R_2 = OCH_2CH_3$	60
c, $R_1 = CH_2CH_3$, $R_2 = OCH_2CH_3$	88
d, $R_1 = CH(CH_3)_2$, $R_2 = OCH_2C_6H_5$	90
e, $R_1 = C_6H_{11}$, $R_2 = OCH_2CH_3$	62 (72)
f, $R_1 = C_6H_{11}$, $R_2 = C_6H_5$	49

the configuration of the products is thus determined by stereoselective conversion of the starting materials to the zwitterionic intermediates.

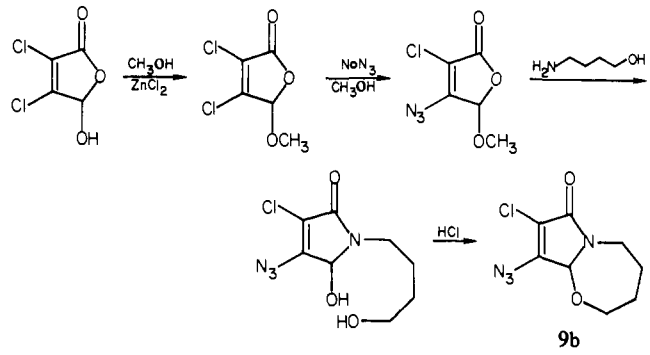
Thermolysis or photolysis of **9a** gave no detectable amount of



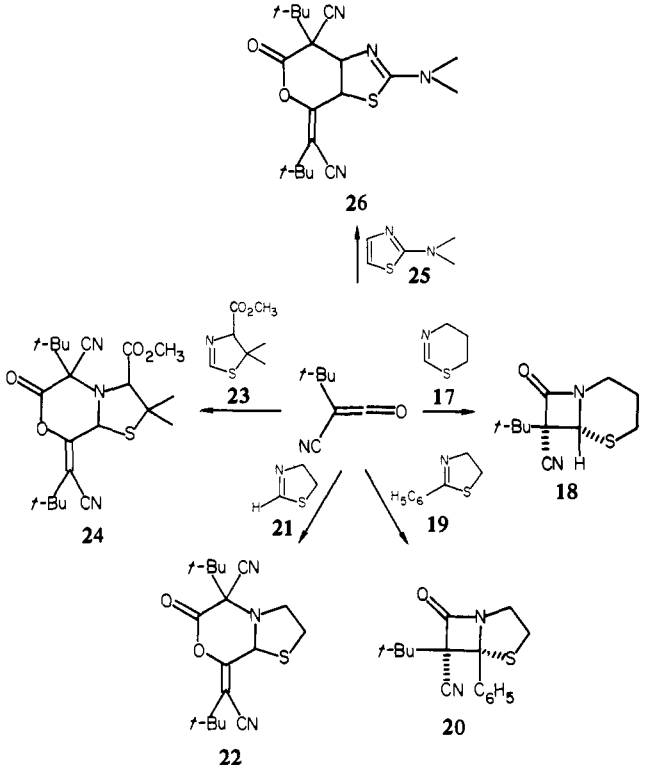
β-lactam product. Instead, the ring-opened amide **16** was isolated in reasonable yields (65%, Δ; 36% $h\nu$). This product is viewed as arising from hydrolytic trapping of the zwitterion **15** by trace amounts of water and thus provides direct evidence for such intermediates in the thermolysis and photolysis of 4-azido-2-pyrrolinones. These results also speak directly to a synthetic limitation in the conversion of 4-azido-2-pyrrolinones to bicyclic cyanoazetidinones. Apparently, the strain energy associated with fusing a cyanoazetidinone to a six-membered ring, in conjunction with the electronic stabilization of the zwitterion, preempts ring closure of **15**.

Analogous, but less severe, limitations have been observed in other synthetic routes to bicyclic cyanoazetidinones, e.g., the cycloadditions of *tert*-butylcyanoketene to thiazines and thiazoles. Here again zwitterions analogous to **15** are the suggested intermediates. The 1:1 cycloaddition products, **18** and **20** arise from

Scheme III



cycloaddition to the corresponding thiazines **17** and **19**. However, the thiazines **21** and **23** give 2:1 products **22** and **24**, and 2-(dimethylamino)thiazole leads to **26**.[5]

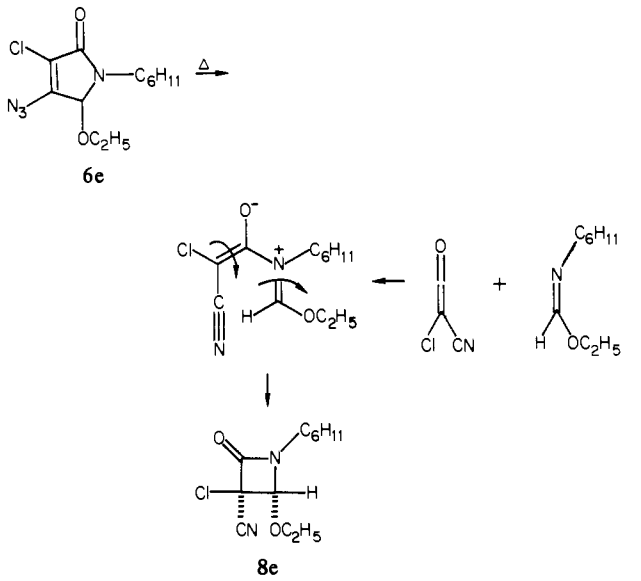


The azidopyrrolinones (**6a–f**, **9a–c**) were prepared from mucochloric acid, a readily available and extensively studies butenolide.[6] Scheme III, illustrating the synthesis of **9b**, represents the general route employed.

Stereochemistry. The stereochemical assignments of the 3-cyano-2-azetidinones described here are based primarily upon analogy to arguments previously developed and utilized in determination of the stereostructures of other members of this series.[7] These include ^{13}C NMR, ^1H NMR, and X-ray crystallographic data.[8] In general, these data have been employed to establish the stereochemistry of a large number of 3-cyano-4-thioalkyl (or thioaryl)-2-azetidinones which were all prepared by the cycloaddition of cyanoketenes to thioformimidates. In all cases the resulting 2-azetidinones are those in which the 3-cyano and the 4-thioalkyl groups reside in a cis relationship. We thus assume analogous stereochemistry for the 3-cyano-4-alkoxy derivatives described here. This assumption is further weighted by the fact

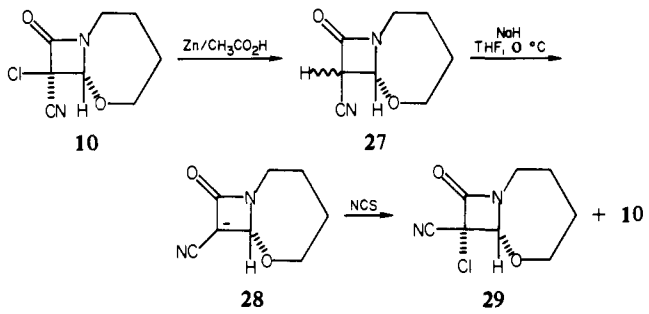
(5) A. Dondoni, A. Medici, C. Venturoli, L. Forlani, and V. Bertolasi, *J. Org. Chem.*, **45**, 621 (1980).
(6) Y. S. Rao, *Chem. Rev.*, **76**, 625 (1976).
(7) R. Chambers, D. Kunert, L. Hernandez, Jr., F. Mercer, and H. W. Moore, *Tetrahedron Lett.*, 933 (1978).
(8) R. J. Doedens and R. Chambers, *Acta Crystallogr.*, in press.

the same stereoisomer is formed from the thermolyses of **6e** as is obtained from the cycloaddition of chlorocyanoketene to *N*-cyclohexyl-*O*-ethylformimidate,[9] i.e.



6e **8e**

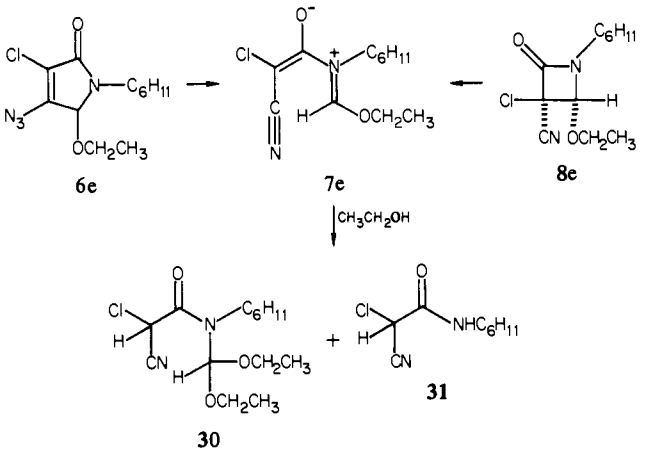
In addition, direct chemical evidence was obtained to substantiate the stereochemistry of the bicyclic azetidinones **10**, **13**, and **14**. Specifically, when 7,8-dihydro-6-oxa-9-oxo-1-azabicyclo[5.2.0]nonane (**10**) was treated with zinc in acetic acid, the



10 **27** **28** **29**

dihydro derivative **27** was formed as a mixture of the *E* and *Z* isomers in a respective ratio of 2:1.[10] Rechlorination of the mixture was accomplished by generation of the enolate **28** (NaH, THF, 0 °C) and treatment of this with *N*-chlorosuccinimide. Here a 5:1 ratio of, respectively, **10** and its diastereomer, **29**, was obtained. The predominance of **10** was anticipated by reasonably assuming rechlorination from the least hindered side of the enolate anion.[11] In addition, the ^{13}C NMR spectra of **10** and **29** reveal the cyano carbon in the former to absorb at higher field (112.4 ppm) than that in the latter (114.2 ppm). This observation is in agreement with that previously reported for the *E* and *Z* isomers of a series of 3-chloro-2-cyano-4-thioalkyl-2-azetidinones, i.e., the cyano which is cis to the heteroatom is less deshielded than that which is trans.[7] In an analogous set of reactions **13** and **14** were dechlorinated and the resulting dihydro derivative was rechlorinated to again give a 5:1 ratio of **13** to **14**; the cyano group in the former appeared at 111.2 ppm and in the latter at 112.6 ppm.

Mechanism. Zwitterions were established as intermediates in the azidopyrrolinone ring contractions by a series of trapping experiments. As mentioned earlier, thermolysis of **9c** in moist toluene results in a 65% yield of the acyclic amide **16**, a product most reasonably resulting from interception of the zwitterion **15**. The thermolysis of **6e** in anhydrous ethanol was also investigated.



6e **7e** **8e** **30** **31**

This gave a mixture of products which were not completely resolved. However, the results are significant in some regards. The four major products are ethyl chlorocyanoacetate, *N*-cyclohexyl-1-chloro-1-cyanoacetamide (**31**), *N*-cyclohexyl-*N*-(diethoxymethyl)-1-chloro-1-cyanoacetamide (**30**), and the β-lactam **8e**, and these are formed in a ratio of 4.0:3.0:2.3:1.0. The ester and β-lactam were identified by analysis of the ^{13}C and ^{1}H NMR spectra of the crude reaction mixture with and without authentic samples added. The amides **30** and **31** were isolated in pure form and identified by spectral and analytical properties which are all in strict accord with their formulated structures. In a control experiment it was shown that **30** is partially converted to **31** under the reaction conditions. In addition to the above products, several minor and as yet unidentified compounds were also detected. However, the critical observation is that the amides **30** and **31** are formed in reasonable yields, and these are products anticipated to arise directly from ethanolysis of zwitterion **7e**. It is also most interesting to note that the amide **31** (20%) was also formed, however, at a slower rate, when the β-lactam **8e** was subjected to alcoholysis in refluxing anhydrous ethanol. This is a remarkable result since it demonstrates the lability of the C_3–C_4 bond rather than the N_1–C_2 bond of this 3-cyano-2-azetidinone.

In another series of zwitterion-trapping experiments a most interesting synthetic route to heteroaromatic betaines was discovered.[12] Specifically, when the 4-azido-2-pyrrolinone (**6e**) was subjected to thermolysis in refluxing benzene for an extended period of time (48 h), **33** (~10%) was isolated in addition to the major β-lactam product, **8e**. The betaine, **33**, which represents an example of a rare class of compounds,[13] was easily isolated since it precipitates from the reaction solution during the course of the thermolysis. It was also observed that the same product is formed when one equivalent each of chlorocyanoketene and the corresponding formimidate was subjected to the same reaction conditions. Synthesis of **33** on a more viable preparative scale (>70%) can be accomplished by carrying out the thermolyses (96 h) in the presence of excess (2–12 equiv) formimidate. During the course of these reactions one can observe the initial formation of the β-lactam which slowly disappears as the betaine forms.

A mechanism describing the formation of **33** is outlined in Scheme IV. The most salient experimental observation is that this product arises from three independent starting materials, i.e., chlorocyanoketene/formimidate, a 3-cyano-2-azetidinone, and a 4-azido-2-pyrrolinone. Thus, a common zwitterionic intermediate is strongly suggested. The most consistent interpretation is that the zwitterion, once formed, is in equilibrium with chlorocyano-

(9) H. W. Moore, R. Chambers, and L. Hernandez, Jr., *J. Am. Chem. Soc.*, **100**, 2245 (1978).

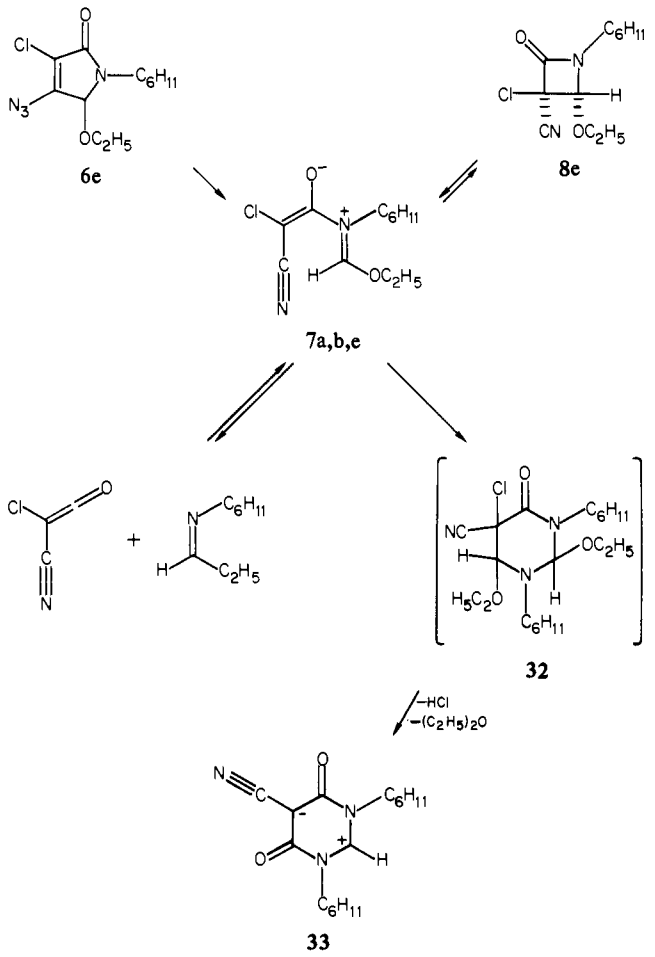
(10) The stereochemistry was readily assigned on the basis of coupling constants for the methine protons. See K. D. Banrow and T. M. Spotswood, *Tetrahedron Lett.*, 3325 (1965).

(11) Such stereospecificity in the halogenation of enolates of monocyclic 3-cyano-2-azetidinones has been unambiguously established. See ref 2.

(12) F. Mercer, L. Hernandez, Jr., and H. W. Moore, *Heterocycles*, **12**, 45 (1979).

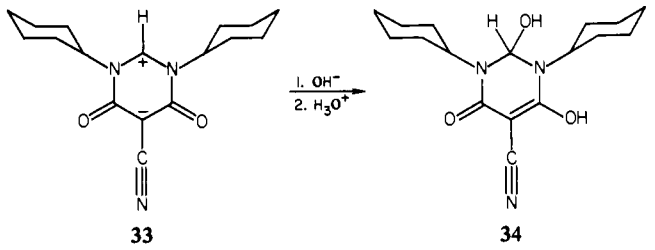
(13) Y. Maki, S. Sako, and M. Suzuku, *J. Chem. Soc., Chem. Commun.*, 999 (1972); Th. Kappe and W. Lube, *Monatsh. Chem.*, **102**, 781 (1971); M. Prystas, *Collect. Czech. Chem. Commun.*, **32**, 4241 (1967); K. T. Potts and M. Sorm, *J. Org. Chem.*, **37**, 1422 (1972).

Scheme IV



ketene and the formimidate. The formimidate thus generated cycloadds to the zwitterion to give **32**, and this in turn suffers the loss of the equivalent of hydrogen chloride and a diethyl ether to give **33**.

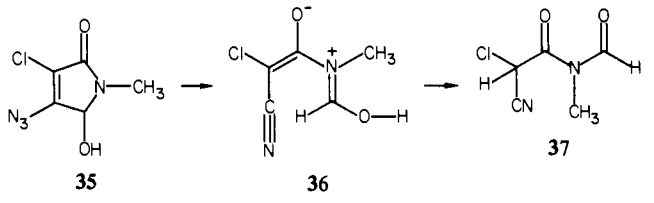
The structural assignment of **33** is based upon spectral and

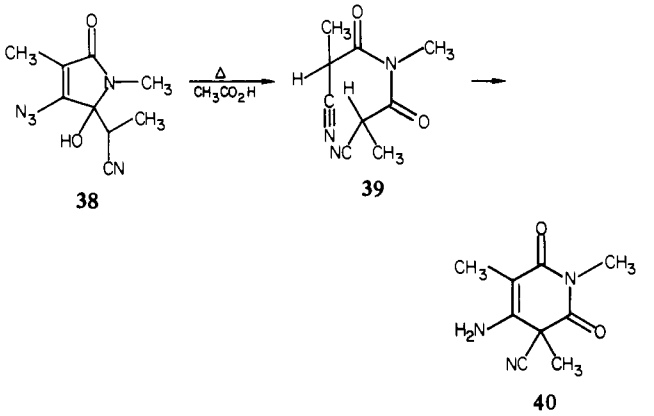


analytical properties as well as its expected hydrolysis (5% NaOH) to 5-cyano-1,3-dicyclohexyl-2,4-dihydroxy-6-oxo-1,2,3,6-tetrahydropyrimidine (**34**) in 92% isolated yield.

In addition to the above trapping experiments which provide direct evidence for zwitterions arising in the thermolysis of 4-azido-2-pyrrolinones, other experiments were conducted which generally focus on the possibility of such intermediates in related vinyl azide thermolyses. For example, 4-azido-5-hydroxy-2-pyrrolinones would be expected to give zwitterions capable of proton transfer (path c, Scheme I) and this was observed for the conversion of 4-azido-3-chloro-5-hydroxy-1-methyl-2-pyrrolinone (**35**) to the imide **37** (26%). The zwitterion 36 is viewed as the intermediate.

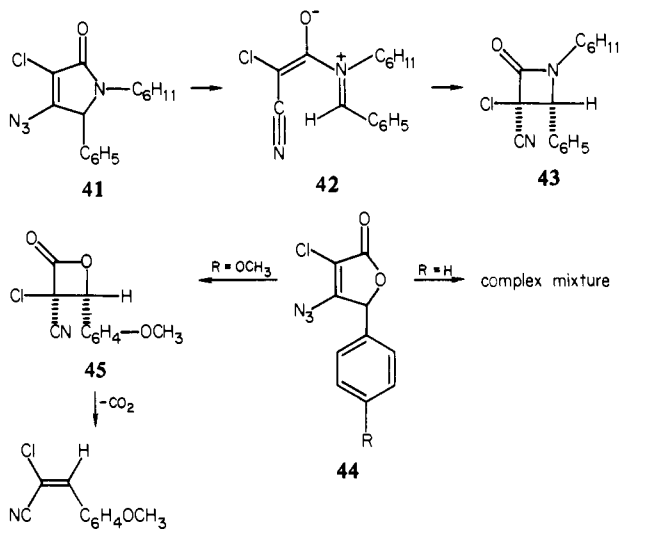
In a related experiment, 4-azido-5-hydroxy-5-(1-cyanoethyl)-1,3-dimethyl-2-pyrrolinone (**38**) cleaves to the symmetrical imide **39** in hot acetic acid. This product which was formed in high yield (~90%) was not isolated in analytical purity since it easily undergoes ring closure to the cyclic imide **40** in 68% isolated yield upon attempted vacuum distillation. Again, the initial





conversion of **38** to **39** most reasonably involves a dipolar intermediate analogous to **36**.

Based upon the results thus far presented, one would anticipate zwitterion formation from 4-azido-5-aryl-2-pyrrolinones since the cationic center would experience benzylic stabilization as well as additional resonance stabilization due to the nonbinding electron pair on the amide nitrogen. Thus, 4-azido-3-chloro-1-cyclohexyl-5-phenyl-2-pyrrolinone (**41**) was found to ring contract to

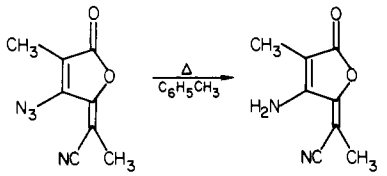


the β-lactam **43**, when subjected to thermolysis in refluxing benzene. Interestingly, when the analogous butenolide **44** (R = H) was thermolyzed under the same conditions, a very complex reaction mixture resulted. However, the 4-methoxyphenyl derivative **44** (R = OCH_3) smoothly ring contracts to the β-lactone **45** and ultimately to the alkene **46** (78%).[14] Thus, as expected, zwitterion formation is sensitive to carbocation-stabilizing effects, and these data speak to some limitations of this process.

Thermolysis of 4-azido-5-alkylidene-2(5*H*)-furanones would not be expected to give products arising from a zwitterionic intermediate since the 5-alkylidene moiety would not stabilize an incipient positive charge. In fact, when 4-azido-5-cyanoethylidene-3-methyl-2(5*H*)-furanone (**47**) was pyrolyzed in refluxing toluene for 5 days, only the β-amino derivative **48** was

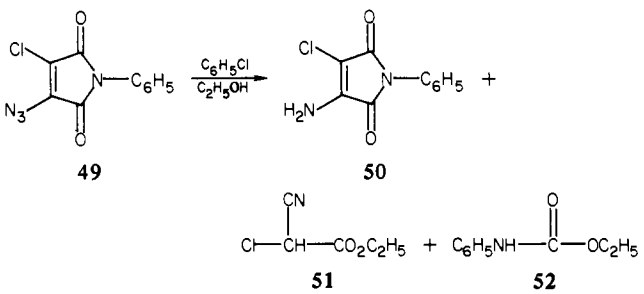
(14) H. W. Moore, F. Mercer, D. Kunert, and P. Albaugh, *J. Am. Chem. Soc.*, **101**, 5435 (1979).

detected in addition to unreacted starting material.



47 48

Finally, one last example which is consistent with the generalized mechanism presented in Scheme I will be mentioned. Azido-substituted maleimides would be expected to thermally cleave to cyanoketenes and isocyanates since the carbonyl adjacent to the azide group would stabilize a positive charge in the zwitterionic intermediate. Such a transformation would be analogous to the previously reported fragmentation of 4-azido-3-chloro-5-methoxy-2(5*H*)-furanone to chlorocyanoketene and methyl formate[1] as well as the cleavage of 4-azido-2-cyanocyclopentene-1,3-diones to 2 equiv of cyanoketenes.[15] Thus, when the azidomaleimide **49** was thermolized in chlorobenzene in the presence of 5 equiv of ethanol, the ester **51** (22%), carbamate **52** (32%), and the aminomaleimide **50** (20%) were isolated. The ester and



49 50 51 52

carbamate arise from ethanolysis of the respective cumulenes. The amino compounds **50** is of particular note since its formation suggests a nitrene may precede zwitterion formation and is trapped by hydrogen atom abstraction.

In conclusion, we wish to emphasize the significant points to result from this investigation. (1) A new β-lactam synthesis involving the thermal and photolytic ring contraction of 4-azido-2-pyrrolinones has been discovered. (2) This ring contraction appears to be quite general for the construction of monocyclic 3-cyano-2-azetidinones; however, for bicyclic examples, it has thus far been impossible to make examples in which a ring smaller than seven members is fused to the β-lactam nucleus. (3) The ring contraction itself has been established to involve a zwitterionic intermediate.

Experimental Section

General Comments. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on Perkin-Elmer 137, Perkin-Elmer 283, and Beckman (Acculab 2) spectrophotometers. The absorptions are reported in inverse centimeters, and, unless otherwise indicated, were obtained as Nujol mulls. Nuclear magnetic resonance (NMR) spectra were recorded by using a Varian EM 360 and a Bruker (90-MHz) spectrometers and, unless otherwise indicated, were run in deuteriochloroform. Chemical shifts are reported on the δ scale with tetramethylsilane (Me_4Si) as the internal standard.

4-Azido-3-chloro-5-methoxy-2(5*H*)-furanone. To a cold stirred solution of 15 g (82.3 mmol) of 2,3-dichloro-5-methoxy-2(5*H*)-furanone[1] in 150 mL of methanol was added 5.37 g (82.6 mmol) of sodium azide. After 1 h water was added and the resulting white solid (14.1 g, 91%) was collected: mp 67–68 °C dec; IR 2145 (N_3), 1780 (C=O), 1640 (C=C) cm^{-1}; NMR (acetone-d_6) δ 3.50 (s, 3 H); 5.64 (s, 1 H). Satisfactory microanalysis could not be obtained on this azide.

4-Azido-3-chloro-1-methyl-5-methoxy-2-pyrrolinone (6a). A solution of 9.8 g (51.5 mmol) of 4-azido-3-chloro-5-methoxy-2(5*H*)-furanone in 150 mL of dichloromethane was stirred at −78 °C while a solution of 5.0 g (162 mmol) of methylamine in 50 mL of chloroform was added dropwise. After the mixture was stirred overnight at −10 °C, the volatiles were removed at 0 °C in vacuo and the resulting pale yellow oil was dissolved in 225 mL of methanol. The solution was stirred in an ice bath, and hydrogen chloride gas was added in excess without allowing the temperature to rise above 15 °C. After 24 h at ambient temperature the reaction solution was poured into 0.5 L of ice. Sodium bicarbonate was added slowly with hand stirring until gas evolution ceased. The methylated product was extracted with two 125-mL portions of dichloromethane and dried over anhydrous II magnesium sulfate and concentrated. The residue was passed through a short column of silica gel, and the yellow band was collected to give 4.1 g (40%) of **6a**: IR 2120 (N_3) 1720 (C=O), 1650 (C=C) cm^{-1}; NMR δ 2.91 (s, 3 H) 3.17 (s, 3 H), 5.26 (s, 1 H).

Anal. Calcd for $C_6H_7N_4ClO_2$: C, 35.55; H, 3.46. Found: C, 35.47; H, 3.75.

4-Azido-3-chloro-5-ethoxy-1-methyl-2-pyrrolinone (6b). A solution of 1.5 g (48.4 mmol) of methylamine in 10 mL of chloroform was added to 3.0 g (15.8 mmol) of 4-azido-3-chloro-5-methoxy-2(5*H*)-furanone in 50 mL of dichloromethane at 0 °C. The solution was stirred overnight at −10 °C and filtered, and the solvent was removed at 0 °C in vacuo to give the carbinolamide as a yellow oil. At room temperature this oil decomposes with evoluation of nitrogen. Spectra properties of the carbinolamine follow: IR (film) 3330 (OH), 2170 (N_3), 1690 (C=O), 1655 (C=C) cm^{-1}; NMR δ 2.86 (s, 3 H), 4.11 (br s, 1 H), 5.16 (s, 1 H).

Without further purification the oil was dissolved in 40 mL of ethanol and cooled, and an excess of HCl gas was slowly added. After 12 h at room temperature, the solution was poured over ice water, neutralized with sodium bicarbonate, and extracted with chloroform. The organic phase was dried (magnesium sulfate) and the solvent removed in vacuo to give 2.7 g of crude 4-azido-2-pyrrolinine as a yellow oil. Chromatography on silica gel (chloroform/hexane, 1:2) gave 0.88 g (26%) of **6b** as a clear oil: IR (film) 2130 (N_3), 1734 (C=O), 1651 (C=C) cm^{-1}; NMR δ 1.22 (t, 3 H), 2.87 (s, 3 H), 3.32 (q, 2 H), 5.20 (s, 1 H). Satisfactory microanalysis could not be obtained on this azide.

4-Azido-3-chloro-1-ethyl-5-ethoxy-2-pyrrolinone (6c). Ethylamine (6.0 g, 0.133 mol) in 50 mL of chloroform was added (30 min) to a cold stirred solution of 6.2 g (32.9 mmol) of 4-azido-3-chloro-5-methoxy-2-(5*H*)-furanone in 150 mL of dichloromethane. After the mixture was stirred for 24 h at room temperature, the solvent was removed under reduced pressure to give a yellow oil. A peak in the NMR spectrum of the crude product at 5.34 (s) and IR absorptions at 3400 (OH), 2122 (N_3), 1710 (C=O), 1648 (C=C) cm^{-1} were consistent with carbinolamide formation. Without further purification the oil was dissolved in 100 mL of ethanol (0 °C) and HCl gas was slowly added (20 min). After 17 h at room temperature the solution was poured over ice water, neutralized with sodium bicarbonate, and extracted with dichloromethane. The organic phase was dried (magnesium sulfate) and the solvent removed in vacuo to give 6.4 g of the pyrrolinone **6c** as an oil. Chromatography (benzene) gave 2.0 g (27%) of **6c** as a clear oil: IR (film) 2120 (N_3), 1714 (C=O), 1649 (C=C) cm^{-1}; NMR (C_6D_6) δ 0.83 (overlapping t's, 6 H, J = 6 Hz), 2.45–3.35 (m, 4 H), 4.40 (s, 1 H).

Anal. Calcd for $C_8H_{11}N_4ClO_2$: C, 41.65; H, 4.77; N, 24.30; Cl, 15.40. Found: C, 41.95; H, 4.89; N, 24.03; Cl, 15.61.

4-Azido-5-(benzyloxy)-3-chloro-1-isopropyl-2-pyrrolinone (6d). A solution of 4 g (74.2 mmol) of isopropylamine in 50 mL of dichloromethane was added dropwise to a cold stirred solution of 8.2 g (43.2 mmol) of 4-azido-3-chloro-5-methoxy-2(5*H*)-furanone in 100 mL of dichloromethane. The solution was stirred at 10 °C for 6 days. After being washed four times with water, the organic phase was dried (magnesium sulfate) and concentrated in vacuo to a red oil: IR (film) 2180 (N_3), 1700 (C=O), 1655 (C=C) cm^{-1}; NMR δ 1.28 (d, 6 H), 4.07 (septet, 1 H), 5.43 (s, 1 H).

Without further purification the oil was dissolved in 100 mL of benzene and 4.6 g (42.6 mmol) of benzyl alcohol was added. While the solution was stirred in an ice water bath, HCl gas was slowly added (10 min). After 12 h at 10 °C the benzene solution was washed with water, dried (magnesium sulfate), and concentrated in vacuo to give 5.64 g of a tan oil. Purification by column chromatography (benzene/chloroform) gave 1.3 g (10%) of the pyrrolinone, mp 61–63 °C. Recrystallization (dichloromethane/hexane) gave the analytical sample: mp 62.5–64 °C; IR 2120 (N_3), 1727 (C=O), 1654 (C=C) cm^{-1}; NMR δ 1.19 (d, 6 H), 4.21 (m, 3 H), 5.50 (s, 1 H), 7.36 (s, 5 H).

Anal. Calcd for $C_{14}H_{15}N_4ClO_2$: C, 54.82; H, 4.89; N, 18.27; Cl, 11.57. Found: C, 54.57; H, 5.04; N, 17.98; Cl, 11.71.

4-Azido-3-chloro-1-cyclohexyl-5-ethoxy-2-pyrrolinone (6e). A solution of 34.1 g (340 mmol) of cyclohexylamine in 200 mL of dichloromethane was added dropwise to a cold stirred solution of 16.24 g (85.9 mmol) of 4-azido-3-chloro-5-ethoxy-2(5*H*)-furanone in 500 mL of dichloromethane. The solution was stirred at −10 °C for 4 weeks. The reaction

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

solution was washed twice with 250 mL of a cold 2.5 M HCl solution, dried (magnesium sulfate), and concentrated to a red oil in vacuo: IR (film) 3300 (OH), 2120 (N_3), 1690 (C=O) cm^{-1}; NMR δ 1.0–2.0 (m, 10 H), 3.75 (br s, 1 H), 5.6 (br s, 2 H).

Without further purification the crude oil was dissolved in 75 mL of absolute ethanol (0 °C) and HCl gas was slowly added to the solution for 20 min. After being stirred for 2 days at 10 °C, the ethanol solution was poured into ice water and neutralized with sodium bicarbonate, and the aqueous phase was extracted with dichloromethane. The organic layer was dried (magnesium sulfate) and concentrated to a red oil. The crude product was chromatographed (chloroform) to give 7.58 g (31%) of the pyrrolinone **6e**, mp 61–63 °C. An analytical sample was obtained by preparative TLC (dichloromethane): mp 62–65 °C dec; IR (film) 2120 (N_3), 1710 (C=O), 1650 (C=C) cm^{-1}; NMR δ 1.0–2.0 (m, 13 H), 3.1–4.1 (3 H, ABX_3 doublet of quartets centered at δ 3.37, with a overlapping broad singlet at δ 3.76), 5.53 (s, 1 H); ^{13}C NMR δ 164.1, 144.4, 112.1, 83.2, 58.9, 52.8, 31.4, 30.6, 25.9, 25.4, 14.7.

Anal. Calcd for $C_{12}H_{17}N_4ClO_2$: C, 50.62; H, 5.98. Found: C, 50.81, H, 5.97.

7-Azido-8-chloro-5-oxa-9-oxo-1-azabicyclo[4.3.0]non-7-ene (9a). To a solution of 25.3 g (0.134 mol) of 4-azido-3-chloro-5-methoxy-2-(5*H*)-furanone dissolved in 1 L of dichloromethane at −12 °C was added dropwise a solution of 30.2 g (0.402 mol) of 3-amino-1-propanol in 500 mL of dichloromethane (precooled to −12 °C). After the addition, the solution was stirred at −12 °C for 24 h with formation of an insoluble brown oil. The insoluble brown oil was decanted (accurate weight was not possible due to gas evolution of oil at 24 °C), and the solution was warmed to 0 °C. Hydrogen chloride gas was bubbled slowly into the solution for 20 min. The solution was warmed to 24 °C, and nitrogen gas was bubbled through the solution for 1 h. Neutralization was accomplished by saturated aqueous sodium bicarbonate solution. The dichloromethane phase was washed with water and saturated aqueous sodium chloride solution. The organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated to yield 6.55 g (23%) of a yellow oil. The yellow oil was purified by column chromatography using 300 g of silica gel and chloroform as the eluant. The first material that eluted was the starting azide, 1.45 g. The second compound was the azide **9c** and was obtained as a yellow solid, 2.90 g (10%): mp 101–102.5 °C dec; IR (KBr) 2135 (N_3), 1715 (C=O), 1645 (C=C) cm^{-1}; NMR δ 1.30–2.23 (m, 2 H), 2.73–4.47 (m, 4 H), 5.17 (s, 1 H); MS–CI (mass calcd for $C_7H_7ClN_4O_2$ is 214), *m/e* 217 (32%, M + 3), 215 (100% M + 1), 189 (16%), 187 (22%), 114 (11%).

8-Azido-9-chloro-6-oxa-10-oxo-1-azabicyclo[5.3.0]dec-8-ene (9b). To a solution of 3.50 g (18.5 mmol) of 4-azido-3-chloro-5-methoxy-2-(5*H*)-furanone in 300 mL of dichloromethane at −12 °C was added dropwise a solution of 5.00 g (56 mmol) of 4-aminobutanol in 200 mL of dichloromethane (precooled to −12 °C). The solution was then maintained at −12 °C for 72 h. The solution was warmed to 0 °C, and hydrogen chloride gas was bubbled slowly into the reaction solution for 20 min. The solution was warmed to 24 °C, and nitrogen was bubbled through the reaction solution for 1 h. Neutralization was accomplished by adding saturated aqueous sodium bicarbonate solution. The dichloromethane phase was washed with water and saturated aqueous sodium chloride solution. The organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated to 2.70 g of a yellow oil. The oil was purified by column chromatography using 300 g of silica gel and chloroform. The first compound to be eluted was the starting azide, 270 mg. The second compound was **9b** and was obtained as a yellow oil which solidified, 1.64 g (39%): mp 53–56 °C dec; IR (Nujol) 2110 (N_3), 1710 (C=O), 1650 (C=C) cm^{-1}; NMR δ 1.73 (br m, 4 H), 2.83–4.28 (br m, 4 H), 5.61 (s, 1 H); MS–CI (mass calcd for $C_8H_9ClN_4O_2$ is 228), *m/e* 231 (42%, M + 3), 229 (100%, M + 1), 203 (23%), 201 (46%), 165 (4%).

9-Azido-10-chloro-7-oxa-11-oxo-1-azabicyclo[6.3.0]undec-9-ene (9c). To a solution of 3.05 g (16.2 mmol) of 4-azido-3-chloro-5-methoxy-2-(5*H*)-furanone in 500 mL of dichloromethane at −12 °C was added dropwise a solution of 5.00 g (48 mmol) of 5-aminopentanol dissolved in 200 mL of dichloromethane (precooled to −12 °C). The solution was stirred at −12 °C for 72 h. The solution was warmed to 0 °C, and hydrogen chloride gas was slowly bubbled into the solution for 20 min. The solution was warmed to room temperature and saturated with nitrogen gas for 1 h. Neutralization was accomplished by the addition of saturated aqueous sodium bicarbonate solution. The dichloromethane phase was washed with water and saturated aqueous sodium chloride solution. The organic phase was dried with anhydrous sodium sulfate, filtered, and evaporated to yield 3.10 g of a yellow oil. The yellow oil was purified by column chromatography using 300 g of silica gel and dichloromethane as the eluant. The first compound to be eluted was the starting azide, 1.49 g. The second band was **9c**, 55 mg (2%) as a white solid: mp 91.5–92.5 °C dec; IR (KBr) 2110 (N_3), 1700 (C=O), 1650 (C=C) cm^{-1}; NMR δ 1.00–2.10 (br m, 6 H), 2.73–4.37 (br m, 4 H), 5.53 (s, 1 H); MS–CI (mass calcd for $C_9H_{11}ClN_4O_2$ is 242), *m/e* 245 (55%, M + 3), 243 (100%, M + 1), 215 (38%), 187 (14%).

1-Methyl-4-methoxy-3-chloro-3-cyano-2-azetidinone (8a). A solution of 1.0 g (4.9 mmol) of **6a** was refluxed in 50 mL of anhydrous benzene for 8.5 h. The light orange solution was filtered and the solvent removed in vacuo to give 0.86 g of an oil. After microdistillation 0.47 g (55%) of the β-lactam **8a** was obtained: IR (film) 2300 (CN), 1800 (C=O) cm^{-1}; NMR δ 2.90 (s, 3 H), 3.64 (s, 3 H), 4.84 (s, 1 H); MS–EI (relative abundance), *m/e* 145 (74%), 143 (2%), 119 (26%), 117 (78%), 73 (26%), 58 (16%), 42 (100%); MS–CI (relative abundance), *m/e* 175 (100%).

Anal. Calcd for $C_6H_7N_2ClO_2$: C, 41.26; H, 4.01. Found: C, 41.05; H, 4.23.

3-Chloro-3-cyano-4-ethoxy-1-methyl-2-azetidinone (8b). A solution of 0.88 g (4.08 mmol) of **6b** in 20 mL of anhydrous benzene was refluxed for 9 h. An insoluble precipitate (104 mg) was recovered by filtration of the reaction solution: mp >200 °C dec; IR 2208 (CN), 1695 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 3.24 (s, 6 H), 9.68 (s, 1 H). The mother liquor was concentrated under reduced pressure to give 0.46 g (60.5%) of the β-lactam (**8b**) as a light brown oil: IR (film) 2260 (CN), 1800 (C=O) cm^{-1}; NMR δ 1.35 (t, 3 H), 2.88 (s, 3 H), 3.78 (q, 2 H), 4.80 (s, 1 H).

3-Chloro-3-cyano-4-ethoxy-1-ethyl-2-azetidinone (8c). A solution of 2.0 g (8.85 mmol) of **6c** in 100 mL of anhydrous benzene was refluxed for 12 h. The light red solution was filtered to remove a trace of a tan solid, mp 288–291 °C dec. Removal of the solvent in vacuo gave 1.69 g (88%) of the β-lactam (**8c**) as an oil, and this showed the same spectral properties as the analytical sample. An analytical sample was prepared by molecular distillation of a sample of the crude product: IR (film) 2246 (CN), 1800 (C=O) cm^{-1}; NMR δ 1.29 (overlapping triplets forming a 1:3:3:1 quartet with J = 7 Hz, 6 H); 3.28 (q, 2 H, J = 7 Hz); 3.78 (q, 2 H, J = 7 Hz), 4.85 (s, 1 H).

Anal. Calcd for $C_8H_{11}N_2ClO_2$: C, 47.41; H, 5.43, N, 13.83; Cl, 17.53. Found: C, 47.15; H, 5.58; N, 13.92; Cl, 17.80.

4-(Benzyloxy)-3-chloro-3-cyano-1-isopropyl-2-azetidinone (8d). A solution of 1.0 g (3.33 mmol) of **6d** in 100 mL of anhydrous chlorobenzene was heated at 115 °C under nitrogen. After 4 h the solvent was removed, leaving 0.83 g (90%) of the β-lactam **8d** as a light brown oil: IR (film) 2245 (CN); 1801 (C=O) cm^{-1}; NMR δ 1.17 (d, 6 H), 3.60 (sep, 1 H), 4.65 (d of d, 2 H, J = 11 Hz), 4.90 (s, 1 H), 7.42 (s, 5 H). Molecular distillation of a sample of the crude product gave a clear oil which showed a molecular weight (MS) of 278.

3-Chloro-3-cyano-1-cyclohexyl-4-ethoxy-2-azetidinone (8e). A solution of 1.6 g (6.42 mmol) of **6e** in 100 mL of anhydrous chlorobenzene was heated to 100 °C for 9 h. Removal of the solvent in vacuo gave 1.3 g of the β-lactam **8e**. Chromatography on Florisil (ethyl acetate/hexane, 1:4) gave 0.88 g (62%) of the β-lactam **8e** as a light yellow oil: IR (film) 2240 (CN), 1795 (C=O) cm^{-1}; NMR δ 0.9–2.2 (m, 13 H), 3.4 (br s, 1 H), 3.76 (q, 2 H), 4.85 (s, 1 H); ^{13}C NMR δ 154.3, 111.6, 90.0, 65.7, 60.2, 53.1, 30.6, 29.5, 24.7, 24.4, 14.7.

Anal. Calcd for $C_{12}H_{17}N_2ClO_2$: C, 56.15; H, 6.63. Found: C, 55.93; H, 6.62.

3-Chloro-3-cyano-1-cyclohexyl-4-ethoxy-2-azetidinone (8e). Pyrrolinone **6e** (200 mg, 0.704 mmol) in 20 mL of dichloromethane was subjected to photolysis at 0 °C under a nitrogen atmosphere by using a 200-W medium-pressure Hanovia mercury lamp and Pyrex filter. After 105 h, analysis of the crude reaction mixture by NMR indicated the presence of 73% of the azetidinone **8e**. The solvent was evaporated in vacuo to give 170 mg of a yellow oil. Preparative layer chromatography using chloroform as the eluant yielded one band (R_f = 0.46) of a light yellow oil, 130 mg (72%). This compound was in all respects identical with the azetidinone **8e**, prepared by the thermolysis of **6e**.

1-Cyclohexyl-3,4-dichloro-5-phenyl-2-pyrrolinone. To a solution of phenyl magnesium bromide, prepared from 3.5 g (22.2 mmol) of bromobenzene and 0.53 g (21.8 mmol) of magnesium turnings in 35 mL of anhydrous ethyl ether, was added dropwise a solution of 2.5 g (8.3 mmol) of 1-cyclohexyl-3,4-dichloro-5-hydroxy-2-pyrrolinone[16] in 50 mL of ethyl ether. The solution was refluxed for 30 min and poured into a mixture of 100 g of ice and 50 mL of 50% H_2SO_4. The organic layer was separated, and the aqueous layer was washed with ether. The combined organic fractions were washed with water (100 mL) and dried over sodium sulfate. Concentration in vacuo afforded an oil residue. Chromatography (silica gel, 10% ethyl acetate/hexanes) yielded the title compound as a yellow oil (130 mg, 4.1%): IR (film) 1790, 1637 cm^{-1}; NMR δ 7.52 (m, 5 H), 6.68 (s, 1 H), 3.90 (m, 1 H), 0.9–2.1 (m, 10 H).

(16) F. Mercer, Ph.D. Thesis, University of California, Irvine, 1979. The pyrrolinone was prepared from 3,4-dichloro-5-methoxy-2(5*H*)-furanone upon treatment with cyclohexylamine.

Anal. Calcd for $C_{16}H_{17}Cl_2NO$: C, 61.95; H, 5.52. Found: C, 61.82; H, 5.02.

Preparation and Thermolysis of 4-Azido-3-chloro-1-cyclohexyl-5-phenyl-2-pyrrolinone (6f). Synthesis of 3-Chloro-1-cyclohexyl-3-cyano-4-phenyl-2-azetidinone (8f). A mixture of 100 mg (0.32 mmol) of 1-cyclohexyl-3,4-dichloro-5-phenyl-2-pyrrolidinone and 32 mg (0.50 mmol) of sodium azide in 10 mL of dimethylformamide was stirred at 10 °C for 5 days. The mixture was then poured into 25 mL of water and extracted with 40 mL of carbon tetrachloride. The organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo. The yellow oil was used directly without further purification: IR (film) 2115, 1780, 1635 cm^{-1}; NMR δ 7.52 (m, 5 H), 6.64 (s, 1 H), 3.90 (m, 1 H), 0.9–2.1 (m, 10 H). A solution of 75 mg of this azide in 5 mL of anhydrous chlorobenzene was maintained at 100 °C for 8 h. The brown solution was concentrated in vacuo. Chromatography (silica gel, 15% ethyl acetate/hexanes) afforded 36 mg of **8f**. This was identical with a sample prepared by the cycloaddition of chlorocyanoketene to benzylidenecyclohexylamine as described below.

3-Chloro-3-cyano-1-cyclohexyl-4-phenyl-2-azetidinone (8f). A mixture of 0.50 g (2.6 mmol) of 4-azido-3-chloro-5-methoxy-2(5*H*)-furanone and 0.46 g (2.4 mmol) of benzylidenecyclohexylamine in 20 mL of anhydrous benzene was maintained at 80 °C for 8 h. The solvent was removed *in vacuo* and the solid product was sublimed (110 °C (0.035 torr)) to afford 0.43 g (57%) of **8g**: mp 116–117 °C; IR 1789 cm^{-1}; NMR δ 7.50 (s, 5H), 4.81 (s, 1 H), 3.25 (m, 1 H), 2.30–1.60 (m, 10 H).

Anal. Calcd for $C_{16}H_{17}ClN_2O$: C, 66.55; H, 5.93. Found: C, 66.57; H, 5.86.

8-Chloro-8-cyano-6-oxa-9-oxo-1-azabicyclo[5.2.0]nonane (10). A solution of 200 mg (0.877 mmol) of **9b** was refluxed in 20 mL of toluene for 1 h. The toluene was evaporated in vacuo to yield 170 mg (97%) of a clear, colorless oil which solidified upon standing. Sublimation of 100 mg of the crude reaction product at 40 °C (0.001mmHg) yielded **10** as a white solid (90 mg): mp 70–71 °C; IR (KBr) 2240 (C≡N), 1800 (C=O) cm^{-1}; NMR δ 1.37–2.30 (br m, 4 H), 2.97–4.43 (b m, 4 H), 5.25 (s, 1 H); MS (mass calcd for $C_8H_9ClN_2O_2$ is 200), *m/e* 203 (0.74%), 200 (3%), 102 (10%), 98 (70%), 71 (22%), 70 (12%), 56 (82%), 55 (100%).

Anal. Calcd for $C_8H_9ClN_2O_2$: C, 48.00; H, 4.50. Found: C, 47.80; H, 4.61.

8-Cyano-6-oxa-9-oxo-1-azabicyclo[5.2.0]nonane. To a solution of 200 mg (1.00 mmol) of azetidinone **10**, dissolved in 7 mL of glacial acetic acid and 2 drops of acetic anhydride was added 650 mg (10 mmol) of zinc at room temperature. The reaction mixture was stirred for 15 min and was then quenched with water. Chloroform was added and the reaction mixture was then washed with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride solution. The organic phase was dried with anhydrous magnesium sulfate, filtered, and evaporated to yield the title compound as a clear, colorless oil, 132 mg (79%). The oil was kugelrohred at 63 °C (5μmHg) to give 60 mg (36%) of a colorless oil: IR (neat) 2250 (C≡N), 1780 (C=O) cm^{-1}; NMR δ benzene-d_6) 0.60–1.43 (br m, 4 H), 2.40–3.73 (br m, 5 H with 2 overlapping doublets at δ 3.43 and 3.60, J = 2 Hz, J = 5 Hz, respectively), 4.40 (d, J = 5 Hz, 0.34 H), 4.73 (d, J = 2 Hz, 0.66 H); MS-CI (mass calcd for $C_8H_{10}N_2O_2$ is 166), *m/e* 167 (100%, M + 1), 100 (17%). Mass calcd for $C_8H_{10}N_2O_2$: 166.074. Obsd (MS): 166.075.

8-Chloro-8-cyano-6-oxa-9-oxo-1-azabicyclo[5.2.0]nonane (10, 29). To a solution of 40 mg (0.24 mmol) of 8-cyano-6-oxa-9-oxo-1-azabicyclo-[5.2.0]nonane dissolved in 10 mL of freshly distilled toluene cooled to −78 °C was added 12 mg (0.25 mmol) of 50% sodium hydride. The reaction mixture was stirred at −78 °C for 15 min and was quenched with 32 mg (0.24 mmol) of *N*-chlorosuccinimide. Water was added and the reaction mixture was extracted with chloroform. The organic phase was washed with saturated aqueous sodium chloride solution and dried with anhydrous magnesium sulfate. The organic phase was evaporated in vacuo to yield a yellow oil. The product was passed through 10 g of silica gel using chloroform as eluant to yield 30 mg (63%) of a clear, colorless oil which by ^1H NMR analysis was shown to be a 5:1 mixture of respectively, **10** and **29**: IR (neat) 2240 (C≡N), 1800 (C=O) cm^{-1}; NMR δ 1.77–2.30 (br m, 4 H), 2.97–4.43 (br m, 4 H), 5.23 (s, 0.4 H), 5.47 (s, 0.6 H); MS (mass calcd for $C_8H_9ClN_2O_2$ is 200), *m/e* 203 (0.74%), 200 (3%), 102 (10%), 98 (70%), 71 (22%), 70 (12%), 56 (82%), 55 (100%). Mass calcd for $C_8H_9ClN_2O_2$: 200.035. Obsd (MS): 200.036.

9-Chloro-9-cyano-7-oxa-10-oxo-1-azabicyclo[6.2.0]decane (13, 14). A solution of 55 mg (0.227 mmol) of **9c** in toluene was refluxed for 2 h. The toluene was removed in vacuo to yield a 5:1 mixture of **13** and **14**, 45 mg (94%), as a light yellow oil. Kugelrohr distillation of the oil at 65 °C (0.001mmHg) yielded a clear colorless oil (20 mg, 42%): IR (neat) 2240 (C≡N), 1800 (C=O) cm^{-1}; NMR δ 1.13–2.23 (br m, 6 H), 2.66–4.43 (br m, 4 H), 5.20 (s, 0.85 H), 5.48 (s, 0.15 H). Mass calcd for $C_9H_{11}ClN_2O_2$: 214.051. Obsd (MS): 214.050.

9-Cyano-7-oxa-10-oxo-1-azabicyclo[6.2.0]decane. To a solution of 50 mg (0.247 mmol) of a 5:1 mixture of **13** and **14** dissolved in 3 mL of glacial acetic acid and 2 drops of acetic anhydride was added 177 mg (2.72 mmol) of zinc. The reaction mixture was stirred at room temperature for 10 min and then quenched with water. Chloroform was added and washed with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride solution. The organic phase was dried with anhydrous magnesium sulfate, filtered, and evaporated in vacuo to yield the title compound as a light yellow oil, 43 mg (98%). The oil was Kugelrohr distilled at 60 °C (5μmHg) to yield 21 mg (48%) of product as a colorless oil: IR 2240 (C≡N), 1780 (C=O) cm^{-1}; NMR (benzene-d_6) δ 0.66–1.46 (br m, 6 H), 1.93–2.50 (br m, 2 H), 3.00–4.00 (br m, 5 H) (broad multiplet with 2 doublets overlapping at δ 3.30 and 3.37, J = 2 Hz, J = 5 Hz, respectively, 5 H), 4.36 (d, J = 5 Hz, 0.58 H), 4.68 (d, J = 2 Hz, 0.42 H). Mass calcd for $C_9H_{12}N_2O_2$: 180.090. Obsd (MS) 180.090.

9-Chloro-9-cyano-7-oxa-10-oxo-1-azabicyclo[6.2.0]decane (13, 14). To a solution of 55 mg (0.305 mmol) of 9-cyano-7-oxa-10-oxo-1-azabicyclo[6.2.0]decane dissolved in 20 mL of diethyl ether cooled to −78 °C was added 16 mg (0.329 mmol) of 50% sodium hydride. The reaction mixture was stirred at −78 °C for 10 min and then quenched with 44 mg (0.328 mmol) of *N*-chlorosuccinimide. Water was added to the reaction mixture, and the organic phase was separated. The aqueous phase was extracted with diethyl ether which was combined with the organic phase, dried with anhydrous magnesium sulfate, filtered, and evaporated in vacuo to yield 70 mg of a light yellow oil. The product was passed through 10 g of silica gel using chloroform as the eluant to yield 30 mg of a clear, colorless oil (46%). This product was in all respects identical with the product obtained upon thermolysis of **9c**, i.e., a 5:1 ratio of **13** to **14**.

4-Aza-2-chloro-7-(formyloxo)-3-oxoheptanitrile (16). A solution of 100 mg (0.46 mmol) of **9a** was maintained under a nitrogen atmosphere to 87 °C in 10 mL of freshly distilled toluene for 4 h. The toluene was evaporated in vacuo to yield 90 mg (97%) of a brown oil. Preparation layer chromatography using chloroform as the eluant (R_f = 0.45) yielded 16 as a clear, colorless oil, 60 mg (65%): IR 3320 (NH), 1760 and 1660 (C=O) cm^{-1}; NMR δ 1.67–2.23 (m, 2 H), 3.43 (q, 2 H), 4.33 (t, 2 H), 5.15 (s, 1 H), 6.25 (br s, 1 H), 8.17 (br s, 1 H); NMR ($CDCl_3$, D_2O) quartet at δ 3.43 became triplet and singlet as the δ 6.25 absorption disappears. Mass calcd for $C_7H_9ClN_2O$: 204.030. Obsd (MS): 204.029.

1-Chloro-1-cyano-2-oxo-3-aza-6-hexyl Formate (16). Photolysis, using oven dried apparatus and a 450-W medium-pressure Hanovia mercury lamp with a Pyrex filter, was conducted on 300 mg (1.40 mmol) of **9a** in 100 mL of acetone (distilled from potassium permanganate onto activated 4A molecular sieves then redistilled under nitrogen) at 10 °C under a nitrogen atmosphere for 4 h. The solvent was evaporated in vacuo to yield a yellow oil, 275 mg (96%). Preparative layer chromatography using ethyl acetate as the eluant yielded 100 mg (36%) (R_f = 0.45) of **16** as a clear, colorless oil. The product was identical with the sample prepared from the thermolysis of **9a**.

8-Chloro-8-cyano-6-oxa-9-oxo-1-azabicyclo[5.2.0]nonane (10). Photolysis, using a 450-W medium-pressure Hanovia mercury lamp and Pyrex filter, was conducted on 100 mg (0.438 mmol) of **9b** in 50 mL of carbon tetrachloride under a nitrogen atmosphere at room temperature for 1.5 h. The solvent was evaporated in vacuo to a colorless, clear oil which solidified upon standing to yield 86 mg (98%) of **10**. Sublimation of the solid at 45 °C (0.001mmHg) yielded **10** as a white solid (79 mg (91%)), mp 70–71 °C. This compound was in all respects identical with the azetidinone prepared previously from the thermolysis of **9b**.

9-Chloro-9-cyano-7-oxa-10-oxo-1-azabicyclo[6.2.0]decane (13, 14). Photolysis, using a 450-W medium-pressure Hanovia mercury lamp and Pyrex filter, was conducted on 100 mg (0.413 mmol) of azide **9c** in 50 mL of carbon tetrachloride under a nitrogen atmosphere at room temperature for 1.5 h. The solvent was evaporated in vacuo to yield a colorless, clear oil, 80 mg (91%). Kugelrohr distillation of the oil at 65 °C (0.001mmHg) yielded a 5:1 mixture of **13** and **14** as a clear, colorless oil (40 mg, 45%) which was in all respects identical with the azetidinone mixture obtained previously from the thermolysis of **9c**.

Methanolysis of 3-Chloro-3-cyano-1-cyclohexyl-4-ethoxy-2-azetidinone (8e). Preparation of *N*-Cyclohexylchlorocyanoacetamide (31). A solution of 3.7 g (14.5 mmol) of **8e** in 75 mL of anhydrous methanol was refluxed for 25 h. The volatiles were removed in vacuo, leaving an oil/solid mixture. Recrystallization (chloroform/hexane) gave 0.57 g (20%) of the acyclic amide **31** as a white solid, mp 110–118 °C. The analytical sample melted at 118–119 °C: IR 3270 (NH), 1669 (C=O), 1570 (NH bend) cm^{-1}; NMR δ 1.2–2.0 (m, 10, H), 3.7 (br s., 1, H), 4.96 (s, 1, H), 6.40 (br s, 1, NH); ^{13}C NMR δ 158.5, 113.7, 50.1, 42.3, 32.5, 25.3, 24.6.

Anal. Calcd for $C_9H_{13}N_2ClO$: C, 53.88; H, 6.48. Found: C, 53.84; H, 6.46.

Thermolysis of 3-Azido-4-chloro-1-cyclohexyl-5-ethoxy-2-pyrrolinone (6e) in Ethanol. Trapping of the Zwitterionic Intermediate (7e). A solution of 3.0 g (0.0106 mol) of **6e** in 75 mL of anhydrous ethanol was refluxed for 11 h under a static nitrogen atmosphere. The volatiles were removed in vacuo, leaving 2.6 g of a light red oil. By spiking the ^1H NMR sample of the crude reaction mixture with **8e**, ethyl chlorocyanoacetate, and **31**, it was possible to identify the peaks at δ 4.95 (s) as the C-4 hydrogen of the β-lactam **8e** and δ 5.24 (s) and 5.56 (s) as the methine hydrogens of the ester and amide, respectively. The peaks at δ 5.56 (s) and 6.10 (s) were ascribed to the CH(Cl)CN and $CH(OEt)_2$ methine hydrogens, respectively, of the tertiary amide **30**. The relative proportion by ^1H NMR analysis of the crude product mixture of **8e**/**30**/**31**/ester was 1.0:2.33:3.0:4.0. The crude ^{13}C NMR indicated the presence of **8e** and **31** by comparison with the known spectra of these compounds, and tentative peak assignments of **30** could be made. The crude IR showed 1791 (C=O, **8e**), 1760 (C=O, ester), 1700 (C=O, **30** and **31**) cm^{-1}. About 0.5 g of the crude mixture was separated on four preparative TLC plates. The tertiary amide (**30**) was isolated as a white solid (56 mg) as the second highest band: mp 75–80 °C; IR 1685 (C=O) cm^{-1} NMR δ 1.27 (d of t, 6, H), 1.1–1.9 (m, 10, H), 3.62 (d of q, 4, H), 4.23 (br, s, 1, H), 5.17 (s, 1 H), 6.04 (s, 1 H); ^{13}C NMR δ 162.2 (C=O), 114.6 (CN), 103.1 (N-C), 63.7 (OCH_2), 63.3 (OCH_2), 54.8 (ClCHCN), 42.1 (cyclohexyl, C-1), 31.4, 31.3 (cyclohexyl, C-2, C-2′), 25.9 (cyclohexyl, C-3), 25.4 (cyclohexyl, C-4); MS (relative abundance), *m/e* 259.31 (0.4), 257.31 (1.4), 177.21 (6), 175.18 (8), 131.12 (26), 103.12, (100), 84.15 (29), 75.09 (36), 67.09 (22).

From the lowest band of four TLC plates, 17 mg of a white solid was isolated, mp 109–112 °C. Its IR was identical with the spectrum of an authentic sample of **31**. The β-lactam (**8e**) and ester were not isolated.

Photolysis of 4-Azido-3-chloro-1-cyclohexyl-5-ethoxy-2-pyrrolinone (8e). Trapping of Zwitterionic Intermediate (7e). Photolysis, using a 450-W medium-pressure Hanovia mercury lamp and Pyrex filter, was conducted on 500 mg (1.76 mmol) of azide **6e** in 50 mL of absolute ethanol under a nitrogen atmosphere at room temperature. After 2 h the solvent was evaporated in vacuo to yield a light yellow oil 510 mg. Analysis of the crude reaction mixture by ^1H NMR indicated it to be composed of essentially the same products as are formed in the thermolysis of **8e** in ethanol.

Anhydro-5-cyano-1,3-dicyclohexyl-4-hydroxy-6-oxopyrimidine Betaine (33). A mixture of 0.50 g (2.6 mmol) of 4-azido-3-chloro-5-methoxy-2(5*H*)furanone and 5.0 g (32 mmols) of ethyl *N*-cyclohexylformimidate in 20 mL of anhydrous benzene was heated at 80 °C for 96 h. The black solution was filtered, and the tan solid was recrystallized from acetone to yield 0.57 g (72%) of **33** as a white solid: mp 329–331 °C dec; IR 2220, 1706 cm^{-1}; NMR (Me_2SO-d_6) δ 9.49 (s, 1 H), 4.41 (m, 2 H), 1.55 (m, 20 H); ^{13}C NMR (Me_2SO-d_6) δ 158.6, 150.6, 116.6, 74.6, 56.5, 30.5, 25.2, 24.3.

Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.70; H, 7.68; N, 13.91. Found: C, 67.72; H, 7.49; N, 13.75.

Thermolysis of 3-Chloro-3-cyano-1-cyclohexyl-4-ethoxy-2-azetidinone (8e) in the Presence of Ethyl *N*-Cyclohexylformimidate. A mixture of 0.20 g (0.8 mmol) of **8e** and 1.0 g (6.4 mmol) of ethyl *N*-cyclohexylformimidate in 10 mL of anhydrous benzene was heated to 80 °C for 72 h. The solution was filtered, and the tan solid was recrystallized from acetone to yield 0.07 g (30%) of **33**.

5-Cyano-1,3-dicyclohexyl-2,4-dihydroxy-6-oxo-1,2,3,6-tetrahydropyrimidine (34). A suspension of 0.15 g (0.50 mmol) of **33** in 5 mL of 5% sodium hydroxide solution was heated to 70 °C until all the solid dissolved. Dilute hydrochloric acid was added until the solution was acidic. The resulting solid was filtered and recrystallized from acetone to yield 0.14 g (92%) of 34 as a white solid, mp 139–140 °C; IR 2198, 1760, 1660 cm^{-1}; NMR (Me_2SO-d_6) δ 0.80–2.10 (m, 2 H).

Anal. Calcd for $C_{17}H_{25}N_3O_3$: C, 63.89, H, 7.89; N, 13.15. Found: C, 64.10; H, 7.97; N, 13.10.

4-Azido-3-chloro-5-hydroxy-1-methyl-2-pyrrolinone (35). To a cold stirred solution of 1.0 g (5.3 mmol) of 4-azido-3-chloro-5-methoxy-2-(5*H*)-furanone in 100 mL of chloroform was added a solution of 0.5 g (15.9 mmol) of methylamine in 20 mL of chloroform over a 5-min period. After the mixture was stirred for 12 h at −10 °C, the volatiles were removed at 0 °C in vacuo. The resulting yellow oil was crystallized (chloroform/hexane) to give 310 mg (31%) of a white solid: mp 111–114° dec; IR 3230 (OH), 2120 (N_3), 1690 (C=O), 1635 (C=C) cm^{-1}; NMR δ 2.92 (s, 3, H), 4.50 (br, s, 1, H), 5.28 (s, 1, H).

Anal. Calcd for $C_5H_5N_4ClO_2$: C, 31.83; H, 2.65. Found: C, 31.86; H, 3.00.

***N*-Formyl-*N*-methylchlorocyanoacetamide (37).** A solution of 310 mg (1.7 mmol) of **35** was thermolized in anhydrous toluene at 100 °C. After 6.5 h the azide absorption (2120 cm^{-1}) was absent by IR examination of the reaction solution. The solvent was removed in vacuo, and the resulting oil was purified by molecular distillation, giving 69 mg (26%) of **35** as a clear oil: IR 3330 (OH), 1720 (CHO), 1680 (C=O) cm^{-1}; NMR δ 3.17 (s, 3, H) 6.46 (s, 1, H), 9.42 (s, 1, H); MS, *m/e* 160.1 (M), 162.1 (M + 2).

Anal. Calcd for $C_5H_5N_2ClO_2$: C, 37.38; H, 3.11. Found: C, 37.36; H, 3.03.

4-Azido-5-(1-cyanoethyl)-1,3-dimethyl-5-hydroxy-2-pyrrolinone (38). A solution of 10 g (52.6 mmol) of α-methyl-β-azido-γ-cyanoethylidene-$\Delta^{\alpha,\beta}$-butenolide in 300 mL of chloroform was stirred in an ice bath, and methylamine gas was bubbled through the solution for 1 h. The reaction was monitored by thin layer chromatography with ethyl acetate/cyclohexane (1:1) as the eluting solvent. After the reaction was complete, the solvent was removed in vacuo to give a brown solid. Chloroform (10 mL) was added to the brown solid, and the mixture was filtered to collect a white solid. Recrystallization from aqueous ethanol gave 9.2 g of **38** as white crystals (79% yield): mp 128–130 °C dec; IR 3100, 2240, 2105, 1690 cm^{-1}; NMR δ 0.97 (d, J = 7 Hz, 3 H), 1.77 (s, 3 H), 2.67 (s, 3 H), 3.55 (q, J = 7 Hz, 1 H), 7.38 (s, 1 H, acidic proton); MS, *m/e* 193 (M − 28).

Anal. Calcd for $C_9H_{11}N_5O_2$: C, 48.87; H, 5.01; N, 31.66. Found: C, 48.91; H, 5.56; N, 30.97.

4-Amino-3-cyano-1,3,5-trimethyl-1,3-dihydro-1*H*-pyridine-2,6-dione (40). From the Thermolysis of 4-Azido-1,3-dimethyl-5-(1-cyanoethyl)-5-hydroxy-2-pyrrolinone (38). A solution of 1.6 g (7.24 mmol) of 4-azido-1,3-dimethyl-5-(1-cyanoethyl)-5-hydroxy-2-pyrrolinone (**38**) in 50 mL of glacial acetic acid was heated at 80 °C under a nitrogen atmosphere for 5 h. The reaction was monitored by thin layer chromatography with diethyl ether/petroleum ether (1:1) as the eluting solvent. Upon complete reaction, the solution was poured into water and extracted three times with chloroform. The organic extract was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo to give 1.33 g of imide **39** as a pale yellow oil (90% yield): IR 2255, 1740 cm^{-1}; NMR δ 1.58 (d, J = 7 Hz, 6 H), 3.38 (s, 3 H), 4.32 (q, J = 7 Hz, 2 H, acidic protons); NMR ($CDCl_3$ + D_2O) δ 1.58 (s, 6 H), 3.38 (s, 3 H).

Attempted purification of the imide **39** by molecular distillation (84 °C (2.5 torr)) gave the cyclized product **40**. This white solid was recrystallized from benzene to give **40** as white crystals in 68% y ield: mp 178–181 °C; IR 3310, 3280, 2245, 1640 cm^{-1}; NMR (acetone-d_6) 1.85 (s, 3 H), 2.02 (s, 3 H), 3.13 (s, 3 H), 6.17 (m, 2 H, acidic protons); MS, *m/e* 193.

Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.65; H, 5.92; N, 21.81.

α-Methyl-β-amino-γ-(1-cyanoethylidene)-$\Delta^{\alpha,\beta}$-butenolide (48) via Thermolysis of α-Methyl-β-azido-γ-(1-cyanoethylidene)-$\Delta^{\alpha,\beta}$-butenolide. A solution of 500 mg (2.63 mmol) of α-methyl-β-azido-γ-(1-cyanoethylidene)-$\Delta^{\alpha,\beta}$-butenolide (**47**)[17] in 8 mL of toluene was refluxed for 3 h. The reaction was monitored by thin layer chromatography (silica gel, ethyl acetate/cyclohexane, 1:1). The known aminobutenolide[18] **48** was the only product isolated (165 mg).

2-Azido-3-chloro-*N*-phenylmaleimide. To a cold stirred solution of 4.9 g (2.0 mmol) of 2,3-dichloro-*N*-phenylmaleimide in 250 mL of dry acetonitrile was added 1.32 g (2.0 mmol) of sodium azide at once. After the mixture was stirred at 0 °C for 5 h, the precipitate was removed by gravity filtration. Removal of the volatiles in vacuo gave 3.9 g (77%) of the title compound as a yellow solid: mp 113 °C dec; IR 2125 (N_3), 1725 (C=O), 1655 (C=C) cm^{-1}; NMR δ 7.53 (s, arom); MS (relative abundance), *m/e* 250 (1.2, M^+ + 2), 249 (0.47, M^+ + 1), 248 (3.19, M^+), 120 (8), 119 (100), 91 (28).

Thermolysis of 2-Azido-3-chloro-*N*-phenylmaleimide in the Presence of Ethanol. Preparation of Ethyl Chlorocyanoacetate (51), Ethyl *N*-Phenylcarbamate (52), and 2-Amino-3-chloro-*N*-phenylmaleimide (50). A solution of 1.0 g (4.0 mmol) of 2-azido-3-chloro-*N*-phenylmaleimide and 1.0 g (2.17 mmol) of absolute ethanol in 50 mL of anhyd chlorobenzene was heated at 100 °C under a static nitrogen atmosphere. After 2 h the azide stretch at 2120 cm^{-1} could no longer be detected in the IR spectrum of the reaction solution. The light orange solution was filtered to remove a white precipitate that was formed in low yield. The volatiles were then removed in vacuo to give 0.83 g of a red oil. Inspection of the NMR spectrum of the crude product indicated that the ester (**51**) and carbamate (**52**) were formed in nearly equal amounts. A silica gel chromatographic separation of the crude mixture with benzene as the eluant gave (a) ethyl chlorocyanoacetate (**51**) (131 mg, (22%)) [IR 1750 (C=O) cm^{-1}; NMR δ 1.33 (t, 3 H, J = 7 Hz), 4.26 (q, 2 H, J = 7 Hz), 4.87 (s, 1 H)], (b) ethyl *N*-phenylcarbamate (52) [mp 44–48 °C (lit.[18] mp 53 °C); IR 3330 (NH), 1725 (C=O), 1600 (arom) cm^{-1}; NMR δ

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1.27 (t, 3 H, J = 7 Hz), 4.13 (q, 2 H, J = 7 Hz), 6.7–7.5 (m, 6 H)], and (c) 2-amino-3-chloro-*N*-phenylmaleimide (**50**) [mp 138–141 °C; IR 3500, 3330 (NH_2), 1725, 1670 (C=O) cm^{-1}; NMR (acetone-d_6) δ 7.10 (br s, 2 H), 7.47 (s, 5 H); MS (relative abundance), m/e 224 (32, M^+ + 2), 222 (100, M^+), 196 (9), 194 (29), 180 (5), 178 (11), 143 (39), 131 (9), 119 (21), 77 (31), 75 (57), 68 (30)].

Anal. Calcd for $C_{10}H_7N_2ClO_2$: C, 53.93; H, 3.14; N, 12.58, Cl, 15.95. Found: C, 53.49; H, 3.21, N, 12.31; Cl, 15.88.

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A Study of the Synthesis and Properties of [2₆](1,2,3,4,5,6)Cyclophane (Superphane)[1]

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Abstract: A synthesis of [2₆](1,2,3,4,5,6)cyclophane (**9**) is described. This molecule, the ultimate in a multibridged [2$_n$]cyclophane, has been given the trivial name "superphane" and was synthesized in ten steps, as outlined in Scheme I, starting from 2,4,5-trimethylbenzyl chloride (**14**). The key to the successful synthesis of superphane lay in employing gas-phase dimerization of *o*-xylylene intermediates to introduce more than one bridge at a time. This provides a convenient overall synthesis suitable for preparing superphane in multigram quantities. X-ray crystallographic analysis has shown superphane to be a highly symmetrical (D_{6h}) molecule with the benzene decks being planar hexagons separated by 2.624 Å. The ^1H NMR spectrum of superphane shows a singlet at δ 2.98 and the ^{13}C NMR spectrum singlets at δ 144.2 and 32.2, reflecting this high degree of symmetry. Superphane forms hard, white crystals, mp 325–327 °C, which are rather insoluble and relatively inert, showing no evidence of thermal rupture of the bridges as occurs with many of the [2$_n$]cyclophanes. However, superphane does exhibit the Birch reduction and undergoes electrophilic attack by alkyl cations and benzylic substitution with *N*-bromosuccinimide. Although superphane readily forms a charge-transfer complex with tetracyanoethylene (TCNE), it does not give the normal, Diels–Alder, barrelene-type adduct with either TCNE or dicyanoacetylene. In the presence of aluminum chloride, though, superphane reacts with dicyanoacetylene to form an unusual structure (**50**), involving formation of novel intramolecular bonds. With ethyl diazoacetate in the presence of cupric sulfate, superphane undergoes carbene addition to give **44**, which can be converted readily to the corresponding tropylium ion (**46**). In a remarkable reaction, the tropylium ion (**46**) in the presence of moisture regenerates superphane.

The cyclophane nomenclature and the cyclophane era were ushered in by the work of Cram and Steinberg in 1951.[2] The availability of [2.2]cyclophanes via 1,6-eliminations or by Wurtz coupling reactions[3] attracted much interest because the rigid geometry of these molecules made them ideal for studying questions of bonding, strain energy, and transannular π-electron interactions. The introduction of the dithiacyclophane–sulfur extrusion approach[4,5] greatly facilitated syntheses of cyclophanes and opened the possibility of preparing multibridged [2$_n$]-cyclophanes, as shown by the synthesis of [2₃](1,3,5)cyclophane.[6] The possibility of constructing additional bridges with known cyclophanes by stepwise manipulation was exploited in syntheses of [2₃](1,2,4)cyclophane[7] and [2₄](1,2,4,5)cyclophane.[8] Further, Hopf introduced a very convenient method for synthesizing multisubstituted [2.2]paracyclophanes.[9] Even so, the further elaboration of these substituted [2.2]paracyclophanes to give multibridged cyclophanes such as [2₄](1,2,3,5)cyclophane[10] and [2₄](1,2,3,4)cyclophane[11] remained a somewhat tedious chore.

In thinking about the further elaboration of multibridged cyclophanes and the possible synthesis of the ultimate member of the series, [2₆](1,2,3,4,5,6)cyclophane (superphane[12]), we felt that a new approach was needed, especially if superphane were to be made available in sufficient quantity for adequate chemical studies. It had been shown by Cava and Deana that the pyrolysis of 1,3-dihydroisothianaphthene 2,2-dioxide (**1**) in diethyl phthalate solution at 300 °C gave [2.2]orthocyclophane (**3**) in 48% yield.[13] Presumably, this reaction proceeds via *o*-xylylene (**2**) as an intermediate. Similarly, Jensen, Coleman, and Berlin have shown that benzocyclobutene (**4**) dimerizes to [2.2]orthocyclophane (**3**), when being boiled under reflux.[14] However, Errede had found that pyrolysis of (2-methylbenzyl)trimethylammonium hydroxide (**5**) followed by condensation of the volatile products at low temperature gave mainly the spirotriene **6**, with only a modest quantity of **3** being formed.[15] Whereas the Diels–Alder dimerization of *o*-xylylene (**2**) to the spirotriene **6** is an allowed process in terms of the conservation of orbital symmetry, the

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