Synthetic Applications of Ketene Cycloadditions; Lactams and Coumarins

Dissertation

Presented to the Graduate Council of the
North Texas State University of Partial
Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

By

Chia-Hui Shieh, B.S.
Denton, Texas
August, 1984

Shieh, Chia-Hui, Synthetic Applications of Ketene Cycloadditions; Lactams and Coumarins. Doctor of Philosophy (Chemistry), August, 1984, 86 pp., 7 tables, bibliography, 98 titles.

The objective of this study was to develop new synthetical routes to natural and industrial products utilizing ketene cycloaddition reactions.

The cycloaddition of diphenylketene with α,β-unsaturated imines yields (2+2) cycloaddition products, β-lactams. However, electron donating groups, such as dimethylamino, in the 4-position of the α,β-unsaturated imines result in (4+2) cycloaddition products, δ-lactams. Dichloroketene reacted with α,β-unsaturated imines to yield (4+2) cycloaddition products, β-lactams. Large substituents in the 4-position of α,β-unsaturated imines resulted in a (2+2) cycloaddition product, β-lactam. The δ-lactams derived from dichloroketene are easily dehydrochlorinated to the corresponding 2-pyridones.

These results are consistent with a two-step cycloaddition process involving a dipolar intermediate. The substitution in the 4-position of the α,β-unsaturated imines, along with the substituents on the ketene functionality, play a key role in the cyclization step to yield (2+2) and/or (4+2) cycloaddition products; i.e., this ring closing step is sterically controlled.

The cycloaddition of diphenyl- and phenylethylketenes with 1,3-diazacycloocta-1,2-diene yielded both 1:1 and 2:1 cycloaddition products depending on the ratio of ketenes and cyclic carbodiimide. The cycloaddition of diphenyl- and phenylketene with 1,3-diazacyclotetradeca-1,2-diene yielded only 1:1 adducts even in the presence of an excess of ketene. Chloroketenes reacted with cyclic carbodiimides to yield (2+2) cycloaddition products, β-lactams that were very susceptible to hydrolysis to N-substituted cycloureas. A trapping experiment indicated that these reactions proceed through a stabilized dipolar intermediate. The ring strain in 1,3-diazacycloocta-1,2-diene apparently enhances the reactivity of the residual carbon nitrogen double bond of the 1:1 cycloaddition product and results in the 2:1 adduct.

The in situ cycloaddition of chloroketenes with α-methoxymethylenecyclohexanones yields (4+2) cycloaddition products, 3,4-dihydro-2-pyranones. The chlorine atom is reductively removed and methanol is spontaneously eliminated to yield the 5,6,7,8-tetrahydrocoumarins. Dehydrogenation of these compounds results in the formation of 3-substituted coumarins. The 3,4-dihydro-2-pyranones could be dehydrogenated before the zinc reduction followed by dehydrochlorination to yield 4-methoxy-3-substituted coumarins. The substituents on the cyclohexanone ring

also provide the opportunity to introduce substituents in the benzene ring of the coumarin system.

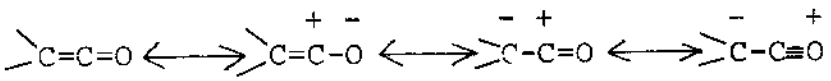
TABLE OF CONTENTS

LIST OF TABLES

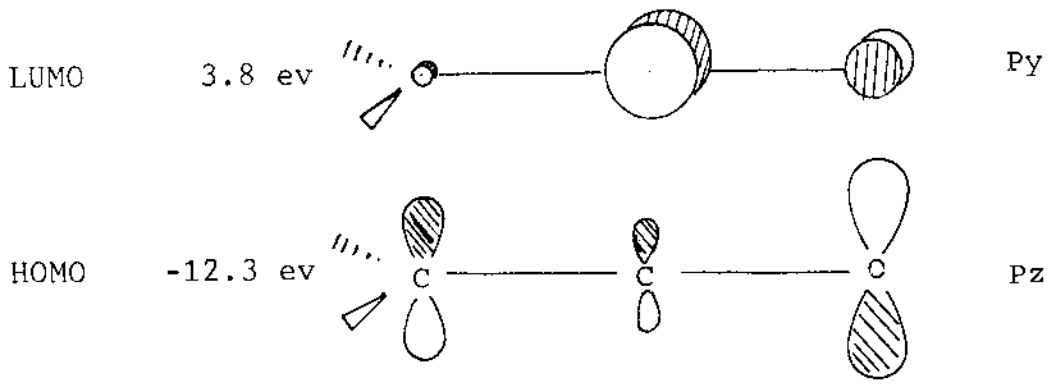
CHAPTER I

INTRODUCTION

Ketenes are highly reactive electrophilic molecules containing an olefinic and carbonyl group in cumulative linkage. Most ketenes are not isolable, and are usually trapped <u>in situ</u> with suitable nucleophiles. (1, 2, 3, 4, 5, 6) The most reactive or electron deficient site of ketenes is the sp-hybridized carbon of the carbonyl group as demonstrated by several theoretical studies. (7, 8

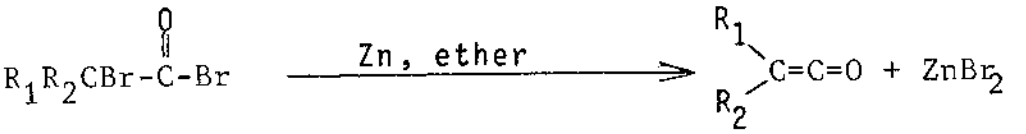


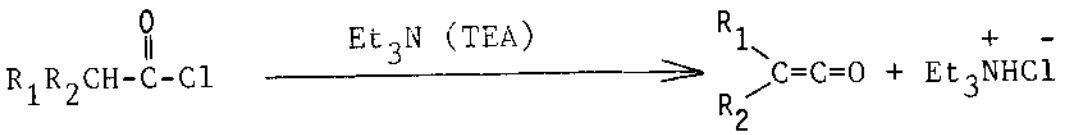
9, 10) The frontier molecular orbitals and energies are shown whereby the larger lobes represent the larger coefficients of the carbon atoms of the ketene. (11)



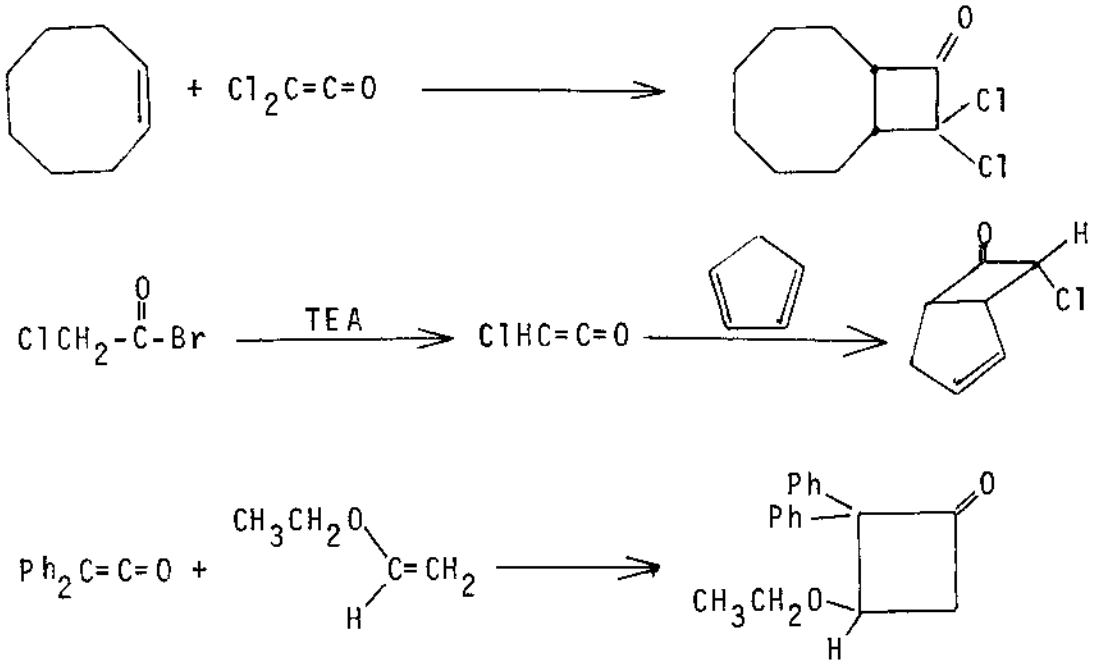
Electron-withdrawing substituents on the ketene lower the energy of the LUMO and therefore increase the reactivity. A general order of reactivity of various substituted ketenes in cycloaddition reactions with olefinic compounds is as follows (5): $Cl_2C=C=O$ > $Ph_2C=C=O$ > $Me_2C=C=O$ > $H_2C=C=O$.

Most monosubstituted and halogenated ketenes are usually not stable at room temperature, but can be trapped <u>in situ</u> in the presence of a suitable ketenophile. Only a few disubstituted ketenes (i.e. diphenylketene, phenylethylketene, diethylketene, etc.) are relatively stable and isolable at room temperature. (12, 13, 14) There are many methods which have been reported for the preparation of ketenes but the two most common methods are the dehydrohalogenation and dehalogenation of suitable acid halides as illustrated. (15, 16)



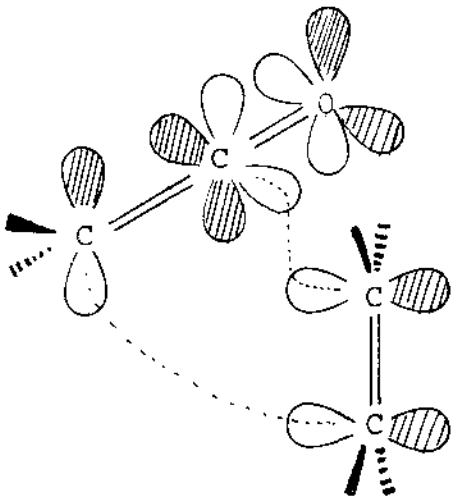


The most synthetically useful reaction of ketenes is the (2+2) cycloaddition of ketenes with unsaturated compounds to yield compounds containing four member rings. There are many reports in the literature on the cycloaddition of ketenes with symmetrical and unsymmetrical olefins to give stereo and regiospecific products as shown below. (17, 18, 19, 20, 21, 22, 23) These results are consistant



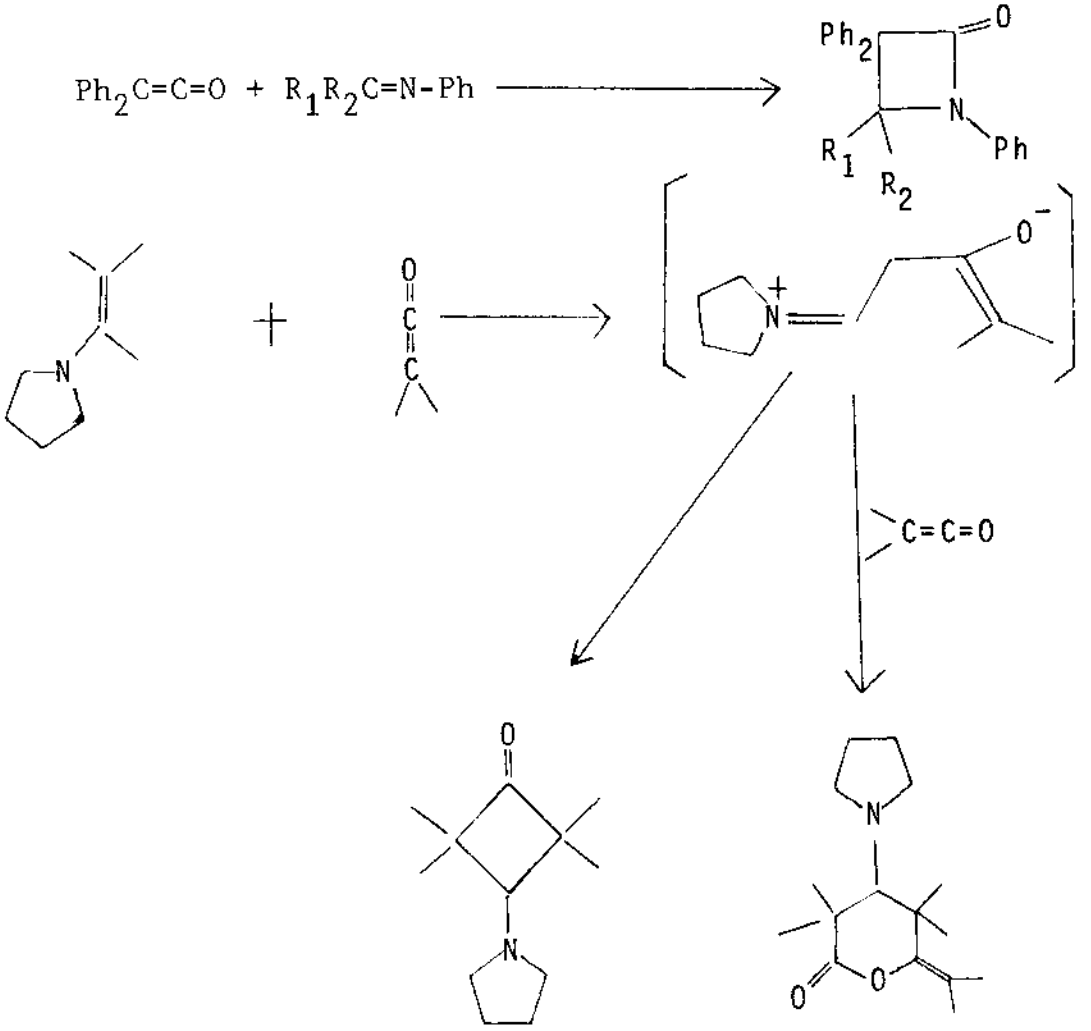
with a concerted mechanism. A lot of evidence has been reported in the literature including negative activation entropy, negligible solvent effects of rate, and an observed secondary isotope effect that suggest a concerted mechanism which follows a ($\pi_2 s + \pi_2 a$) pathway. Thus, one end of the π-bond of the olefin develops overlap to the p_y

orbital of the central carbon atom of the ketene, while the other end of the π-bond of the olefin develops overlap to the p_z orbital of the terminal carbon atom of the ketene functionality. (24) Therefore, the regioselectivity was explained by the fact that the largest



coefficient carbon of the HOMO of the olefin overlaps with the largest coefficient carbon of the LUMO of the ketenes.

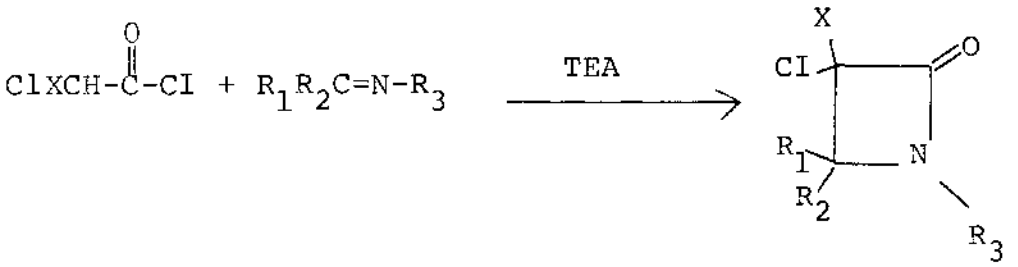
Although the cycloaddition of ketenes with olefins by a concerted mechanism successfully explains the stereochemistry of ketene cycloadditions, there are many reports of ketene cycloadditions that occur by a stepwise pathway. The cycloaddition of ketenes with imines, (25, 26, 27, 28, 29, 30, 31, 32, 33, 34) and highly activated olefins (35, 36, 37, 38) are representative.



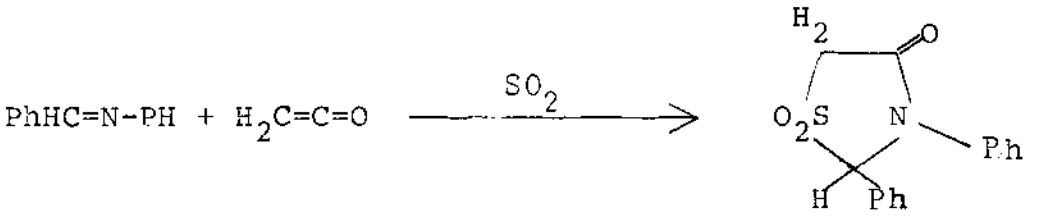
The first synthesis of a β-lactam by the cycloaddition of ketenes with imines was reported by Staudinger in 1970. Staudinger investigated the cycloaddition of various

types of ketenes with imines and reported the first review of ketene cycloaddition reactions in 1912. (33)

In an extension of the Staudinger synthesis of β-lactams, Ghosez and Duran reported the cycloaddition of haloketenes with imines to yield halogenated-β-lactams which are potential precursors of various functionally substituted β-lactams. (35)

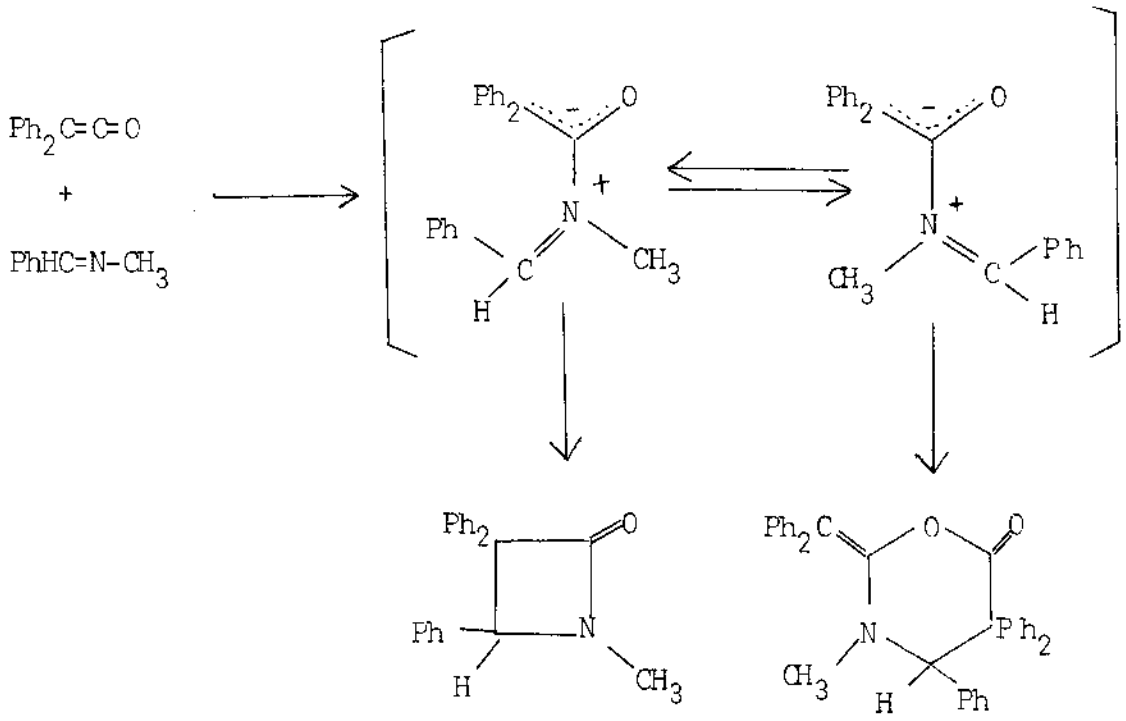


The mechanism of this reaction has been recently elucidated and established to be a two-step process involving a dipolar intermediate. In 1967, Gomes and Foullie reported the cycloaddition of ketene with benzylideneaniline in sulphur dioxide as the solvent with the resultant formation of a compound containing sulphur dioxide in 52%. (40) It was concluded that this reaction



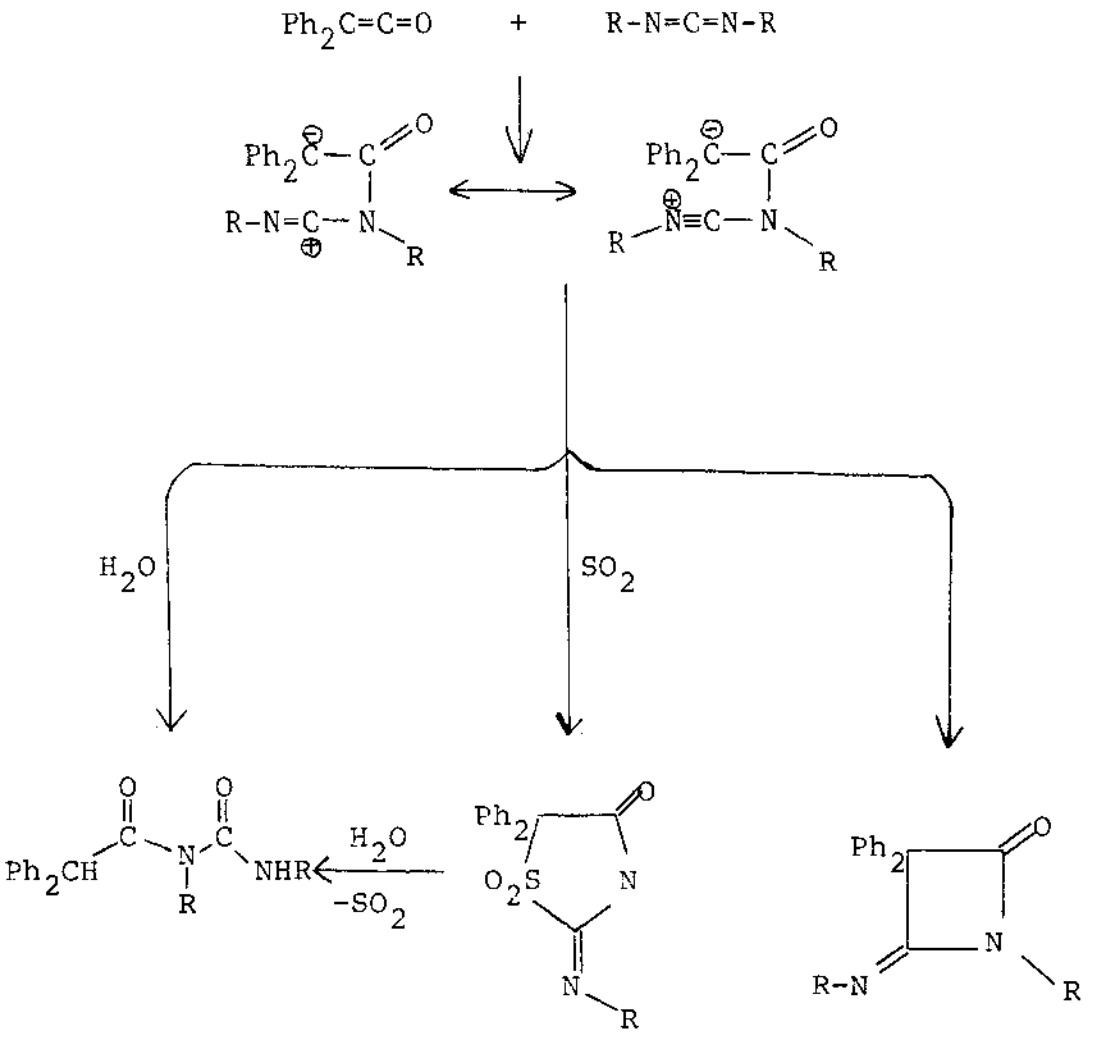
likely undergoes a two-step process involving a dipolar intermediate which was successfully trapped by the sulphur dioxide.

Huisgen and coworkers have also reported evidence for the formation of a 1,4-dipolar intermediate in the cycloaddition of diphenylketene and benzylidenemethylamine. (27) The use of excess of diphenylketene resulted in the



isolation of both a 1:1 and 2:1 cycloadduct. Clearly, this 2:1 cycloadduct is derived from the addition of a second molecule of diphenylketene to the 1,4-dipolar intermediate.

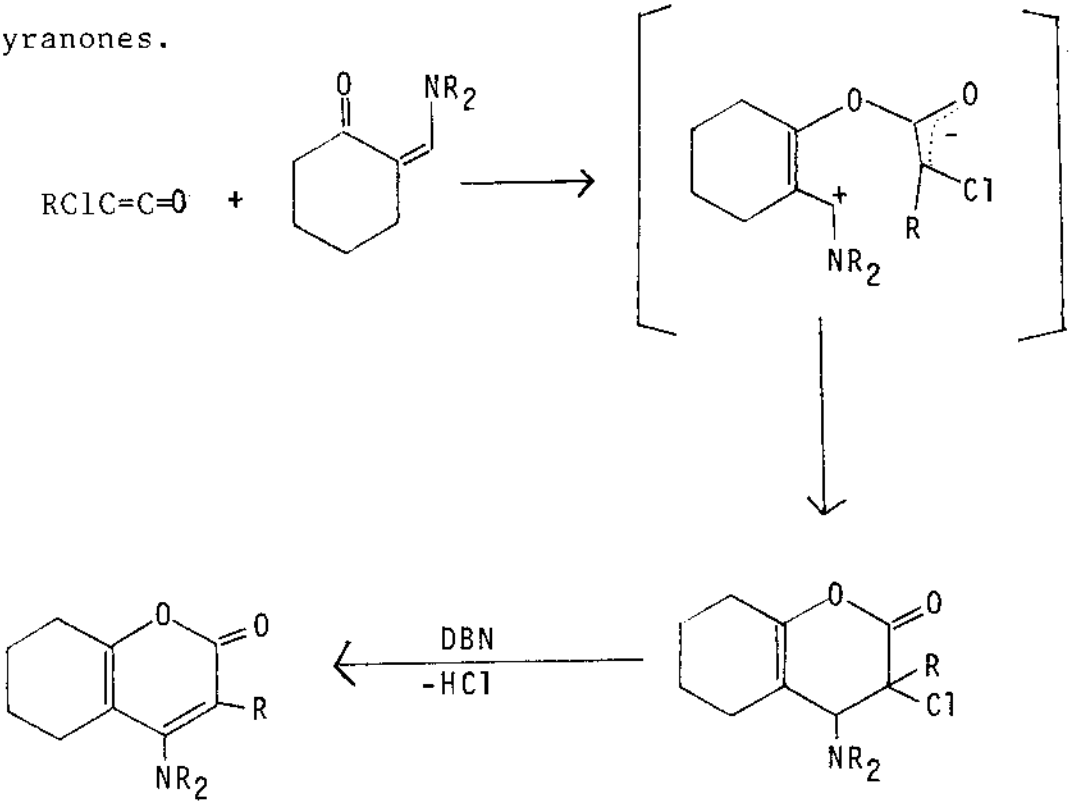
More recently, Brady and Dorsey reported the cycloaddition of ketenes with carbodiimides to yield β-iminoyl-β-lactams. (41) These reactions were demonstrated to occur by a two-step process involving a dipolar intermediate as the intermediate was successfully trapped. (42)



Besides the (2+2) ketene cycloadditions, there are some scattered reports on the (4+2) cycloaddition of ketenes with activated vinyl ketones, (43, 44, 45, 46) and α,β-unsaturated imines. (35, 47, 48)

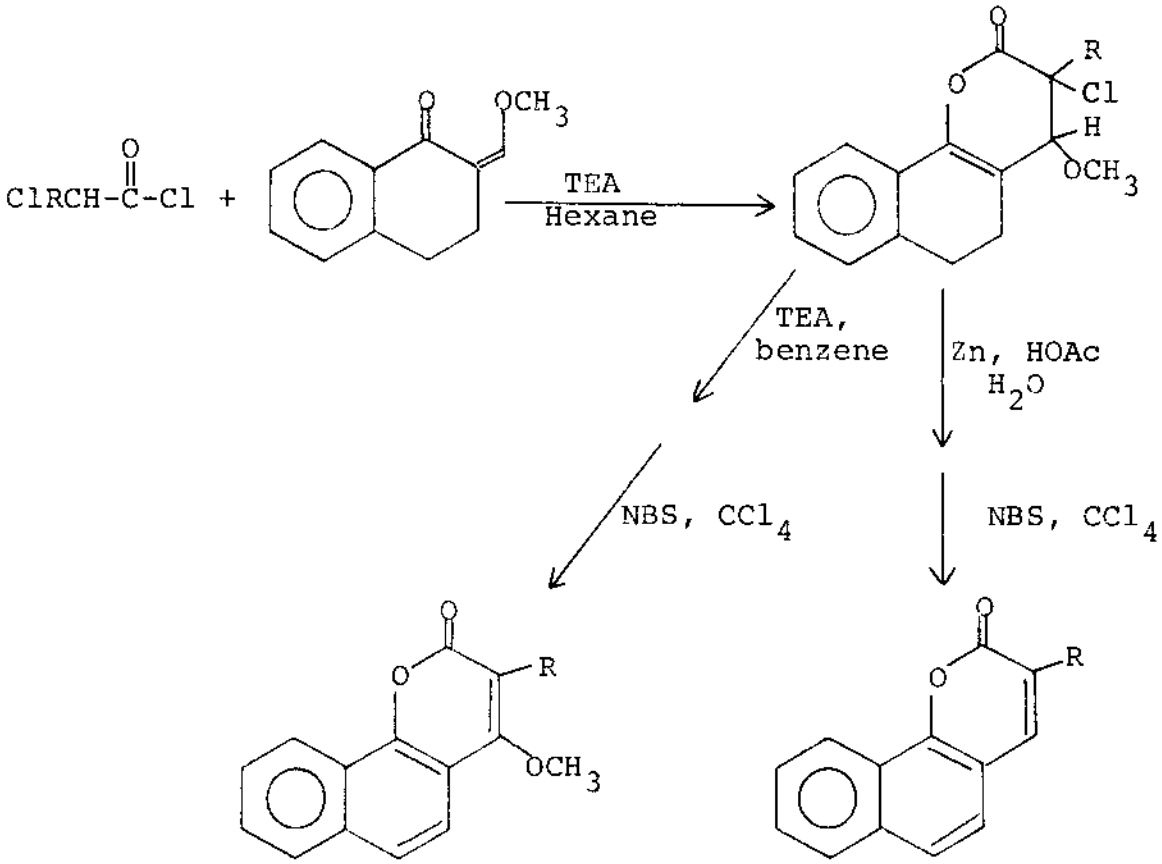
Schenone and coworkers have reported a series of cycloadditions of ketenes with various types of N,N-disubstituted 2-aminomethylene cyclic ketones to give

dihydropyranones. (49, 50, 51, 52, 53, 54, 55, 56) A two-step mechanism was proposed involving a dipolar intermediate. The cycloaddition products resulting from chloroketenes may be dehydrochlorinated to the 2-pyranones.

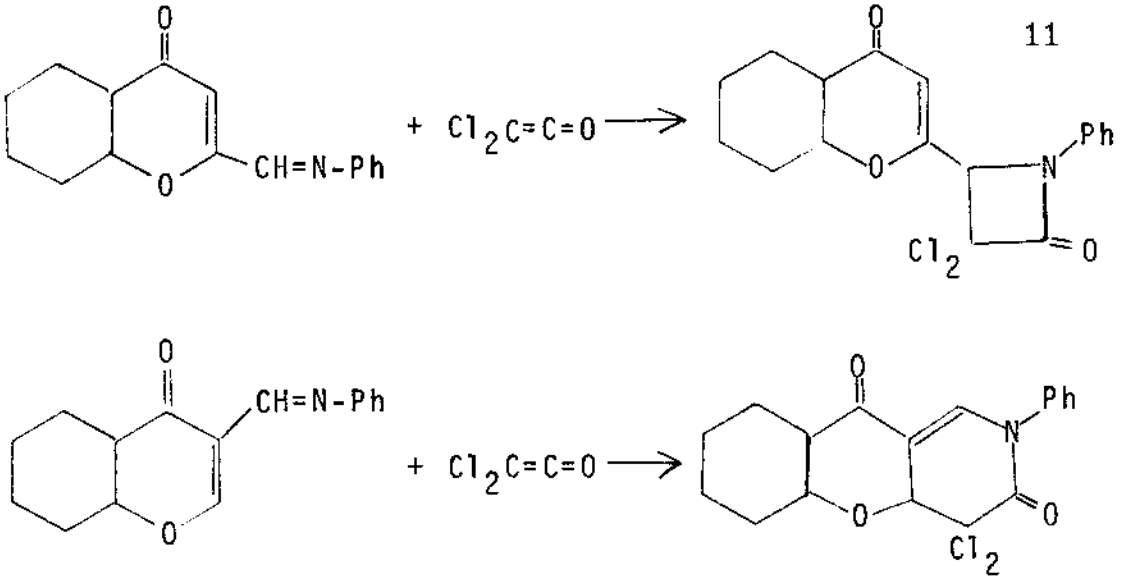


Recently, Brady and Agho investigated the cycloaddition of diphenyl- and various chloroketenes with β-methoxy-α,β-unsaturated ketones to yield (4+2) cycloaddition products. The products resulting from chloroketenes and β-(methoxymethylene)-α-tetralone were readily converted to dihydro-2-pyranones on treatment with zinc in moist acetic acid or with triethylamine in refluxing benzene. The treatment of the dihydro-2-pyranones with

N-bromosuccinimide in refluxing carbon tetrachloride resulted in good yields of substituted 7,8-benzocoumarins. (57)

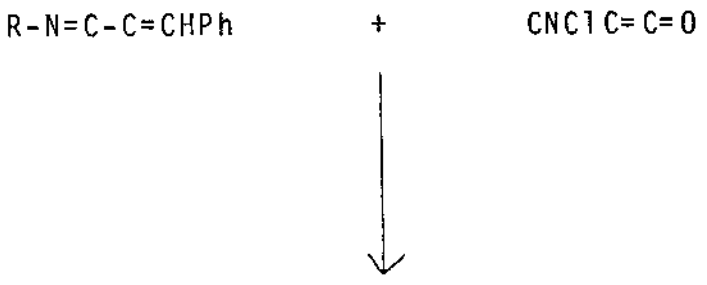


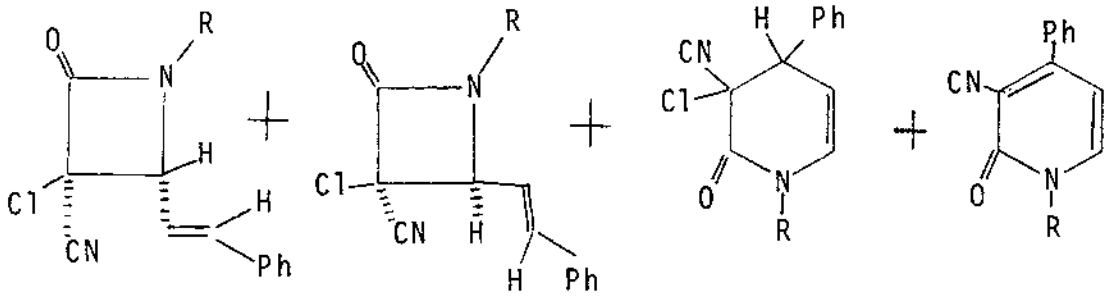
Similarly, there are a couple of isolated reports on the cycloaddition of α,β-unsaturated imines to give (4+2) cycloadditions. Fitterns and coworkers studied the cycloaddition of 2 and 3-(aryliminomethyl-)chromones with dichloroketene to yield (4+2) and (2+2) cycloaddition products, respectively. (47)



11

During the course of this dissertation study, Moore and Hughes reported the cycloaddition of chlorocyanoketene with cinnamylideneamines to give β-lactams, δ-lactams, and 2-pyridones. The stereoselectivity of these cycloadditions is dependant on the N-substituent as well as the C-substituents of the imines. (48)





It is interesting to note that there is no detailed and systematized study of the cycloaddition of ketenes with α,β-unsaturated imines in the literature. Since it is well established that the cycloaddition of ketenes with imines occured via a dipolar intermediate, α,β-unsaturated imines do, in fact, offer the possibility for ring closure from the dipolar intermediate to (4+2) cycloaddition products. This could be a significant synthetic development for the preparation of β-lactams and/or δ-lactams. Therefore, it was proposed to study the reaction of diphenylketene and dichloroketene with various α,β-unsaturated imines to determine the synthetic utility of this reaction for the preparation of β-and δ-lactams. Therefore, part I of this dissertation is a study of ketene cycloaddition reactions with α,β-unsaturated imines.

Recently, a new synthesis for cyclic carbodiimides has been reported and as expected the ring size of the cyclic carbodiimides effects the stability and the reactivity of the carbodiimide moiety. (58, 59, 60) It was expected that this ring would also effect the cycloaddition of ketenes with cyclic carbodiimides. Consequently, it was proposed to study the cycloaddition of ketenes with cyclic carbodiimides to determine the

synthetic usefulness of this reaction for the preparation of dicyclo-β-lactams. Therefore part II of this dissertation is concerned with ketene cycloadditions with cyclic carbodiimides.

Coumarins are derivatives of 2-pyranones and are widespread in nature being found primarily in the plant kingdom. Both natural and synthetic coumarins are known to exhibit useful and varied physiological activities. (61, 62, 63) Brady and Agho reported the synthesis of benzocoumarins from halogenated ketenes and α-methoxy-β-tetralone. It was proposed to extend this synthetic methodology to a new general synthetic route for substituted coumarins from the cycloaddition of halogenated ketenes with β-methoxymethylene cyclohexanones. Hence, part III of this study is a new synthesis for substituted coumarins.

CHAPTER BIBLIOGRAPHY

1. Brady, W.T., Synthesis, 8, 415 (1971).

2. Brady, W.T., Tetrahedron, 37, 1939 (1981).

3. Ward, R.S., The chemistry of ketenes, allenes and related compounds, part 1, edited by Patai, S., New York, Interscience Publishers, Inc., 1980, p. 223.

4. Hanford, W.E., Sauer, J.C., Organic reactions, edited by Adams, R., Vol. 3, Wiley Interscience, London, 1946, Chapter 3, p. 108.

5. Ruden, R.A., J. Org. Cham., 39, 2607 (1974).

6. Luknitskii, F.I., Vovsi, B.A., Russ. Chem. Rev., 38, 387 (1969).

7. Pople, T.A., Gordon, M., J. Amer. Chem. Soc., 89, 4253 (1967).

8. Weimann, L.J., Christoffersen, R.E., J. Amer. Chem. Soc., 95, 2074 (1973).

9. Hopkinson, A.C., Csizmadia, I.G., Can. J. Chem., 52, 546 (1974).

10. Houk, K.N., Strozier, R.W., Hall, T.A., Tetrahedron Letters, 897 (1974).

11. Fleming, I., Frontier Orbitals and Organic Chemical Reactions, Chichester-New York-Brisbane-Toronto, John Wiley, 1978.

12. Krapcho, A.P., Lesser, J.H., J. Org. Chem., 31, 2030 (1966).

13. Newman, M.S., Leggwate, A., J. Org. Chem., 33, 2144.

14. Tsunetsugn, T., Arimoro, K., Fueno, T., Furukawa, J., Die Makromolekulace Chemie. 112, 210 (1968).

15. Hassner, A., Fletcher, V.R., Hamon, D.P.G., J. Amer. Chem. Soc., 93, 264 (1971).

16. Brady, W.T., Hoff, E.F., Roe, R., Parry, F.H., J. Amer. Chem. Soc., 91, 5679 (1969).

17. Ghosez, L., Montaigne, R., Vanlierde, H., Dumay, F., Angewante Chemie Int. Ed. Engl., 7, 221 (1968).

18. Brady, W.T., Lloyd, R.M., J. Org. Chem., 44, 2560 (1979).

19. Brady, W.T., Watts, R.D., J. Org. Chem., 45, 3525 (1980).

20. Zaitseva, G.S., Baukov, V.I., Matsev, V.V., Lutsenko, I.F., Zh. Obshch. Khim., 44, 1415 (1974).

21. Kato, T., Yamamoto, Y., Takeda, S., Yakugaku Zasshi, 94, 884 (1974), as seen in Chem. Abst., 81, 37514u (1974).

22. Fleming, I., Chem. Ind. (lond.), 449 (1975).

23. Brady, W.T., Lloyd, R.M., J. Org. Chem., 45, 2025 (1980).

24. Brady, W.T., Lloyd, R.M., J. Org. Chem., 46, 1322 (1981).

25. Bose, A.K., Spiegelman, G., Manhas, M.S., Tetrahedron Letters, 3167 (1971).

26. Pfleger, R., Jager, A., Chem. Ber., 90, 2460 (1957).

27. Huisgen, R., Davis, B.A., Morikawa, M., Angewandte Chemie Int. Ed. Eng., 77, 826 (1968).

28. Kirmse, W., Horner, L., Chem. Ber., 89, 2759 (1956).

29. Bose, A.K., Chiang, Y.H., Manhas, M.S., Tetrahedron Letters, 4991 (1972).

30. Bose, A.K., Manhas, M.S., Chiang, Y.H., Tetrahedron 25, 4421 (1969).

31. Ziegler, E., Wimmer, Th., Mittelbach, H., Monatsh Chem., 99, 2128 (1968).

32. Nelson, P.A., J. Org. Chem., 37, 1447 (1972).

33. Staudinger, H., "Die Ketene", Ferdinand Enke, (Stuttgart, 1912).

34. Ziegler, E., Kleinberg, G., Monatsh Chem., 96, 1296 (1965).

35. Hoffman, R.W., Angewandte Chemie Int. Ed. Engl., 11, 324 (1972).

36. Bellus, D., Fisher, H.P., Greuter, H., Martin, P., Helv. Chim. Acta., 61, 1784 (1978).

37. Bellus, D., J. Amer. Chem. Soc., 44, 100 (1979).

38. Bellus, D., J. Org. Chem., 44, 1208 (1979).

39. Ghose, L., Duran, F., Tetrahedron Letters, 245 (1970).

40. Gomes, A., Joullie, M.M., Chem. Commu., 935 (1967).

41. Brady, W.T., Dorsey, E.D., J. Org. Chem., 34, 2846 (1969).

42. Brady, W.T., Dorsey, E.D., J. Org. Chem., 35, 2732 (1970).

43. Scarpati, R., Scia, D., Santacroce, C., Tetrahedron, 20, 2735 (1964).

44. Brady, W.T., Watts, R.D., J. Org. Chem., 46, 4047 (1981).

45. Hasek, R.H., Gott, P.G., Martin, J.C., J. Org. Chem., 29, 2513 (1964).

46. Martin, J.C., Gott, P.G., Goodlett, V.W., Hasek, R.H., J. Org. Chem., 30, 4175 (1965).

47. Fitton, A.O., Frost, J.R., Houghton, P.G., Suschitzky, H., J. Chem. Soc., Perkin Trans. 1, 1450 (1977).

48. Moore, H.W., Hughes, G., Tetrahedron Letters, 23, 4003 (1982).

49. Schenone, P., Bignardi, G., Evangelisti, F., Ann. Chim. (Rome), 61, 326 (1971).

50. Schenone, P., Bignardi, G., Bargagna, A., J. Heterocycl. Chem., 9, 1971 (1972).

51. Schenone, P., Bignardi, G., Bargagna, A., Evangelisti, F., J. Heterocycl. Chem., 13, 1105 (1976).

52. Schenone, P., Bignardi, G., Mosti, L., Evangelisti, F., J. Heterocycl. Chem., 13, 1201 (1976).

53. Schenone, P., Bargagna, A., Cafaggi, S., J. Heterocycl. Chem., 14, 249 (1977).

54. Schenone, P., Mosti, L., Menozzi, G., J. Heterocycl. Chem., 15, 181 (1978).

55. Schenone, P., Bargagna, A., Evangelisti, F., J. Heterocycl. Chem., 16, 93 (1979).

56. Schenone, P., Mosti, L., Menozzi, G., J. Heterocycl. Chem., 16, 913 (1979).

57. Brady, W.T., Agho, M.O., J. Org. Chem., 48, 5337 (1983).

58. Richter, R., Tucker, B., Ulrich, H., J. Org. Chem., 43, 1544 (1978).

59. Damrauer, R., Soucy, D., Winkler, P., Eby, S., J. Org. Chem., 45, 1315 (1980).

60. Richter, R., Tucker, B., Ulrich, H., J. Org. Chem., 48, 1694 (1983).

61. Soimae, T.O., J. Pharm. Sci., 53, 231 (1964).

62. Arora, R.B., Mathur, C.N., Br. J. Pharmacol., 20, 29 (1963).

63. Ichibagase, H., J. Pharm. Soc. Jpn., 75, 1475 (1955).

CHAPTER II

EXPERIMENTAL

Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a 60 MHZ Hitachi Perkin-Elmer R-24B spectrometer, employing deuteriochloroform as the solvent with tetramethylsilane as the internal standard. Carbon-13 nmr spectra were obtained on a JEOL FX-90Q FT nuclear magnetic resonance spectrometer. Deuteriochloroform was used as a lock solvent and as the internal standard, and all chemical shifts are reported in parts per million (ppm). The infrared (ir) spectra were obtained on a Beckmann 1330 spectrophotometer. All melting points were determined on a Thomas Hoover capillary melting point apparatus, and like boiling points, are uncorrected. Elemental analyses were carried out by Midwest Microlab, Ltd., Indianapolis, Indiana.

Hexane, tetrahydrofuran and ether were dried and purified before using by distillation from sodium-potassium alloy under a nitrogen atmosphere. Benzene and triethylamine were distilled from sodium metal. All acid chlorides were distilled immediately before using. Diphenylketene was prepared from diphenylacetyl chloride as previously described. (1)

Part I. The Cycloaddition of Ketenes with α,β-Unsaturated Imines

Typical Procedure For Imine Synthesis. (2, 3, 4, 5)

(a) From α,β-Unsaturated Aldehydes. A solution of 0.2 mol of freshly distilled amine was added over 10 min. to a stirred solution of 0.2 mol of α,β-unsaturated aldehydes in 50 ml of dry ether. The resulting mixture was allowed to stand at ambient temperature for about 30 min., and then the ether was evaporated under reduced pressure. The imines were vacuum distilled or recrystalized from 95% ethanol.

(b) From α,β-Unsaturated Ketones. A solution of 0.2 mol of the amine, 0.2 mole of the α,β-unsaturated ketone, and a catalytic amount of zinc chloride in 80 ml of benzene was refluxed under a water separator until water ceased to be formed. The zinc chloride was removed by filtration, the benzene was removed under reduced pressure, and the imines were recrystallized from 95% ethanol.

Typical Procedure For Diphenylketene Cycloadditions With α,β-Unsaturated Imines. To a stirred solution of 0.021 mol of the α,β-unsaturated imine in 100 ml of dry ether was added 0.020 mol of freshly distilled diphenylketene

in 30 ml of dry ether under a nitrogen atmosphere at ambient temperature. When the ketene band in the ir at 2100 cm^{-1} had disappeared (usually about 1 hour), the solution was concentrated on a rotatory evaporator and the residue recrystallized from 95% ethanol and benzene.

N,3,3-Triphenyl-4-styryl-2-azetidinone, 1a. From diphenylketene and the N-phenyl imine of cinnamaldehyde was obtained 5.9 g (74%) of compound 1a; m.p. 172-173° C; ir ($CDCl_3$) 1732 cm^{-1} (C=O); nmr, δ, 4.95 (d, 1 H), 5.35 (dd, 1 H), 6.45 (d, 1 H), 6.8 (m, 20 H).

Anal. Calcd. for $C_{29}H_{23}NO$: C, 86.78; H, 5.73. Found: C, 86.69; H, 5.61.

N,3,3-Triphenyl-4-(1-methylstyryl)-2-azetidinone, 1b. From diphenylketene and the N-phenyl imine of α-methyl-cinnamaldehyde was obtained 5.9 g (72%) of compound 1b; m.p. 131.5-133.5° C; ir ($CDCl_3$) 1738 cm^{-1} (C=O); nmr, δ, 1.2 (s, 3 H), 5.0 (s, 1 H), 6.4 (s, 1 H), 6.9 (m, 20 H).

Anal. Calcd. for $C_{30}H_{25}NO$: C, 86.74; H, 6.02. Found: C, 86.70; H, 5.80.

N,3,3-Triphenyl-4-methyl-4-styryl-2-azetidinone, 1c. From diphenylketene and the N-phenyl imine of 4-phenyl-3-buten-2-one was obtained 5.2 g (63%) of compound 1c; m.p. 146.5-148° C; ir ($CDCl_3$) 1739 cm^{-1} (C=O); nmr, δ, 1.7 (d, 3 H), 5.87 (d, 1 H), 6.4 (d, 1 H), 7.2 (m, 20 H).

Anal. Calcd. for $C_{30}H_{25}NO$: C, 86.74; H, 5.2; N, 3.37. Found: C, 87.01; H, 6.04; N, 3.50.

N,3,3-Triphenyl-4-(2-furfuryl)-2-azetidinone, 1d. From diphenylketene and the N-phenyl imine of furfural was obtained 4.5 g (62%) of compound 1d; m.p. 145.5-146.5° C; ir ($CDCl_3$) 1742 cm^{-1} (C=O); nmr, δ, 5.5 (s, 1 H), 5.75 (d, 2 H), 6.9 (m, 16 H).

Anal. Calcd. for $C_{25}H_{29}NO_2$: C, 82.19; H, 5.20; N, 3.84. Found: C, 82.45; H, 4.99; N, 3.87.

N,3,3-Triphenyl-5,5,7-trimethyl-1-aza-2-oxospiro[5,3]-non-7-ene, 1e. From diphenylketene and the N-phenyl imine of isophorone was obtained 6.2 g (76%) of compound 1e; m.p. 130-131.5° C; ir ($CDCl_3$) 1742 cm^{-1} (C=O); nmr, δ, 0.65 (s, 3 H), 1.68 (s, 3 H), 1.79 (s, 3 H), 5.18 (s, 1 H), 7.2 (m, 15 H).

Anal. Calcd. for $C_{29}H_{29}NO$: C, 84.79; H, 7.13; N, 3.27. Found: C, 85.18; H, 6.87; N, 3.22.

N-Isopropyl-3,3-diphenyl-4-styryl-2-azetidinone, 1f. From diphenylketene and the N-isopropyl imine of cinnamaldehyde was obtained 5.3 g (77%) of compound 1f; m.p. 110-111° C; ir ($CDCl_3$) 1730 cm^{-1} (C=O); nmr, δ, 1.1 (d, 3 H), 1.22 (d, 3 H), 3.75 (m, 1 H), 4.15 (d, 1 H), 5.4 (d, 1 H), 6.4 (d, 1 H), 6.9 (m, 15 H).

Anal. Calcd. for $C_{26}H_{25}NO$: C, 85.01; H, 6.81; N, 3.81. Found: C, 84.75; H, 6.87; N, 3.81.

N,3,3-Triphenyl-4-methyl-4-(2-methylpropenyl)-2-azetidinone, 1g. From diphenylketene and the N-phenyl imine of 4-methyl-3-pentene-2-one there was obtained 5.1 g (70%) of compound 1g; m.p. 135.5-136° C; ir ($CDCl_3$) 1720 cm^{-1} (C=O); nmr, δ, 1.05 (s, 3 H), 1.4 (s, 3 H), 1.55 (s, 3 H), 5.2 (s, 1 H), 7.1 (m, 15 H).

Anal. Calcd. for $C_{26}H_{25}NO$: C, 85.01; H, 6.52; N, 7.61. Found: C, 85.14; H, 6.52; N, 7.46.

N,3,3-Triphenyl-4-(5,6-dihydro-2H-pyran-3-yl)-2-azetidinone, 1h. From diphenylketene and the N-phenyl imine of 5,6-dihydro-2H-pyran-3-carboxaldehyde there was obtained 6.4 g (84%) of compound 1h; m.p. 144-146° C; ir ($CDCl_3$) 1740 cm^{-1} (C=O); nmr, δ, 1.95 (s, 3 H), 3.18 (t, 3 H), 3.42 (s, 3 H), 4.9 (s, 1 H), 7.0 (m, 15 H).

Anal. Calcd. for $C_{26}H_{25}NO_2$: C, 81.69; H, 6.04; N, 3.67. Found: C, 81.38; H, 5.83; N, 3.51.

N-Cyclohexyl-3,3-diphenyl-4-styryl-2-azetidinone, 1i. From diphenylketene and the N-cyclohexyl imine of cinnamaldehyde there was obtained 7.6 g (82%) of compound 1i; m.p. 139-140° C; ir ($CDCl_3$) 1730 cm^{-1} (C=O); nmr, δ, 1.5 (m, 10 H), 3.2 (m, 1 H), 4.65 (d, 1 H), 5.38 (dd, 1 H), 6.45 (d, 1 H), 7.0 (m, 15 H).

Anal. Calcd. for $C_{29}H_{29}NO$: C, 85.50; H, 7.13; N, 3.44. Found: C, 85.38; H, 7.14; N, 3.34.

N,3,3-Triphenyl-4-(2-phenylstyryl)-2-azetidinone, 1j. From diphenylketene and the N-phenyl imine of β-phenylcinnamaldehyde there was obtained 8.0 g (84%) of 1j; m.p. 199-200.5° C; ir ($CDCl_3$) 1734 cm^{-1} (C=O); nmr, δ, 5.24 (d, 1 H), 5.49 (d, 1 H), 7.04 (m, 20 H).

Anal. Calcd. for $C_{35}H_{27}NO$: C, 88.05; H, 5.66; N, 2.94. Found: C, 88.10; H, 5.36; N, 2.71.

N-tert-Butyl-3,3-diphenyl-4-styryl-2-azetidinone, 1k. From diphenylketene and the N-tert-butyl imine of cinnamaldehyde there was obtained 6.3 g (83%) of 1k; m.p. 158-159.5° C; ir ($CDCl_3$) 1729 cm^{-1} (C=O); nmr, δ, 1.3 (s, 9 H), 4.6 (d, 1 H), 5.35 (dd, 1 H), 6.4 (d, 1 H), 6.9 (m, 15 H).

Anal. Calcd. for $C_{27}H_{27}NO$: C, 85.04; H, 7.09; N, 3.67. Found: C, 85.15; H, 6.98; N, 3.58.

N,3,3-Triphenyl-4-(dimethylamino)-3,4-dihydro-2-pyridone, 2a. From diphenylketene and the N-phenyl imine of 3-(dimethylamino)-2-propenal there was obtained 4.7 g (64%) of 2a; m.p. 129.5-131° C; ir ($CDCl_3$) 1675 cm^{-1} (C=O); nmr, δ, 2.15 (s, 6 H), 3.8 (d, 1 H), 5.2 (dd, 1 H), 6.0 (d, 1 H), 6.9 (m, 15 H).

Anal. Calcd. for $C_{25}H_{24}N_2O$: C, 81.52; H, 6.51; N, 7.61. Found: C, 81.34; H, 6.52; N, 7.46.

Typical Procedure For Dichloroketene Cycloadditions With α,β-Unsaturated Imines. A solution of 0.020 mol of freshly distilled dichloroacetyl chloride in 50 ml of dry ether was added over a 1 hour period to a stirred solution of 0.021 mol of α,β-unsaturated imine and 0.022 mol of triethylamine in 200 ml of dry ether at ambient temperature under a nitrogen atmosphere. The resulting mixture was stirred an additional 30 min. and the amine salt removed by filtration. The filtrate was concentrated on a rotatory evaporator, and the residue was recrystallized from 95% ethanol and benzene.

3,3-Dichloro-3,4-dihydro-N,4-diphenyl-2-pyridone, 2b. From dichloroketene and the N-phenyl imine of cinnamaldehyde there was obtained 3.1 g (49%) of 2b; m.p. 147-148° C; ir ($CDCl_3$) 1680 cm^{-1}(C=O); nmr, δ, 4.1 (dd, 1 H), 5.15 (dd, 1 H), 6.95 (m, 10 H).

Anal. Calcd. for $C_{17}H_{13}Cl_2NO$: C, 64.16; H, 3.87; N, 4.40. Found: C, 64.42; H, 3.87; N, 4.12.

3,3-Dichloro-3,4-dihydro-5-methyl-N,4-diphenyl-2-pyridone, 2c. From dichloroketene and the N-phenyl imine of α-methylcinnamaldehyde there was obtained 4.4 g (66%) of 2c; m.p. 113-114.5° C; ir ($CDCl_3$) 1700 cm^{-1} (C=O)

nmr, δ, 1.55 (s, 3 H), 3.7 (s, 1 H), 5.85 (s, 1 H), 6.9 (m, 10 H).

Anal. Calcd. for $C_{18}H_{15}Cl_2NO$: C, 65.08; H, 4.55; N, 4.22. Found: C, 65.28; H, 4.37; N, 4.35.

3,3-Dichloro-N-phenyl-4-(2-phenylstyryl)-2-azetidinone, 11. From dichloroketene and the N-phenyl imine of β-phenylcinnamaldehyde there was obtained 4.8 g (61%) of 11; m.p. 136.5-137° C; ir ($CDCl_3$) 1785 cm^{-1} (C=O); nmr, δ, 4.66 (d, 1 H), 5.24 (d, 1 H), 7.05 (m, 15 H).

Anal. Calcd. for $C_{23}H_{17}Cl_2NO$: C, 70.05; H, 4.31; N, 3.55. Found: C, 70.30; H, 4.30; N, 3.48.

The Dehydrochlorination of Compound 2b, 3-chloro-N,4-diphenyl-2-pyridone, 3a. A 1.0 g portion of compound 2b was refluxed in 100 ml of o-dichlorobenzene for 3 hours. After cooling to room temperature, the resulting mixture was recrystallized from 95% ethanol and benzene to give 0.87 g (98%) of compound 3a; m.p. 185.8-187° C; ir ($CDCl_3$) 1661 cm^{-1} (c=O), nmr, δ, 6.0 (d, 1 H), 6.95 (d, 1 H), 7.1 (m, 10 H).

Anal. Calcd. for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.26; N, 4.97. Found: C, 72.17; H, 4.06; N, 5.09.

The Dehydrochlorination of Compound 2c, 3-Chloro-5-methyl-N,4-diphenyl-2-pyridone, 3b. A 1.0 g portion of compound 2c was refluxed in 100 ml of o-dichlorobenzene

for 3 hours. After cooling to room temperature, the resulting mixture was filtered, and then concentrated on a rotatory evaporator. The residue was recrystallized from 95% ethanol and benzene to give 0.89 g (100%) of compound 3b, m.p. 166-167.5° C; ir ($CDCl_3$) 1650 cm^{-1} (C=O); nmr, δ, 1.7 (s, 3 H), 7.0 (m, 11 H).

Anal. Calcd. for $C_{18}H_{14}ClNO$: C, 73.1; H, 4.74; N. 4.74. Found: C, 72.91; H, 4.74; H, 4.78.

The Hydrogenation of Compound 2c, 3-Chloro-3,4-dihydro-5-methyl-N,4-diphenyl-2-pyridone, 2d. A 1.0 g portion of 3,3-dichloro-3,4-dihydro-5-methyl-N,4-diphenyl-2-pyridone, 0.2 g of palladium black, and 20 ml of benzene were agitated in a hydrogenation apparatus for 8 hours. The resulting mixture was filtered and then concentrated on a rotatory evaporator to give 0.87 g (98%) of compound 2d; m.p. 120-122° C; ir ($CDCl_3$) 1685 cm^{-1} (C=O); nmr, δ, 1.5 (s, 3 H), 3.45 b(d, 1 H), 4.85 (d, 1 H), 5.95 (d, 1 H), 6.95 (m, 10 H).

Anal. Calcd. for $C_{18}H_{16}ClNO$: C, 72.60; H, 5.38; N, 4.71. Found: C, 72.42; H, 5.15; N, 4.63.

Part II. The Cycloaddition of Ketenes With Cyclic Carbodiimides

All of the cyclic carbodiimides were made from commercially available lactams by treatment with

dimethylsulfate, hydroxyamine, methanesulfonyl chloride followed by a Tiemann Rearrangement with ring enlargement as previously described. (6, 7, 8, 9, 10)

1-Methoxy-2-azacyclohept-1-ene. (6) A solution of 19 ml (0.2 mol) of dimethylsulfate, 22.3 g (0.197 mol) of 2-azacycloheptanone and 50 ml of dry benzene was refluxed for 24 hours under a nitrogen atmosphere. After cooling to room temperature, a 100 ml of 2 N potassium carbonate solution was slowly added. The resulting mixture was filtered, and the organic layer was separated. The benzene was evaporated on a rotatory evaporator and the residue was vacuum-distilled at 70-75° C (20 mm) to give 15.6 g (70%) of 1-methoxy-2-azacyclohept-1-ene.

1-Methoxy-2-azacyclotridec-1-ene. (7) A solution of 91 g (0.46 mol) of 2-azacyclotridecanone in 116 g (0.92 mole) of dimethylsulfate was heated at 70° C for 4 hours. After cooled to room temperature, a solution of 55.2 g (1.38 mol) of NaOH in 193 g water was added at one portion. The resulting mixture was stirred an additional 15 min. The organic layer was separated, dried over sodium sulfate and vacuum distilled at 85-90° C (0.1 mm) to give 48.53 g (50%) of 1-methoxy-2-azacyclotridec-1-ene.

Typical Procedure For Lactam-Oxime. (8) A solution of 0.049 mol of 0-methyl lactam, 0.065 mol of hydroxylamine hydrochloride and 0.065 mol of sodium bicarbonate in 200 ml methanol was refluxed for 3 hours. The resulting mixture was cooled, filtered and the solvent evaporated under reduced pressure to give the corresponding lactam-oxime.

Typical Procedure For The Preparation of 1-[[(methylsulfonyl)oxy]imino]-2-azacyclic alkene. (9) To a stirred and ice cooled suspension of 0.04 mol of lactam oxime in 30 ml pyridine was added dropwise 0.04 mol of methanesulfonyl chloride. After additional stirring for 2 hours, pyridine was removed in vacuo, and the remaining oily residue was triturated with 20-30 ml of water which generally leads to separation of the mesylates as colorless solids which are filtered and recrystallized from methylene chloride and hexane solution.

1,3-Diazacycloocta-1,2-diene. (10) To a stirred solution of 0.01 mol of 1-azacycloheptan-2-one 0-(methylsulfonyl) oxime in 20 ml of methylene chloride was added a solution of 10 ml of 10 N NaOH containing 100 mg of aliquat 336.* The resulting reaction was monitored by infrared, and when the carbonyl band had disappeared (usually 2.5-3 hours), the solution was washed several

times with small portions of water, dried over sodium sulfate, and concentrated in vacuo, leaving a mobil, colorless, strong smelling liquid. This liquid underwent polymerization during distillation, consequently this cyclic carbodiimide was used in the cycloadditions without further purification.

1,3-Diazacyclotetradeca-1,2-diene. (11) A suspension of 42 g (0.375 mol) of potassium tert-butoxide in 200 ml of dimethoxyethane was slowly added to a slurry of 0.3 mol of 1-azacyclotridecan-2-one O-(methylsulfonyl) oxime over a period of 30 min. The reaction mixture was stirred for an addition 1.5 hours. The inorganic salt was filtered, and the organic solution concentrated on a rotatory evaporator. The residue was dissolved in 200 ml of methylene chloride, and extracted 3 or 4 times with 20 ml portions of water. The methylene chloride solution was dried over sodium sulfate, concentrated, and vacuum-distilled at 85-86° C (0.1 mm).

Typical Procedure For Diphenylketene Cycloaddition With Cyclic Carbodiimides.

(a) Equal Molar Amounts of Ketene and Cyclic Carbodiimide. An 0.01 mol portion of diphenylketene was added to a stirred solution of 0.01 mol of the cyclocarbodiimide

in 10 ml of ether under a nitrogen atmosphere. The reaction mixture was stirred for an additional hour and the solvent removed under reduced pressure and the residue recrystallized from benzene and hexane to yield the β-lactams.

(b) 2:1 Molar Ratio of Ketene and Cyclic Carbodiimide. A solution of 0.01 mol of 1,3-diazacycloocta-1,2-diene in 30 ml of ether was added to a stirred solution of 0.02 mol of diphenylketene in 5 ml of ether under a nitrogen atmosphere. The reaction mixture was stirred overnight and the solvent removed under reduced pressure. The residue was recrystallized from chloroform and hexane to give the 2:1 cycloaddition products.

Cycloaddition of diphenylketene With 1,3-Diazacyclo-octa-1,2-diene, 11a. There was obtained 2.8 g (93%) of 11a; m.p. 112-114° C; ir ($CDCl_3$) 2920, 1795, 1665, 1370 cm^{-1}; nmr, δ , 1.3-2.2 (m, 6 H), 3.45-4.0 (m, 2 H), 7.1-7.8 (m, 10 H).

Anal. Calcd. for $C_{20}H_{20}ON_2$: C, 78.95; H, 6.58. Found: C, 79.08; H, 6.51.

Cycloaddition of Diphenylketene With 1,3-Diazacyclo-nona-1,2-diene, 11b. There was obtained 2.9 g (91%) of 11b; m.p. 128-130° C; ir ($CDCl_3$), 2920, 1795, 1680,

1350 cm^{-1}; nmr, δ, 0.9-1.95 (m, 8 H), 3.3-3.9 (m, 4 H), 6.9-7.7 (m, 10 H).

Anal. Calcd. for $C_{21}H_{22}ON_2$: C, 79.25; H, 6.92. Found: C, 79.11; H, 6.92.

Cycloaddition of Diphenylketene With 1,3-Diazacyclotetradeca-1,2-diene, 11c. There was obtained 3.5 g (91.5%) of 11c; m.p. 156.5-157.5° C; ir, ($CDCl_3$) 2900, 2840, 1790, 1665, 1430, 1380 cm^{-1}; nmr, δ, 0.34-3.0 (m, 18 H), 3.24-3.64 (m, 4 H), 7.2-7.4 (m, 10 H).

Anal. Calcd. for $C_{26}H_{32}ON_2$: C, 80.4; H, 8.35. Found: C, 80.28; H, 8.11.

Cycloaddition of a 2:1 Molar Ratio of Diphenylketene and 1,3-Diazacycloocta-1,2-diene, 12a. There was obtained 4.5 g (91%) of 12a; m.p. 236-238° C; ir ($CDCl_3$) 3020, 3010, 2920, 1720, 1430, 1380, 1160 cm^{-1}; nmr, δ, 1.0-1.6 (m, 6 H), 1.8-2.2 (m, 2 H), 3.2-3.7 (m, 2 H), 6.6-8.0 (m, 10 H).

Anal. Calcd. for $C_{34}H_{30}O_2N_2$: C, 81.92; H, 6.02. Found: C, 81.04; H, 5.85.

Cycloaddition of a 2:1 Molar Ratio of Phenylethylketene and 1,3-Diazacycloocta-1,2-diene, 12b. There was obtained 3.6 g (91%) of 12b; m.p. 271.5-273° C; ir ($CDCl_3$) 2920, 2860, 1740, 1440, 1370 cm^{-1}; nmr, δ, 1.03 (t, 6 H),

1.2-1.6 (m, 8 H), 2.11-2.73 (m, 4 H), 2.96-3.44 (m, 2 H), 7.2-7.5 (m, 10 H).

Anal. Calcd. for $C_{26}H_{30}O_2N_2$: C, 77.61; H, 7.46. Found: C, 77.32; H, 7.38.

Typical Procedure For the Cycloaddition of in situ Generated Ketenes With Cyclic Carbodiimides. A solution of 0.02 mol of freshly distilled acid chloride in 100 ml of dry hexane was added over a 2 hours period to a stirred solution of 0.02 mol of the cyclic carbodiimide and 0.04 mol of triethylamine in 150 ml of hexane under a nitrogen atmosphere. The resulting mixture was stirred an additional hour and the amine salt removed by filtration. The solvent was evaporated under reduced pressure and the residue recrystallized from benzene and hexane or benzene and 95% ethanol.

Cycloaddition of Phenylketene With 1,3-Diazacyclotetradeca-1,2-diene, 13a. There was obtained 2.9 g (94%) of 13a; m.p. 75-76° C; ir ($CDCl_3$), 2890, 2840, 1790, 1660, 1430, 1380 cm^{-1}; nmr, δ, 0.84-2.2 (m, 18 H), 2.93-3.55 (m, 2 H), 3.35 (t, 2 H), 4.87 (s, 1 H), 7.1-7.4 (m, 5 H).

Anal. Calcd. for $C_{20}H_{28}ON_2$: C, 80.00; H, 8.64. Found: C, 79.86; H, 8.79.

Cycloaddition of Dichloroketene With 1,3-Diazacyclo-octa-1,2-diene, 14a. There was obtained 1.5 g (62%) of 14a; m.p. 267.5-268.5° C; ir (DMSO), 2920, 2860, 1660 (broad), 1500, 1250 cm^{-1}; nmr, δ, 1.0-1.6 (m, 6 H), 2.9-3.3 (m, 4 H), 7.9-8.3 (m, 2 H); Mass Spect., M/e 238, 155, 140, 127, 112, 110, 100, 70, 68, 41.

Anal. Calcd. for $C_8H_{12}O_2N_2Cl_2$: C, 40.16; H, 4.02. Found: C, 40.19; H, 5.12.

Cycloaddition of Dichloroketene With 1,3-Diazacyclo-tetradeca-1,2-diene, 14b. There was obtained 2.1 g (65%) of 14b; m.p. 109.5-110° C; ir ($CDCl_3$) 3320, 2920, 2845, 1688, 1510, 1455 cm^{-1}; nmr, δ, 1.1-2.1 (m, 1 H), 3.4 (t, 2 H), 3.88 (t, 2 H), 6.6 (s, 1 H), 7.5-8.3 (m, 1 H).

Anal. Calcd. for $C_{14}H_{24}O_2N_2Cl_2$: C, 59.50; H, 8.93. Found: C, 59.34; H, 8.95.

N-Diphenylacetyl-1,3-diazacyclooctan-2-one, 16. A solution containing 0.01 mol of diphenylketene in 50 ml of benzene was added to a solution of 0.01 mol of 1,3-diazacycloocta-1,2-diene in 100 ml of benzene at 0° C under a nitrogen atmosphere. This reaction solution was quenched with 100 ml of water after 4 min. The solvent and water were evaporated under reduced pressure and the residue dissolved in 100 ml of chloroform. The chloroform solution was extracted several times with dil. NaOH

solution. The chloroform solution was then evaporated to dryness with a rotatory evaporator and the residue was fractionally recrystallized from chloroform and hexane to yield 0.55 g (17%) of 16; m.p. 178-180° C; ir (DMSO) 1640 cm^{-1} (broad, C=O); nmr, δ , 1.2-1.9 (m, 6 H), 3.0-3.7 (m, 4 H), 5.0 (s, 1 H), 5.2-5.6 (m, 1 H), 7.0-7.4 (m, 10 H).

Anal. Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.51; H, 6.88. Found: C, 75.06; H, 7.44.

Part III. A New Synthesis For Substituted Coumarins

All of the substituted coumarins were made from the cycloadditions of chloroketenes with substituted (Z)-2-methoxymethylene cyclohexanones and (Z)-2-methoxymethylene cyclohexanone followed by zinc reduction and dehydrogenation. (12) The synthesis of α-methoxymethylene cyclohexanones is easily accomplished from cyclohexanones and ethyl formate as previously described. (11)

General Procedure for Substituted (Z)-2-Methoxymethylenecyclohexanone. (12) A solution of 24.2 g (0.175 mol) of anhydrous potassium carbonate, 15 g (0.119 mol) of dimethylsulfate and 0.117 mol of freshly distilled corresponding α-hydroxymethylenecyclohexanone (11) in 300 ml of dry acetone was refluxed for 24 hours. On cooling, the

mixture was filtered, concentrated and distilled to give corresponding α-methoxymethylenecyclohexanone.

General Procedure For Chloroketene Cycloaddition With α-Methoxy-α,β-unsaturated Ketones (3,4-dihydro-2-pyranones). A solution of 0.0125 mol of the freshly distilled chlorinated acetyl chloride in 50 ml of dry hexane was added over a 2 hour period to a stirred, refluxing solution of 0.0125 mol of the α-methoxy-α,β-unsaturated ketone and 0.0125 mol of trimethylamine in 100 ml of dry hexane under a nitrogen atmosphere. The resulting mixture was stirred for an additional 30 minute period. The amine salt was then removed by filtration, and the filtrate was concentrated on a rotatory evaporator. The residue was not stable at room temperature and treated with zinc in acetic acid without further purification.

Zinc/Acetic Acid Reduction (tetrahydrocoumarins). To the concentrated residue from the chloroketene cycloadditions was added 40 ml of acetic acid and 2 ml of water. The mixture was stirred at room temperature, and 4 g of powdered zinc was added in one portion. The mixture was then stirred for 24 hours. Excess zinc and the zinc salt were filtered and washed with 40 ml of

chloroform. The filtrate was placed in a separatory funnel and washed several times with water until the aqueous layer tested neutral with litmus paper. The chloroform layer was dried over magnesium sulfate and concentrated to give the corresponding 5,6,7,8-tetrahydrocoumarins.

3-Chloro-5,6,7,8-tetrahydrocoumarin, 22a. From dichloroacetyl chloride, (Z)-2-methoxymethylene cyclohexanone and triethylamine there was obtained, after zinc reduction and recrystallization, 1.1 g (48%) of compound 22a; m.p. 124-125° C; ir ($CDCl_3$) 1700 cm^{-1} (C=O), 1625 cm^{-1} (C=C); nmr, δ, 1.5-1.9 (m, 4 H), 2.1-2.6 (m, 4 H), 7.3 (s, 1 H).

3-Phenyl-5,6,7,8-tetrahydrocoumarin, 22b. From phenylchloroacetyl chloride, (Z)-2-methoxymethylene cyclohexanone and triethylamine there was obtained, after zinc reduction and recrystallization, 1.5 g (52%) of compound 22b; m.p. 116-117° C; ir ($CDCl_3$) 1690 cm^{-1} (C=O), 1625 cm^{-1} (C=C); nmr, δ, 1.4-1.7 (m, 4 H), 2.1-2.6 (m, 4 H), 7.0-7.6 (m, 6 H).

8-Methyl-3-phenyl-5,6,7,8-tetrahydrocoumarin, 22c. From phenylchloroacetyl chloride, (Z)-2-methoxymethylene-4-methyl cyclohexanone and triethylamine there was obtained, after zinc reduction and recrystallization,

1.7 g (58%) of compound 22c; m.p. 112-114.5° C; ir ($CDCl_3$) 1685 cm^{-1} (C=O), 1622 cm^{-1} (C=C); nmr, δ , 1.0-3.0 (m, 10 H), 7.0-7.9 (m, 6 H).

6-Methyl-3-phenyl-5,6,7,8-tetrahydrocoumarin, 22d. From phenylchloroacetyl chloride, (Z)-2-methoxymethylene-6-methyl cyclohexanone and triethylamine there was obtained, after zinc reduction and recrystallization, 1.1 g (44%) of compound 22d; m.p. 117-117.5° C; ir ($CDCl_3$) 1685 cm^{-1} (C=O), 1622 cm^{-1} (C=C); nmr, δ , 1.0 (d, 3 H), 1.2-1.8 (m, 7 H), 7.1 (s, 1 H), 7.2-7.8 (m, 5 H).

3-Chloro-6-methyl-5,6,7,8-tetrahydrocoumarin, 22e. From dichloroacetyl chloride, (Z)-2-methoxymethylene-6-methyl cyclohexanone there was obtained, after zinc reduction and recrystallization, 1.65 g (55%) of compound 22e; m.p. 94.5-96° C; ir 1700 cm^{-1} (C=O), 1622 cm^{-1} (C=C); nmr, δ , 1.1 (d, 3 H), 1.3-2.8 (m, 7 H), 7.3 (s, 1 H).

General Procedure For Dehydrogenation of Tetrahydrocoumarins (substituted coumarins). A solution of 1 g of the 5,6,7,8-tetrahydrocoumarin in 200 ml of chlorobenzene was refluxed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone for 18 hours. The mixture was filtered and the solvent removed under reduced pressure. The

residue was purified by chromatography on a column of acidic alumina upon elution with hexane/ethyl acetate (1:1) to yield the substituted coumarin.

3-Chlorocoumarin, 23a. (12) From 1 g (0.0054 mol) of 3-chloro-5,6,7,8-tetrahydrocoumarin and 3.69 g (0.016 mol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone there was obtained 0.39 g (41%) of 23a; m.p. 129.5-131° C; ir ($CDCl_3$) 1700 cm^{-1} (C=O), 1600 cm^{-1} (C=C); nmr, δ , 7.20-7.67 (m, 4 H), 7.88 (s, 1 H).

Anal. Calcd. for $C_9H_5O_2Cl$: C, 59.83; H, 2.77. Found: C, 59.43; H, 2.73.

3-Phenylcoumarin, 23b. (12) From 1 g (0.0044 mol) of 3-phenyl-5,6,7,8-tetrahydrocoumarin and 3.01 g (0.013 mol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone there was obtained 0.43 g (44%) of 23b; m.p. 107.5-109° C; ir ($CDCl_3$) 1695 cm^{-1} (C=O), 1600 cm^{-1} (C=C); nmr, δ, 7.23-7.70 (m, 9 H), 7.80 (s, 1 H).

Anal. Calcd. for $C_{15}H_{10}O_2$: C, 79.51; H, 6.02. Found: C, 79.28; H, 6.26.

8-Methyl-3-phenylcoumarin, 23c. From 1 g (0.0042 mol) of 8-methyl-3-phenyl-5,6,7,8-tetrahydrocoumarin and 2.85 g (0.013 mol) of 2,3-dichloro-5,6-dicyano,1,4-benzoquinone there was obtained 0.45 g (45.3%) of 23c;

m.p. 112-114° C; ir ($CDCl_3$) 1695 cm^{-1} (C=O), 1595 cm^{-1} (C=C); nmr, δ , 2.47 (s, 3 H), 7.02-7.70 (m, 9 H).

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.11. Found: C, 80.49; H, 4.99.

3-Chloro-6-methylcoumarin, 23d. From 1 g (0.005 mol) of 3-chloro-6-methyl-5,6,7,8-tetrahydrocoumarin and 3.43 g (0.015 mol of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone there was obtained 0,40 g (40.2%) of 23d; m.p. 121-123° C; ir ($CDCl_3$) 1720 cm^{-1} (C=O), 1600 cm^{-1} (C=C); nmr, δ , 2.3 (s, 3 H), 7.0-7.5 (m, 3 H), 7.7 (s, 1 H).

Anal. Calcd. for $C_{10}H_7ClO_2$: C, 61.70; H, 3.60. Found: C, 61.97; H, 3.63.

6-Methyl-3-phenylcoumarin, 23e. From 1 g (0.0044 mol) of 6-methyl-3-phenyl-5,6,7,8-tetrahydrocoumarin and 3.1 g (0.013 mol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was obtained 0.41 g (42.2%) of 23e; m.p. 147-147.5° C; ir ($CDCl_3$) 1695 cm^{-1} (C=O), 1595 cm^{-1} (C=C); nmr, δ , 2.3 (s, 3 H), 7.0-7.9 (m, 9 H).

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.11. Found: C, 81.10; H, 4.87.

6-Methyl-4-methoxy-3-phenylcoumarin, 23f. A 1 g portion of the cycloadduct of phenylchloroketene and 4-methyl-2-methoxymethylenecyclohexanone was refluxed

with 2.25 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in chlorobenzene for 18 hours. The mixture was filtered and dried under reduced pressure. The residue was passed through a column of acidic alumina by elution with hexane/ethyl acetate (1:1) to yield 6-methyl-4-methoxy-3-chloro-3-phenyl-3,4-dihydrocoumarin. This compound was refluxed with 2 ml of triethylamine in 60 ml of benzene for 24 hours. The amine salt was removed by filtration the solvent evaporated under reduced pressure. The residue was recrystallized from 95% ethanol and benzene to give 0.36 g (41%) of 23f; m.p. 156.5-158° C; ir ($CDCl_3$) 1685 cm^{-1} (C=O), 1595 cm^{-1} (C=C); nmr, δ , 2.4 (s, 3 H), 3.45 (s, 3 H), 7.0-7.6 (m, 6 H).

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.69; H, 5.26. Found: C, 76.64; H, 5.11.

CHAPTER BIBLIOGRAPHY

1. Taylor, E.C., McKillop, A., Hawks, G.H., Org. Syn., 52, 36 (1972).

2. Lucius, A.B., Harry, E., Org. Syn., Coll. Vol. 1, 80 (1943).

3. Sprung, M.M., Chem. Rev., 26, 297 (1940).

4. Layer, R.W., Chem. Rev., 63, 489 (1963).

5. Grewe, R., Hamann, R., Jacobsen, G., Nolte, E., Riecke, K., Ann. Chem., 581, 85 (1953).

6. Benson, R.E., Cairns, T.L., Org. Syn., Coll. Vol. IV, Wiley, New York, 1963, p. 588.

7. Lussi, H., Ang. Chimia, 27, 65 (1973).

8. Behringer, H., Meier, H., Annalen, 607, 67 (1957).

9. Ulrich, H., Tucker, B., Richter, R., J. Org. Chem., 43, 1544 (1978).

10. Richter, R., Tucker, B., Ulrich, H., J. Org. Chem., 48, 1694 (1983).

11. Ainsworth, C., Org. Synth., 39, 27 (1959).

12. Brady, W.T., Agho, A.O., J. Org. Chem., 48, 5337 (1983).

*Aliqnat 336 is tricaprylmethylammonium chloride

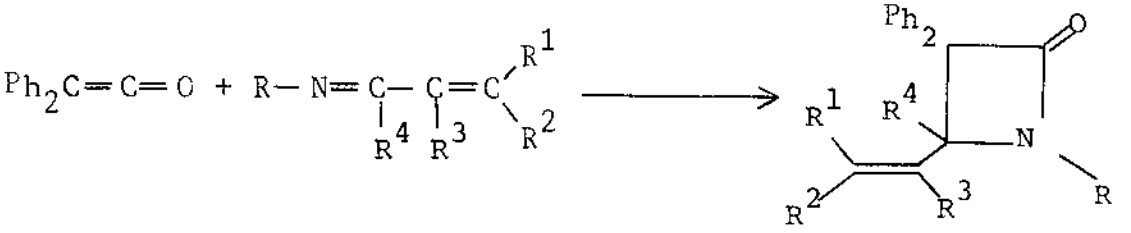
CHAPTER III

RESULTS AND DISCUSSION

Part I. The Cycloaddition of Ketenes With α,β-Unsaturated Imines to Yield β-Lactams And δ-Lactams

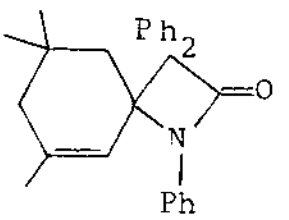
Imines are highly electron rich heteroolefins which have recently been widely used in the synthesis of β-lactams by cycloadditions with ketenes. (1, 2, 3, 4) The highly nucleophilic nature of the nitrogen atom on the imines makes them a very suitable ketenophile. The mechanism of these reactions has been established to occur by a two step process involving a dipolar intermediate. (5, 6) α,β-Unsaturated imines, conjugated heterodienes containing a carbon-carbon double bond adjacent to the imine function, offer the possibility of both (4+2) and (2+2) cycloaddition reactions with ketenes to yield β-lactams and/or δ-lactams.

The cycloaddition of freshly distilled diphenylketene with α,β-unsaturated imines occurs readily in good yields at ambient temperature to give the (2+2) cycloaddition products, 1a-1k. The reactions were monitored by infrared, and the solid products were easily isolated and purified by recrystallization.

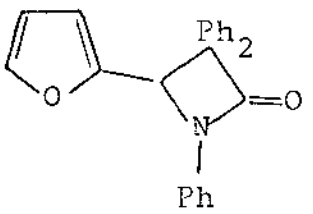


	R	R^1	R^2	R^3	R^4
1a.	Ph	Ph	H	H	H
1b.	Ph	Ph	H	CH_3	H
1c.	Ph	Ph	H	H	CH_3
1f.	i-pr	Ph	H	H	H
1g.	Ph	CH_3	CH_3	H	CH_3
1i.	C_6H_{11}	Ph	H	H	H
1j.	Ph	Ph	Ph	H	H
1k.	t-Bu	Ph	H	H	H

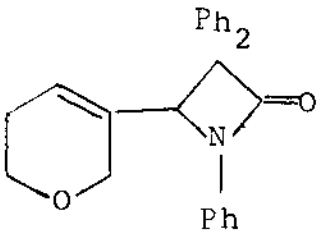
1e.



1d.



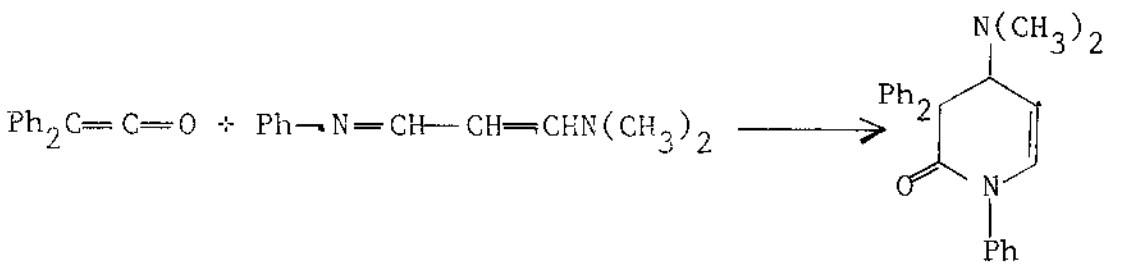
1h.



The infrared spectra of 1a-1k showed the characteristic β-lactam carbonyl absorption ranging from 1720-1740 cm^{-1}. It is well established in the literature that the carbonyl absorption of β-lactams in the infrared occurs in the 1740 cm^{-1} range. (7, 8) There were no bands in the infrared spectra between 1650-1700 cm^{-1} suggesting the absence of

the (4+2) cycloaddition products, the δ-lactams. The ^{1}H-nmr spectra reveals a signal at δ 5.0-5.5 which is the proton on the carbon of the 4- position of the β-lactam ring. Compounds 1a, 1i and 1k showed ABX patterns for the hydrogens on the 4-, and 5- and 6 positions which suggests a slight coupling between the hydrogens on the 4-, 5- and 6 positions. The ^{13}C-nmr spectra exhibited 3 signals in the completely decoupled spectra for the β-lactam ring as shown in Table I. Assignments were based on the off resonance decoupled spectra. All of these spectral characteristics are consistent with literature reports on similar compounds. (9, 10)

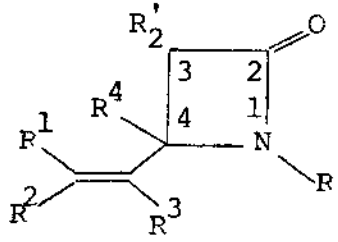
The α,β-unsaturated imines were selected so that the steric requirement on both the N substituent and substitution on the carbon skelton would be varied. A wide variation in the substituents on the imines did not give any (4+2) cycloaddition with diphenylketene except the cycloaddition of diphenylketene with the N-phenyl imine of 3-(dimethylamino)-2-propenal, as this imine yielded a (4+2) cycloaddition product, δ-lactam, 2a. The infrared spectrum of compound 2a revealed a typical



2a.

TABLE I

C-13 NMR Chemical Shifts and Assignments for β-Lactams 1a-l



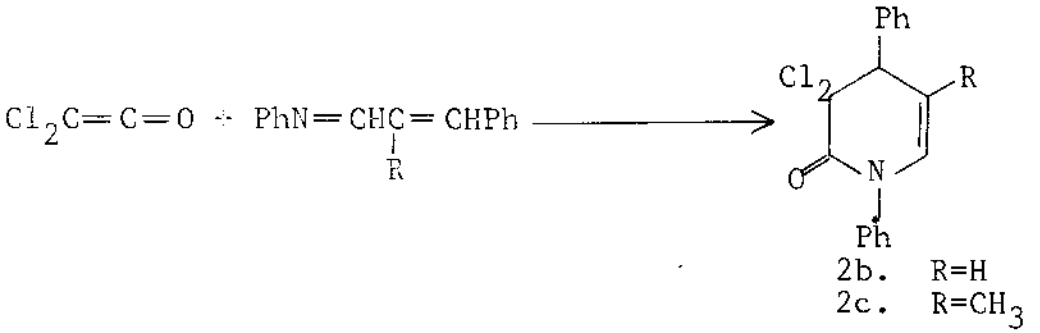
Compound	REFERENCE SOLVENT, $CDCl_3$ ~ 77.0 ppm			
	C-2	C-3	C-4	other C-atoms
1a	166.5	70.62	66.01	117.05, 123.9, 125.4, 126.1, 126.3, 126.7, 127.5, 128.5, 129.4, 129.8, 135.1, 135.7, 137.3, 137.9, 140.1
1b	166.6	70.50	70.13	14.4, 116.8, 124.0, 126.7, 127.2, 127.9, 128.5, 128.6, 130.6, 133.4, 136.5, 137.5, 138.0, 140.5
1c	166.9	68.82	74.56	20.7, 118.2, 124.1, 126.6, 127.0, 127.2, 128.0, 128.4, 128.6, 128.8, 129.0, 131.5, 133.2, 136.2, 137.2, 138.1, 138.8
1d	166.58	71.36	61.2	110.0, 110.6, 115.3, 122.3, 128.1, 125.3, 125.6, 125.7, 126.0, 126.8, 127.0, 135.4, 135.6, 138.1, 140.8, 146.5
1e	167.85	69.58	74.45	119.2, 124.2, 124.6, 126.8, 127.1, 127.6, 128.8, 129.4, 130.0, 136.3, 136.9, 138.5, 138.8

TABLE I (contd)

Compound	REFERENCE SOLVENT, $CDCl_3$ - 77.0 ppm			
	C-2	C-3	C-4	other C-atoms
1f	167.86	69.64	64.93	126.3, 126.9, 127.9, 128.1, 128.3, 133.8, 135.8, 137.8, 140.6
1g	167.09	68.87	75.1	10.0, 25.6, 27.6, 117.8, 123.9, 124.2, 126.5, 126.9, 127.2, 128.1, 128.3, 128.9, 137.4, 139.0, 139.1, 139.3
1h	166.4	70.7	66.1	25.0, 63.5, 65.1, 116.2, 124.1, 125.6, 127.3, 128.0, 128.1, 128.6, 129.0, 132.4, 137.5, 137.8, 140.6
1i	169.5	68.7	66.2	19.1, 37.7, 59.2, 39.6, 41.7, 112, 112.3, 112.4, 114.2, 116.5, 116.6, 117.2, 118.8, 128.3, 128.5, 146.3, 147.8
1j	166.5	73.0	64.9	109.2, 114.7, 116.4, 117.3, 117.8, 118.0, 118.1, 118.6, 118.8, 125.9, 126.7, 127.1, 128.1, 132.7, 148.6
1k	168.2	68.7	65.5	28.6, 54.7, 126.5, 127.0, 127.2, 128.0, 128.2, 128.5, 129.4, 133.4, 136.3, 138.2, 140.9
1l	157.72	84.0	69.4	117.4, 120.9, 125.3, 127.7, 128.3, 129.2, 129.7, 136.0, 137.7, 140.0, 151.4

δ-lactam carbonyl band at 1675 cm^{-1} which is consistent with the literature. (11) The completely decoupled ^{13}C-nmr spectrum, Table II, exhibited 5 resonances for the δ-lactam ring carbon atoms with the characteristic carbonyl carbon signal appearing at 170.56 ppm. The proton nmr and the elemental analysis are also consistent with the assigned structure.

The *in situ* generation of dichloroketene from dichloroacetyl chloride with triethylamine in the presence of the N-phenyl imine of cinnamaldehyde and the N-phenyl imine of -methylcinnamaldehyde resulted in the formation of the (4+2) cycloaddition products, the 3,4-dihydro-2-pyridones, 2b and 2c.

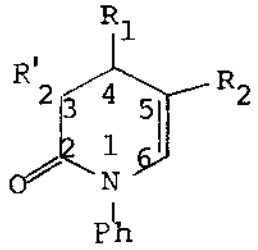


2b. R=H
2c. R=CH_3

The infrared spectra for compounds 2b and 2c revealed the carbonyl absorption in the range of 1680-1700 cm^{-1}. The presence of substituents such as chlorine atoms in the α-position of δ-lactams results in a shifting of the carbonyl absorption in the infrared to the 1690 cm^{-1} range.

TABLE II

C-13 NMR Chemical Shifts and Assignments for δ-Lactams 2a-d.

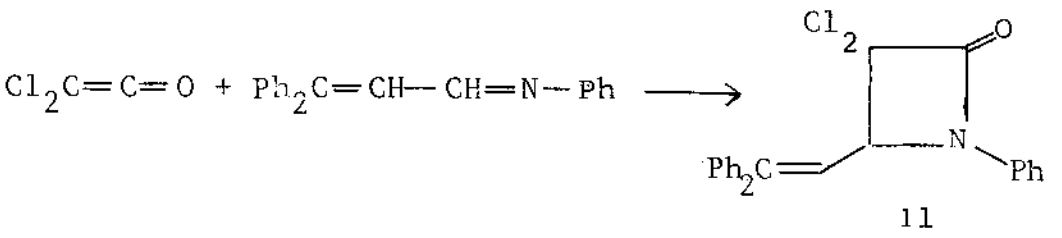


Compound	REFERENCE SOLVENT $CDCl_3$ - 77.0 ppm				
	C-2	C-3	C-4	C-5	C-6 and other C-atoms
2a	170.6	59.1	65.1	102.35	41.2, 125.6, 126.0, 126.1, 126.9, 127.2, 127.5, 127.8, 128.4, 128.8, 130.2, 131.1, 141.0, 141.6, 142.2
2b	159.2	84.7	53.7	107.6	123.8, 126.0, 126.4, 126.7, 127.4, 128.0, 128.6, 137.7, 138.2
2c	158.1	83.9	60.2	116.9	16.7, 122.9, 123.6, 125.7, 126.7, 126.8, 126.9, 127.4, 133.2, 138.2
2d	163.2	60.5	50.8	118.8	18.2, 125.4, 125.8, 126.7, 127.1, 127.8, 128.4, 128.8, 129.0, 135.0, 135.2, 140.1

The proton nmr spectrum of compound 2b revealed an ABX pattern for the hydrogenson the 4-, 5- and 6 positions. suggesting slight couplings between the three protons. Compound 2c exhibited two singlets at δ 3.7 and 5.85 for the hydrogens at the 4- and 6 position, and a singlet at δ 1.55 for the hydrogens on the methyl group. Both the infrared and proton nmr spectral data are consistent with reports in the literature on 2-pyridones. (12)

The ^{13}C-nmr spectra of 2b and 2c showed 5 resonances for the δ-lactam ring carbon atoms in the completely decoupled spectra as shown in Table II. The carbonyl carbon atom bands of 2b and 2c shift to 159 ppm probably due to the inductive effect of the two chlorine atoms in the 3-position of the 2-pyridones. (13)

The cycloaddition of <u>in situ</u> generated dichloroketene with the N-phenyl imine of β-phenylcinnamaldehyde resulted in the formation of the (2+2) cycloaddition product, the 2-azetidinone, 11. The structure of this cycloadduct was



11

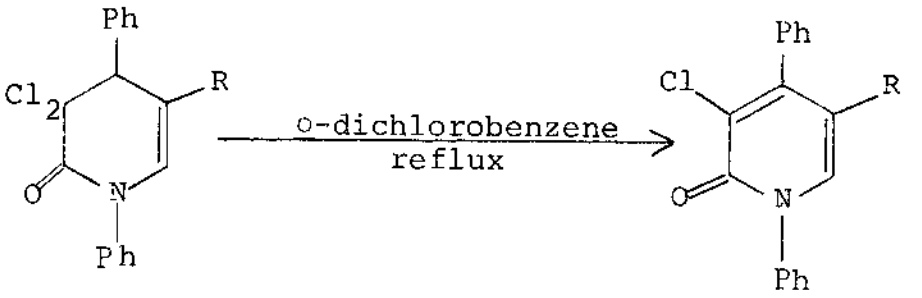
assigned on the basis of the carbonyl band in the infrared at 1785 cm^{-1} and the proton and ^{13}C-nmr spectrum (Table I) as well as the elemental analysis.

In an attempt to improve the yields of compound 2a-c, dichloroketene was generated by the zinc dechlorination of trichloroacetyl chloride instead of generation by the triethylamine dehydrochlorination of dichloroacetyl chloride. An α,β-unsaturated imine-zinc chloride salt was formed rather than obtaining the expected β- and δ-lactams. Clearly, the α,β-unsaturated imines reacted with zinc chloride before the cycloaddition occurred.

In all of the above described cycloadditions, an aliquot of the reaction mixture was removed after the reaction had occurred and analyzed by infrared spectroscopy. There were no cycloadducts in which both the 1740 and 1660 cm^{-1} bands in the infrared appeared. Hence, the cycloadditions occurred to give either the (2+2) or (4+2) cycloaddition products as far as could be determined. The yields of the dichloroketene cycloadditions were significantly lower (49-66%) than the diphenylketene cycloadditions (62-84%), and these cycloadditions were accompanied by the formation of dichloroketene polymer. Reactions of dichloroketene with other α,β-unsaturated imines did not result in isolable products.

In order to determine if the (4+2) cycloaddition products could be formed from the (2+2) cycloadducts, several of the (2+2) cycloadducts were refluxed in

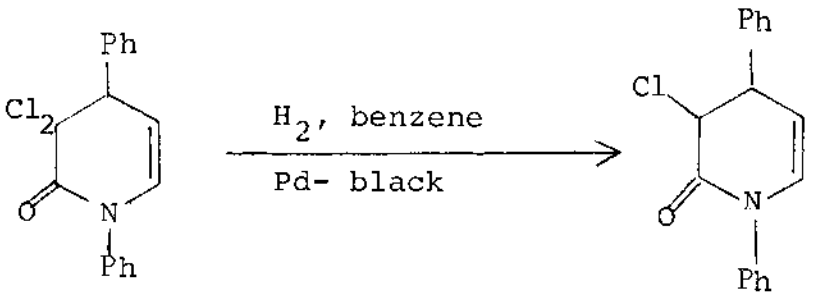
o-dichlorobenzene overnight with no change. However, refluxing the δ-lactams derived from dichloroketene in o-dichlorobenzene resulted in dehydrochlorination to yield the 2-pyridones 3a and 3b. Similar dehydrochlorination



3a. R=H
3b. R=CH_3

of α-chloro-δ-lactams have been reported. (14) Apparently, the conjugation is the driving force for the facile dehydrochlorination.

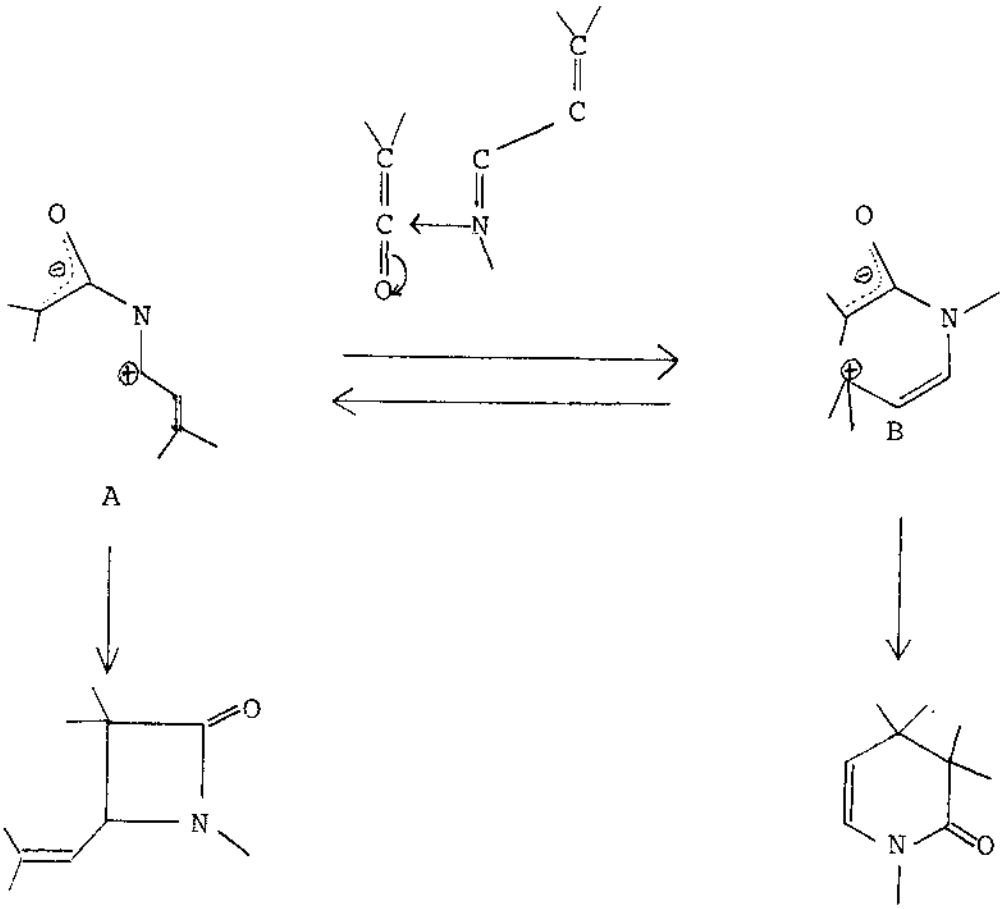
The hydrogenation of the 3,4-dihydro-2-pyridone, 2b, with palladium black resulted in the reductive removal of only one of the α-chlorine atoms to yield compound 2d which revealed a carbonyl band in the infrared spectrum at



2d

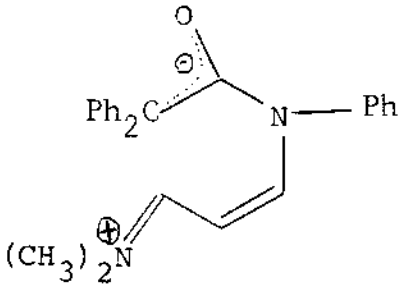
1685 cm^{-1}. The proton nmr spectrum showed two doublets at δ,3.45 and 4.85 which were the two hydrogens at the 3- and 4 position. The ^{13}C-nmr spectral data (Table II) is consistent with the assigned structure.

The most reasonable explanation of the above-described results is a two-step process involving a dipolar intermediate. The dipolar intermediate is apparently formed by the initial nucleophilic attack of the nitrogen atom of the imines on the electrophilic sp-hybridized carbon atom of the ketene molecule. Conformations of a dipolar intermediate that would lead to the (4+2) and the (2+2) cycloaddition products are shown as A and B below. If the steric interaction between the ketene substituents and the substituents in the 4- position of the imines is large enough to prevent ring-closure to give (4+2) cycloaddition products, δ-lactams, then the reaction occurs from A to yield the (2+2) cycloaddition products, β-lactams. Conversely, if there is not a large steric interaction, then ring closure would occur from B rather than A to give the more stable (4+2) cycloaddition products, δ-lactams. Apparently, in the cycloaddition of diphenylketene with α,β-unsaturated imines the large phenyl groups provide significant steric hindrance in B, and cycloaddition occurs from A rather than B, leading to



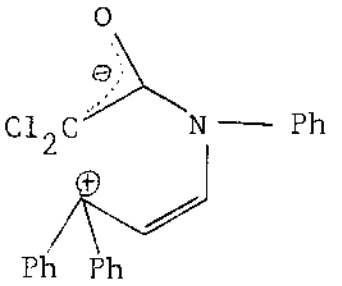
the (2+2) cycloaddition products. However, in the case of dichloroketene, the chlorine atoms do not present the steric problems that the phenyl groups do, and the cycloaddition generally yields the more stable (4+2) cycloadducts. It was not surprising that the cycloaddition of the N-phenyl imine of 3-(dimethylamino)-2-propenal with diphenylketene yields the (4+2) cycloadducts, δ-lactams. The strong electron-releasing ability of the dimethylamino group would be expected to cause

resonance structure C to make a strong contribution to the structure of the dipolar intermediate, thus leading to the (4+2) cycloadduct.



C

Other strong evidence for the two step mechanism is offered by the cycloaddition of the N-phenyl imine of β-phenylcinnamaldehyde and dichloroketene whereby the (2+2) cycloaddition product is formed rather than the (4+2) cycloadduct. Again, this result is expected when an examination of the conformation of the dipolar



intermediate that would lead to the (4+2) cycloadduct is made. The steric problems for ring closure parallel the above-described case for the diphenylketene cycloadditions.

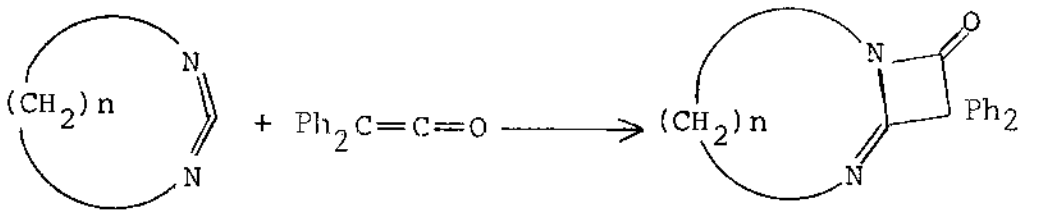
In summary, the results described in this study suggest that the cycloaddition of ketenes with α,β-unsaturated imines are primarily controlled by steric effects in the proposed dipolar intermediate. Since both β-lactams and δ-lactams are well known biologically active compounds (15, 16, 17) and continue to be of much interest, this study should provide a good synthetic pathway for δ-lactams and 4-vinyl-β-lactams.

Part II. The Cycloaddition of Ketenes With Cyclic Carbodiimides

Ketene and carbodiimides was reported to undergo a (2+2) cycloaddition reaction to yield β-iminonyl-β-lactams. (18, 19) Treatment of the carbodiimides with an excess of diphenylketene did not yield any isolable 2:1 cycloaddition products. Recently, cyclocarbodiimides have been prepared from commercially available lactams by treatment with dimethylsulfate, hydroxylamine, methanesulfonyl chloride followed by a Tiemann Rearrangement with a ring enlargement reaction. (20, 21) It was found that the ring size of the cyclocarbodiimide affects the stability and the reactivity of the carbodiimide moiety. A study of the cycloaddition of ketenes with which cyclocarbodiimides was expected to yield 2:1 and 1:1

cycloaddition products, as well as give some insight to ketene cycloadditions with the cyclo carbodiimide moiety.

The reaction of equal molar amounts of freshly distilled diphenylketene with cyclic carbodiimides occurred readily at room temperature to give (2+2) cycloaddition products, 11a,11b,11c, in 90+% yields. These solid products were easily isolated and purified

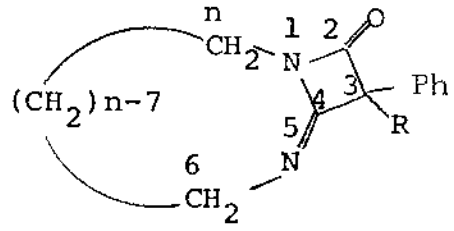


11a. n=5
b. n=6
c. n=11

by recrystallization. The infrared spectra revealed a strong band for the carbonyl group at 1790-1800 cm^{-1} and a strong band for the imino function at 1660-1698 cm^{-1}. The ^{13}C-nmr spectra showed a pair of carbon signals at 39.73-46.72, 43.5-45.3 and 39.13-49.23 ppm for the methylene carbons adjacent to the nitrogen atoms as shown in Table III. The proton nmr spectra also exhibited a multiplet at δ, 3.2-4.0 for the methylene protons adjacent

TABLE III

C-13 NMR Chemical Shifts and Assignments for Cyclo-β-iminoyl-β-lactams, 11a-c, 13.

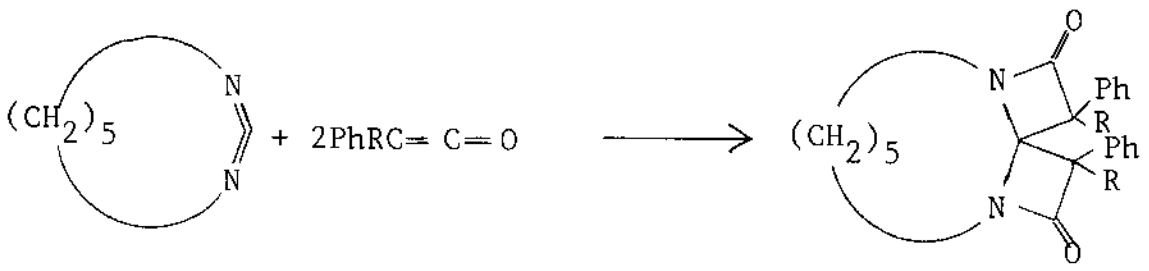


11a. n=10, R=ph
11b. n=11, R=ph
11c. n=16, R=ph
13. n=16, R=H

Compound	REFERENCE SOLVENT $CDCl_3$ - 77.0 ppm					
	C-2	C-3	C-4	C-6	C-n	other C-atoms
11a	170.6	70.98	155.3	46.72	39.73	21.9, 27.7, 29.4, 126.6, 127.4, 128.4, 137.4
11b	171.76	70.76	152.6	45.3	43.3	22.3, 25.9, 30.2, 31.5, 126.6, 127.7, 128.3, 137.3
11c	170.8	76.08	153.1	49.3	39.1	22.9, 24.6, 24.8, 25.0, 25.4, 25.8, 26.0, 28.8, 127.9, 128.1, 128.7, 136.1
13	168.7	62.2	152.1	50.4	39.1	23.5, 24.5, 24.9, 25.5, 25.8, 26.2, 28.7, 127.6, 127.9, 128.9, 131.5

to nitrogen atoms. Both the proton and ^{13}C-nmr spectra are consistent with literature reports on similar structures. (12)

The reaction of a 2:1 molar ratio of diphenyl- and phenylethylketenes with 1,3-diazacycloocta-1,2-diene slowly gave a 2:1 cycloaddition product, 12a and 12b, in 91+% yield as illustrated below. The structure of 12a and 12b



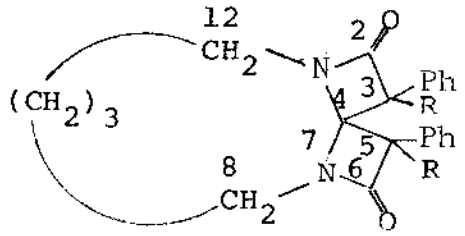
12a. R=Ph

12b. R=Et

were assigned on the basis of the carbonyl bands at 1720-1740 cm^{-1} and no bands in the 1600-1700 cm^{-1} range for the imino group. The ^{13}C-nmr spectra revealed only one signal at 39-41 ppm for the two methylene groups adjacent to the nitrogen atoms. The ^{13}C-nmr data for compounds 12a and 12b are shown in Table IV. It is interesting to note that the reaction of a 2:1 molar ratio of diphenylketene and 1,3-diazacyclotetradeca-1,2-diene resulted in only the 1:1 cycloaddition product, 11c. Apparently, the greater ring strain in 11a is manifested in a greater

TABLE IV

C-13 NMR Chemical Shifts and Assignments for di-β-lactams, 12a,b.



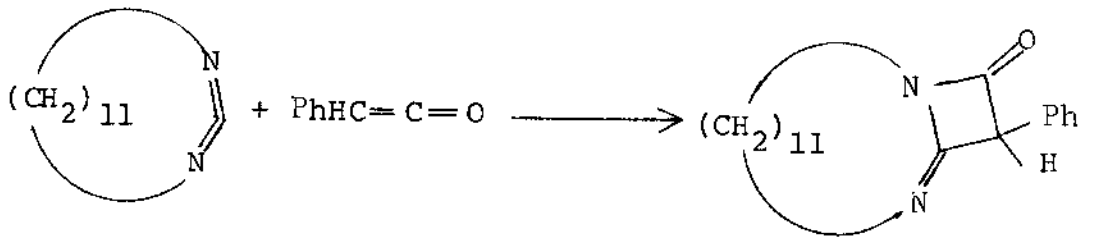
12a. R=Ph

12b. R=Et

Compound	REFERENCE SOLVENT $CDCl_3$ - 77.0 ppm				
	C-2+C-6	C-3+C-5	C-4	C-n+C-8	other C-atoms
12a	169.7	72.99	90.7	41.08	23.8, 25.1, 126.5, 127.5, 127.6, 127.9, 128.3, 128.5, 135.3, 136.2
12b	169.96	70.06	87.7	39.4	9.29, 24.4, 24.8, 31.3, 127.4, 128.5, 136.2

reactivity of the residual carbon nitrogen double bond toward a second molecule of ketene as compare to 11c.

The <u>in situ</u> generation of an equimolar amount of phenylketene by the triethylamine dehydrochlorination of phenylacetyl chloride in the presence of 1,3-diazacyclotetradeca-1,2-diene resulted in the formation of the 1:1 cycloaddition product, 13. The infrared spectra of this cycloadduct revealed a β-lactam carbonyl carbon atom band

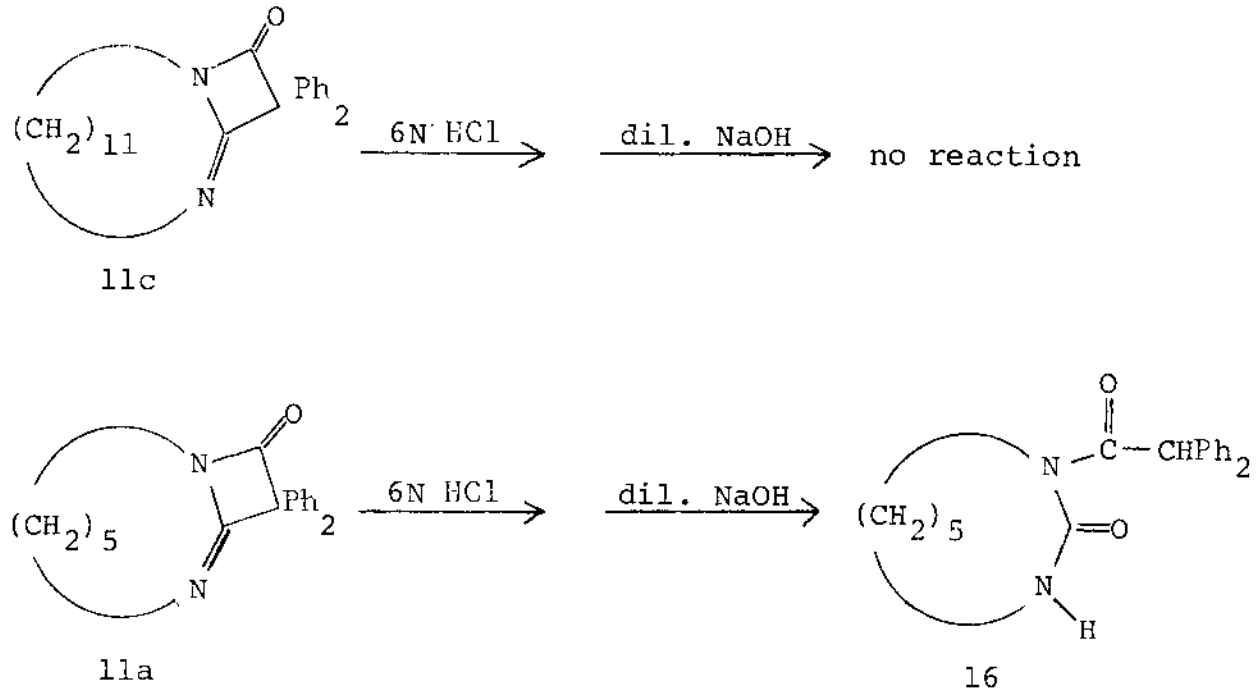


13

at 1790 cm^{-1}. The ^{13}C-nmr spectrum of 13 showed a pair of carbon signals at 50.4-39.13 ppm which are the two methylene groups adjacent to the nitrogen atoms. The proton nmr spectrum and elemental analysis are also consistent with the assigned structure.

The reaction of 13 with additional phenylketene did not give any isolable 2:1 cycloadduct. This result is consistent with the results observed on the cycloaddition of diphenylketene and 1,3-diazacyclotetradeca-1,2-diene. Thus, the cycloaddition of less ring strained cyclocarbodiimides with excess ketenes only yields the 1:1

cycloaddition products. In order to get further evidence of this ring strain argument, compound 11c was stirred with 100 ml of 6N hydrochloric acid for 24 hours with no change. However, stirring compound 11a with 100 ml 6N hydrochloric acid resulted in the formation of N-diphenylacetyl-1,3-diazacyclooctan-2-one, 16. Apparently, the



11c

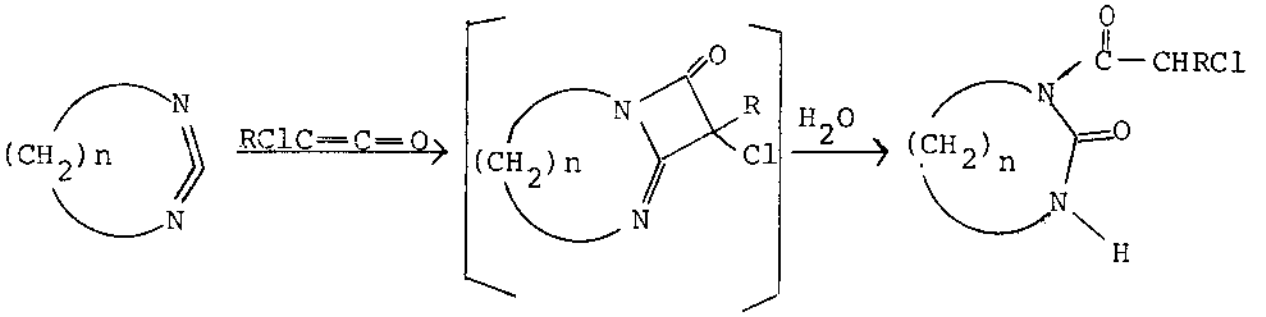
11a

16

higher the ring strain of the 1:1 cycloadducts of ketenes with cyclocarbodiimides, the higher the reactivity of the second carbon nitrogen double bond of the cycloadducts.

The cycloaddition of *in situ* generated dichloro- and methylchloroketenes in the presence of 1,3-diazacyclotetradeca-1,2-diene and 1,3-diazacycloocta-1,2-diene resulted in the formation of only the 1:1 cycloadducts,

14a, 14b, and 14c in yields ranging from 60-80%. The ir spectra of these crude products revealed a β-lactam carbonyl band at 1780 cm^{-1}. In an attempt to purify these compounds by recrystallization from benzene and 95% ethyl alcohol, the ring opened hydrolysis products, 15a, 15b, and 15c were formed. Even standing exposed to the



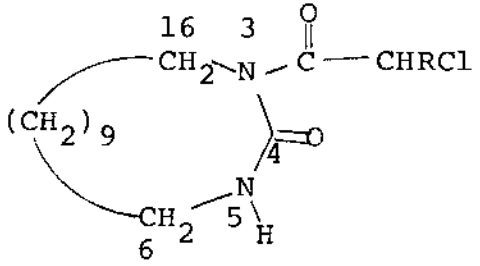
14a. n=5, R=Cl
14b. n=11, R=Cl
14c. n=11, $R=CH_3$

15a. n=5, R=Cl
15b. n=11, R=Cl
15c. n=11, $R=CH_3$

atmosphere at ambient temperatures results in this hydrolysis. The ring opened products do not have any band around 1790 cm^{-1} but do have a broad band at 1680-1690 cm^{-1}. The ^{13}C-nmr spectra (Table V) reveal a pair of triplets at 39-45 ppm and a doublet at 51-65 ppm which are the two methylene groups adjacent to the two nitrogen atoms and the carbon atom adjacent to the halogen atom respectively.

TABLE V

C-13 NMR Chemical Shifts and Assignments for Compound 14b and 14c.



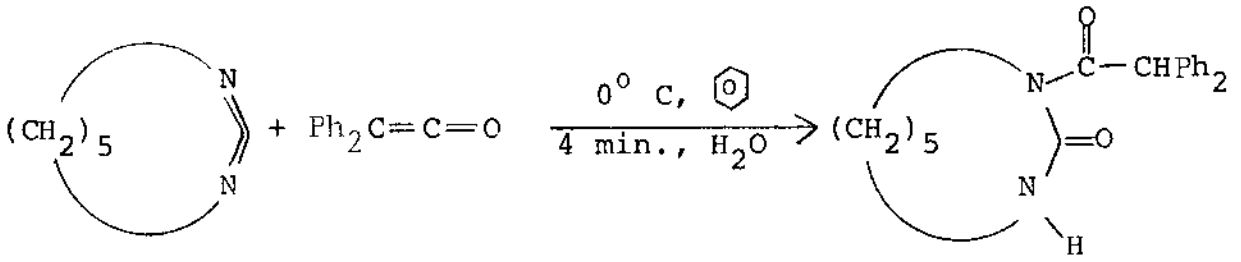
14b. R=Cl

14c. R=CH_3

Compound	REFERENCE SOLVENT , $CDCl_3$ - 77.0 ppm					
	C-1	C-2	C-4	C-6	C-16	other C-atoms
14b	65.8	166.5	153.7	45.04	40.22	23.3, 24.02, 24.94, 25.6, 25.9, 26.5, 26.8
14c	51.8	172.5	154.4	44.28	39.95	20.9, 23.2, 24.02, 25.37, 26.08, 26.89

It was very surprising that all the chloroketene cycloaddition products, including the 1,3-diazacyclotetradeca-1,2-diene, were so susceptible to hydrolysis. Apparently, the electron withdrawing affects of the chlorine atom(s) coupled with the strain involved in the carbon nitrogen double bond provided the impetus for the hydrolysis reaction.

The cycloadditions of ketenes with carbodiimides has been demonstrated to occur by a two-step process involving a dipolar intermediate. (19) The cycloaddition of ketenes with cyclocarbodiimides are also expected to occur by this two-step mechanism. In an attempt to trap the dipolar intermediate in these cycloaddition reactions, the reaction of diphenylketene with 1,3-diazacycloocta-1,2-diene in benzene at 0° C was quenched after four minutes by the addition of water. N-Diphenylacetyl-1,3-diazacyclooctan-2-one, 16 was isolated in a 17% yield. Diphenylacetic acid and 11a were also isolated from this reaction



16

mixture. Control experiments demonstrated that 16 was not produced from 11a under identical reaction conditions.

Also, it was demonstrated that 16 was not formed from the reaction of the ketene hydrolysis product, diphenylacetic acid, and the cyclic carbodiimide. Thus, the reaction of diphenylacetic acid and 1,3-diazacycloocta-1,2-diene resulted in the formation of 1,3-diaza-2-diphenylacetoxy-1-cyclooctene and diphenylacetic anhydride but no evidence for the formation of 16. Clearly, 16 was formed by the reaction of the dipolar intermediate with water. The high yield of the trapped compound, 16, is probably a reflection of the resonance stabilization of the dipolar intermediate.

In conclusion the cycloadditions involving the 8-membered ring cyclic carbodiimide, 1,3-diazacycloocta-1,2-diene, with ketenes yields both 1:1 and 2:1 cycloaddition products depending on the ratio of ketene and carbodiimide. However, the cycloadditions of the larger ring cyclic carbodiimide, 1,3-diazacyclotetradeca-1,2-diene, yielded only the 1:1 adducts even in the presence of an excess of ketene. It was reported that the cycloaddition of acyclic carbodiimides with ketenes yields only the 1:1 cycloaddition products. (18, 19) Clearly, these results suggest that the ring strain in the 1:1 cycloadducts of 1,3-diazacycloocta-1,2-diene is responsible for the addition of the second ketene molecule to the residual carbon nitrogen double bond.

Since penicillin was found to inhibit the growth of bacteria in 1929 (22), β-lactams have served as one of the most important synthetic goals for the organic chemist. Neither the bicyclo-β-iminoyl-β-lactams nor the tricyclo-di-β-lactams have previously been synthesized. Therefore, this study demonstrates a new synthetic method for the synthesis of bicyclic and tricyclic mono and di-β-lactams which should be very interesting for biological testing.

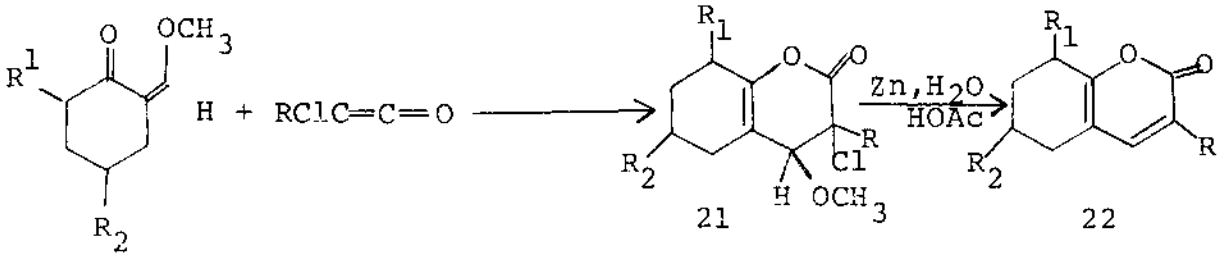
Part III. A New Synthesis for Substituted Coumarins

Coumarins are naturally occurring compounds which represent a challenging synthetic goal to organic chemists because of the useful and varied physiological activities (23, 24, 25) exhibited by these compounds and their use in fluorescent whiteners (26, 27), dyes (28, 29, 30), and photographic sensitizers. (31)

The synthesis of coumarins have been mostly through the traditional Von Pechmann and Knoevenagle methods. (32, 33) However, there have recently appeared some varied methods for the synthesis of these compounds. (34, 35, 36, 37) Benzocoumarins have recently been synthesized by an elegant three-step synthesis (38); the cycloaddition of chloroketenes with β-methoxymethylene-α-tetralone, the reductive removal of an α-chlorine

atom with the spontaneous loss of methanol, followed by dehydrogenation. This study involves an extension of this synthesis whereby coumarins are prepared by the cycloaddition of chloroketenes with (Z)-2-methoxymethylene cyclohexanone followed by zinc reduction and dehydrogenation.

The cycloaddition of <u>in situ</u> generated dichloro- and phenylchloroketenes with substituted (Z)-2-methoxymethylene cyclohexanones in refluxing hexane resulted in the formation of (4+2) cycloaddition products, the 3,4-dihydro-2-pyranones, 21 a-e. These cycloaddition products were not isolated, but treated with excess zinc in moist acetic acid to give the substituted 5,6,7,8-tetrahydrocoumarins, 22 a-e, in overall yields of about 50%. The tetrahydrocoumarins are solid products



21a.	R_1=H, R_2=H, R=1	22a.	R_1=H, R_2=H, R=1
21b.	R_1=H, R_2=H, R=Ph	22b.	R_1=H, R_2=H, R=Ph
21c.	R_1=CH_3, R_2=H, R=Ph	22c.	R_1=CH_3, R_2=H, R=Ph
21d.	R_1=H, R_2=CH_3, R=Cl	22d.	R_1=H, R_2=CH_3, R=Cl
21e.	R_1=H, R_2=CH_3, R=Ph	22d.	R_1=H, R_2=CH_3, R=Ph

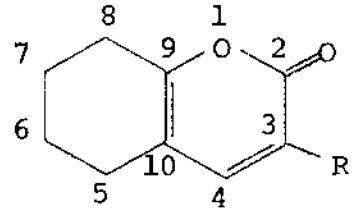
at room temperature and easily purified by recrystallization from 95% ethanol. It was very surprising to find when benzene, ether or tetrahydrofuran was used as the solvent instead of hexane in the cycloaddition step, no isolable products were isolated after the zinc reduction. After the cycloaddition reaction, an ir spectrum of the crude reaction mixture did not show the characteristic 2-pyranone band. Apparently, the greater polarity of these solvents relative to hexane increases the rate of polymerization of the chloroketenes.

The infrared spectra of compounds 22a-e revealed a carbonyl absorption in the 1685-1700 cm^{-1} range and an absorption at 1622-1625 cm^{-1} for the two carbon-carbon double bonds. The proton nmr spectra revealed a singlet for the vinyl protons at δ,7.1-7.3, and the methylene protons appeared at δ,1.0-3.0. The ^{13}C-nmr spectra, Table VI, revealed five resonances for the pyranone ring carbon atoms with the characteristic carbonyl carbon atom signal at 158-162 ppm. All these spectra are consistent with the assigned tetrahydrocoumarin as well as literature data on these compounds.

An attempt to dehydrogenate the tetrahydrocoumarins with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DDQ, in refluxing benzene was unsuccessful. Even refluxing over

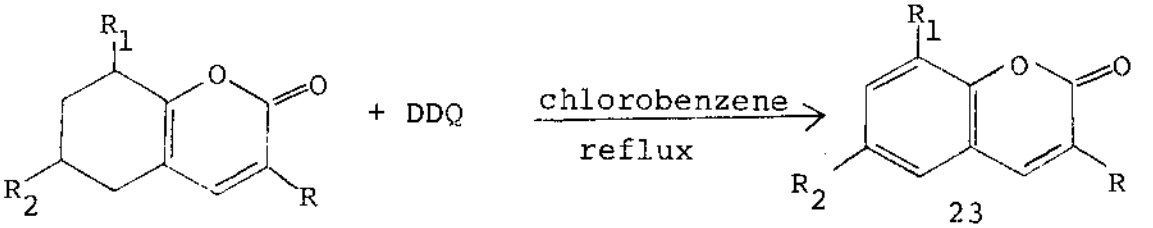
TABLE VI

C-13 NMR Chemical Shifts and Assignments for tetrahydrocoumarins, 22a-e.



Compound	REFERENCE SOLVENT, $CDCl_3$ - 77.0 ppm									
	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	other C-atoms
22a	158.4	118.5	142.8	24.8	20.9 or 21.2		26.6	112.4	158.1	
22b	161.7	124.1	142.7	25.0	21.2 or 21.6		26.8	112.7	158.5	127.2, 127.8, 134.6
22c	162.0	124.6	142.8	26.0	19.7	30.1	31.8	112.5	158.3	127.8, 127.9, 128.0, 134.8, 18.4
22d	161.6	124.2	142.6	33.3	27.9	29.2	26.7	112.2	158.3	20.6, 127.1, 127.8, 128.0, 134.7
22e	158.2	118.3	142.7	32.8	27.4	28.7	26.2	111.8	157.8	20.2

an extended period of time (72 hours) did not yield any coumarins. However, this dehydrogenation could be accomplished with DDQ by using chlorobenzene as the solvent. Refluxing in this solvent for 24 hours yielded the substituted coumarins in 50% yields.



22

23

23a. R_1=H, R_2=H, R=Cl

23b. R_1=H, R_2=H, R=Ph

23c. R_1=CH_3, R_2=H, R=Ph

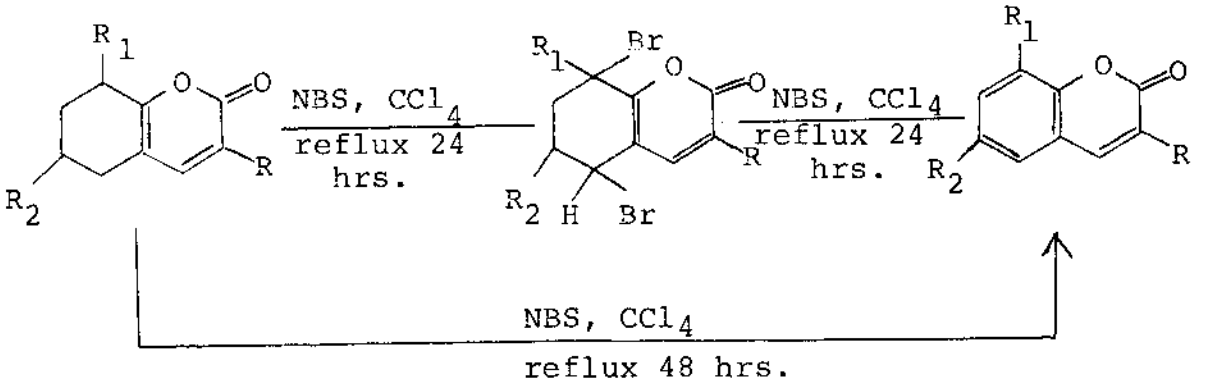
23d. R_1=H, R_2=CH_3, R=Cl

23e. R_1=H, R_2=CH_3, R=Ph

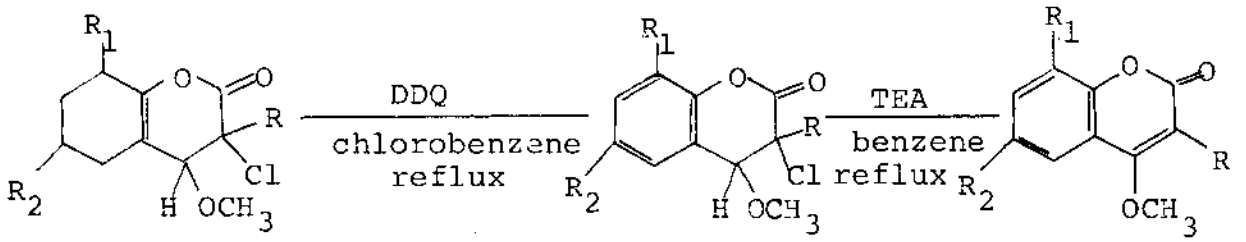
Apparently, the use of chlorobenzene allowed a higher reaction temperature which resulted in the dehydrogenation. The infrared spectra of the coumarins revealed a carbonyl band at 1695-1700 cm^{-1} and the proton nmr spectra exhibited typical absorptions of coumarin hydrogens at δ, 7.0-7.9. Compounds 23 c-e showed singlets at δ, 2.3-2.47 which are the protons on the methyl groups.

The hydrogen on the 4-position was centered around δ, 7.7-7.9, and occurred as a singlet. The completely decoupled ^{13}C-nmr spectra of compounds 23a and 23d, Table VII, exhibited 9 resonances for the ring carbons with the characteristic carbonyl carbon signal at 157-160 ppm. The phenyl group on compounds 23b, 23c and 23e revealed 4 signals at 127-134 ppm in the completely decoupled ^{13}C-nmr spectra which were not distinguishable from the carbon signals for the 5,6,7,8-positions as shown in Table VII. All of these spectra are consistent with literature reports on similar compounds. (39) All of the substituted coumarins are solid at room temperature and easily purified by chromatography on a column of acidic alumina by elution with hexane/ethyl acetate. The substituted coumarins were obtained in overall yields of about 30% for all three steps of this synthesis. In an attempt to find another method for accomplishing the dehydrogenation, the tetrahydrocoumarins were treated with N-bromosuccinimide and a trace amount of benzoyl peroxide in refluxing carbon tetrachloride for 24 hours to yield. 5,8-dibromo-5,6,7,8-tetrahydrocoumarins. The dibromo-tetrahydrocoumarins spontaneously underwent dehydrobromination to yield the coumarins upon refluxing for about 24 hours. Hence, it was found that treatment of the

tetrahydrocoumarins with N-bromosuccinimide and a trace of peroxide in carbon tetrachloride at reflux for 24 hours resulted in a 40-59% yield of the coumarins.



An alternate method to generate substituted coumarins from the chloroketene cycloaddition products (21a-e) is the treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in refluxing benzene. This procedure will yield the substituted 4-methoxycoumarin as demonstrated with 21e. The structure of the methoxycoumarin, 23f, was established



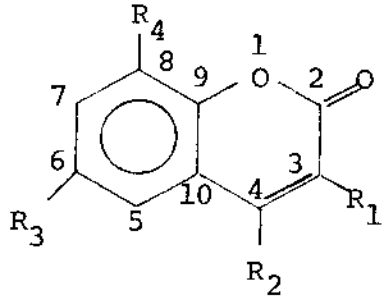
from the spectroscopic data. The infrared spectrum revealed the carbonyl absorption at 1685 cm^{-1}. The proton nmr spectrum revealed two singlets at δ, 2.4 and 3.45 for the protons of the methyl group at the 6-position and the protons of the methoxy group. The ^{13}C-nmr spectrum (Table VII) is consistent with the assigned structure with the carbonyl carbon absorption at 163.2 ppm. Dehydrogenations of the dichloroketene cycloaddition products with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone prior to loss of methanol were not successful. It is likely that the chloro substituents deactivate the systems toward dehydrogenation with DDQ. (40)

Several attempts were made to use monosubstituted ketenes in the cycloaddition step followed by the elimination of methanol and dehydrogenation. These syntheses did not give any isolable coumarins. The difficulty is probably in the cycloaddition step since it is well known that monosubstituted ketenes generally give lower yields of cycloaddition products.

Methylchloro- and other alkyl chloroketenes readily undergo (4+2) cycloaddition with substituted (Z)-2-methoxymethylene cyclohexanones, which could be converted to the 3- and 4- substituted coumarins derived from dichloroketene cycloaddition products, 3-chlorocoumarins,

TABLE VII

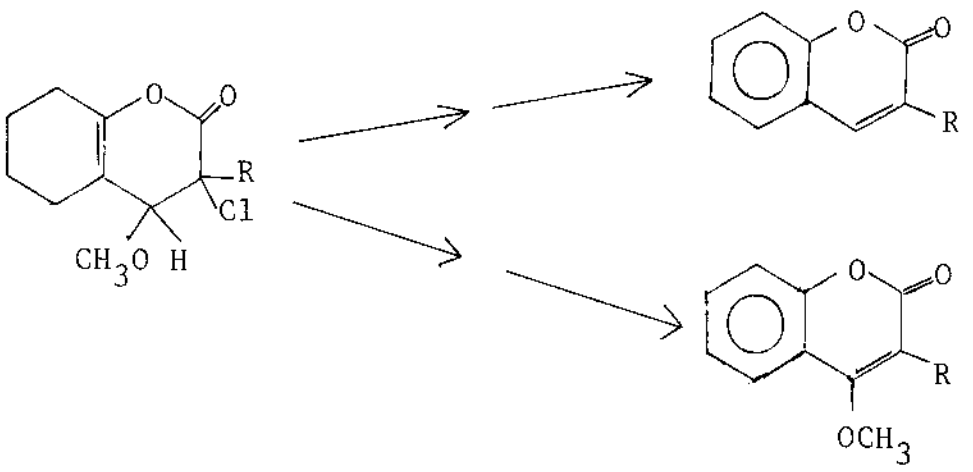
C-13 NMR Chemical Shifts and Assignments for Coumarins, 23a-f.



Compound	REFERENCE SOLVENT, $CDCl_3$ - 77.0 ppm					
	C-2	C-3	C-4	C-5	C-6	other C-atoms
23a	156.9	122.1	139.8	118.7	152.5	116.5, 124.9, 127.2, 131.7
23b	160.3	128.3	139.2	119.5	153.4	116.3, 119.6, 124.4, 127.8, 128.4, 128.7, 131.2, 134.6
23c	160.4	128.0	140.1	119.3	151.8	15.3, 124.0, 125.6, 125.7, 128.4, 128.5, 128.6, 132.6, 134.8
23d	157.0	121.8	139.8	118.3	150.5	20.44, 116.0, 126.8, 132.7, 134.8, 139.8

TABLE VII (contd)

Compound	REFERENCE SOLVENT, $CDCl_3$ - 77.0 ppm					
	C-2	C-3	C-4	C-5	C-6	other C-atoms
23e	157.0	121.8	139.8	118.3	150.5	20.49, 115.8, 127.8, 128.3, 128.5, 132.2, 133.9, 134.6
23f	162.7	117.1	163.2	110.8	150.4	20.66, 60.85, 115.8, 123.3, 127.9, 130.7, 132.3, 132.6, 133.5



also afford the potential to be converted to other functional groups in the 3- position of coumarins, i.e., 3-chlorocoumarins could be converted to the 3-alkoxy derivatives by reaction with metal alkoxides. (41)

In summary, the above described synthesis provides a method for the preparation of 3- and 4-substituted coumarins from commercially available starting compounds. The substituents on the cyclohexanone ring also provide the opportunity to introduce substituents in the benzene ring of the coumarin system. Therefore, this synthesis provides for various substitution in the 3-position of coumarin system, alkoxy substituents in the 4-position and the opportunity for substituents on the benzene ring of the coumarin.

CHAPTER BIBLIOGRAPHY

1. Sheehan, J.C., Corey, E.J., "The Synthesis of -Lactams", Adams, R., Ed., Organic Reactions, Vol. 9, p. 388, Wiley, New York, 1957.

2. Clarke, H.T., Robinson, J.R., "The Chemistry of Penicillin", Princeton University, press, 1949.

3. Cama, L.D., Christensen, B.G., J. Amer. Chem. Soc. 96, 7582 (1974).

4. Bachi, M.D., Vaga, J., J. Org. Chem., 44, 4393 (1979).

5. Nelson, D.A., Tetrahedron Letter, 2543 (1971).

6. Huisgen, R., Davis, B.A., Morikawa, M., Angew. Chem. Int. Ed., 7, 826 (1968).

7. Hall, D.M., J. Chem. Soc., 1603 (1948).

8. Staudinger, H., Jelagin, S., Chem. Ber., 44, 365 (1911).

9. Sheradsky, T., Zbaida, D., J. Org. Chem., 45, 2165 (1980).

10. Bender, D.R., Brennan, J., Rapoport, H., J. Org. Chem., 43, 3354 (1978).

11. Fitton, A.O., Frost, J.R., Houghton, P.G., Suschitzky, H., J. Chem. Soc., Perkin Trans. 1, 1450 (1977).

12. Moore, H.W., Hughes, G., Tetrahedron Letter, 23, 4003 (1982).

13. Levy, G.C., Lichter, R.L., Nelson, G.L., "C-13 NMR Spectroscopy", John Wiley and Sons, New York, 1980, p. 144.

14. Duran, F., Ghosez, L., Tetrahedron Letter, 245 (1970).

15. Abraham, E.P., Newton, G.G.F., Biochem. J., 79, 377 (1961).

16. Hodgkin, D.C., Maslen, E.N., Biochem. J., 79, 363 (1961).

17. Brown, A.G., Butterworth, D., Cole, M., Hanscomb, G., Hood, J.D., Reading, C., J. Antibiotics, 24, 668 (1976).

18. Brady, W.T., Dorsey, E., Parry, F.H., J. Org. Chem., 34, 2846 (1969).

19. Brady, W.T., Dorsey, E., J. Org. Chem., 35, 2732 (1970).

20. Ritcher, R., Tucker, B., Ulrich, H., J. Org. Chem., 48, 1694 (1983).

21. Ritcher, R., Tucker, B., Ulrich, H., J. Org. Chem., 43, 1544 (1978).

22. Fleming, A., Berit. J. Exp. Pathol., 10, 226 (1929).

23. Soinae, T.O., J. Pharm. Sci., 53, 231 (1964).

24. Arora, R.B., Mathur, C.B., Br. J. Pharmacol., 20, 29 (1963).

25. Ichibagase, H., J. Pharm. Soc. Jpn., 75, 1475 (1955).

26. Schlaepfer, H., German Patent (DOS) 2329991 (1974); as seen in Chem. Abst., 81, 51143 (1974).

27. Dorlars, A., Schellhammer, C.W., Schroeder, J., Angew. Chem. Int. Ed. Engl., 14, 665 (1975).

28. Drexhage, K.H., Reynolds, G.A., Opt. Commun., 13, 22 (1975).

29. Drexhage, K.H., Erikson, G.R., Hawks, G.H., Reynolds, R.G., Opt. Commun., 15, 399 (1975).

30. Drexhage, D.H., Topics in Applied Physics, Vol. 1, Dye Lasers, New York, Springer Verlage, 1973, p. p. 161.

31. Kandall, J.D., Waddington, H.R.J., Duffin, G.F., British Patent, 867592 (1962); as seen in Chem. Abst., 55, 21927 (1961).

32. Sethna, S., Phadke, R., Org. React., 7, 1 (1953).

33. Horning, E.C., Horning, M.G., Dimmig, D.A., Org. Synth., 3, 165 (1955).

34. Woods, L.L., Scapp, J., J. Org. Chem., 30, 312 (1965).

35. Bissel, E.F., Synthesis, 846 (1982).

36. Kraus, G.A., Pezzanite, J.O., J. Org. Chem., 44, 2480 (1979).

37. Tayler, R.T., Cassel, R.A., Synthesis, 672 (1983).

38. Brady, W.T., Agho, M., J. Org. Chem., 48, 5337 (1983).

39. Tantivatana, P., Ruangrungsi, N., Vaisiriroj, V., Lankin, D.C., Bhacca, N.S., Borris, R.P., Cordell, G.A., Johnson, L.F., J. Org. Chem., 48, 268 (1983).

40. Conley, R.A., Heindel, N.D., J. Org. Chem., 40, 3169 (1975).

41. Newman, M.S., Perry, C.Y., J. Org. Chem., 28, 116 (1963).

BIBLIOGRAPHY

1. Abraham, E.P., Newton, G.G.F., Biochem. J., 79, 377 (1961).

2. Ainsworth, C., Org. Synth., 39, 27 (1959).

3. Arora, R.B., Mathur, C.N., Br. J. Pharmacol., 20, 29 (1963).

4. Bachi, M.D., Vaga, J., J. Org. Chem., 44, 4393 (1979).

5. Behringer, H., Meier, H., Ann., 607, 67 (1957).

6. Bellus, D., Fisher, H.P., Greuter, H., Martin, P., Helv. Chim. Acta., 61, 1784 (1978).

7. Bellus, D., J. Amer. Chem. Soc., 44, 100 (1979).

8. Bellus, D., J. Org. Chem., 44, 1208 (1979).

9. Bender, D.R., Brennan, J., Rapoport, H., J. Org. Chem., 43, 3354 (1978).

10. Benson, R.E., Cairns, T.L., Org. Syn. Coll. Vol. IV, Wiley, New York, 1963, p. 588.

11. Bissel, E.R., Synthesis, 846 (1982).

12. Bose, A.K., Chiang, Y.H., Manhas, M.S., Tetrahedron Letters, 4091 (1972).

13. Bose, A.K., Manhas, M.S., Chiang, Y.H., Tetrahedron, 25, 4421 (1969).

14. Bose, A.K., Spiegelman, G., Manhas, M.S., Tetrahedron Letters, 3167 (1971).

15. Brown, A.G., Butterworth, D., Cole, M., Hanscomb, G., Hood, J.D., Readling C., J. Antibiotics, 24, 668 (1976).

16. Brady, W.T., Dorsey, E.D., J. Org. Chem., 34, 2846 (1969).

17. Brady, W.T., Hoff, E.F., Roe, R., Parry, F.H., J. Amer. Chem. Soc., 91, 5679 (1969).

18. Brady, W.T., Dorsey, E.D., J. Org. Chem., 35, 2732 (1970).

19. Brady, W.T., Synthesis, 8, 415 (1971).

20. Brady, W.T., Lloyd, R.M., J. Org. Chem., 44, 2560 (1979).

21. Brady, W.T., Lloyd, R.M., J. Org. Chem., 45, 2025 (1980).

22. Brady, W.T., Watts, R.D., J. Org. Chem., 45, 3525 (1980).

23. Brady, W.T., Tetrahedron, 37, 2949 (1981).

24. Brady, W.T., Lloyd, R.M., J. Org. Chem., 46, 1322 (1981).

25. Brady, W.T., Watts, R.D., J. Org. Chem., 46, 4047 (1981).

26. Brady, W.T., Agho, M.O., J. Org. Chem., 48, 5337 (1983).

27. Cama, L.D., Christensen, B.G., J. Amer. Chem. Soc., 96, 7582 (1972).

28. Clarke, H.T., Robinson, J.R., "The Chemistry of Penicillin", Princeton University Press, 1949.

29. Conley, R.A., Hindel, N.P., J. Org. Chem., 40, 3169 (1975).

30. Damrauer, R., Soucy, D., Winkler, P., Eby, S., J. Org. Chem., 45, 1315 (1980).

31. Dorlars, A., Schellhammer, C.W., Schroeder, J., Angew. Chem. Int. Ed., 14, 665 (1975).

32. Drexhage, K.H., Topics in Applied Physics, Vol. 1, Dye Lasers, New York, Springer Verlage, 1973, p. 161.

33. Drexhage, K.H., Reynolds, G.A., Opt. Commun., 13, 22 (1975).

34. Drexhage, K.H., Erikson, G.R., Hawks, G.H., Reynolds, R.G., Opt. Commu., 15, 399 (1975).

35. Fitton, A.O., Frost, J.R., Houghton, P.G., Suschitzky, H., J. Chem. Soc., Perkin Trans. 1, 1450 (1977).

36. Fleming A., Berit. J. Exp. Pathol., 10, 226 (1929).

37. Fleming, I., Chem. Ind. (Lond.), 449 (1975).

38. Fleming, I., Frontier Orbitals and Organic Chemical Reactions, Chichester-New York-Brisbane-Toronto, John Wiley, 1978.

39. Ghosez, L., Montaigne, R., Vanlierde, H., Dumay, F., Angewante Chemie Int. Ed. Engl., 7, 221 (1968).

40. Ghose, L., Duran, F., Tetrahedron Letters, 245 (1970).

41. Gomes, A., Joullie, M.M., Chem. Commu., 935 (1967).

42. Grewe, R., Hamann, R., Jacobsen, G., Nolte, E., Riecke, K., Ann. Chem., 581, 85 (1953).

43. Hanford, W.E., Sauer, J.C., Organic Reactions, edited by Adams, R., Vol. 3, Wiley Interscience, London, 1946, Chapter 3, p. 108.

44. Hasek, R.H., Gott, P.G., Martin, J.C., J. Org. Chem., 29, 2513 (1964).

45. Hassner, A., Fletcher, V.R., Hamon, D.P.G., J. Amer. Chem. Soc., 93, 264 (1971).

46. Hodgkin, D.C., Maslen, E.N., Biochem. J., 79, 363 (1961).

47. Hoffman, R.W., Angewandte Chemie Int. Ed. Engl., 11, 324 (1972).

48. Hopkinson, A.C., Csizmadia, I.G., Can. J. Chem., 52, 546 (1974).

49. Horning, E.C., Horning, M.G., Dimming, D.A., Org. Synth., 3, 165 (1955).

50. Houk, K.N., Strozier, R.W., Hall, T.A., Tetrahedron Letters, 897 (1974).

51. Huisgen, R., Davis, B.A., Morikawa, M., Angewandte Chemie Int. Ed. Engl., 7, 826 (1968).

52. Ichibagase, H., J. Pharm. Soc. Jpn., 75, 1475 (1955).

53. Kandall, J.D., Waddington, H.R.J., Duffin, G.F., British Patent, 867592 (1962); as seen in Chem. Abst., 55, 21927 (1961).

54. Kato, T., Yamamoto, Y., Takeda, S., Yakugaku Zasshi, 94, 884 (1974), as seen in Chem. Abst., 81, 37514u (1974).

55. Kirmse, W., Horner, L., Chem. Ber., 89, 2759 (1956).

56. Krans, G.A., Pezzanite, J.O., J. Org. Chem., 44, 2480 (1979).

57. Krapcho, A.P., Lesser, J.H., J. Org. Chem., 31, 2020 (1966).

58. Layer, R.W., Chem. Rev., 63, 489 (1963).

59. Levy, G.C., Lichter, R.L., Carbon-13 NMR Spectroscopy, John Wiley & Sons, New York, 1980, p. 144.

60. Lucius, A.B., Harry, E., Org. Syn., Coll. Vol. 1, John Wiley & Sons, New York, 1955, p. 80.

61. Luknitskii, F.I., Vovsi, B.A., Russ. Chem. Rev., 38, 487 (1969).

62. Lussi, H., Ang. Chimia, 27, 65 (1973).

63. Martin, J.C., Gott, P.G., Goodlett, V.W., Hasek, R.H., J. Org. Chem., 30, 4175 (1965).

64. Moore, H.W., Hughes, G., Tetrahedron Letters, 23, 4003 (1982).

65. Nelson, D.A., Tetrahedron Letters, 2543 (1971).

66. Nelson, P.A., J. Org. Chem., 37, 1447 (1972).

67. Newman, M.S., Perry, C.Y., J. Org. Chem., 28, 116 (1963).

68. Newman, M.S., Leggwate, A., J. Org. Chem., 33, 2144 (1968).

69. Pfleger, R., Jager, A., Chem. Ber., 90, 2460 (1957).

70. Pople, T.A., Gordon, M., J. Amer. Chem. Soc., 89, 4253 (1967).

71. Richter, R., Tucker, B., Ulrich, H., J. Org. Chem., 43, 1544 (1978).

72. Richter, R., Tucker, B., Ulrich, H., J. Org. Chem., 48, 1694 (1983).

73. Ruden, R.A., J. Org. Chem., 39, 3607 (1974).

74. Scarpati, R., Scia, D., Santacroce, C., Tetrahedron, 20, 2735 (1964).

75. Schlaepfer, H., German Patent (DOS) 2329991 (1974); as seen in Chem. Abst., 81, 51143 (1974).

76. Schenone, P., Bignardi, G., Evangelisti, F., Ann. Chim. (Rome), 61, 326 (1971).

77. Schenone, P., Bignardi, G., Bargagna, A., J. Heterocycl. Chem., 9, 1971 (1972).

78. Schenone, P., Bignardi, G., Bargagna, A., Evangelisti, F., J. Heterocycl. Chem., 13, 1105 (1976).

79. Schenone, P., Bignardi, G., Mosti, L., Evangelisti, F., J. Heterocycl. Chem., 13, 1201 (1976).

80. Schenone, P., Bargagna, A., Cafaggi, S., J. Heterocycl. Chem., 14, 249 (1977).

81. Schenone, P., Mosti, L., Menozzi, G., J. Heterocycl. Chem., 15, 181 (1978).

82. Schenone, P., Bargagna, A., Evangelisti, F., J. Heterocycl. Chem., 16, 93 (1979).

83. Schenone, P., Mosti, L., Menozzi, G., J. Heterocycl. Chem., 16, 913 (1979).

84. Sethna, S., Phadke, R., Org. Reaction, 7, 1 (1953).

85. Sheehan, J.C., Corey, E.J., The Synthesis of -Lactams, Adams, R., Ed., Organic Reaction, Vol. 9, Wiley, New York, 1957, p. 388.

86. Sheradsky, T., Zbaida, D., J. Org. Chem., 45, 2165 (1980).

87. Soimae, T.O., J. Pharm. Sci., 53, 321 (1964).

88. Sprung, M.M., Chem. Rev., 26, 297 (1940).

89. Staudinger, H., Jelagin, S., Chem. Ber., 44, 365 (1911).

90. Staudinger, H., "Die Ketene", Ferdinand Enke, (Stuttgart, 1912).

91. Tantivatana, P., Ruangrungsi, N., Vaisiriroj, V., Lankin, D.C., Bhacca, N.S., Borris, R.P., Cordell, G.A., Johnson, L.F., J. Org. Chem., 48, 268 (1983).

92. Taylor, E.C., Mikillop, H., Hawks, G.H., Org. Synth., 52, 36 (1972).

93. Tsunetsugn, T., Arimoro, K., Fueno, T., Furukawa, J., Die Makromolekulace Chemie. 112, 210 (1968).

94. Weimann, L.J., Christoffersen, R.E., J. Amer. Chem. Soc., 95, 2074 (1973).

95. Ward, R.S., The chemistry of ketenes, allenes and related compounds, part I edited by Patai, S., New York, Interscience Publishers, Inc., 1980, p. 223.

96. Zaitseva, G.S., Baukov, V.I., Matsev, V.V., Lutsenko, I.F., Zh. Obshch. Khim., 44, 1415 (1974).

97. Ziegler, E., Kleinberg, G., Monatsh Chem., 96, 1296 (1965).

98. Ziegler, E., Wimmer, Th., Mittelbach, H., Monatsh Chem., 99, 2128 (1968).