INVESTIGATIONS ON SYNTHETIC ROUTES TO STRUCTURAL MOIETIES RELATED TO THE NONADRIDE CLASS OF MOLD METABOLITES

by

EDWARD JACKSON CONE

A DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in
the Department of Chemistry in
the Graduate School of the
University of Alabama

UNIVERSITY, ALABAMA

1971

ACKNOWLEDGMENTS

I am grateful to Dr. Robert H. Garner for his encouragement and guidance in this research and for his flexibility in allowing me to pursue certain studies.

To Dr. A. Wallace Hayes I express my appreciation for his interest and cooperation in this investigation.

I express my gratitude to Dr. Billy W. Ponder for his generous gift of three samples used in this study.

A special note of thanks is due my wife, Eleanor, whose devotion and faith in my abilities have been very important to me.

Financial support during 1967-70 was provided by an NDEA Title IV Fellowship and by an assistantship from the University of Alabama during 1970-71.

TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

LIST OF TABLES

LIST OF ILLUSTRATIONS

"Die Schöpfung ist niemals vollendet."

--Immanuel Kant

CHAPTER I

INTRODUCTION

The purpose of this research was to investigate several synthetic schemes leading to structural moieties related to the nonadride class of mold metabolites. This dissertation describes the investigation of three such synthetic approaches to nine-membered ring derivatives along with related spectral and chemical studies of key intermediate compounds.

The first general approach involved bromination and oxidation studies of derivatives of cycloheptadiene. Several compounds were synthesized and characterized.

The second approach was an investigation of the reaction of cyclic five and six-membered ring enamino ketones with dimethyl acetylenedicarboxylate. The characterization of the products from these reactions is described and a mechanism for this type of reaction is proposed. Also, described are studies on spectral and chemical properties of enamino ketones. The results are interpreted in terms of nitrogen lone pair electron delocalization in this system. Two cyclooctadienone derivatives prepared by this approach were subjected to a variable temperature nmr study, and free energies of

activation for ring inversion were calculated from the data obtained.

The third synthetic approach to a nine-membered ring system was a study of the reaction of enamines with activated dienes. The results of six reactions of this type are described.

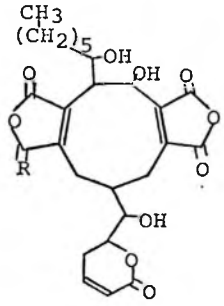
CHAPTER II

HISTORICAL BACKGROUND

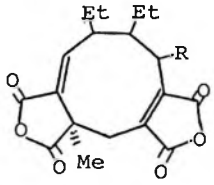
Within the past decade, the study of mycotoxin chemistry has become an area of increasing research activity. With the outbreaks in 1960 of "Turkey X" disease (53) in England and trout hepatoma (53) in the United States, contamination of foodstuff by toxic mold metabolites was recognized as a severe problem in food storage. The isolation and characterization of the toxic metabolite, aflatoxin (22, 42) and the demonstration of aflatoxin B_1 as an extremely potent carcinogen (53) highlighted the possible threat to world health by the presence of mold-produced contaminants.

Similarly, other toxic metabolites were found and characterized. The report by Burnside, et.al.(24) on the toxigenicity of Penicillium rubrum eventually lead to isolation and structural elucidation (55, 56) of two toxic compounds, designated rubratoxin A and B. The report by Moss (56) proposes structures 1 and 2, respectively for the toxins A and B. This structural assignment was confirmed and the absolute stereochemistry was defined by Büchi, et.al., (23) by use of x-ray crystallography.

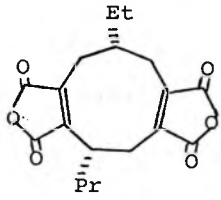
The bisanhydride ring derivatives 1 and 2 bear a structural relationship with the nonadride mold metabolites (6, 10) including glauconic, (8, 9, 32) glaucanic, (8, 9) and byssochlamic acids, (7, 63) shown respectively as 3, 4, and 5. The isolation of glauconic and galucanic



1, R = H, OH
2, R = O



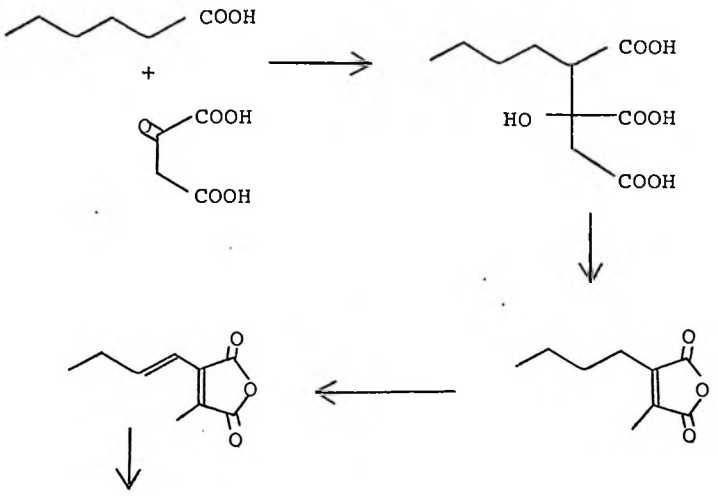
3, R = OH
4, R = H



5

acids from Penicillium glaucum, later reclassified as Penicillium purpurogenum (10), was described by Wijkman (73) in 1931. The toxicity of byssochlamic acid was recognized by Raistrick and Smith (64) who isolated it from Byssochalmys fulva Olliver and Smith in 1933. A more recent report by Rose and Moss (66) compared the toxicity of glauconic and byssochlamic acid to rubratoxin A and B, with the results indicating that the A and B toxins were far more toxic than the nonadride derivatives.

The collective name, nonadrides, reflects their probable biogenetic origin. Sutherland, et.al. (16, 54) has produced convincing evidence that glauconic, glaucanic and byssochlamic acids are derived from dimerization of two C_9 units. The basic C_9 unit could be derived from a combination of a hexanoic acid derivative and oxaloacetic acid as shown in Scheme 1 for the glaucanic acid toxin. Moss et.al. (55) has proposed the analogous pathway for production of rubratoxin B, derived from two C_{13} units, each arising by coupling of a decanoic acid derivative with oxaloacetic acid.

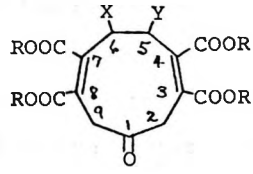


glaucanic acid

Scheme 1

Although there is little remaining doubt that the structural assignments of metabolites 1-5 are correct, the final proof of structure would be total synthesis by an umambigious route. However, there have been no reports in the literature of attempts to synthesize these compounds. In addition to structural confirmation, such a synthesis should provide a synthetic route for derivativization of these compounds, a process which would be helpful in establishing the toxic site of these structures.

The synthesis of any of these metabolites would require the construction of a nine-membered ring with appropriately placed substituents. For example, the initial goal of such a synthetic approach could be the nine-membered carbocyclic ring 6, with carboxyl groups placed at C-3, C-4, C-7, and C-8 for later conversion into bisanhydride units, and a carbonyl group at C-1.



6

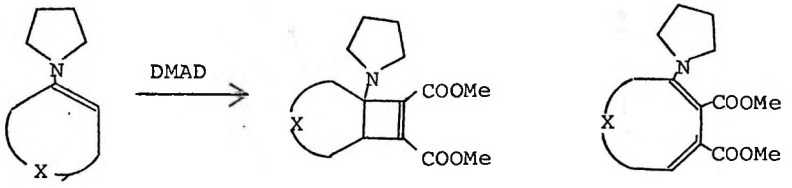
Ultimately, the C-1 carbonyl group could serve as the site for a selective addition reaction designed to add a side chain at C-1. Also, the allylic positions C-2

and C-9 and those at C-5 and C-6 should exhibit varying degrees of reactivity making possible the selective introduction of substituent groups such as those found in byssochlamic acid and rubratoxin B. Furthermore, if a synthesis of 6 were developed which possessed sufficient flexibility in the placement of substituents, the toxins 1, 3, and 4 might be synthesized utilizing similar intermediates.

A survey of synthetic methods that could be used for the construction of nine-membered rings leads to the consideration of several general approaches to the problem. The most frequently encountered method of closure of medium and large ring systems is the acyloin condensation (51). As applied to the present case, however, the inclusion of appropriate functional groups compatible with this reaction would appear to present formidable problems.

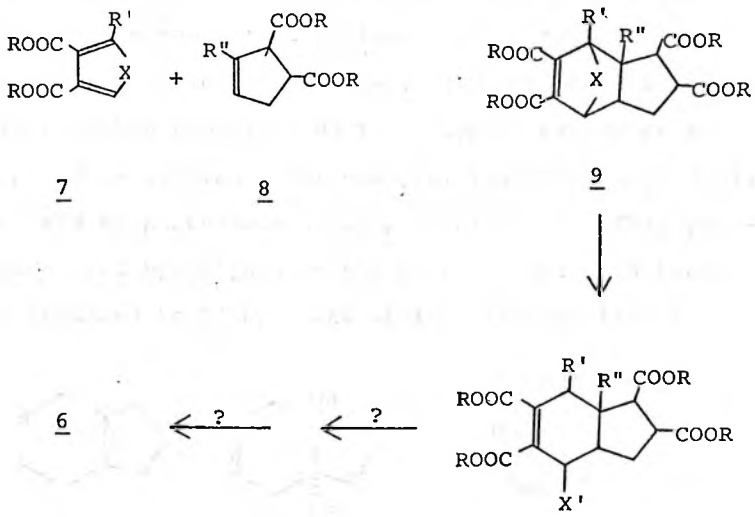
Another synthetic approach to derivatives of 6 could be the use of a ring-expansion reaction in which a carbocyclic ring is enlarged by one or more carbon atoms. The choice of the type of ring-expansion reaction would be governed by the number of carbons needed for enlargement of a selected compound to the desired nine-membered ring system. This approach would appear more favorable if the introduction of appropriately placed carboxyl groups accompanied the ring-expansion step.

Such a reaction was reported simultaneously by three different groups (18, 20, 45) in 1963. In these reports a cyclic enamine was reacted with dimethyl acetylene-dicarboxylate to give a cyclobutene intermediate which



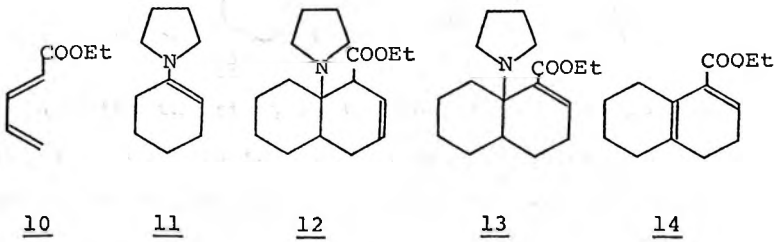
rearranged to a ring-expanded product containing vicinyl carboxyl groups. A two-fold application of this type of ring-expansion reaction to an appropriate five-membered ring would lead to a nine-membered ring derivative of the type 6 containing the four necessary carboxyl groups.

A different synthetic approach to the preparation of nine-membered ring derivatives could involve construction of the ring system with carboxyl groups intact in a one-step cycloaddition reaction of an appropriate diene with a dienophile as shown in Scheme 2. Scission of a bond to the bridging X group with concurrent or subsequent cleavage of the C-1 to C-6 bond could lead to derivative of the type 6. A cycloaddition reaction of this nature



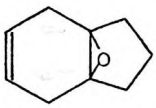
Scheme 2

employing the activated diene 10 with the pyrrolidino enamine 11 was reported (12, 28) giving 12 along with the isomer 13 and the elimination product 14. Hence, it is reasonable to expect that properly substituted 7 and an enamine 8 (R"=NR_2) might combine to give the tricyclic derivative 9 (R"=NR_2).

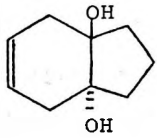


10 11 12 13 14

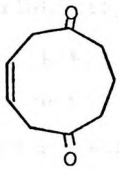
The subsequent opening of the internal bonds of 9 leading to 6 might follow several reaction paths, depending on the nature of the bridging X group. A number of examples are available (25, 26) in which a carbon-carbon bond forming the bicyclic bridge of a compound is cleaved. For example, the epoxide 15 (70), prepared by perbenzoic acid epoxidation of 4,7-dihydroindane, was hydrolyzed to the diol 16, which in turn was oxidized to 17 by means of lead tetraacetate in



15

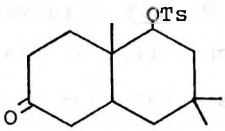


16

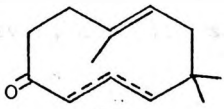


17

trichloracetic acid. A different type of internal bond cleavage was reported by Mukharji and Das Gupta (57). The bicyclic ketotosylate 18 was subjected to potassium t-butoxide in t-butyl alcohol giving the cyclodecadienone derivative 19. These examples could serve as



18



19

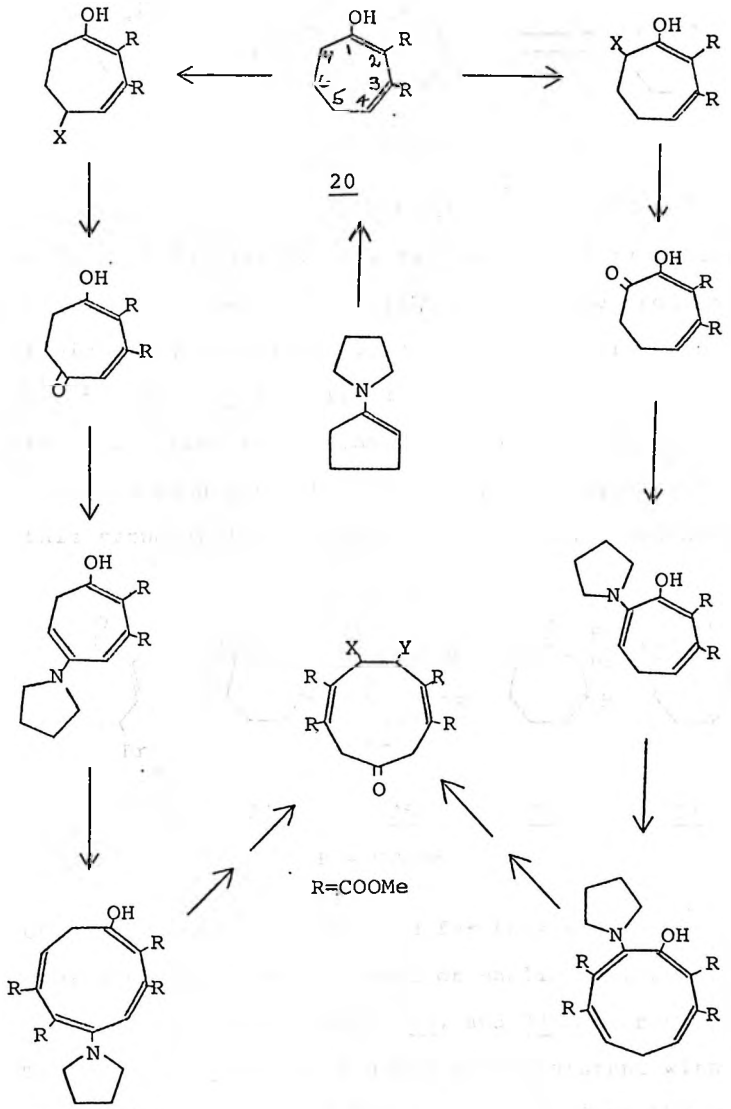
models for the study of the chemistry of compounds corresponding to the generalized structure 9 in which analogous types of bond rearrangements could be accomplished.

CHAPTER III

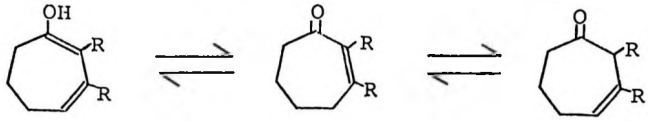
DISCUSSION OF EXPERIMENTAL WORK

A. Reactions of 1-Hydroxy-2,3-dicarbomethoxy-1,3-cycloheptadiene and Its Derivatives

One approach to construction of the generalized nonadride ring system 6 consists of the reaction sequence shown in Scheme 3. This approach offered the advantage of utilizing the ready availability of intermediate 20 (13, 20, 45) which was prepared from the reaction of 1-morpholinocyclopentene with dimethyl acetylenedicarboxylate (DMAD) followed by acid hydrolysis. An anticipated problem of this approach was the selective introduction of an appropriate substituent at C-5 or C-7 for later conversion to a carbonyl group for use in the condensation ring-expansion sequence leading to 6. Spectral measurements (43, 62) indicate that 20 exists almost exclusively in the enol form shown. Thus, reactivity at C-5 and C-7 would be expected. However, a tautomeric equilibrium involving keto forms 20a and 20b must be considered as possible contributors in a reaction and C-2 and C-4 also were potential reactive sites. The initial attempt to introduce an additional functional group into 20 employed reaction with N-bromosuccinimide in carbon tetrachloride solution without



21 Scheme 3 22

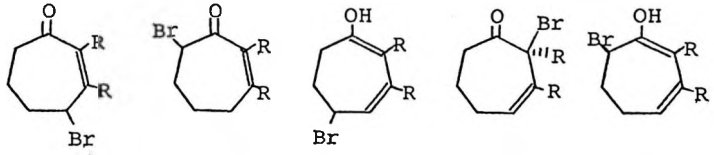


20a

20 20b

R = COOMe

a radical initiator. Reaction was rapid as indicated by the appearance of succinimide, and the product, isolated by removal of solvent from the filtered solution, was tentatively identified as 23 or 24, presumably resulting from ionic bromination (44) at C-4 or C-7. In addition to a correct elemental analysis, evidence for this structural assignment was based on spectral data and



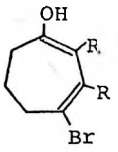
23 24 25 26 27

R = COOMe

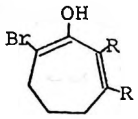
chemical properties observed for this compound. The nmr showed no evidence for vinyl or enolic protons, thus eliminating structures 25, 26, and 27 from consideration. The nmr absorption at 5.4 ppm was consistent with that expected for either the C-4 proton in 23 or the C-8 proton in 24, based on the assumption of large coupling

with the cis vicinyl proton and small coupling with trans vicinyl proton.

The bromine substituent proved to be unusually resistant to displacement or elimination. Treatment with either aqueous or alcoholic base converted the bromination product into an isomeric compound exhibiting distinctly different physical properties. This same isomerization was observed when a sample, prepared for nmr analysis ($CDCl_3$), was treated with two drops of triethylamine. Absorptions of the isomeric compound appeared within 15 minutes and the isomerization was apparently complete in eight hours. The isomeric compound showed enolic, but no vinylic proton absorptions in the nmr. These spectral characteristics were consistent with either 28 or 29, the tautomeric enols of 23 and 24, respectively.



28

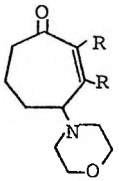


29

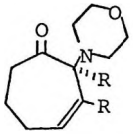
R = COOMe

It was found that treatment of the bromination product with a secondary amine brought about displacement of bromine rather than isomerization. Reaction with excess morpholine in benzene solution produced morpholine

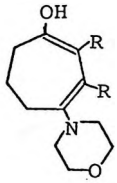
hydrobromide and a compound containing a morpholino group, but no bromine. The nmr of this product exhibited vinyl, but no enolic proton absorptions. Direct substitution of 23 would produce 30, a structure with no vinyl protons and one which might be expected under these conditions to isomerize to the enolic form 32. However, allylic displacement of bromine via an S_N2' mechanism in 23 by morpholine would lead to 31, a structure consistent with the spectral data of the product. Reaction of 24 with morpholine could proceed only by direct displacement to yield 33 or 34, structures



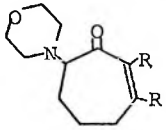
30



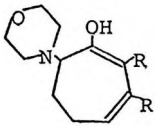
31



32



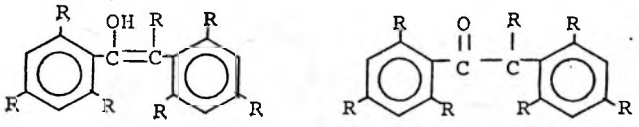
33 R = COOMe



34

not compatible with the spectral data. Therefore, the evidence favors 23 as the structure of the bromination product of 20, and 28 as the isomeric enol.

The facile tautomerization of 23 to the vinylic bromide 28 under most reaction conditions would be expected since the transformation extends conjugation. Also, the possibility of intramolecular hydrogen bonding of the enol 28 is evident. Taking six Kcal/mole as the average stabilization associated with intramolecular hydrogen bonding (39) and ignoring other structural effects, the enol/keto ratio for this system at equilibrium should be approximately 10^4. This accounts for the unusual difficulty experienced in eliminating or substitution of bromine in 23. It should be noted that the individual isolation and characterization of tautomers 23 and 28 is unusual, but not without precedent. For example, Fuson et.al. (36, 37) were able to isolate tautomers 35 and 36 in crystalline form and characterize



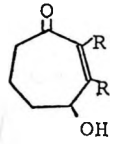
35 36

R = CH_3

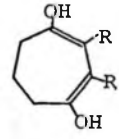
them. The enol tautomer 35 was found to be unusually stable and was converted to 36 only when refluxed in methanolic hydrochloric acid for an extended period of time. Also, there are other examples (68) of isolation of stable enol and keto isomers.

Another observation on the chemical behavior of 23 was that it was easily reduced to 20 by bisulfite ion in aqueous ethanol. However, despite these interesting observations, it was apparent that 23 was not a useful intermediate in the projected synthetic scheme, and therefore, the chemistry of this compound was not investigated further.

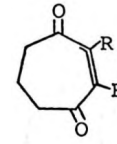
Compound 20 was subjected to selenium dioxide oxidation under a variety of conditions in a new attempt at introducing a functional group at C-5 or C-7. The most promising effort, using acetic acid as solvent, produced a crystalline substance tentatively identified as 37 by nmr, mass spectrometry, and elemental analysis.



37



38



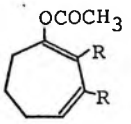
39

R = COOMe

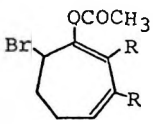
In an attempt at further characterization a small amount of 37 was subjected to oxidation with active manganese dioxide. The nmr of the product mixture indicated the presence of 38 and possibly 39 along with unreacted 37.

It should be noted that 38 is the dienolic tautomer of 37 and the conversion of 37 to 38 is analogous to the isomerization of 23 to 28.

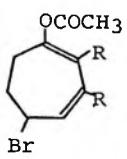
The preceding experiments suggested that use of the enol acetate derviative 40 would be preferable to 20 in attempts to achieve reaction at allylic positions C-5 and C-7. Reaction of 40 with N-bromosuccinimide in carbon tetrachloride in the presence of a radical initiator yielded a mixture of relatively unstable products that could not be separated by distillation or column chromatography. The nmr of the mixture exhibited absorptions reasonably consistent with that expected for the -CHBr- and vinyl protons in 41 and 42. Although either of these compounds constitute useful intermediates, their instability and the problems associated with separation and purification of a single isomer seemed



40



41



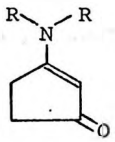
42

R = COOMe

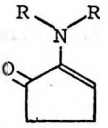
substantial, and this synthetic approach was not pursued further.

B. Reactions of Cyclic Enamino Ketones with Dimethyl Acetylenedicarboxylate

The second synthetic approach was a variation of the reaction sequence outlined in Scheme 3. The difference in this approach was that the keto group required for the second ring-expansion reaction using DMAD was incorporated in the starting five-membered ring structure rather than being introduced after the first ring-expansion step. Therefore, this approach utilized a cyclic enamino ketone as the key starting material. Two types of cyclic enamino ketone systems are possible in five-membered rings and are represented by structures 43 and 44.

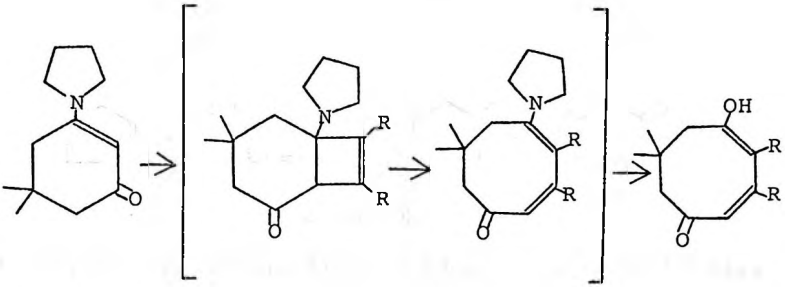


43



44

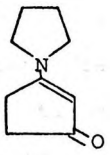
Utilization of these types of intermediates would lead to 6 through intermediates 21 and 22, respectively, shown in Scheme 3. Both types of cyclic enamino ketones are reported in the literature, but the only report of reaction with DMAD was in the case of the monoenamine derivative of dimedone (45) 45. In this reported case, only the hydrolysis product 48 was isolated and the yield was unspecified. Therefore, the initial effort of this



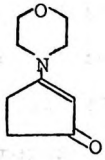
45 46 47 48

R = COOMe

investigation was a repetition of the reported reaction. The desired product 48 was obtained in reasonable yield and this approach seemed encouraging. Hence, the analogous five-membered ring enamino ketones 49 and 50 were prepared from 1,3-cyclopentadione. An adequate

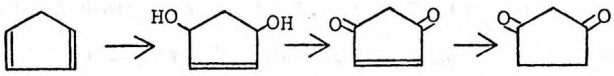


49



50

preparation of 1,3-cyclopentadione via a three-step synthesis starting with cyclopentadiene as shown in Scheme 4 was developed. Treatment of both pyrrolidino



Scheme 4

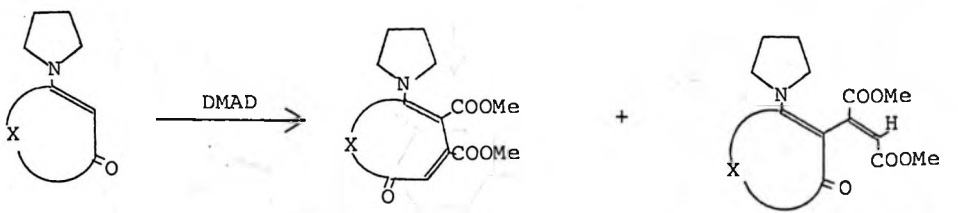
and morpholino enamino ketones 49 and 50 with DMAD gave indications of reaction, but initial efforts to isolate a product from the reaction mixture were unsuccessful. On the basis of these results it was decided that the reaction of cyclic enamino ketones with DMAD should be investigated more thoroughly with attention directed to the effect on the course of the reaction of structural variations, e.g., ring size and ring substitution, in the enamino ketone system.

In studying the reactions of enamino ketones it was desirable to isolate as many of the reaction intermediates as possible. The reported results (45) on the reaction of 45 with DMAD indicated that isolation of the cyclobutene intermediate 46 would not be feasible. However, the attempt to isolate intermediate 47 was successful. Therefore, in contrast to the reported study (45) of 45, separation and identification of products from all reaction mixtures were made prior to hydrolysis. A thorough study

of the reactions of the three enamino ketones 45, 52, and 49 with DMAD was made with regard to choice of solvent, mode of addition of reagents, influence of temperature, and isolation procedures. A ring-expanded product was isolated for each of the three enamino ketones as shown in Table 1. In addition a second compound was isolated from each product mixture which corresponded to the Michael adducts 51, 54, and 56, also shown in Table 1. Products derived from such adducts of enamines and propiolate esters have been previously reported, (21, 45) but no examples of Michael adducts of enamines with DMAD were found in literature. In the case of each product it was possible to isolate and purify a crystalline sample which gave satisfactory elemental analysis. Table 1 also includes the maximized percent yields of identifiable products under optimum conditions and chemical shifts for the vinyl protons of the respective compounds. Structural assignments were based largely on the spectral similarities, principally the vinyl proton chemical shifts of 53 and 55 to 47, and 54 and 56 to 51. In turn, 47 was correlated by hydrolysis to the known structure 48 (45). Assignments of structures to products 51, 54, and 56 were based partly on the observation of higher field vinyl proton absorptions for these products as compared to the ring-expanded structures 47, 53, and 55. It would be expected

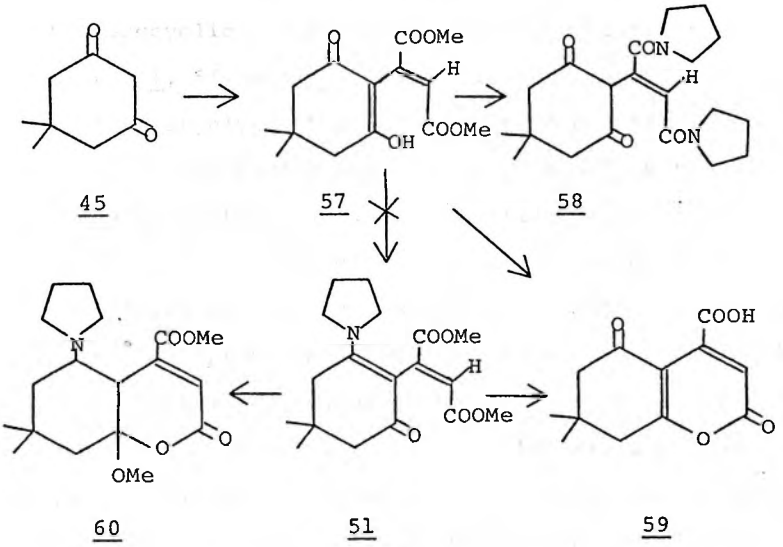
TABLE 1

PERCENT YIELD AND NMR VINYL PROTON CHEMICAL SHIFTS OF PRODUCTS FROM THE REACTION OF CYCLIC ENAMINO KETONES WITH DIMETHYL ACETYLENEDICARBOXYLATE



	Reactant	Ring-Expanded Product	Percent Yield	Vinyl Proton Chemical Shift (ppm)	Michael Product	Percent Yield	Vinyl Proton Chemical Shift (ppm)
X = $-CH_2C(CH_3)_2CH_2-$	45	47	32	6.48	51	66	5.32
X = $-(CH_2)_3-$	52	53	48	6.45	54	50	5.33
X = $-(CH_2)_2-$	49	55	18	6.85	56	10	5.65

that vinyl protons in the cross-conjugated systems of 51, 54, and 56 would experience greater shielding effects. However, structure correlation by an independent synthesis of 51 also was undertaken by means of the reactions in Scheme 5. Dimedone was condensed with DMAD using sodium hydride to give the expected adduct 57 for which confirming spectral and elemental analysis data were obtained. Reaction of 57 with pyrrolidine did not yield



Scheme 5

the desired monoenamine derivative 51, but instead gave a clean, white solid tenatively identified by spectral means as the dipyrrolidino amide 58. Successful correlation was obtained through the intermediate 59, a product which was obtained by hydrolysis of either 57 or 51 in aqueous hydrobromic acid.

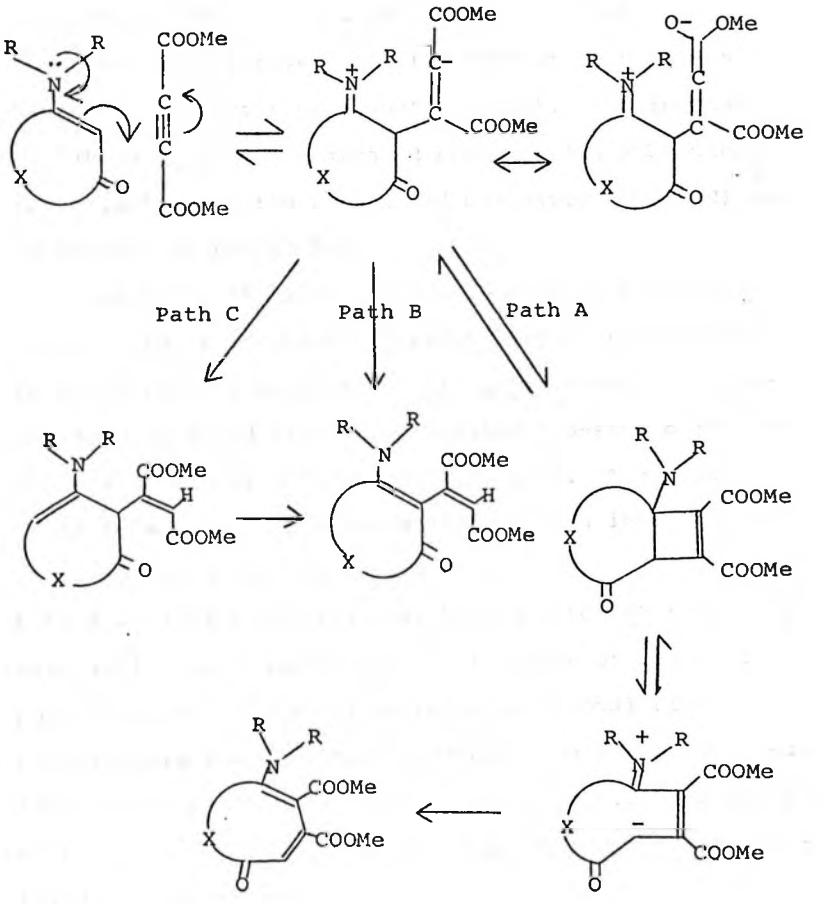
The assignment of the pyrone-type structure for 59 was supported by nmr, mass spectra, and elemental analysis. Also, the formation of pyrone from analogous structural systems under similar reaction conditions is reported in the literature (35). The trans assignment to the exocyclic double bond in the Michael reaction products 51, 54, and 56 and the dimedone-DMAD adduct 57 was based largely on the fact that pyrone formation occurred in the hydrolysis of both 57 and 51 with the products accounting for a major portion of the material. It is evident that the cis isomer could not cyclize without first undergoing isomerization. Also, nmr data indicated the presence of only one type of isomer in all cases. Another indication of trans geometry lay in the similarity of the chemical shift of the vinyl proton of 57 (6.85 ppm) to that of ethyl fumarate (6.73 ppm) (14).

It is interesting to note that the pyrrolidino group could not be removed from 51 under conditions that normally accomplish hydrolysis of enamines. Instead, room temperature reaction in a dilute hydrochloric acid-methanol

mixture brought about isomerization to a product identified as 60. Further studies on this isomerization were not undertaken.

The two types of reaction products, shown in Table 1 accounted for approximately the entire product mixture in the cases of reactions of 45 and 52, but less than 30% of the product mixture obtained from 49. It did not prove possible to isolate and identify any other components of the latter reaction product mixture, but the physical appearance and nmr spectra of the residual material indicated the presence of substantial amounts of polymerized DMAD.

A reasonable mechanism by which both types of products in Table 1 could be formed is outlined in Scheme 6. Initial formation of a zwitterion adduct is in keeping with the suggestion by Stork (70) for addition of enamines to activated olefins such as acrylonitrile. Cyclization of the zwitterion to form a cyclobutene derivative (Path A) is undoubtedly the reaction path ultimately leading to ring-expanded products. Such cyclobutene intermediates actually have been isolated in certain cases of reactions with enamines (20, 45), but not in reactions with enamino ketones. Nevertheless, the intermediacy of a cyclobutene structure is inferred on the basis of the nature of the products isolated. The subsequent opening of the cyclobutene ring to give a ring-expanded product must be



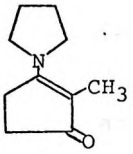
Scheme 6

a process in which the nitrogen lone pair of electrons participates since a simple thermal cyclobutene to butadiene transformation would be required to proceed *via* a sterically unfavorable conrotatory process (75). Formation of the Michael addition product is explained most simply by irreversible transfer of a proton in the initial zwitterion adduct (Path B). The initial formation of the unconjugated enamine with subsequent isomerization to the conjugated derivative (Path C) is an equivalent possibility.

The ratio of ring-expanded to Michael addition products in reactions of 45 and 52 may be rationalized in terms of this mechanism. The *gem*-dimethyl substituents in 45 would create unfavorable 1,3-steric interactions in the cyclobutene intermediate. The result would be a decrease in the amount of this intermediate in equilibrium with the zwitterion adduct. Thus, reaction Path A is less competitive with Path B for 45 than is the case in the reaction of 52. In the case of the cyclopentenone derivative 49, where no additional ring substituents are present, ring-expansion again competes favorably with Michael addition, but conditions could not be found in which either process prevailed over unidentified side reactions.

In order to assess the effect of alkyl substituents at the 2-position of the enamino ketone system, an attempt was made to condense 61 with DMAD. The proposed zwitterion

adduct would be expected to proceed only by reaction paths A and C since no proton would be available at C-2 for removal to form a conjugated Michael adduct. Hence, it was thought that greater relative amounts of ring-expanded products might be observed in this case. However, only starting material could be recovered from the reaction mixture. Apparently, the methyl substituent at C-2 interferes with the initial addition of the enamine to DMAD, probably through a steric effect.

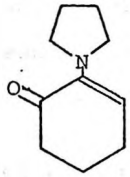


61

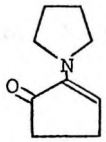
Also, an attempt was made to condense 45 and 49 with ethyl propiolate (HC≡CCOOEt) to determine if the ratio of Michael addition to ring-expansion products differed substantially in comparison with reactions of DMAD. Unfortunately, under conditions similar to those employed in reactions with DMAD, only starting materials were recovered in the ethyl propiolate reaction.

Examples of the enamino ketone system illustrated by structure 44 (2-amino-2-cycloalkenones) are less frequent in the literature. The derivative, 62 has

been reported to be unreactive toward addition to ethyl acrylate and resistant to hydrolysis in aqueous acid, (27) thus indicating less nucleophilicity at C-3 than at the carbon terminus of simple enamines. The

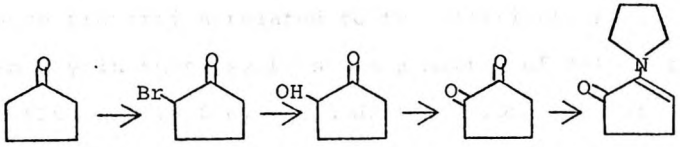


62



63

analogous five-membered ring derivative 63 is not reported, but was prepared from 1,2-cyclopentadione, which in turn was available by a previously established synthetic route from cyclopentanone (1) as shown in Scheme 7. These monoenamines derived from 1,2-diones, especially 63,



Scheme 7

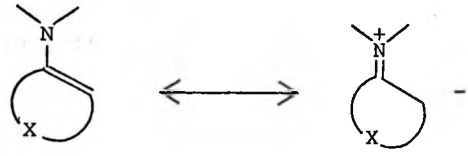
were less stable than the corresponding 1,3-dione derivatives, as evidenced by rapid discoloration. Reaction of either 62 or 63 with DMAD under conditions similar to those employed for 45, 52, and 49 yielded dark oily residues which exhibited no distinguishing spectral

characteristics, and from which no identifiable components could be separated. It is possible that the reaction with DMAD was prevented by the thermal instability of 62 and 63 or the weak nucleophilicity of the 1,2-enamino ketone system. Due to these unpromising results the reactions of 62 and 63 were not investigated further.

C. Studies of Properties Related to Electron Distribution in Enamines and Enamino Ketones

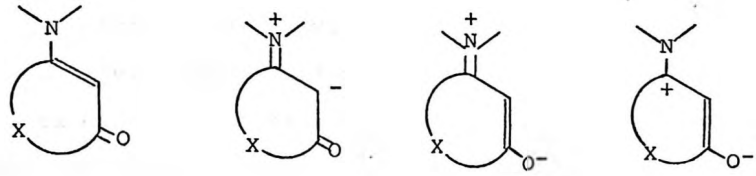
The major impetus of the synthetic effort described in this dissertation involved reactions of enamines or enamino ketones with DMAD. Consequently, it was felt that a thorough study of the effects of structural variations on the properties of cyclic enamines and enamino ketones might provide useful data for anticipating or explaining reaction results. In particular, those properties related to the distribution of electron density in these systems was a matter of interest. The possibilities of electron distribution are most easily illustrated by use of cannonical structures considered to make significant contribution to each resonance hybrid. Figure 1 depicts the various possibilities of delocalization of electron density for each type of system. Evidence related to electron distribution was obtained by four lines of experimentation.

Enamines



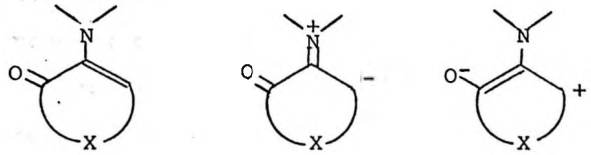
A B

3-Amino-2-cycloalkenones



C D E F

2-Amino-2-cycloalkenones



G H I

2-Cycloalkenones

J K

Figure 1 Cannonical Forms of Enamines, Cyclic Enamino Ketones and 2-Cycloalkenones

a. NMR Chemical Shifts of Vinyl Protons and Other Spectral Data

A total of 19 enamines and enamino ketones were prepared in this investigation. A summary of vinyl proton chemical shifts of these compounds and two related cycloalkenones is given in Table 2. Also included are infrared and ultraviolet data for selected compounds.

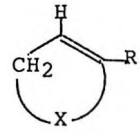
Chemical shifts of vinyl protons have been interpreted previously as evidence for steric and electronic effects on delocalization of the nitrogen lone pair electrons in simple enamines (40, 59). Increases of electron density at the carbon terminus of the enamine provide greater shielding of the vinyl proton and result in upfield shifts in the nmr absorptions of the vinyl proton. Inspection of the data for simple enamines, 64-71, reveals several interesting points regarding ring size effects. First, the vinyl proton shifts of five-membered ring enamines are consistently smaller than those of the analogous six-membered ring systems (64>65, 66>67, 68>69, 70>71). This trend indicates that the nitrogen lone pair electrons are more extensively delocalized into five than six-membered rings, an observation consistent with that made by two other groups (40, 59).

The dependance of the vinyl proton shift on the structure of the amino group is also apparent. The

TABLE 2

NMR CHEMICAL SHIFTS OF VINYL PROTONS AND OTHER SPECTRAL DATA OF ENAMINES AND ENAMINO KETONES

Enamines



Pyrrolidine = Py

Morpholine = Mp

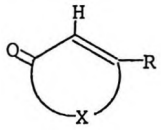
Dimethylamine = Dm

Piperidine = Pp

Compound	Chemical Shift of Vinyl Proton (ppm)	Infrared C=O C=C (cm^{-1})	Ultraviolet λmax (log ε) (nm)
64[a] R = Py, X = $-(CH_2)_3-$	4.27	-	-
65 R = Py, X = $-(CH_2)_2-$	4.00	-	-
66[b] R = Mp, X = $-(CH_2)_3-$	4.57	-	-
67 R = Mp, X = $-(CH_2)_2-$	4.37	-	-
68 R = Dm, X = $-(CH_2)_3-$	4.46	-	-
69 R = Dm, X = $-(CH_2)_2-$	4.16	-	-
70[b] R = Pp, X = $-(CH_2)_3-$	4.53	-	-
71[b] R = Pp, X = $-(CH_2)_2-$	4.25	-	-

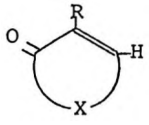
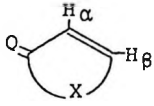
TABLE 2 (Continued)

3-Amino-2-cycloalkenones



52	R = Py, X = $-(CH_2)_3-$	5.06	1595 1546	302 (4.54)
45	R = Py, X = $-CH_2C(CH_3)_2CH_2-$	5.04	1598 1548	303 (4.53)
49	R = Py, X = $-(CH_2)_2-$	4.87	1646 1543	279 (4.40)
72[a]	R = Mp, X = $-(CH_2)_3-$	5.24	-	-
50	R = Mp, X = $-(CH_2)_2-$	5.05	1650 1550	281 (4.70)
73	R = Dm, X = $-CH_2C(CH_3)_2CH_2-$	5.14	-	305 (4.41)
74	R = Dm, X = $-(CH_2)_2-$	4.92	1635 1575	278 (4.12)

TABLE 2 (Continued)

2-Amino-2-cycloalkenones 				
62 R = Py, X = $-(CH_2)_3-$	5.54	1674 1600	217 (3.68) 298 (3.48)	
63 R = Py, X = $-(CH_2)_2-$	5.82	1699 1606	-	
75 R = Py, X = $-CH(CH_3)CH_2-$	5.72	1700 1610	214 (3.78) 314 (3.48)	
76[a] R = Mp, X = $-(CH_2)_2-$	6.32	-	-	
2-Cycloalkenones 				
77[c] X = $-(CH_2)_3-$	H_α5.93	1691	225 (4.14)	
	H_β6.99	1621		
78[c] X = $-(CH_2)_2-$	H_α6.10	1720	217 (4.06)	
	H_β7.75	1593		

[a]The preparation procedures for these compounds are not found in Experimental, but were prepared by usual procedures and exibited spectral characteristics confirming assigned structures.

[b]Data taken from reference (59).

[c]Data taken from reference (72).

pyrrolidine enamines in which nitrogen is incorporated in a five-membered ring provide greater shielding of the vinyl proton than either morpholino or piperidino enamines in which nitrogen is part of a six-membered ring. The acyclic dimethylamino derivatives exhibit intermediate levels of shielding for vinyl protons. Thus, the order of chemical shifts with respect to the amine group is as follows: morpholine>piperidine> dimethylamine>pyrrolidine; e.g., 66>70>68>64 and 67>71 69>65.

In general, nucleophilicity at a reaction site parallels electron density. For example, the reaction of phenoxide ion with ethyl iodide is found to have a negative rho value (41). Reasoning on this basis suggests that enamines derived from cyclopentanone should be more nucleophilic than the corresponding cyclohexanone derivatives and that for a given ketone the pyrrolidino enamine should be the most nucleophilic derivative of those included in this investigation.

Enamino ketones can be considered as α,β-unsaturated ketones with an amino substituent at either the α- or β-position. The amino and keto groups, respectively electron releasing and electron withdrawing, exert opposing effects on the electron densities at the enamine carbon termini of both types of enamino ketones. Hence, the vinyl proton signals in the enamino ketones are observed at lower field than those of the simple enamines and at

higher field than those of the corresponding α- or β-protons in the conjugated ketones. Inspection of structures of C-I in Figure 1 reveals that the conjugative electron withdrawal of the keto group is greater at the β-position than the α-position. Therefore, the vinyl proton signals of the 2-amino-2-cycloalkenones appear at lower field than those of the 3-amino-2-cycloalkenones, a comparison that is qualitatively similar to the relative chemical shifts of α- and β-protons in the cycloalkenones 77 and 78. Thus, a greater electron density is indicated at the enamine carbon termini for the 3-amino-2-cycloalkenones than is the case for the 2-amino-2-cycloalkenones.

The vinyl proton chemical shifts are found to be smaller for the five-membered rings with respect to the six in the 3-amino-2-cycloalkenone systems. This is consistent with the previously mentioned factor of greater delocalization of nitrogen lone pair electrons into five vs six-membered rings. Then, structure D is indicated to be relatively more important in the case of the five-membered ring.

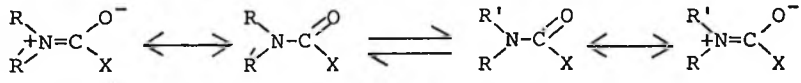
The infrared data indicate that the 3-pyrrolidino group is more effective in lowering the carbonyl frequency in six than five-membered rings ($\Delta\nu$ for 52 vs 77 = 96 cm^{-1} compared to $\Delta\nu$ for 45 vs 78 = 74 cm^{-1}). The pyrrolidino group also produces a larger bathochromic shift in the ultraviolet for six than five-membered ring derivatives

($\Delta\lambda$ for 52 vs 77 = 77 nm compared to $\Delta\lambda$ for 45 vs 78 = 62 nm). This indicates greater importance of structure E in six than in five-membered rings. The combined evidence favors a greater electron density at C-2 for 3-amino-2-cyclopentenones than 3-amino-2-cyclohexenones.

In the case of the 2-amino-2-cycloalkenones the larger shifts of vinyl protons in 63 and 76 compared to 62 and 75 appear to contradict the generalization that nitrogen lone pair delocalization is greater into five than six-membered rings. However, this point is clarified by the fact that the β-proton in 78 is markedly less shielded than the β-proton in 77 ($\Delta\nu$ = 0.76 ppm), an indication that a ring-size effect allows greater electron withdrawal from the β-proton of α,β-unsaturated ketones in five than six-membered rings. It should be noted that the difference between the chemical shifts for the vinyl proton of 63 and the β-proton of 78 (1.93 ppm) is greater than that between 62 and the β-proton of 77 (1.45 ppm). Thus, greater delocalization of nitrogen lone pair electrons into five than six-membered rings also applies to the 2-amino-2-cycloalkenone systems, but the trend toward smaller chemical shifts for the five-membered ring derivatives is reversed by the greater electron withdrawal effect of the keto group in five than six-membered rings. Consequently, structures H and I are more important in five than six-membered rings.

b. The Rotational Barriers of the C-N Bond in Enamino Ketones

The analysis of temperature dependent changes in nmr spectra is the principal method used presently to study the phenomenon of hindered rotation of groups about single bonds in organic molecules. The classical example is the case of hindered rotation about the C-N bond in amides (69). Since the amide nitrogen substituents R and R' experience different environments in the two rotameric forms A and B, separate signals for R and R' are observed in the nmr spectrum under conditions such that the rate constant for rotation k is less than the quantity $\pi\Delta\nu/\sqrt{2}$, where $\Delta\nu$ is the difference in frequency of the signals for R and R'. Increases in temperature increase the rate of rotation and at the temperature at which k is equal to $\pi\Delta\nu/\sqrt{2}$, the signals for R and R' coalesce. The treatment of such nmr data for the calculation of rotational



Rotamer A Rotamer B

barriers has been the subject of numerous articles and reviews (11, 50, 69). In the case of rotation about the C-N bond in amides, the height of the rotational barrier can be taken as a measure of the extent of nitrogen lone pair electron delocalization as shown for rotamers A and B.

Since the 3-amino-2-cycloalkenone system may be considered to be a vinylogous amide it was apparent that this nmr method of determining differences in rotational barriers about the C-N bond could be used for evaluating differences in the extent of nitrogen lone pair electron delocalization in these systems. The only analogous nmr studies on rotational barriers of vinylogous amide systems is a report (48) on acyclic systems such as 3-dimethylaminoacrolein, $(CH_3)_2NCH=CHCHO$, in which an activation free energy for rotation at the coalesence temperature was reported to be 15.8 Kcal/mole. In the present case the dimethylamine derivatives 73 and 74 were chosen for study since the R and R' group would exhibit singlets in the nmr, thus simplifying the analysis procedure. The nmr spectra for the N,N-dimethyl signals of 73 and 74 over a temperature range including the coalesence point are shown in Figure 2 and 3. In the case of 73 the methyl signals are separated by a frequency difference of 17.5 Hz and coalesce at -9°C. The separation of methyl signals in 74 is 12 Hz and coalesence occurs at 33°C.

The most accurate calculations of thermodynamic parameters from temperature dependent nmr spectra are based on complete line shape analysis in which theoretically calculated spectra are matched with experimental spectra obtained at various temperatures. Lack of

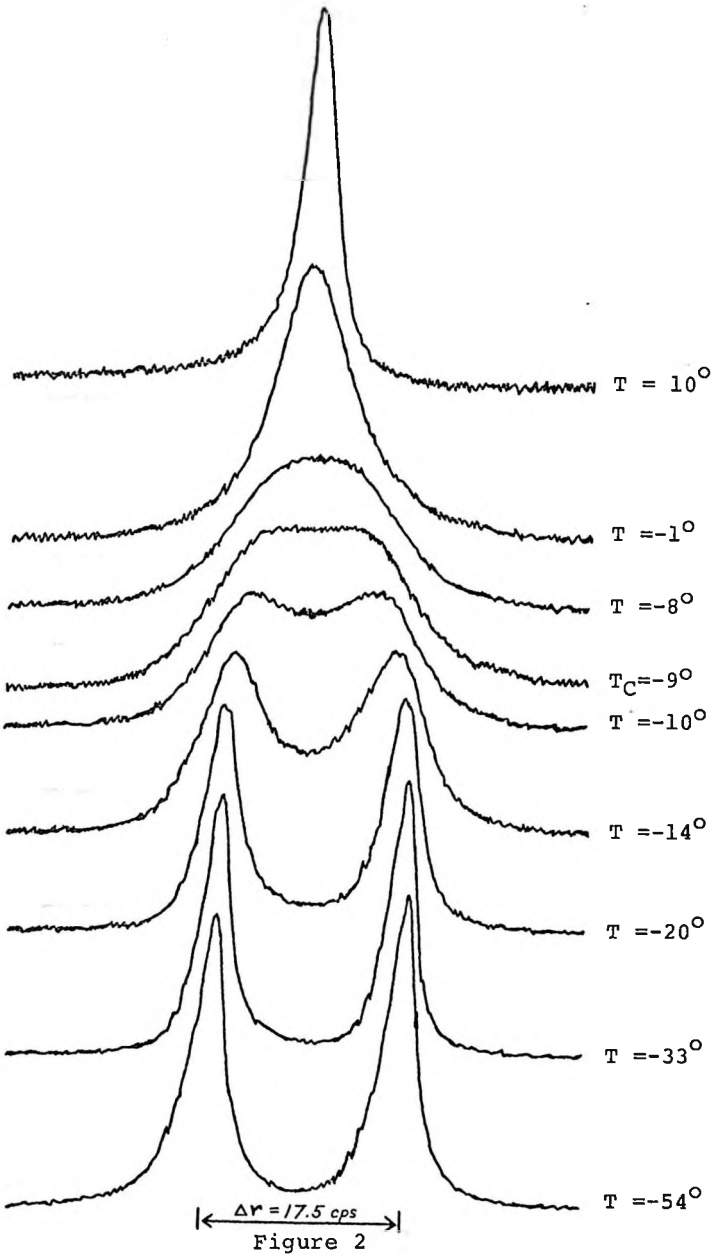


Figure 2

Partial NMR Spectra of 5,5-Dimethyl-N,N-dimethyl-3-aminocyclohex-2-en-1-one at Various Temperatures

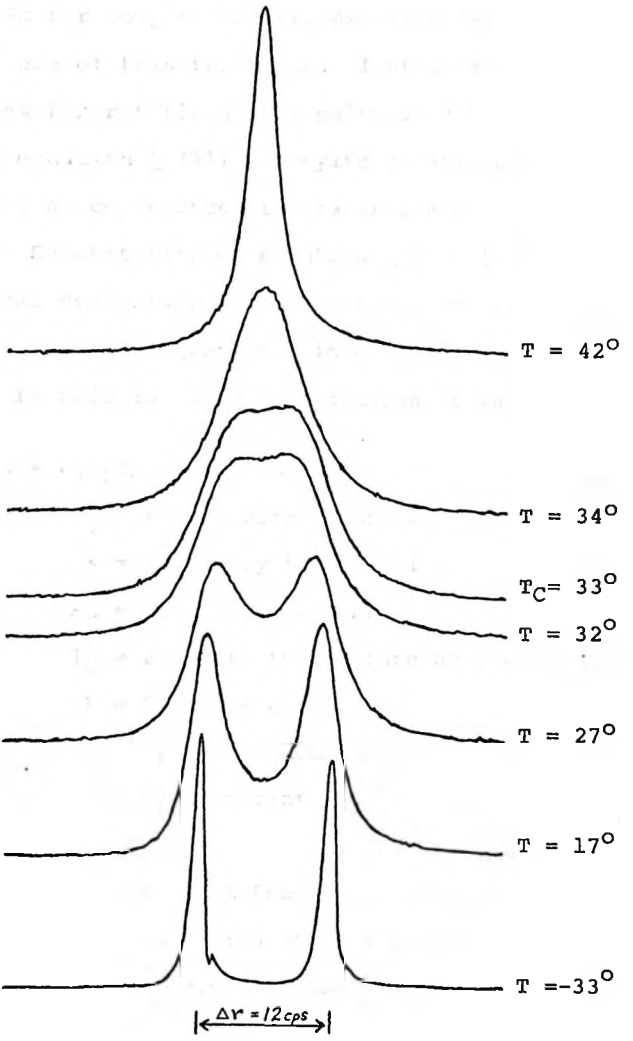


Figure 3

Partial NMR Spectra of N,N-Dimethyl-3-amino-cyclopent-2-en-1-one at Various Temperatures

facilities for plotting calculated spectra in a manner suitable for comparison with experimental spectra prevented the use of this technique. Instead activation free energies for rotations were calculated by use of the Erying equation 1 (11) employing rotational rate constants measured at coalesence temperatures according to equation 2. Substitution of equation 2 into 1 followed by numerical evaluation of constants and rearrangement of terms yields the equation 3 in which the activation free energy is calculated by substitution of values of T_C and

$$k_C = \kappa(k_B T_C/h)\exp(-\Delta G^*/RT_C) \qquad 1$$

where k_C = rate constant for rotation

κ = frequency factor = 1

k_B = Boltzman constant

T_C = absolute temperature at coalesence point

h = Planck's constant

ΔG^* = free energy of activation

R = gas constant

$$k_C = \pi\Delta\nu/\sqrt{2} \qquad 2$$

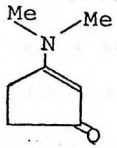
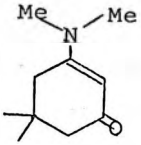
where $\Delta\nu$ = maximum frequency difference in cps in region of slow exchange

$$\Delta G^* = 4.5765T_C(9.9720 + \log T_C/\Delta\nu) \qquad 3$$

$\Delta\nu$. The data and results of the calculations are summarized in Table 3. Although systematic errors in the method employed may introduce considerable uncertainty

TABLE 3

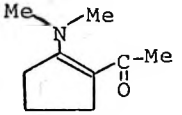
ACTIVATION FREE ENERGIES FOR ROTATION ABOUT THE C-N BOND IN ENAMINO KETONES

	$T_C(C^O)$	$\Delta\nu$	ΔG^*(Kcal/mole)	$\Delta\Delta G^*$
 74	33	12.0	15.9	2.4
 73	-9	17.5	13.5	

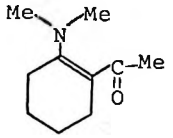
regarding the absolute accuracy of the results, comparison of the two results obtained by this method should be meaningful. Therefore, the 2.4 Kcal/mole greater activation free energy for 74 is a significant indication of a higher rotational barrier for the C-N bond in the five-membered ring derivative compared to the six-membered analog. Also, the higher rotational barrier in 74 indicates greater nitrogen lone pair electron delocalization in this system, a conclusion in agreement with that previously presented in Part C-a.

In addition to nmr temperature studies of 73 and 74 the qualitative observation was made that in the ambident temperature spectra of 45 and 49, the signals for the $-CH_2-N-$ protons of 49 were partially resolved into a set of triplets. The analogous signals for 45 were unresolved, indicating a lower coalesence temperature and probably a lower free energy of activation for the six-membered ring derivative 45.

An attempt to determine the effect of the fixed trans geometry of the double bond in 73 and 74 on the free energy of activation was made by comparison to that of the cis-enamino ketones 79 and 80. The synthesis of 79 and 80 involved acetylation of the simple enamines 68 and 69. Inspection of the nmr spectra of the distilled products of these reactions of 68 and 69 with acetyl chloride and triethylamine indicated that both 79 and 80 were



79

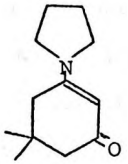


80

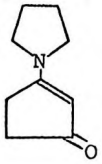
present in an approximately 1:1 ratio with the corresponding, unconjugated double bond isomers, an observation similar to other reported cases of acetylation of enamines (60). No convenient separation of these isomeric product mixtures was devised; however, the nmr spectrum of both product mixtures containing 79 and 80 was examined at various temperatures. No changes were noted in either spectra as low as -60°C, indicating a relatively low coalesence temperature and free energy of activation compared to the trans enamino ketones, 73 and 74.

c. The ^{13}C-H Coupling Constants of Vinyl Protons in Enamino Ketones

The ^{13}C-H coupling constant has been demonstrated to be proportional to the fractional s character of the carbon atomic orbital used to form the bonding C-H molecular orbital. Such data have been successfully employed to demonstrate bonding characteristics in substituted methanes (58) and strained saturated ring systems (34). The ^{13}C-H constants for the vicinyl protons of 45 and 49 were determined by nmr repetitive scan techniques to be



45



49

respectively 159.0 Hz and 167.5 Hz. Application of the equation $\%\underline{s} = 0.20J_{CH}$, developed by Muller and Pritchard (58), leads to the conclusion that the carbon atomic orbital of the vinyl C-H bond in 45 has 31.8% s character corresponding to $sp^{2.14}$ hybridization, whereas the analogous orbital of the vinyl C-H bond in 49 has 33.5% s character corresponding to $sp^{1.98}$ hybridization.

One analysis of these results is based on the explanation that for a carbon bonded to three substituents, s character for sigma bonding orbitals will be at a maximum in a planar bonding geometry and will decrease with increasing pyrimidal character. On this basis the data could be taken to indicate that the geometry of the substituents at C-2 of the five-membered ring has greater planarity than the corresponding geometry of the six-membered ring. Such a conclusion leads to the expectation that in comparison with the five-membered ring derivative the electron density at C-2 in the six would be greater (higher field vinyl proton chemical shift), and influence of the nitrogen lone pair electron delocalization

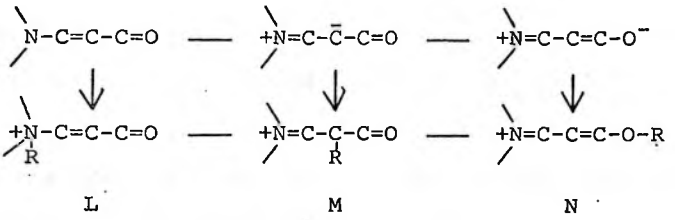
less extended to the carbonyl group (lesser influence of amino group on lowering the carbonyl stretching frequency and a smaller bathochromic shift in the ultraviolet). These expectations are at variance with the observed results discussed in Part C-a.

An alternate and more acceptable analysis of these data assumes that the geometry of sigma bonds at the C-2 carbon is essentially planar for both enamino ketone systems. Comparison of the sigma bond frameworks of 45 and 49 indicates that the angle between ring bonding orbitals at C-2 in 49 would be more constricted than is the case in 45. Therefore, in comparison with the six-membered ring, the ring sigma bonding orbitals at C-2 in the five would have increased p character, allowing the bonding orbital to hydrogen to have relatively greater s character. Thus, since the electron distribution in the enamino ketone system may be considered entirely a pi bond phenomenon, the J_{CH} values may bear no direct relationship to the question of nitrogen lone pair electron delocalization.

d. Protonation and Alkylation of Cyclic Enamino Ketones

The study of electron distribution in 3-amino-2-cycloalkenone systems leads naturally to the consideration of the actual site of protonation and alkylation during a reaction. Three atoms in this system (nitrogen, C-2 carbon, and oxygen) could be considered potential

centers of high electron density. Hence, for reactions in which these systems play a nucleophilic role, e.g, reaction with anhydrous acid or ethyl iodide, there are three possible initial products L, M, and N, reflecting nitrogen, carbon, and oxygen protonation or alkylation.



Some indication of the relative nucleophilicity of carbon, nitrogen, and oxygen in these systems may be inferred from the nature of the products of these reactions.

Leonard and Adamcik (49) reported the first systematic attempt to determine sites of alkylation of enamino ketones. They found that although acyclic enamino ketones were alkylated mainly at carbon, the cyclic enamino derivative 45 was alkylated exclusively at oxygen. It also was concluded and later confirmed by Alt and Speziale (3) that 45 was protonated at oxygen. Similarly, Meyers (52) reported that cyclic cis-enamino ketones yielded both C- and O-alkylation products in aprotic solvents, but that cyclic trans-enamino ketones undergo only O-alkylation. These results indicate that delocalization of the nitrogen lone pair electrons in the enamino ketone ring

system is extensive and that nitrogen is probably the least nucleophilic while oxygen apparently is the most nucleophilic of the three sites.

In an effort to determine if five-membered ring enamino ketones exhibited similar reactivity to that of the six the reactions of 45 and 49 with ethyl iodide and 45 and 50 with anhydrous hydrogen chloride were studied. The corresponding O-ethyl iodide salts 81 and 82, as shown in Table 4, were isolated from the reaction of the enamino ketones in refluxing ethyl iodide. Assignment of structure 82 was based largely on the similarity of the absorptions of the O-ethyl group of 82 (quartet at 4.37 ppm in CD_3OD) to that of 81 (quartet at 4.22 ppm in CD_3OD). The extreme hydroscopic nature of 82 made further characterization results uncertain. Hence, attention was turned to characterization of the hydrochloride salts 83 and 84, also shown in Table 4, which were obtained from the reactions of 45 and 50 with anhydrous hydrogen chloride. Alt and Speziale (3) had previously pointed out the similarity of the uv spectra of 83 (303 nm) to 45 (298 nm), using this as evidence of O-protonation. A comparison of the uv spectra of 84 (278 nm) to 50 (277 nm) supports assignment of the structure of 84 as the O-protonated form. However, it was found that the nmr spectra of 83 and 84 in deuterium oxide or methanol-d^4 did not contain absorptions

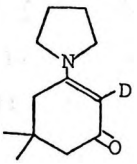
TABLE 4

ALKYLATION AND PROTONATION OF CYCLIC ENAMINO KETONES

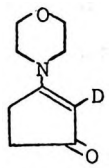
45,	Y = $-(CH_3)_2-$ R = pyrrolidino	81,	Y = $-C(CH_3)_2-$ R = pyrrolidino R'= $-CH_2CH_3$ X = I
49,	Y = - R = pyrrolidino	82,	Y = - R = pyrrolidino R'= $-CH_2CH_3$ X = I
45,	Y = $-C(CH_3)_2-$ R = pyrrolidino	83,	Y = $-C(CH_3)_2-$ R = pyrrolidino R'= H X = Cl
50,	Y = - R = morpholino	84,	Y = - R = morpholino R'= H X = Cl

attributable to a vinyl proton, which were observed in the spectrum of 83 determined in water. The exchange of the vinyl protons is logically attributed to a tautomeric equilibrium of the enol to the keto form.

In a further attempt to verify the exchange phenomenon, solutions of 83 and 84 in deuterium oxide were neutralized with anhydrous potassium carbonate and extracted with chloroform. Removal of solvent followed by recrystallization in benzene-hexane yielded the enamino ketones 45-d^1 and 50-d^1, respectively which exhibited identical mp and uv spectra with 45 and 50. The nmr spectrum of both 45-d^1 and 50-d^1 was also identical with 45 and 50



45-d^1



50-d^1

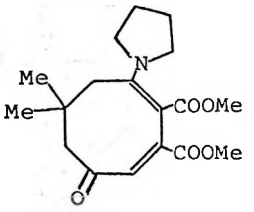
except for the absence of a vinyl proton absorption (less than 5%). Also, the mass spectrum of 45-d^1 contained a parent ion peak at 194 m/e in contrast to 193 m/e obtained for 45.

This evidence clearly supports the exchange phenomenon observed for the O-protonated salts, 83 and 84.

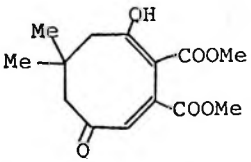
In addition, it should be noted that although the nucleophilic oxygen of the enamino ketone system apparently is the more stable protonation site, fast exchange of hydrogen at carbon does occur. Thus, delocalization of nitrogen lone pair electrons is extensive in 45 and 49 with both oxygen and carbon being sites of protonation in solution.

D. Conformational Inversion in 2,4-Cyclooctadienone Systems

It was observed that the nmr spectrum of 47, the ring-expansion product of the reaction of the monoenamine derivative of dimedone with dimethyl acetylenedicarboxylate, was characterized by two signals for the geminal-ring methyl substituents and two AB patterns for the adjacent methylene groups (Figure 4). Hydrolysis of 47 produced 48 which exhibited similar patterns for these same protons (Figure 5). The nonequivalence of the methylene ring protons of 48 had been noted in the



47



48

Figure 4 NMR Spectra of 3,4-Dicarbomethoxy-7,7-dimethyl-5-pyrrolidino-cycloocta-2,4-dien-1-one

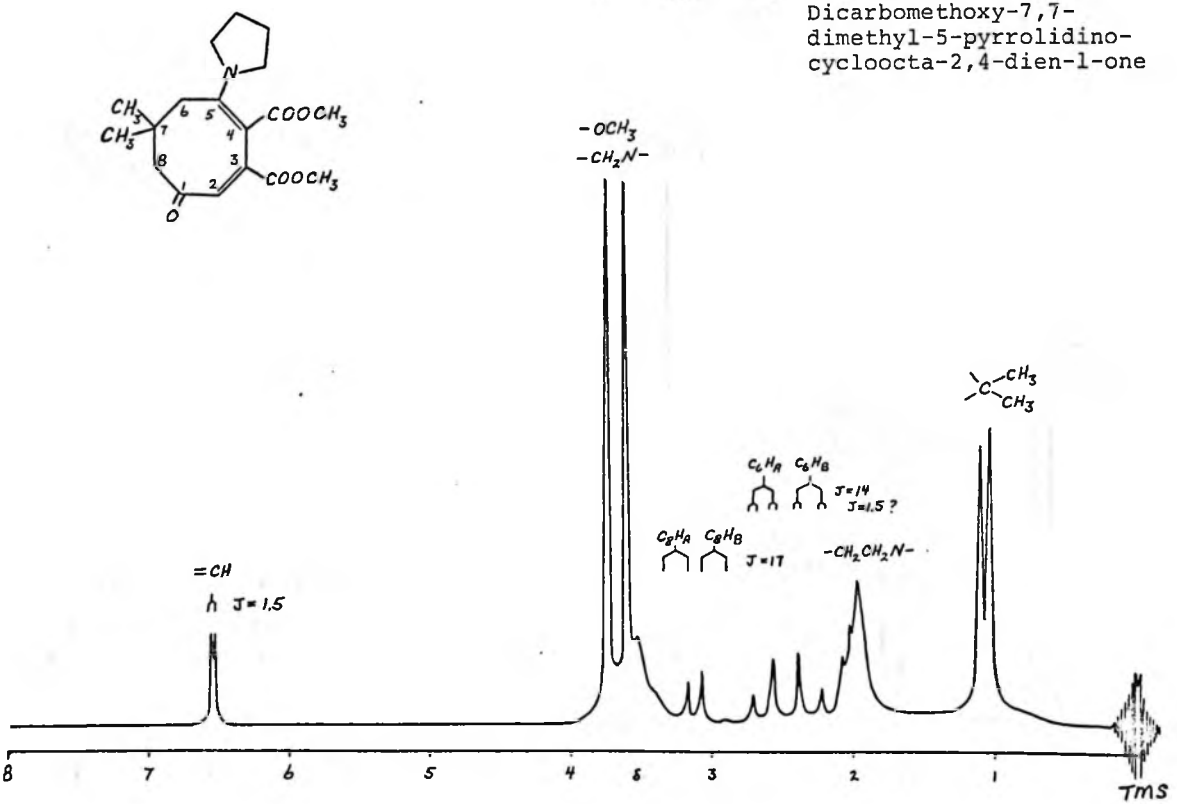
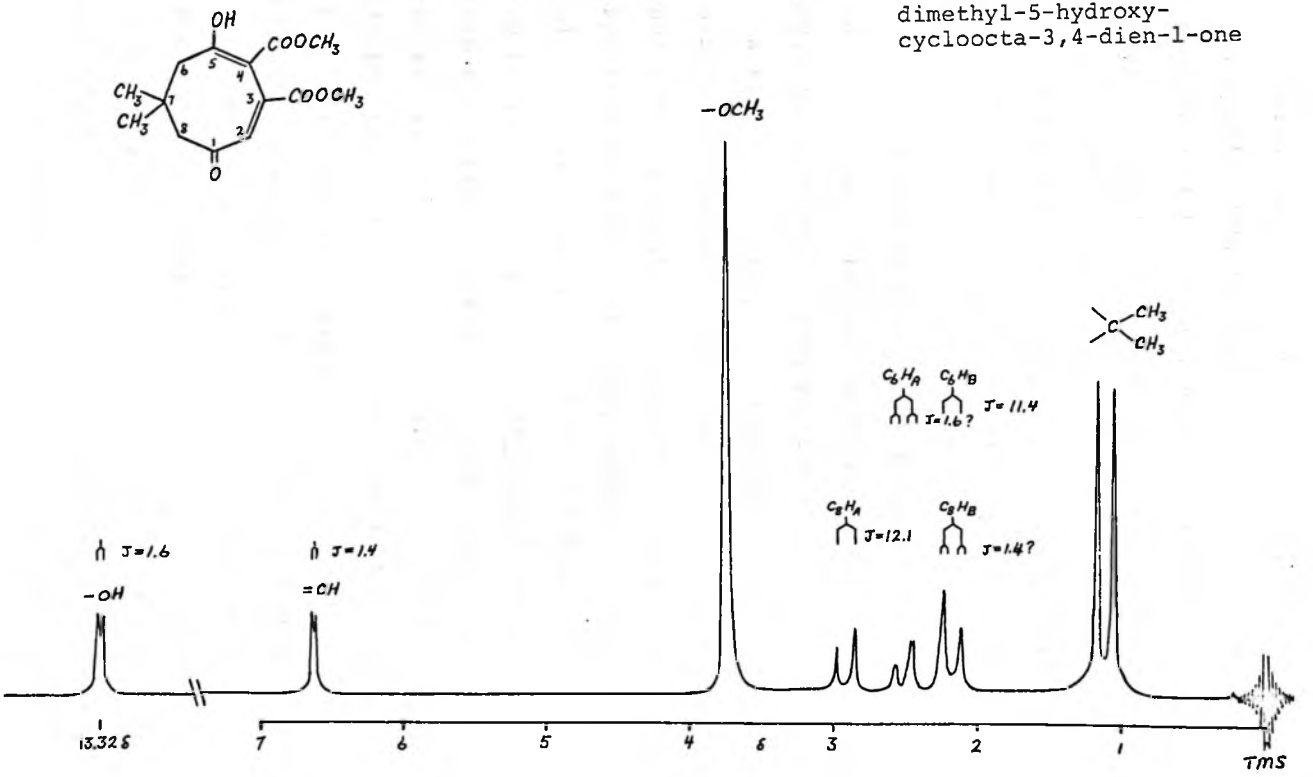


Figure 5 NMR Spectra of 3,4-Dicarbomethoxy-7,7-dimethyl-5-hydroxy-cycloocta-3,4-dien-1-one



experimental description of the preparation of 48 by Huebner, et.al. (45), but no mention was made of the nonequivalence of the geminal-ring methyl groups and no explanation of the nonequivalence was offered. The detailed interpretation of 47 and 48 are given in Figures 4 and 5 respectively. The assignment of ring methylene protons in 48 is based on Huebner's interpretation of the 60 MHz spectrum of this compound.

Nonequivalence in these cases is unquestionably due to high barriers to ring inversion similar to that observed in other medium ring systems (4, 38). Therefore, a study of the temperature dependence of this nonequivalence was undertaken. Although both the ring-geminal groups exhibit this nonequivalence, analysis of the spectral data was most easily accomplished for the methyl signals. Shown in Figure 6 and 7 are nmr scans of the geminal methyl signals of 47 and 48 over a temperature range including the coalesence point. Because of the required temperature range, the solvent for 47 and 48 was tetrachloroethane. As shown in Table 5 the nmr methyl signals in 47 are separated by 8 Hz in the region of slow exchange and coalesence occurs at 45°C, whereas the methyl groups in 48 are separated by 13 Hz and coalesence occurs at 90°C. Activation free energies for these ring inversions were calculated by the use of equation 3, described in Part C-b of this discussion. These data indicate that the 5-pyrrolidino derivative 47

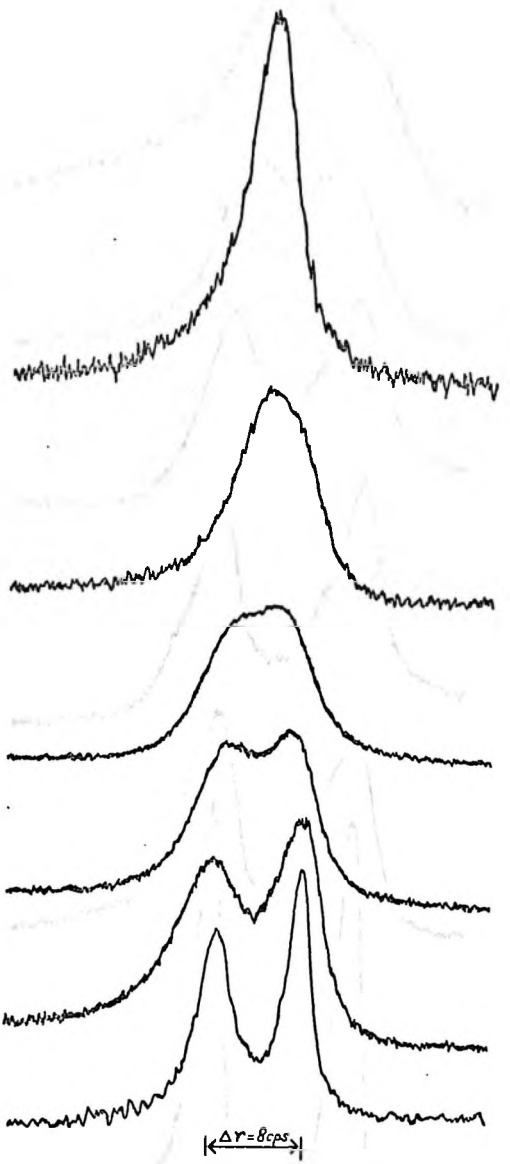


Figure 6

Partial NMR Spectra of 3,4-Dicarbomethoxy-7,7-dimethyl-5-pyrrolidinocycloocta-2,4-dien-1-one

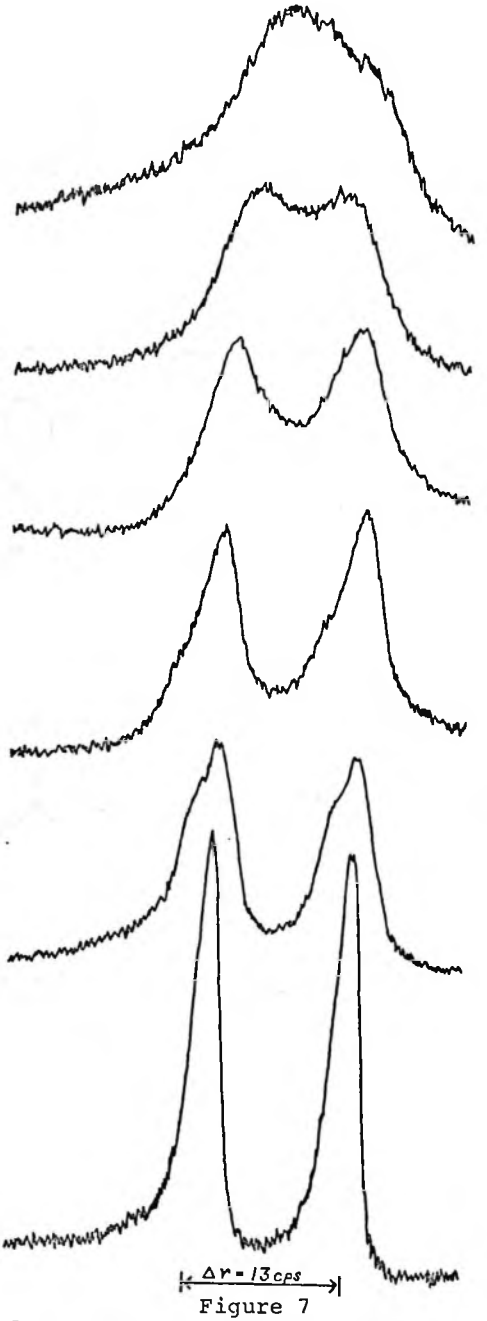
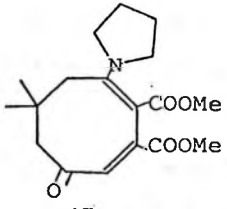
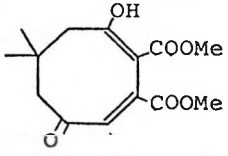


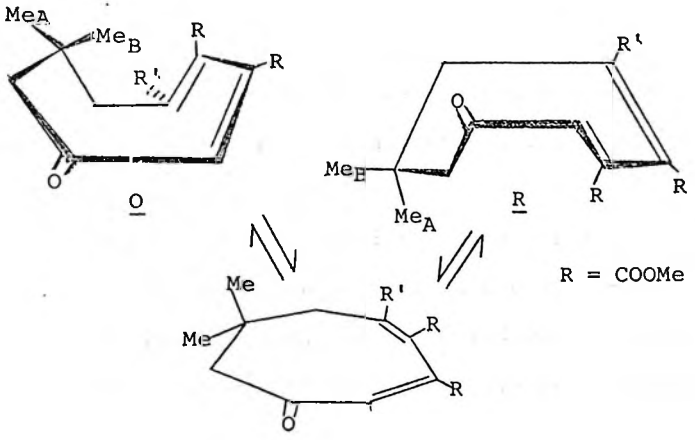
Figure 7
Partial NMR Spectra of 3,4-Dicarbomethoxy-7,7-dimethyl-5-hydroxycycloocta-3,4-dien-1-one

TABLE 5

ACTIVATION FREE ENERGIES FOR RING INVERSION IN CYCOOCTADIENONES

	T_C(C°)	Δν	ΔG*(Kcal/mole)	ΔΔG*
 47	45	8	16.8	2.7
 48	99	13	19.5	

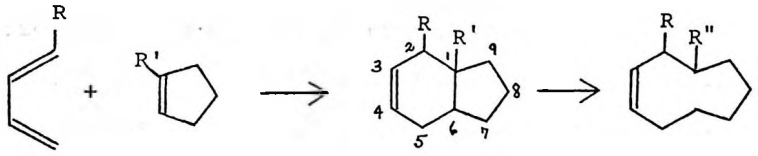
has a lower barrier to inversion than the 5-hydroxy derivative 48. A reasonable assumption in these cases is that the ground state conformations of 47 and 48 would be the nonplanar tub structures O or R (47 R' = pyrrolidino, 48, R'= OH) which would be interconverted through a planar or nearly planar transition state P. The lower barrier to inversion of 47 compared to 48 may be ascribed to a more nearly planar ground state conformation caused by extensive delocalization of the nitrogen lone pair electrons. Other aspects of these spectra are also interpretable on the basis of these conformational properties. For example, the upfield signals for the geminal-ring methyl groups and C-6 and C-8 methylene protons are reasonably assigned to the endo-substituent in each instance since these nuclei would experience anisotropic shielding by the pi



electrons of the conjugated system. Furthermore, the fact that the methylene signals at C-8 are farther downfield in 47 than 48 can be attributed to less shielding of these nuclei in 47, due to a more planar conformation.

E. Reaction of Enamines with Activated Dienes

The third general synthetic approach to a nine-membered ring system bearing substituents capable of being related to the nonadride-type nucleus was based on a key condensation step in which a cyclopentene derivative adds to an activated diene in a cycloaddition reaction to form a bicyclo [4.3.0] nonane carbon skeleton.

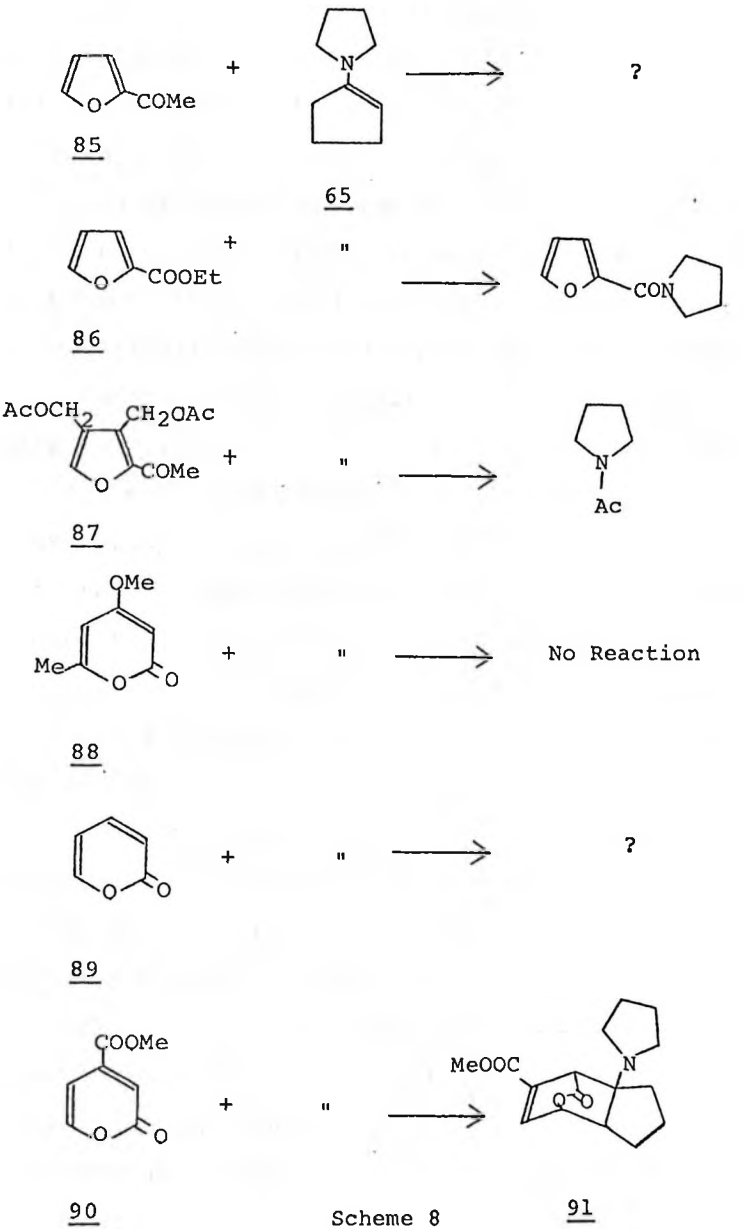


Design of the reactants in such a way as to allow subsequent cleavage of the C-1 to C-6 bond in the bicyclic ring would provide a route to the desired nine-membered ring compound.

The type of condensation chosen for study was the addition of a cyclic enamine to a diene activated toward nucleophilic addition. The reported condensation of the cyclopentanone enamine with ethyl 2,4-pentadienoate

(12, 28) served as an appropriate model. An amino group at C-1 of the bicyclic system should be useful in releasing electrons for displacing the bridging C-1 to C-6 bond concurrent with a bond displacement at C-5. The use of cyclic dienes in this scheme also seemed preferable to acyclic derivatives for several

reasons. Cyclic diene systems with appropriate substituents were more readily available than the acyclic analogs. Also, the necessary cisoid geometry of the cyclic systems should favor ring-closure following initial nucleophilic addition by the enamine. Finally, cyclic dienes containing an appropriate X group would furnish the needed leaving group to be displaced in a concerted manner with the cleavage of the C-1 to C-6 bond. Furans, activated by a carbonyl substituent at C-2, and 2-pyrones are cyclic diene systems having these characteristics and therefore were chosen for study. In the latter case the carbonyl group bridging the diene terminal carbons also would provide activation of the diene toward nucleophilic addition. The reactions attempted in this study are summarized in Scheme 8.


COMe
85
65
?
COOEt
86
CON
AcOCH2
CH2OAc
COMe
87
N
Ac
OMe
Me
88
No Reaction
89
?
COOMe
90
MeOOC
91

Scheme 8

The condensation of the enamine 65 with 2-acetylfuran, 85 and with ethyl 2-furoate, 86, failed to give the desired type of adduct under a variety of conditions. In the latter case, the only identifiable product isolated was 2-pyrrolidinofuroamide (This is the first of two instances in which esters were observed to undergo amidation in reactions with pyrrolidino enamines.) Also, it was decided to attempt the condensation with an activated furan derivative appropriately substituted at the 3- and 4-positions. Commercial 3,4-dicarboethoxyfuran could not be acetylated at C-2, and therefore the acetylation step was preceded by hydride reduction of the carboalkoxy groups to primary carbinol groups which were then protected by esterification. This trisubstituted furan 87 also failed to yield any addition products in reaction with 65. However, pyrrolidinoacetamide was isolated (the second example of amidation of esters in reaction with enamines).

The three 2-pyrone systems chosen for study represented a spectrum of substituent effects. The methyl and methoxy groups of commercially available 88 are electron releasing in contrast to the electron withdrawing carbomethoxy group of 90, which was prepared by conversion of D,L-malic acid to coumalic acid (74), followed by esterification (19). The unsubstituted pyrone 89 was prepared by thermal decarboxylation of coumalic acid (76).

The attempted reaction of 88 with 65 in refluxing benzene led only to recovery of starting materials. Treatment of 89 with 67 in refluxing diglyme gave signs of reaction, but no identifiable products could be detected by nmr analysis or isolated by column chromatography. However, instantaneous reaction of 90 with 67 was observed at room temperature in a variety of solvents. Reaction in p-dioxane solution containing a trace of hydroquinone gave a product mixture from which a minute quantity of a crystalline substance was isolated by means of column chromatography. The nmr of this product was reasonably consistent with the structure 91, which represents the desired addition-cyclization product. It was observed that treatment of the crude product mixture from this reaction resulted in immediate evolution of a gas, presumably carbon dioxide. The small quantities of materials available in these reactions prevented additional characterization of this product at the present time, but the results constitute a promising basis for further experimentation.

CHAPTER IV

EXPERIMENTAL

General Remarks.--Standard taper Pyrex glassware was used in all reactions unless otherwise noted. Reaction vessels were protected by calcium chloride tubes in cases where the effect of moisture on the reaction was uncertain. Melting points were obtained on a Fisher-Johns Melting Point apparatus. Both melting and boiling points are reported uncorrected. The refractive indices were obtained on an Abbe-3L, Bausch & Lomb Refractometer. All elemental analysis were performed by Chemalytics, Inc.*

Infrared spectra were obtained using a Perkin-Elmer Model 337 Infrared Spectrophotometer or a Perkin-Elmer Model 127 Infracord Spectrophotometer. Values for absorption bands are reported in cm^{-1}. The nmr spectra were obtained using a Varian Model HA-100 High Resolution NMR Spectrometer. The lock signal employed for spectra determined in deuteriochloroform and methanol-d^4 solvents was tetramethylsilane. For spectra determined in deuterium oxide (D_2O) and water (H_2O) solvents, sodium-2,2-dimethyl-2-silapentane-5-sulphonate (Merck Sharp & Dohme

---

*Chemalytics, Inc., 2330 S. Industrial Park Drive, Temple, Arizona 85281.

of Canada Limited, MX-1061) was employed as the lock signal. Chemical shifts are reported as ppm downfield from the lock signal. Mass spectra were obtained using a CEC Type 21-104 Mass Spectrometer. The ultraviolet and visible spectra were obtained using a Perkin-Elmer Model 202 Ultraviolet-Visible Spectrometer. Values for absorption maxima are reported in nm along with ($\log\varepsilon$).

Preparation of 1-Morpholinocyclopentene (67).--1-Morpholinocyclopentene was prepared by the method of Stork, et.al., (70) and purified by distillation: bp 111-115° (19 mm), lit. (70) bp 104-106° (12 mm). It was necessary to store the product under nitrogen in a refrigerator.

Preparation of 1-Morpholino-2,3-dicarbomethoxy-1,3-cycloheptadiene.--1-Morpholino-2,3-dicarbomethoxy-1,3-cycloheptadiene was prepared by a procedure similar to that used by Huebner, et.al. (45) for the preparation of 1-pyrrolidino-2,3-dicarbomethoxy-1,3-cycloheptadiene. Ten g of dimethyl acetylenedicarboxylate (D 13,840-1, Aldrich Chemical Company, Inc.) was added over a period of five min to a solution of 10.8 g of 1-morpholino-cyclopentene in 12 ml of diglyme with rapid stirring. Instant red coloration was observed. The reaction was exothermic and the temperature rose to ca. 110°. The mixture was allowed to cool whereupon crystallization occurred. The crystals were filtered and washed with

cold ethyl acetate to produce a clean yellow product: mp 168-170°; lit. (13) mp 167-168°.

Preparation of 2,3-Dicarbomethoxy-3-cycloheptenone (20).--2,3-Dicarbomethoxy-3-cycloheptenone 20 was prepared by a procedure similar to that of Huebner, et.al. (45). 1-Morpholino-2,3-dicarbomethoxy-1,3-cycloheptadiene (4.0 g) was added to 20 ml of 15% hydrochloric acid solution at room temperature with rapid stirring. Instant dissolution followed by cloudiness occurred. The solution was allowed to sit at room temperature for ca. two hr, after which the crystallized product was filtered and washed thoroughly with water. The white, crystalline product was sufficiently pure for use without further crystallization: 98% yield; mp 61-62°, lit. (13) mp 63.5-64°.

Bromination of 2,3-Dicarbomethoxy-3-cycloheptenone (20).--Ten g of 20 and 7.88 g of N-bromosuccinimide (B-382 Fisher Scientific Co.) were placed in 100 ml of carbon tetrachloride which had been purified according to a procedure by Fieser (33). The mixture was heated under reflux for ca. 1.5 hr. The color of the solution gradually turned bright orange. The solution was allowed to cool, and the solid succinimide was filtered and washed with cold carbon tetrachloride. Removal of the solvent under vacuum at room temperature gave a viscous yellow oil which crystallized on cooling. The crystalline material, corresponding to a 30% yield, was filtered and washed with cold

carbon tetrachloride. The yellow solid, identified as 4-bromo-2,3-dicarbomethoxy-2-cyclohepten-1-one, 23, was recrystallized in acetone-water and was found to be unstable at room temperature, but could be stored indefinitely at 0°: mp 73-74°; ir (KBr) 1730, 1680 (C=O), 1620 (C=C); nmr ($CDCl_3$) 5.4 (d, J = 5 Hz, 1H, CHBr), 3.75-3.80 (2s, 6H, OCH_3), 2.9-3.3 (m, 1H, CBrCH), 2.5-2.8 (m, 1H, CBrCH), 1.9-2.5 (m, 4H, CH_2CH_2CO); uv (95% ethanol) 225 (3.88); mass spectrum (70eV) m/e (rel intensity) 275 (11), 274 (10), 273 (11), 272 (9), 247 (18), 245 (18), 194 (63), 193 (47), 166 (32), 165 (100), 137 (30). Anal. Calcd for $C_{11}H_{13}O_5Br$: C, 43.30; H, 4.29; Br, 26.19. Found: C, 43.40; H, 4.09; Br, 26.31.

Isomerization of 4-Bromo-2,3-dicarbomethoxy-2-cyclohepten-1-one (23) to 4-Bromo-2,3-dicarbomethoxy-1-hydroxy-1,3-cycloheptadiene (28) in Methanolic Sodium Methoxide.--A solution of sodium methoxide in methanol was prepared from the reaction of 5.5 g of sodium with 100 ml of methanol. To this solution, maintained at ca. 0-5° by means of an ice water bath, was added 3.0 g of 23 in 40 ml of methanol over a period of ca. 15 min. The solution gradually turned bright yellow as addition progressed. Cooling and stirring was maintained for an additional 30 min whereupon the solution was allowed to warm to room temperature and stirred for one hr. The yellow solution was treated with dilute hydrochloric acid solution until it was just acid to litmus. At this point the yellow

color of the solution faded. By cooling the solution, a white crystalline material formed which was filtered and washed with water. The solid precipitate of 28 was recrystallized in acetone-water: 60% yield; mp 106-107°; ir (KBr) 1725 (C=C), 1650 (enol chelate), 1595 (diene); nmr ($CDCl_3$) 12.8 (s, 1H, OH), 3.8 (2s, 6H, OCH_3), 2.4-2.9 (m, 6H, CH_2); uv (95% ethanol) 210 (3.65); mass spectrum (70eV) m/e (rel intensity) M+ 306 (17), M+ 304 (18), 274 (96), 272 (100), 246 (14), 244 (14), 219 (20), 217 (22), 193 (30), 165 (91), 137 (50). Anal. Calcd for $C_{11}H_{13}O_5Br$: C, 43.30; H, 4.29; Br, 26.19. Found: C, 43.39; H, 4.15; Br, 26.51.

Isomerization of 4-Bromo-2,3-dicarbomethoxy-2-cycloheptenone (23) to 4-Bromo-2,3-dicarbomethoxy-1-hydroxy-1,3-cycloheptadiene (28) in Sodium Hydroxide Solution.--One g of 23 was stirred in 50 ml of five percent sodium hydroxide solution at room temperature for two hr. The solid gradually dissolved forming a yellow solution. The solution was made just acid to litmus by addition of dilute nitric acid solution. A light, pink solid precipitated which was filtered and washed with water: mp 103-104°. The solid substance was identical with that formed in the isomerization of 23 in methanolic sodium methoxide.

Isomerization of 4-Bromo-2,3-dicarbomethoxy-2-cyclohepten-1-one (23) to 4-Bromo-2,3-dicarbomethoxy-1-hydroxy-1,3-cycloheptadiene (28) with Triethylamine.--Two drops of triethylamine was added to a sample of 23 in

deuteriochloroform and the nmr spectra was examined. Within 30 min over one-half of 23 had isomerized to 28. Isomerization was complete after eight hours.

Reaction of 4-Bromo-2,3-dicarbomethoxycyclohept-2-en-1-one (23) with Morpholine.--Seven g of morpholine was added slowly to 18 g of 23 in 200 ml of dry benzene. The mixture was stirred vigorously and heated at reflux for one hour. Evaporation of the solvent gave an oily solid which was dissolved in boiling methanol. Addition of ether and cooling caused precipitation to occur. The solid morpholine hydrobromide was filtered and stored in a vacuum desiccator. The salt was readily soluble in water and silver bromide precipitated when the solution was treated with silver nitrate solution. A sample of morpholine hydrobromide prepared by reaction of morpholine with hydrobromic acid solution was identical in all respects with the collected sample.

The mother liquor was evaporated to give solid 2,3-dicarbomethoxy-2-morpholinocyclohept-3-en-1-one, 31, which was filtered, washed sparingly with cold methanol, and recrystallized in boiling carbon tetrachloride: 20% yield; mp 158-159°; ir (KBr) 1740, 1720, 1690 (C=O), 1620 (C=C); nmr ($CDCl_3$) 7.15-7.30 (t, J = 6Hz, 1H, =CH), 3.6-3.7 (m, 10H, OCH_3, CH_2O), 3.0-3.3 (m, 2H, CH_2CO), 2.3-2.9 (m, 6H, $=CCH_2$, CH_2N), 1.8-2.0 (m, 2H, CH_2); uv (95% ethanol) 240 (3.91), 265 (3.96); mass spectrum (70eV) m/e (rel intensity) M+ 311 (5), 255 (8), 253 (10), 225 (100),

224 (14), 196 (16), 166 (5), 164 (6). Anal. Calcd for $C_{15}H_{21}O_6N$: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.70; H, 6.64; N, 4.60.

Reduction of 4-Bromo-2,3-dicarbomethoxy-2-cycloheptenone (23) to 2,3-Dicarbomethoxy-1-hydroxy-1,2-cycloheptadiene (20).--To one g of 23 in two ml of ethanol was added a saturated solution of sodium bisulfite until no further red color developed in the solution. During addition an oil formed on the bottom of the flask. The solution was decanted from the oil and the oil was crystallized by cooling. The crystals were filtered, washed with water and dried in a vacuum desiccator. The crystalline substance had a mp 60-61° and was found to be identical in all respects with the sample of 20 prepared by hydrolysis of 1-morpholino-2,3-dicarbomethoxy-1,3-cycloheptadiene.

Selenium Dioxide Oxidation of 2,3-Dicarbomethoxy-1-hydroxycyclohepta-1,3-diene (20).--The procedure used was similar to that developed by Schaefer, Horvath, and Klein (67) for the oxidation of olefins. A solution of 5.0 g of 20 in 100 ml of glacial acetic acid was added to 1.23 g of selenium dioxide (Alfa Inorganics, No.68101) in 1.0 ml water. The mixture was heated at reflux for 20 min and cooled rapidly in an ice bath. The selenium was filtered and the filtrate was poured into one-liter of water. The solution was extracted three times with ether, and the ether was washed successively with water,

dilute sodium carbonate, and water, and dried over anhydrous sodium sulfate. Evaporation of the ether solution provided a crystalline substance. Recrystallization in carbon tetrachloride-pentane solution gave 0.9 g of light yellow crystals. This compound was tentatively identified as 2,3-dicarbomethoxy-4-hydroxycyclohept-2-en-1-one, 37. A sufficient amount of 37 was not obtained for thorough purification, and hence elemental analysis was not satisfactory. Physical and spectral data was as follows: 17% yield; mp 72-73°; ir (KBr) 3330 (OH), 1730, 1715 (C=O), 1645 (C=C); nmr ($CDCl_3$) 5.2 (s, 1H, OH), 5.0 (s, 1H, OCH), 5.80 (s, 3H, OCH_3), 5.74 (s, 3H, OCH_3), 1.8 (m, 6H, CH_2); uv (95% ethanol) 210 (3.81); mass spectrum (70eV) m/e (rel intensity) 211 (10), 210 (9), 183 (69), 151 (100), 123 (12), 117 (12), 79 (18), 59 (24), 55 (28). Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 53.43; H, 5.53.

Attempted Manganese Dioxide Oxidation of 2,3-Dicarbomethoxy-4-hydroxycyclohept-2-en-1-one (37).--To a solution of 0.5 g of 37 in benzene was added one g of active manganese dioxide prepared by the method of Attenburrow, et.al. (5). The mixture was heated under reflux for three hr using a water separator. The mixture was cooled, the solid filtered, and solvent removed by vacuum distillation. The presence of 37, and 2,3-dicarbomethoxycyclohept-2-en-1,4-dione, 39, and/or 2,3-dicarbomethoxy-1,4-

dihydroxycyclohepta-1,3-diene, 38, was indicated by the nmr ($CDCl_3$) of the residual oil: 12.38 (s, OH), 5.0 (s, OCH), 3.7-3.9 (3s, OCH_3), 2.8 (t, J = 6Hz, CH_2CO), 1.4-2.3 (m, CH_2).

Preparation of 1-Acetoxy-2,3-dicarbomethoxy-1,3-cycloheptadiene (40).--To a solution of 10.0 g of 2,3-dicarbomethoxy-1-hydroxycyclohepta-1,3-diene and 22.35 g of freshly distilled triethylamine in 100 ml of dry benzene was added 17.4 g of acetyl chloride over a period of 15 min while vigorous stirring was maintained. The reaction was exothermic and the temperature rose to reflux as a white solid formed. After addition was complete the mixture was heated under reflux for six hr. The mixture was cooled and the solid triethylamine hydrochloride was filtered and washed with benzene. After removal of solvent, the residual oil was distilled to give pure 40: bp 126-131° (0.6 mm); nmr ($CDCl_3$) 7.4 (t, J = 7 Hz, 1H, =CH), 3.7 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 2.2-2.35 (s on m, 10H, CH_3CO, CH_2).

Reaction of 1-Acetoxy-2,3-dicarbomethoxy-1,3-cycloheptadiene (40) with N-Bromosuccinimide.--To a solution of 5.0 g of N-bromosuccinimide in 30 ml of specially purified carbon tetrachloride (33) was added 3.0 g of 40 and 0.1 g of 2,2'-azobis-(2-methylpropionitrile) (Eastman Chemicals, No. 6400). The mixture was heated under reflux for ca. four hours. The mixture was cooled and the solid succinimide was filtered and washed with carbon

tetrachloride. After removal of solvent, the residual oil was distilled. The fraction collected at 148-155° (1 mm) was a yellow oil which was identified as a mixture of 1-acetoxy-5-bromo-2,3-dicarbomethoxy-1,3-cyclohepta-diene, 42, and 1-acetoxy-7-bromo-2,3-dicarbomethoxy-1,3-cycloheptadiene, 41, and exhibited the following nmr ($CDCl_3$) spectral data: 7.17 (d, J = 5Hz, 1H), 7.07 (t, J = 7 Hz, 1H), 6.24 (q, J = 5Hz, J = 10 Hz, 1H), 5.80 (d of t, J = 7 Hz, J = 10 Hz, 1H), 3.7 (3s, 10H, OCH_3), 2.7(s on m, 4H, CH_3CO), 2.2 (m, 6H, CH_2). The oil was unstable and darkened considerably over a period of three days at room temperature.

Preparation of 1,3-Cyclopentanedione.--1,3-Cyclopentadione was prepared according to the procedure of DePuy and Zaweski (29). Two g of cyclopentene-1,4-dione (65) in 100 ml of glacial acetic acid was added over a period of 45 min to a vigorously stirred* mixture of 20 g of zinc dust in 100 ml of glacial acetic acid in a one-liter flask maintained at 85° by means of an oil bath. The mixture was cooled and the solid was filtered and washed with 100 ml glacial acetic acid. The filtrate and washings were combined and evaporated at room temperature under vacuum. A clean white solid (mp 140-146°) remained which was stored in a desiccator over NaOH to remove last traces of acid. The dried product was sufficiently pure

*Vigorous stirring is necessary at this point. On separate attempts where vigorous stirring was not maintained, an inferior product resulted.

for use without crystallization: 64% yield; mp 149-150° lit. (17) mp 151.5-152.5°; uv (0.1N HCl) 242 (4.23) lit. (17) uv (0.1N HCl) 242 (4.32); ir (KBr) 1600 (C=O), lit (17) ir (Nujol Mull) 1600.

Preparation of 1,2-Cyclopentanedione.--1,2-Cyclopentanedione was prepared according to the procedure of Acheson (1). The exact procedure was followed with the exception of substituting molar equivalents of ferric chloride hexahydrate in place of anhydrous ferric chloride: bp 75° (4 mm), lit. (1) bp 78-86° (8 mm); mp 53-55°, lit. (1) mp 55-56°.

General Procedure for Preparation of Cyclic Morpholino and Pyrrolidino Enamino Ketones.--The procedure used was similar to that of Stork, et.al. (70) for the preparation of enamines, where a 1:1.3 mole equivalent ratio of dicarbonyl compound and secondary amine in benzene was heated under reflux. Water was separated from the reaction by use of a Dean-Stark trap. Reflux was generally continued for ca. one hr after the theoretical amount of water had been removed, whereupon the mixture was cooled, and the excess benzene and amine was removed by vacuum distillation. The residue was then either recrystallized or distilled.

Preparation of 5,5-Dimethyl-3-pyrrolidinocyclohex-2-en-1-one (45).--The general procedure for preparation of cyclic pyrrolidino enamino ketones was followed giving a solid residue after evaporation of solvent. The product

was recrystallized twice in benzene-hexane solvent affording clean, yellow crystals of 45: mp 134-135°, lit. (49) mp 131-133°, ir (10% by weight in $CHCl_3$) 1598 (C=O), 1548 (C=C), lit. (49) ir (CCl_4, 2%) 1619, 1573; uv (0.1N NaOH) 303 (4.53), lit. (49) uv 303 (4.54); nmr ($CDCl_3$) 5.04 (s, 1H, =CH), 3.1-3.6 (m, 4H, NCH_2), 2.3 (s, 2H, CHCO), 2.15 (s, 2H, CHC=C), 1.90-2.05 (m, 4H, CH_2), 1.1 (s, 6H, CH_3), lit. (2) nmr ($CDCl_3$) 5.02 (=CH); mass spectrum (70eV) m/e (rel intensity) M+ 193 (50), 178 (9), 165 (17), 164 (16), 150 (36), 137 (38), 123 (8), 109 (100), 108 (29), 70 (30), 68 (40), 67 (25).

Preparation of 3-Pyrrolidinocyclohex-2-en-1-one (52).--The general procedure for preparation of cyclic pyrrolidino enamino ketones was followed giving a semi-solid residue after evaporation of solvent. The residue was redissolved in benzene and cooled in an ice bath. A black oily impurity separated upon addition of hexane, and the mother liquor was decanted. More hexane was added and the procedure repeated until the solution became noticeably lighter in color, whereupon a solid precipitate formed. The solid was filtered and washed with hexane. The compound was again recrystallized giving solid yellow 52: mp 86-88°, lit. (61) mp 84-88°; ir (10% by weight in $CHCl_3$) 1595 (C=O), 1546 (C=C); nmr ($CDCl_3$) 5.06 (s, 1H, =CH), 3.10-3.60 (m, 4H, NCH_2), 2.30 (t, J = 6.0 Hz, 2H, CHCO), 2.50 (t, J = 6.0 Hz, 2H, CHC=C), 2.0 (m, 6H, CH_2);

uv (0.1N NaOH) 302 (4.54); mass spectrum (70eV) m/e (rel intensity) M+ 165 (9), 164 (49), 137 (46), 109 (100), 108 (31), 94 (20), 81 (21), 68 (43).

Preparation of 3-Pyrrolidino-2-cyclopenten-1-one (49). --The general procedure for preparation of cyclic pyrrolidino enamino ketones was followed using two g of 1,3-cyclopentadione and 1.5 g of pyrrolidine. Removal of the solvent after reflux gave a dark, solid residue. Solution in benzene followed by addition of hexane and cooling gave a dark, oily substance from which the mother liquor was decanted. Addition of more hexane caused crystallization to occur. The product was filtered and recrystallized giving light yellow crystals of 49: 49% yield; mp 104-105°; ir (10% by weight in $CHCl_3$) 1646 (C=O), 1543 (C=C); nmr ($CDCl_3$) 4.87 (s, 1H, =CH), 3.10-3.55 (2t, J = 6 Hz, 4H, CH_2N), 2.25-2.70 (2t, J = 4 Hz, 4H, $=CCH_2-CH_2$), 1.90-2.20 (m, 4H, CH_2); uv (0.1N NaOH) 279 (4.42); mass spectrum (70eV) m/e (rel intensity) M+ 151 (77), 123 (24), 122 (100), 108 (38), 95 (67), 94 (32), 81 (16), 70 (27). Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.90; H, 8.52; N, 8.88.

Preparation of 2-Pyrrolidinocyclohex-2-en-1-one (62). --The general procedure for preparation of cyclic pyrrolidino enamino ketones was followed using 1,2-cyclohexadione (C6720 Columbia Organic Chemical Co. Inc.) as the starting diketone. After reflux and evaporation of solvent the residue was distilled giving pure 62:

bp 68-70° (0.1 mm), lit. (46) bp 70-71° (0.2 mm); n_D^{27} 1.5355; ir (10% by weight in $CHCl_3$) 1674 (C=O), 1600 (C=C), lit. (46) ir (neat) 1680, 1600; nmr ($CDCl_3$) 5.54 (t, J = 5 Hz, 1H, =CH), 3.0-3.2 (t, J = 7 Hz, 4H, NCH_2), 2.3-2.6 (m, 4H, $CH_2C=$ and CH_2CO), 1.7-2.1 (m, 6H, CH_2), lit. (46) nmr (neat) 5.44 (t, J = 5 Hz, 1H), 2.9-3.2 (m, 4H), 2.1-2.5 (m, 4H), 1.6-2.05 (m, 6H); uv (0.1N NaOH) 217 (3.68), 298 (3.48); mass spectrum (70eV) m/e (rel intensity) M+ 165 (87), 164 (48), 150 (31), 137 (38), 136 (100), 109 (35), 108 (39), 81 (45), 70 (58).

Preparation of 2-Pyrrolidino-2-cyclopenten-1-one (63).--The general procedure for preparation of cyclic pyrrolidino enamino ketones was followed giving a dark, oily residue. The residue was redissolved in benzene and pentane was added with cooling. A black tarry substance separated and the solution was decanted from the tar. The solution was then evaporated to an oily residue and distilled under vacuum to give 63: bp 83-84° (0.5 mm); ir (10% by weight in $CHCl_3$) 1699 (C=O), 1606 (C=C); n_D^{28} 1.5375; nmr ($CDCl_3$) 5.82 (t, J = 3 Hz, 1H, =CH), 3.1-3.4 (t, J = 7 Hz, 4H, NCH_2), 2.25-2.55 (m, 4H, CH_2CH_2CO), 1.65-2.0 (m, 4H, CH_2).

Preparation of 2-Methyl-3-pyrrolidinocyclopent-2-en-1-one (61).--The general procedure for preparation of cyclic pyrrolidino enamino ketones was followed using

2-methyl-1,3-cyclopentadione (Aldrich 11,702-1) as the starting diketone. However, in this case less than the theoretical yield of water was collected during the usual 2-5 hr reflux period. The mixture was cooled and the solvent was evaporated to give a solid residue. The residue was recrystallized in benzene-chloroform-hexane giving a fluffy white powder. This solid was identified as pyrrolidinium 3-oxo-1-cyclopentenolate, 93, from the following spectral and physical data: mp 90-94°; ir (KBr) 1625; nmr ($CDCl_3$), 8.6 (s, 2H, NH), 3.2 (m, 4H, CH_2N), 2.1 (s, 4H, CH_2CO), 2.0 (m, 4H, CH_2), 1.5 (s, 3H, CH_3); uv (95% ethanol) 267 (4.39); mass spectrum (70eV) m/e (rel intensity) 112 (50), 70 (100). Addition of deuterium oxide eliminated the NH absorptions in the nmr spectra. Also, the salt was found to be very soluble in water and gave an intense violet color when treated with ferric chloride solution. When the reflux period was extended to 48 hr a theoretical amount of water was separated. The solution was cooled and the solvent was removed leaving a solid residue. The residue was recrystallized in pet ether (60-110) giving tan crystals of 61; mp 96-97°, lit. (61) mp 100°; ir (10% by weight in $CHCl_3$) 1640 (C=O), 1550 (C=C), lit. (61) ir (?) 1661, 1558; nmr ($CDCl_3$) 3.6 (m, 4H, CH_2N), 2.5 (m, 2H, CH_2CO), 2.3 (m, 2H, $=CCH_2$), 1.8-2.1 (s on m, 7H, CH_2, CH_3); uv (95% ethanol) 294 (4.51), lit. (61) uv (ethanol) 296 (4.55).

The enamino ketone 61 also could be prepared by heating a sample of 93 in benzene containing excess pyrrolidine over ca. a 24 hr period. Products from both preparations were identical.

General Procedure for Reaction of an Enamino Ketone with Dimethyl Acetylenedicarboxylate.--An equimolar quantity of DMAD was added over a period of 10-15 min to a rapidly stirred solution of enamino ketone in glyme preheated to ca. 85°. Heating was continued for one hr after addition was complete. Both the addition and heating processes were carried out under a nitrogen atmosphere. The mixture was allowed to cool, and the products were isolated by crystallization or column chromatography using unactivated silica gel (60-200 mesh) as the stationary phase and benzene-chloroform as eluting solvents. Each chromatographic fraction was analyzed by TLC, using Silica Gel G as adsorbant. The developing solvent consisted of 5% methanol, 15% acetone, 20% ethyl acetate and 60% $CHCl_3$ unless otherwise stated.

The percent of the ring-expanded product and the Michael adduct for each reaction was calculated directly from the initial product mixture by use of nmr analysis. Amounts of starting materials (enamino ketone and DMAD) were weighed on an analytical balance and weights recorded to four decimal places. Upon completion of reaction the solution was transferred quantatively to a tared flask, and the solvent was removed at 40° (0.1mm).

Then the flask and contents were weighed and a correction factor calculated, when needed, for traces of unremoved solvent and other extraneous material. A weighed aliquot of the product residue and a weighed amount of N,N-dimethylformamide (DMF) were combined and diluted with deuteriochloroform for nmr analysis. Since the ring-expanded product and the Michael adduct exhibited characteristically different vinyl proton chemical shifts (over one ppm difference in all cases studied) the integration traces of the spectral region, 4.0-8.5 Hz (the -CHO proton of DMF is found at 8.05), provided the ratio of unknown products to the known DMF standard on a 1:1:1 basis, and the percent yield of both products could be conveniently calculated. At least three integration traces were obtained for each spectra and at least two product ratios were calculated for each reaction by use of the following equations:

$$M_X = MI_X/I$$

where M_X = moles of reaction product

M = moles of added DMF

I_X = integration value of vinyl proton of reaction product

I = integration value of -CHO proton of DMF

$$P = 100M_XAC/B$$

where P = percent yield of product

A = molecular weight of product

B = weight of product residue

C = correction factor = weight of product residue/ weight of reactants

This method provided a convenient method of studying the optimum conditions yielding maximum percent yields. Hence, the figures reported represent an average of those obtained at the conditions found to give maximum yield.

Reaction of 5,5-Dimethyl-3-pyrrolidinocyclohex-2-en-1-one (45) with Dimethyl Acetylenedicarboxylate.--The general procedure for reaction of an enamino ketone with DMAD was followed giving a dark, oily solution. The solution was cooled and pentane was added until the solution turned cloudy. A yellow crystalline precipitate of dimethyl 2-(5,5-dimethyl-6-oxo-3-pyrrolidinocyclohexenyl)-fumarate, 51, formed which was filtered and washed with cold ether. The precipitate was recrystallized in carbon tetrachloride: 66% yield; mp 133-134°; ir (KBr) 1720, 1700 (C=O), 1505 (diene); nmr ($CDCl_3$) 5.32 (s, 1H, =CH), 3.74 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.2-3.4 (m, 4H, NCH_2), 2.50 (s, 2H, CH_2CO), 2.17 (s, 2H, $=C(N)CH_2$), 1.8-2.0 (m, 4H, CH_2), 1.04 (s, 6H, CH_3); uv (95% ethanol) 224 (3.94), 324 (4.11), 350 (shoulder) (3.79); mass spectrum (70eV) m/e (rel intensity) M+ 335 (6), 304 (4), 303 (4), 289 (10), 277 (20), 276 (100), 216 (37), 200 (7). Anal. Calcd for $C_{18}H_{25}O_5N$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.28; H, 7.35; N, 4.06.

The filtrate was evaporated to an oily residue and chromatographed on a 1x12" column of silica gel. A single colored band was eluted from the column using benzene/chloroform mixtures. Evaporation of solvent gave a yellow oily residue. TLC analysis of the residue from a 20% acetone, 80% ethyl acetate elution gave a single spot with R_F 0.6. The oil was crystallized by cooling and recrystallized in carbon tetrachloride-pet ether (30-60°) to give a 32% yield of 3,4-dicarbomethoxy-7,7-dimethyl-5-pyrrolidinocycloocta-2,4-dien-1-one, 47: mp 119-120°; ir (KBr) 1730, 1710 (C=O), 1640, 1525 (diene); nmr ($CDCl_3$) 6.48 (d, J = 1.5 Hz, 1H, =CH), 3.2-3.8 (2s on m, 10H, OCH_3, NCH_2), 2.4 (2d, J = 14 Hz, 2H, $=C(N)CH_2$), 3.1 (2d, J = 17 Hz, 2H, CH_2CO), 1.8-2.1 (m, 4H, CH_2), 1.0-1.1 (2s, 6H, CH_3); uv (95% ethanol) 222 (4.01), 317 (4.04), 400 (3.71); mass spectrum (70eV) m/e (rel intensity) M+ 335 (41), 320 (25), 304 (26), 292 (59), 276 (91), 250 (34), 248 (40), 244 (62), 220 (43), 119 (30), 83 (67), 70 (100). Anal. Calcd for $C_{18}H_{25}O_5N$: C, 46.46; H, 7.51; N, 4.18. Found: C, 64.63; H, 7.34; N, 4.05.

Reaction of 3-Pyrrolidinocyclohex-2-en-1-one (52) with Dimethyl Acetylenedicarboxylate.--The general procedure for reaction of an enamino ketone with DMAD was followed. The solution was cooled and ether was added, whereupon crystallization of 3,4-dicarbomethoxy-5-pyrrolidinocycloocta-2,4-dien-1-one, 53, occurred. The

yellow solid was filtered, washed with ether and recrystallized in carbon tetrachloride: 48% yield; mp 172-173.5°; ir (KBr) 1730, 1705, 1640 (C=O), 1520 (diene); nmr ($CDCl_3$) 6.45 (s, 1H, =CH), 3.1-3.8 (2s superimposed on m, 10H, OCH_3, CH_2N), 2.4-2.8 (m, 4H, CH_2CO, $=CCH_2$), 1.8-2.2 (m, 6H, CH_2); uv (95% ethanol) 224 (4.37), 304 (4.19), 404 (4.00); mass spectrum (70eV) m/e (rel intensity) M+ 307 (29), 279 (20), 276 (20), 248 (100), 200 (95), 192 (20), 160 (22), 91 (21), 70 (62). Anal. Calcd for $C_{16}H_{21}O_5N$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.39; H, 6.76; N, 4.42.

The filtrate was evaporated to orginal volume and the glyme removed at 40° (2 mm). The residue was chromotographed on a silica gel column using mixtures of benzene and chloroform as the eluting solvent. The fractions were analyzed by TLC. Fractions containing the compound corresponding to the spot at R_F = 0.6 were combined and rechromatographed on silica gel. This process was continued until a relatively pure sample of dimethyl 2-(3-oxo-1-pyrrolidino-1-cyclohexenyl)-fumarate, 54, was obtained. The compound was then purified by recrystallization in ether-hexane: 50% yield; mp 132.5-133.5°; ir (KBr) 1730, 1630, 1585 (C=O), 1505 (diene); nmr ($CDCl_3$) 5.33 (s, 1H, =CH), 3.75 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.1-3.5 (m, 4H,CH_2N), 2.66 (t, J = 6Hz, 4H, CH_2CO), 2.25 (t, J = 7H, 4H, $=CCH_2$), 1.7-2.1 (m, 6H, CH_2); uv (0.1 N NaOH) 224 (3.81), 310 (4.33); mass

spectrum (70eV) m/e (rel intensity) M+ 307 (6), 275 (4), 247 (100), 187 (24), 91 (5). Anal. Calcd for $C_{16}H_{21}O_5N$: C, 62.53; H, 6.89; N, 4.55. Found: C, 62.12; H, 6.26; N, 4.38.

Reaction of 3-Pyrrolidinocyclopent-2-en-1-one (49) with Dimethyl Acetylenedicarboxylate.--The general procedure for reaction of an enamino ketone with DMAD was followed giving a dark, oily solution. The solution was cooled and the glyme was removed under vacuum at 40° (2 mm). The residue was chromatographed on a silica gel column using chloroform-acetone mixtures as the eluting solvent. Fractions containing a yellow spot at R_F 0.3 on TLC were combined and rechromatographed until a relatively uncontaminated mixture of 3,4-dicarbomethoxy-5-pyrrolidinocyclohept-2,4-diene-1-one, 55, and dimethyl 2-(1-pyrrolidino-3-oxo-1-cyclopentenyl)-fumarate, 56, was obtained. This mixture was separated on a silica gel column using chloroform as eluting solvent. Initially pure 56 was eluted, followed by a mixture of 55 and 56 and finally pure 55 was eluted from the column. The oily product 55 was crystallized in an ether-benzene-pentane mixture forming orange platelets: 19% yield; mp 91-93°; ir (KBr) 1725, 1655, 1630 (C=O), 1570 (diene); nmr ($CDCl_3$) 6.85 (s, 1H, =CH), 3.75 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.2-3.65 (m, 4H, CH_2N), 2.7 (m, 2H, CH_2CO), 2.45 (m, 2H, $=CCH_2$), 1.8-2.0 (m, 4H, CH_2); uv (95% ethanol) 213 (4.08), 283 (4.6); mass spectrum

(70eV) m/e (rel intensity) M+ 293 (12), 262 (5), 235 (16), 234 (100),202 (8), 174 (22), 118 (7), 70 (9). Anal. Calcd for $C_{15}H_{19}O_5N$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.27; H, 6.62; N, 4.59.

The oily residue of 56 was crystallized in ether-hexane forming a yellow powder. The elemental analysis of 56 was unsatisfactory due to the lack of a sufficient amount of material for thorough purification, however, the spectral data was consistent with the assignment of structure: 10% yield; mp 65-66°; ir (KBr) 1730 (C=O), 1555 (diene); nmr ($CDCl_3$) 5.65 (s, 1H, =CH), 3.8 (s, 3H, OCH_3), 3.7 (s, 3H, OCH_3), 3.4 (m, 4H, CH_2N), 2.6 (m, 2H, CH_2CO), 2.4 (m, 2H, $=CCH_2$), 1.9 (m, 4H, CH_2); uv (95% ethanol) 208 (3.67), 280 (3.91); mass spectrum (70eV) m/e (rel intensity) M+ 293 (10), 262 (6), 235 (17), 234 (100), 202 (9), 174 (30), 146 (6), 118 (7), 70 (11). Anal. Calcd for $C_{15}H_{19}O_5N$: C, 61.42; H, 6.53; N, 4.78. Found: C, 59.11; H, 6.12; N, 3.98.

Reaction of 2-Pyrrolidino-2-cyclopent-2-en-1-one (63) and 2-Pyrrolidino-2-cyclohex-2-en-1-one (62) with Dimethyl Acetylenedicarboxylate.--The general procedure for reaction of an enamino ketone with DMAD was followed in the reactions of both 63 and 62. In both cases a darkening of the reaction mixture occurred during reflux. However, removal of solvent from the reaction mixtures gave dark residues from which no identifiable products could be detected or isolated.

Attempted Reaction of 2-Methyl-1-Pyrrolidinocyclopent-2-en-1-one (61) with Dimethyl Acetylenedicarboxylate. --The general procedure for reaction of an enamino ketone with DMAD was followed. After a two hr heating period the mixture was cooled in an ice bath and hexane added until the solution turned cloudy. A precipitate which formed was filtered, washed sparingly with ether and identified by mp and nmr as the starting material 61 (70% recovery).

Hydrolysis of 3,4-Dicarbomethoxy-7,7-dimethyl-5-pyrrolidinocycloocta-2,4-dien-1-one (47).--Five g of 47 was added to 25 ml of 15% hydrochloric acid solution. After standing at room temperature for 48 hr a colorless, crystalline precipitate of 3,4-dicarbomethoxy-7,7-dimethyl-5-hydroxycycloocta-3,4-dien-1-one, 48, formed which was filtered, washed with water, and recrystallized in ethanol: 90% yield; mp 150-151°, lit. (45) mp 147-149°; ir (KBr) 1730 (C=O), 1640 (enol), 1580 (C=C), lit. (45) ir (?) 1745, 1727, 1603; nmr ($CDCl_3$) 13.3 (d, J = 1.6 Hz, 1H, OH), 6.6 (d, J = 1.4 Hz, 1H, =CH), 3.75 (s, 6H, OCH_3), 2.9 (d, J = 12.1 Hz, 1H, CHCO), 2.3 (q, J = 11.4 Hz, 2H, $=C(OH)CH_2$), 2.2 (d, 1H, J = 12.1 Hz, CH_2CO), 1.15 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), uv (95% ethanol) 230 broad (3.95), 315 (3.41); mass spectrum (70eV) m/e (rel intensity) M+ 282 (21), 251 (17), 250 (41), 222 (43), 208 (26), 198 (31), 194 (70), 167 (34), 166 (64), 138 (30), 93 (33), 83 (100).

Hydrolysis of 3,4-Dicarbomethoxy-5-pyrrolidinocyclo-octa-2,3-dien-1-one (92).--Four g of 92 was dissolved in 40 ml of methanol and 40 ml of 15% hydrochloric acid solution and stirred at room temperature for 14 hr. The solution was neutralized with solid potassium carbonate, extracted with chloroform, and dried over anhydrous magnesium sulfate. Evaporation of solvent provided an oily residue which crystallized upon storage in the refrigerator. The crystalline 3,4-dicarbomethoxy-5-hydroxycycloocta-2,4-dien-1-one was recrystallized in ether-hexane: 75% yield; mp 76-77°; ir (KBr) 1735, 1655, (C=O), 1610 (C=C); nmr ($CDCl_3$) 13.24 (m, 1H, OH), 6.65 (m, 1H, =CH), 3.8 (s, 6H, OCH_3), 1.95-3.1 (m, 6H, CH_2). Addition of D_2O eliminated the long range coupling of the enol proton resulting in a sharpening of the vinyl and multiplet signals. The coupling constant of the vinyl proton to one of the C-8 methylene protons is J = 1.3 Hz. Other spectral data were as follows: uv (95% ethanol) 230 broad (3.92), 315 (3.40); mass spectrum (70eV) m/e (rel intensity) M+ 254 (20), 222 (100), 198 (22), 194 (91), 180 (47), 166 (82), 163 (60), 152 (52), 138 (36), 93 (46), 59 (52). Anal. Calcd for $C_{12}H_{14}O_5$: C, 56.69; H, 5.55. Found: C, 56.17; H, 5.23.

Preparation of Dimethyl 2-(1-Hydroxy-5,5-dimethyl-3-oxocyclohexenyl)-fumarate (57).--A solution of 14 g of dimedone in 300 ml of tetrahydrofuran was added to 4.21 g of sodium hydride (57% dispersion in mineral oil) which

had been slurried with dry hexane and the hexane decanted. To this mixture was added 14.2 g of DMAD over a period of three min. The temperature rose from 35° to 60° and the color changed to dark yellow. The mixture was stirred for 0.5 hr and 50 ml of water was added slowly. After the reaction subsided the mixture was poured into 600 ml of water. The solution was made acid to litmus with 6N hydrochloric acid solution and extracted with ether. The ether extract was washed once with water and dried over anhydrous sodium sulfate. The ether was evaporated leaving a yellow oil. The oil was crystallized in methylene chloride-ether-hexane giving 57 in 63% yield: mp 137-138°, ir (KBr) 1720 (C=O), 1570 (C=C); nmr ($CDCl_3$) 10.06 (s, 1H, OH), 6.85 (s, 1H, =CH), 3.7 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 2.35 (s, 4H, CH_2CO), 1.1 (s, 6H, CH_3); uv (95% ethanol) 208 (4.28), 259 (4.36); mass spectrum (70eV) m/e (rel intensity) 251 (5), 250 (28), 219 (13), 194 (100), 191 (39), 166 (24), 163 (10), 138 (33), 110 (10), 108 (9), 93 (33), 83 (15). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.87; H, 6.28.

Reaction of Dimethyl 2-(5,5-Dimethyl-1-hydroxy-3-oxo-1-cyclohexenyl)-fumarate (57) with Pyrrolidine.--To 3.7 g of 57 in benzene was added 1.3 g of pyrrolidine. Instant yellow coloration occurred. The mixture was heated under reflux for ca. one hr using a Dean-Stark trap to remove traces of water. Removal of solvent

left a semi-solid residue. Ether was added, and the solid was filtered and washed with ether to yield a white solid precipitate of bis-(dipyrrolidinyl)-2-(1-hydroxy-3-oxo-1-cyclohexenyl)-fumaramide: mp 149-150°; ir (KBr) 1645, 1615 (C=O), 1585 (C=C); nmr ($CDCl_3$) 11.0 (broad s, OH), 6.1 (s, 1H, =CH), 3.5 (m, 8H, CH_2N), 2.3 (s, 4H, CH_2CO), 1.9 (m, 8H, CH_2), 1.05 (s, 6H, CH_3); uv (95% ethanol) 295 (4.19), shoulder 330 (3.95); mass spectrum (70eV) m/e (rel intensity) 289 (16), 220 (3), 192 (10), 191 (10), 98 (78), 71 (18), 70 (100), 55 (57).

Hydrolysis of Dimethyl 2-(5,5-Dimethyl-1-hydroxy-3-oxocyclohexenyl)-fumarate (57) to 4-Carboxy-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrocoumarin (59).--A mixture of 1.0 g of 54 in 20 ml of 23% hydrobromic acid solution was heated under reflux for 12 hr. During this time a white solid formed, which was removed by filtration of the cooled reaction mixture. The solid was washed with water to give white crystals of 59 which were dried in a vacuum desiccator: 72% yield; mp 230-232°; ir (KBr) 1760, 1725, 1625 (C=O), 1540 (C=C); nmr (CD_3OD) 6.15 (s, 1H, =CH), 2.8 (s, 2H, CH_2CO), 2.4 (s, 2H, $=CCH_2$), 1.1 (s, 6H, CH_3); uv (95% ethanol) 259 (3.87), shoulder 292 (3.62); mass spectrum (70eV) m/e (rel intensity) M+ 236 (33), 192 (60), 180 (85), 164 (57), 152 (100), 136 (45), 124 (93), 108 (62), 93 (64), 83 (31), 66 (37), 55 (49). Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.05; H, 5.12. Found: C, 60.53; H, 4.91.

Hydrolysis of 2-(5,5-Dimethyl-3-oxo-1-pyrrolidinocyclohex-1-enyl)-fumarate (51) to 4-Carboxy-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrocoumarin (59).--A mixture of 1.0 g of 51 in 20 ml of 23% hydrobromic acid solution was heated under reflux for 14 hr. A white solid formed during the reflux period. The mixture was allowed to cool to room temperature and the solid was filtered, washed with water, and dried in a vacuum desiccator to give a 60% yield of 59. This sample of 59 was identical in all respects with that prepared by hydrolysis of 57.

Hydrolysis of Dimethyl 2-(5,5-Dimethyl-3-oxo-1-pyrrolidinocyclohex-1-enyl)-fumarate (51) to 7,7-Dimethyl-9-methoxy-5-pyrrolidino-6,7,8,9-tetrahydrocoumarin (60).--To a mixture of five ml of methanol and ten ml of 15% hydrochloric acid solution was added 1.0 g of 51. The mixture was stirred at room temperature for three days and then made just basic to litmus with either potassium carbonate or sodium hydroxide. Upon neutralization the color of the solution turned from light yellow to orange. The basic solution was extracted three times with chloroform and the extract dried over anhydrous sodium sulfate. Removal of solvent gave a bright yellow oil which was crystallized by cooling and recrystallized in an ether-chloroform-hexane mixture to yield bright yellow crystals. The solid was characterized as 60, however, difficulty experienced in purification procedures caused elemental

analysis to be unsatisfactory. The physical and spectral data of 60 was as follows: mp 144-145°, ir (KBr) 1730, 1625, 1605 (C=O), 1540 (C=C), nmr ($CDCl_3$) 6.6 (s, 1H, =CH), 3.75 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.2 (m, 4H, CH_2N), 2.5 (s, 2H, $CNCH_2$), 2.35 (d, J = 15 Hz, 1H, $CHCO_2$), 2.1 (d, J = 15 Hz, 1H, $CHCO_2$), 1.9 (m, 4H, CH_2), 1.09 (s, 3H, CH_3), 1.06 (s, 3H, CH_3); uv (95% ethanol) 212 (4.10), 310 (4.41); mass spectrum (70eV) m/e (rel intensity) M+ 335 (17), 303 (9), 276 (100), 244 (6), 216 (44), 133 (7), 132 (7), 91 (9), 70 (20). Anal. Calcd for $C_{18}H_{25}O_5N$: C, 64.46; H, 7.51; N, 4.18. Found: C, 65.51; H, 7.09; N, 4.49.

Attempted Reaction of 3-Pyrrolidinocyclopent-2-en-1-one (49) with Ethyl Propiolate.--To 0.6 g of 49 in eight ml of glyme heated to 80° was added 0.39 g of ethyl propiolate (Aldrich Chemical Co., E 4660-7) over a period of ten min. Heating at 80-85° was continued for 1.5 hr after addition. Both addition and heating processes were carried out under nitrogen. The solution was cooled in an ice bath and treated successively with 15 ml each of ether and hexane. A precipitate formed which was filtered, washed with ether, and found by mp and nmr spectrum to be identical with the starting material 49 (83% recovery).

Attempted Reaction of 5,5-Dimethyl-3-Pyrrolidinocyclohex-2-en-1-one (45) with Ethyl Propiolate.-- The procedure followed was the same as the attempted reaction of 49 with ethyl propiolate. After the heating period was

complete the solution was cooled in an ice bath, and hexane was added until the solution turned cloudy. A precipitate formed which was filtered, washed with ether and found by mp and nmr spectrum to be identical with the starting material, 45 (60% recovery after some material was lost by spillage.)

Preparation of 5-Methyl-2-pyrrolidino-2-cyclopenten-1-one (75).--Five g of 1-methylcyclopentene-2-ol-3-one (m-424, Research Organic Chemicals) was reacted with pyrrolidine according to the general procedure for preparation of cyclic pyrrolidino enamino ketone. After the reflux period the solvent was removed, and the residue was distilled giving 75 as a yellow oil which partially crystallized: 80% yield; bp 69-70° (1 mm); ir (NaCl) 1700 (C=O), 1610 (C=C); nmr ($CDCl_3$) 5.72 (t, J = 3.5 Hz, 1H, =CH), 3.1-3.5 (m, 4H, CH_2N), 2.7 (d of q, J = 18 Hz, J =6 Hz, J = 3.5 Hz, 1H, =CCH), 2.3 (o, J = 7 Hz, J = 1.8 Hz, 1H, CHCO), 2.05 (d of m, J = 18 Hz, 1H, =CCH), 1.9 (m, 4H, CH_2), 1.1 (d, J = 7 Hz, 3H, CH_3); uv (95% ethanol) 214 (3.78), 314 (3.48).

Preparation of 5,5-Dimethyl-N,N-dimethyl-3-aminocyclohex-2-en-1-one (73).--A pressure flask was charged with five g of dimedone in 100 ml of dry ether and ten g of anhydrous calcium chloride, and cooled in an ice bath. After addition of eight g of dimethylamine, the flask was sealed and heated at ca. 60° in an oil bath overnight. The flask was cooled and the mixture was filtered.

The residue was washed sparingly with chloroform and the solvent was removed. The remaining yellow oil was dissolved in benzene, filtered, and the benzene was removed. The oily residue of 73 was crystallized in ether*: 60% yield; mp 79-80°; nmr ($CDCl_3$) 5.14 (s, 1H, =CH), 3.0 (s, 6H, CH_3N), 2.3 (s, 2H, CH_2CO), 2.1 (s, 2H, $=CCH_2$), 1.06 (s, 6H, CH_3); uv (0.1N NaOH) 305 (4.41), (0.1N HCl) 288 (4.11); mass spectrum (70eV) M+ 167.

Preparation of N,N-Dimethyl-3-aminocyclopent-2-en-1-one (74).--A pressure flask was charged with two g of 1,3-cyclopentadione in 100 ml of p-dioxane and five g of anhydrous sodium carbonate, and cooled in an ice bath. After addition of nine g of dimethylamine, the flask was sealed and heated overnight at ca. 80° in an oil bath. The flask was cooled and the contents were filtered and washed with chloroform. The solvent was removed leaving a solid residue which was recrystallized in a methylene chloride-ether-pentane mixture to give a 70% yield of 74. This product gave an unsatisfactory elemental analysis (due to difficulty of removing starting material), but other data were acceptable: mp 123-124°; ir (KBr) 1635 (C=O), 1575 (C=C); nmr ($CDCl_3$) 4.92 (s, 1H, =CH), 3.0 (broadened s, 6H, CH_3N), 2.6 (m, 2H, CH_2CO), 2.4 (m, 2H, $=CCH_2$); uv (0.1N NaOH) 278 (4.12), (0.1N HCl), 270 (4.01);

*This product still contained a minor amount of dimedone.

mass spectrum (70eV) m/e (rel intensity) M+ 125 (100), 110 (10), 97 (13), 96 (23), 82 (35), 69 (85), 68 (45), 43 (53). Anal. Calcd for $C_7H_{11}ON$: C, 67.17; H, 8.86; N, 11.19. Found: C, 68.81; H, 8.32; N, 10.29.

Acetylation of N,N-Dimethyl-1-aminocyclohexene (68). --The procedure followed was similar to that used by Eistert and Wissendorf (30) for acetylation of 65. A solution of 6.7 g of acetyl chloride in 25 ml chloroform was added over a period of 60 min to a sealed flask at 0° containing ten g of 68 (15) and 9.1 g of triethylamine in 90 ml of chloroform. The mixture was stirred for one additional hr at 0° and overnight at room temperature. Then the solution was filtered and the triethylamine hydrochloride was washed with 70 ml of chloroform. The solvent was evaporated and the residue was distilled to give a single fraction containing both 6-acetyl-1-N,N-dimethylaminocyclohexene and 2-acetyl-1-N,N-dimethylaminocyclohexene, 80: 75% yield; bp 62-64° (0.1 mm); $n_D^{28.5}$ 1.5131; ir (NaCl) 1750, 1700 (C=O), 1630 (C=C); nmr ($CDCl_3$) 4.75 (m, =CH), 2.8 (s), 2.25-2.5 (s, m), 2.05 (s), 1.4-1.8 (m).

Acetylation of N,N-Dimethyl-1-aminocyclopentene.--The same procedure as that used for acetylation of N,N-dimethyl-1-aminocyclohexene was followed giving a yellow oily residue which was distilled to give a single fraction containing both 5-acetyl-1-N,N-dimethylaminocyclopentene and 2-acetyl-1-N,N-dimethylaminocyclopentene, 79: 60%

yield; bp 69-70° (0.5 mm); ir (NaCl) 1748, 1710 (C=O), 1630 (C=C); nmr ($CDCl_3$) 5.1 (m, =CH), 3.0 (s, CH_3), 1.7-2.8 (2s superimposed on m).

Preparation of 3-Morpholino-2-cyclpenten-1-one (50). --The general procedure for preparation of cyclic morpholino enamino ketones was followed using 1.5 g of 1,3-cyclopentadione and 1.8 g of morpholine. Removal of solvent gave a yellow solid which was recrystallized in benzene-hexane to give yellow crystals of 50: 65% yield; mp 106-107°; ir (10% by weight in $CHCl_3$) 1650 (C=O), 1550 (C=C); nmr ($CDCl_3$) 5.05 (s, 1H, =CH), 3.7-3.8 (t, J = 6Hz, 4H, OCH_2), 3.35-3.45 (t, J = 6 Hz, 4H, NCH_2), 2.3-2.7 (2t, J = 7 Hz, 4H, CH_2CH_2CO); uv (0.1N NaOH) 281 (4.70); mass spectrum (70eV) m/e (rel intensity) M+ 167 (100), 137 (4), 110 (29), 109 (26), 108 (29), 85 (38), 81 (48), 55 (70). Anal. Calcd fot $C_9H_{13}O_2N$: C, 64.65; H, 7.84; N, 8.37. Found: C, 64.39; H, 7.94; N, 7.86.

Preparation of 1-Pyrrolidinocyclopentene (65).--The preparation of 65 was the same as that used by Stork, et.al., (70). The product was purified by distillation: bp 93-94° (18 mm), lit. (70) bp 88-92° (15 mm). It was necessary to store the product under a nitrogen atmosphere in a refrigerator.

Procedure for Obtaining NMR Variable Temperatures Spectra.--The nmr spectra were obtained on a Varian HA-100 Spectrometer using a Varian Variable Temperature

Controller. Freshly distilled 1,1,2,2-tetrachlorethane was used as solvent for obtaining spectra in the 30-100° range with an internal capilliary containing 63% sulfuric acid solution as the lock signal. Each temperature measurement in this range was calibrated with ethylene glycol.

Deuteriochloroform was the solvent used for temperature measurements in the -60 to 30° range with tetramethylsilane as the lock signal. A standard methanol sample was employed for temperature calibration. All samples were allowed to reach thermal equilibrium with the probe temperature before measurement was begun and at least three runs were made at each temperature.

Determination of ^{13}C Coupling Constants.--The ^{13}C coupling constants for the vinyl protons of 5,5-dimethyl-3-pyrrolidinocyclohex-2-en-1-one and 3-pyrrolidinocyclopent-2-en-1-one were obtained in deuteriochloroform by time average employing a Varian Data Systems Model No. 620-i computer. The spectra were obtained using an RF level of 40 db and 250 sweep width. Sweep time was 250 sec. The number of repetitive scans employed were 264 and 180 respectively.

Preparation of 5,5-Dimethyl-3-pyrrolidinocyclohex-2-en-1-one Ethiodide (81).--The procedure used for preparation of 81 was the same as that used by Leonard and Adamcik (49). The compound was obtained in 92% yield: mp 175-177°, lit. (49), mp 176-177°; ir (KBr) 1630, 1650,

lit. (49) ir (Nujol Mull) 1626, 1607; nmr (D_2O) 5.7 (s, 1H, =CH), 4.2 (q, J = 7Hz, 2H, OCH_2), 3.8 (m, 4H, CH_2N), 2.7 (s, 2H, $=C(OEt)CH_2$), 2.4 (s, 2H, $N=CCH_2$), 2.1 (m, 4H, CH_2), 1.4 (t, J = 7 Hz, 3H, CH_3), 1.1 (s, 6H,CH_3); uv (95% ethanol) 217 (4.13), 285 (4.36).

Preparation of 3-Pyrrolidinocyclopent-2-en-1-one Ethiodide (82).--One g of 3-pyrrolidinocyclopent-2-en-1-one was heated under reflux in 20 ml of ethyl iodide for ca. two hr. After the reflux period an insoluble oily layer of 82 floated on top of the mixture. Storage in the refrigerator for two days provided crystalline 82, which was filtered and washed with pentane. The compound was very hydroscopic and was stored under hexane. The material was quite soluble in water, but insoluble in chloroform. An aqueous solution of 82 precipitated silver iodide when treated with silver nitrate solution. The nmr (D_2O) of 82 was as follows: 5.93 (s, =CH), 4.4 (q, J = 7.5 Hz, OCH_2), 3.2-3.8 (m, CH_2N), 2.7-3.0 (m, $=CCH_2CH_2$), 1.9-2.2 (m, CH_2), 1.4 (t, J = 7.5 Hz, CH_3)

Preparation of 5,5-Dimethyl-3-pyrrolidinocyclohex-2-en-1-one Hydrochloride (83).--The procedure used for preparation of 83 was the same as that used by Alt and Speziale (2). The pure white compound was obtained in 95% yield: mp 215-220°, lit. (2) mp 229-230°; ir (KBr) 1595, 1560; nmr (CD_4OD) 3.8 (m, 4H, CH_2N), 2.7 (s, 2H, $=CCH_2$), 2.4 (s, 2H, $N=CCH_2$), 2.1 (m, 4H, CH_2), 1.1 (s,

6H, CH_3); nmr (H_2O) 5.7 (s, =CH), lit. (2) nmr ($CDCl_3$) 6.21 (=CH); uv (95% ethanol) 299 (4.44) lit. (2) uv (ethanol) 298 (4.43).

Preparation of 3-Morpholinocyclopent-2-en-1-one Hydrochloride (84).--One g of 3-morpholinocyclopent-2-en-1-one was dissolved in 40 ml of dry benzene. Dry hydrogen chloride was passed through the solution until initial cloudiness of the benzene solution cleared. A solid precipitate of 84 was deposited, which was filtered, washed with benzene, and stored in a desiccator over sodium hydroxide: 90% yield; mp 155-165°; ir (KBr) 1645, 1500; nmr (D_2O) 3.8 (2m, 8H, OCH_2CH_2N), 2.95 (2m, 4H, CH_2CH_2); uv (95% ethanol) 278 (4.41).

Preparation of 5,5-Dimethyl-3-pyrrolidinocyclohex-2-en-1-one-d^1 (45-d^1) and 3-Morpholinocyclopent-2-en-1-one-d^1 (50-d^1).--The same procedure was followed for the preparation of 45-d^1 and 50-d^1. Solutions of 45 and 50 in deuterium oxide were made basic to litmus with anhydrous potassium carbonate, followed by extraction with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and evaporated to an oil at room temperature under vacuum. The oils were crystallized by cooling and recrystallized in benzene-hexane to give clean, crystalline samples of 45-d^1 and 50-d^1. Both compounds exhibited identical melting points and nmr spectra with corresponding undeuterated compound, with

the exception of the absence of the nmr vinyl proton absorptions. The mass spectrum (70eV) m/e of 45-d^1 contained M+ 194 as compared to M+ 193 for 45.

Attempted Reaction of 2-Acetylfuran (85) with 1-Pyrrolidinocyclopentene (65) in Glyme.--To 30 ml of glyme was added 5.0 g of 85 and 6.23 g of 65, and the mixture was heated under reflux (95°). Both the addition and reflux processes were carried out under a nitrogen atmosphere. After heating for eight hr the mixture showed no detectable loss of 85 by gas-liquid partition chromatography, and hence, the reaction was terminated.

Reaction of 2-Acetylfuran (85) with 1-Pyrrolidinocyclopentene (65) in a Sealed Tube.--One g of 65 and 0.80 g of 85 (Aldrich Chemical Co., A 1625-4) was placed in an annealed Pyrex tube. The tube was flushed with nitrogen, sealed, and heated for 18 hr at 200°. After cooling to room temperature the tube was opened and found to contain a black, hard substance which was only slightly soluble in chloroform. The nmr spectra of this substance showed no discernable characteristics, and no further characterization was attempted.

Attempted Reaction of 2-Ethyl Furoate (86) with 1-Pyrrolidinocyclopentene (65) in Diglyme.--To 5.0 g of 86 (Aldrich Chemical Co., E 2850-1) in 30 ml of diglyme was added 4.9 g of 65 and the mixture was heated under reflux (165°) for 48 hr. Both the addition and heating processes were carried out under a nitrogen atmosphere. The mixture

was cooled to room temperature, poured into 200 ml of water and extracted three times with ether. The ether layer was washed once with water, dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. An nmr spectrum of the residual oil indicated the sample was starting material contaminated with diglyme.

Reaction of 2-Ethyl Furoate (86) with 1-Pyrrolidinocyclopentene (65) in a Sealed Tube.--One g of 65 and 1.02 g of 86 was placed in an annealed Pyrex tube. The tube was flushed with nitrogen, sealed, and heated 18 hr at 200°. After cooling to room temperature the tube was opened and the contents were sampled for nmr. The nmr spectrum clearly indicated a mixture of 86 and a new compound containing three aromatic protons with slightly different chemical shifts. An attempt at distillation of the mixture yielded pure 86 solidifying in the condenser at ca. 100° (0.1 mm) and a yellow oil which was collected at ca. 140-160° (0.1 mm). The nmr spectrum of the oil included minor absorptions corresponding to 86 as well as absorptions consistent with that expected of 2-pyrrolidinofuroamide: 7.55 (s, =CHO), 7.0 (d, J = 4 Hz, =CH), 6.4 (q, J = 2 Hz, J = 4 Hz, =CH), 3.7 (m, CH_2N), 1.9 (m, CH_2).

Preparation of Diisobutyl 3,4-Furandicarboxylate (94).--A mixture of 10 g of 3,4-furandicarboxylic acid and 0.1 g of p-toluenesulfonic acid dissolved in 150 ml of

benzene and 40 ml of isobutyl alcohol was heated under reflux for three days using a Dean-Stark trap for separation of water. Removal of the solvent and distillation of the residual oil provided a quantitative yield of 94. bp 105-113° (0.2 mm), n 21 D 1.4643; nmr ($CDCl_3$) 7.9 (s, 2H, =CH), 4.0 (d, J = 6 Hz, 4H, OCH_2), 2.0 (sep, J = 6 Hz, 2H, CH), 1.0 (d, J = 6Hz, 12H, CH).

Preparation of n-Dibutyl 3,4-Furandicarboxylate (95). --A mixture of 14.3 g of 3,4-furandicarboxylic acid 50 ml of n-butyl alcohol, 250 ml of benzene, and 0.1 g of p-toulenesulfonic acid was heated under reflux for two days using a Dean-Stark trap. Removal of the solvent and distillation of the residual oil provided 95 in 92% yield: bp 129-135° (0.2 mm); nmr (CCl_4) 7.9 (s, 2H, =CH), 4.2 (t, J = 6 Hz, 4H, OCH_2), 1.3-1.9 (m, 12H, CH_2), 0.95 (t, J = 6 Hz, 6H, CH_3).

Preparation of 2-Acetyl-3,4-bis-(acetoxymethyl)-furan (87).--The method of Elming and Clauson-Kass (31) was followed for the preparation of 87 using either 94, 95 or 3,4-dicarboethoxyfuran as the starting ester. The yields of the lithium aluminum hydride reduction step were 10, 67, and 80% respectively for the preparation of 3,4-bis(acetoxymethyl)-furan, 96: bp 81-90° (0.1 mm), lit. (31) bp 88-90° (0.1 mm); mp 28-29°, lit. (31) mp 29-31°; n 25 D 1.4666; nmr (CCl_4) 7.4 (s, 2H, =CH), 4.95 (s, 4H, CH_2), 2.0 (s, 6H, CH_3). Acetylation of 96 with acetic

anhydride and boron fluoride-ethyl ether produced 87 in 60% yield: bp 135-145° (0.5 mm), lit. (31) bp 127-129° (0.1 mm); nmr (CCl_4) 7.55 (s, 1H, =CH), 5.3 (s, 2H, CH_2), 4.95 (s, 2H, CH_2), 2.4 (s, 3H, CH_3CO), 2.0 (s, 6H, CH_3COO).

Reaction of 1-Pyrrolidinocyclopentene (65) with 2-Acetyl-3,4-bis-(acetoxymethyl)-furan (87).--A mixture of 3.00 g of 87 and 1.62 g of 65 in 20 ml of diglyme was heated under reflux in a nitrogen atmosphere for three days. Distillation of the residue gave two distinct fractions in addition to the solvent: bp 54-60° (0.5 mm), bp 125-140° (0.5 mm). The lower boiling fraction was identified as pyrrolidinyl acetamide by comparison of spectral and chromatographic evidence with that of an authentic sample prepared by reaction of pyrrolidine with acetyl chloride. An nmr spectrum indicated that the higher boiling fraction was a complex mixture of components which were not identified. The same results were obtained when 65 and 87 were reacted in a sealed tube at 130° for four hr in the absence of a solvent.

Attempted Reaction of 4-Methoxy-6-methyl-2H-pyran-2-one (88) with 1-Pyrrolidinocyclopentene (65).--To 20 ml of benzene was added 1.0 g of 88 (Aldrich Chemical Co., 15,428-8) and 0.98 g of 65. The mixture was heated under reflux for 18 hr in a nitrogen atmosphere. After cooling, the solvent was removed leaving a solid substance. The material was filtered and washed with ether giving 0.9 g

(90% recovery) of the starting material 88.

Reaction of 2-Pyrone (89) with 1-Pyrrolidinocyclopentene (65).--To five ml of diglyme was added 0.75 g of 89 (76) and 1.07 g of 65. The mixture was heated under reflux for 30 hr in a nitrogen atmosphere. At this point gas-liquid partition chromatography showed no trace of 89 remaining in the mixture. The solvent was removed at 40-60° (0.1 mm) and the mixture was placed on a silica gel column (Baker, 60-200 mesh) with benzene. Various fractions were eluted using solvent mixtures of benzene-chloroform and chloroform-acetone. The nmr of these fractions exhibited no discernable characteristics and no further characterization was attempted.

Reaction of 1-Pyrrolidinocyclopentene (65) with Methyl Coumalate (90).--To a mixture of 1.0 g of 90, (19) and 0.1 g of hydroquinone in ten ml of p-dioxane was added 0.89 g of 65. Immediate red coloration occurred. The mixture was stirred at room temperature for three days. The solvent was removed and the residue was chromatographed on a silica gel column (Baker, 60-200 mesh) using benzene and mixtures of benzene-chloroform for elution. The fractions eluted from mixtures containing 20-50% chloroform were combined and the solvent was removed. The oily residue which crystallized was triturated with cold pet ether (30-60°) and the solid was filtered. The solid was tentatively identified as 3—carbomethoxy-10-oxa-1-pyrrolidinotricyclo-[4.3.0.$2^{2,5}$]—3-undecen-11-one, 91:

ir (KBr) 1690, 1640 (C=O), 1605 (C=C); nmr ($CDCl_3$) 7.6 (d, $\underline{J}$ = 13 Hz, 1H, =CH), 4.45 (d, $\underline{J}$ = 13 Hz, 1H, COOCH), 3.6 (s on m, 4H, OCH_3, OOCCH), 3.2 (m, 4H, CH_2N), 1.8-2.2 (m, 8H, CH_2), 0.8-1.3 (m, ?H, CH_2).

REFERENCES CITED

(1) Acheson, R. H., "Some Experiments with Cyclopentanones," J. Chem. Soc., 4236 (1956).

(2) Alt, G. H. and Speziale, A. J., "Reactions of Enamines. IV. The Formation of Chloroiminium Salts from Certain Enamino Ketones," J. Org. Chem., 29,794 (1963).

(3) Alt, G. H. and Speziale, A. J., "Reactions of Enamines. VI. The Protonation of Enamino Ketones," J. Org. Chem., 30,1407 (1965).

(4) Anet, F. A. L., Bourn, A. J. R. and Lin, Y. S., "Ring Inversion and Bond Shift in Cyclooctatetraene Derivatives," J. Am. Chem. Soc., 86, 3276 (1964).

(5) Attenburrow, J., Cameron, A. F. B., Chapman, J. H., Evans, R. M., Hems, B. A., Jansen, A. B. A. and Walker, T., "A Synthesis of Vitamin A from Cyclohexanone," J. Chem. Soc., 1094 (1952).

(6) Baldwin, J. E., Barton, D. H. R., Bloomer, J. L., Jackman, L. M., Rodriguez-Hahn, L. and Sutherland, J. K., "The Constitution of Glauconic, Glaucanic, and Byssochlamic Acids," Experientia, 18, 345 (1962).

(7) Baldwin, J. E., Barton, D. H. R. and Sutherland, J. K., "The Nonadride. Part IV. The Constitution and Stereochemistry of Byssochlamic Acid," J. Chem. Soc., 1787 (1965).

(8) Barton, D. H. R., Godinho, L. D. S. and Sutherland, J. K., "The Nonadrides. Part III. The Absolute Configuration of Glauconic and Glaucanic Acids," J. Chem. Soc., 1779 (1965).

(9) Barton, D. H. R., Jackman, L. M., Rodiguez-Hahn, L. and Sutherland, J. K., "The Nonadrides. Part II. The Constitution of Glauconic and Glaucanic Acids," J. Chem. Soc., 1772 (1965).

REFERENCES (Continued)

(10) Barton, D. H. R. and Sutherland, J. K., "The Nonadrides. Part I. Introduction and General Survey," J. Chem. Soc., 1769 (1965).

(11) Bensch, G., "Topics in Stereochemistry," Vol. 3., Interscience Publishers, New York, N. Y., 1968, p. 122.

(12) Berchtold, G. A., Ciabattoni, J. and Tunick, A. A., "Synthesis of 1,3-Cyclohexadienes by the Reaction of Enamines with Methyl trans-2,4-Pentadienoate," J. Org. Chem., 30, 3679 (1965).

(13) Berchtold, G. A. and Uhlig, G. F., "The Reaction of Enamines of Cyclic Ketones with Dimethyl Acetylenedicarboxylate," J. Org. Chem., 28, 1459 (1963).

(14) Bhacca, N. S., Johnson, L. F. and Shoolery, J. N., "High Resolution NMR Spectra Catalog," National Press, USA, 1965, No. 213.

(15) Blanchard, E. P., "The Preparation of N,N-Dimethyl- and N,N-Diethylenamines from Ketones," J. Org. Chem., 28, 1397 (1963).

(16) Bloomer, J. L., Moppett, C. E. and Sutherland, J. K., "The Nonadrides. Part V. Biosynthesis of Glauconic Acid," J. Chem. Soc. (C), 588 (1968).

(17) Boothe, J. H., Wilkinson, R. G., Kushner, S. and Williams, J. H., "Synthesis of Aureomycin Degradation Products," J. Am. Chem. Soc., 75, 1732 (1953).

(18) Bose, A. K., Mina, G., Manhas, M. S. and Rzucidlo, A., "Steroids II. Bis-Homosteroids Via Enamines," Tetrahedron Lett., 1467 (1963).

(19) Boyer, J. H. and Schoen, W., "Organic Synthesis," Vol. 36, ed. N. J. Leonard, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 44.

(20) Brannock, K. C., Burpitt, R. D., Goodlett, V. W. and Thweatt, J. G., "Enamine Chemistry. II. Reactions with Acetylenedicarboxylates," J. Org. Chem., 28, 1464 (1963).

REFERENCES (Continued)

(21) Brannock, K. C., Burpitt, R. D., Goodlett, V. W. and Thweatt, J. G., "Enamine Chemistry. IV. Reactions with Propiolates," J. Org. Chem., 29, 818 (1964).

(22) Büchi, G., Moulkes, D. M., Kurono, M., Mitchell, G. F. and Schneider, R. S., "The Total Synthesis of Racemic Aflatoxin B_1," J. Am. Chem. Soc., 89, 6745 (1967).

(23) Büchi, G., Snader, K. M. and White, J. D., "Structures of Rubratoxins A and B," J. Am. Chem. Soc., 92, 6639 (1970).

(24) Burnside, J. E., Sippel, W. L., Forgacs, J., Carll, W. T., Atwood, M. B. and Doll, E. R., "A Disease of Swine and Cattle Caused by Eating Moldy Corn. II. Experimental Production with Pure Cultures of Molds," Am. J. Vet. Res., 18,817 (1957).

(25) Cambie, R. C. and Gallager, R. T., "Chemistry of the Podocarpacea," Tetrahedron, 24, 4631 (1968).

(26) Corey, E. J., Mitra, R. B. and Uda, H., "Total Synthesis of d,l-Isocaryophyllene," J. Am. Chem. Soc., 86, 485 (1964).

(27) Danishefsky, S. and Cavanaugh, R., "Reaction of Enamines with Aromatic Nitro-compounds," Chemistry and Industry, 2171 (1967.

(28) Danishefsky, S. and Cunningham, R., "The Reaction Enamines with Activated Butadienes. A One-Step Synthesis of Benzenes," J. Org. Chem., 30, 3676 (1965).

(29) DePuy, C. H. and Zaweski, E. F., "Cyclopentene-3,5-dione. I. Synthesis and Properties," J. Am. Chem. Soc., 81, 4920 (1959).

(30) Eistert, B. and Wessendorf, T., "Eine Methode zur Identifizierung von aus unsymmetrischen-β-Diketonen und Hydrazinderivaten erhältlichen Pyrosolderivaten," Chem. Ber., 94, 2590 (1961).

(31) Elming, N. and Clauson-Kass, N., "A New Synthesis of Pyrridoxine," Acta. Chem. Scand., 9, 23 (1955).

REFERENCES (Continued)

(32) Ferguson, G., Sim, G. A. and Robertson, J. M., "The Stereochemistry of Glauconic Acid," Proc. Chem. Soc., 1962, 385.

(33) Fieser, L. F., "Experiments in Organic Chemistry," Third Edition, D. C. Heath and Company, Boston, Mass., 1955, p. 283.

(34) Foote, C. S., "The Effect of Bond Angle on Hybridization," Tetrahedron Lett., 579 (1963).

(35) Fried, J. and Elderfield, R. C., "Studies on Lactones Related to the Cardiac Aglycones. V. Synthesis of 5-Alkyl-2-Pyrones," J. Org. Chem., 6, 566 (1941).

(36) Fuson, R. C., Byers, D. J. and Raljons, N., "Vinyl Alcohols. II. 1,2-Dimesityl-1-propen-1-ol," J. Am. Chem. Soc., 63, 2639 (1941).

(37) Fuson, R. C., Corse, J. and McKeever, C. H., "A Stable Vinyl Alcohol, 1,2-Dimesityl-1-propen-1-ol," J. Am. Chem. Soc., 42, 3250 (1940).

(38) Ganter, C., Pokras, S. M. and Roberts, J. D., "Nuclear Magnetic Resonance Spectroscopy. Ring Inversion in 3,5,7-Cyclooctatrienone," J. Am. Chem. Soc., 4235 (1966).

(39) Gould, E. S.,"Mechanism and Structure in Organic Chemistry," Holt, Reinhart and Winston, New York, N. Y., 1959, p. 377.

(40) Gurowitz, W. D. and Joseph, M. A., "Enamines II. Factors Determining the Structure of Enamines of 2-Substitituted Ketones," J. Org. Chem., 32, 3289 (1967).

(41) Hammett, L. P., "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 190.

(42) Hartley, R. D., Nesbitt, B. F. and O'Kelly, J., "Toxic Metabolites of Aspergillus Flavus," Nature, 198, 1056 (1963).

(43) Hirsch, J. A. and Cross, F. J., "Medium-Ring 3-Carboxyalkanines. Synthesis and Keto-Enol Equilibria," J. Org. Chem.,36, 955 (1971).

REFERENCES (Continued)

(44) House, H. O., "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p. 145.

(45) Huebner, C. F., Dorfman, L., Robison, M. M., Donoghue, E., Pierson, W. G. and Strachan, P., "Reactions of Acetylenic Esters with Enamines," J. Org. Chem., 28, 3134 (1963).

(46) Jerussi, R. A., "The Oxygenation of Enamines. Ketonization at the β-Position to give α-Amino Ketones," J. Org. Chem., 34, 3648 (1969).

(47) Korach, M., Nielsen, D. R. and Rideout, W. H., "Organic Synthesis," Vol. 42, ed. V. Boekelheide, John Wiley and Sons, Inc., New York, N. Y., 1962, p. 50.

(48) Kramer, H. E. A. and Gompper, R., "NMR-Untersuchungen an α, β-ungesattigten β-Aminocarbonylverbindugen: Gehinderte innerte Rotation," Z. Phys. Chem. (Frankfurt am Main), 43, 292 (1964).

(49) Leonard, N. J. and Adamcik, J. A., "Unsaturated Amines. XII. The Sites of Alkylation and Protonation in Certain Enamino Ketones. Substituted Trimethinium Compounds from O-Alkylated Enamino Ketones," J. Am. Chem. Soc., 81, 595 (1959).

(50) Lowe, J. R., "Progress in Physical Organic Chemistry," Vol. 6, ed. A. Streitwieser and R. W. Taft, Interscience Publishers, New York, N. Y., 1968, p. 1.

(51) McElvain, S. M., "Organic Reactions," Vol. IV, ed. Roger Adams, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 256.

(52) Meyers, A. I., Reine, A. H. and Gault, R., "The Chemistry of Cyclic Enamino Ketones. IV. Factors Affecting C and O Alkylation," J. Org. Chem., 34, 698 (1968).

(53) Miller, J. A., "Toxicants Occurring Naturally in Foods," National Academy of Sciences, National Research Council, Washington, D. C., 1966, p. 26.

REFERENCES (Continued)

(54) Moppett, C. E. and Sutherland, J. K., "The Biosynthesis of Glauconic Acid: C_9 Precursors," Chem. Commun., 21, 772 (1966).

(55) Moss, M. O., Robinson, F. V., Wood, A. B., Paisley, H. M. and Feeney, J., "Rubratoxin B, a Proposed Structure for a Bis-anhydride from Penicillium rubrum Stoll," Nature, 220, 776 (1968).

(56) Moss, M. O., Wood, A. B. and Robinson, F. V., "The Structure of Rubratoxin A., A Toxic Metabolite of Penicillium Rubrum," Tetrahedron Lett., 367 (1969).

(57) Mukharji, P. C. and Das Gupta, T. K., "Alicyclic Compounds. II. Action of Base on Bicyclic Ketotosylates-Fragmentation of a Decalone Tosylate to a Cyclodecadienone," Tetrahedron, 25, 5275 (1969).

(58) Muller, N. and Pritchard, D. E., "C^{13} Splittings in Proton Magnetic Resonance Spectra. II. Bonding in Substituted Methanes," J. Chem. Phys., 31, 1471 (1959).

(59) Nagarajan, K. and Rajappa, S., "NMR Spectral Studies on Cyclic Enamines," Tetrahedron Lett., 2293 (1969).

(60) Opitz, G. and Tempel, E., "Sulfene as a Dienophile," Angew Chem. internat., Edit., 3, 754 (1964).

(61) Panouse, J. J. and Sannie, C., "Recherches sur la synthese totale du noyau sterolique. V. Aminocetones cycliques insatures. 2) Sur les amino-1 cyclene-1 ones-3 N-disubstitutees," Bull. Soc. Chim. Fr., 1374 (1956).

(62) Paquette, L. A. and Begland, R. W., "Stabilized Derivatives of cis, cis, cis-1,3,5-Cyclodecatriene. Keto-Enol Tautomerism in 2,3-Dicarbomethoxy-cis, cis-3,5-cyclodecadienones and cis-3-Cycloalkenones," J. Am. Chem. Soc., 88, 4685 (1966).

(63) Paul, I. C., Sim. G. A., Hamor, T. A. and Robertson, J. M., "Fungal Metabolites. Part II. The Structure of Byssochlamic Acid: X-Ray Analysis of Byssochlamic Acid Bis-p-bromophenylhydrazide," J. Chem. Soc., 5502 (1963).

REFERENCES (Continued)

(64) Raistrick, H. and Smith, G., "Studies in the Biochemistry of Micro-organisms. XXXV. The Metabolic Products of Byssochalmys Fulva Olliver and Smith," Biochem. J., 27, 1814 (1933).

(65) Rasmusson, G. H., House, H. O., Zaweski, E. F. and DePuy, C. H., "Organic Synthesis," Vol. 42, ed. V. Boekelheide, John Wiley and Sons, Inc., New York, N. Y., 1962, p.36.

(66) Rose, H. M. and Moss, M. O., "The Effect of Modifying the Structure of Rubratoxin B on the Acute Toxicity to Mice," Biochem. Pharmacol, 19, 612 (1970).

(67) Schaefer, J. P., Horvath, B. and Klein, H. P., "Selenium Dioxide Oxidation. III. The Oxidation of Olefins," J. Org. Chem., 33, 2647 (1968).

(68) Schulenberg, J. W., "Isolation of Crystalline Keto-Enol Tautomers. Conversion into Indoles and Oxindoles," J. Am. Chem. Soc., 90, 1367 (1968).

(69) Stewart, W. E. and Siddall, III, T. H., "Nuclear Magnetic Resonance Studies of Amides," Chem. Rev., 70, 517 (1970).

(70) Stork, G., Brizzolara, A., Landesman, H., Szmusovisz, J. and Terrell, R., "The Enamine Alkylation and Acylation of Carbonyl Compounds," J. Am. Chem. Soc., 85, 207 (1963).

(71) Untch, K. G., "sym-cis, cis, cis-1,4,7-Cyclononatriene, An Unusual Cyclic Six Pi Electron System," J. Am. Chem. Soc., 85, 345 (1963).

(72) Waight, E. S. and Al-Jallo, H. N. A., "Absorption Spectra of Conjugated Carbonyl Compounds. Part II. Infrared, Ultraviolet, and Nuclear Magnetic Resonance Spectra of Cyclopent-2-enones and Cyclohex-2-enones," J. Chem. Soc. (B), 73 (1966).

(73) Wijkman, N., "Uber einige neue durch Schimmelpozle gebildete Substanzen," Ann. Chem., 485, 61 (1931).

REFERENCES (Continued)

(74) Wiley, R. H. and Smith, R. N., "Organic Synthesis," Vol. 31, ed. R. S. Schreiber, John Wiley and Sons, Inc., New York, N. Y.,1951, p. 23.

(75) Woodward, R. B. and Hoffman, R., "The Conservation of Orbital Symmetry," Angew. Chem. internat. Edit., 8, 781 (1969).

(76) Zimmerman, H. E., Grunewald, G. L. and Paufler, R. M., "Organic Synthesis," Vol. 46, ed. E. J. Corey, John Wiley and Sons, Inc., New York, N. Y., 1966, p. 101.