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DIELS-ALDER CYCLOADDITIONS OF 1,3,4,-OXADIAZIN-6-ONES WITH ELECTRON RICH PI SYSTEMS

ALBERT PADWA* and PHILIPP EISENBARTH

Department of Chemistry
Emory University
Atlanta, Georgia 30322

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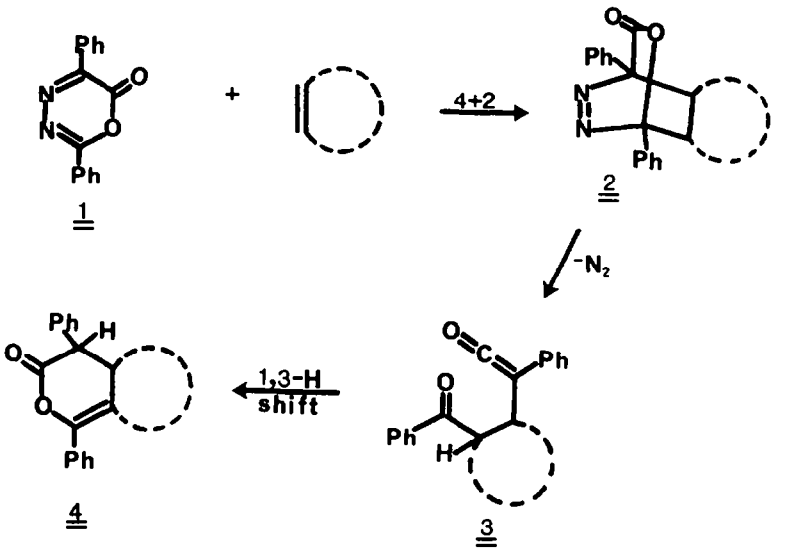
Abstract: A study of the cycloaddition behavior of several 2,5-disubstituted 1,3,4-oxadiazin-6-ones with electron rich pi bonds has been carried out. trans-1-Propenylpyrrolidine was found to react with the oxadiazinone ring system to give rise to a ring opened diazatrienyl substituted carboxylic acid. Further heating of the acid results in decarboxylation, hydrolysis, cyclization and pyrrolidine elimination to produce a disubstituted pyrazole. Reaction with the trisubstituted enamine 1-(2-methyl-propenyl)pyrrolidine, was also studied in some detail. The cycloadditions encountered can be rationalized as proceeding by an initial Diels-Alder reaction followed by cheletropic extrusion of nitrogen to produce a ketoketene intermediate. The fate of the ketene is markedly dependent upon the overall pattern of substitution. Some of the products formed can be explained in terms of a competitive migration of the pyrrolidino group to the ketene and benzoyl groups. With one system the major cycloadduct is derived from the Diels-Alder reaction of a transient azaketene tautomer formed by an electrocyclic opening of the oxadiazinone ring.

The Diels-Alder reaction represents one of the most versatile routes for the construction of carbocycles.[1,2] In one step, two new carbon-carbon bonds are formed, and the stereochemistry as well as the regiochemistry can be controlled by the proper choice of reactants.[3-10] Appropriate selection of dienes and dienophiles allows for a wide range of structural and functional variations in the adducts. In this respect, the recent availability of highly functionalized dienes has considerably widened the scope of the reaction.[11-16] Dienes substituted with two nitrogen atoms have attracted some interest in recent years because of their value in natural product synthesis.[17-19] There are numerous reports in the literature indicating that 1,2-, 1,3- and 1,4-diazabutadienes can act as 4π-components in Diels-Alder reactions.[20] On the other hand, there are few examples of 2,3-diazabutadienes participating in [4+2]-cycloaddition reactions.[21-26] The 2,3-diazabutadiene unit is incorporated in the structure of 6-oxo-1,3,4-oxadiazines. Recently, the preparation and cycloaddition behavior of the first member of this class of heterocycles has been described by Steglich and coworkers.[27] In the reactions studied, oxadiazine 1 behaves as an electron deficient 2,3-diazabutadiene whose Diels-Alder reaction results in the formation of a γ-ketoketene (3) after loss of nitrogen from the initially produced cycloadduct 2. When strained

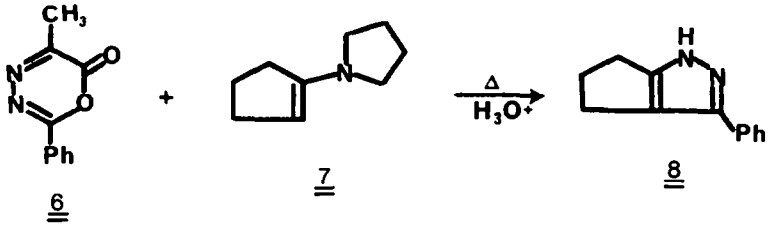
cycloalkenes were used as the dienophile, ketene 3 undergoes a subsequent cyclization to produce an α-pyrone derivative 4.[27,28] The chemistry of the oxadiazinone ring system is still largely unexplored. In this paper we wish to report on the cycloaddition behavior of several new oxadiazinones with enamines and enol ethers.



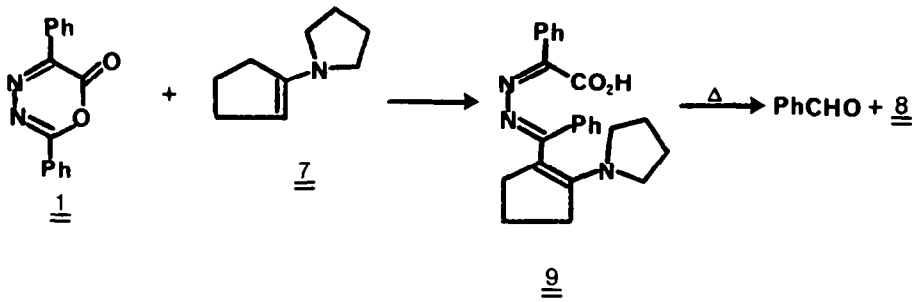
Results and Discussion

As our first model we chose to investigate the reaction of 5-methyl-2-phenyl-1,3,4-oxadiazin-6-one (6) with 1-pyrrolidinocyclopentene (7). The unknown 5-methyl substituted oxadiazinone 6 was prepared by the dehydration of syn-pyruvic acid benzoylhydrazone with dicyclohexylcarbodiimide according to the general procedure of Steglich and coworkers.[27,29] Heating a benzene solution of 6 and 7 at 85°C followed by silica gel chromatography afforded 3-phenyl-4,5-cyclopentenopyrazole (8) in high yield. The structure of 8 was established by comparison with an authentic sample[30].

The same pyrazole was also formed together with benzaldehyde when 2,5-diphenyloxadiazinone 1 was heated with enamine 7. However, when the reaction was carried out at 25°C, a yellow crystalline solid was isolated in 77% yield whose structure was assigned as diazatriene 9, mp 151-152°C, on the basis of its spectral properties. Heating this material in wet benzene afforded pyrazole 8 and benzaldehyde in good yield.

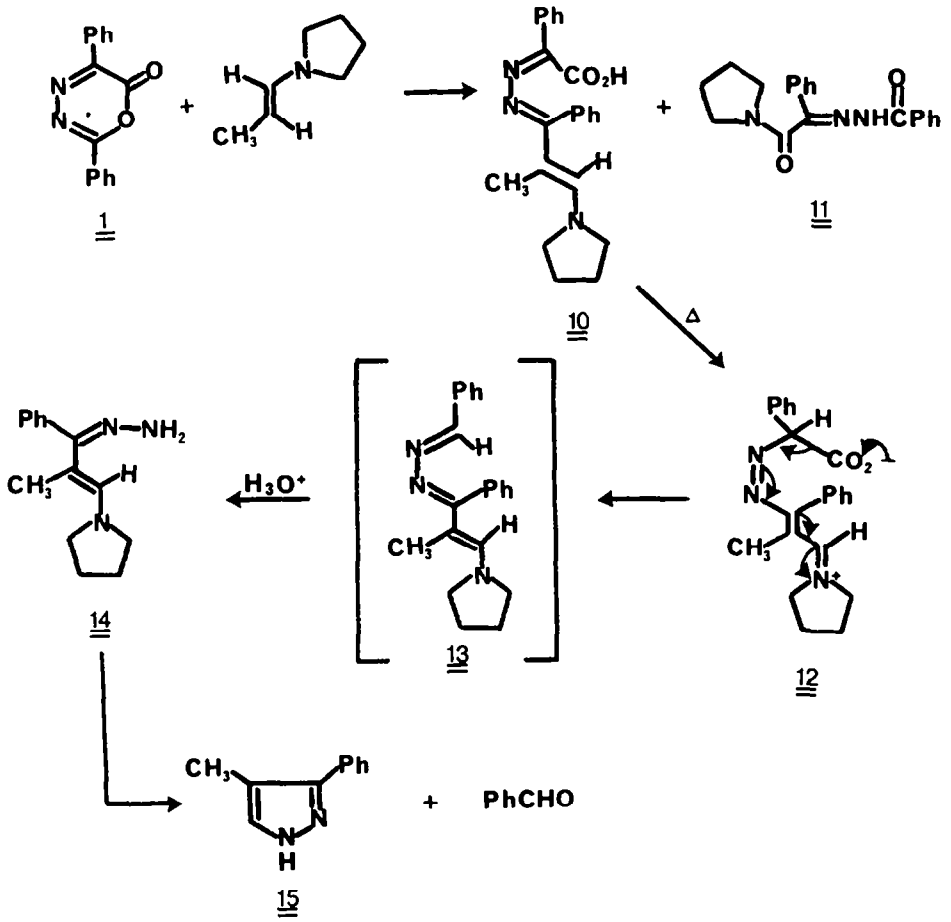


Under identical conditions the addition of trans-1-propenylpyrrolidine to oxadiazinone 1 furnished a mixture of cycloadduct 10 as well as benzoyl-N-pyrrolidinoformamide benzoylhydrazone (11). Heating a sample of 10 in benzene gave rise to benzaldehyde and 3-methyl-4-phenylpyrazole (15).



Conversion of the pyrrolidino derivatives 9 and 10 to the corresponding pyrazoles can be envisaged as proceeding by an initial decarboxylation to give 13 followed by hydrolysis, cyclization and pyrrolidine elimination as outlined in Scheme I.

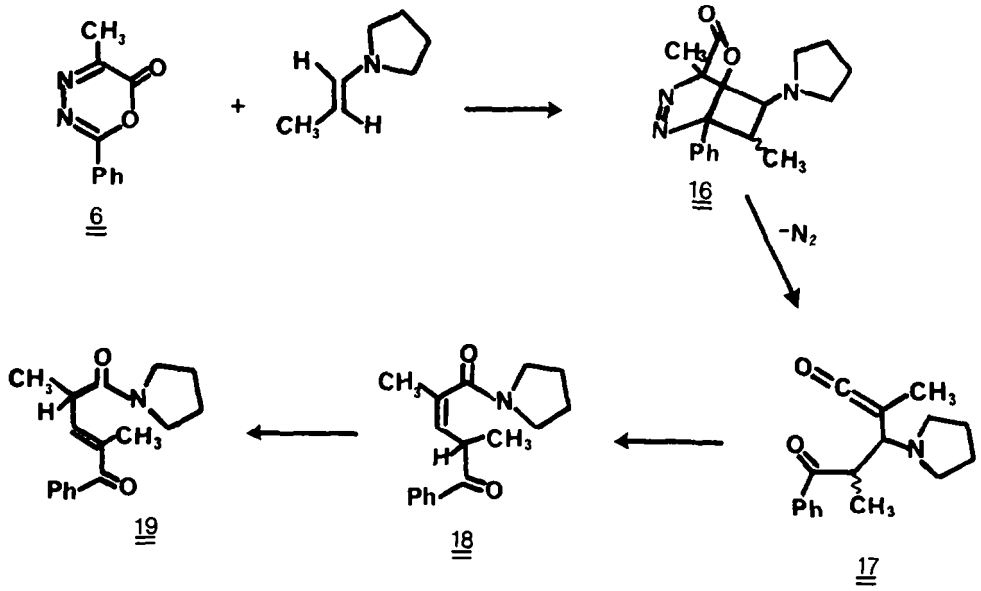
Scheme I



The formation of diazatrienes 9 and 10 can be explained by attack of the enamine carbon atom on the 2-position of the heterocyclic ring followed by a subsequent hydrogen shift. Structure 11 is a minor by-product and is derived from the reaction of pyrrolidine with the oxadiazinone.

A totally different profile of reactivity toward cycloaddition was encountered in the reaction of 5-methyl-2-phenyl-oxadiazinone (6) with trans-1-propenylpyrrolidine. The major product (49%), to which the

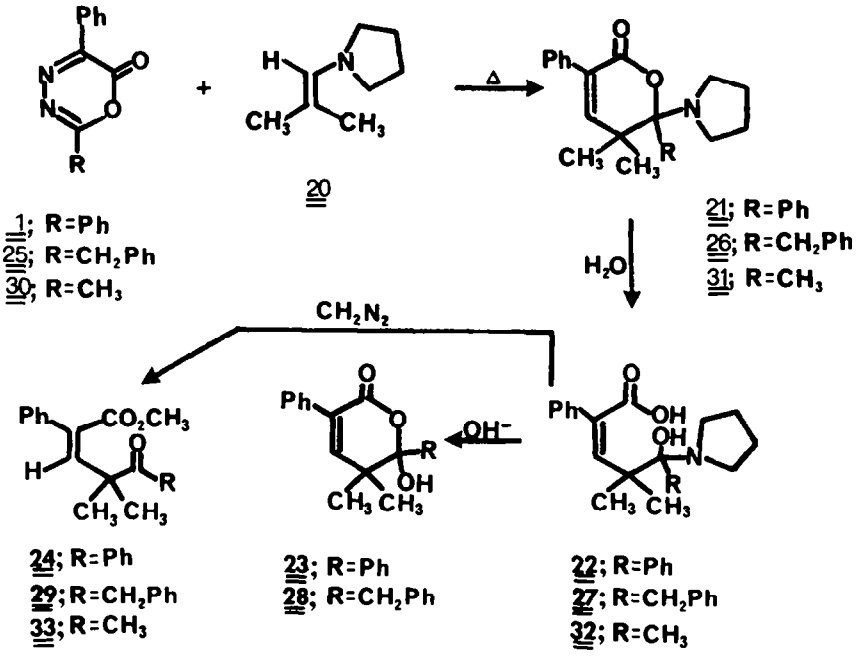
2,4-dimethyl-5-oxo-5-phenyl-3-pentenoic acid pyrrolidinamide structure (19) has been assigned, exhibits doublets for the methyl groups at 1.30δ(J=6.2 Hz) and 2.02 (J=1.5 Hz) as well as doublet of quartets at 3.63 (J=9.75 and 6.2 Hz) and 6.40 (J=9.75 and 1.5 Hz). A study by NMR spectroscopy of this particular cycloaddition reaction established that a 2:1 mixture of E and Z-2,4-dimethyl-5-oxo-5-phenyl-2-pentenoic acid pyrrolidinamide (18) were first formed. These compounds isomerized to the thermodynamically more stable enone 19 when chromatographed on a silica gel column. The formation of structure 18 can be rationalized in terms of the intermediacy of γ-ketoketene 17 which is



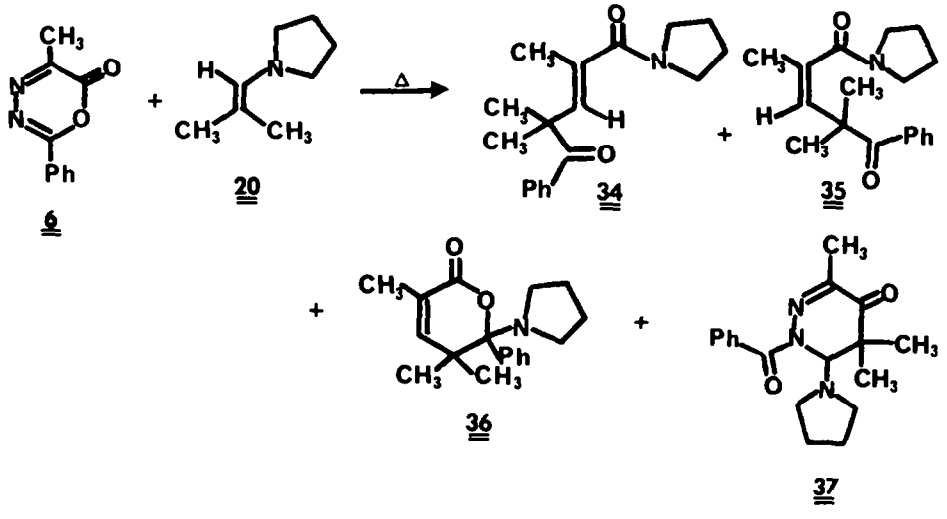
produced by extrusion of nitrogen from the primary cycloadduct 16. Since a 1,3-hydrogen shift is not possible here, the pyrrolidino group undergoes a 1,3-sigmatropic shift to the ketene carbonyl group. The enhanced electrophilicity that the 5-phenyl substituent imparts to the oxadiazinone ring is evidently sufficient to lead to preferential ring opening rather than Diels-Alder cycloaddition. This would account for the difference in behavior of oxadiazinones 1 and 6 toward trans-1-propenylpyrrolidine.

The reaction of oxadiazinone 1 with 1-(2-methylpropenyl)pyrrolidine (20) was also investigated and was found to afford a single 1:1-cycloadduct. The structure of this material was assigned as δ-pyrrolidino lactone 21 on the basis of its characteristic spectral data (see Experimental Section) and hydrolytic behavior. Stirring an aqueous THF solution of 21 at room temperature for two days resulted in its conversion to 4,4-dimethyl-2,5-diphenyl-5-hydroxy-5-pyrrolidino-2-pentenoic acid 22. Further treatment of 22 with potassium hydroxide in ethanol afforded lactol 23 whereas reaction with diazomethane produced 4,4-dimethyl-5-oxo-2-phenyl-2-hexenoate (24) in quantitative yield. Unequivocal proof of cycloadduct 21 derives from a single crystal X-ray structure analysis.[31] An analogous set of reactions occurred when the corresponding 2-benzyl (25) and 2-methyl-substituted oxadiazinones (28) were treated with enamine 20.

From the reaction of 5-methyl oxadiazinone 6 with 1-(2-methylpropenyl)pyrrolidine, four products (34-37) were isolated by column chromatography. The formation of compounds 34-36 is closely analogous to the results previously encountered. Structure 37 was assigned as

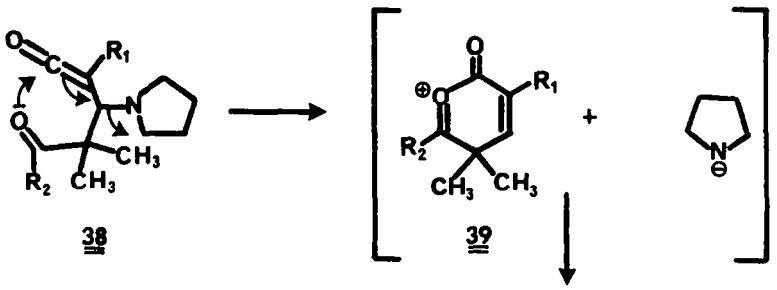


1-benzoyl-1,4,5,6-tetrahydro-6-pyrrolidino-3,5,5-trimethyl-1,2-diazin-4-one on the basis of its spectral data and molecular formula which corresponds to $C_{18}H_{23}N_3O_2$. This material exhibits bands in the infrared at 1660 (C=O) and 1565 cm^{-1} (PhCONN=<). The ^1H NMR spectrum of 37 showed singlets at δ1.21 (3H), 1.28 (3H), 1.97 (3H) and 5.82 (1H). The ^{13}C NMR spectrum ($CDCl_3$) showed pertinent peaks at 16.42 (q), 18.73 (q), 23.60 (t), 24.76 (q), 44.80 (s), 49.67 (t), 77.65 (d), 171.81 (s) and 193.82 (s).



The mechanism by which the oxadiazinones react with enamine 20 is worthy of comment in view of the subtle variations in product distribution. The cycloaddition reactions can be rationalized as proceeding by an initial Diels-Alder reaction followed by extrusion of nitrogen to produce a ketoketene intermediate (i.e. 38). The concentration of the ketene is very low since we were unable to detect it by IR spectroscopy. The fate of the ketene is markedly dependent upon the overall pattern of substitution. Since a 1,3-hydrogen shift is not possible here, the neighboring benzoyl group undergoes addition to the

ketene carbonyl and this is followed by pyrrolidino group ejection to give intermediate 39. This species then reacts with the pyrrolidine moiety to give either 35 or 36 depending on the site of attack. An alternate possibility is that a 1,3-sigmatropic shift of the pyrrolidine group to the ketene carbonyl occurs in competition with benzoyl group attack at the ketene center. This



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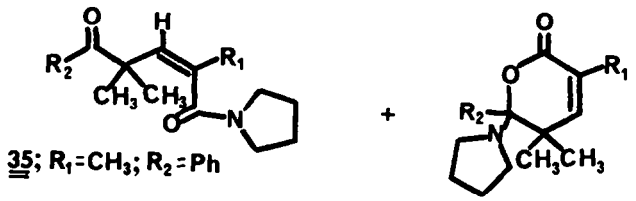
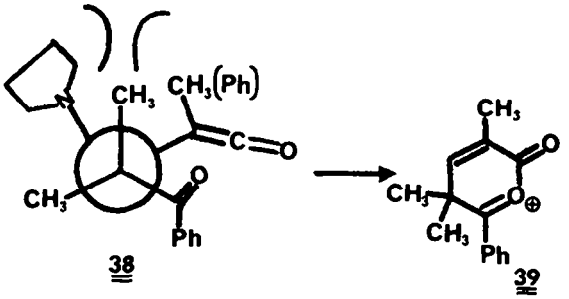


35; R_1=CH_3; R_2=Ph

36; R_1=CH_3; R_2=Ph

latter pathway would account for the formation of a mixture of isomeric amides (i.e. 34 and 35). In fact, some combination of both pathways seems likely. From molecular models it appears that considerable non-bonded interactions between the methyl group and the pyrrolidine hydrogens must develop in the transition state which leads to structure 39. These unfavorable interactions are avoided when a phenyl group is attached to the ketene π-system. This would account for the high regioselectivity of cyclization in the phenyl series and the lack of selectivity with the methyl system. Finally, the formation of cycloadduct 37 from the reaction of oxadiazinone 6 can be rationalized in terms of an electrocyclic ring opening to an azaketene tautomer (i.e. 40) followed by a Diels-Alder cycloaddition with the added enamine.



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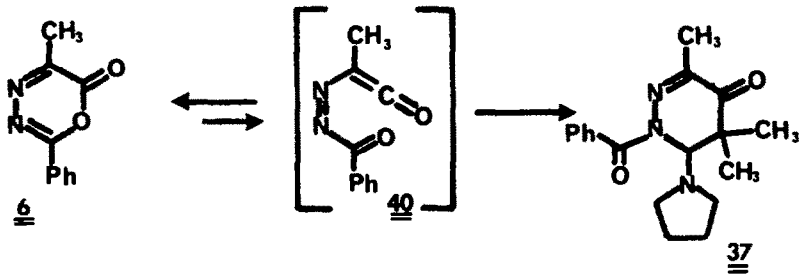
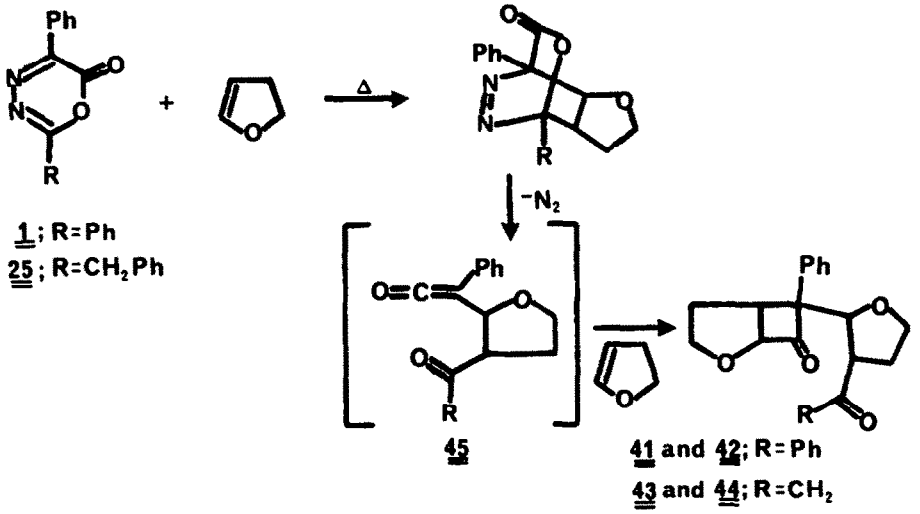
As a continuation of our work in this area we have also studied the cycloaddition behavior of the oxadiazinone system with an enol ether. From the thermal reaction of 1 with dihydrofuran, two crystalline diastereomeric adducts were isolated by preparative thick-layer chromatography. The nitrogen deficient 2:1-adducts have been assigned as cyclobutanones 41 and 42 on the basis of



their spectral data (see Experimental Section). Most importantly, the infrared spectra show carbonyl bands at 1780 and 1670 cm^{-1}. A similar set of products were formed from the reaction of dihydrofuran with the 2-benzyl substituted oxadiazinone 25. Infrared and NMR spectra of cycloadducts 43 and 44 are closely related to those of 41 and 42. The cycloadducts obtained are most simply explained by invoking loss of nitrogen from the initially formed Diels-Alder adduct. The resulting ketoketene intermediate 45 then undergoes a subsequent 2+2-cycloaddition with another molecule of dihydrofuran.



In conclusion, our results show that oxadiazinones undergo ready cycloaddition with enamines and enol ethers via mechanistically intriguing processes. We are continuing to examine the cycloaddition behavior of the oxadiazinone ring system and will report additional findings at a later date.

Experimental Section. All melting points and boiling points are uncorrected. Experimental analyses were performed by Atlantic Microlabs, Atlanta, Ga. The infrared absorption spectra were determined on a Perkin-Elmer 467 infrared spectrophotometer. The ultraviolet absorption spectra were measured with a Cary Model 14 recording spectrophotometer, using 1-cm matched cells. The proton magnetic resonance spectra were determined at 90 MHz by using a Varian EM-390 spectrometer at an ionizing voltage of 70 eV. All thermolyses were carried out in a 20% pyridine-benzene mixture in a sealed Carius tube. The crude reaction mixtures were chromatographed on silica gel using hexane as the eluent.

Reaction of 5-Methyl-2-phenyl-1,3,4-oxadiazin-6-one (6) with 1-Pyrrolidinocyclopentene (7). To a solution containing 0.565 g of 5-methyl-2-phenyl-1,3,4-oxadiazin-6-one[29] (6) in 5 ml of benzene at 85°C was

added 0.44 g of 1-pyrrolidinocyclopentene (7) under a nitrogen atmosphere. The mixture was kept at this temperature for 20 min and was then cooled to room temperature. The solvent was removed under reduced pressure and the resulting oil was subjected to silica flash chromatography using ethyl acetate as the eluent. The resulting oil was rechromatographed on a silica gel thick layer plate using a 2:1 chloroformethyl acetate mixture as the eluent. The major component contained 400 mg (72%) of 3-phenyl-4,5-cyclopentenopyrazole (8). This structure was assigned by comparison of its spectral data with those of an authentic sample[30].

Reaction of 2,5-Diphenyl-1,3,4-oxadiazin-6-one (1) with 1-Pyrrolidinocyclopentene (7). To a stirred solution containing 1.25 g of 2,5-diphenyl-1,3,4-oxadiazin-6-one (1)[27] in 15 ml of dry benzene at room temperature was rapidly added 0.82 g of 1-pyrrolidinocyclopentene (7)[32]. After stirring for 30 min, the deep yellow precipitate which had formed was filtered to give 1.5 g (77%) of a yellow solid. Crystallization from hot methanol-ethyl acetate gave 0.96 g (50%) of diazatriene 9 as bright orange crystals; mp 151-152°C (dec.); IR (KBr) 2975, 1690, 1605, 1580, 1525, 1490, 1440, 1340, 1270, 1115, 835, 775, 700 cm^{-1}; NMR ($CDCl_3$,90MHz)δ 1.60-2.20 (m, 6H), 2.65-3.25 (m, 8H), 7.30-8.12 (m,10H) and 10.6 (brs,1H); UV (95% ethanol) 400 nm (ε 13000), 300 nm (ε 14900); m/e 341, 250, 234, 221, 149, 131 (base), 120, 117, 115, 107, 91 and 77, 65; Anal. Calcd. for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.52; N, 10.84; Found: C, 74.21; H, 6.54; N, 10.75.

A solution containing 100 mg of 9 in 4 ml of benzene was heated at reflux under a nitrogen atmosphere for 45 min. The solvent was removed under reduced pressure and the remaining red oil was chromatographed on a silica gel thick layer plate using a 1:1 chloroform-ether mixture as the eluent. The first fraction was identified as benzaldehyde. The second fraction contained 40 mg (82%) of 3-phenyl-4,5-cyclopentenopyrazole (8). The structure of this material was assigned by comparison of its spectral data with a known compound[30] as well as by its elemental analysis: Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.20; Found: C, 78.03; H, 6.60; N, 15.17.

Reaction of 2,5-Diphenyl-1,3,4-oxadiazin-6-one (1) with trans-1-Propenylpyrrolidine. To a stirred solution containing 1.0 g of 2,5-diphenyl-1,3,4-oxadiazin-6-one (1) in 10 ml of benzene under a nitrogen atmosphere at 25°C was added 0.67 g of trans-1-propenylpyrrolidine[33]. Stirring was continued for 30 min during which a yellow precipitate was formed. The mixture was concentrated under reduced pressure and filtered to give 0.23 g of 10 as a deep yellow and very moisture sensitive powder; NMR ($CDCl_3$,90MHz)δ 1.70-2.03 (m), 2.30 (s), 3.00-3.22 (br t), 3.50-3.73 (br t), 6.88 (br s), 7.15-7.95 (m) and 10.7 (brs,1H); IR (KBr) 1685, 1610, 1500, 1450, 1415, 1385, 1325, 1110, 830 cm^{-1}; UV (95% ethanol) 400 nm.

The mother liquor was concentrated under reduced pressure to leave behind a red oil which was dissolved in 10 ml of dichloromethane. The solution was filtered and then 20 ml of ether was added. Crystallization afforded 0.105 g (8%) of benzoyl-N-pyrrolidinoformamide-benzoylhydrazone (11) as a white crystalline solid; mp 155-156°C; NMR ($CDCl_3$,90MHz)δ1.73-2.02 (m, 4H), 3.05-3.23 (br t, 2H), 3.65-3.83 (br t, 3H), 7.38-7.98 (m, 11H); IR (KBr) 3160, 2900, 1700, 1630, 1550, 1450, 1270, 1145 cm^{-1}. The mother liquor was concentrated under reduced pressure and the residue was chromatographed on a silica gel thick layer plate using a 1:1 hexane-ether mixture as the eluent. The first fraction contained 100 mg of benzaldehyde. Further elution of the column with a 1:1 chloroform-ether mixture gave 400 mg (63%) of 3-methyl-4-phenylpyrazole

(15), mp 118-119°C (lit.[34] 117-118°C); NMR ($CDCl_3$,90MHz)δ2.22 (s, 3H), 7.30-7.56 (m, 6H), 9.0 (brs, 1H).

Reaction of 5-Methyl-2-phenyl-1,3,4-oxadiazin-6-one (6) with trans-1-(2-Propenyl)pyrrolidine. To a solution containing 1.13 g of 5-methyl-2-phenyl-1,3,4-oxadiazin-6-one (6) in 12 ml of benzene at 25°C was added 0.89 g of trans-1-(2-propenyl)pyrrolidine. Stirring was continued for an additional 1.5 hr. NMR analysis of the solution showed the presence of E- and Z-2,4-dimethyl-5-oxo-5-phenyl-2-pentenoic acid pyrrolidinamide (18) as the main product; NMR ($CDCl_3$) 1.28, 1.32 (2 d), 1.50-2.00 (m), 1.87, 1.93 (2 d), 3.00-3.70 (m), 4.20-4.50 (m), 5.57, 5.78 (2 d with fine splitting, J=9.0Hz), 7.35-8.00 (m); IR ($CDCl_3$) 1685, 1620 cm^{-1}. The mixture was concentrated under reduced pressure to leave behind an oil which was chromatographed on a silica gel thick layer plate using a 3:1:1 hexane-chloroformether mixture. The major product contained 0.8 g (49%) of 2,4-dimethyl-5-oxo-5-phenyl-3-pentenoic acid pyrrolidinamide (19) as a yellow liquid; bp 90°C (0.3 mm); IR (neat) 2990, 2890, 1670 (sh), 1640, 1600, 1580, 1430, 1305, 1250, 1165, 1010, 750, 710 cm^{-1}; NMR ($CDCl_3$,90 MHz)δ1.30 (d, J=6.2Hz, 3H), 1.73-2.05 (m, 4H), 2.02 (d, J=1.5Hz, 3H), 3.35-3.60 (m, 4H), 3.63 (dq, J=9.75 and 6.2Hz, 1H), 6.40 (dq, J=9.75 and 1.5Hz, 1H), 7.35-7.75 (m, 5H); UV (methanol) 246 (ε14100), 320 nm (ε 360); m/e 271 (M^+), 166 (base), 105; Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16; Found: C, 75.10; H, 7.84; N, 5.16.

Reaction of 5-Methyl-2-phenyl-1,3,4-oxadiazin-6-one (6) with 1-(2-Methylpropenyl)pyrrolidine (20). A stirred solution containing 0.793 g of 5-methyl-2-phenyl-1,3,4-oxadiazin-6-one (6) and 0.626 g of 1-(2-methylpropenyl)pyrrolidine[33] (20) in 10 ml of dry benzene was heated at reflux for 4 hr under a nitrogen atmosphere. Analysis of the crude reaction mixture by NMR spectroscopy indicated the presence of four products (34-37) in a ratio of 36:30:25:9. The reaction mixture was concentrated under reduced pressure and the resulting oil was chromatographed on a silica gel column. The first fraction contained a crystalline solid, mp 124-125°C, whose structure was assigned as 1-benzoyl-1,4,5,6-tetrahydro-6-pyrrolidino-3,5,5-trimethyl-1,2-diazin-4-one (37), IR (KBr) 1660, 1565, 1380, 1350, 1155, 1125, 980 cm^{-1}; NMR ($CDCl_3$,90MHz)δ1.21 (s, 3H), 1.28 (s, 3H), 1.53-1.80 (m, 4H), 1.97 (s, 3H), 2.46-2.78 (m, 4H), 5.82 (s, 1H), 7.30-7.78 (m, 5H); C^{13}-NMR ($CDCl_3$,20 MHz)δ 16.42 (q), 18.73 (q), 23.60 (t), 24.76 (q), 44.80 (s), 77.65 (d), 127.54 (d), 129.93 (d), 130.73 (d), 134.24 (s), 142.88 (s), 171.81 (s), 193.80 (s); UV (95% ethanol) 300 nm (ε 8150), 226 nm (ε 7750); m/e 313 (M^+), 244, 208, 125, 110, 105 (base), 96, 91 and 77; Anal. Calcd. for $C_{18}H_{23}N_3O_2$: C, 68.69; H, 7.40; N, 13.41; Found: C, 68.82; H, 7.44; N, 13.30.

The second fraction was assigned as lactone 36 mp 115-116°C; IR (KBr) 2935, 1690, 1445, 1360, 1270, 1245, 1150, 1020, 915, 815, 770, 715 cm^{-1}; NMR ($CDCl_3$,90MHz)δ0.63 (br s, 3H), 1.24 (br s, 3H), 1.52-1.75 (m, 4H), 1.92 (d, J=1.5Hz, 3H), 2.23-2.90 (m, 4H), 6.25 (q, J=1.5Hz, 1H), 7.17-7.73 (m, 5H); UV (acetonitrile) 225 nm (ε 6600); m/e 285 (M^+), 226, 215, 200, 176, 173, 110, 105 (base), 95, 91, 77, 67; Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91; Found: C, 75.82; H, 8.13; N, 4.86.

The third fraction was a colorless oil and was assigned as E-1-(4-benzoyl-2,4,4-trimethyl-2-butenoyl)- pyrrolidine (34): IR (neat) 2990, 2890, 1680, 1620, 1430, 1255, 1170, 980, 800, 755, 725, 695 cm^{-1}; NMR ($CDCl_3$,90MHz)δ1.47 (s, 6H), 1.54 (d, J=1.5Hz, 3H), 1.74-1.94 (m, 4H), 3.20-3.60 (m, 4H), 6.05 (q, J=1.5Hz, 1H), 7.27-8.11 (m, 5H); C^{13}-NMR ($CDCl_3$, 20MHz)δ14.33 (q), 24.05 (br t), 26.10 (br t), 27.42 (q), 45.54 (br t), 47.71, 48.18 (br t),

127.98, I29.34, 132.22, 135.11, 135.25, 136.58, 171.11, 203.53; UV (95% ethanol) 243 nm (ε10900); m/e 285 (M^+), 242, 180, 152, 111, 109, 105 (base), 95, 81 and 77; Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91; Found: C, 74.75; H, 8.17; N, 4.76.

The last fraction contained Z-1-(4-benzoyl-2,4,4-trimethyl-2-butenoyl)-pyrrolidine (35); mp 58-59°C; IR (neat) 2940, 2875, 1670, 1620, 1440, 1355, 1255, 1160, 780, 720 cm^{-1}; NMR (CCl_4,90MHz)δ1.32 (s, 6H), 1.70-2.00 (m, 4H), 1.85 (d, J=1.6Hz, 3H), 3.20-3.55 (m, 4H), 5.40 (q, J=1.6Hz, 1H), 7.27-8.07 (m, 5H); UV (methanol) 241 nm (ε 9900); m/e 285 (M^+), 180, 105 (base), 77; Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91; Found: C, 74.63; H, 8.11; N, 5.08.

Reaction of 2,5-Diphenyl-1,3,4-oxadiazin-6-one (1) with 1-(2-Methylpropenyl)pyrrolidine (20). To a stirred solution containing 1.25 g of 2,5-diphenyl-1,3,4-oxa-3,4-diazin-6-one (1) in 20 ml of benzene at 25°C was added 0.626 g of 1-(2-methylpropenyl)pyrrolidine (20). Stirring was continued for 4 hr after which time the solution was filtered and concentrated under reduced pressure. Crystallization of the residue from ether resulted in a mixture of lactone 21 and benzoyl-N-pyrrolidinoformamide-benzoylhydrazone (11). The crude residue was chromatographed on a silica gel column using a 1:1 chloroform-ether mixture to give 0.17 g (11%) of 11 as a pale yellow solid; mp 155-156°C; IR (KBr) 3160, 2900, 1700, 1630, 1550, 1450, 1270, 1145 cm^{-1}; NMR ($CDCl_3$,90MHz)δ1.73-2.02 (m, 4H), 3.05-3.23 (br t, 2H), 3.65-3.83 (br t, 3H), 7.38-7.98 (m, 10H), 10.8 (br s, 1H). The second fraction contained 1.0 g (60%) of 5,5-dimethyl-3,6-diphenyl-6-pyrrolidino-5,6-dihydro-2-pyranone (21) as a white crystalline solid; mp 194-195°C; IR (KBr) 2980, 1690, 1450, 1365, 1200, 1155, 980, 925, 900, 810, 760, 705 cm^{-1}; NMR ($CDCl_3$,90MHz)δ0.77 (br s, 3H), 1.33 (s, 3H), 1.50-1.83 (m, 4H), 2.30-2.97 (m, 4H), 6.47 (s, 1H), 7.18-7.53 (m, 8H), 7.60-7.77 (m, 2H); C^{13}-NMR ($CDCl_3$, 20MHz)δ23.48 (q), 23.69 (t), 28.63 (q), 39.61, 49.67 (t), 104.36, 127.65, 127.71, 127.91, 128.10, 128.25, 129.54, 135.47, 139.70, 150.21 (d), 163.96; UV (95% ethanol) 251 nm (ε9930); m/e 347 (M^+), 242, 200, 172, 149, 129, 117, 105, 95, 91 (base)and, 77; Anal. Calcd. for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03; Found: C, 79.30; H, 7.30; N, 3.99.

A solution containing 130 mg of 5,5-dimethyl-3,6-diphenyl-6-pyrrolidino-5,6-dihydro-2-pyranone (21) in 5 ml of a 4:1 tetrahydrofuran-water mixture was stirred for 48 hr at 25°C. The solvent was removed under reduced pressure to give 135 mg (99%) of Z-4,4-dimethyl-2,5-diphenyl-5-hydroxy-5-pyrrolidino-2-pentenoic acid (22) as a labile yellow oil; IR (neat) 2970, 2760, 2470, 1680, 1630, 1570, 1410, 1320, 1245, 1160, 980, 940, 700 cm^{-1}; NMR ($CDCl_3$,90 MHz)δ1.40 (s, 6H), 1.53-1.75 (m, 4H), 2.77-2.97 (m, 4H), 6.20 (s, 1H), 7.22-8.08 (m, 10H), 8.00 (brs,2H); UV (methanol) 249 nm (ε 8460); m/e 294 , 245, 223, 172, 160, 105, 91, 71 (base) and 70.

A solution containing 180 mg of 22 and 50 mg of potassium hydroxide in 4 ml of absolute ethanol was heated at reflux for 15 min. The solution was concentrated under reduced pressure and acidified with 2 N hydrochloric acid. Extraction of the mixture with ether followed by drying the organic layer over anhydrous magnesium sulfate and evaporation of the solvent gave 130 mg (77%) of lactol 23 as a white solid; mp 184-185°C; IR (KBr) 3310, 2993, 1700, 1385, 1238, 1198, 1103, 1015, 1005, 975, 755 cm^{-1}; NMR ($CDCl_3$, 90MHz)δ1.16 (s,6H), 4.05 (br s, 1H), 6.65 (s, 1H), 7.28-7.75 (m, 10H); UV (95% ethanol) 248 nm (ε 10620); Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16; Found: C, 77.32; H, 6.18.

To a solution containing 100 mg of 4,4-dimethyl-2,5-diphenyl-5-hydroxy-5-pyrrolidino-2-pentenoic acid (23) in 3 ml of ether was added a

freshly prepared solution of diazomethane in 1 ml ether. The resulting mixture was allowed to stand for 30 min at room temperature. The solvent was removed under reduced pressure to leave behind 80 mg (95%) of pure methyl Z-4,4-dimethyl-2,5-diphenyl-5-oxo-2-pentenoate (24) as a yellow oil which was purified by distillation at 105°C (0.3 mm); IR (neat) 2990, 1715, 1670, 1440, 1425, 1355, 1200, 1005, 905, 705 cm^{-1}; NMR ($CDCl_3$,90 MHz)δ1.56 (s, 6H), 3.53 (s, 3H), 6.53 (s, 1H), 7.25-8.05 (m, 10H); UV (methanol) 244 nm (ε16600); m/e 308 (M^+), 172, 143, 128, 105 (base), 77; Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54; Found: C, 77.28; H, 6.83.

Reaction of 2-Benzyl-5-phenyl-1,3,4-oxadiazin-6-one (25) with 1-(2-Methylpropenyl)pyrrolidine (20). To a stirred solution containing 1.06 g of 2-benzyl-5-phenyl-1,3,4-oxadiazin-6-one (25) in 10 ml of benzene at room temperature was added 0.55 g of 1-(2-methylpropenyl)pyrrolidine (20). Stirring was continued for an additional 2 hr after which time the solution was concentrated under reduced pressure. The oily residue that remained was crystallized from dichloromethaneether to give 0.84 g (54%) of lactone 26 as a white solid, mp 200-201°C; IR (KBr) 2970, 1695, 1500, 1450, 1365, 1220, 1175, 1140, 990, 890, 775, 715 cm^{-1}; NMR ($CDCl_3$,90MHz)δ0.88 (br s, 3H), 1.32 (br s, 3H), 1.67-2.00 (br m, 4H), 2.80-3.30 (br m, 4H), 3.30 and 3.78 (AB q, 2H), 6.37 (s, 1H), 7.18-7.55 (m, 10H); C^{13}-NMR ($CDCl_3$, 20MHz)δ23.49 (t), 25.15 (q), 26.86 (q), 40.17, 42.09 (t), 49.37 (t), 104.85, 126.74, 127.97, 128.20, 128.27, 128.34, 128.37, 130.15, 135.44, 135.88, 151.79 (d), 164.07; UV (methanol) 248 nm (12960); m/e 361 (M^+), 315, 270, 242, 226, 184, 172, 149, 129, 117, 115, 105, 98, 95 and, 91 (base); Anal. Calcd. for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87; Found: C, 79.64; H, 7.56; N, 3.86.

A solution containing 200 mg of 6-benzyl-5,5-dimethyl-3-phenyl-6-pyrrolidino-5,6-dihydro-2-pyranone (26) in 5 ml of a 4:1 tetrahydrofuran-water mixture was stirred for 48 hr at 25°C. The solvent was removed to give 205 mg (98%) of a white solid whose structure was assigned as Z-4,4-dimethyl-2,6-diphenyl-5-hydroxy-5-pyrrolidino-2-hexenoic acid (27) on the basis of its spectral data; mp 116-117°C; IR (KBr) 2985, 2750, 2610, 2480, 1705, 1625, 1560, 1500, 1415, 1315, 1045, 735, 665 cm^{-1}; NMR ($CDCl_3$,90 MHz)δ 1.35 (s, 6H), 1.60-1.80 (m, 4H), 2.85-3.05 (m, 4H), 4.03 (s, 2H), 5.94 (s, 1H), 7.25-7.60 (m, 10H), 9.1 (brs,2H); UV (methanol) 253 nm (ε9580); Anal. Calcd. for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69; Found: C, 76.02; H, 7.75; N, 3.65.

A solution containing 200 mg of 27 and 50 mg of potassium hydroxide in 4 ml of absolute ethanol was heated at reflux for 10 min. To the cooled solution was added 10 ml of a 1N hydrochloric acid solution and the mixture was extracted with ether. The ether layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 150 mg (88%) of lactol 28 as a white crystalline solid; mp 120-121°C; IR (KBr) 3290, 3040, 1700, 1605, 1500, 1385, 1240, 1210, 1050, 990, 970, 895, 755, 705 cm^{-1}; NMR ($CDCl_3$,90 MHz)δ 1.35 (s, 6H), 2.87 (br s, 1H), 3.15 (s, 2H), 6.58 (s, 1H), 7.23-7.55 (m, 10H), C^{13}-NMR ($CDCl_3$,20 MHz)δ23.48 (q), 40.21, 40.80 (t), 127.84, 128.11, 128.31, 128.89, 130.29, 131.55, 132.61, 135.18, 150.32, 162.85; UV (95% ethanol) 254 nm (9630); m/e 308 (M^+), 290, 275, 262, 247, 217, 189, 172, 159, 149, 143, 141, 129, 105, 91 (base) and 77; Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54; Found: C, 78.00; H, 6.61.

To a solution containing 106 mg of 4,4-dimethyl-2,6-diphenyl-5-hydroxy-5-pyrrolidino-2-hexenoic acid (27) in 5 ml of tetrahydrofuran was added a freshly prepared solution of diazomethane in 2 ml of ether. The resulting mixture was allowed to stand at room temperature for 30 min. The solvent was

removed under reduced pressure to give 85 mg (94%) of methyl 4,4-dimethyl-2,6-diphenyl-5-oxo-2-hexenoate (29) as a yellow oil which was distilled at 95°C (0.3 mm); IR (neat) 2980, 1725, 1600, 1495, 1430, 1360, 1265, 1205, 1045, 1015, 730, 700 cm^{-1}; NMR ($CDCl_3$,90 MHz)δ1.39 (s, 6H), 3.77 (s, 3H), 3.90 (s, 2H), 6.23 (s, 1H), 7.15-7.40 (m, 10H); UV (methanol) 253 nm (ε 9380); m/e 322 (M^+), 204, 172, 143, 128, 105, 91 (base) and 77; Anal. Calcd. for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88; Found: C, 78.11; H, 6.91.

Reaction of 2-Methyl-5-phenyl-1,3,4-oxadiazin-6-one (30) with 1-(2-Methylpropenyl)pyrrolidine (20). To a solution containing 0.753 g of 2-methyl-5-phenyl-1-oxa-3,4-diazin-6-one (30) in 8 ml of benzene at 25°C under a nitrogen atmosphere was added 0.63 g of 1-(2-methylpropenyl)pyrrolidine (20). Stirring of the solution was continued for 1 hr. NMR analysis of the crude residue showed that it contained a mixture of benzoyl-N-pyrrolidinoformamideacetylhydrazone (15%) and lactone 31 (80%) as the major products. The NMR spectrum of lactone 31 showed the following peaks: ($CDCl_3$,90 MHz)δ1.20 (s, 6H), 1.63 (s, 3H), 1.60-1.80 (m, 4H), 2.60-2.90 (m, 4H), 6.48 (s, 1H), 7.20-7.50(m, 5H). The crude mixture was concentrated under reduced pressure and was taken up in 10 ml of ether. Upon standing, 0.13 g (12%) of benzoyl-N-pyrrolidinoformamideacetylhydrazone crystallized out as a pale orange solid; mp 194-195°C , IR (KBr) 1640, 1595, 1535, 1510, 1380, 1330, 1305, 1245, 1060, 830, 770, 700cm-1; NMR ($CDCl_3$,90 MHz) 1.92-2.11 (m, 4H), 2.43 (s, 3H), 3.48-3.73 (m, 4H), 7.30-8.98 (m, 5H), 10.5 (brs, 1H). The mother liquors were evaporated to dryness and dissolved in a small amount of dichloromethane. Upon addition of a 1:1 ether-pentane mixture, 0.66 g (58%) of carboxylic acid 32 precipitated out as a white crystalline solid, mp 150-151°C; IR (KBr) 2990, 2760, 2450, 1710, 1640, 1555, 1415, 1385, 1320, 1120, 845, 775, 705 cm^{-1}; NMR ($CDCl_3$,90 MHz)δ1.32 (s, 6H), 1.67-1.90 (m, 4H), 2.18 (s, 3H), 2.92-3.18 (m, 4H), 5.81 (s, 1H), 7.18-7.53 (m, 5H), 8.15 (brs, 2H); C^{13}-NMR ($CDCl_3$,20 MHz)δ 24.41 (q), 25.94 (t), 26.10, 44.33 (t), 48.90, 127.06, 127.98, 134.32, 140.25, 142.24, 174.11; UV (methanol) 252 nm (ε 10320); m/e 288, 286, 232, 214, 207, 172, 143, 129 (base), 91 and 77; Anal. Calcd. for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62; Found: C, 71.17; H, 8.32; N, 4.59.

To a solution containing 80 mg of 4,4-dimethyl-5-hydroxy-2-phenyl-5-pyrrolidino-2-hexenoic acid (32) in 5 ml of tetrahydrofuran was added a freshly prepared solution of diazomethane in 2 ml ether. The resulting mixture was allowed to stand for 30 min at 25°C. The solvent was removed under reduced pressure to leave behind 60 mg (94%) of pure methyl 4,4-dimethyl-5-oxo-2-phenyl-2-hexenoate (33) as a colorless oil; bp 70°C (0.3 mm); IR (neat) 2980, 1730, 1715, 1630, 1600, 1495, 1435, 1360, 1270, 1210, 1120, 1015, 765, 700 cm^{-1}; NMR ($CDCl_3$,90 MHz)δ1.34 (s, 6H), 2.18 (s, 3H), 3.73 (s, 3H), 6.20 (s, 1H), 7.25-7.60 (m, 5H); UV (methanol) 249 nm (ε 8460); m/e 246 (M^+), 220, 204, 172, 143 (base), 129, 128, 115, 91, 77, 73; Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; Found: C, 72.44; H, 7.43.

Reaction of 2,5-Diphenyl-1,3,4-oxadiazin-6-one (1) with 2,3-Dihydrofuran. A solution containing 0.7 g of 2,5-diphenyl-1,3,4-oxadiazin-6-one (1) in 5 ml of 2,3-dihydrofuran was heated under reflux for 6 hr. The hot mixture was filtered and then 5 ml of pentane was added. Crystallization of the mixture gave 0.5 g (54%) of 7-(3-benzoyl-2-furanyl)-7-phenyl-2-oxabicyclo-[3.2.0]heptan-6-one (41) as a white, crystalline solid, mp 155-156°C; IR (KBr) 3060, 2960, 2870, 1780, 1670, 1600, 1580, 1490, 1445, 1380, 1230, 1145, 1100, 1055, 915, 715, 685 cm^{-1}; NMR ($CDCl_3$,90 MHz)δ1.73-2.40 (m, 4H), 3.67-4.32 (m, 6H), 4.87 (d, 1H, J=7.2Hz), 5.10 (d, 1H,J=6.4Hz), 6.98-7.57 (m, 8H), 7.66-7.82 (m, 2H); C^{13}-NMR ($CDCl_3$,200

MHz)δ28.01 (t), 30.22 (t), 47.40 (d), 62.10 (d), 67.78 (t), 71.12 (t), 76.23 (s), 80.02 (d), 80.82 (d), 127.66 (d), 128.05 (d), 128.16 (d), 128.27 (d), 129.22 (d), 132.43 (d), 134.33 (s), 138.01 (s), 198.18 (s), 209.79 (s); UV (methanol) 245 nm (ε 11585); m/e 362 (M^+), 292, 264, 159, 105 (base) and 77; Anal. Calcd. for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12; Found: C, 75.76; H, 6.25.

The mother liquor was concentrated under reduced pressure and the oily residue that remained was chromatographed on a silica gel thick layer plate using a 2:1 ether-hexane mixture. The major fraction gave 0.09 g (8%) of the other diastereomer (42) as a white solid; mp 101-102°C; IR (KBr) 2890, 1780, 1670, 1595, 1580, 1450, 1390, 1240, 1220, 1175, 1085, 1055, 980, 925, 910, 720, 700, 685 cm^{-1}; NMR ($CDCl_3$,90 MHz)δ1.70-2.45 (m, 4H), 3.63-4.30 (m, 6H), 4.84 (d, 1H, J=5.7Hz), 4.92 (d, 1H, J=6.8Hz), 6.93-7.55 (m, 8H), 7.64-7.80 (m, 2H); m/e 362 (M^+), 292, 264, 159, 146, 105 (base) and 77.

Reaction of 2-Benzyl-5-phenyl-1,3,4-oxadiazin-6-one (25) with 2,3-Dihydrofuran. A solution containing 0.79 g of 2-benzyl-5-phenyl-1,3,4-oxadiazin-6-one (25) in 5 ml of 2,3-dihydrofuran was heated at reflux for 2 hr. The reaction mixture was concentrated to dryness and the resulting residue was chromatographed on a silica gel column using a 1:1 hexane-ether mixture as the eluent. The major fraction contained 0.51 g (42%) of 7-(3-phenylacetyl-2-furanyl)-7-phenyl-2-oxabicyclo[3.2.0]heptan-6-one (43) as a 77:23 mixture of two diastereomers. The major isomer was obtained by fractional crystallization as a colorless solid; mp 97-98°C; IR (KBr) 2980, 2950, 2890, 2870, 1775, 1725, 1495, 1450, 1385, 1315, 1140, 1080, 1055, 765, 705 cm^{-1}; NMR ($CDCl_3$,90 MHz)δ1.53-2.50 (m, 4H), 3.18-4.25 (m, 8H), 4.63 (d, 1H, J=7.1Hz), 5.02 (d, 1H, J=6.0Hz), 7.02-7.50 (m, 10H); m/e 376 (M^+), 306, 199, 187, 159, 143, 131, 128, 115, 105 (base), 91 and 77; Anal. Calcd. for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43; Found: C, 76.60; H, 6.46.

The NMR of the second diastereomer 44 showed signals at 1.50-2.45 (m, 4H), 3.15-4.22 (m, 8H), 4.75 (d, 1H,J=7.1Hz), 5.06 (d, 1H,J=5.7Hz), 7.0-7.5 (m, 10H). A pure sample of this material could not be obtained.

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*Alexander von Humboldt Senior Scientist, 1984-1985; University of Wurzburg.

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