The methanesulfonate salt of **25** was prepared by the addition of equimolar amounts of **25** and methanesulfonic acid to methanol. The resulting salt was precipitated by the addition of ether. Recrystallization of the salt from a mixture of methanol and ether gave the methanesulfonate salt of **25** as pale yellow needles: mp 226–227 °C; IR (KBr) 3440 cm^{-1}; NMR (Me_2SO-d_6) δ 2.46 (s, 3, CH_3), 3.38 (s, 2, C_5 H), 3.43 (s, 4, CH_2CH_2), 3.86 (s, 2, C_3 H), 7.01 (d, J = 2 Hz, 1, arom H), 7.4–7.9 (m, 6, arom H), 8.5 (br s, 1, NH^+).

Anal. Calcd for $C_{19}H_{19}Cl_2NO_3S_3$: C, 47.90; H, 4.02; N, 2.94; S, 20.19. Found: C, 47.99; H, 4.12; N, 2.84; S, 20.23.

Acknowledgment. We thank the following members of our Physical Chemistry Department: Dr. F. Scheidl for elemental analyses, Dr. T. Williams for NMR spectra, Dr. W. Benz for mass spectra, Mr. S. Traiman for IR spectra and Mr. W. May for technical assistance.

Registry No. 4, 2958-36-3; **5** (X = Y = Cl), 76049-50-8; **5** (X = Cl; Y = H), 76049-48-4; **5** (X = Cl; Y = F), 76049-49-5; **5** (X = Y = H), 25187-00-2; **6**, 76049-54-2; **7** (X = Y = Cl; R = phth), 76049-64-4; **7** (X = Cl; Y = H; R = phth), 76049-52-0; **7** (X = Cl; Y = F; R = phth), 76049-53-1; **7** (X = H; Y = Cl; R = phth), 76049-55-3; **7** (X = Y = H; R = phth), 76049-56-4; **7** (X = Y = Cl; R = NH_2), 76049-64-4; **7** (X = Cl; Y = H; R = NH_2), 76049-61-1; **7** (X = Cl; Y = F; R = NH_2), 76049-63-3; **7**·HCl (X = H; Y = Cl; R = NH_2), 76049-66-6; **7**·HCl (X = Y = H; R = NH_2), 76049-67-7; **9** (X = Y = Cl), 76049-70-2; **9** (X = Y = Cl) methanesulfonate, 76049-71-3; **9** (X = Cl; Y = H) methanesulfonate, 58582-23-3; **9** (X = Cl; Y = F), 58583-07-6; **9** (X = H; Y = Cl), 76049-72-4; **9** (X = Y = H) methanesulfonate, 76049-74-6; **9** (X = Cl; Y = F) *N*-oxide, 76049-76-8; **9** (X = Y = Cl) *N*-oxide, 76049-78-0; **10**, 78367-91-6; **11**, 81389-12-0; **12**, 81389-13-1; **13**, 81389-14-2; **15**, 81389-15-3; **16**, 81389-16-4; **17**, 81389-17-5; **18**, 81389-18-6; **19**, 81389-19-7; **19**·HCl, 81389-20-0; **20**, 81389-21-1; **21**, 81389-22-2; **23**, 81389-23-3; **24**, 81389-25-5; **25**, 81389-26-6; **25** methanesulfonate, 81389-27-7; *N*-propargylphthalimide, 7223-50-9.

Supplementary Material Available: Tables VI–IX containing the corresponding final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for compound **16** (4 pages). Ordering information is given on any current masthead page.

Regiochemistry of Intramolecular Munchnone Cycloadditions: Preparative and Mechanistic Implications

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A series of munchnone derivatives containing an internal π bond were generated in situ by treating several *N*-(*o*-allylphenyl)alanines with acetic anhydride. The major product obtained corresponded to intramolecular 1,3-dipolar cycloaddition of the mesoionic species across the olefinic π bond. The structures of the cycloadducts were assigned on the basis of their characteristic spectral data and by an X-ray single-crystal structure analysis. The cycloaddition reactions proceed via an initial N-acetylation of the amino acid followed by cyclodehydration to give an unstable munchnone intermediate. The azomethine ylide functionality of the mesoionic species then participates in an intramolecular 1,3-dipolar cycloaddition with the unactivated carbon–carbon double bond. The regioselectivity of the internal cycloaddition of a series of *N*-(*o*-allylphenyl)-substituted munchnones was found to be markedly dependent on the substituent groups present. It can be presumed that both steric and electronic factors are involved. Intramolecular cycloaddition of munchnones has been found to provide a valuable mechanistic tool for the study of orientational substituent effects.

1,3-Dipolar cycloadditions to olefins have been extensively studied and are now well understood primarily owing to the efforts of Huisgen and co-workers.[1-7] Experience indicates a concerted mechanism[8,9] and frontier molecular orbital theory has successfully explained relative rates and regioselectivity of these cycloadditions.[10-20] During the last decade a new impulse has been given to research in this field when it was found that various mesoionic compounds undergo 1,3-dipolar cycloaddition with different dipolarophiles.[21] Of the known mesoionic heterocycles, the structure, physical properties, and reactions of munchnones and sydnones have drawn the closest scrutiny.[21-24] Huisgen and co-workers have studied the cycloaddition reaction of munchnones with various dipolarophiles in detail and have shown that the reaction constitutes a general synthesis of pyrroles[25] and pyrrolines.[26] The reaction involves a 1,3-dipolar cycloaddition of the munchnone, behaving like a cyclic azomethine ylide, to the corresponding acetylenic or olefinic dipolarophile followed by CO_2 evolution and aromatization or tautomerization.[27,28] The reactions of sydnones closely parallel those of the related munchnones.[29-31] Studies with these two mesoionic systems have generated considerable theoretical interest and have resulted in practical, unique syntheses of nu-

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merous functionalized monocyclic and ring annulated heterocycles.[21]

In spite of the copious literature dealing with bimolecular cycloaddition reactions of mesoionic heterocycles, intramolecular examples have received only a minimum of attention.[32-35] An attractive feature associated with the intramolecular dipolar cycloaddition of mesoionic compounds is the opportunity to control the stereochemistry of the products at several centers. In systems where the dipole and dipolarophile are linked by several atoms, the highly ordered transition state will also induce useful regiochemical control. As part of a research program designed to uncover new cycloadditions of mesoionic heterocycles, we initiated a study dealing with the chemistry of munchnones containing a π bond in close proximity to the dipole center. In this paper we report that munchnones of this type undergo smooth intramolecular 1,3-dipolar cycloaddition to form novel heterocyclic compounds.[36]

Results and Discussion

As our first model we chose to investigate the intramolecular dipolar cycloaddition of the *N*-(*o*-allylphenyl)-munchnone system. Formation of the desired mesoionic compound (i.e., **7**) involved treating the appropriate α-amino acid with acetic anhydride. The required α-amino acids were prepared by reacting ethyl 2-bromopropionate or ethyl α-bromophenylacetate with *o*-allylaniline. The resulting esters were saponified to give the required α-amino acids **3** and **4**. The *N*-benzoyl-substituted α-amino acids **5** and **6** were also available from the α-amino acid esters **1** and **2** via an acylation–saponification sequence. The proton NMR spectra of **5** and **6**, as well as their ester precursors, are noteworthy due to the presence of extra signals which are presumably the result of amide-hindered rotation.[37] For example, the benzylic proton of **6** appears as two different signals in the NMR, while two different sets of doublets and quartets appear for the CH_3CH moiety in the spectrum of **5** and its ester precursor.

With the required α-amino acids in hand, we turned our attention to the generation of munchnones of type **7**. Treatment of *N*-(*o*-allylphenyl)alanine (**3**) with acetic anhydride at 55 °C for 3 h afforded a single compound in good yield whose structure is assigned 3a,4-dihydro-1,3a-dimethyl-1,4-methano-5*H*-oxazolo[3,2-*a*]quinolin-2(1*H*)-one (**8**): mp 115–116 °C; NMR ($CDCl_3$, 100 MHz) δ 1.25 (dd, 1 H, J = 13.0, 2.0 Hz), 1.31 (s, 3 H), 1.53 (s, 3 H), 1.95 (dd, 1 H, J = 13.0, 7.5 Hz), 2.58–2.82 (m, 1 H), 2.81 (dd, 1 H, J = 16.5, 2.5 Hz), 3.16 (dd, 1 H, J = 16.5, 4.0 Hz), 6.96–7.14 (m, 1 H), 7.14–7.36 (m, 3 H). Similarly, treatment of **3** with 2 equiv of benzoic anhydride in refluxing benzene also yielded a single cycloadduct (**9**) in 81% isolated yield. This same cycloadduct was obtained by treating *N*-benzoyl-*N*-(*o*-allylphenyl)alanine (**5**) with acetic anhydride at 55 °C for several hours. In neither case were there any signs of another regioisomer in the crude reaction mixture.

The structure of cycloadduct **9** is assigned as the 1,4-methano-5*H*-oxazolo[3,2-*a*]quinolin-2(1*H*)-one regioisomer, mp 155–156 °C, on the basis of its characteristic spectral data. Most noteworthy is the fact that cycloadducts **8** and **9** have virtually identical ^{13}C chemical shifts at carbon atoms 1, 2, 3a, 4, 5, and 11 (^{13}C NMR, $CDCl_3$): 73 (s), 175 (s), 100 (s), 40 (d), 36 (t), 35 (t) ppm. The structure of oxazoloquinolinone **9** was unequivocally proved by an X-ray single-crystal structure analysis.[38] The crystals of **9** used for X-ray diffraction were monoclinic and belong to space group $p2_1/n$. The unit cell parameters were as follows: a = 10.522 (2) Å, b = 8.858 (1) Å, c = 16.5818 (2) Å, β = 94.46 (1)°, and the calculated density indicate four molecules per unit cell. The structure was derived from Patterson and Fourier syntheses and refined by least-squares methods to R = 0.051 for all the data.

The above cycloaddition reactions proceed via an initial N-acetylation of the amino acid followed by cyclodehydration to give an unstable munchnone intermediate

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Table I. ^{13}C Chemical Shifts of the Oxazoloquinoline and Oxadiazolocinnoline Systems[a]

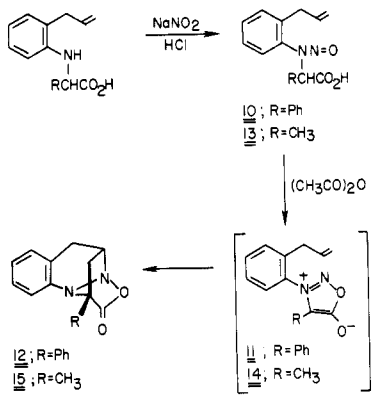
structure	C_1	C_2	C_{3a}	C_4	C_5	C_{11}	CH_3
8	72.9	175.0	99.1	40.1	35.7	34.9	13.1 (C_1), 15.1 (C-3a)
9	73.0	174.7	100.9	39.9	35.7	34.9	13.1
12[b]	81.0	176.1		65.9	36.0	29.1	
15	73.7	177.3		65.3	35.8	32.1	11.0
16	104.6		73.6	34.8	41.2	32.3	16.9
17	79.8	174.0	99.3	39.9	35.0	32.2	15.2
18	106.4		74.3	34.2	38.7	32.4	
19	79.9	173.6	101.0	39.1	35.0	32.1	

[a] Parts per million, $CDCl_3$. [b] Parts per million, HMPA.

(**7a** or **7b**). No attempt was made to isolate the intermediate munchnone, since Huisgen has shown the Δ^2-oxazolium 5-oxide system to be extremely reactive.[39-43] The azomethine ylide functionality of the mesoionic species then participates in an intramolecular 1,3-dipolar cycloaddition with the unactivated carbon–carbon double bond of the allyl group to give the oxazoloquinolinones **8** and **9**.

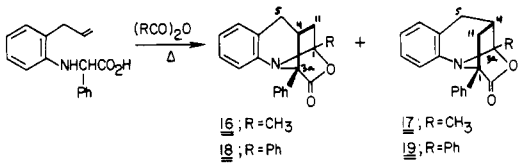
The isolation of the oxazoloquinolinone system represents the first example of an intramolecular dipolar cycloaddition reaction of a munchnone derivative. This reaction is of additional interest in that it involves [3 + 2] cycloaddition with an unactivated olefin, a substrate which is generally unreactive toward munchnones. When azomethine ylides are used as 1,3-dipoles, the dipole HOMO and dipolarophile LUMO interaction will be of greatest importance in stabilizing the transition state. Azomethine ylides are known to react most rapidly with electron-deficient alkenes, since such a pair of addends possesses a narrow dipole HOMO–dipolarophile LUMO gap.[44] Bimolecular reactions of azomethine ylides with 1-alkenes have never been observed, thereby indicating that the dipole LUMO–dipolarophile HOMO interaction is never large. Houk has suggested that the introduction of a carbonyl group into an azomethine ylide[45] (i.e., munchnones) shifts the 1,3-dipole to a type III case (Sustmann's classification).[46] Since the intramolecular cycloaddition of **7** involves an alkyl-substituted π bond, one might inquire why the reaction occurs at all. Undoubtedly, the rate of internal cycloaddition reflects an extremely favorable entropy factor which offsets the unfavorable electronic factor.

The above reaction is also unique in that the product obtained corresponds to a 1:1 cycloadduct which has retained the elements of carbon dioxide. In fact, to our knowledge, this represents the first example of an isolable primary cycloadduct of a munchnone and an olefin. It is interesting to note that the orientation of the cycloadduct derived from munchnone **7** is identical with that observed with the closely related sydnone system. Heimgartner and co-workers[33,34] had reported that treatment of nitroso amino acid **10** with acetic anhydride gave oxadiazolo[3,2-*a*]cinnoline **12** in high yield. The reaction was proposed to



proceed via a transient sydnone (i.e., **11**) which undergoes a rapid intramolecular dipolar cycloaddition to give **12**. We have encountered similar results in our investigation with sydnone **14**. Treatment of *N*-(*o*-allylphenyl)alanine **1** with nitrous acid followed by reaction with acetic anhydride produced oxadiazolocinnoline **15** as the exclusive cycloadduct. The formation of **15** involves a 1,3-dipolar cycloaddition of the sydnone, behaving like a cyclic azomethine imine, to the neighboring π bond.

We have also studied the regiochemical aspects of the cycloaddition of *N*-(*o*-allylphenyl)-2-phenylglycine (**4**) with acetic anhydride. In this case the reaction produced a mixture of two regioisomeric cycloadducts **16** and **17**. The



isomers could easily be separated by fractional crystallization. The major regioisomer formed (62%) was identified as oxazolo[3,4-*a*]quinolinone **16**: mp 165–166 °C; NMR ($CDCl_3$, 100 MHz) δ 1.63 (s, 3 H), 1.65 (dd, 1 H, J = 13.0, 2.0 hZ), 2.34 (dd, 1 H, J = 13.0, 7.), 2.51 (dd, 1 H, J = 17.0, 2.5 Hz), 2.78 (dd, 1 H, J = 17.0, 3.0 Hz), 2.80–3.05 (m, 1 H), 6.80 (d, 1 H, J = 7.0, Hz), 6.89–7.34 (m, 8 H). The minor isomer, mp 189–190 °C, was identified as oxazolo[3,2-*a*]quinoline **17**: NMR ($CDCl_3$, 100 MHz) δ 1.61 (s, 3 H), 1.99 (dd, 1 H, J = 13.0, 2.0 Hz), 2.31 (dd, 1 H, J = 13.0, 7.0 Hz), 2.75–2.95 (m, 1 H), 3.05 (dd, 1 H, J = 16.0, 2.0 Hz), 3.19 (dd, 1 H, J = 16.0, 3.5 Hz), 6.57 (d, 1 H, J = 8.0 Hz), 6.80–7.20 (m, 3 H), 7.36 (s, 5 H). No interconversion of **16** and **17** occurred on heating the isolated regioisomers in boiling toluene for 6 h, thus indicating the observed regiochemistry to result from kinetic control. It should be pointed out that the isolation of **16** as the major cycloadduct stands in marked contrast with the results encountered with the *N*-(*o*-allylphenyl)alanine system (**3**).

The structural assignments for cycloadducts **16** and **17** were based on their respective proton and ^{13}C NMR spectra. Particular attention was given to the chemical shifts of the benzylic and methylenic protons as well as to an appreciably shielded aromatic proton with cycloadduct **17**. The aromatic regions of cycloadducts **8**, **9**, **12**, and **17** were virtually identical, including the presence of an appreciably shielded doublet in each case. Additionally, the ^{13}C chemical shifts for the carbon atoms compare favorably as indicated in Table I. Thus, the ^{13}C chemical shift for carbon C-3a of cycloadducts **8** and **9**, which ap-

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Table II. Relative NMR Chemical Shift Differences of the H_{11} and $H_{11'}$ Protons of the Oxazoloquinoline and Oxadiazolocinnoline Systems

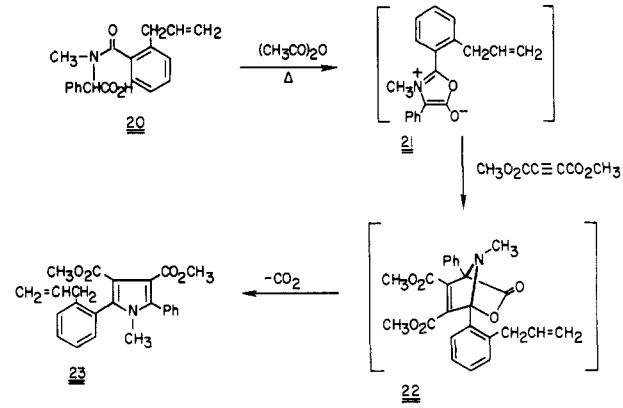
structure	$\delta(H_{11})$	$\delta(H_{11'})$	ΔH_{11}
8	1.95	1.25	0.70
9	2.07	1.41	0.63
12	2.42	2.22	0.20
15	2.01	1.48	0.53
16	2.34	1.65	0.69
17	2.31	1.99	0.32
18	2.52	2.26	0.26
19	2.45	2.18	0.27

pears at 99.1 and 100.9 ppm, compares favorably with the C-3a shift of cycloadduct 17 (99.3 ppm). In addition, the ^{13}C chemical shift of the methyl carbon of cycloadduct 8, which appears at 15.1 ppm, is in good agreement with the C-3a methyl carbon of 17 at 15.2 ppm. Finally, an interesting correlation exists for the relative proton NMR chemical shift differences of the H_{11} and $H_{11'}$ protons ($\Delta H_{11} = \delta H_{11'} - \delta H_{11}$) of the oxazoloquinolines 16 and 17 and the oxadiazolocinnolines 12 and 15. As illustrated in Table II, when the H_{11} and $H_{11'}$ protons are adjacent to a carbon substituted with a phenyl group (i.e., 12, 17–19), ΔH_{11} ranges between 0.2 and 0.3 ppm. However, when the H_{11} and $H_{11'}$ protons are adjacent to a carbon substituted with a methyl group (i.e., 8, 9, 15, and 16), the ΔH_{11} difference corresponds to 0.5–0.7 ppm. The pertinent chemical shifts and coupling constants for these adducts are given in the Experimental Section.

Opposite regioselectivity was encountered in the intramolecular cycloaddition of the munchnone derived from heating 4 with benzoic anhydride in benzene. Under these conditions 4 furnished cycloadducts 18 and 19 in a 1:2 ratio. Regiochemical assignment of the mixture of isomers was easily made by comparison of the proton and ^{13}C NMR spectra (see Tables I and II). The above results clearly indicate that the nature of the substituent groups present on the munchnone ring play an important role in controlling the regioselectivity of cycloaddition. It can be presumed that both steric and electronic factors are involved.[19] Intramolecular cycloaddition of munchnones thus provide a valuable mechanistic tool for the study of orientational substituent effects.

1,3-Dipolar cycloaddition of mesoionic systems have been suggested to be a LU(1,3-dipole)–HO(dipolarophile) controlled process.[44,47] We find it difficult to accommodate our results with a type III process (Sustmann's classification)[46] since this perception cannot easily accommodate the changes in regiochemistry that we observe. In the present case, mesoionic compounds having high local charge densities give rise to a complex inhomogeneous field in the vicinity of the approaching dipolarophile and van der Waals energy considerations[48,49] may be quite important here and provide some insight into the regiochemistry of the cycloadditions. The regiochemistry exhibited in the cycloaddition of sydnones and munchnones with unsymmetrical dipolarophiles is known to be sensitive to substitution and has its basis in all possible frontier interactions. Thus, Frontier MO theory does not easily account for the distribution of products obtained from the above systems. It seems reasonable to assume that steric factors play a role in determining the regiochemical outcome of the above cycloadditions.

In view of the stringent spatial requirements associated with the intramolecular cycloaddition of 1,3-dipoles,[50] we thought it worthwhile to consider what effect a variation in the spatial proximity between the dipole and dipolarophile would have on the course of the intramolecular dipolar cycloaddition reaction. This led us to study the cycloaddition behavior of the munchnone (i.e., 21) derived from *N*-methyl-*N*-(*o*-allylbenzoyl)-2-phenylglycine (20). Unfortunately, all attempts to detect intramolecular cycloaddition from this system failed. When 20 was treated with acetic anhydride in the presence of dimethyl acetylenedicarboxylate, the expected pyrrole 23 was obtained in modest yield. The isolation of pyrrole 23 indicates that the mesoionic system is formed but that intramolecular cycloaddition does not occur.

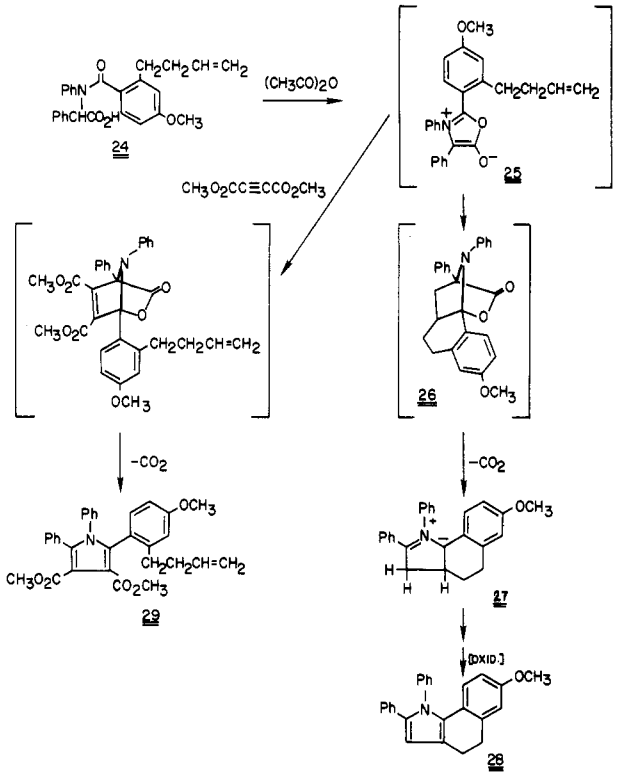


The primary spatial requirement for intramolecular dipolar cycloaddition is that the distance between the two reacting centers should be sufficiently short so that effective three-center overlap of the 1,3-dipole with the dipolarophile should be arranged in such a way as to allow their p orbitals to lie in a plane parallel to the plane of the 1,3-dipole. Examination of molecular models indicates that with munchnone 21, the azomethine ylide portion of the molecule and the π bond cannot approach each other in parallel planes. Consequently, intramolecular 1,3-dipolar cycloaddition does not occur.

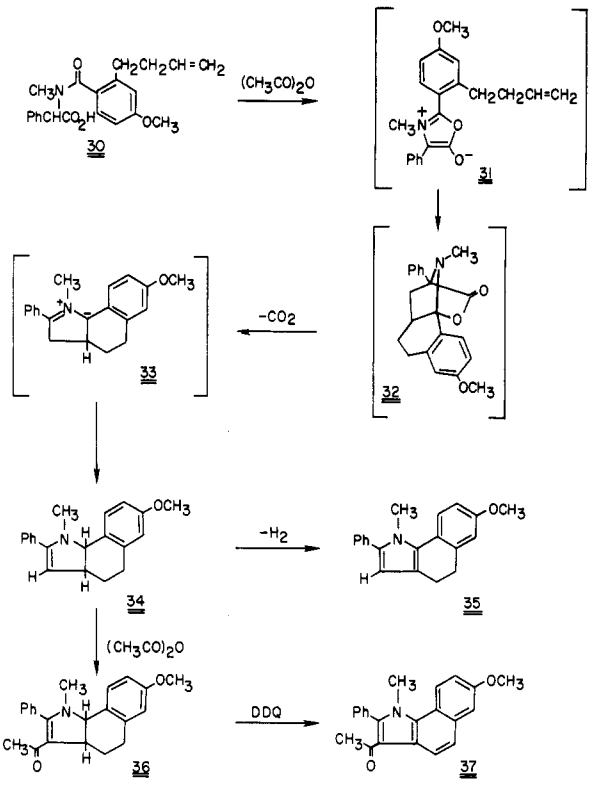
The situation is somewhat different with the homologous unsaturated munchnone 25. With this system, the transition state for cycloaddition allows attainment of the "parallel-plane approach" and intramolecular cycloaddition would be expected to occur. In order to test this prediction, we carried out the reaction of *N*-aroyl amino acid 24 with acetic anhydride. The major product isolated from the reaction mixture corresponded to a primary cycloadduct which had lost the elements of carbon dioxide and hydrogen. Assignment of this material as 4,5-dihydro-1*H*-benz[*g*]indole 28, mp 186–187 °C, was based on its elemental analysis and characteristic spectral data [NMR ($CDCl_3$, 100 MHz) δ 2.61–3.09 (m, 4 H), 3.71 (s, 3 H), 6.15 (d, 1 H, J = 8.0 Hz), 6.32 (s, 1 H), 6.38 (dd, 1 H, J = 8.0, 2.5 Hz), 6.80 (d, 1 H, J = 2.5 Hz), 6.89–7.57 (m, 10 H)]. A plausible mechanism for the formation of 28 is illustrated in Scheme I. Intramolecular dipolar cycloaddition of munchnone 25 produces the primary cycloadduct 26 which readily loses carbon dioxide under the reaction conditions to give the azomethine ylide 27. Tautomerization of 27 furnishes the tetrahydro-1*H*-benz[*g*]indole which is subsequently oxidized to 28. It should be pointed out that every step in this sequence, including the oxidation, has ample precedent in the literature.[26] When the reaction of 24 with acetic anhydride was carried out in the presence

(47) H. Gotthardt and F. Reiter, *Chem. Ber.*, 112, 1193 (1979).
(48) J. Bertran, E. Silla, and J. I. Fernandez-Alonso, *Tetrahedron*, 31, 1093 (1975).
(49) H. Fujimoto and R. Hoffman, *J. Phys. Chem.*, 78, 1874 (1974), and references cited therein.
(50) A. Padwa, *Angew. Chem., Int. Ed. Engl.*, 15, 123 (1976).

Scheme I



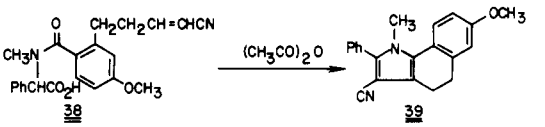
Scheme II



of dimethyl acetylenedicarboxylate, the only product obtained was pyrrole **29**. This observation provides good support for the involvement of munchnone **25**, which in the absence of an added dipolarophile, undergoes intramolecular cycloaddition across the neighboring double bond to eventually give **28**.

An additional system which was also studied involved the reaction of the closely related *N*-aroyl amino acid **30** with acetic anhydride. In this case, the expected 4,5-dihydro-1*H*-benz[*g*]indole **35** was isolated in low yield. The structure of the major product obtained from the reaction mixture was assigned as 3-acetyltetrahydro-1*H*-benz[*g*]indole **36** on the basis of its characteristic spectral properties. The DDQ oxidation of **36** led to the corresponding 1-methyl-2-phenyl-3-acetyl-7-methoxy-1*H*-benz[*g*]indole (**37**), thus providing chemical support to the assigned structure. As indicated in Scheme II, structure **36** is presumed to be formed by the acylation of the enamine functionality of the intermediate tetrahydro-1*H*-benz[*g*]indole **34**. It is worth noting that a product similar to **36** was not observed in the reaction of *N*-aroyl amino acid **24** with acetic anhydride. This is probably related to the lesser reactivity of the tetrahydro-1*H*-benz[*g*]indole ring as a result of the inavailability of the nitrogen lone pair, which is delocalized onto the phenyl ring.

Placement of an electron-withdrawing substituent on the π bond should lower the dipolarophile LU energy and enhance the yield of the 1,3-dipolar cycloaddition. Thus, it became of interest to study the intramolecular cycloaddition of an unsaturated munchnone derivative which possessed an electron-withdrawing substituent on the double bond in order to determine whether this electronic perturbation would promote the intramolecular cycloaddition. To this end we synthesized *N*-methyl-*N*-(*p*-methoxy-*o*-(4-cyano-3-butenyl)benzoyl]-2-phenylglycine (**38**). This compound was prepared by subjecting the ethyl ester of *N*-aroyl amino acid **30** to ozonolysis followed by treatment of this resulting aldehyde with (cyanomethylene)triphenylphosphorane and aqueous hydrolysis of the Wittig product. Treatment of **38** with acetic anhydride at 55 °C for 3 h produced the expected 4,5-dihydro-1*H*-benz[*g*]indole **39** in low yield (i.e., 11%). This



result indicates that activation of the internal dipolarophile with an electron-withdrawing group fails to improve the efficiency of the intramolecular dipolar cycloaddition process. One interesting possibility to account for this "leveling effect" is the high degree of order already present in the transition state. Bimolecular cycloadditions exhibit large negative entropies of activation[2] since the reactants must be precisely aligned with respect to each other. The interplay of entropy and enthalpy will control the rate-determining activation process. The larger entropy term associated with the intramolecular cycloaddition will tend to compress the rate scale. Perhaps this is the key to understanding the "leveling effect", since the smaller the steric requirements of the transition state, the less sensitive the system is toward electronic disturbance.

In conclusion, our results show that the intramolecular dipolar cycloaddition reaction of munchnones containing proximate π bonds is a general, synthetically useful, and mechanistically intriguing process. We are continuing to examine the effects of geometry and substituents on the reaction and will report additional findings at a later date.

Experimental Section[51]

Preparation of *N*-(*o*-Allylphenyl)alanine (3). A mixture containing 9.05 g of ethyl 2-bromopropionate, 6.66 g of *o*-allyl-

(51) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 283 infrared spectrometer. NMR spectra were obtained on a Varian XL-100 spectrometer. Elemental analyses were performed by the Atlantic Microanalytical Laboratory. The ultraviolet absorption spectra were measured with a Cary-14 recording spectrophotometer, using 1-cm matched cells.

aniline,[52] and 5.06 g of triethylamine in 35 mL of toluene was heated at reflux for 48 h. Upon cooling, the reaction mixture was washed with water and then dried over magnesium sulfate. Removal of the solvent left 9.90 g of a yellow liquid which was chromatographed over silica gel with a 5% acetone–hexane mixture to give 5.10 g (44%) of *N*-(*o*-allylphenyl)alanine ethyl ester (**1**) as a light-yellow liquid: IR (neat) 3300, 2899, 1718, 1595, 1577, 1502, 1441, 1302, 1250, 1208, 1161, 1054, 917, 748 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.17 (t, 3 H, J = 7.0 Hz), 1.40 (d, 3 H, J = 6.0 Hz), 3.24 (d, 2 H, J = 6.0 Hz), 3.84–4.36 (m, 4 H), 4.89–5.20 (m, 2 H), 5.62–6.06 (m, 1 H), 6.40 (d, 7.0 Hz, 1 H), 6.55 (t, 1 H, J = 7.5 Hz), 6.78–7.10 (m, 2 H).

A mixture of 2.80 g of the above ester and 720 mg of sodium hydroxide in 6 mL of water and 1.2 mL of ethanol was heated at reflux for 30 min. Upon cooling, the reaction mixture was diluted with water and extracted with ether. The aqueous layer was acidified with 10% hydrochloric acid and extracted with ether. The ether layer was washed with water and dried over magnesium sulfate. Removal of the solvent under reduced pressure left an orange solid which was passed through a short silica gel column using a 20% acetone–hexane mixture as the eluent. The major fraction contained 2.07 g of a yellow solid which was recrystallized from acetone–hexane to give 1.66 g (67%) of *N*-(*o*-allylphenyl)-alanine (**3**) as a light-yellow solid: mp 60–61 °C; IR (KBr) 3235, 3010–2290, 1715, 1582, 1499, 1307, 1211, 1147, 920, 778, 745 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.47 (d, 3 H, J = 6.5 Hz), 3.27 (d, 2 H, J = 6.0 Hz), 4.09 (q, 1 H, J = 6.5 Hz), 4.92–5.24 (m, 2 H), 5.67–6.12 (m, 1 H), 6.49 (d, 1 H, J = 8.0 Hz), 6.66 (*t*, 1 H, J = 7.0 Hz)e, 6.92–7.18 (m, 2 H), 8.00 (br s, 2 H). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.14; H, 7.39; N, 6.78.

Treatment of *N*-(*o*-Allylphenyl)alanine (3) with Acetic Anhydride. A solution containing 616 mg of *N*-(*o*-allylphenyl)alanine (**3**) in 6 mL of acetic anhydride was heated at 55 °C for 3 h. When the solution cooled, 30 mL of water was added. After being stirred for 10 min, the aqueous reaction mixture was extracted with benzene. The combined benzene extracts were washed with water, a saturated aqueous sodium bicarbonate solution, and water. After the extracts were dried over magnesium sulfate, the solvent was removed under reduced pressure to leave 658 mg of a yellow solid which was chromatographed on a silica gel column using a 5% acetone–hexane mixture as the eluent. The major fraction gave, after recrystallization from acetone–hexane, 371 mg (54%) of a solid whose structure was assigned 3a,4-dihydro-1,3a-dimethyl-1,4-methano-5*H*-oxazolo[3,2-*a*]quinolin-2(1*H*)-one (**8**) on the basis of its spectral properties: mp 115–116 °C; IR (KBr) 1773, 1471, 1437, 1372, 1333, 1215, 1100, 1053, 938, 921, 764 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.25 (dd, 1 H, J = 13.0, 2.0 Hz), 1.31 (s, 3 H), 1.53 (s, 3 H), 1.95 (dd, 1 H, J = 13.0, 7.5 Hz), 2.58–2.82 (m, 1 H), 2.81 (dd, 1 H, J = 16.5, 2.5 Hz), 3.16 (dd, 1 H, J = 16.5, 4.0 Hz), 6.96–7.14 (m, 1 H), 7.14–7.36 (m, 3 H); mass spectrum, m/e 229 (M^+, 100), 201, 186, 159, 158, 144, 143, 115, 43. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.30; H, 6.62; N, 6.13. Examination of the crude reaction mixture by NMR spectroscopy failed to show any signs of a regioisomeric tricyclic compound.

The molecular structure of oxazolo[3,2-*a*]quinolinone **8** was unequivocally determined by an X-ray crystal-structure analysis.[53]

Treatment of *N*-(*o*-Allylphenyl)alanine (3) with Benzoic Anhydride. A solution containing 616 mg of *N*-(*o*-allylphenyl)alanine (**3**) and 1.36 g of benzoic anhydride in 4 mL of benzene was heated at reflux for 14 h. Upon cooling, the reaction mixture was diluted with 20 mL of benzene and washed with a saturated sodium bicarbonate solution and water. The benzene extracts were dried over magnesium sulfate and concentrated under reduced pressure to give 861 mg of a yellow solid which was chromatographed over silica with a 10% acetone–hexane mixture as the eluent. The major component contained 708 mg (81%) of a crystalline solid whose structure was assigned as 3a,4-dihydro-1-methyl-3a-phenyl-1,4-methano-5*H*-oxazolo[3,2-*a*]quinolin-2(1*H*)-one (**9**) on the basis of its spectral properties: mp 155–156 °C; IR (KBr) 1776, 1441, 1342, 1242, 1218, 1196, 1142, 986, 917, 773, 759, 702 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.40 (s, 3 H), 1.41 (dd, 1 H, J = 13.0, 2.0 Hz), 2.07 (dd, 1 H, J = 13.0, 7.0 Hz), 2.74 (br s, 2 H), 3.14–3.40 (m, 1 H), 6.96 (d, 1 H, J = 7.0 Hz), 7.04–7.40 (m, 6 H), 7.44–7.64 (m, 2 H); NMR (benzene-d_6, 100 MHz) δ 0.97 (dd, 1 H, J = 13.5, 2.0 Hz), 1.27 (s, 3 H), 1.75 (dd, 1 H, J = 13.5, 7.5 Hz), 2.17 (dd, 1 H, J = 17.0, 2.5 Hz), 2.53 (dd, 1 H, J = 17.0, 3.0 Hz), 2.76–3.02 (m, 1 H), 6.60 (d, 1 H, J = 6.5 Hz), 6.73–7.24 (m, 6 H), 7.41–7.60 (m, 2 H); mass spectrum, m/e 291 (M^+, base), 263, 248, 158, 144, 143, 105, 43. Anal. Calcd fro $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.29; H, 5.88; N, 4.79. Examination of the crude reaction mixture by NMR spectroscopy failed to show any signs of a regioisomeric tricyclic compound.

The molecular structure of oxazolo[3,2-*a*]quinolinone **9** was unequivocally determined by an X-ray crystal-structure analysis.[38] The crystals of **9** used for X-ray diffraction were monoclinic and belong to space group $p2_1/n$. The unit cell parameters were as follows: a = 10.522 (2) Å, b = 8.858 (1) Å, c = 16.5818 (2) Å, β = 94.46 (1)°, V = 1535.0 (4) $Å^3$, ρ = 1.261 g/c^3, and the calculated density indicates four molecules per unit cell. The structure was derived from Patterson and Fourier syntheses and refined by least-squares methods to R = 0.051 for all the data. The final positional and thermal parameters are given in Tables I–III of the supplementary material.

Preparation of *N*-Benzoyl-*N*-(*o*-allylphenyl)alanine (5). A solution containing 1.40 g of *N*-(*o*-allylphenyl)alanine ethyl ester (**1**), 843 mg of benzoyl chloride, and 607 mg of triethylamine in 20 mL of benzene was heated at reflux for 24 h. Upon cooling, the mixture was washed with water, a saturated aqueous sodium bicarbonate solution, and water. The benzene layer was dried over magnesium sulfate and concentrated under reduced pressure to give a yellow oil which was chromatographed over silica gel with a 5% acetone–hexane mixture as the eluent. The major component isolated from the column contained 1.74 g (85%) of *N*-benzoyl-*N*-(*o*-allylphenyl)alanine ethyl ester as a light-yellow oil: IR (neat) 2920, 1725, 1650, 1630, 1481, 1439, 1361, 1307, 1203, 1098, 1043, 1026, 917, 701 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.19–1.45 (m, 5.1 H), 1.64 (d, 0.9 H, J = 7.0 Hz), 3.26 (qd, 2 H, J = 15.0, 6.5 Hz), 4.05–4.33 (m, 2.3 H), 4.67 (q, 0.7 H, J = 7.0 Hz), 4.79–5.10 (m, 2 H), 5.30–5.80 (m, 1 H), 6.83–7.33 (m, 9 H).

A mixture containing 1.35 g of the above ester and 176 mg of sodium hydroxide in 5 mL of water and 2 mL of ethanol was heated at reflux for 30 min. Upon cooling, the reaction mixture was diluted with 10 mL of water and extracted with ether. The aqueous layer was acidified with 10% hydrochloric acid and extracted with methylene chloride. The organic layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to leave a yellow oil which was crystallized from ethyl acetate–hexane to give 1.14 g (92%) of *N*-benzoyl-*N*-(*o*-allylphenyl)alanine (**5**): mp 131–132 °C; IR (KBr) 3335–2410, 1733, 1605, 1558, 1414, 1319, 1212, 820, 801, 771, 746, 723 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.29 (d, 2.1 H, J = 7.0 Hz), 1.63 (d, 0.9 H, J = 7.0 Hz), 3.15 (qd, 2 H, J = 15.0, 6.0 Hz), 4.08 (q, J = 7.0 Hz, 0.3 H), 4.65 (q, J = 7.0 Hz, 0.7 H), 4.72–4.96 (m, 2 H), 5.20–5.62 (m, 1 H), 6.54–7.30 (m, 9 H), 11.0 (s, 1 H). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.83; H, 6.23; N, 4.51.

Treatment of *N*-Benzoyl-*N*-(*o*-allylphenyl)alanine (5) with Acetic Anhydride. A solution containing 619 mg of *N*-benzoyl-*N*-(*o*-allylphenyl)alanine (**5**) in 4 mL of acetic anhydride was heated at 55 °C for 3 h. When the solution cooled, 20 mL of water was added to the reaction mixture. After being stirred for 10 min, the aqueous mixture was extracted with benzene. The benzene extracts were washed with water, a saturated sodium bicarbonate solution, and water. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The resulting yellow solid was recrystallized from ethyl acetate–hexane to give 546 mg (94%) of oxazolo[3,2-*a*]quinolinone **9**, mp 155–156 °C, which was identical with the tricyclic prepared from the reaction of *N*-(*o*-allylphenyl)alanine (**3**) with benzoic anhydride. Examination of the crude reaction mixture by NMR spectroscopy failed to reveal the presence of a regioisomeric tricyclic compound.

(52) C. D. Hurd and W. W. Jenkins, *J. Org. Chem.*, **22**, 1418 (1957).

(53) Details of the X-ray crystal-structure analysis of compound **8** will be reported independently by B. Rubin in a subsequent paper. We thank Dr. Rubin for help in determining the structure of compound **8**.

Preparation of 2-Oxo-1-methyl-1,5-methano-1,2,4,5,6,11-hexahydro[1,2,3]oxadiazolo[3,2-*a*]cinnoline (15). A solution containing 138 mg of sodium nitrite in 1 mL of water was added dropwise to an ice-cooled suspension of 205 mg of *N*-(*o*-allylphenyl)alanine (**3**) in 10 mL of glacial acetic acid and 5 mL of water. The mixture was allowed to stir at 0 °C for 2 h and was then diluted with 5 mL of water and extracted with benzene. The benzene extracts were washed with water and dried over magnesium sulfate. Removal of the solvent under reduced pressure left a yellow oil which was taken up in 2 mL of acetic anhydride and heated at 55 °C for 3 h. After the mixture cooled, 10 mL of water was added and the mixture was allowed to stir for 10 min. Extraction of the aqueous mixture with benzene was followed by washing of the benzene extracts with water, a saturated sodium bicarbonate solution, and water. The benzene layer was dried over magnesium sulfate and concentrated under reduced pressure to give 174 mg of a yellow solid. This material was passed through a short column of silica gel eluting with a 20% acetone–hexane mixture. The major fraction isolated from the column yielded, after recrystallization from ethyl acetate–hexane, 148 mg (69%) of 2-oxo-1-methyl-1,5-methano-1,2,4,5,6,11-hexahydro[1,2,3]oxadiazolo[3,2-*a*]cinnoline (**15**) as colorless needles: mp 131–132 °C; IR (KBr) 1790, 1468, 1441, 1243, 1100, 1088, 872, 835, 763, 682 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.42 (s, 3 H), 1.48 (dd, 1 H, J = 12.5, 3.5 Hz), 2.01 (dd, 1 H, J = 12.5, 6.5 Hz), 2.74 (dd, 1 H, J = 16.5, 2.0 Hz), 3.48 (dd, 1 H, J = 16.5, 4.0 Hz), 4.07–4.30 (m, 1 H), 6.82–6.98 (m, 1 H), 7.03–7.28 (m, 3 H); mass spectrum, *m/e* 144, 130, 129 (base), 128, 127, 115, 44. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.71; H, 5.61; N, 12.98. Examination of the crude reaction mixture by NMR spectroscopy failed to reveal the presence of a regioisomeric tricyclic compound.

Preparation of *N*-(*o*-Allylphenyl)-2-phenylglycine (4). A solution containing 9.72 g of ethyl α-bromophenylacetate, 5.33 g of *o*-allylaniline,[52] and 4.05 g of triethylamine in 30 mL of toluene was heated at reflux for 24 h. Upon cooling, the mixture was washed with water and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 13.2 g of a brown oil which was chromatographed over silica gel with benzene as the eluent. The major fraction contained 8.05 g (68%) of *N*-(*o*-allylphenyl)-2-phenylglycine ethyl ester (**2**) as a crystalline solid, after recrystallization from pentane: mp 52–53 °C; IR ($CHCl_3$) 3425, 3003, 1733, 1605, 1585, 1506, 1449, 1312, 1200, 1025, 922 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.16 (t, 3 H, J = 7.0 Hz), 3.37 (d, 2 H, J = 5.0 Hz), 3.92–4.24 (m, 2 H), 4.96–5.32 (m, 4 H), 5.73–6.18 (m, 1 H), 6.21–7.52 (m, 9 H); mass spectrum, *m/e* 295 (M^+), 223, 222 (base), 91. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.41; H, 7.25; N, 4.57.

A mixture containing 5.91 g of the above ester and 1.20 g of sodium hydroxide in 10 mL of water and 2 mL of ethanol was heated at reflux for 30 min. Upon cooling, the reaction mixture was diluted with 10 mL of water and extracted with ether. The aqueous layer was acidified with 10% hydrochloric acid. The resulting precipitate was collected and recrystallized from 95% ethanol to give 4.76 g of *N*-(*o*-allylphenyl)-2-phenylglycine (**4**) (89%) as a crystalline solid: mp 131–132 °C; IR (KBr) 3390, 3195–2260, 1698, 1597, 1580, 1490, 1399, 1309, 1267, 1256, 1189, 1171, 996, 912, 747, 713 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 3.45 (d, 2 H, J = 5.5 Hz), 5.12 (s, 1 H), 5.94–5.36 (m, 2 H), 5.77–6.20 (m, 1 H), 6.27–7.63 (m, 11 H); mass spectrum, *m/e* 221, 220 (base), 206, 144, 117, 115, 91. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.34; H, 6.60; N, 5.15.

Treatment of *N*-(*o*-Allylphenyl)-2-phenylglycine (4) with Acetic Anhydride. A solution containing 802 mg of *N*-(*o*-allylphenyl)-2-phenylglycine (**4**) in 6 mL of acetic anhydride was heated at 55 °C for 3 h. When the solution cooled, 30 mL of water was added and the mixture was stirred for 10 min. The aqueous mixture was extracted with benzene. The benzene extracts were washed with water, a saturated sodium bicarbonate solution, and water. The benzene layer was dried over magnesium sulfate and concentrated under reduced pressure to give a pale-yellow oil which crystallized on standing. Recrystallization of the crude solid from benzene–pentane afforded 546 mg (62%) of 3-oxo-1-methyl-3a-phenyl-1,5-methano-1,3,4,5,6,11-hexahydro[1,3]oxazolo[3,4-*a*]-quinoline (**16**) as a crystalline solid: mp 165–166 °C; IR (KBr) 1773, 1475, 1441, 1381, 1232, 1158, 1144, 1105, 1005, 998, 912, 772, 758, 751, 700 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.63 (s, 3 H), 1.65 (dd, 1 H, J = 13.0, 2.0 Hz), 2.34 (dd, 1 H, J = 13.0, 7.0 Hz), 2.51 (dd, 1 H, J = 17.0, 2.5 Hz), 2.78 (dd, 1 H, J = 17.0, 3.0 Hz), 2.80–3.05 (m, 1 H), 6.80 (d, 1 H, J = 7.0 Hz), 6.89–7.34 (m, 8 H); mass spectrum, *m/e* 291 (M^+), 263, 248, 247, 221, 220, 206, 205 (base), 135, 91, 78. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.28; H, 5.87; N, 4.84.

Fractional recrystallization of the mother liquors from benzene–pentane gave 91 mg of 2-oxo-3a-methyl-1-phenyl-1,5-methano-1,2,4,5,6,11-hexahydro[1,3]oxazolo[3,2-*a*]quinoline (**17**) as a crystalline solid (10%): mp 189–190 °C; IR (KBr) 1776, 1475, 1382, 1225, 1192, 1143, 1106, 1035, 1007, 983, 927, 766, 758, 717, 700 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.61 (s, 3 H), 1.99 (dd, 1 H, J = 13.0, 2.0 Hz), 2.31 (dd, 1 H, J = 13.0, 7.0 Hz), 2.75–2.95 (m, 1 H), 3.05 (dd, 1 H, J = 16.0, 2.0 Hz), 3.19 (dd, 1 H, J = 16.0, 3.5 Hz), 6.57 (d, 1 H, J = 8.0 Hz), 6.80–7.20 (m, 3 H), 7.36 (s, 5 H); mass spectrum, *m/e* 291 (M^+), 220, 205, 182, 178, 105, 78 (base), 77. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.18; H, 5.95; N, 4.70.

Treatment of *N*-(*o*-Allylphenyl)-2-phenylglycine (4) with Benzoic Anhydride. A solution containing 802 mg of *N*-(*o*-allylphenyl)-2-phenylglycine (**4**) and 1.36 g of benzoic anhydride in 4 mL of benzene was heated at reflux for 18 h. Upon cooling, the reaction mixture was diluted with 20 mL of benzene and washed with a saturated aqueous sodium bicarbonate solution and with water. The benzene solution was dried over magnesium sulfate and was concentrated under reduced pressure to give a yellow solid. Recrystallization of this material from ethyl acetate–hexane gave 684 mg (65%) of 3a,4-dihydro-1,3a-diphenyl-1,4-methano-5*H*-oxazolo[3,2-*a*]quinoline-2(1*H*)-one (**19**) as a crystalline solid: mp 173–174 °C; IR (KBr) 1776, 1435, 1340, 1221, 1206, 1135, 1101, 1013, 992, 904, 769, 756, 747, 696 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.26 (dd, 1 H, J = 13.0, 2.5 Hz), 2.52 (dd, 1 H, J = 13.0, 2.5 Hz), 2.52 (dd, 1 H, J = 13.0, 7.5 Hz), 2.84 (d, 2 H), 3.34–3.56 (m, 1 H), 6.44–7.08 (m, 10 H), 7.12–7.66 (m, 4 H); NMR (benzene-d_6, 100 MHz) δ 1.80 (dd, 1 H, J = 13.0, 2.0 Hz), 2.07 (dd, 1 H, J = 13.0, 7.0 Hz), 2.24 (dd, 1 H, J = 18.0, 2.5 Hz), 2.58 (dd, 1 H, J = 18.0, 3.0 Hz), 2.86–3.15 (m, 1 H), 6.37–6.80 (m, 4 H), 6.86–7.21 (m, 6 H), 7.27–7.42 (m, 2 H), 7.46–7.80 (m, 2 H); mass spectrum, *m/e* 353 (M^+, base), 309, 221, 220, 207, 206, 205, 129, 115, 105, 91, 77. Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.30; H, 5.43; N, 3.78.

The mother liquors obtained from the recrystallization of oxazoloquinolinone **19** were concentrated under reduced pressure. The resulting solid obtained consisted of a mixture of **19** and another regioisomer whose structure was assigned as 4,5-dihydro-1,3a-diphenyl-1,4-methano-1*H*-oxazolo[3,4-*a*]quinolin-3-(3a*H*)-one (**18**). This material could not be obtained completely pure as it always contained 10–20% of regioisomer **19**. A relatively pure sample of **18** showed the following spectral properties: IR (KBr) 1770, 1430, 1335, 1215, 1205, 1130, 1100, 990, 770, 760, 740, 690 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.18 (dd, 1 H, J = 13.0, 2.0 Hz), 2.45 (dd, 1 H, J = 13.0, 7.0 Hz), 2.78 (d, 2 H), 3.0–3.20 (m, 1 H), 6.4–7.6 (m, 14 H); mass spectrum, *m/e* 353 (M^+, base), 309, 221, 91, 77.

Preparation of *N*-Benzoyl-*N*-(*o*-allylphenyl)-2-phenylglycine (6). A solution of 886 mg of *N*-(*o*-allylphenyl)-2-phenylglycine ethyl ester (**2**), 422 mg of benzoyl chloride, and 304 mg of triethylamine in 10 mL of benzene was heated at reflux for 36 h. Upon cooling, the reaction mixture was washed with water, a saturated aqueous sodium bicarbonate solution, and water. The solution was dried over magnesium sulfate and concentrated under reduced pressure to give 1.39 g of an oil which was recrystallized from benzene–pentane to afford 997 mg (83%) of *N*-benzoyl-*N*-(*o*-allylphenyl)-2-phenylglycine ethyl ester as a colorless solid: mp 82–83 °C; IR (KBr) 1742, 1639, 1488, 1443, 1350, 1208, 1166, 790, 726, 698 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.28 (t, 3 H, J = 7.0 Hz), 2.94 (d, 2 H, J = 6.0 Hz), 4.29 (q, 2 H, J = 7.0 Hz), 4.66–5.44 (m, 3 H), 5.53 (s, 0.2 H), 6.14 (s, 0.8 H), 6.70–7.66 (m, 14 H); mass spectrum, *m/e* 399 (M^+), 326, 294, 222, 220, 105 (base), 91, 77. Anal. Calcd for $C_{26}H_{25}NO_3$: C, 78.17; H, 6.31; N, 3.51. Found: C, 78.23; H, 6.36; N, 3.48.

A mixture containing 799 mg of the above ester and 88 mg of sodium hydroxide in 5 mL of water and 2 mL of ethanol was heated at reflux for 45 min. The mixture was diluted with water, acidified with 10% hydrochloric acid, and extracted with methylene chloride. The methylene chloride extracts were dried over

magnesium sulfate and concentrated under reduced pressure to give 630 mg (85%) of *N*-benzoyl-*N*-(*o*-allylphenyl)-2-phenylglycine (**6**) as a colorless solid after recrystallization from chloroform: mp 154–155 °C; IR (KBr) 3450–2340, 1757, 1718, 1637, 1575, 1493, 1445, 1379, 1244, 1199, 1179, 920, 700 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.97 (d, 2 H, J = 6.0 Hz), 4.57–5.41 (m, 3 H), 5.50 (s, 0.25 H), 6.18 (s, 0.75 H), 6.53–7.73 (m, 14 H), 10.90 (br s, 1 H); mass spectrum, m/e 353, 221, 220 (base), 206, 144, 123, 117, 115, 105, 91, 77. Anal. Calcd for $C_{24}H_{21}2NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.53; H, 5.82; N, 3.55.

Treatment of *N*-Benzoyl-*N*-(*o*-allylphenyl)-2-phenylglycine (6) with Acetic Anhydride. A solution containing 371 mg of *N*-benzoyl-*N*-(*o*-allylphenyl)-2-phenylglycine (**6**) in 2 mL of acetic anhydride was heated at 55 °C for 3 h. Upon cooling, 10 mL of water was added. After stirring for 10 min, the aqueous mixture was extracted with benzene. The benzene extracts were washed with water, a saturated aqueous sodium bicarbonate solution and water. The benzene solution was dried over magnesium sulfate and concentrated under reduced pressure to give a white solid. Fractional crystallization of this material afforded 218 mg (67%) of a white solid, mp 173–174 °C, which was identical with oxazolo[3,2-*a*]quinolinone **19** prepared from the reaction of *N*-(*o*-allylphenyl)-2-phenylglycine (**4**) with benzoic anhydride. The minor isomer obtained from the fractional crystallization contained 109 mg (33%) of oxazolo[3,4-*a*]quinolin-3(3a*H*)-one **18**, which was identical with the minor component obtained from the reaction of *N*-(*o*-allylphenyl)-2-phenylglycine (**4**) with benzoic anhydride.

Preparation of *N*-Methyl-*N*-(*o*-allylbenzoyl)-2-phenylglycine (20). A solution containing 1.52 g of oxalyl chloride in 10 mL of anhydrous ether was added dropwise to 1.30 g of *o*-allylbenzoic acid[54] and 58 mg of *N*,*N*-dimethylformamide in 20 mL of anhydrous ether at 0 °C. Upon completion of the addition, the mixture was allowed to stir at 5 °C for 20 h. The solvent was removed under reduced pressure and the residue was taken up in 5 mL of benzene. The benzene solution was then added dropwise to 1.55 g of *N*-methyl-2-phenylglycine ethyl ester[55] and 810 mg of triethylamine in 15 mL of benzene. The mixture was then heated at reflux for 2 h, cooled, washed with a 1% hydrochloric acid solution, a saturated aqueous sodium bicarbonate solution, and water. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give 2.67 g (99%) of a yellow oil: IR (neat) 1742, 1645, 1497, 1453, 1389, 1319, 1198, 1179, 1063, 1035, 773, 752, 701 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.30 (t, 3 H, J = 7.0 Hz), 2.58 (s, 3 H), 3.43 (d, 2 H, J = 6.0 Hz), 4.29 (q, 2 H, J = 7.0 Hz), 4.88–5.28 (m, 2 H), 5.68–6.20 (m, 1 H), 6.58 (s, 1 H), 7.08–7.52 (m, 9 H). Extraneous signals probably due to a second rotamer (hindered rotation) appeared at δ 2.99 (d, J = 7.0 Hz) and 5.42 (d, J = 10.5 Hz). The ratio of the major benzylic doublet at δ 3.43 to the minor benzylic doublet at δ 2.99 is 3:1.

A mixture containing 2.67 g of the above ester and 352 mg of sodium hydroxide in 5 mL of water and 2 mL of ethanol was heated at reflux for 30 min. Upon cooling, the mixture was diluted with 15 mL of water and extracted with methylene chloride. The aqueous layer was acidified with 10% hydrochloric acid and extracted with methylene chloride. The organic layer was washed with water and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 2.27 g (92%) of a viscous yellow oil: NMR ($CDCl_3$, 100 MHz) δ 2.54 (br s, 3 H), 3.41 (d, 2 H, J = 6.0 Hz), 4.80–5.22 (m, 2 H), 5.64–6.16 (m, 1 H), 6.66 (s, 1 H), 6.80–7.56 (m, 9 H), 12.3 (br s, 1 H). Extraneous signals also appeared at δ 2.95 (d, 6.0 Hz) and 5.42 (d, J = 7.0 Hz) which are probably due to a second rotamer (hindered rotation). The ratio of the major benzylic doublet at δ 3.41 to the minor benzylic doublet at δ 2.95 is ca 2:1.

Treatment of *N*-Methyl-*N*-(*o*-allylbenzoyl)-2-phenylglycine (20) with Acetic Anhydride in the Presence of Dimethyl Acetylenedicarboxylate. A solution containing 229 mg of *N*-methyl-*N*-(*o*-allylbenzoyl)-2-phenylglycine (**20**) and 210 mg of dimethyl acetylenedicarboxylate in 1.5 mL of acetic anhydride was heated at 55 °C for 3 h. When the solution cooled, 10 mL of water was added and the mixture was allowed to stir for 10 min. The aqueous mixture was extracted with benzene, and the benzene extracts were washed with water and a saturated sodium bicarbonate solution and dried over magnesium sulfate. Concentration of the solvent under reduced pressure left an orange oil which was chromatographed over a silica gel column using a 40% ether–hexane mixture as the eluent. The major component isolated from the column contained 100 mg (35%) of *N*-methyl-2-(*o*-allylphenyl)-3,4-bis(carbomethoxy)-5-phenylpyrrole (**23**) as a colorless solid: mp 111–112 °C; IR (KBr) 1698, 1477, 1437, 1427, 1290, 1248, 1205, 1172, 770, 705 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 3.03 (s, 3 H), 3.26 (d, 2 H, J = 6.0 Hz), 3.56 (s, 3 H), 3.63 (s, 3 H), 4.72–5.03 (m, 2 H), 5.51–5.93 (m, 1 H), 7.15–4.45 (m, 9 H); mass spectrum, m/e 389 (M^+), 358, 357, 330, 315, 298, 270, 91 (base). Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 74.27; H, 6.01; N, 3.56.

Preparation of *N*-Phenyl-*N*-[*p*-methoxy-*o*-(3-butenyl)benzoyl]-2-phenylglycine (24). A solution containing 1.52 g of oxalyl chloride in 10 mL of anhydrous ether was added dropwise to a 1.65-g suspension of *p*-methoxy-*o*-(3-butenyl)benzoic acid and 58 mg of *N*,*N*-dimethylformamide in 20 mL of anhydrous ether at 0 °C. The reaction mixture was allowed to stir at 5 °C for 20 h and then the solvent was removed under reduced pressure. The residue was taken up in 5 mL of benzene and was added dropwise to 2.04 g of *N*,*C*-diphenylglycine ethyl ester[56] and 810 mg of triethylamine in 15 mL of benzene. After heating at reflux for 24 h, the mixture was cooled, washed with water, 1% hydrochloric acid, a saturated aqueous sodium bicarbonate solution, and water. The benzene layer was dried over magnesium sulfate and concentrated under reduced pressure. The resulting oil was chromatographed over silica gel with chloroform as the eluent. The major fraction contained 3.20 g (90%) of a pale-yellow oil which was used without further purification: IR (neat) 2899, 1727, 1634, 1591, 1481, 1443, 1350, 1321, 1272, 1235, 1192, 1058, 1033, 695 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.23 (t, 3 H, J = 7.0 Hz), 2.14–2.52 (m, 2 H), 2.60–2.90 (m, 2 H), 3.51 (s, 3 H), 4.20 (q, 2 H, J = 7.0 Hz), 4.76–5.16 (m, 2 H), 5.60–6.04 (m, 1 H), 6.17 (s, 1 H), 6.28 (dd, 1 H, J = 8.5, 2.5 Hz), 6.47 (d, 1 H, J = 2.5 Hz), 6.80 (s, 5 H), 6.85 (d, 1 H, J = 8.5 Hz), 7.04 (s, 5 H).

A mixture containing 3.20 g of the above ethyl ester and 320 mg of sodium hydroxide in 5 mL of water and 3 mL of ethanol was heated at reflux for 30 min. The solution was cooled, acidified with 10% hydrochloric acid, diluted with water, and extracted with methylene chloride. The organic layer was washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to give a yellow oil. This material was chromatographed over silica gel, using a 1:1 chloroform–acetone mixture as the eluent. The major fraction isolated was a pale-yellow oil (2.34 g, 78%) whose structure was assigned as *N*-phenyl-*N*-[*p*-methoxy-*o*-(3-butenyl)benzoyl]-2-phenylglycine (**24**): NMR ($CDCl_3$, 100 MHz) δ 2.23–2.54 (m, 2 H), 2.66–2.94 (m, 2 H), 3.60 (s, 3 H), 4.84–5.20 (m, 2 H), 5.6–6.10 (m, 1 H), 6.28 (s, 1 H), 6.32 (dd, 1 H, J = 9.0, 2.5 Hz), 6.53 (d, 1 H, J = 2.5 Hz), 6.89 (s, 5 H), 6.94 (d, 1 H, J = 9.0 Hz), 7.16 (s, 5 H), 10.9 (br s, 1 H).

Treatment of *N*-Phenyl-*N*-[*p*-methoxy-*o*-(3-butenyl)benzoyl]-2-phenylglycine (24) with Acetic Anhydride. A solution containing 312 mg of *N*-phenyl-*N*-[*p*-methoxy-*o*-(3-butenyl)benzoyl]-2-phenylglycine (**24**) in 1.5 mL of acetic anhydride was heated at 55 °C for 3 h. When the solution cooled, 10 mL of water was added and the mixture was stirred for 10 min at 25 °C. The mixture was extracted with benzene, and the benzene extracts were washed with water, a saturated aqueous sodium bicarbonate solution, and water. The benzene layer was dried over magnesium sulfate and concentrated under reduced pressure to give 273 mg of a yellow oil. This material was chromatographed over silica gel, using a 40% ether–hexane mixture as the eluent. The major component isolated contained 45 mg (17%) of 1,2-diphenyl-7-methoxy-4,5-dihydro-1*H*-benz[*g*]indole (**28**) as a crystalline solid: mp 186–187 °C; IR (KBr) 1600, 1497, 1458, 1383, 1299, 1280, 1244, 1044, 845, 817, 762, 697 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.61–3.09 (m, 4 H), 3.71 (s, 3 H), 6.15 (d, 1 H, J = 8.0 Hz), 6.32 (s, 1 H), 6.38 (dd, 1 H, J = 8.0, and 2.5 Hz), 6.80 (d, 1 H, J = 2.5 Hz), 6.89–7.57 (m, 10 H); mass spectrum, m/e 351 (M^+, base), 350, 349, 336. Anal. Calcd for $C_{25}H_{21}NO$: C, 85.44; H, 6.02;

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N, 3.99. Found: C, 85.34; H, 6.04; N, 3.97.

The munchnone intermediate could be trapped externally when the reaction was carried out in the presence of excess dimethyl acetylenedicarboxylate. A solution containing 337 mg of *N*-phenyl-*N*-[*p*-methoxy-*o*-(3-butenyl)benzoyl]-2-phenylglycine (**24**) and 230 mg of dimethyl acetylenedicarboxylate in 1.5 mL of acetic anhydride was heated at 55 °C for 3 h. When the mixture cooled, 10 mL of water was added to the mixture. After being stirred for 10 min, the mixture was extracted with benzene. The benzene extracts were washed with water, a saturated aqueous sodium bicarbonate solution, and water. After drying over magnesium sulfate, the solvent was removed under reduced pressure to give 462 mg of a brown oil. This material was chromatographed over silica gel, using a 40% ether–hexane mixture as the eluent. The major component isolated contained 133 mg (33%) of 1,5-diphenyl-2-[*p*-methoxy-*o*-(3-butenyl)phenyl]-3,4-bis(carbomethoxy)pyrrole (**29**) as a crystalline solid: mp 111–112 °C; IR (KBr) 1698, 1603, 1553, 1464, 1435, 1346, 1266, 1198, 1160, 1053, 769, 703 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.84–2.64 (m, 4 H), 3.58 (s, 3 H), 3.66 (s, 6 H), 4.68–5.02 (m, 2 H), 5.42–5.88 (m, 1 H), 6.40–7.32 (m, 13 H); mass spectrum, *m/e* 495 (M^+), 181, 180, 179, 167, 165, 107. Anal. Calcd for $C_{31}H_{29}NO_5$: C, 75.13; H, 5.90; N, 2.83. Found: C, 75.14; H, 5.93; N, 2.84.

Preparation of *N*-Methyl-*N*-[*p*-methoxy-*o*-(3-butenyl)benzoyl]-2-phenylglycine (30). A solution containing 7.78 g of 2-[*p*-methoxy-*o*-(3-butenyl)phenyl]-4,4-dimethyl-Δ^2-oxazoline in 12 mL of methyl iodide was heated at reflux for 20 h. Removal of the excess methyl iodide under reduced pressure left the crude methiodide salt as a yellow solid. A solution of this salt and 6.0 g of sodium hydroxide in 150 mL of tetrahydrofuran and 450 mL of water was heated at reflux for 26 h. The mixture was concentrated under reduced pressure and the residue was diluted with 450 mL of water and extracted with ether. The aqueous layer was acidified with a 5% aqueous acetic acid solution and extracted with benzene. The benzene layer was washed with water, dried over magnesium sulfate, and evaporated under reduced pressure to give 5.10 g of a solid which was recrystallized from benzene–hexane to give 3.95 g (64%) of *p*-methoxy-*o*-(3-butenyl)benzoic acid: mp 109–110 °C; IR (KBr) 3225–2300, 1681, 1603, 1554, 1299, 1266, 1244, 1155, 886, 778 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.37 (q, 2 H, J = 7.5 Hz), 3.10 (t, 2 H, J = 7.5 Hz), 3.80 (s, 3 H), 4.84–5.12 (m, 2 H), 5.64–6.08 (m, 1 H), 6.60–6.80 (m, 2 H), 7.98 (d, 1 H, J = 8.6 Hz), 12.0 (br s, 1 H); mass spectrum, *m/e* 206 (M^+), 177, 165 (base), 122, 105. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.96; H, 6.88.

A solution containing 571 mg of oxalyl chloride in 4 mL of anhydrous ether was added dropwise to a stirred suspension of 619 mg of *p*-methoxy-*o*-(3-butenyl)benzoic acid and 22 mg of *N*,*N*-dimethylformamide in 8 mL of anhydrous ether at 0 °C. Upon completion of the addition, the mixture was stirred at 5 °C for 19 h. The solvent was removed under reduced pressure and the residue was taken up in 2 mL of benzene. This solution was added dropwise to 580 mg of *N*-methyl-2-phenylglycine ethyl ester[55] and 304 mg of triethylamine in 6 mL of benzene at 0 °C. After being stirred at 25 °C for 8 h, the mixture was washed with water, a 1% hydrochloric acid solution, a saturated aqueous sodium bicarbonate solution, and water. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give 1.14 g (100%) of *N*-methyl-*N*-[*p*-methoxy-*o*-(3-butenyl)benzoyl]-2-phenylglycine ethyl ester as a colorless oil: IR (neat) 2899, 1736, 1631, 1608, 1451, 1381, 1318, 1245, 1183, 1063, 1035, 920, 824, 766, 701 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.27 (t, 3 H, J = 7.0 Hz), 2.43 (br q, 2 H, J = 7.0 Hz), 2.58 (br s, 3 H), 2.51–3.13 (m, 2 H), 3.72 (s, 3 H), 4.25 (q, 2 H, J = 7.0 Hz), 4.77–5.15 (m, 2 H), 5.53–6.05 (m, 1 H), 6.50 (s, 1 H), 6.65 (d, 1 H, J = 8.0 Hz), 6.69 (s, 1 H), 7.04 (d, 1 H, J = 8.0 Hz), 7.25 (s, 5 H).

A mixture containing 3.25 g of the above ester and 352 mg of sodium hydroxide in 5 mL of water and 2 mL of ethanol was heated at reflux for 30 min. Upon cooling, the mixture was diluted with 100 mL of water and extracted with methylene chloride. The aqoeuos layer was acidified with 10% hydrochloric acid and extracted with methylene chloride. The organic layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent left 2.65 g (94%) of a pale oil whose structure was assigned as *N*-methyl-*N*-[*p*-methoxy-*o*-(3-butenyl)benzoyl]-2-phenylglycine (**30**): NMR ($CDCl_3$, 100 MHz) δ 2.30 (br q, 2 H, J = 6.0 Hz), 2.58 (br s, 3 H), 2.61–3.17 (m, 2 H), 3.71 (s, 3 H), 4.65–5.11 (m, 2 H), 5.47–5.97 (m, 1 H), 6.59 (s, 1 H), 6.68 (d, 1 H, J = 8.0 Hz), 6.72 (s, 1 H), 7.09 (d, 1 H, J = 8.0 Hz), 7.29 (s, 5 H), 11.6 (s, 1 H).

Treatment of *N*-Methyl-*N*-[*p*-methoxy-*o*-(3-butenyl)benzoyl]-2-phenylglycine (30) with Acetic Anhydride. A solution containing 937 mg of *N*-methyl-*N*-[*p*-methoxy-*o*-(3-butenyl)benzoyl]-2-phenylglycine (**30**) in 5 mL of acetic anhydride was heated at 55 °C for 3 h. When the solution cooled, 25 mL of water was added. After being stirred for 10 min, the mixture was extracted with benzene. The benzene extracts were washed with water, a saturated aqueous sodium bicarbonate solution, and water. After the extracts dried over magnesium sulfate, the benzene layer was evaporated under reduced pressure to give 385 mg of a brown oil. The oil was subjected to silica gel chromatography, using a 10% acetone–hexane mixture as the eluent. The first fraction eluted contained 17 mg (2%) of a crystalline solid whose structure was assigned as 1-methyl-2-phenyl-7-methoxy-4,5-dihydro-1*H*-benz[*g*]indole (**35**) on the basis of its spectral data: mp 181–182 °C; IR (KBr) 1575, 1493, 1453, 1292, 1280, 1247, 1122, 1044, 760, 700 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.53–2.95 (m, 4 H), 3.76 (s, 6 H), 6.08 (s, 1 H), 6.57–6.81 (m, 2 H), 7.12–7.47 (m, 6 H); mass spectrum, *m/e* 289 (M^+, base), 288, 287, 274, 73. Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.73; H, 6.71; N, 4.77.

The second fraction isolated from the column was assigned as 1-methyl-2-phenyl-3-acetyl-7-methoxy-3a,4,5,9b-tetrahydro-1*H*-benz[*g*]indole (**36**) on the basis of its NMR spectrum ($CDCl_3$, 100 MHz) which exhibited methyl singlets at δ 1.58, 2.28, and 3.77, as well as one-proton doublet centered at δ 4.64 (J = 10.5 Hz). This material was not purified but was instead oxidized directly. A mixture consisting of the above mentioned material and 281 mg of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 5 mL of benzene was heated at reflux for 5 h. The mixture was diluted with 5 mL of chloroform and chromatographed through a short alumina column using a 50% benzene–chloroform mixture as the eluent. The major fraction obtained from the column consisted of a crystalline solid (40 mg, 5%) whose structure was assigned as 1-methyl-2-phenyl-3-acetyl-7-methoxy-1*H*-benz[*g*]indole (**37**) on the basis of the following data: mp 158–159 °C; IR (KBr) 1620, 1393, 1374, 1283, 1255, 1231, 1167, 1124, 1043, 1030, 858, 822, 773, 704 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.94 (s, 3 H), 3.89 (s, 3 H), 3.94 (s, 3 H), 7.12–7.76 (m, 8 H), 8.39 (d, 1 H, J = 9.5 Hz), 8.66 (d, 1 H, J = 9.0 Hz); mass spectrum, *m/e* 329 (M^+), 314, 105, 91, 77. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.03; H, 5.84; N, 4.21.

Preparation of *N*-Methyl-*N*-[*p*-methoxy-*o*-(4-cyano-3-butenyl)benzoyl]-2-phenylglycine (38). Ozone was bubbled through a solution containing 1.14 g of *N*-methyl-*N*-[*p*-methoxy-*o*-(3-butenyl)benzoyl]-2-phenylglycine ethyl ester in 200 mL of methylene chloride at −78 °C until a dark color persisted. The reaction mixture was purged with nitrogen for 10 min and then 50 mL of methyl sulfide was added. The mixture was stirred at 25 °C for 2 h and was then concentrated under reduced pressure to give a brown oil. This material was chromatographed over silica gel, using chloroform as the eluent. The resulting aldehyde (620 mg, 54%) was used in the next step without further purification: IR (neat) 2915, 2825, 2725, 1735, 1631, 1449, 1385, 1314, 1247, 1211, 1185, 1063, 1032, 702 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.26 (t, 3 H, J = 7.0 Hz), 2.56 (br s, 3 H), 2.64–3.12 (m, 4 H), 3.71 (s, 3 H), 4.24 (q, J = 7.0 Hz, 2 H), 6.43 (s, 1 H), 6.68 (d, 1 H, J = 7.5 Hz), 6.72 (s, 1 H), 7.06 (d, 1 H, J = 7.5 Hz), 7.28 (s, 5 H), 9.67 (s, 1 H).

A solution containing 614 mg of the above aldehyde and 482 mg of (cyanomethylene)triphenylphosphorane[57] in 10 mL of methylene chloride was stirred for 12 h at 25 °C. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed over silica gel, using ether as the eluent. The major fraction contained 629 mg (97%) of a light-yellow oil, which was used further without purification: IR (neat) 2933, 2222, 1736, 1634, 1451, 1389, 1248, 1211, 1119, 1062, 1034, 759, 703 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.31 (t, 3 H, J = 7.0 Hz), 2.60 (s, 3 H), 2.37–3.15 (m, 4 H), 3.78 (s, 3 H), 4.28 (q, 2 H, J = 7.0 Hz), 5.18

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(d, 0.35 H (*Z* isomer), J = 10.0 Hz), 5.37 (d, 0.65 H (*E* isomer), J = 16.0 Hz), 6.25–6.99 (m, 4 H), 7.12 (d, 1 H, J = 8.5 Hz), 7.34 (s, 5 H).

A mixture containing 629 mg of the above *E* and *Z* isomers of *N*-methyl-*N*-[*p*-methoxy-*o*-(4-cyano-3-butenyl)benzoyl]-2-phenylglycine ethyl ester and 68 mg of sodium hydroxide in 3 mL of water and 2 mL of ethanol was heated at reflux with stirring for 30 min. The mixture was cooled, acidified with 10% hydrochloric acid, diluted with 15 mL of water, and extracted with methylene chloride. The organic layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting oil was chromatographed over silica gel with a 1:1 chloroform–acetone mixture as the eluent to give 301 mg (51%) of (*E*- and (*Z*)-*N*-methyl-*N*-[*p*-methoxy-*o*-(4-cyano-3-butenyl)benzoyl]2-phenylglycine (**38**) as a pale oil: IR ($CHCl_3$) 3300–2450, 2203, 1712, 1613, 1595, 1381, 1199, 1112, 1062, 1033 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.60 (s, 3 H), 2.30–3.28 (m, 4 H), 3.79 (s, 3 H), 5.08 (d, 0.35 H (*Z* isomer), J = 10.0 Hz), 5.31 (d, 0.65 H, (*E* isomer), J = 16.0 Hz), 6.27–6.90 (m, 4 H), 7.14 (d, 1 H, J = 9.0 Hz), 7.36 (s, 5 H), 10.9 (s, 1 H).

Treatment of *N*-Methyl-*N*-[*p*-methoxy-*o*-(4-cyano-3-butenyl)benzoyl]-2-phenylglycine (38) with Acetic Anhydride. A solution containing 301 mg of (*E*)- and (*Z*)-*N*-methyl-*N*-[*p*-methoxy-*o*-(4-cyano-3-butenyl)benzoyl]-2-phenylglycine (**38**) in 1.5 mL of acetic anhydride was heated at 55 °C for 3 h. When the solution cooled, 10 mL of water was added and the mixture was stirred for an additional 10 min. Extraction of the aqueous mixture with benzene was followed by washing of the benzene extracts with water, a saturated aqueous sodium bicarbonate solution, and water. The benzene layer was dried over magnesium sulfate and concentrated under reduced pressure to give 134 mg of a brown oil. This oil was chromatographed over silica gel, using a 40% ether–hexane mixture as the eluent. The major component isolated from the column contained 27 mg (11%) of 1-methyl-2-phenyl-3-cyano-7-methoxy-4,5-dihydro-1*H*-benz[*g*]indole (**39**) as a crystalline solid: mp 183–184 °C; IR (KBr) 2193, 1570, 1490, 1464, 1294, 1277, 1247, 1045, 810, 766, 700 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.64–3.08 (m, 4 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 6.76–6.97 (m, 2 H), 7.38–7.66 (m, 6 H); mass spectrum, m/e 314 (M^+, base), 299, 129, 128, 109, 104, 91. Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.09; H, 5.80; N, 8.90.

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Registry No. **1**, 81278-07-1; **2**, 63499-45-6; **3**, 81278-08-2; **4**, 77219-99-9; **5**, 81278-09-3; **5** ethyl ester, 81278-10-6; **6**, 81278-11-7; **6** ethyl ester, 81278-12-8; **8**, 77226-66-5; **9**, 77219-98-8; **12**, 63499-47-8; **15**, 81278-13-9; **16**, 77220-00-9; **17**, 77226-67-6; **18**, 77220-01-0; **19**, 77220-02-1; **20**, 81278-14-0; **20** ethyl ester, 81278-15-1; **23**, 81278-16-2; **24**, 81278-17-3; **24** ethyl ester, 81278-18-4; **28**, 81278-19-5; **29**, 81278-20-8; **30**, 81278-21-9; **30** ethyl ester, 81278-22-0; **35**, 81278-23-1; **36**, 81278-24-2; **37**, 81278-25-3; (*E*)-**38**, 81278-26-4; (*E*)-**38** ethyl ester, 81278-27-5; (*Z*)-**38**, 81278-28-6; (*Z*)-**38** ethyl ester, 81278-29-7; **39**, 81278-30-0; ethyl 2-bromopropionate, 535-11-5; *o*-allylaniline, 32704-22-6; ethyl α-bromophenylacetate, 2882-19-1; *o*-allybenzoic acid, 61436-73-5; *N*-methyl-2-phenylglycine ethyl ester, 81278-31-1; dimethyl acetylenedicarboxylate, 762-42-5; *p*-methoxy-*o*-(3-butenyl)benzoic acid, 81278-32-2; *N,C*-diphenylglycine ethyl ester, 5634-58-2; 2-[*p*-methoxy-*o*-(3-butenyl)phenyl]-4,4-dimethyl-Δ^2-oxazoline, 81278-33-3; 2-[*p*-methoxy-*o*-(3-butenyl)phenyl]-4,4-dimethyl-Δ^2-oxazoline methiodide, 81278-34-4; *N*-methyl-*N*-[*p*-methoxy-*o*-(3-oxopropyl)benzoyl]-2-phenylglycine ethyl ester, 81278-35-5.

Supplementary Material Available: The positional and thermal parameters obtained from the least-squares refinement of structure **9** (3 pages). Ordering information is given on any current masthead page.

New Synthesis of Diazepam and the Related 1,4-Benzodiazepines by means of Palladium-Catalyzed Carbonylation

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A new synthesis of diazepam (**5**) was achieved by application of palladium-catalyzed carbonylation to the compound **3** prepared from *o*-bromoaniline derivative **1** and the amino acid **2**, and this procedure was also used for the synthesis of poisonous metabolites *dl*-cyclopeptine (**7**), *dl*-cyclopenin (**8a**), and *dl*-cyclopenol (**8b**), having a 1,4-diazepine skeleton.

Palladium-catalyzed carbonylation of aryl and vinyl halides has been developed by us as a useful method for the synthesis of heterocyclic compounds such as benzolactams,[1a] benzolactones,[1b] cyclic imides,[1c] and α-methylene lactams and lactones.[1d] The chemistry was further extended to the synthesis of the alkaloid sendaverine[1e] and a formal synthesis of a monocyclic β-lactam antibiotic, nocardicin A.[1f] The most remarkable feature of this reaction is that the synthesis of four-, five-, six-, and seven-membered lactams and lactones can be simply realized by variation of the length of carbon chain of the starting material.

In the course of synthetic studies, we have been particularly interested in exploration of a new route to 1,4-benzodiazepine derivatives having pharmacological activity in the series of the synthetic and naturally occurring products.

It was expected that our method should be extended to the synthesis of 3,4-dihydro-1*H*-benzodiazepine-2,5-dione (**4**) by insertion of carbon monoxide into aryl halide **3** (Scheme I), which could be prepared from *o*-bromoaniline derivative **1** and amino acid **2**. Now report the synthesis of the key intermediate for diazepam (**5**), and of diazepine

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