Reactions of Azines with Electron-Deficient Alkynes. Formation of 1,5-Dihydropyrazolo[1,2-*a*]pyrazoles, α,β-Unsaturated Azines, and *N*-Allyl- and *N*-Propenylpyrazoles

Steven Evans,[1a] Richard C. Gearhart, Lloyd J. Guggenberger,[1b] and Edward E. Schweizer*

Department of Chemistry, University of Delaware, Newark, Delaware 19711, and Contribution No. 2470 from the Central Research Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

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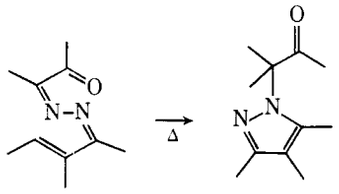
The reactions of simple acyclic azines with dimethyl acetylenedicarboxylate or methyl propiolate have been shown to yield either α,β-unsaturated azines or *N*-allyl- and/or *N*-propenylpyrazoles depending on the nature of the azine. The intermediacy of 1,5-dihydropyrazolo[1,2-*a*]pyrazoles has been demonstrated and the stereochemistry of the reaction probed. An x-ray crystallographic structure determination on one of the *N*-allylpyrazoles is also reported.

The thermolysis of α,β-unsaturated azines is a simple and efficient route to the pyrazole ring system. For example, azines (1) derived from α-diketone monohydrazones and α,β-unsaturated carbonyl compounds readily rearrange[2] on heating to α-pyrazolyl ketones (2). Similarly, cinnamaldehyde azine



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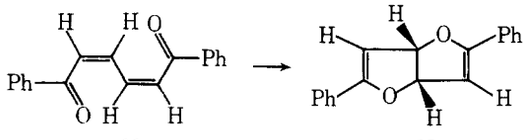
(3a) yields[3] *N-cis*-propenylpyrazole (5a) on pyrolysis. These reactions are quite general, requiring only that one of the substituents on the terminal double bond of the azine be a proton. The proposed[4] mechanism for the conversion of **3a** to **5a** involves formation of azomethine imine **4a** followed by intramolecular hydrogen transfer (path A, Scheme I).

Maier's report[5] of the ring closure of 1,4-dibenzoylbutadiene (11) to furano[3,2-*b*]furan **12** suggests an alternative mecha-



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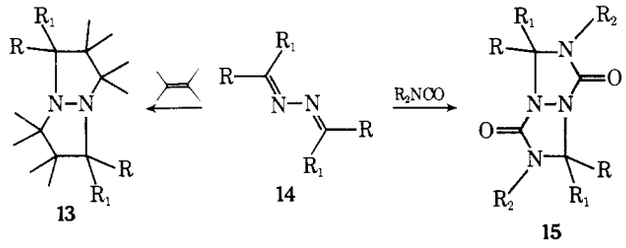
nistic possibility for the **3a** → **5a** conversion involving bicyclic heterocycle **7a** (path B, Scheme I). A synthesis of examples of **7** and investigation of their thermal behavior would offer a test, in part, of this hypothesis. When none of the substituents in the 1 and 5 positions is a proton, reversion to **3** would be expected (either directly or via **4**), while if at least one proton is in the 1 or 5 position, **5** and/or **6** may result as well.

The 1,5-dihydropyrazolo[1,2-*a*]pyrazoles **7** were unknown at the beginning of this investigation. However, simple ald- and ketazines (14) are known to react with olefins[6] and isocyanates[7,8] to yield related perhydro systems **13** and **15**, re-



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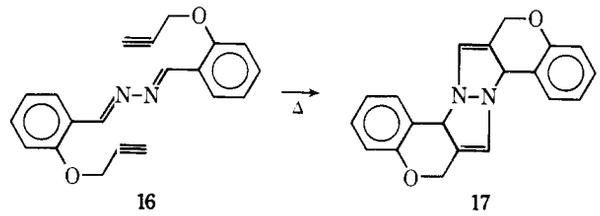
spectively. We reasoned that this "criss-cross" [7] cycloaddition could be extended to alkynes as a synthetic approach to **7**. During the course of this study, several reports appeared in the literature which confirmed, to some extent, our thinking. Hexafluoroacetone azine **10a** reacts at room temperature with phenylacetylene (**9a**) or acetylene (**9b**) to yield[9] dihydropyrazolopyrazoles **7b** and **7c**, respectively. At higher temperatures[10] or upon thermolysis or photolysis[9] of **7b** or **7c**, unsaturated azines **3b** or **3c** result. Recently, Suschitsky et al. re-



16 17

ported[11] that dihydropyrazolopyrazole 17 results from rearrangement of the azine of salicylaldehyde propargyl ether (**16**) in refluxing diethylaniline. We wish to report the results of our investigations into the reactions of azines with electron-deficient alkynes.

Results and Discussion

Benzophenone azine (**10b**) reacts slowly with dimethyl acetylenedicarboxylate (**9c**) to form a single product, isolated in 82% yield as a bright yellow solid. Analytical data indicate the formation of 2:1 (alkyne:azine) adduct. The ^{13}C and ^{1}H NMR spectra show only two distinct carbomethoxy groups and the lack of any saturated carbons (other than the ester methyl carbons). This indicates a fully unsaturated, symmetrical structure which is consistent with the product being the acyclic azine **3d**, resulting from rearrangement of intermediate **7d** analogously to the **7b/c** → **3b/c** conversion.

Reaction of benzaldehyde (**10c**) or benzaldehyde–benzophenone (**10d**) azines with **9c** under similar conditions yields colorless, crystalline 2:1 adducts in approximately 80% isolated yield. The ^{13}C NMR spectra of both products distinctly show four nonequivalent carbomethoxy groups and a single, nonester methyl saturated carbon at about 60 ppm. In the proton spectrum of the **10c–9c** product, two one-proton singlets (at δ 5.88 and 7.93 ppm) are observed for the nonaromatic/methyl hydrogens. The single proton of this type in the **10d–9c** adduct resonates at 5.49 ppm. Of the possible products for this reaction, dihydropyrazolopyrazoles **7e/f**, azines **3e/f**, and *N*-propenylpyrazoles **5e/f** are clearly inconsistent with these spectral data. The *N*-allylpyrazoles **6e/f** are consistent with the data but since a wide variety of compounds containing the C–N double bond form dihydropyridines when allowed to

Table I. Selected ^{1}H NMR Parameters for *N*-Allyl- (6) and *N*-Propenyl- (5) pyrazoles

Compd	R_2[a]	R_8	R_4	R_3	R_5
6e	7.93[b]	5.88	*c*	*c*	*c*
6f	C_6H_5	5.49	*c*	*c*	*c*
6g	7.99	6.08	*c*	*c*	*c*
6i	6.24 d, J = 16.0	5.35 d, J = 6.5	*c*	6.65 dd, J = 16.0, 6.5	7.96
6j	7.92 (7.95)	4.85, 2 H		*c*	7.92 (7.95)
6k	C_6H_5	5.41 d, J = 10.0	*c*		7.97
6l	C_6H_5	4.78, 2 H		*c*	7.92
5i	3.26, 2 H d, J = 7.5		*c*	*d*	8.07
5j	4.34, 2 H		7.61	*c*	8.04
5l	C_6H_5		7.59	*c*	7.91

[a] Numbering refers to Scheme I. [b] One proton singlets, parts per million (δ) vs. Me_4Si except as noted. [c] CO_2CH_3, δ 3.4–3.85 ppm. [d] Obscured by aromatic region.

Table II. Pertinent ^{13}C NMR Parameters for *N*-Allyl- (6) and *N*-Propenyl- (5) pyrazoles

Compd	C-4[a]	C-6	C-8	CO_2CH_3	CO_2CH_3
6e	114.4[b]	58.6	*c*	51.7, 52.2, 52.5, 52.8	162.4, 162.9, 166.5, 167.9
6f	114.0	63.0	*c*	51.8, 52.0 (2), 53.2	162.1, 163.1, 168.0, 168.7
6i	112.7	63.1	*c*	51.1, 52.4	163.0 (2)
6j	*d*	46.4	*c*	51.0, 52.2	163.2, 166.8
6k	112.3	60.0	*c*	51.0, 53.0	163.1, 169.1
6l	112.5	51.7	*c*	51.0, 51.7	163.4, 169.0
5i	112.7	*c*	34.2	51.1, 53.0	163.0, 168.3
5j	115.8	*c*	31.8	51.4, 52.2	162.7, 167.9
5l	113.6	*c*	46.9	51.3, 51.7	162.6, 167.2

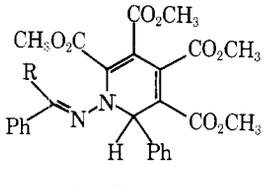
[a] Numbering as in Scheme I. [b] Parts per million (δ) vs. Me_4Si. [c] Not assigned. [d] Obscured by baseline noise.

Table III. Selected Interplanar Angles[a] for 6f

Plane 1[b]	Plane 2	Angle, deg
N2–C1–C2–C25	C1–C25–O1–O2	2.2
C1–C2–C3–C27	C2–C27–O3–O4	65.5
C4–C5–C6–C29	C5–C29–O5–O6	44.0
N1–C3–C2–C19	C3–C19–C20–C24	67.5
C5–C6–C7–C13	C6–C7–C8–C12	53.7
C5–C6–C7–C13	C6–C13–C14–C18	40.8

[a] Angle between the normals to the calculated planes. [b] Labels refer to Figure 1 (text).

react with **9c**,[12] we were forced to consider structures **18a** and **18b** as likely candidates for these products. Although consistent with the NMR data, we rule out these structures since most dihydropyridines are colored to some extent[13] and we are unable to detect benzaldehyde or benzophenone upon acid hydrolysis. We thus assign the structure of the products resulting from the reaction of azines **10c** and **10d** with alkyne **9c** as the *N*-allylpyrazoles, **6e** and **6f**. Pertinent ^{1}H and ^{13}C NMR parameters are listed in Tables I and II, respectively.



18a, R = H
b, R = Ph

We have confirmed this assignment by x-ray crystallography. The ORTEP[14] perspective drawing of **6f** based on the x-ray analysis is shown in Figure 1 and clearly shows the pyrazole ring (N1–N2–C1–C2–C3) with its substituents. Table III lists selected angles between calculated planes containing the indicated atoms which reflect the orientations of the phenyl and carbomethoxy groups. It is interesting to note that the phenyl ring in the 5 position of the pyrazole ring (i.e., C19 → C24) is tilted approximately 67.5° from the plane of the

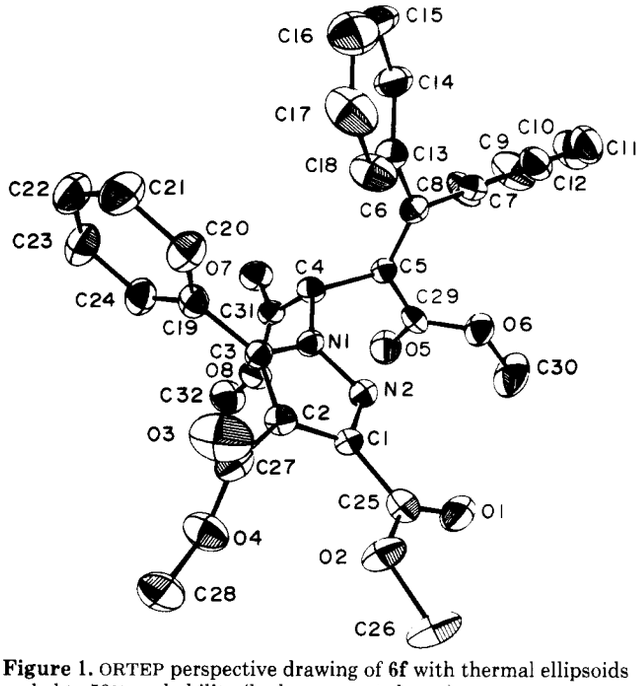
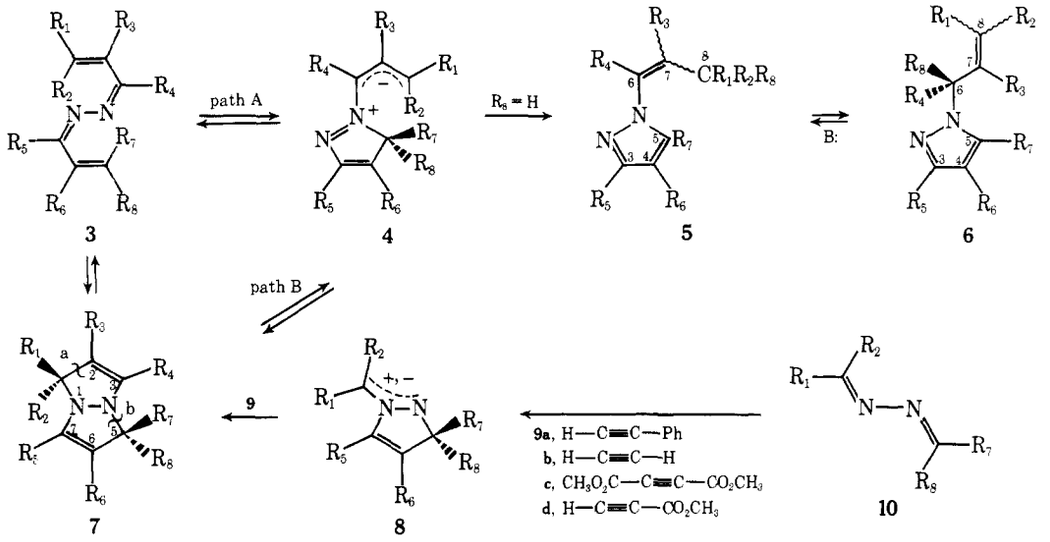


Figure 1. ORTEP perspective drawing of **6f** with thermal ellipsoids scaled to 50% probability (hydrogens not shown).

Scheme I



Compd	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
10a	CF_3	CF_3					CF_3	CF_3
b	Ph	Ph					Ph	Ph
c	Ph	H					Ph	H
d	Ph	Ph					Ph	H
e	3,4-(OCH₃)₂C₆H₃	H					3,4-(OCH₃)₂C₆H₃	H
3–8a	Ph	H	H	H	H	H	Ph	H
b	CF_3	CF_3	H	Ph	Ph	H	CF_3	CF_3
c	CF_3	CF_3	H	H	H	H	CF_3	CF_3
d	Ph	Ph	CO_2CH_3	CO_2CH_3	CO_2CH_3	CO_2CH_3	Ph	Ph
e	Ph	H	CO_2CH_3	CO_2CH_3	CO_2CH_3	CO_2CH_3	Ph	H
f	Ph	Ph	CO_2CH_3	CO_2CH_3	CO_2CH_3	CO_2CH_3	Ph	H
g	3,4-(OCH₃)₂C₆H₃	H	CO_2CH_3	CO_2CH_3	CO_2CH_3	CO_2CH_3	3,4-(OCH₃)₂C₆H₃	H
h	CF_3	CF_3	H	CO_2CH_3	H	CO_2CH_3	CF_3	CF_3
i	Ph	H	H	CO_2CH_3	H	CO_2CH_3	Ph	H
j	Ph	H	CO_2CH_3	H	H	CO_2CH_3	Ph	H
k	Ph	Ph	H	CO_2CH_3	H	CO_2CH_3	Ph	H
l	Ph	Ph	CO_2CH_3	H	H	CO_2CH_3	Ph	H

heterocyclic ring. Acoplanarity of the 5-phenyl and pyrazole rings has been cited as a reason for the different ^1H[15] and ^{13}C[16] NMR spectra of 3- and 5-phenylpyrazoles. All bond lengths and angles in **6f** are within expected ranges.[17] Owing to the obvious spectral similarities of **6f** and **6e**, it is assumed that the structural assignment of the latter is also correct.

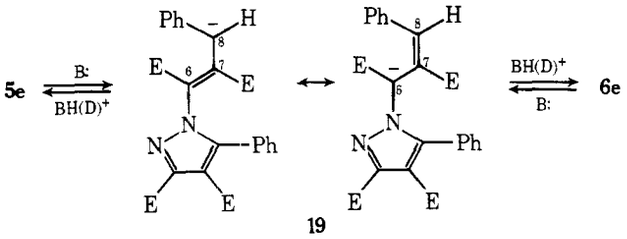
The structures of the products isolated thus far (**3d, 6e,** and **6f**) imply the intermediacy of dihydropyrazolopyrazoles **7d–f,** but we cannot detect them. Presumably they rearrange to the observed products as fast as or faster than they are formed. Criss-cross cycloaddition has been shown[18] to be a two-step reaction involving initial formation of azomethine imines **8** (Scheme I). We reasoned that introducing electron-donating groups into the aromatic rings of **10c** would facilitate the formation of **8**. Since the 1,3-dipolar cycloaddition of **8** with a second mole of acetylene should be relatively fast, we hoped to be able to detect or isolate **7** using a more electron-rich azine.

In fact, 3,4-dimethoxybenzaldehyde azine **10e** reacts slowly at room temperature with **9c** to form the expected *N*-allylpyrazole **6g** and a second 2:1 adduct in approximately a 1:2 ratio. ^{13}C NMR spectroscopy of the second product shows the presence of only two nonequivalent carbomethoxy groups and a single saturated carbon (other than ester methyl and ring methoxy carbons) resonating at 67.5 ppm. A two-proton singlet at δ 5.64 ppm characterizes the proton spectrum. Based on this spectral data and the facile thermal (1 h, 100 °C) and photochemical transformation into **6g,** we assign the structure of this second product as the dihydropyrazolopyrazole **7g.**

Azomethine imine **4** is presumably an intermediate in the transformation of **7** (or **3**) to **5** and/or **6.** However, when **7g** is thermolyzed in CH_3OD, essentially no deuterium is found at C-8 in **6g** formed. The same lack of deuterium incorporation is observed in the rearrangement of **3a** to **5a** in benzyl alcohol-*O*-*d*. In addition, **6g** is formed exclusively when **7g** is heated in the presence of excess maleic anhydride or phenyl isocyanate. These results imply that if **4g** is being generated, intramolecular hydrogen transfer is occurring much faster than either external protonation (deuteration) or reaction with dipolarophiles. Further work on the nature of the **7** to **5/6** transformation is warranted and currently underway in these laboratories.

None of the *N*-propenyl isomers **5e–g** could be detected even though they are presumably precursors for the observed products since hydrogen transfer in the **3a** → **4a** → **5a** conversion is proposed[4] to be intramolecular and to C-8 exclusively. Assuming this is true, the conversion of **5** to **6** most likely involves an allyl carbanion such as **19** (Scheme II). Any of a number of nitrogen bases present in the reaction mixture could act as the requisite base catalyst. The relative rates of

Scheme II

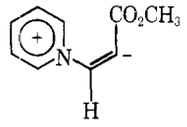


19

E = CO_2CH_3

H/D exchange at carbons 6 and 8 in **6e** support this view as well as the preference for the *N*-allyl isomer in this system. Hydrogen is completely exchanged for deuterium at C-6 within 15 min when a $CDCl_3$ solution of **6e** is exposed to D_2O/triethylamine. It takes 8 days to effect 80% deuterium incorporation at C-8. Thus, **19** is readily formed but greatly prefers deuteration (protonation) at C-6. If **5e** is formed deprotonation/reprotonation will lead rapidly to **6e.** Allyl–propenylpyrazole interconversion has been directly observed in a related system (see below).

The use of symmetrical alkyne **9c** clouds the stereochemistry of these reactions. Examination of the literature reveals that symmetrically substituted tetra- or dihydropyrazolopyrazoles result from the reaction of azines with unsymmetrical olefins[6] and alkynes,[9] respectively. The rationale for this stereochemistry is that the initial reaction between the azine and dienophile to form an azomethine imine (e.g., **8**) should proceed to bond the relatively electron-rich azine nitrogen to the more electrophilic dienophile carbon. Analogous behavior is observed with imines (e.g., pyridine) which react with electron-deficient alkynes via 1,4 dipoles such as **20.**[19] Sym-



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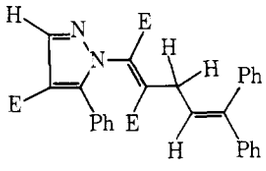
metrical pyrazolopyrazoles will result if the 1,3-dipolar cycloaddition of the azomethine imine thus formed with a second mole of dienophile proceeds as if nitrogen is the electron-rich end of the dipole. This is the normal mode of azomethine imine cycloaddition but steric and electronic factors may alter the direction of addition.[20]

The recent report[21] that the unsymmetrical dihydropyrazolopyrazole **7h** is the major product of the reaction between hexafluoroacetone azine (**10a**) and methyl propiolate (**9d**) indicated that the stereochemical course of these reactions described above is not inviolate and prompted us to investigate the reactions of azines **10c** and **10d** with unsymmetrical alkyne **9d.** Four major products result from the reaction of **10c** with **9d** in refluxing toluene. In addition to unreacted **10c** (10%), we have identified *N*-allylpyrazoles **6i** (32%) and **6j** (10%) along with their *N*-propenyl isomers **5i** (37%) and **5j** (8%) as the products of this reaction based on analyses of their NMR spectra. We expected, based on our earlier results, that the products would be substituted pyrazoles, and this is confirmed in all cases by the presence in the ^{13}C NMR of a peak at about 114 ppm assignable to C-4 of the pyrazole ring (Table II). In a series of 4-unsubstituted pyrazoles, C-4 is found[16] to resonate at 105–107 ppm. Replacement of the proton by a carbomethoxy group should result in a 5–10-ppm deshielding.[22] In addition, a peak at δ 7.9–8.1 ppm in the ^1H NMR indicates that the pyrazole ring is unsubstituted in the 3 position (R_5, Table I).

The remaining peaks in the ^1H NMR define the structure of the three carbon pyrazole side chains. For **6i** the expected AXY pattern is readily discernible and the magnitude of the coupling between the olefinic protons (16 Hz) indicates a trans double bond. The C-8 methylene in **5i** is a doublet and the carbon chemical shift of C-8 agrees quite well with the value of 33.3 ppm which we observe for the analogous carbon in **5a.** As a final proof, **5i** and **6i** are interconverted simply by heating. Similarly the ^1H and ^{13}C NMR data (Tables I and II) for **5j**[23] and **6j** are consistent with the proposed structures. The difference in chemical shift for the C-8 methylene protons in **5i** and **5j** may reflect a difference in conformation about the double bond (see discussion below).

The substituent patterns in these products bespeak their origin. Thus, the major route apparently involves unsymmetrical intermediate **7i,** which yields **5i** and **6i** by ring opening at a (Scheme I) followed by proton transfer and equilibration. Minor products **5j** and **6j** arise by similar processes from symmetrical dihydropyrazolopyrazole **7j.** Assuming that azomethine imine **8i/j** is a common intermediate, the product ratio (**5i** + **6i**)/(**5j** + **6j**) of 3.8 reflects an apparent kinetic preference for **8i/j** to react with methyl propiolate as if the carbon is the negative end of the dipole. Interestingly, no products resulting from ring cleavage of **7i** at b can be detected. This may reflect the dual resonance stabilization afforded the carbanionic portion of **4i** by the carbomethoxy and phenyl substituents which is lacking in the analogous dipole resulting from ring opening of **7i** at b.

Finally, we have investigated the reaction of azine **10d** with **9d.** Reaction in refluxing toluene for an extended period of time (22 days) yields a mixture containing unreacted **10d** (7%) and *N*-allylpyrazoles **6k** (26%) and **6l** (18%) as determined by quantitative NMR analysis. In addition, column chromatography allows the isolation of *N*-propenylpyrazole **5l** (26%) and a small amount (~5%) of a 3:1 adduct, identified as the *N*-pentadienylpyrazole **21.**



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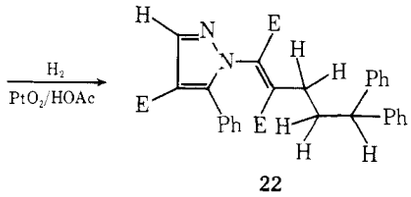
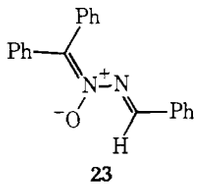


22

E = CO_2CH_3

Once again, peaks at 112–113 ppm in the ^{13}C and 7.95–8.05 ppm in the ^1H NMR for all products, including **21,** indicate a 3-unsubstituted pyrazole nucleus. The remaining NMR parameters collected in Tables I and II support the structural assignments.

Since azine **10d** is unsymmetrical, discrimination between N-1 and N-2 in the formation of **8** is possible. In reactions with peracids **10d** has been shown[24] to form azine oxide **23** exclu-



23

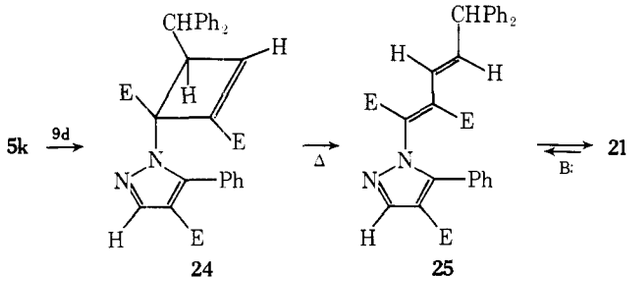
sively. This reflects the greater ability of the benzhydrilidene carbon to stabilize charge buildup. The products of the **10d–9d** reaction (**5l, 6k, 6l,** and **21**) can all be derived from common

intermediate **8k/l** in which the exocyclic benzhydrilidene carbon shares the charge. Reaction of **8k/l** with a second mole of **9d** as if the nitrogen bears the excess electron density yields symmetrical intermediate **7l**, the precursor for **5l** and **6l**. Reaction of **8k/l** in the opposite manner yields **6k** via unsymmetrical dihydropyrazolopyrazole **7k**. The (**5l** + **6l**)/(**6k**) ratio of 1.7 reflects the apparent kinetic preference for **8k/l** to react with **9d** as if the nitrogen is the more electron-rich center in the 1,3 dipole.

Our assignment of structure **21** to the 3:1 adduct is based in part on analysis of the spectral data. Three distinct carbomethoxy groups are readily apparent in both the ^{13}C and ^{1}H NMR spectra, and elemental analysis confirms that the product is a 3:1 adduct. In addition, the ^{13}C spectrum shows a single saturated carbon at 33.9 ppm while a one-proton triplet (δ 5.69 ppm) and a two-proton doublet (δ 2.76 ppm) characterize the ^{1}H spectrum. The best fit for this data is pentadienyl pyrazole **21**. Hydrogenation affords a dihydro derivative whose NMR and mass spectra are consistent with **22**.

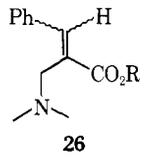
A mechanistic scheme which accounts for the formation of **21** requires that **5k** react as an enamine[25] with a third mole of **9d** to form cyclobutenyl pyrazole **24** (Scheme III), although

Scheme III



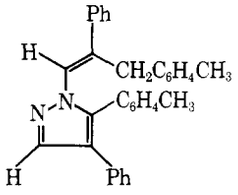
it has been stated,[26] without explanation, that vinyl pyrazoles do not behave as enamines. Thermal ring opening of the cyclobutene ring to **24** followed by double bond migration would yield **21**. However neither **6k** (which would yield **5k** by double bond migration), **5a**, nor a **5i/6i** mixture reacted with excess **9d** to yield products analogous to **21**. This mechanism must therefore remain a tentative proposal at this time.

We have delayed our discussion on the configuration of the double bonds in the various products since, with the exception of **6i**, we are unable to unambiguously define the stereochemistry. However, reasonable assignments may be made utilizing model compounds and empirical additivity relationships which have been developed[27] for predicting olefinic chemical shifts in a wide variety of alkenes. In addition, Trofimenko[26] has extended this concept to vinyl pyrazoles. Using the relationship $\delta = 5.25 + Z_{gem} + Z_{trans} + Z_{cis}$ and literature[27] Z values, chemical shifts of 7.7 and 7.0 ppm are predicted for the E and Z isomers of the α-(dialkylaminomethyl)cinnamate **26** as a model for **6e**, **6g**, and **6j**. The observed (Table I) values of 7.9–8.0 are much closer to the calculated shift for **26**-E and we assign this stereochemistry to these products.



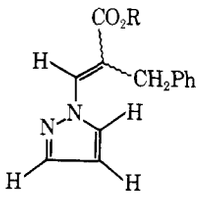
26

In attempting to assign the stereochemistry of the double bond in the N-propenylpyrazoles **5i**, **5j**, and **5l**, several model compounds are available for comparison. The benzyl methylene protons in **5a** and **27**[4] resonate at δ 3.91 and 4.33 ppm, respectively, which is very close to the value observed for the analogous protons in **5j** (4.34 ppm). Since **5a** and **27** are known[3,4] to have the pyrazole and benzyl groups cis, we assign



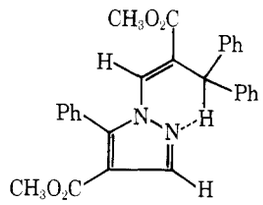
27

E stereochemistry to **5j**. In addition, the observed chemical shift for the C-6 proton of 7.61 in **5j** is closer to the value calculated for **28**-*E* (7.8) than for **28**-*Z* (7.2). The benzyl methylene protons in **5i** resonate at considerably higher field (more shielded) than those in either **27** or **5a**. Methyl groups trans to the pyrazole ring in N-propenylpyrazoles are known[26] to appear at higher field than when cis. Such a "trans" configuration in **5i** might also be favored on steric grounds. Thus we feel fairly confident in assigning *E* stereochemistry to the double bond in **5i**.



28

The remaining product of unknown stereochemistry is N-propenylpyrazole **5l**. The chemical shift of the vinyl proton in this product (7.59) is similar to that observed for **5j** and suggests similar stereochemistry. However, the C-8 proton resonates at significantly lower field than expected (chemical shifts of 6.0–6.3 ppm have been reported[28] for protons in similar environments). An intramolecular interaction between the C-8 proton and the pyrazole nitrogen as shown below may



5l

be involved. Such an interaction resembles the "carbinyl hydrogen bonding" invoked[29] to explain larger than expected acylation chemical shifts and Eu(fod)$_3$ gradients in certain acylated alcohols.

Conclusion

We have demonstrated that the reaction of azines with electron-deficient alkynes is a general route to 1,5-dihydropyrazolo[1,2-*a*]pyrazoles (**7**) and their rearrangement products, either acyclic azines (**3**) or N-substituted pyrazoles (**5** and/or **6**) depending on the availability of a proton at C-1 or 5 of **7**. In addition, we have probed the stereochemistry of this reaction in some detail. The nature of the products formed in these reactions and preliminary experiments on the nature of the **7** → **5/6** transformation are consistent with the proposal that **7a** is involved in the rearrangement of **3a** to **5a** but do not constitute proof of this hypothesis. Nonetheless, the reactions of aldazines and alkynes provide a simple and efficient route

to pyrazoles which would be difficult to prepare by standard routes.

Experimental Section

General. Azines used in this investigation were prepared by standard procedures. Dimethyl acetylenedicarboxylate (**9c**, Aldrich) and methyl propiolate[30] (**9d**) were distilled and stored in a desiccator prior to use. Reaction solvents were dried by standard methods and glassware was baked for a minimum of 4 h at 110–120 °C. A dry nitrogen atmosphere was maintained in all reactions. ^{1}H NMR spectra were obtained on either a Varian A-60A or Perkin-Elmer R-12b while a Bruker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data system operating at 22.63 MHz was used to collect the ^{13}C data. Mass spectra were recorded using a Du Pont CEC21-110D instrument. Chemical shifts are reported as parts per million (δ) vs. Me_4Si as an internal standard in $CDCl_3$ as solvent. Melting points obtained with a Hoover-Thomas apparatus are uncorrected. Elemental analyses were performed by Micro-Analysis Inc., Wilmington, Del.

X-Ray Crystallography for $C_{32}H_{28}N_2O_8$ (6f). Crystals were received as colorless, prismatic crystals showing clear triclinic morphology. The crystal chosen for study was approximately 0.40 × 0.16 × 0.13 mm in dimension and was mounted with the longest direction corresponding to the ϕ axis. This direction coincides with the crystal c^* axis.

The data were collected using Zr-filtered Mo Kα radiation (λ = 0.7107 Å) out to a maximum of 40° in 2θ. Each peak was scanned at a rate of 2.5°/min over a range of 2° plus the K_{α_1}–K_{α_2} dispersion. Backgrounds of 10-s duration were taken at each limit of the scan. A total of 2702 reflections were measured of which 160 were classified as unobserved. Reflection standard deviations were calculated based upon counting statistics. Structure factors with $F_o < 1.5\sigma(F_o)$ were given zero weight in the refinement. No crystal decomposition was detected and no correction for absorption was deemed necessary.

Precision lattice constants were obtained by least-squares refinement of eight carefully centered reflections. The pertinent cell parameters are as follows: space group $P\bar{1}$, a = 11.587 (21), b = 11.626 (6), c = 11.420 (8) Å, $\cos\alpha$ = −0.1485 (4), $\cos\beta$ = −0.2975 (14), $\cos\gamma$ = 0.0550 (14), Z = 2, ρ_{calcd} = 1.31 g/cm^3, μ = 1.023 cm^{-1}. Numbers in parentheses refer to standard deviations.

The structure was resolved by direct method tangent refinement techniques using the ORTEP program to search for a possible molecule from peaks observed in several trial e maps. One trial model incorporated all but one peak as possible atoms.

Subsequent cycles of difference Fourier maps and least-squares refinement[31] proved the model correct, located the additional nonhydrogen atom, and showed $P\bar{1}$ rather than $P1$ to be the correct space group. Anisotropic temperature factors were then introduced and hydrogen positions calculated by placing them at expected bond distances from the nonhydrogen atoms.

Cycles of refinement were continued, resulting in a final R = 0.054 and R_w = 0.065 where $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$.

Seven strong reflections with low 2θ values and $F_a < F_c$ were given negligible weight in the refinement owing to likely extinction problems.

The scattering factors used were for the neutral atoms and the function $\Sigma w(|F_o| - |F_c|)^2$ was minimized in the refinement. A final difference Fourier map showed no electron density greater than 0.5 e/Å^3.

Preparation of Methyl 2-Oxo-3-carbomethoxy-4,4-diphenylbut-3-enoate Azine (3d). A solution of 2.12 g (15 mmol) of alkyne **9c** and 1.81 g (5 mmol) of azine **10b** was heated at reflux in dry acetonitrile for 40 days. TLC (silica gel, CH_2Cl_2) showed incomplete reaction. On cooling, the product (**3d**) and unreacted **10b** cocrystalliized from the reaction mixture. After chilling at 0–5 °C for 2 h the solid was filtered, yielding 2.31 g of a yellow powder. Fractional crystallization from ethanol yielded 1.60 g (82% based on recovered azine) of **3d** as a yellow solid, mp 194–196 °C. Recrystallization from ethanol yielded an analytical sample: mp 195–197 °C; ^{1}H NMR δ 3.26, 3.54 (s, 6 H each, $-CO_2CH_3$), 7.00–7.40 (m, 20 H, aromatic); ^{13}C NMR 52.1, 52.4 ($-CO_2CH_3$), 156.9 (C=N), 162.4, 166.2 ppm ($-CO_2CH_3$). Anal. Calcd. for $C_{38}H_{32}N_2O_8$: C, 70.80; H, 5.00. Found: C, 70.55; H, 5.05.

Preparation of Methyl 2-(3,4-Dicarbomethoxy-5-phenylpyrazolyl)-3-carbomethoxy-4-phenylbut-3-enoate (6e). A solution of 5.2 g (0.025 mol) of azine **10c** and 10.5 g (0.074 mol) of **9c** in 40 ml of dry acetonitrile was heated at reflux for 60 h. The solvent was removed in vacuo and the residual amber oil dissolved in 40 ml of methanol. Crystallization was initiated by cooling in an ice–salt bath while scratching the vessel walls with a glass rod. Chilling at 0 °C for several hours, filtration, and vacuum drying yielded 9.7 g (79%) of **6e** as a white solid, mp 71–74 °C. Crystallization from methanol afforded an analytical sample: mp 80–81 °C; ^{1}H NMR δ 3.45, 3.56, 3.77, 3.81 (s, 3 H each, $-CO_2CH_3$), 5.88 (s, 1 H, C-6 H), 7.14 (br s, 10 H, aromatic), 7.93 (s, 1 H, C-8 H). Anal. Calcd for $C_{26}H_{24}N_2O_8$: C, 63.42; H, 4.90. Found: C, 63.57; H, 4.84.

Preparation of Methyl 2-(3,4-Dicarbomethoxy-5-phenylpyrazolyl)-3-carbomethoxy-4,4-diphenylbut-3-enoate (6f). A solution of 1.42 g (0.005 mol) of azine **10d** and 2.12 g (0.015 mol) of **9c** in 20 ml of dry acetonitrile was heated at reflux for 146 h. Workup as above afforded 2.38 g (84%) of **6f** as a white solid, mp 145–148 °C. Recrystallization from ethanol afforded an analytical sample: mp 149–151 °C; ^{1}H NMR δ 3.48, 3.56, 3.65, 3.76 (s, 3 H each, $-CO_2CH_3$), 5.49 (s, 1 H, C-6 H), 7.10 (br s, 15 H, aromatic). Anal. Calcd for $C_{32}H_{28}N_2O_8$: C, 67.60; H, 4.96. Found: C, 67.70; H, 4.95.

Preparation of Methyl 2-[3,4-Dicarbomethoxy-5-(3,4-dimethoxyphenyl)pyrazolyl]-3-carbomethoxy-4-(3,4-dimethoxyphenyl)but-3-enoate (6g). A solution of 1.64 g (0.005 mol) of azine **10e** and 1.5 g (0.0106 mol) of **9c** in 20 ml of dry acetonitrile was heated at reflux for 20 h. Workup as above yielded 2.11 g (69%) of **6g** as a pale yellow solid, mp 87–93 °C, essentially pure by NMR. Repeated crystallization from methanol afforded a colorless analytical sample: mp 131–132 °C; ^{1}H NMR δ [3.30 (s, 6 H), 3.63 (s, 3 H), 3.76 (br s, 6 H), 3.85 (br s, 12 H), all $C_6H_3(OCH_3)_2$ or $-CO_2CH_3$], 6.08 (s, 1 H, C-6 H), 6.59–7.58 (m, 6 H, aromatic), 7.99 (s, 1 H, C-8 H). Calcd for $C_{30}H_{32}N_2O_{12}$: C, 58.82; H, 5.26. Found: C, 58.50; H, 5.27.

Preparation of 1,5-Bis(3,4-dimethoxyphenyl)-2,3,6,7-tetrakis(carbomethoxy)-1,5-dihydropyrazolo[1,2-*a*]pyrazole (7g). A slurry of 1.00 g (3.05 mmol) of azine **10e** in 2.13 g (15.0 mmol) of **9c** and 2 ml of dry $CHCl_3$ was stirred in the dark at ambient temperatures for 10 days. The chloroform was removed in vacuo at less than 35 °C. Methanol was added and the resulting slurry was chilled and filtered, yielding 0.17 g (17%) of unreacted **10e.** Removal of methanol in vacuo (<35°) followed by column chromatography (silica gel, 0.5% MeOH in CH_2Cl_2) afforded in order of elution (a) unreacted **9c;** (b) 0.90 g (48%) of **7g** as an amorphous, amber solid; (c) 0.42 g (22%) of **6g.** Attempts at further purification of **7g** failed owing to the lability of the product. ^{1}H NMR δ [3.48 (br s, 6 H), 3.75 (brs, 12 H), 3.86 (brs s, 6 H), all $C_6H_3(OCH_3)_2$ or $-CO_2CH_3$], 5.64 (s, 2 H, C-1 H, C-5 H), 6.55–7.53 (m, 6 H, aromatic).

Thermal Rearrangement of 7g. $CDCl_3$ Solvent. A solution of **7g** (200 mg) in 0.5 ml of $CDCl_3$ in a sealed 5-mm NMR tube was heated in a thermostated oil bath at 65 °C. At intervals, the sample tube was cooled in ice and its NMR spectrum recorded. From this, the half-life for the conversion of **7g** to **6g** was estimated to be 2.5 h at this temperature. Only peaks corresponding to **6g** were detected.

Methanol Solvent. A solution of 100 mg of **7g** in 3 ml of MeOH was heated in a capped pyrolysis tube at 100 °C for 1.5 h. A ^{1}H NMR spectrum of the crude product after removal of solvent showed only **6g.**

Methanol-*O*-*d* Solvent. A solution of 100 mg of **7g** in 3 ml of MeOD (99.5% D) was heated at 100 °C for 1.5 h as above. The NMR spectrum of the crude product showed 0.95 H at C-8 (~5% D incorporation).

In the Presence of Maleic Anhydride. A solution of 100 mg (0.163 mmol) of **7g** and 100 mg (1.02 mmol) of maleic anhydride in 0.5 ml of dry CH_3CN was heated for 1.25 h at 100 °C as above. The NMR spectrum of the crude product showed only **6g** and maleic anhydride.

In the Presence of Phenyl Isocyanate. A mixture of 80 mg (0.13 mmol) of **7g** and 0.22 g (1.85 mmol) of PhNCO (freshly distilled) was heated for 1.5 h at ~100 °C as above. The crude product was partitioned between ether and 5% HCl. The layers were separated, and the organic phase washed with 5% HCl and H_2O, dried (Na_2SO_4), and evaporated in vacuo. The ^{1}H NMR showed the presence of **6g** only.

Photolysis of 7g. A solution of 20 mg of **7g** in 2 ml of benzene in a Pyrex test tube was irradiated with a 140-W Hanovia mercury lamp at 20 °C. The conversion of **7g** to **6g** was conveniently monitored by TLC (0.5% MeOH in CH_2Cl_2, silica gel) and was complete after 12 h.

Reaction of 10c with Methyl Propiolate (9d). A solution of 1.04 g (5 mmol) of azine **10c** and 1.05 g (12.5 mmol) of **9d** in 15 ml of dry toluene was heated at reflux for 97 h. Solvent and excess **9d** were removed in vacuo (40 °C, 0.5 mm) to yield 1.88 g (theory 1.88) of a thick, golden oil. Quantitative NMR analysis indicated the presence of 0.47 mmol (10%) of **10c,** 1.58 mmol (32%) of **6i,** 1.85 mmol (37%) of **5i,** 0.41 mmol (8%) of **5j,** and 0.52 mmol (10%) of **6j.** The crude product was

then chromatographed (silica gel, 0.5% MeOH in CH_2Cl_2 as eluent) to yield the following, in order of elution. (a) **10c,** identical by NMR with authentic **10c.** (b) **5j,** white solid, mp 108.5–110 °C (MeOH); ^1H NMR δ 3.55, 3.64 (s, 3 H each, $-CO_2CH_3$), 4.34 (s, 2 H, C-8 H_2), 6.93–7.54 (m, 10 H aromatic), 7.61 (s, 1 H, C-6 H), 8.04 (s, 1 H, C-3 H). Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36. Found: C, 69.98, 5.45. (c) **5i + 6i,** pale yellow oil. We were unable to completely separate these isomers but fractions enriched in one or the other allowed complete assignment of spectral data. ^1H NMR δ 3.26 (d, J = 7.5 Hz, 2 H, **5i,** C-8 H_2), 3.52, 3.57, 3.64 (3 s, total 6 h, **5i + 6i,** $-CO_2CH_3$), 5.35 (d, J = 6.5 Hz, 1 H, **6i,** C-6 H), 6.24 (d, J = 16.0 Hz, 1 H, **6i,** C-8 H), 6.65 (dd, J = 6.5, 16.0 Hz, 1 H, **6i,** C-7 H), 6.90–7.50 (m, 11 H, **5i + 6i,** aromatic and **5i,** C-7 H), 7.96 (s, 1 H, **6i,** C-3 H), 8.07 (s, 1 H, **5i,** C-3 H). A fraction containing isomers **5i, 6i,** and **6j** in approximate ratio of 2:1:0.5 was prepared for analysis by short-path, bulb-to-bulb distillation at 180 °C (0.05 mm). Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36. Found: C, 69.92; H, 5.23. (d) **6j,** brown oil contaminated with **5i, 6i,** and some dark, tarry material. Bulb-to-bulb distillation yielded a pale yellow oil containing mostly **6j** with some **5i** and **6i.** ^1H NMR δ 3.62, 3.71 (s, 3 H each, $-CO_2CH_3$), 4.85 (s, 2 H, C-6 H_2), 6.93–7.64 (m, 10 H, aromatic), 7.92, 7.95 (s, 1 H each, C-3 H, C-8 H).

Thermal Equilibration of 5i and 6i. A mixture of **5i** and **6i** (**6i/5i** = 2.4) was heated at reflux in acetonitrile for 48 h. The solvent was removed in vacuo and an NMR analysis showed the **6i/5i** ratio to be 0.8.

Reaction of 10d with Methyl Propiolate (9d). A solution of 1.42 g (5 mmol) of azine **10d** and 1.25 g (1.5 mmol) of **9d** in 15 ml of dry toluene was heated at reflux for 22 days. The solvent and excess **9d** were removed in vacuo (40 °C, 0.5 mm) to yield 2.33 g (theory 2.26) of a yellow, amorphous solid. Quantitative NMR analysis indicated the presence of 0.34 mmol (7%) of **10d,** 1.31 mmol (26%) of **6k,** and 0.91 mmol (18%) of **61.** The crude product was then chromatographed (silica gel, 0.5% MeOH in CH_2Cl_2 as eluent) to yield the following, in order of elution.

(a) **10d,** identical by NMR with authentic **10d.**

(b) **5l.** 0.59 g (1.30 mmol, 26%); white solid, mp 122.5–123.5 °C (MeOH); ^1H NMR δ 3.38, 3.60 (s, 3 H each, CO_2CH_3), 6.93 (s, 1 H, C-8 H), 6.95–7.50 (m, 15 H, aromatic), 7.59 (s, 1 H, C-6 H), 7.96 (s, 1 H, C-3 H). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.34. Found: C, 74.50; H, 5.36.

(c) **6k.** White solid, mp 142–143 °C (MeOH); ^1H NMR δ 3.55, 3.59 (s, 3 H each, CO_2CH_3), 5.41 (d, J = 10.0 Hz, C-6 H), 6.60 (d, J = 10.0 Hz, C-7 H), 7.10 (br s, 10 H, aromatic), 7.97 (s, 1 H, C-3 H). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.34. Found: C, 74.52; H, 5.35.

(d) **6l.** White solid, mp 111.5–112.5 °C (MeOH); ^1H NMR δ 3.25, 3.54 (s, 3 H each, CO_2CH_3), 4.78 (s, 2 H, C-6 H_2), 6.78–7.56 (m, 15 H, aromatic), 7.92 (s, 1 H, C-3 H). Anal. Calcd for $C_{28}H_{24}N_2O_4$: C 74.32; H, 5.34. Found: C, 74.11; H, 5.21.

(e) **21.** 100 mg (0.19 mmol, 4%); white solid, mp 162.5–163.5 °C (MeOH); ^1H NMR δ 2.76 (d, J = 7.5 Hz, 2 H, C-8 H_2), 3.22, 3.40, 3.57 (s, 3 H each, CO_2CH_3), 5.69 (t, J = 7.5 Hz, 1 H, C-9 H), 6.53–7.23 (m, 15 H, aromatic), 7.72 (s, 1 H, C-3 H). ^{13}C NMR 33.9 (C-8), 51.0, 51.7, 51.8 (CO_2CH_3), 112.5 (C-4), 162.9, 169.0, 169.7 (CO_2CH_3). Anal. Calcd for $C_{32}H_{28}N_2O_6$: C, 71.63; H, 5.26. Found: C, 71.57; H, 5.18.

Hydrogenation of 21. A solution of 150 mg of **21** in 10 ml of glacial acetic acid and 3 ml of methylene chloride was hydrogenated at 5–10 psi H_2 for 21 h over 10 mg of PtO_2. The catalyst was removed by filtration and the solvents removed in vacuo. The residue was dissolved in 20 ml of ether, extracted with 2 × 5 ml of 5% NaOH and 1 × 5 ml of H_2O, the organic phase dried (Na_2SO_4), and the ether removed in vacuo to yield 0.14 g (93%) of **22** as an off-white solid. Crystallization from CH_2Cl_2–heptane yielded a colorless analytical sample: mp 197–198 °C; ^1H NMR δ 1.99–2.99 (br m, 4 H, C-8 H_2, C-9 H_2), 3.34, (s, 6 H, $-CO_2CH_3$), 3.58 (s, 3 H, $-CO_2CH_3$), 5.05 (m, 1 H, C-10 H), 6.33–7.73 (m, 15 H, aromatic), 7.90 (s, 1 H, C-3 H). ^{13}C NMR 29.6, 30.7 (C-8, C-9), 51.1, 51.5 (br) (CO_2CH_3), 58.8 (C-10). Mass spectum m/e 538 (M^+). Anal. Calcd for $C_{32}H_{30}N_2O_6$: C, 71.36; H, 5.61. Found: C, 71.22; H, 5.70.

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Registry No.—3d, 60896-16-4; **5i,** 60896-17-5; **5j,** 60896-18-6; **5l,** 60896-19-7; **6e,** 60896-20-0; **6f,** 60896-21-1; **6g,** 60896-22-2; **6i,** 60896-23-3; **6j,** 60896-24-4; **6k,** 60896-25-5; **6l,** 60896-26-6; **7g,** 60896-27-7; **9c,** 762-42-5; **9d,** 922-67-8; **10b,** 983-79-9; **10c,** 588-68-1; **10d,** 13118-38-2; **10e,** 17745-86-7; **21,** 60896-28-8; **22,** 60934-68-1.

Supplementary Material Available. Tables of positional and thermal parameters for the structure of **6f** (4 pages). Ordering information is given on any current masthead page.

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