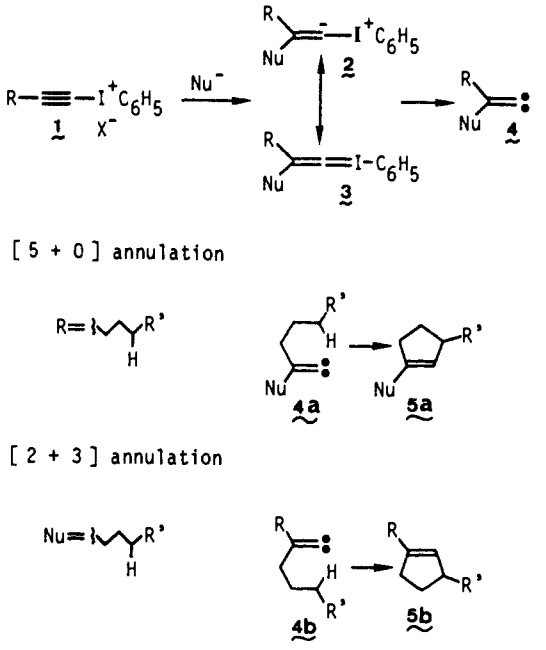
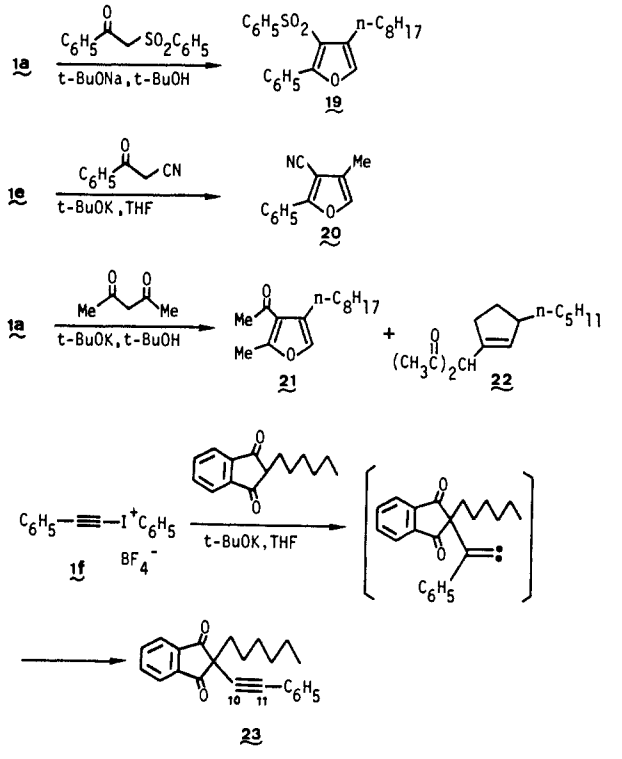
Scheme I



Scheme II



may reasonably explain the formation of these furans.[12] Exclusive formation of the furan **19** clearly shows that the intramolecular 1,5 insertion into C–H bonds of methylene groups cannot compete with that into O–H bonds of enols. However, the stereochemistry of enolized carbene intermediates plays an important role in the furan synthesis. Thus the tandem MCI reaction of **1a** with acetylacetone afforded a mixture of furan **21** and cyclopentene **22** in a 64:36 ratio in 61% yield (Scheme II).

The new MCI reaction has some limitation. The attempted [2 + 3] annulation using (phenylethynyl)iodonium salt **1f** and 2-hexyl-1,3-indandione gave no cyclopentene derivative but alkyne **23** in 74% yield. Beringer and co-workers reported similar results and concluded that the substitution reaction occurs on the α-acetylenic carbon atom of alkynyliodonium salts.[4a] However, we found on the basis of a ^{13}C NMR experiment that the formal substitution reaction proceeds via Michael addition of nucleophiles toward iodonium salts followed by 1,2-phenyl migration of the resulting alkylidene carbenes (or carbenoids).[13,14]

The tandem MCI reaction not only offers many advantages including high efficiency and mildness of the reaction conditions but also provides general and simple access to a diverse spectrum of complex cyclopentenes and substituted furans.

Supplementary Material Available: Tables of the X-ray diffraction analysis of **12** including atomic coordinates, bond lengths and angles, and thermal parameters and the molecular structure of **12** (6 pages). Ordering information is given on any current masthead page.

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(13) When phenyl(phenylethynyl-2-^{13}C)iodonium tetrafluoroborate (99% enriched) was used, the enrichment at the acetylenic carbons of **23** obtained was determined as 94% (C-10) and 6% (C-11) from the ^{13}C NMR spectrum.

(14) The facile 1,2-aryl migration of unsaturated carbenoids has been reported.[2a]

Novel Fluorescent 1,4-Dihydropyridines[1]

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Malondialdehyde (MDA) is produced in mammalian tissues as a side product of prostaglandin and thromboxane biosynthesis and, along with other aldehydes, as an end product of unsaturated lipid peroxidation.[2,3] Aldehydes have been implicated in degenerative processes in vivo,[4] and MDA particularly may be of considerable importance physiologically because of its ability to modify and cross-link biological macromolecules.[5-8] Although vinylogous amidine linkages have been suggested as being formed in lipofuscins, a seemingly ubiquitous group of fluorescent pigments which have been linked to aging,[9] the chromophoric component responsible for the fluorescence of lipofuscins or other cross-linked biomolecules[10,11] remains unknown. UV–visible and fluorescence data[12,13] appear to be consistent with the formation of vinylogous amidines as well as highly fluorescent heterocyclic systems of unknown structure. This paper reports on model studies with MDA that involve the isolation and structural characterization of novel heterocyclic adducts of similar UV and fluorescence data as those reported in the aforementioned biological studies.

We have discovered that when MDA (**1**) was allowed to react with amino acids (e.g., glycine methyl ester) under aqueous acidic conditions for prolonged periods (72 h), the UV spectrum shifted gradually from a single absorption at about 250 nm to absorptions

(1) Dedicated to Professor Nelson J. Leonard on the occasion of his 70th birthday.

(2) Pryor, W. A. *Free Radicals in Biology*; Academic: New York, 1976–1984; Vol. I–VI.
(3) *Autoxidation in Food and Biological Systems*; Simic, M. G.; Karel, M., Eds.; Plenum: New York, 1980.
(4) Marnett, L. J.; Hurd, H. K.; Hollstein, M. C.; Levin, D. E.; Esterbauer, H.; Ames, B. N. *Mutat. Res.* **1985**, *148*, 25.
(5) Basu, A. K.; Marnett, L. J. *Cancer Res.* **1984**, *44*, 2848.
(6) Munkres, K. D. *Mech. Ageing Dev.* **1979**, *10*, 249.
(7) Nair, V.; Vietti, D. E.; Cooper, C. S. *J. Am. Chem. Soc.* **1981**, *103*, 3030.
(8) Nair, V.; Turner, G. A.; Offerman, R. J. *J. Am. Chem. Soc.* **1984**, *106*, 3370.
(9) Munkres, K. D.; Rana, R. S. *Mech. Ageing Dev.* **1978**, *7*, 407.
(10) Reiss, U.; Tappel, A. L.; Chio, K. S. *Biochem. Biophys. Res. Commun.* **1972**, *48*, 921.
(11) Summerfield, F. W.; Tappel, A. L. *Anal. Biochem.* **1981**, *111*, 77.
(12) Chio, K. S.; Tappel, A. L. *Biochemistry* **1969**, *8*, 2821.
(13) Chio, K. S.; Tappel, A. L. *Biochemistry* **1969**, *8*, 2827.

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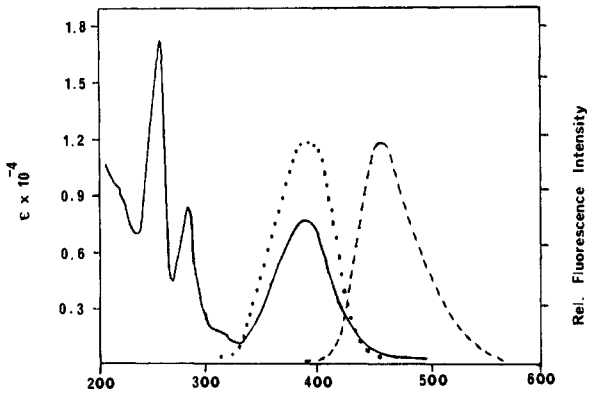
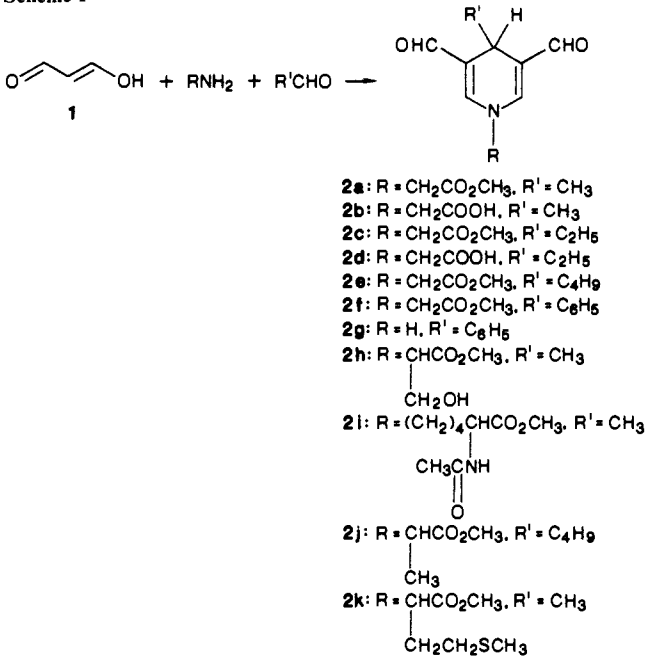


Figure 1. Ultraviolet absorption (—), fluorescence excitation (···), and corrected fluorescence emission spectra (---) of 1,4-dihydropyridine **2a** in water, pH 7.0

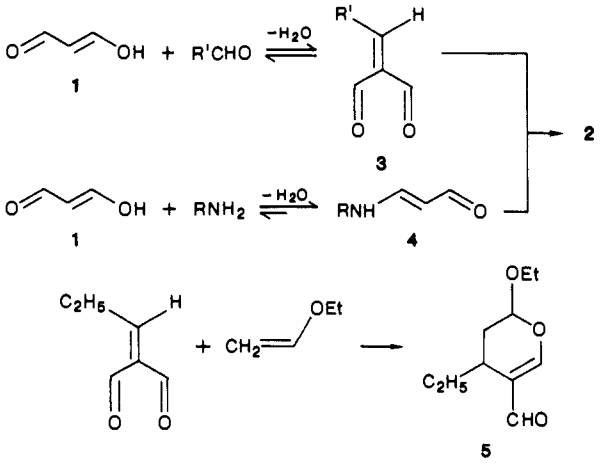
Scheme I



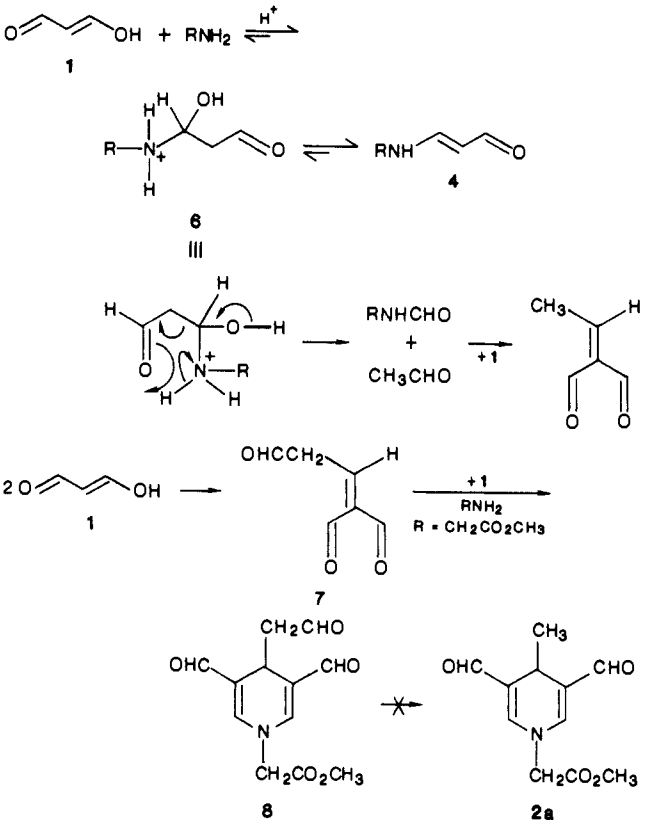
at about 240, 265, and 390 nm. Workup and purification gave low yields of a product with UV absorptions (in H_2O) at 236 (ϵ = 18 900), 262 (ϵ = 7900), and 384 nm (ϵ = 8800). The compound was highly fluorescent, emitting at 454 nm upon excitation at 386 nm with a relative quantum efficiency (Φ) of 0.36 (Figure 1).[14] The mass spectrum showed a molecular ion at m/z 223. The high-field ^1H NMR spectrum (in $CDCl_3$) showed two equivalent aldehyde protons as a singlet at δ 9.30, two equivalent protons as a singlet at δ 6.64, and a multiplet at δ 3.84 integrating for four protons. Additional doublet and singlet resonances integrating for three and two protons at δ 1.14 and 4.20, respectively, were also observed. Taken collectively, the data suggested that the product was the 4-methyl-1,4-dihydropyridine-3,5-dicarboxaldehyde **2a** (Scheme I). Further support for the structures came from the delayed-decoupled 90.6-MHz ^{13}C NMR spectral data, which showed eight distinct resonances with multiplicities consistent with the assigned structure.

The identical product **2a** was obtained in about 50% yield when MDA was allowed to react with glycine methyl ester in the presence of acetaldehyde at pH 4.3[15] for 7 h. The generality of the reaction of MDA with amino acids in the presence of additional aldehydes was established by isolation of related 1,4-dihydropyridines in similar yields from alanine, serine, methionine, and lysine methyl esters with acetaldehyde, propanal, pentanal, and benzaldehyde (Scheme I). Unprotected amino acids can also be used in these reactions (e.g., glycine), but use of the esters makes isolation of products somewhat easier.

Scheme II



Scheme III



It is very probable that alkylidenemalondialdehydes **3** are the intermediates in the mechanism of these transformations (Scheme II). These reactive species[16] are apparently produced in situ from the condensation of MDA with the additional aldehyde and behave as Michael acceptors for the enaminals **4**. The latter are 1:1 adducts formed rapidly from the condensation of MDA with the amino acids.[7] Evidence for the formation and consumption of the enaminals came from UV data (~280 nm) obtained during the course of the reaction and from the formation of the same dihydropyridines from the reaction of isolated enaminals. The intermediacy of the alkylidene MDA was inferred by a Diels–

(14) Relative quantum yield vs. quinine sulfate (0.70) in 0.1 N H_2SO_4. Scott, T. G.; Spencer, R. D.; Leonard, N. J.; Weber, G. *J. Am. Chem. Soc.* **1970**, *92*, 687.

(15) The pH was adjusted to just below the pK_a of MDA (4.46).

(16) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbruggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852.

Alder trapping experiment[17] using ethyl vinyl ether to yield **5** (Scheme II).

The formation of the 1,4-dihydropyridine **2a** from the reaction of MDA with glycine methyl ester in the absence of added second aldehyde may be rationalized by the mechanism shown in Scheme III, where the very slow formation of acetaldehyde from the thermal cleavage of the amino alcohol (hydrated enaminal) **6** results in the eventual formation of an alkylidene MDA which can be trapped by a second molecule of enaminal. Malondialdehyde itself could behave as the "second aldehyde" in this reaction forming the alkylidene MDA **7** which would then result in the dihydropyridine **8**. However, **8** was not isolated in this reaction. In order to prove that dihydropyridine **2a** was not produced by the in situ decarbonylation of **8**, an authentic sample of **8** was prepared by an alternative route. It was found to be thermally stable under the conditions used to produce the 1,4-dihydropyridines.

We conclude from these initial studies that MDA is able to modify amino acid residues to fluorescent 1,4-dihydropyridines. These findings may be of significance in understanding the biological chemistry of MDA in vivo and may explain some of the spectral disparities reported earlier on the interaction of MDA with amino acids and proteins.[12,13] In addition, some of the dihydropyridines produced in this study may be of interest as fluorescent biological probes of the calcium channel in living systems.[18] Further studies on the dihydropyridines as well as the alkylidene malondialdehydes are in progress.

Acknowledgment. We thank the National Science Foundation for support of this research.

Supplementary Material Available: Tables of NMR (^1H and ^{13}C), UV, fluorescence, and mass spectral data for adducts (10 pages). Ordering information is given on any current masthead page.

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Drug-Metal Interactions: An Unusual Four-Membered Ring Copper Phenobarbital Complex

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Phenobarbital (**1**) is among the anticonvulsant drugs used in the treatment of most forms of epilepsy.[1,2] The drug may be administered orally, intramuscularly, or intravenously following which it is transported to the plasma. Since most of the labile copper in human plasma[3] is loosely bound to albumin, this metal can bind to amino acids and other chelating ligands. It is of interest, therefore, to determine the copper binding properties of phenobarbital and its sodium salt. Monodentate 2:1 copper complexes of barbiturates have been studied by various authors[4,5] using spectroscopic methods. During our studies of copper-phenobarbital interactions, a new type of a bidentate, 2:1 copper complex was obtained.

This report describes the synthesis, characterization, and the chemical structure of disodium bis(phenobarbiturato)copper(II), ($Cu^{II}(PB)_2$). The blue-green complex was prepared by combining methanolic solutions of $Cu^{II}Cl_2 \cdot 2H_2O$ and sodium phenobarbital in a 1:2 molar ratio.[6,7] ESR and infrared data indicate that the copper atom is coordinated to two nitrogen atoms from each phenobarbital in a square-planar arrangement forming unusual four-membered rings. To our knowledge this is the first report on the synthesis and characterization of a copper complex containing this number of ring atoms.

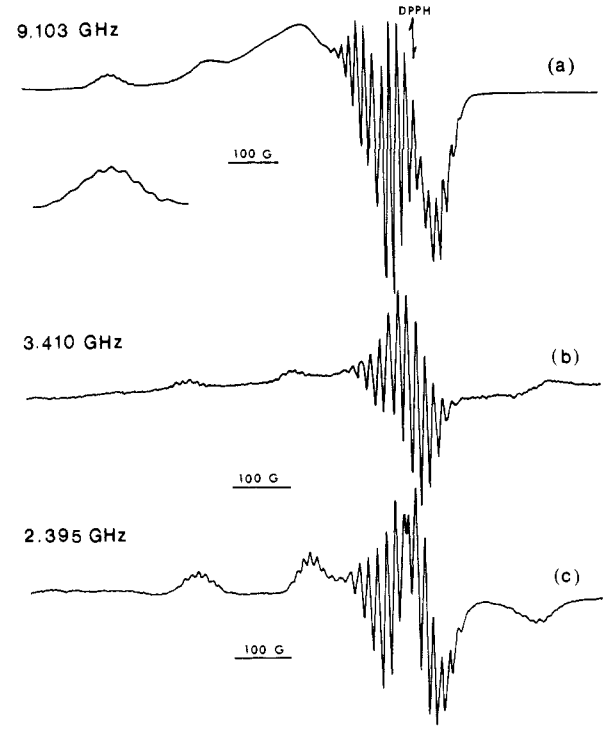
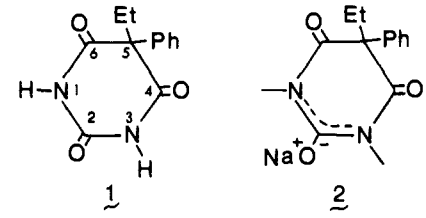


Figure 1. Multifrequency ESR spectra of $Cu^{II}(PB)_2$ complex in frozen MTHF glass at 77 K.

The carbonyl region of the infrared spectrum of $Cu^{II}(PB)_2$ shows two bands of approximately equal intensity at 1625 and 1672 cm^{-1} and a weak band at 1710 cm^{-1}. All three bands are bathochromically shifted with respect to positions observed for the free acid.[8] In addition, a strong peak near 1620 cm^{-1} was observed which is not present in the free ligand. The infrared spectrum of the carbonyl region resembles in form and intensity patterns that reported for sodium phenobarbital.[8] For reference, the latter compound is based on an enolized C=O group in the 2-position[8] with a deprotonated nitrogen atom. In the copper complex under study, both nitrogen atoms are deprotonated resulting in resonance structure **2**. Thus, the three carbonyls would



no longer be expected to have the same intensity and, based upon previous work,[8] the high-frequency weak C=O band is assigned to the 2-position. The two remaining carbonyls in the 4- and 6-positions, however, are in the same environment and are coupled

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(2) Quattrone, A.; Crunelli, V.; Samarin, R. *Neuropharm.* **1978**, *17*, 643.
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(4) Pezeshk, A.; Greenaway, F. T.; Sorenson, J. R. J. *Inorg. Chim. Acta* **1983**, *80*, 191.
(5) Wang, B. C.; Walker, W. R.; Li, N. C. *J. Coord. Chem.* **1973**, *3*, 179.
(6) The reaction mixture initially formed a green-brown precipitate which was isolated and characterized to be disodium tetrakis(phenobarbiturato)-copper(II) dihydrate. Anal. Calcd for $Na_2(CuC_{48}H_{46}N_8O_{12} \cdot 2H_2O)$: C, 53.76; H, 4.66; N, 10.44. Found: C, 53.68; H, 4.98; N, 10.84. The intermediate was then suspended in hot methanol and stirred for 15 min, losing two molecules of phenobarbital to yield the desired product.
(7) Anal. Calcd for $Na_2(CuC_{24}H_{22}N_4O_6 \cdot 4H_2O)$: C, 44.77; H, 4.66; N, 8.70. Found: C, 44.52; H, 4.62; N, 8.74.
(8) Mesley, R. J. *Spectrochim. Acta, Part A* **1970**, *26A*, 1427.

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