(4) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963); D. L. Hall and R. B. Perfetti, *ibid.*, **39**, 111 (1974).
(5) Satisfactory elemental analyses were obtained for compounds **4**, **6**, **7**, **9**, **12**, and **15**. All other compounds were characterized by spectroscopic methods.
(6) L. Zervas and I. Photaki, *J. Am. Chem. Soc.*, **84**, 3887 (1962).
(7) Prepared by esterification of bromopyruvic acid with diphenyldiazomethane in benzene at room temperature.
(8) Difficulties in similar dehydrations have been reported. See, for example, German patent 2 337 447.
(9) M. Gorman and C. W. Ryan in "Cephalosporins and Penicillins; Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, Chapter 12.
(10) Prepared by esterification of 3-bromo-2-oxobutyric acid with *N,N'*-diisopropyl-*O*-*tert*-butylpseudourea in methylene chloride at room temperature for 2 days.
(11) Functionalization of 3-methyl-3-cephem esters by allylic bromination fails although 2-cephem esters may be functionalized in this way: J. A. Webber, G. W. Huffman, R. E. Koehler, C. F. Murphy, C. W. Ryan, E. M. Van Heymingen, and R. T. Vasileff, *J. Med. Chem.*, **14**, 113 (1971); see also ref 9, Chapter 4.
(12) C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez, and K. Smith, *Tetrahedron Lett.*, 2417 (1974).
(13) Unpublished data, J. Hoover and D. Jakas.
(14) L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7582 (1974); R. N. Guthikonda, L. D. Cama, and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7584 (1974).

D. Boles Bryan, Ralph F. Hall, Kenneth G. Holden
William F. Huffman, John G. Gleason*
Research & Development Division
Smith Kline & French Laboratories
Philadelphia, Pennsylvania 19101
Received October 26, 1976

Decarboxylative 1-Aza-1′-oxa [3,3]Sigmatropic Rearrangements of Enolizable or Enolized *N*-Aryl-*N,O*-diacylhydroxylamines to *o*-(*N*-Acylamino)aryl Ketones, Esters, and Amides: a New Synthetic Method for Ortho Alkylation

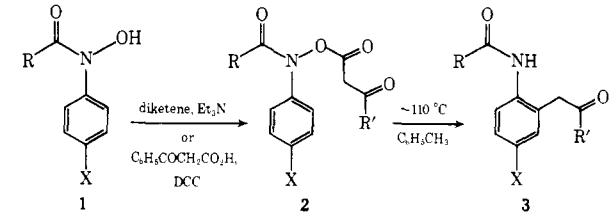
Sir:

The introduction of allyl substituents into the ortho position of phenols by the Claisen rearrangement of allyl aryl ethers is a long-known and effective synthetic process.[1] Although the scope of the more recently discovered amino-Claisen rearrangement for the synthesis of ortho allyl anilines is at present less well defined,[2] the high temperatures or acid catalysts usually employed for this reaction would appear to impose certain limitations on its utility, and indeed a number of side reactions have already been encountered.[3] The ortho alkylation of anilines may also be accomplished through [2,3]sigmatropic rearrangements of N-aryl azasulfonium ylides albeit with a subsequent reduction to remove the sulfur function from the side chain.[4] We wish to report a new regiospecific synthesis of anilides having carbonyl-functionalized alkyl groups in the ortho position by means of 1-aza-1′-oxa [3,3]sigmatropic rearrangements[5] of enolizable or enolized *N*-aryl-*N,O*-diacylhydroxylamines.

Although a number of reactions which appear to involve rearrangements of this type has been reported in the literature,[6,7] apart from the acid-catalyzed isomerization of O-aryl ketoximes to *o*-hydroxyphenylketimines or benzofurans,[6c] the synthetic applications of this 1′-aza analogue of the Claisen rearrangement have been restricted. One factor which has no doubt impeded the exploitation of this inherently exothermic transformation[8] is the instability of the requisite *N,O*-divinyl- and *N*-aryl-*O*-vinylhydroxylamines. Accordingly we choose to model our initial approach after the Carroll reaction,[9] a variant of the Claisen rearrangement in which the vinyl ether grouping is generated simply by enolization of an allyl acetoacetate.

N-Aryl-*N*-hydroxyamides (**1**), readily available by partial reduction of nitroarenes to *N*-arylhydroxylamines[10,11] and selective N-acylation,[11,12] are transformed into *O*-acetoacetyl derivatives (**2**) by reaction with diketene in the presence of a catalytic amount of triethylamine (1.1 equiv of diketene, 1:1 chloroform–ether, 0 °C, overnight). The two phenyl substituted intermediates (**2c** and **2e**) were obtained in a complementary manner by the dicyclohexylcarbodimide(DCC)-induced condensation of benzoylacetic acid with the appropriate *N*-hydroxy amides. Since these compounds proved, with two exceptions, to be liquids and rather unstable, they were for the most part purified only by extraction (5–10% sodium bicarbonate) to remove any unreacted *N*-hydroxyamide and characterized chiefly by infrared and NMR spectral data.[13]

Scheme I



	X	R	R′	2 Yield (%)	3 Yield (%)
a, H		CH_3	CH_3	71	55
b, H		C_6H_5	CH_3	77	46
c, H		CH_3	C_6H_5	—[a]	51[b]
d, CH_3		CH_3	CH_3	81	82
e, CH_3		CH_3	C_6H_5	—[a]	50[b]
f, CH_3		C_6H_5	CH_3	88	61
g, Cl		CH_3	CH_3	85	44
h, CO_2CH_3		CH_3	CH_3	70	40

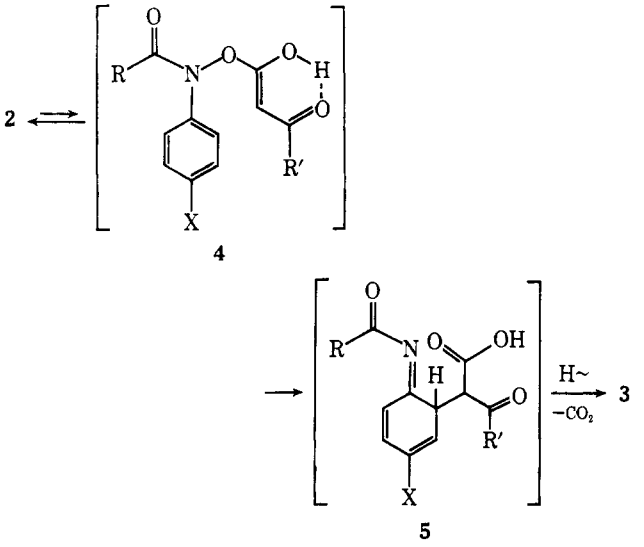
[a] Yield not determined at this stage. [b] Overall yield from 1.

When heated in toluene at reflux temperature (~110 °C for 30–90 min, the β-keto esters undergo decarboxylation and give rise to *o*-(*N*-acylamino)aryl ketones (**3**) as major products in 40–82% yield after purification by chromatography on silica gel.[13b,14] Two of the products were identified as the known 2′-acetonylacetanilide (**3**, X = H; R = R′ = CH_3; mp 134–136 °C)[15a] and 2′-acetonylbenzanilide (**3**, X = H; R = C_6H_5; R′ = CH_3; mp 115–117 °C)[15b] by the correspondence of melting points and spectral data. The structural assignments for the others are based upon the similarity of the spectra and analogy.

According to the analogy with the Carroll reaction,[9] one plausible mechanism for this reaction consists of a [3,3]sigmatropic rearrangement of the ketene hemiacetal tautomer **4**, prototropic rearomatization, and decarboxylation of the resulting β-keto acid intermediate. Although the apparent absence of appreciable amounts of the para isomer of **3**[16] would seem inconsistent with a dissociative mechanism involving free radicals or ions, the possibility of radical or ion pair pathways cannot be discounted. It is pertinent to note that these reactions occur at much lower temperature (~110 °C as opposed to ≥ 150 °C) than is required to isomerize *N*-aryl-*N,O*-diacylhydroxylamines to *o*-acyloxyanilides[17] and that there are indications that the ortho alkylation step precedes decarboxylation (see below).

Hydrolysis of four of the *o*-(*N*-acylmino)aryl ketones (**3a**, **3c**, **3d**, and **3g**) with 10% hydrochloric acid in 95% ethanol for 15 min at reflux afforded the corresponding substituted indoles in 79–91% yield, a reaction which provides both additional support for the structures proposed and a practical application for the 1′-aza Claisen rearrangement. In this connection it is noteworthy that the uncyclized ketones (**3**) produced in this ortho alkylation reaction (**2** → **3**) may be isolated and, in principle, utilized for other purposes, in contrast to the spontaneous cyclization which occurs in the Fischer[18] and Gassman[4b,d] indole syntheses. The only alternative synthesis of *o*-(*N*-acylamino)aryl ketones (**3**) of which we are aware

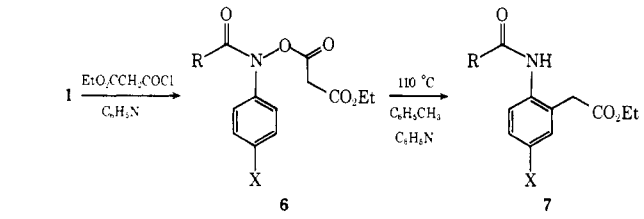
Scheme II



involves a photochemical rearrangement and hydrolysis of quinoline N-oxides.[15,19]

The following two variations upon this 1′-aza Claisen rearrangement serve to illustrate further the synthetic utility of the reaction. Mixed malonates (**6**)[13b] are readily prepared in 60–86% yield by acylation of the *N*-aryl-*N*-hydroxyamides with ethylmalonyl chloride[20] (1 equiv of pyridine, methylene chloride, 25 °C, 30 min). Thermolysis of these esters in toluene containing approximately 1 equiv of pyridine at reflux (1–7 h) gave rise to 55–80% yields of the *o*-(*N*-acylamino)aryl acetates **7**,[13b] two of which have been previously reported in the literature.[21–23] In this case, it proved possible to detect the formation of an intermediate by TLC analysis during the reaction which could be isolated in 11% yield and identified as the monoethylmalonic acid corresponding to **7d.** This finding indicates that decarboxylation occurs subsequent to the ortho alkylation step.

Scheme III

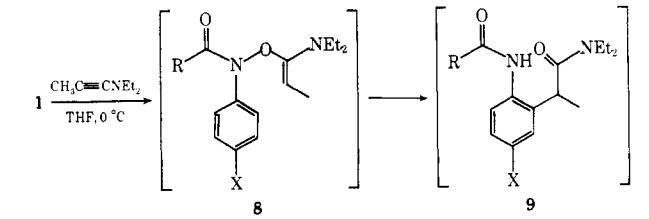


X	R	6 Yield (%)	7 Yield (%)
a, H	CH_3	77	60
b, H	C_6H_5	85	53
c, CH_3	CH_3	60	70
d, CH_3	C_6H_5	86	80
e, Cl	CH_3	76	70
f, CO_2CH_3	CH_3	83	55

A modification of the Claisen rearrangement involves the addition of allylic alcohols to ynamines and subsequent [3,3]sigmatropic rearrangement of the resulting allyloxy enamines to γ,δ-unsaturated amides.[24] We find that *N*-aryl-*N*-hydroxyamides react spontaneously with the ynamine, *N,N*-diethyl-1-amino-1-propyne, at 0 °C to form *o*-(*N*-acylamino)arylpropionamides **9** in yields ranging from 42 to 67%,[13b] presumably by way of adduct **8.** A minor side product consistently encountered in these reactions is the simple anilide (18–34%) arising from deoxygenation of the starting *N*-hydroxyamide.

Although the product yields in these 1′-aza-Claisen rearrangements are moderate (40–70% in most cases), the mild

Scheme IV



X	R	Yield (%)
H	CH_3	53
H	C_6H_5	67
CH_3	CH_3	44
CH_3	C_6H_5	42

conditions and the ready availability of a variety of substrates suggest that the reaction will provide a useful method for the introduction of functionalized alkyl groups onto aromatic rings.

Acknowledgment. We wish to thank the National Science Foundation for financial assistance.

References and Notes

(1) (a) D. S. Tarbell, *Org. React.*, **2**, 2 (1944); (b) S. J. Rhoads and N. R. Raulins, *ibid.*, **22**, 1 (1975), and references cited therein.

(2) (a) C. D. Hurd and W. W. Jenkins, *J. Org. Chem.*, **22**, 1418 (1957).(b) For other examples and references see M. Schmid, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **56**, 105 (1973); S. Jolidon and H.-J. Hansen, *Chimica*, **30**, 21, 23 (1976).

(3) The side reactions include cleavage of the allyl group, cyclization of the initially formed ortho allyl anilines to indolines and indoles, rearrangement without allylic transposition, and polymerization.[2]

(4) (a) P. G. Gassman and G. D. Gruetzmacher, *J. Am. Chem. Soc.*, **96**, 5487 (1974); (b) P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *ibid.*, **96**, 5495 (1974); (c) P. G. Gassman and T. J. van Bergen, *ibid.*, **96**, 5508 (1974); (d) P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, *ibid.*, **96**, 5512 (1974).

(5) This numbering system for heteroanalogues of [3,3]sigmatropic rearrangements has recently been proposed by F. Vögtle and E. Goldschmidt, *Chem. Ber.*, **109**, 1 (1976).

(6) (a) C. H. Hassall and A. E. Lippman, *J. Chem. Soc.*, 1059 (1953); (b) E. H. Huntress, T. E. Lesslie, and W. M. Hearon, *J. Am. Chem. Soc.*, **78**, 419 (1956); (c) A. Mooradian and P. E. Dupont, *Tetrahedron Lett.*, 2867 (1967), and references cited; See also I. I. Grandberg and V. I. Sorokin, *Russ. Chem. Rev.*, **43**, 115 (1974); *Usp. Khim.*, **43**, 266 (1974); (d) T. Sheradsky, *Tetrahedron Lett.*, 25 (1970); (e) T. Sheradsky and G. Salemnick, *J. Org. Chem.*, **36**, 1061 (1971); (f) I. C. Calder and P. J. Williams, *J. Chem. Soc., Chem. Commun.*, 891 (1972); (g) B. S. Thyagarajan, J. B. Hillard, K. V. Reddy, and K. C. Majumdar, *J. Heterocycl. Chem.*, **11**, 369 (1974); (h) Y. Makisumi and S. Takada, *Chem. Pharm. Bull.*, **24**, 770 (1976).

(7) For a recent review on heteroanalogues of the Cope reaction see E. Winterfeldt, *Fortschr. Chem. Forsch.*, **16**, 75 (1970).

(8) The 1-aza-1′-oxa [3,3]sigmatropic rearrangement of *N,O*-divinylhydroxylamine has been estimated to be exothermic by approximately 90 kcal/mol: J. B. Hendrickson, *Angew Chem., Int. Ed. Engl.*, **13**, 47 (1974).

(9) (a) M. F. Carroll, *J. Chem. Soc.*, 704, 1266 (1940); 507 (1941); (b) W. Kimel and A. C. Cope, *J. Am. Chem. Soc.*, **65**, 1992 (1943); (c) R. K. Hill and M. E. Synerholm, *J. Org. Chem.*, **33**, 925 (1968); (d) W. Hoffmann, H. Paseduch, H. Pommer, and W. Reif, *Justus Liebigs Ann. Chem.*, **747**, 60 (1971).

(10) (a) C. S. Marvel and O. Kamm, "Organic Syntheses," Col. Vol. I, Wiley, New York, N.Y., 1932, p 445; (b) B. Zech and H. Metzger, "Methoden der Organischen Chemie", Vol. 10, Part 1, E. Müller, Ed., George Thieme Verlag, Stuttgart, 1971, pp 1138–1150; (c) H. E. Baumgarten, A. Staklis, and E. M. Miller, *J. Org. Chem.*, **30**, 1203 (1965).

(11) *CAUTION:* Many *N*-arylhydroxylamines and *N*-arylhydroxamic acids with two or more aromatic rings are dangerous carcinogens: C. Heidelberger, *Annu. Rev. Biochem.*, **44**, 79 (1975); J. H. Weisburger and E. K. Weisburger, *Pharmacol. Rev.*, **25**, 1 (1973).

(12) V. K. Gupta and S. G. Tandon, *J. Indian Chem. Soc.*, **46**, 831 (1969).

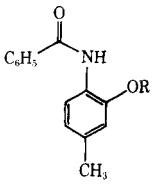
(13) (a) Satisfactory microanalyses were obtained for the crystalline acetoacetates **2d** (mp 90–91 °C) and **2h** (mp 83–85 °C). However, only three of the six liquid acetoacetates afforded satisfactory combustion analyses. (b) Acceptable microanalyses and appropriate infrared and NMR spectral data were secured for all of the other new compounds mentioned in this paper.

(14) The formation of *o*-(*N*-acetoacetyl)aryl ketones in 4–15% from the reaction of *N*-arylhydroxylamines with diketene has recently been reported: T. Kato, K. Tabei, and E. Kawashima, *Chem. Pharm. Bull.*, **24**, 1544 (1976).

(15) (a) O. Buchardt, J. Becher, and C. Lohse, *Acta Chem. Scand.*, **20**, 2467 (1966); (b) O. Buchardt, *ibid.*, **21**, 1841 (1967).

(16) Although a significant proportion of the starting material remains unaccounted for, it is nevertheless evident that no major, identifiable by-product was formed. Only very minor amounts of several substances were found in the chromatography fractions flanking those which contained the major product.

(17) L. Horner and H. Steppan, *Justus Liebigs Ann. Chem.*, **606**, 24 (1957).
(18) (a) B. Robinson, *Chem. Rev.*, **69**, 227 (1969); (b) R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, N.Y., 1970; (c) R. K. Brown, *Chem. Heterocycl. Compd.*, **25**, 227 (1972).
(19) For a recent review on the photochemistry of aromatic *N*-oxides see F. Bellamy and J. Streith, *Heterocycles*, **4**, 1391 (1976).
(20) D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1286 (1944).
(21) **7a**, mp 64–65 °C (lit.[22] mp 66 °C); **7b**, mp 80–82 °C, (lit.[22] 82 °C).
(22) P. W. Neber, *Chem. Ber.*, **55**, 826 (1922).
(23) In the absence of pyridine the reaction times are considerably longer (6–24 h) and the yields of rearranged esters are generally lower (33–55%). In the case of malonate **6d**, the major products from the uncatalyzed reaction are i and ii which arise via 1,3 oxygen migration.[17]



i (R = $COCH_2CO_2Et$, 50%)
ii (R = H, 35%)

(24) J. Ficini and C. Barbara, *Tetrahedron Lett.*, 6425 (1966).
(25) Fellowship from The National University of Malaysia, Kuala Lumpur, Malaysia; 1972–1976.

Robert M. Coates,* Ikram Md. Said[25]
Department of Chemistry, University of Illinois
Urbana, Illinois 61801
Received September 3, 1976

The Copper–Cadmium *N*-Methyltetraphenylporphyrin Electrophilic Substitution Reaction: Evidence for a Cis Attack

Sir:

The kinetics of the substitution of one metal ion in solution for another coordinated to a porphyrin molecule usually follow a rate law first order in replacing ion and first order in metalloporphyrin, with no evidence for rate retardation by the departing ion.[1] One common interpretation is that the activated complex has the form [M-P-M*], with the entering and leaving metal ions on opposite sides of the porphyrin plane. Such activated complex geometries in solutions are also suggested by solid state crystal structures of several dimetallic mononuclear porphyrins.[2] We report a kinetic study of copper replacing cadmium from the Cd(II) *N*-methyltetraphenylporphin (Cd-N-MeTPP$^+$) complex. The *N*-methyl group prohibits the copper from occupying a position on the distal side of the porphyrin plane from the cadmium ion.[3]

The kinetics were run at 25 °C in DMF at an ionic strength of 0.36 using $(Et)_4NBF_4$. Using the mole ratio method, cadmium forms only a 1:1 complex with the *N*-methylporphyrin,[4] even at concentrations of cadmium/porphyrin of 30:1. The $Cu(BF_4)_2$/Cd-N-MeTPP$^+$ reaction, followed spectrophotometrically, went clearly to Cu-N-MeTPP$^+$. Isosbestic points were found at 597, 575, and 435 nm, and no evidence for the demethylation[5] of Cu-N-MeTPP$^+$ into Cu-TPP was observed during the course of the reaction. Under pseudo-first-order conditions with at least a 20-fold excess of copper to porphyrin, the reaction was first order in porphyrin. As shown in Figure 1, the reaction was also first order in copper, and independent of added cadmium. The second-order rate constant was 25.7 $\pm$ 2.2 M^{-1} min^{-1}.

The lack of rate inhibition by added cadmium tends to rule out a mechanism whereby cadmium first dissociates before copper incorporation. Since the *N*-methyl group sterically blocks one face of the porphyrin toward metal ion coordination, the simplest interpretation is that cadmium and copper are on

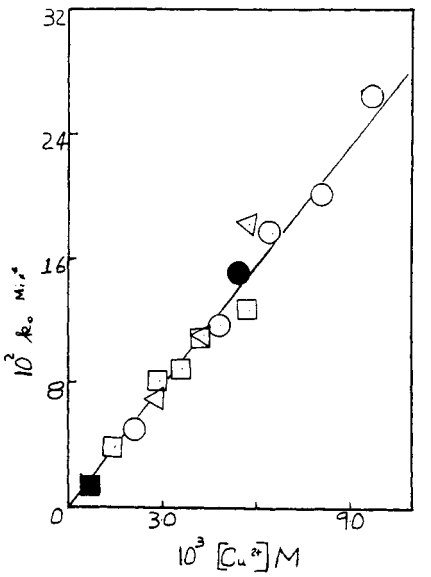
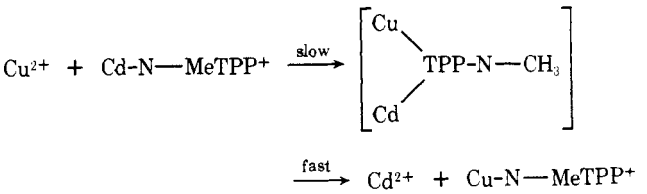


Figure 1. Plot of the observed rate constant k_{obsd} vs. $(Cu^{2+})_0$ for the Cu^{2+}/Cd-N-MeTPP$^+$ reaction at 25 °C in DMF at an ionic strength of 0.36 [$(Et)_4BF_4$]. The $Cd(BF_4)_2$ concentrations are: ■ = 7.2×10^{-4} M, ○ = 14.8×10^{-4} M, □ = 35.1×10^{-4} M, ● = 50×10^{-4} M, △ = 1.76×10^{-2} M.

the same side of the porphyrin plane during the substitution process.



The observations on *N*-methylporphyrins imply that either or both cis and trans geometries may occur during electrophilic substitution reactions of metaloporphyrins themselves.

Preliminary work indicates that, consistent with their basicities, the Cu/Cd-TPP reaction is orders of magnitude faster than that of Cu/Cd-N-MeTPP$^+$. In addition, the former reaction is also faster than the Cu/H_2-TPP process, where N-H bond breaking may be the rate limiting step.

Acknowledgment. We thank ERDA, Contract No. E-(40-1)-4047, for financial support.

References and Notes

(1) (a) C. Grant and P. Hambright, *J. Am. Chem. Soc.*, **91**, 4195 (1969); (b) S. Cheung, L. Dixon, F. Fleischer, D. Yeter, and M. Krishnamurthy, *Bioinorg. Chem.*, **2**, 281 (1973); (c) H. Baker, P. Hambright, and L. Ross, *Inorg. Chem.*, **12**, 2200 (1973).
(2) M. Tsutsui and G. Taylor in "Porphyrins and Metalloporphyrins", K. M. Smith, Ed., Elsevier, Amsterdam, 1975, Chapter 7, and references therein.
(3) Molecular steric models (see D. Lavallee and A. Gebala, *Inorg. Chem.*, **13**, 2004 (1974)) indicate that the *N*-methyl side of the porphyrin plane cannot coordinate metal ions. Crystal structures of two chlorocobalt(II)*N*-alkylporphyrins (O. P. Anderson and D. K. Lavallee, *J. Am. Chem. Soc.*, **98**, 4670 (1976), and D. E. Goldberg and K. M. Thomas, *ibid.*, **98**, 913 (1976)) show the metal to be on the opposite face of the porphyrin from the alkyl group. In addition, while tetraphenylporphyrin forms dimetallic mononuclear adducts with mercury(II), only monometallic mononuclear species are obtained with the corresponding *N*-methylporphyrin (H. F. Hudson and K. M. Smith, *Tetrahedron*, **32**, 597 (1976)).
(4) The molar extinction coefficients of Cd-N-MeTPP$^+$ under the reaction conditions are 1.24×10^4 at 615 nm, 8.93×10^3 at 650 nm, and 7.26×10^3 at 570 nm.
(5) C. Stinson and P. Hambright, *Inorg. Chem.*, **15**, 3181 (1976).

Charlie Stinson, Peter Hambright*
Chemistry Department, Howard University
Washington, D.C. 20059
Received December 10, 1976