mass calcd for $C_{29}H_{48}N_3O_5$ 518.3594, found 518.3599.

Acknowledgment. The spectroscopic and analytical staff at Abbott Laboratories is gratefully acknowledged. We are especially indebted to David Whittern for NOE studies.

Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra for compounds characterized by high-resolution mass spectroscopy, ^1H NMR spectra for imidazolidones **16–19** and **23**, and X-ray structural data for **11** including ORTEP representation (44 pages). Ordering information is given on any current masthead page.

New Syntheses and Reactions of Some Halogenated Porphyrins

Ohannes M. Minnetian, Ian K. Morris, Kevin M. Snow, and Kevin M. Smith*

Department of Chemistry, University of California, Davis, California 95616

Received April 12, 1989

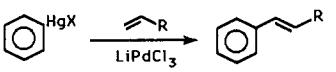
Efficient syntheses of 2,4-dibromo- and 2,4-diiododeuteroporphyrin IX have been carried out by treating zinc(II) 2,4-bis(chloromercurio)deuteroporphyrin IX dimethyl ester (**2**) with bromine or iodine. Unavoidable meso-chlorination occurs when **2** is treated with chlorine and with other free-radical chlorinating agents. Regioselective meso-chlorination and peripheral (β) bromination are shown to occur from brief treatment of copper(II) deuteroporphyrin IX or β-unsubstituted a,c-biladienes with the corresponding copper(II) halide in refluxing dimethylformamide. Protoporphyrin IX has been synthesized by vinylation of **2** via ethylene/$LiPdCl_3$ (35% yield), with vinyl bromide and Wilkinson's catalyst (63%), or from 2,4-dibromodeuteroporphyrin IX with ethenyltributylstannane/$(Ph_3P)_4Pd^0$ (85%).

Introduction

Mercurated aryl systems have been shown to undergo a myriad of transformations;[1] the most notable of these were discovered by Heck[2,3] and involve the transmetalation of an aryl mercurial with lithium chloropalladate in the presence of an olefin, efficiently generating the coupled aryl–olefin compound (Scheme I). We have recently developed a number of effective new procedures, utilizing these mercuration procedures, for the creation of new carbon–carbon bonds at the porphyrin periphery.[4,5] For example, zinc(II) deuteroporphyrin IX dimethyl ester (**1**) can be mercurated by simply warming the porphyrin in the presence of an excess of mercury(II) acetate in tetrahydrofuran. After forming the chloride salt, the mercurated deuteroporphyrin **2** is obtained in high yield. Attempts to form protoporphyrin IX dimethyl ester (**3**) by reaction of **2** with ethylene and $LiPdCl_3$ (in acetonitrile) gave ≤5% yields, but methyl acrylate added readily to the 2- and 4-positions, forming the bis-acrylate porphyrin **4** in 37% yield.[6–8] A variety of other biologically important porphyrins were also synthesized,[5] including deoxophylloerythroetioporphyrin, deoxophylloerythrin methyl ester,[9] and regioselectively deuteriated protohemes.[10]

Arylmercurials can ordinarily be halogenated with bromine and iodine in a facile manner.[11] Introduction of bromine and iodine has proven invaluable in determining the position of mercury within a new compound or for establishing the ratio of isomers of an inseparable mixture of arylmercurials. Aryl bromides and iodides are also extremely useful as synthetic intermediates leading to amines, carboxylic acids and esters, ethers, nitriles, and a host of organometallic compounds.[12] Chlorination on the other hand has received little attention and appears limited to only certain arylmercuric salts.

Scheme I



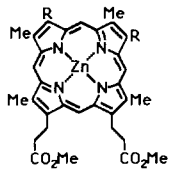
2,4-Brominated and -Iodinated Derivatives of Deuteroporphyrin IX. Using a procedure developed by Larock et al.,[13] we attempted to couple vinyl bromide with bis-mercurated deuteroporphyrin IX **2** via Wilkinson's catalyst in the hope of achieving a more efficient transformation of deuteroporphyrin IX into protoporphyrin IX. The coupling in DMSO/THF gave a very poor yield (≤10%) of protoporphyrin IX dimethyl ester (**3**), but marked improvements were observed (63%) when the more polar solvent, hexamethylphosphoramide, was used. Generalization of this coupling reaction by using 2,3-dibromopropene, surprisingly, resulted only in isolation of the dimethyl esters of 2- and 4-monobromodeuteroporphyrins (**5** and **6**, respectively), in 8% total yield, and 2,4-dibromodeuteroporphyrin (**7**) (20%). Treatment of bis-mercurated deuteroporphyrin IX **2** in tetrahydrofuran/chloroform with 2.2 equiv of bromine in chloroform gave a more acceptable 72% yield of 2,4-dibromodeuteroporphyrin IX dimethyl ester (**7**). Excess of bromine caused meso-bromination to occur (NMR).

(1) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer-Verlag: New York; 1985.
(2) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.
(3) Heck, R. F. *Organotransition Metal Chemistry*; Academic Press: New York, 1974.
(4) Smith, K. M.; Langry, K. C. *J. Chem. Soc., Chem. Commun.* **1980**, 217; **1981**, 283.
(5) Smith, K. M.; Langry, K. C. *J. Org. Chem.* **1983**, *48*, 500.
(6) Morsingh, F.; MacDonald, S. F. *J. Am. Chem. Soc.* **1960**, *82*, 4377.
(7) Jackson, A. H.; Kenner, G. W.; Wass, J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1475.
(8) Kenner, G. W.; McCombie, S. W.; Smith, K. M. *Liebigs Ann. Chem.* **1973**, 1329.
(9) Smith, K. M.; Langry, K. C.; Minnetian, O. M. *J. Org. Chem.* **1984**, *49*, 4602.
(10) Smith, K. M.; Miura, M.; Morris, I. K. *J. Org. Chem.* **1986**, *51*, 4660.
(11) Reference 1, pp 168–178.
(12) March, J. *Advanced Organic Chemistry*; 2nd ed.; McGraw-Hill: New York, 1977; pp 437, 563, 566, 596–598, 603–606, 656.
(13) Larock, R. C.; Narayanan, K.; Hershberger, S. S. *J. Org. Chem.* **1983**, *48*, 4377.

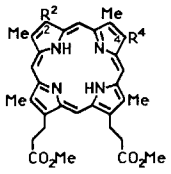
0022-3263/89/1954-5567$01.50/0

Larock et al.[14] have reported that Wilkinson's catalyst may also be used to couple methyl iodide to arylmercurials, and this appeared to provide a possible new access to 2,4-dimethyldeuteroporphyrin IX dimethyl ester (**8**), which has previously been synthesized by reduction of 2,4-diformyldeuteroporphyrin IX dimethyl ester (**9**)[15] or by total synthesis from monopyrroles,[16] and has found several applications in heme protein reconstitutions.[17] Application of this reaction to the bis-mercurated deuteroporphyrin dimethyl ester **2** resulted only in formation of the monoiodinated (**10** and **11**) and diiodinated (**12**) deuteroporphyrins, each in 7% yield. Treatment of **2** with iodine and sodium iodide afforded a 93% yield of diiododeuteroporphyrin IX dimethyl ester, **12**. We suspect that an electrophilic or free-radical mechanism is operative.[11]

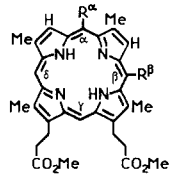
In order to investigate whether or not the nature of the mercury counterion in **2** was important in these 2,4-halogenation reactions, and whether the halogen introduced by replacement of the mercury was transferred intramolecularly or just from extraneous external halide, the four derivatives (**2**, **13**–**15**) were synthesized; **2** was obtained as described previously[5] by treatment of the zinc(II) bis(mercurio)porphyrin diacetate **16** with sodium chloride, and the others (**13**–**15**) by treatment of **16** with sodium fluoride, sodium bromide, or sodium iodide, respectively. The difluoro, dichloro, dibromo, and diiodo compounds (**13**, **2**, **14**, and **15**, respectively) all gave only the 2,4-diiododeuteroporphyrin IX dimethyl ester (**12**) when treated with iodine. Likewise, treatment with bromine gave the corresponding dibromodeuteroporphyrin **7**, clearly indicating that the newly introduced halogen atom is derived from the added oxidant. Use of chlorine resulted in a mixture of meso-chlorinated products with the chloromercurated derivative **2**.



1 R = H
2 R = HgCl
13 R = HgF
14 R = HgBr
15 R = HgI
16 R = HgOAc



3 $R^2 = R^4 = CH{=}CH_2$
4 $R^2 = R^4 = CH{=}CHCO_2Me$
5 $R^2 = Br$; $R^4 = H$
6 $R^2 = H$; $R^4 = Br$
7 $R^2 = R^4 = Br$
8 $R^2 = R^4 = Me$
9 $R^2 = R^4 = CHO$
10 $R^2 = I$; $R^4 = H$
11 $R^2 = H$; $R^4 = I$
12 $R^2 = R^4 = I$
17 $R^2 = R^4 = Cl$
18 $R^2 = R^4 = H$



19 $R^\alpha = Cl$; $R^\beta = H$
20 $R^\alpha = H$; $R^\beta = Cl$

Both 2,4-dibromo- and 2,4-diiododeuteroporphyrin IX dimehyl ester (**7** and **12**, respectively) have previously been prepared from deuteroporphyrin IX. Bromination was described as early as 1937 by Fischer[18] and more recently by Caughey et al.[19] and Gradyushko et al.[20] Fischer and Gradyushko et al. utilized bromine in various solvent systems while Caughey et al. used pyridinium bromide perbromide. As far as can be discerned, only Treibs[21] has reported the synthesis of diiododeuteroporphyrin IX **12**, the reaction being carried out with iodine in pyridine–chloroform.

Chlorination of Porphyrins. Every attempt to synthesize 2,4-dichlorodeuteroporphyrin IX dimethyl ester (**17**) from bis-mercurated deuteroporphyrin IX **2** failed in our hands. While arylmercurials have been shown to replace mercury with chlorine upon treatment of sulfuryl chloride,[22] free-radical chlorination of porphyrins with H_2O_2–HCl mixtures in tetrahydrofuran or acetic acid[23] or with sulfuryl chloride in chloroform[24] is known to lead to meso-tetrachlorinated porphyrins. Preparation of mono- or dichlorinated porphyrins in large quantities are difficult and is usually performed in carefully controlled two-phase reactions.[24]

When the bis-mercurated deuteroporphyrin IX **2** was treated at room temperature with an excess of sulfuryl chloride (20 equiv) in dimethylformamide, a more mobile yellow-brown compound having an optical spectrum devoid of a Soret band (the major absorption around 400 nm which is characteristic of the aromatic porphyrin macrocycle) or even longer wavelength satellite bands, was formed. Decreasing the quantity of sulfuryl chloride to 2.5 equiv, to avoid overchlorination of the porphyrin, followed by demetalation with TFA, afforded (TLC) two products in roughly equal quantities; a mobile band having a phyllo-type (meso-substituted; 25% yield) optical spectrum [λ_{max} 404 (Soret), 504 (band IV), 534 (III), 576 (II), 628 (I) nm; phyllo pattern intensity Soret > IV > II > III > I], and a less mobile band with an etio-type spectrum [λ_{max} 399 (Soret), 496 (band IV), 528 (III), 568 (II), 620 (I) nm; etio pattern intensity Soret > IV > III > II > I]. ^1H NMR analysis indicated that the etio band was deuteroporphyrin IX dimethyl ester (**18**). The absorption maxima of the meso-substituted compound are very similar to those reported by Bonnett et al.[24] for meso-monochlorooctaethylporphyrin [λ_{max} 406, 507, 540, 578, 628 nm]. Moreover, the ^1H NMR spectrum displayed six meso proton singlets (δ 10.01, 9.98, 9.93, 9.91, 9.88, 9.86 ppm), and two sets of "β"-proton singlets (δ 9.44, 9.42, and 9.04, 9.01 ppm). The NMR spectrum strongly suggested that the phyllo compound is an equal mixture of α- and β-chlorodeuteroporphyrins **19** and **20**, respectively, with three meso protons for each isomer between 10.01 and 9.86 ppm, two β-protons (adjacent to the meso-chloro position) at ~9.43 ppm, and the other two β-protons at ~9.03 ppm. Kulish et al.[25] have also reported that β-protons adjacent to a meso-chloro atom are shifted downfield by ~0.4 ppm. Low-resolution EI mass spectroscopy (*m/e*: (M^+) 572, (M^+

(14) Larock, R. C.; Hershberger, S. S. *J. Organomet. Chem.* **1982**, *225*, 31. Larock, R. C.; Bernhardt, J. C. *J. Org. Chem.* **1977**, *42*, 1680.
(15) Parker, S. E.; Brinigar, W. S. *Bioinorg. Chem.* **1976**, *5*, 325.
(16) Smith, K. M.; Kehres, L. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2329.
(17) La Mar, G. N.; Emerson, S. D.; Lecomte, J. T. J.; Pande, U.; Smith, K. M.; Craig, G. W.; Kehres, L. A. *J. Am. Chem. Soc.* **1986**, *108*, 5568.
(18) Fischer, H.; Orth, H. *Die Chemie des Pyrrols*; Akademische Verlag: Leipzig, 1973; Vol. II, Part 1, p 279.
(19) Caughey, W. S.; Alben, J. O.; Fujimoto, W. Y.; York, J. L. *J. Org. Chem.* **1966**, *31*, 2631.
(20) Gradyushko, A. T.; Kozhich, D. T.; Sokolev, K. N.; Tsvirko, M. P. *Opt. Spectrosc.* **1974**, *37*, 510.
(21) Treibs, A. *Naturwissenschaften* **1952**, *39*, 281.
(22) Jensen, F. R.; Gale, L. H.; Rogers, J. E. *J. Am. Chem. Soc.* **1968**, *90*, 5793. Schöllkopf, U.; Gerhart, F.; Reetz, M.; Frasnelli, H.; Schumacher, H. *Liebigs Ann. Chem.* **1968**, *716*, 204.
(23) Bonnett, R.; Gale, I. A. D.; Stephenson, G. F. *J. Chem. Soc. C.* **1966**, 1600.
(24) Voigt, H. Dissertation, Universitat Braunschweig, 1964.
(25) Kulish, M. A.; Mironov, A. F.; Rozynov, B. V.; Evstigneeva, R. P. *Zh. Obshch. Khim.* **1971**, *41*, 2743. Kulish, M. A.; Kozhich, D. T.; Mironov, A. F.; Evstigneeva, R. P. *Bioorg. Khim.* **1978**, *4*, 1237.

– Cl) 538) provided further evidence that the porphyrins **19** and **20** possess only one chlorine atom per macrocycle. This general type of chlorination is not without precedent. Johnson and Oldfield[26] reported that the attempted Vilsmeier formylation of etioporphyrin with phosphorous oxychloride and dimethylformamide did not give the expected formylporphyrin, but instead gave the meso-monochloro product in 16% yield.

We wished to discover if the presence of mercury on zinc(II) deuteroporphyrin was a necessary requirement for the reaction, or if the same isomers **19** and **20** could be prepared simply by treating zinc(II) deuteroporphyrin IX dimethyl ester (**1**) with 2.5 equiv of sulfuryl chloride in dimethylformamide. Following demetalation and chromatography, a more mobile meso-substituted [phyllo: λ_{max} 402, 502, 532, 574, 628 nm] band was isolated in 17% yield, followed by a 24% yield of deuteroporphyrin IX dimethyl ester (**18**). However, the proton NMR spectrum of the material from chlorination of zinc(II) deuteroporphyrin was far more complicated, showing all four meso-monochloro isomers [δ 10.09–9.82 ppm (cluster of at least nine overlapping singlets), a set of β-singlets at 9.45 and 9.44 ppm, and at least four overlapping β-singlets at 9.09, 9.06, 9.02, 8.97 ppm]. Thus, it appears that mercury does mediate the selective meso-chlorination of deuteroporphyrin IX.

Although copper(II) chloride and copper(II) bromide have been shown to chlorinate and brominate arylmercurials in dimethylformamide,[27] we were only able to produce complicated mixtures of meso-chlorinated porphyrins with copper(II) chloride. Treatment of zinc(II) bis-mercurated deuteroporphyrin IX **2** with a 30-fold excess of copper(II) chloride in dimethylformamide at room temperature gave one band upon alumina chromatography. While the optical spectrum indicated that only one chlorine is present on the macrocycle [phyllo: λ_{max} 410, 506, 538, 578, 632 nm] and it is at a meso position, ^{1}H NMR spectra were difficult to interpret. Using only 2.5 equiv of copper(II) chloride at room temperature provided no detectable change after 3 h, and no improvement was observed by heating the mixture at 80 °C. Addition of catalytic amounts of lithium palladium chloride[28] with 5 equiv of copper(II) chloride gave only meso-chlorinated porphyrin.

Repetition of the experiment with 5 equiv of copper(II) bromide in dimethylformamide revealed that meso-bromination also occurs. The optical spectrum of the isolated product(s) suggested them to be a mixture of meso- and non-meso-brominated 2,4-dibromodeuteroporphyrins. Satellite bands [phyllo: λ_{max} 506 (broad), 534, 578 (shoulder at 570), 624 nm] similar to those of 2,4-dibromodeuteroporphyin IX dimethyl ester (**7**) [etio: λ_{max} 502, 534, 570, 624 nm] were apparent. The ^{1}H NMR spectrum showed two different NH peaks at –4.2 and –4.6 ppm and three broad meso singlets at 9.85, 9.75, and 9.60 ppm, the β-protons being absent. Treatment with only 2.0 equiv of copper(II) bromide afforded no reaction after 30 min; however, after addition of another 4 equiv, a highly mobile compound was detected. Optical and ^{1}H NMR spectroscopy again suggested that the products were a mixture of meso- and non-meso-brominated 2,4-dibromodeuteroporphyrins.

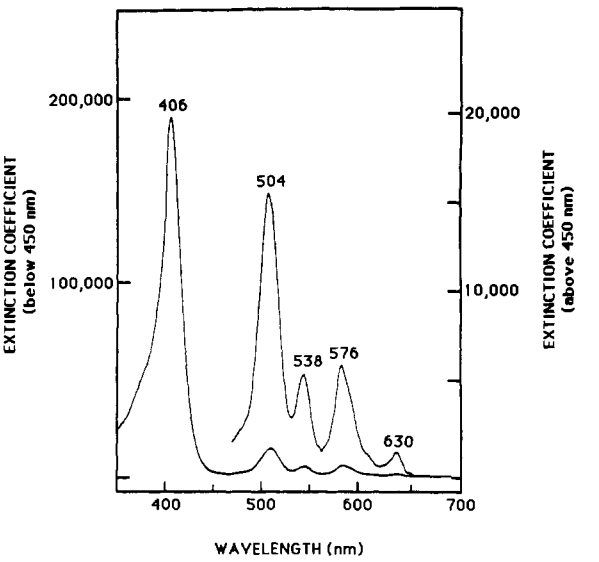


Figure 1. Optical spectrum, in dichloromethane, of meso-chloroporphyrin **23**.

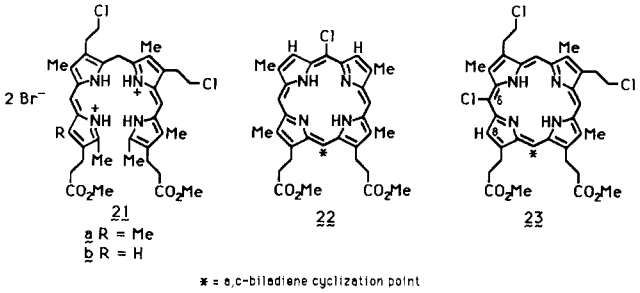
Chlorine gas dissolved in CCl_4/pyridine, as described by Salomon,[29] was also used as a chlorinating agent. A moderate excess of chlorine at –40 °C gave only a polar green compound with complete disappearance of the Soret absorption band and a new absorbance at 456 nm. A more promising result came from treatment of the porphyrin **2** with only 2 equiv of chlorine. However, NMR and spectrophotometry indicated a complex mixture of meso-substituted chlorinated products. *tert*-Butylhypochlorite in THF also gave polar green materials.

Santaniello and Ferraboschi[30] reported the replacement of mercury chloride on a regioselectively mercurated estradiol derivative with bromine, iodine, and chlorine. They found that treating the substrate with *N*-chlorosuccinimide (NCS) in dichloromethane resulted in a 90% conversion to the chloro estradiol. Treatment of mercurated deuteroporphyrin **2** with 2.5 equiv of NCS in refluxing dichloromethane afforded no product after 3 h. Switching to dimethylformamide with 5 equiv of NCS and heating at 50 °C gave only one nonpolar product which, upon demetalation with trifluoroacetic acid, had an optical spectrum devoid of satellite bands and a red-shifted Soret band at 426 nm. A similar result was observed when the quantity of NCS was cut back to 2.5 equiv. Being far more reactive than bromine and iodine, free-radical and electrophilic chlorinating agents are consequently less selective. In line with this general trend it should be mentioned that Bonnett and co-workers[31] have recently accomplished meso-fluorination of octaethylporphyrin using cesium fluoroxysulfate.

Meso-Chlorinated Porphyrins from Copper(II) Chloride Promoted *a,c*-Biladiene Cyclizations. Oxidative cyclizations of *a,c*-biladiene dihydrobromides (e.g. **21a**) can be carried out with either copper(II) chloride or copper(II) acetate. The copper(II) chloride mediated cyclization generally provides higher yields of porphyrin, but several workers[26,32] have realized that unexpected side products can be isolated. Copper(II) acetate, on the other hand, produces fewer side products, but the yield of porphyrin is frequently lower. During the course of an un-

(26) Johnson, A. W.; Oldfield, D. *J. Chem. Soc. C.* **1966**, 794.
(27) Artamkina, G. A.; Beletskaya, I. P.; Reutov, O. A. *J. Org. Chem. USSR* **1973**, *9*, 1795. Beletskaya, I. P.; Artamkina, G. A.; Reutov, O. A. *J. Organomet. Chem.* **1975**, *99*, 343. Razuvaev, G. A.; Fedotov, M. S. *J. Gen. Chem. USSR* **1952**, *22*, 547.
(28) Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.
(29) Salomon, R. G. *J. Org. Chem.* **1976**, *41*, 1529.
(30) Santaniello, E.; Ferraboschi, P. *J. Chem. Soc., Chem. Commun.* **1981**, 217.
(31) Andrews, L. E.; Bonnett, R.; Kozyrev, A. N.; Appelman, E. H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1735.
(32) Smith, K. M.; Minnetian, O. M. *J. Org. Chem.* **1985**, *50*, 2073.

related synthetic study, the *a,c*-biladiene **21b** was cyclized to porphyrin with copper(II) chloride. The first experiment followed standard procedure: the *a,c*-biladiene was refluxed for 5 min with 20 equiv of anhydrous copper(II) chloride in dimethylformamide. Aqueous workup, demetalation with H_2SO_4/CF_3CO_2H and chromatography afforded only one porphyrin. The optical spectrum (Figure 1) was of the phyllo-type [λ_{max} 406 nm (ϵ 197 000), 504 (15 500), 538 (5500), 576 (6000), 630 (1300)], normally indicative of a meso-substituted porphyrin. Moreover, the profile and absorption maxima were very close to those reported by Bonnett et al.[24] for meso-chlorooctaethylporphyrin [λ_{max} 406 nm (ϵ 161 000), 507 (14 800), 540 (5300), 578 (5600), 628 (1600)]. Electron impact mass spectroscopy confirmed the presence of a third chlorine atom on the porphyrin. ^1H NMR spectra clearly showed that only one porphyrin was formed from cyclization, this bearing three meso protons (9.83, 9.64, and 9.58 ppm) and one β-proton (9.32 ppm). Based on the general structural assignment, the chemical yield of the meso-chloroporphyrin was 15%.

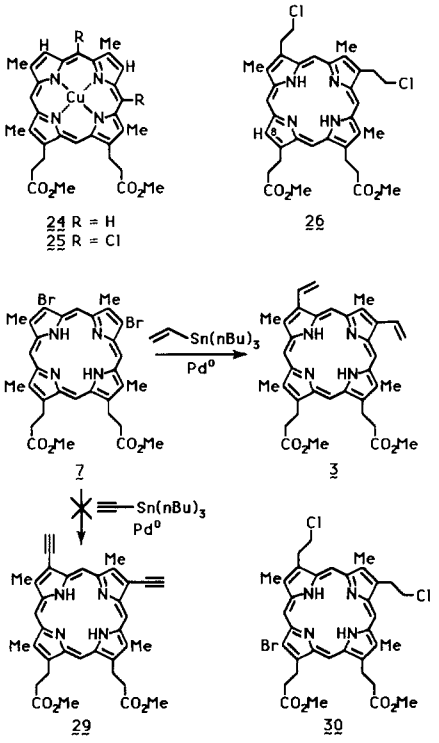


Having deduced that the porphyrin contained only one chlorine atom located at a meso position, it was necessary to establish which meso position was substituted. Kulish et al.[26] reported a low yield (6.7%) of meso-chloroporphyrin **22** from the copper(II) chloride cyclization of the corresponding di-unsubstituted *a,c*-biladiene, assigning the chlorine to the α-meso position. Having based this assignment on the comparison of the proton NMR chemical shift data of its proposed structure with that of the nonchlorinated analogue only by proton NMR, and because we suspected that the chlorine atom might be introduced via a terminal chloromethyl group during our *a,c*-biladiene cyclization (and therefore located at the locus of cyclization), we considered this assignment to require further investigation. To determine the precise location of chlorine on our porphyrin, a complete series of nuclear Overhauser enhancement (NOE) experiments were carried out. All results confirmed the structure as **23**, but the key observation was that irradiation of the 8-β-proton (9.32 ppm) gave an NOE observed at one of the α-methylene groups of a propionate side chain but *not* at a meso proton. Therefore, the chlorine must occupy the δ-meso position adjacent to the 8-β-free position (i.e. **23**).

The one feature common to our meso-chloroporphyrin **23** and the Kulish et al. porphyrin **22** is that they both have β-free positions adjacent to a meso carbon. The question which then arose was does chlorination precede or accompany cyclization or is the chlorine introduced after cyclization has taken place? To address this question, copper(II) deuteroporphyrin IX dimethyl ester (**24**) was refluxed with 20 equiv of copper(II) chloride for 5 min. The porphyrin was isolated as one band after demetalation and flash chromatography on silica gel. The phyllo-type optical spectrum (λ_{max} 412, 512, 544, 588, 644 nm) resembled that reported by Bonnett et al.[24] for α,γ-dichlorooctaethylporphyrin [λ_{max} 411 nm (ϵ 185 000), 514 (12 700), 548 (3200), 586 (4100), 637 (600)]. Although the ^1H NMR spectrum indicated the presence of a minor component, two meso protons (9.75 and 9.70 ppm) and two β-protons (9.45 and 9.35 ppm) could be clearly distinguished, and low-resolution mass spectroscopy confirmed the presence of two chlorine atoms. Based on the evidence given, the major isolated product is assigned the α,β-dichlorodeuteroporphyrin IX dimethyl ester structure (**25**), illustrating that chlorine can be introduced after cyclization occurs.

Room-temperature cyclization of *a,c*-biladienes with copper(II) chloride were also investigated. Following the usual protocol,[33] the *a,c*-biladiene **21b** was stirred for 2 h at room temperature in dimethylformamide with 20 equiv of copper(II) chloride. After demetalation of the resulting porphyrin with H_2SO_4/CF_3CO_2H, TLC indicated that two main products were present; one was a highly mobile red porphyrin, and the other a less mobile green porphyrin. The two bands were easily separated by alumina column chromatography, and the optical spectrum of the red band appeared to be a composite of phyllo- and etio-type profiles, suggesting the red band to be a mixture of porphyrins. Neither alumina nor silica gel TLC offered any hope of separating these compounds by normal chromatographic methods.

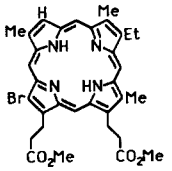
^1H NMR spectroscopy confirmed that the red band is a mixture of two porphyrins. Nine singlets are present in the downfield meso region and two sets of NH protons are upfield. The chemical shifts of the δ-meso-chloroporphyrin **23** were reproduced as a fingerprint in the NMR spectrum of the mixture, leaving us to conclude that the mixture is composed of δ-meso-chloroporphyrin **23** and the desired β-free-porphyrin **26** in a ratio of 2:3, respectively. The total yield of porphyrin in the red band was 30%.



Cyclization of the *a,c*-biladiene **21b** with copper(II) bromide in refluxing DMF [as with copper(II) chloride] gave only one product. The optical spectrum [λ_{max} 402 nm (rel intensity), 502 (1.0), 538 (0.98), 566 (0.69), 620 (0.36)] of the demetalated species deviated slightly from the etio spectrum of the desired compound (**26**) and is very similar

(33) Smith, K. M.; Minnetian, O. M. *J. Chem. Soc., Perkin Trans. 1* 1986, 277.

to the β-bromoporphyrin **31** reported by Mironov [λ_{max} = 401 nm, 500 (1.0), 535 (0.91), 567 (0.59), 621 (0.2)].[25] The β-proton is absent from the ^{1}H NMR spectrum, and the low-resolution mass spectrum showed the presence of one bromine atom on the porphyrin ring. The evidence clearly points to the assigned structure of the β-bromoporphyrin **30**, obtained in 10% yield.



31

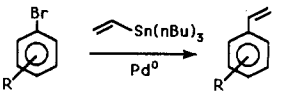
Again, to show that bromination can occur after cyclization, we treated copper(II) deuteroporphyrin IX dimethyl ester with 20 equiv of copper(II) bromide in refluxing dimethylformamide for 5 min and isolated 2,4-dibromodeuteroporphyrin IX dimethyl ester (**7**) in 61% yield. Thus, treatment with copper(II) chloride gave the meso-halogenated porphyrin exclusively whereas copper(II) bromide gave the β-halogenated porphyrin.

Oxidative cyclization of the *a,c*-biladiene **21b** with copper(II) acetate proceeded in the expected manner providing the desired porphyrin **26** in 15–20% yield. Cyclization with copper(II) fluoride was also investigated, but no aldehyde or meso-fluoro product was observed; the yield of porphyrin **26** was 15%.

Efficient Synthesis of Protoporphyrin IX from Deuteroporphyrin IX. Synthesis of vinylporphyrins from β-unsubstituted porphyrins such as deuteroporphyrin IX is normally a lengthy process. The most common route involves insertion of copper(II) or iron(III) followed by acetylation of the metalloporphyrin with acetic anhydride and tin(IV) chloride and removal of the metal. The resultant 2,4-diacetylporphyrin is reduced to the corresponding 2,4-bis(1-hydroxyethyl) derivative, which is dehydrated to give the desired divinylporphyrin.[34] Any methodology able to shorten this labor-intensive process would be a welcome improvement. Mercuration procedures described above yielded initially ≤5% yield of protoporphyrin IX dimethyl ester (**3**),[5] and this has now been improved to 34% using the same general methodology or to 63% by treating bis-mercurated deuteroporphyrin IX **2** and vinyl bromide with Wilkinson's catalyst in hexamethylphosphoramide (see the Experimental Section for both procedures).

Stille[35] has demonstrated that the cross-coupling of organotin reagents with various electrophiles in the presence of catalytic quantities of palladium is a highly efficient method for the synthesis of a wide variety of organic compounds. The reaction proceeds under neutral conditions, is generally not particularly sensitive to water or oxygen, and possesses a high degree of selectivity with regard to the transfer of specific organic groups from unsymmetrical tin reagents. Stille[36] recently reported the preparation of highly functionalized styrene derivatives (**28**) by the palladium-catalyzed coupling of aryl bromides (**27**) with commercially available tri-*n*-butylethenylstannane (Scheme II). Stille found that conversion to the styrene derivative was dependent on the nature of the aryl

Scheme II



27 28

bromide, viz. electron-withdrawing systems reacted rapidly (1–4 h), whereas electron-rich systems require additional catalyst and reaction times for complete conversion to the olefin in yields ranging from 62 to 85%. We felt that applying Stille's methodology to 2,4-dibromodeuteroporphyrin IX dimethyl ester (**7**), prepared as described above from 2,4-bis(chloromercurio)deuteroporphyrin IX dimethyl ester (**2**), would provide an excellent means for preparation of protoporphyrin IX dimethyl ester (**3**). 2,4-Dibromodeuteroporphyrin IX dimethyl ester (**7**) was refluxed with tri-*n*-butylethenylstannane and tetrakis(triphenylphosphine)palladium(0) in toluene. Within 1 h, the optical spectrum of the starting material [λ_{max} 402, 502, 534, 570, 624 nm] had changed to resemble that of protoporphyrin IX [λ_{max} 404, 508, 542, 574, 630 nm] and after another 1 h was identical with that of protoporphyrin IX [λ_{max} 404, 506, 540, 576, 630 nm]; no change was observed after a third hour. Following aqueous workup and chromatography on alumina an 85% yield of protoporphyrin IX dimethyl ester (**3**) was obtained. No attempt was made to optimize the conversion.

We envision that this methodology will provide an expedient means of preparing deuterated, carbon-13 labeled, carbon-14 labeled, and vinyl-fluorinated derivatives of protoporphyrin IX. An attempt was also made to prepare 2,4-diethynyldeuteroporphyrin IX dimethyl ester (**29**) by treating 2,4-dibromodeuteroporphyrin IX dimethyl ester (**7**) with tri-*n*-butylethynylstannane and tetrakis(triphenylphosphine)palladium(0) in toluene, but this method failed to give any characterizable products. This finding was substantiated by Stille and co-workers[37] who were able only to prepare 10% of the required product in a coupling of tri-*n*-butylethynylstannane with 4-bromophenyl acetate.

Conclusions

We have shown that porphyrins can be halogenated using a variety of methods and halogenating agents. Our studies show that the site of halogenation is determined by the size and reactivity of the halogen in question, with meso-chlorination being favored by the smaller more reactive chlorine, and β-halogenation by the larger less reactive halogens (bromine, iodine). Bromine, being of intermediate size amongst the halogens, shows a propensity for β-bromination, but bromine will meso-brominate porphyrins if an excess is used. Meso-fluorination would be expected from fluorine. No meso-iodination was observed in our studies.

Copper(II) chloride and bromide provide a controlled method for chlorination and bromination of peripherally unsubstituted porphyrins. This control is not seen with mercurated porphyrins, but anomalous multihalogenation of certain arylmercurials is not without precedent.[38] While copper(II) chloride ordinarily provides efficient conversion of most *a,c*-biladienes to porphyrins, it is now clear that copper(II) chloride and bromide should be avoided as oxidizing agents for cyclization of β-unsubstituted *a,c*-biladienes.

(34) E.g.: Smith, K. M.; Fujinari, E. M.; Langry, K. C.; Parish, D. W.; Tabba, H. D. *J. Am. Chem. Soc.* **1983**, *105*, 6638.
(35) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.
(36) McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 422.
(37) See note 9 in ref 36.
(38) Reference 1, page 176. Nefedov, V. A. *Zh. Obshch. Khim.* **1969**, *39*, 665; *J. Gen. Chem. USSR* **1969**, *39*, 630.

With methods now available for efficient synthesis of 2,4-dibromo- and 2,4-diiododeuteroporphyrin IX, effort is presently being directed in our laboratories toward exploitation of useful transformations common to aryl halides, but with specific emphasis on labeled derivatives of protoporphyrin IX.

Experimental Section

General. Melting points are uncorrected and were measured on a Thomas/Bristoline hot stage apparatus. Electronic absorption spectra were measured on a Hewlett-Packard 8450A spectrophotometer using solutions in dichloromethane. Mass spectra were obtained on a VG Analytical ZAB-HS instrument (70 eV, EI, mass reference perfluorokerosene). Proton NMR spectra (^{1}H NMR) were obtained in $CDCl_3$ either at 90 MHz (Varian EM390) or at 300 MHz (GE QE300) with chemical shifts reported in ppm relative to internal standards of tetramethylsilane (0 ppm, 90 MHz spectra) or chloroform (7.258 ppm, 300 MHz). NOE studies were carried out at 360 MHz (Nicolet NT360 spectrometer) at 30 °C in $CDCl_3$ solution. Elemental analyses were performed at the Microchemical Analysis Laboratory, University of California, Berkeley. Reactions were usually carried out in the dark (aluminum foil) under nitrogen and were monitored using thin-layer chromatography, TLC) on commercially available Merck silica sheets. Gravity and flash column chromatography employed either Merck neutral alumina (70–230 mesh) or Merck silica gel 60. The alumina was usually deactivated with 6% water (Brockmann Grade III) before use.

Zinc(II) 2,4-Bis(chloromercurio)deuteroporphyrin IX Dimethyl Ester (2). The title compound was prepared in yields varying between 85 and 105% by the method previously described in detail.[4,5] As previously, attempts to obtain a satisfactory elemental analysis were unsuccessful.

Zinc(II) 2,4-Bis(fluoromercurio)deuteroporphyrin IX Dimethyl Ester (13). Zinc(II) deuteroporphyrin IX dimethyl ester (1) (220 mg, 0.365 mmol) in tetrahydrofuran (30 mL) was treated with mercury(II) acetate (373 mg, 3.2 equiv) in methanol (5 mL) containing acetic anhydride (2 mL) for 5 h at 65 °C with stirring. After this time, TLC showed all material to have been retained on the base line. The mixture was cooled to room temperature, and then a saturated solution of sodium fluoride in water (25 mL) was added. The mixture was stirred for 15 min and extracted with chloroform (2 × 100 mL), which was then washed several times with water. Evaporation of the solvent gave a deep purple solid, which was triturated with 95% ethanol to give iridescent crystals (402 mg, 106%) presumably contaminated with a little trimercurated material.[5,9] The material did not melt but decomposed above 300 °C. NMR spectroscopy gave only very broad lines. λ_{max} (relative intensity, CH_2Cl_2): 410 (14.2), 540 (1.1), 576 nm (1.0).

Zinc(II) 2,4-Bis(bromomercurio)deuteroporphyrin IX Dimethyl Ester (14). This compound was prepared from zinc(II) deuteroporphyrin IX dimethyl ester (1) (220 mg) in a manner similar to compound **13**, except that a saturated solution of sodium bromide was used in place of the sodium fluoride. The title porphyrin was obtained as bright purple microprisms (342 mg, 81%), mp 276–277 °C. NMR spectroscopy gave only very broad lines. λ_{max} (relative intensity, CH_2Cl_2): 386 (8.8), 410 (12.9), 540 (1.0), 578 (nm) (1.0).

Zinc(II) 2,4-Bis(iodomercurio)deuteroporphyrin IX Dimethyl Ester (15). This compound was also prepared from zinc(II) deuteroporphyrin IX dimethyl ester (1) (220 mg) as above, except that a saturated solution of sodium iodide was used in place of the sodium fluoride. The title porphyrin was obtained in 69% yield (315 mg), mp 263–265 °C. NMR spectroscopy gave only very broad lines. λ_{max} (relative intensity, CH_2Cl_2): 408 (14.8), 538 (1.1), 576 nm (1.0).

Protoporphyrin IX Dimethyl Ester (3). (A) Using Ethylene and Palladium Exchange on 2. The bis-mercurated zinc(II) porphyrin **2** (50 mg) in tetrahydrofuran (3 mL) was treated with $LiPdCl_3$ [prepared from $PdCl_2$ (25 mg) and LiCl (10 mg) in acetonitrile (3 mL)] and degassed by bubbling with nitrogen. The mixture was the placed under 30 psi of ethylene (cylinder), and the mixture was stirred vigorously at room temperature for 12 h. The mixture was then filtered through a bed of Celite, which was washed well with dichloromethane/tetrahydrofuran, and the solvents were evaporated to give a residue. This was taken up in dichloromethane (50 mL) and washed several times with 3 N HCl (to remove the chelated zinc) and then water, dried over Na_2SO_4, and evaporated to give a red residue, which was quickly filtered through a column of alumina (Brockmann Grade III), eluting with dichloromethane. Evaporation of the red eluates gave a residue, which was crystallized from dichloromethane/hexane to give the title porphyrin (9.5 mg, 34%), mp 224–225 °C (lit.[39] mp 224–226 °C). The proton NMR spectrum was identical with that obtained from method C (vide infra), and the product was shown to be identical with an authentic sample of protoporphyrin IX dimethyl ester obtained from hemin.[40]

(B) Using Wilkinson's Catalyst, Vinyl Bromide, and the Bis(mercurio)porphyrin 2. The mercurated porphyrin **2** (80 mg) in hexamethylphosphoramide (10 mL) containing Wilkinson's catalyst (20 mg) and lithium chloride (96 mg) was cooled to 0 °C and then treated with vinyl bromide (1.1 mL, 200 equiv). The mixture was stirred for 6 h at 60 °C in a sealed tube, diluted with dichloromethane (20 mL), and washed six times with 10% aqueous HCl, once again with 1 N sodium hydroxide, and finally twice with water. After evaporation of the solvent, the red residue was chromatographed on a silica gel column, eluting with 2.5% methanol in dichloromethane; evaporation of the solvent containing the major red band gave a residue which was recrystallized from dichloromethane/hexane to give **3** (22.7 mg; 63%) as deep purple needles, mp 224–225 °C (lit.[39] mp 224–226 °C). The proton NMR spectrum, though concentration-dependent, was identical with that obtained from methods A and C, and the material was identical in all respects with an authentic sample of protoporphyrin IX dimethyl ester (**3**).

(C) Using Tri-*n*-butylethenylstannane. Tri-*n*-butylethenylstannane (Aldrich) (20 μL, 22 mg, 3.8 equiv) was added to a stirring solution of 2,4-dibromodeuteroporphyrin IX dimethyl ester (**7**) (13 mg, 1 equiv), tetrakis(triphenylphosphine)palladium(0) (Aldrich) (12.2 mg, 0.6 equiv), and butylated hydroxytoluene (BHT) (few small grains) in dry toluene (8.0 mL) under an atmosphere of nitrogen. The optical spectrum of the reaction mixture after heating the solution at reflux for 1 h was almost identical with that of the desired product. After an additional 2 h of reflux, the solution was cooled to room temperature. Adhering to Stille's[37] procedure, pyridine (0.5 mL) was added to the solution followed by the addition of 1.0 mL of a solution of HF/pyridine and tetrahydrofuran [prepared by adding 0.4 mL of a 70/30 HF/pyridine solution (Aldrich) to 10.0 mL of dry tetrahydrofuran and 1.5 mL of dry pyridine]. The resulting mixture was stirred overnight under nitrogen at ambient temperature. The solution then was diluted with dichloromethane and washed with water, three times with 2 N HCl, with water again, and then with brine. The organic layer was dried over Na_2SO_4 before the solvent was stripped off on a rotovapor. The residue was chromatographed on a 0.5 × 30 cm alumina (Brockmann Grade III) column, eluting with dichloromethane. The major fraction was collected, and after evaporation to dryness it was crystallized from dichloromethane/petroleum ether to afford protoporphyrin IX dimethyl ester as red needles (9.2 mg, 85%), mp 223–225 °C (lit.[39] mp 224–226 °C). ^{1}H NMR ($CDCl_3$): δ −3.72 (s, 2 H, NH), 3.27 (t, 4 H, CH_2CH_2CO), 3.61, 3.62 (each s, 3 H, ring CH_3), 3.66 (s, 6 H, ring CH_3), 3.69, 3.70 (each s, 3 H, OCH_3), 4.39 (t, 4 H, CH_2CH_2CO), 6.19 (d, $J_{\alpha\beta}$ = 11.1 Hz, 2 H, cis β-vinyl CH), 6.37 (d, $J_{\alpha\beta}$ = 17.7 Hz, 2 H, trans β-vinyl CH), 8.28 (m, 2 H, α-vinyl CH), 10.02, 10.06, 10.15, 10.20 (each s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} 404, 506, 540, 576, 630. The material was identical by mixture melting point, proton NMR, and spectrophotometry with an authentic sample of protoporphyrin IX dimethyl ester (**3**).

2,4-Dibromodeuteroporphyrin IX Dimethyl Ester (7). (A) Using Wilkinson's Catalyst, 2,3-Dibromopropane, and the Bis-Mercury(II) Porphyrin 2. Bis-mercurated zinc(II) deuteroporphyrin IX dimethyl ester **2** (80 mg), lithium chloride (96 mg), and Wilkinson's catalyst (50 mg) in hexamethylphosphoramide (3 mL) were treated with 2,3-dibromopropene (4 mL), and

(39) Grinstein, M. *J. Biol. Chem.* **1947**, *167*, 515.
(40) Fuhrhop, J.-H.; Smith, K. M. In *Porphyrins and Metalloporphyrins*; Smith, K. M., Ed.; Elsevier: Amsterdam, 1975; p 771.

the mixture was heated at 60 °C for 18 h. After cooling to room temperature the solution was diluted with chloroform (50 mL) and washed with water, five times with 1 N sodium hydroxide, three times with 10% aqueous HCl, and finally with water again. The organic layer was dried over Na_2SO_4 and evaporated to give a red residue. Chromatography on silica gel preparative TLC plates, eluting with 1.5% methanol in dichloromethane, gave two bands. The slower running band, after extraction from the silica gel and crystallization from dichloromethane/hexane, gave the title compound (10.4 mg, 20%), mp 270–272 °C (lit.[41] mp 274–277 °C). ^1H NMR ($CDCl_3$): δ −5.03 (s, 2 H, NH), 3.20 (m, 4 H, CH_2CH_2CO), 3.48, 3.56 (each s, 3 H, ring CH_3), 3.49 (s, 6 H, ring CH_3), 3.64, 3.65 (each s, 3 H, OCH_3), 4.32 (t, 4 H, CH_2CH_2CO), 9.59, 9.63, 9.75, 9.80 (each s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} 400 nm (ϵ 170000), 500 (14000), 534 (9600), 570 (6600), 624 (3900). LR mass spectrum: m/e 699 (30), 697 (21), 695 (22), 619 (100), 617 (98), 559 (23). Anal. Calcd for $C_{32}H_{32}Br_2N_4O_4$: C, 55.19; H, 4.63; N, 8.05. Found: C, 55.11; H, 4.67; N, 7.83. The faster running band afforded 17.3 mg (50%) of deuteroporphyrin IX dimethyl ester (**18**). When fewer equivalents of 2,3-dibromopropane (1.3 mL) were used, along with shorter reaction times (6 h at 70 °C), monobrominated products (**5**, **6**) were isolated, but these were not further investigated.

(B) Using Bromine and Bis-Bromomercurated Porphyrin 14. The zinc(II) bis(bromomercurio)porphyrin **14** (269 mg) in tetrahydrofuran (10 mL) and dichloromethane (30 mL) containing aluminum trichloride (75 mg, 1.5 mol equiv) was treated rapidly but dropwise with bromine (75 mg, ca. 2.2 equiv) in dichloromethane (10 mL). After 15 min water was added, and the mixture was extracted with dichloromethane, which was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was taken up in trifluoroacetic acid, set aside for 5 min, and then diluted with chloroform and water. Several further washings of the organic phase with water, followed by drying (Na_2SO_4) and evaporation to dryness, gave a red-brown residue, which was chromatographed on alumina (Brockmann Grade III), eluting with dichloromethane. Evaporation of the red eluates gave a residue, which was crystallized from dichloromethane/hexane to afford the title porphyrin (105 mg, 65%), identical in all respects with the material described above. When the reaction was repeated with the same zinc(II) bis(bromomercurio)porphyrin (**14**, 158 mg) and in the absence of aluminum trichloride, a slightly improved yield of the title porphyrin (68 mg, 72%) was obtained. With the bis(iodomercurio)porphyrin **15**, a slightly reduced yield (42%) of the title compound was isolated. Use of larger excesses of bromine resulted in isolation (column chromatography) of small amounts of a (presumably meso-brominated) byproduct possessing a phyllo-type electronic absorption spectrum [λ_{max} (relative intensity, CH_2Cl_2), 510 nm (14.7), 544 (4.0), 582 (5.3), 632 (1.0)].

(C) Using Copper(II) Bromide and Copper(II) Deuteroporphyrin IX Dimethyl Ester. Copper(II) bromide (750 mg) was dissolved in dry dimethylformamide (20 mL), and the solution was heated to reflux. To this refluxing mixture was added copper(II) deuteroporphyrin dimethyl ester (**24**) (78 mg), and the resultant mixture was stirred at reflux for 5 min. The solution was cooled briefly before pouring onto ice water. Dichloromethane was added, and the organic phase was washed once with 2 N HCl, twice with water, and once with brine before being dried over Na_2SO_4 and evaporated to dryness. The residue was taken up in trifluoroacetic acid (10 mL), and to it was added concentrated H_2SO_4 (2 mL). After 45 min the acidic solution was poured onto ice water, neutralized with Na_2CO_3, and washed twice with water and once with brine. The solution was dried over Na_2SO_4 before evaporation to dryness. The residue was chromatographed on a 1.5 × 40 cm flash silica gel column, eluting with 1% methanol in dichloromethane, and the product was collected as the major band. The eluates were evaporated to give a residue, which was crystallized from dichloromethane/petroleum ether to give 55 mg (61%), mp 281–284 °C (lit.[41] mp 274–277 °C). This material was identical, spectroscopically and by TLC, with the samples prepared above.

2,4-Diiododeuteroporphyrin IX Dimethyl Ester (12). The zinc(II) bis-bromomercurated porphyrin **14** (20 mg) in tetrahydrofuran (2 mL) and chloroform (5 mL) was stirred at room temperature while iodine (10.3 mg, 2.1 equiv) in chloroform (10 mL) was added rapidly but dropwise. After 15 min the mixture was diluted with water (40 mL) and extracted with chloroform (2 × 20 mL). The organic layer was washed with water, dried over Na_2SO_4, and then evaporated to dryness to give a red residue. Trifluoroacetic acid (1 mL) was added, and after 5 min the mixture was diluted with chloroform (50 mL) and washed several times with water to give a red-brown residue after evaporation of the solvent. Chromatography on silica gel, eluting with 3% methanol in dichloromethane, gave the title compound after evaporation of the eluates and crystallization from dichloromethane/hexane, in 96% yield (13.1 mg), mp 258–259 °C. ^1H NMR: ($CDCl_3$) δ −4.61 (br s, 2 H, NH), 3.21 (t, 4 H, CH_2CH_2CO), 3.53, 3.58 (each s, 3 H, ring CH_3), 3.60, 3.65 (each s, 6 H, ring CH_3 and OCH_3), 4.35 (t, 4 H, CH_2CH_2CO), 9.74, 9.76, 9.83, 9.86 (each s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} 402 nm (ϵ 164000), 502 (13800), 536 (10400), 570 (6600), 626 (4300). LR mass spectrum: m/e 791 (100), 665 (90), 593 (20). Anal. Calcd for $C_{32}H_{32}I_2N_4O_4$: C, 48.63; H, 4.08; N, 7.09. Found: C, 48.50; H, 3.94; N, 6.93. In an analogous manner, the mercurated analogues **2**, **13**, **15**, when treated with iodine, gave the title compound in 29, 46, and 93% yields, respectively. Physical and spectroscopic properties of these materials were identical with those described above.

2,4-Bis(2-chloroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5-trimethylporphyrin (26). Method A. The title porphyrin was prepared, in yields ranging from 15 to 20%, by the oxidative cyclization of the β-unsubstituted *a,c*-biladiene **21b** with copper(II) acetate by the standard cyclization method.[42] Use of copper(II) fluoride gave a 15% yield of **26**. **Method B.** Oxidation of the *a,c*-biladiene **21b** with copper(II) chloride and demetalation of the resulting copper(II) porphyrin with CF_3CO_2H/H_2SO_4 (85:15) was carried out by standard methods.[42] The use of copper(II) chloride resulted in formation of a mixture of meso-chloroporphyrin **23** and the desired β-unsubstituted porphyrin **26**. This mixture was converted into **26** by catalytic hydrogenation to the porphyrinogen, followed by reoxidation to porphyrin with 2,3-dichloro-5,6-dicyanobenzoquinone. Full details of these experiments have been published elsewhere.[43]

8-Bromo-2,4-bis(2-chloroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5-trimethylporphyrin (30). The title porphyrin was prepared in 10% yield from the *a,c*-biladiene **21b** by the standard method[42] using copper(II) bromide in boiling dimethylformamide, mp 202–205 °C. ^1H NMR ($CDCl_3$): δ −4.13 (s, 2 H, NH), 3.28 (m, 4 H, CH_2CH_2CO), 3.55, 3.62, 3.64 (each s, 3 H, ring CH_3), 3.66, 3.67 (each s, 3 H, OCH_3), 4.28–4.44 (m, 12 H, 2 CH_2CH_2CO, 2 CH_2CH_2Cl, 2 CH_2CH_2Cl), 9.86, 9.91, 10.07, 10.16 (each s, 1 H, meso H). UV–vis (CH_2Cl_2): λ_{max} 402 nm (ϵ 181000), 502 (12700), 538 (12900), 566 (7470), 620 (1910). LR mass spectrum: m/e (%) 732 (15), 731 (24), 730 (58), 729 (30), 728 (100), 727 (26), 726 (63). HR mass spectrum: calcd for $C_{35}H_{37}BrCl_2N_4O_4$ 726.1375, found 726.1382.

δ-Chloro-2,4-bis(2-chloroethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5-trimethylporphyrin (23). This porphyrin was prepared using copper(II) chloride by the same method as previously described for the synthesis of β-bromoporphyrin **30** in 15% yield, mp 204–208 °C. ^1H NMR ($CDCl_3$): δ 3.22 (t, 2 H, CH_2CH_2CO), 3.42 (t, 2 H, CH_2CH_2CO), 3.45 (s, 3 H, ring CH_3), 3.53 (s, 6 H, ring CH_3), 3.67, 3.82 (each s, 3 H, OCH_3), 4.08–4.38 (m, 12 H, 2 CH_2CH_2CO, 2 CH_2CH_2Cl, 2 CH_2CH_2Cl), 9.32, 9.58, 9.64, 9.83 (each s, 1 H, β-H and 3 meso *H*). UV–vis (CH_2Cl_2): λ_{max} 406 nm (ϵ 197000), 504 (15500), 538 (5530), 576 (6010), 630 (1290). LR mass spectrum: m/e (%), 687 (8), 686 (31), 685 (30), 684 (100), 683 (34), 682 (99), 651 (14), 650 (32), 649 (26), 648 (54), 647 (9). HR mass spectrum: calcd for $C_{35}H_{37}Cl_3N_4O_4$ 682.1880, found, 682.1869.

α,β-Dichloro-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin (25). The title compound was prepared in 66% yield by treatment of copper(II) deuteroporphyrin IX dimethyl ester (**24**) with copper(II) chloride (20 equiv) following method C previously described for the porphyrin **7**, mp 205–209 °C. ^1H NMR ($CDCl_3$): δ −3.75 (s, 2 H, NH), 3.20 (m, 4 H,

(41) Fisher, H.; Orth, H. *Die Chemie des Pyrrols*; Akademische Verlag: Leipzig, 1937; Vol. II, part 1, p 257.

(42) Smith, K. M.; Craig, G. W. *J. Org. Chem.* **1983**, *48*, 4302.

(43) Snow, K. M.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 3270.

CH_2CH_2CO), 3.30–3.70 (m, 18 H, 4 ring CH_3 and 2 OCH_3), 4.30 (m, 4 H, CH_2CH_2CO), 9.35, 9.45 (each s, 1 H, 2,4-H), 9.70, 9.75 (each s, 1 H, meso H). UV-vis (CH_2Cl_2): λ_{max} 412 nm (ϵ 192000), 512 (13890), 544 (3930), 588 (3800), 654 (760). LR mass spectrum: *m/e* 606 (100), 572 (42), 533 (14), 499 (13). HR mass spectrum: calcd for $C_{32}H_{32}Cl_2N_4O_4$ 606.1801, found 606.1800.

Acknowledgment. This research was supported by grants from the National Science Foundation (CHE-86-19034) and the National Institutes of Health (HL 22252).

Displacements at the Nitrogen of Lithioalkoxylamides by Organometallic Reagents

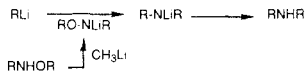
Peter Beak* and Gordon W. Selling

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Received March 20, 1989

The conversions of *N*-(*o*-bromobenzyl)methoxylamine to *N*-acetylbenzoazetine (**1**), of *N*-[3-(*o*-bromophenyl)-*n*-propyl]methoxylamine to *N*-acetyltetrahydroquinoline (**2**), and of *N*-[4-(*o*-bromophenyl)-*n*-butyl]-methoxylamine to *N*-acetylbenzazapine (**3**) illustrate the use of this displacement reaction to form nitrogen-containing rings in an exocyclic reaction mode. An X-ray structural determination is reported for **1**. The formations of anilides by amination of aromatic organolithium reagents with lithium methoxylamide is also reported. Lithium reagents are found to be more effective than Grignard, copper, or zinc reagents in these displacements, and the yields decrease as the size of the substituents around nitrogen increases. The endocyclic restriction test is used to show that this displacement on nitrogen cannot occur within the endocyclic confines of a seven-membered ring. A S_N2 reaction pathway in a lithium complex is considered to be supported by these results.

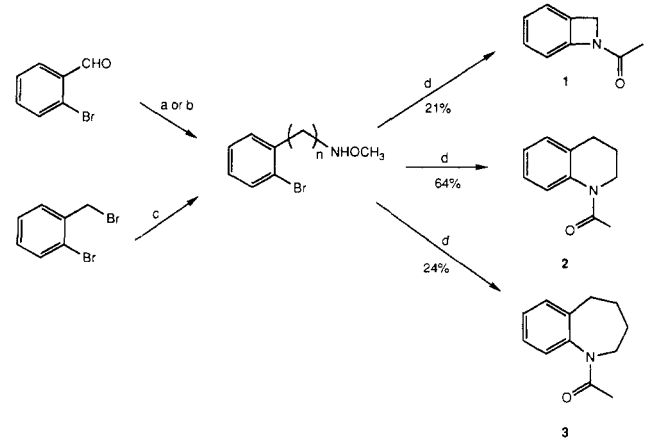
The formal displacement of an alkoxy group from an alkoxylamine, by an organolithium reagent, has been developed as a useful amination method.[1,2] Synthetically it has been shown that the species formed by lithiation of alkoxylamines and *N*-alkylalkoxylamines can aminate organolithium reagents. Mechanistically the endocyclic restriction test has been used to support our suggestion that the reaction occurs in an aggregated lithium complex of the reactants in which the entering and leaving groups are disposed at 180°.[3] In this paper we report synthetic uses of this amination, including a convenient preparation of a benzoazetine, and further investigation of the reaction mechanism.



Results and Discussion

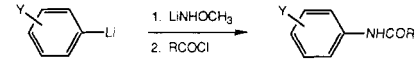
Cyclizations. This amination strategy can be used to form nitrogen-containing rings. The sequence which begins with the preparation of the appropriate (*o*-bromophenyl)alkanylmethoxylamine by straightforward methodology is illustrated by the synthesis of *N*-acetylbenzoazetine (**1**), *N*-acetyltetrahydroquinoline (**2**), and *N*-acetylbenzazapine (**3**). The key step is double lithiation of the aryl bromide to give an (*o*-lithiophenyl)alkyllithiomethoxylamide which then undergoes an exocyclic ring closure. Earlier we showed that indoline could be formed in this way, and in this work we have found that we could not prepare a benzazocine by this approach. This later failure is consistent with the slower rate of cyclization expected for an exocyclic ring closure of an eight-membered ring.[4]

Scheme I[a]



[a] (a) n = 1, NH_2OCH_3–HCl; BH_3–pyridine (78%); (b) n = 3, $Ph_3P{=}CHCO_2CH_3$; Mg, CH_3OH; DIBAL; NH_2OCH_3–HCl, BH_3–pyridine (39%); (c) $BrMgCH_2CH{=}CH_2$, BH_3–THF; H_2O_2, NaOH; oxallyl chloride, NH_2OCH_3–HCl; BH_3–pyridine (36%); (d) CH_3Li; t-C_4H_9Li; RCOCl.

Scheme II



4, Y = H, R = Ph (91%); **5**, Y = *p*-CH_3, R = Ph (93%); **6**, Y = *o*-C_2H_5, a mixture R = CH_3 (25%) and R v $CH_3CH{=}COCH_3$ (53%); **7**, Y = *o*-OCH_3, R = Ph (98%); **8**, Y = *m*-OCH_3, R = Ph (73%); **9**, Y = *p*-OCH_3, R = Ph (28%); **10**, Y = *m*-Cl, R = CH_3 (46%)

The structure of the benzoazetine **1** was assigned by standard methods, including vapor pressure osmometry, and confirmed by a single-crystal X-ray structure determination. The crystal structure for **1**, in space group P_{21c} with a = 9.529 (3) Å, b = 8.984 (2) Å, c = 9.439 (3) Å, β = 108.80 (2)°, Z = 4, was solved by direct methods and

(1) Sheverdina, N. I.; Kocheshkov, Z. *J. Gen. Chem. USSR* **1938**, *8*, 1825, appear to have been the first to observe this reaction.
(2) Beak, P.; Basha, A.; Kokko, B. J.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 1511 and references cited therein.
(3) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. This reaction, which formally brings together two negatively charged species for a bonding interaction, appears to be an example of the complex-induced proximity effect.
(4) Illuminate G.; Mandolini, L. *Acc. Chem. Res.* **1988**, *14*, 95. The slower cyclization presumably is then not competitive with the decomposition of the lithioalkoxyamide.

0022-3263/89/1954-5574$01.50/0