Preparation of Substituted Tetrabenzotriazaporphyrins and a Tetranaphthotriazaporphyrin: A Route to Mono-*meso*-substituted Phthalocyanine Analogues

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The synthesis, by treatment of phthalonitriles or 6-*tert*-butyl-2,3-dicyanonaphthalene with Grignard reagents, of novel substituted derivatives of tetrabenzotriazaporphyrins and a substituted tetranaphthotriazaporphyrin are described. Mono-*meso*-substituted tetrabenzotriazaporphyrins, soluble in organic compounds, were the major products, but byproducts of phthalocyanines and, in one case, tetrabenzodiazaporphyrins were obtained.

Introduction

The syntheses of symmetrical tetra,[1,2] octa,[1,3] and even hexadecaphthalocyanines[1,4] are relatively straightforward using the appropriately substituted phthalonitrile as the sole precursor. Unsymmetrical phthalocyanines, containing different substituents in the benzo groups, are extremely difficult to obtain. Strategies of synthesis, based on using statistical condensation reactions of two different substituted phthalonitriles, give mixtures of products which cannot be readily separated by chromatographic methods, probably due to the pronounced aggregation[5] effects in phthalocyanines, although 2-phosphazinylphthalocyanine[6] and some nonidentically substituted octasubstituted phthalocyanines[7] were isolated by this method.

Using specifically designed directed synthesis, some disubstituted[8] and monosubstituted phthalocyanines[9,10] have been prepared, but the precursors are more complicated and the yields are low.

Unsymmetrical porphyrins, bearing substituents in the pyrrolic or *meso* positions, have been used in a wide variety of applications,[11] such as the four-electron reduction of oxygen[12] and in photodynamic therapy of cancer,[13] but in some of these applications, the porphyrin nuclei were too unstable[12] as catalysts or absorbed at too low wavelengths for efficient use.[13] Unsymmetrical tetrabenzoporphyrins[14] and phthalocyanines[15] may alleviate these problems, but these systems are difficult to prepare and phthalocyanines cannot be substituted at the *meso* position.

The tetrabenzo[5,10,15]triazaporphyrin (**1a**) (TBTAP) ring system is differentiated from that of phthalocyanine (**2**) by a methine group, instead of a nitrogen, at a *meso* position (Figure 1). This single *meso*-carbon may provide an additional site for the attachment of substituent groups; however, the few studies of the TBTAP ring system, reported mostly in the older literature, have not provided evidence for the possibility of this type of substitution.[16-19] It has been shown, by Barrett et al.[16] that if a stochiometric amount of methylmagnesium iodide was added to phthalonitrile in ether and the crude product of this initial reaction heated, in a higher boiling solvent, a good yield of the magnesium derivative of TBTAP **1b** could be obtained. It was proposed that an iminoisoindoline derivative was formed during the initial addition of the Grignard reagent to phthalonitrile, which underwent subsequent addition to unreacted phthalonitrile to produce a tetrameric species. During the higher temperature step this tetrameric species underwent a cyclization reaction to form **1a**. The possibility of introducing substituents attached to the *meso*-carbon was explored, in the same paper, using the analogous reaction between *n*-butyllithium and phthalonitrile. The UV/vis spectrum of the pigment resulting from this reaction implied that a mixture of a TBTAP and magnesium phthalocyanine was produced; however, a pure TBTAP could not be isolated. A similar attempt to prepare the 27-phenyl TBTAP derivative, using benzylmagnesium chloride, yielded no other pigment than magnesium phthalocyanine.

In this paper we examined the possibility of preparing TBTAP derivatives with alkyl and aryl substituents attached to the *meso*-carbon as a route to monosubstituted phthalocyanine types of compounds in which substitution at a *meso* position is possible. In addition, the synthesis

(1) Moser, F. H.; Thomas, A. H. *The Phthalocyanines*; CRC Press: Boca Raton, FL, 1983; Vols. I and II. Leznoff, C. C. In *Phthalocyanines—Properties and Applications*; Leznoff, C. C., Lever, A. B. P., Eds.; VCH: New York, 1989; Chapter 1.

(2) Derkacheva, V. M.; Luk'yanets, E. A. *Zh. Obshch. Khim.* **1980**, *50*, 2313. Snow, A. W.; Griffith, J. R.; Marullo, N. P. *Macromolecules* **1984**, *17*, 1614. Shirai, H.; Maruyama, A.; Kobayashi, K.; Hojo, N.; Urushido, K. *Makromol. Chem.* **1980**, *181*, 575. Metz, J.; Schneider, O.; Hanack, M. *Inorg. Chem.* **1984**, *23*, 1065.

(3) Pawlowski, G.; Hanack, M. *Synthesis* **1980**, 287. Wöhrle, D.; Meyer, G.; Wahl, B. *Makromol. Chem.* **1980**, *181*, 2127.

(4) Bonderman, D.; Cater, E. D.; Bennett, W. E. *J. Chem. Eng. Data* **1970**, *15*, 396.

(5) White, W. I. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. V, Chapter 7. Kobayashi, N.; Lever, A. B. P. *J. Am. Chem. Soc.* **1987**, *109*, 7433 and references therein.

(6) Allcock, H. R.; Neenan, T. X. *Macromolecules* **1986**, *19*, 1496.

(7) Piechocki, C.; Simon, J. *J. Chem. Soc., Chem. Commun.* **1985**, 259. Cook, M. J.; Daniel, M. F.; Harrison, K. J.; McKeown, N. B.; Thomson, A. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1148. Duggan, P. J.; Gordon, P. F. Eur. Pat. Appl. 1985, E.P. 1557890; *Chem. Abstr.* **1986**, *105*, 70242r.

(8) Idelson, E. M. U.S. Patent 1977, No. 4,061,654; *Chem. Abstr.* **1978**, *88*, 171797m.

(9) Leznoff, C. C.; Greenberg, S.; Khouw, B.; Lever, A. B. P. *Can. J. Chem.* **1987**, *65*, 1705. Leznoff, C. C.; Greenberg, S. *Tetrahederon Lett.* **1989**, *29*, 5555.

(10) Leznoff, C. C.; Hall, T. W. *Tetrahedron Lett.* **1982**, *23*, 3023. Hall, T. W.; Greenberg, S.; McArthur, C. R.; Khouw, B.; Leznoff, C. C. *Nouv. J. Chim.* **1982**, *6*, 653. Wöhrle, D.; Krawczyk, G. *Polym. Bull.* **1986**, *15*, 193. Gaspard, S.; Giannotti, C.; Maillard, P.; Schaeffer, C.; Tran-Thi, T-H. *J. Chem. Soc., Chem. Commun.* **1986**, 1239.

(11) *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vols. I and II.

(12) Collman, J. P.; Anson, F. C.; Barnes, C. E.; Bencosme, C. S.; Geiger, T.; Evitt, E. R.; Kreh, R. P.; Meier, K.; Pettman, R. B. *J. Am. Chem. Soc.* **1983**, *105*, 2694. Fillers, J. P.; Ravichandran, K. V.; Abdalmundi, I.; Tulinsky, A.; Chang, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 417 and references therein.

(13) Dougherty, T. J.; Potter, W. R.; Weishaupt, K. R. In *Porphyrin Localization and Treatment of Tumors*; Doirin, D. R., Gomer, C. J., Eds.; Alan R. Liss Inc.: New York, 1984; pp 301-314. Brown, S. G.; Tralau, C. J.; Coleridge Smith, P. D.; Akademir, D.; Weiman, T. J. *Br. J. Cancer* **1986**, *54*, 43 and references therein.

(14) Kopranenkov, V. N.; Dashkevich, S. N.; Shevtsov, V. K.; Luk'yanets, E. A. *Khim. Geterosiki. Soedin.* **1984**, 6.

(15) Spikes, J. D. *Photochem. Photobiol.* **1986**, *43*, 691. Rosenthal, I.; Ben-Hur, E. In *Phthalocyanines-Properties and Applications*; Leznoff C. C., Lever, A. B. P., Eds.; VCH: New York, 1989; Chapter 6.

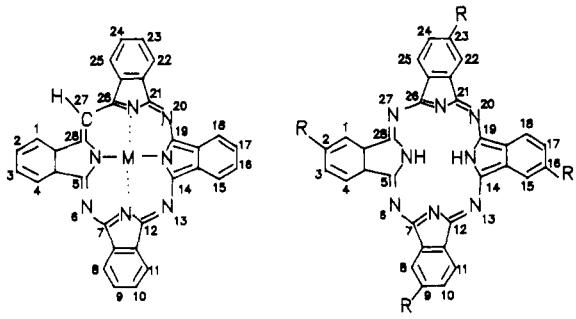
(16) Barrett, P. A.; Linstead, R. P.; Tuey, G. A. P.; Robertson, J. M. *J. Chem. Soc.* **1939**, 1809.

(17) Barrett, P. A.; Linstead, R. P.; Tuey, F. G.; Tuey, G. A. P. *Ibid.* **1940**, 1079.

(18) Dent, C. E. *J. Chem. Soc.* **1938**, 1.

(19) Helberger, J. H. *Ann. Chem.* **1937**, *529*, 205.

0022-3263/90/1955-2186$02.50/0



1a M = H_2
1b M = Mg

2 R = H
3 R = $OCH_2C(CH_3)_3$
4 R = $C(CH_3)_3$

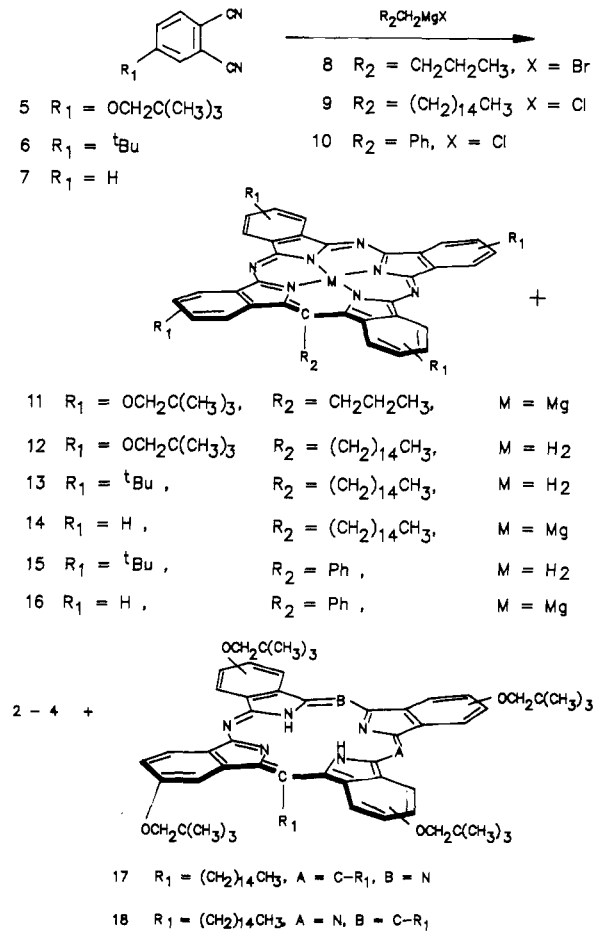
Figure 1.

of TBTAP's with sterically bulky groups located at the peripheral benzo positions should, by analogy with the properties of tetraneopentoxyphthalocyanine (**3**)[20] and tetra-*tert*-butylphthalocyanine (**4**),[21] produce derivatives readily soluble in organic solvents. The tetrabenzotriazaporphyrins can incorporate the flexibility of substitution of porphyrins along with the stability and spectroscopic properties of phthalocyanines.

Results and Discussion

Treatment of a variety of phthalonitriles (**5–7**) with different Grignard reagents (**8–10**) led to the substituted tetrabenzotriazaporphyrins **11–16**, as metal-free or magnesium derivatives, along with phthalocyanines **2–4** as byproducts and in one case a mixture of isolable *meso*-disubstituted tetrabenzodiazaporphyrins **17** and **18** (Scheme I). When an ether solution of *n*-butylmagnesium bromide (**8**) was added to an ether solution of 4-neopentoxyphthalonitrile (**5**), the ether evaporated, and the product heated in water, only trace amounts of pigment were produced. When the product of the Grignard reaction was heated in quinoline, however, a 35% yield of pigment was formed. The UV/vis spectrum of the resultant dyes appeared to be consistent with that of a mixture of 2,9,16,23-tetraneopentoxyphthalocyanine (**3**) and the desired 27-propyl-2,9,16,23-tetraneopentoxytetrabenzo[5,10,15]triazaporphyrin[22] (**11**). A mass spectrum of this mixture showed parent ions at 800 and 921 consistent with the presence of **3** and **11**. In retrospect, our first choice of a phthalonitrile and a Grignard reagent proved to be a poor one as **3** and **11** proved to be inseparable by a variety of chromatographic methods. This initial problem confirmed the difficulty Linstead's group[16] experienced in their unsuccessful attempts to obtain pure *substituted* TBTAP's. On the other hand, treatment of **5** with a hexadecylmagnesium chloride (**9**) in ether gave, after heating in quinoline and demetalation with glacial acetic acid, a mixture of **3**, the desired 27-pentadecyl-2,9,16,23-tetraneopentoxytetrabenzo[5,10,15]triazaporphyrin (**12**) in 14% yield, and a trace of a tetrabenzodiazaporphyrin, which could be formulated as either the 20,27-dipentadecyl-2,9,16,23-tetraneopentoxytetrabenzo[5,10]diazaporphyrin (**17**) or the 13,27-dipentadecyl-2,9,16,23-tetraneopentoxy[5,15]diazaporphyrin (**18**) isomer

Scheme I



5 R_1 = $OCH_2C(CH_3)_3$
6 R_1 = ^tBu
7 R_1 = H

8 R_2 = $CH_2CH_2CH_3$, X = Br
9 R_2 = $(CH_2)_{14}CH_3$ X = Cl
10 R_2 = Ph, X = Cl

11 R_1 = $OCH_2C(CH_3)_3$, R_2 = $CH_2CH_2CH_3$, M = Mg
12 R_1 = $OCH_2C(CH_3)_3$ R_2 = $(CH_2)_{14}CH_3$, M = H_2
13 R_1 = ^tBu, R_2 = $(CH_2)_{14}CH_3$, M = H_2
14 R_1 = H, R_2 = $(CH_2)_{14}CH_3$, M = Mg
15 R_1 = ^tBu, R_2 = Ph, M = H_2
16 R_1 = H, R_2 = Ph, M = Mg

17 R_1 = $(CH_2)_{14}CH_3$, A = C–R_1, B = N
18 R_1 = $(CH_2)_{14}CH_3$, A = N, B = C–R_1

or a mixture of **17** and **18**.[23] In this and subsequent examples, flash chromatography[24] was successful in separating the TBTAP's from the phthalocyanine and diaza byproducts as the long chain alkyl *meso* substituent altered the solubility and mobility of the TBTAP's sufficiently to effect separation. In a similar manner, 4-*tert*-butylphthalonitrile (**6**), on treatment with Grignard **9**, gave 27-pentadecyl-2,9,16,23-tetra-*tert*-butyltetrabenzo[5,10,15]triazaporphyrin (**13**) in 19% yield, along with some 2,9,16,23-tetra-*tert*-butylphthalocyanine (**4**), but no tetrabenzodiazaporphyrins were isolated. In an attempt to prepare a tetrabenzotriazaporphyrin with the single *meso* substituent but no substituents on the benzo rings (peripheral substituents), phthalonitrile (**7**) was treated with Grignard **9** as above to give a very insoluble TBTAP which could not be separated from the even more insoluble phthalocyanine (**2**). If the demetalation step is omitted, however, it turned out that (27-pentadecyltetrabenzo[5,10,15]triazaporphyrin)magnesium (**14**) is sufficiently soluble in coordinating solvents, such as pyridine and tetrahydrofuran (THF), to facilitate its separation from the very insoluble **2** and **14** was isolated in 9% yield by flash chromatography. Phthalocyanines **2–4** were not purified in their entirety but generally constituted at least 50% of the crude pigment mixture.

An aromatic substituent was incorporated into the *meso* position of TBTAP by the reaction of commercially available benzylmagnesium chloride (**10**) with 4-*tert*-bu-

(20) Leznoff, C. C.; Greenberg, S.; Marcuccio, S. M.; Minor, P. C.; Seymour, P.; Lever, A. B. P.; Tomer, K. B. *Inorg. Chem. Acta* **1984**, *89*, L35. Leznoff, C. C.; Marcuccio, S. M.; Greenberg, S.; Lever, A. B. P.; Tomer, K. B. *Can. J. Chem.* **1985**, 623.

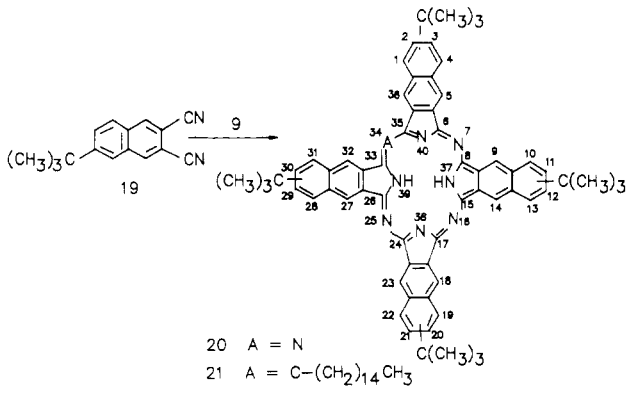
(21) Mikhalenko, S. A.; Barkanova, S. V.; Lebedev, O. L.; Luk'yanets, E. A. *Zh. Obsch. Khim.* **1971**, *41*, 2735.

(22) See Experimental Section for Chemical Abstract name: Heathcock, C. H. *J. Org. Chem.* **1989**, *54*, 10A.

(23) The terms "adjacent" and "opposite" have been used for similar types of isomers in the porphyrin series. See: Milgrom, L. R.; Mofidi, N.; Jones, C. C.; Harriman, A. *J. Chem. Soc., Perkin Trans. 2* **1989**, 301.

(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Scheme II



tylphthalonitrile (**6**) or phthalonitrile (**7**) in ether under conditions similar to those described for Grignard (**9**) to afford 2,9,16,23-tetra-*tert*-butyl-27-phenyltetrabenzo[5,10,15]triazaporphyrin (**15**) and (omitting the demetalation step) (27-phenyltetrabenzo[5,10,15]triazaporphyrin)magnesium (**16**) in 12 and 15% yields respectively.

The attempt by Linstead's group[16] to prepare **16** produced only magnesium phthalocyanine, as judged by the UV/vis spectrum of the crude pigment from the reaction. However, it was possible that the benzylmagnesium chloride used was at fault, as the preparation of this Grignard by techniques in Linstead's time often resulted in the reagent being heavily contaminated by the Wurtz coupled product.

Naphthalocyanines[25] are similar in structure to phthalocyanines and porphyrins, but having naphtho substituents at each of the pyrrole rings and absorbing light at higher wavelengths. This latter property makes them possible candidates for use in photodynamic therapy.[13,15] For this reason, we wished to prepare a *meso*-substituted tetranaphthotriazaporphyrin derivative. As unsubstituted naphthalocyanines are even more insoluble than phthalocyanines we used a substituted 2,3-dicyanonaphthalene as a suitable precursor. Thus, treatment of 6-*tert*-butyl-2,3-dicyanonaphthalene[26] (**19**) with hexadecylmagnesium chloride (**9**), as above, gave naphthalocyanine (**20**) and 2,11,20,29-tetra-*tert*-butyl-34-pentadecyltetranaphtho[5,10,15]triazaporphyrin (**21**) (Scheme II). Chromatographic separation of **21** from **20** proved difficult, because of the greater insolubility of naphthalocyanines and their tendency to aggregate, but a pure sample of **21** was obtained in 3% yield, which exhibited no contamination by **20** when characterized by FAB mass spectroscopy and elemental analysis. All other TBTAP's isolated (**11–16**) also exhibited parent ions in their FAB mass spectra, with no concurrent peaks, consistent with phthalocyanine contamination. It should also be noted that TBTAP's **11–16** and **21** each exists as a mixture of 10 possible isomers.[27]

The UV/vis spectra of compounds **11–16** and **21** correspond closely to the published spectra of metal-free TBTAP and magnesium TBTAP, respectively.[16,28,29] The spectra of the magnesium derivatives **14** and **16** exhibits a distinct Q-band splitting, unlike magnesium phthalocyanine (D_{4h} symmetry), due to the lower symmetry (C_{2v}) of the TBTAP molecule. Similarly, the UV/vis spectrum of the highly substituted mixture of tetrabenzodiazaporphyrin **17** and **18** is analogous to that of the unsubstituted compound.[29] The UV/vis spectrum of compound **21** is of interest as, unlike that of the metal-free tetra-*tert*-butylnaphthalocyanine, the Q-band is split.[30]

A comparison of the ^{1}H NMR spectra of **14** with that of magnesium phthalocyanine also shows the lower symmetry of the TBTAP ring system. The nonequivalence of the protons in the aromatic region of the spectrum of **14** being more obvious in that the 1,4 protons give rise to a 2:4:2 group of peaks centered around 9.8 ppm.

In this paper we have shown that, by simple modifications to the existing synthetic route to unsubstituted TBTAP, novel derivatives with aryl and alkyl groups attached to the meso carbon of TBTAP can be prepared. This method provides a facile (a one-step procedure using readily available starting materials) synthesis of monosubstituted phthalocyanine analogues. In addition, metal-free TBTAP's rendered soluble in organic solvents by bulky peripheral substituents have been prepared which will allow for more research into the physical properties of the rarely studied TBTAP ring system.

Experimental Section

General Methods. Matheson high purity argon was used to maintain inert atmosphere conditions. Infrared (IR) spectra were recorded on a Pye Unicam SP1000 infrared spectrophotometer using KBr disks. Nuclear magnetic resonance (NMR) spectra for protons and carbons were recorded on a Bruker AM300 NMR spectrometer. The position of signals are reported in δ units. (The splitting of the signal is described as singlets (s), doublets (d), triplets (t), quartets (q), doublets of doublets (dd) or multiplets (m).) The ^{1}H NMR spectra of 10^{-3} M solutions of the phthalocyanine analogues were obtained by averaging 500–3000 scans over the absorption range. The ultraviolet–visible spectra (UV) were recorded on a Hewlett-Packard HP8451A Diode Array spectrophotometer. Mass spectra (MS) were recorded at 70 eV on a VG Micromass 16F mass spectrometer in the EI mode. The FAB spectra were obtained with a Kratos MS-50 triple analyzer mass spectrometer equipped with a FAB ion source of standard Kratos design and Ion Tech atom gun. The sample was dissolved in chloroform, and 1 μL of the resulting solution added to 1 μL of *m*-nitrobenzyl alcohol on the probe tip. The spectra of the molecular ions of the phthalocyanines were obtained by signal averaging up to 256 scans over the appropriate mass range. The number in parentheses after the indicated ion shows the percentage of the base peak represented by that ion. Melting points (mp) were determined using a Kofler hot stage melting point apparatus and are uncorrected. Flash chromatography was performed using silica gel of particle size 20–45 μm. All reactions, except the one which required sonication, were stirred with a magnetic stirrer. Ultrasound activation was carried out using a Branson 1200 sonicator. All solvents were freshly distilled before use. Microanalyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario. Thin-layer chromatography (TLC) was performed using silica gel G as the absorbent.

2,9,16,23-Tetrakis(2,2-dimethylpropoxy)-27-pentadecyl-29*H*,31*H*-tetrabenzo[*b*,*g*,*l*,*q*][5,10,15]triazaporphine (12).[22] Hexadecylmagnesium chloride (**9**) in dry diethyl ether solution (4 mL), prepared from hexadecyl chloride (1.5 g, 5.8 mmol) and an excess of magnesium (0.2 g, 8.3 mmol), was added dropwise to a stirred solution of 4-neopentoxyphthalonitrile (**5**) (1.2 g, 5.8 mmol) in diethyl ether (5 mL), causing a reaction in which a purple color developed. The reaction was maintained at room tem-

(25) Bradbrook, E. F.; Linstead, R. P. *J. Chem. Soc.* **1936**, 1739, 1744. Kaplina, M. L.; Lovinger, A. J.; Reents, W. D., Jr.; Schmidt, P. H. *Mol. Cryst. Liq. Cryst.* **1984**, *112*, 345.

(26) Kovshev, E. I.; Puchnova, V. A.; Luk'yanets, E. A. *Zh. Org. Khim.* **1971**, *7*, 369.

(27) For discussions on regioisomers in tetrasubstituted phthalocyanines, see: Wöhrle, D.; Gitzel, J.; Okura, I.; Aono, S. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1171. Greenberg, S.; Lever, A. B. P.; Leznoff, C. C. *Can. J. Chem.* **1987**, *66*, 1059.

(28) Sevchenko, A. N.; Shkirman, S. F.; Mashenkov, V. A.; Solovev, K. N. *Dokl. Akad. Nauk. S.S.R.* **1967**, *175*, 545.

(29) Solovev, K. N.; Mashenkov, V. A.; Kachura, T. F. *Opt. Spectrosc.* **1969**, *27*, 24.

(30) Kovshev, E. I.; Luk'yanets, E. A. *Zh. Obshch. Khim.* **1972**, *42*, 696.

perature, under anhydrous conditions for 2 h. The solvent was then removed by passing a stream of dry argon through the reaction vessel for 15 min. Sufficient quinoline was added to dissolve the resultant brown solid, and the temperature was raised to 200 °C. Over a period of 2 h the reaction underwent a color change from a reddish-brown to a dark green. The reaction was allowed to stir for a further 22 h at 200 °C. The reaction mixture was cooled, and the crude product was demetalated by addition of 50 mL of glacial acetic acid followed by heating the acidified mixture to reflux for 1 h.

The resultant pigment was initially purified by elution through a silica (flash chromatography grade) column, using hexane/toluene (2:1) as the eluant. This chromatography separated the required product from the tetraneopentoxyphthalocyanine (**3**) and tetrabenzodiazaporphyrin byproducts. Reprecipitation from a concentrated solution of toluene (10 mL) by methanol (100 mL) gave pure 2,9,16,23-tetraneopentoxy-27-pentadecyltetrabenzo[5,10,15]triazaporphyrin (**12**) (210 mg, 14% yield) as a green amorphous powder: IR (KBr) 3280, 3062, 2962, 2938, 2862, 1620, 1400, 1235, 1028 cm^{-1}; UV (THF) 696 (ϵ 84 500), 652 (ϵ 5200), 624 (ϵ 27 500), 386 (ϵ 58 900), 364 (ϵ 52 600); ^1H NMR (300 MHz, benzene-d_6) −3.50 to −2.60 (2 H, m), 0.89 (3 H, t), 1.20–1.68 (60 H, m), 1.73 (2 H, m), 3.63 (2 H, m), 3.93 (8 H, m), 7.41–9.18 (12 H, m); MS m/z 1067 (M^+, 100). Anal. Calcd for $C_{66}H_{89}N_7O_4$: C, 76.44; H, 8.40; N, 9.18. Found: C, 76.71; H, 8.30; N, 9.03.

The tetrabenzodiazaporphyrin byproducts obtained from the above column were reprecipitated from a toluene solution (2 mL) using methanol (10 mL) to give 2,9,16,23-tetraneopentoxy-20,27-dipentadecyltetrabenzo[5,10]diazaporphyrin (**17**) and 2,9,16,23-tetraneopentoxy-13,27-dipentadecyl[5,10]diazaporphyrin (**18**) (10 mg, 0.5% yield) as a green powder: UV (THF) 694 (ϵ 78 300), 652 (ϵ 47 900), 624 (ϵ 41 400), 400 (ϵ 82 100), 424 (ϵ 78 300), 394 (ϵ 68 000); MS m/z 1285 (M^+, 100). Anal. Calcd for $C_{84}H_{120}N_6O_4$: C, 78.95; H, 9.47; N, 6.58. Found: C, 79.28; H, 9.65; N, 6.49.

2,9,16,23-Tetrakis(2,2-dimethylethyl)-27-pentadecyl-29*H*,31*H*-tetrabenzo[*b*,*g*,*l*,*q*][5,10,15]triazaporphine (13). Hexadecylmagnesium chloride (**9**) in dry diethyl ether solution (4 mL), prepared from hexadecyl chloride (0.7 g, 2.7 mmol) and an excess of magnesium (0.1 g, 4.2 mmol), was added dropwise to a stirred solution of 4-*tert*-butylphthalonitrile (**6**) (0.5 g, 2.7 mmol) in diethyl ether (3 mL), causing a reaction in which a purple color developed. The reaction proceeded as before, and the resultant pigment was purified by elution through a silica (flash chromatography grade) column, using hexane/toluene (7:3) as the eluant. This procedure separated the required product from the tetra-*tert*-butylphthalocyanine (**4**) byproduct. Reprecipitation from a concentrated solution of toluene (5 mL) by methanol (50 mL) gave pure 2,9,16,23-tetra-*tert*-butyl-27-pentadecyltetrabenzo[5,10,15]triazaporphyrin (**13**) (120 mg, 19% yield) as a green amorphous powder: mp 119 °C; IR (KBr) 3280, 3062, 2978, 2942, 2875, 1624, 1493, 1038 cm^{-1}; UV (THF) 688 (ϵ 170 000), 648 (ϵ 112 000), 630 (ϵ 44 800), 620 (ϵ 44 700), 590 (ϵ 26 900), 440 (ϵ 28 200), 388 (ϵ 91 200), 364 (ϵ 70 800); ^1H NMR (300 MHz, benzene-d_6) −3.20 to −1.60 (2 H, m), 0.89 (3 H, t), 1.20–1.38 (22 H, m), 1.65–2.00 (38 H, m), 2.13 (2 H, m), 3.80 (2 H, m), 7.75–9.80 (12 H, m); MS m/z 947 (M^+, 100). Anal. Calcd for $C_{64}H_{81}N_7$: C, 81.05; H, 8.61; N, 10.34. Found: C, 81.05; H, 8.98; N, 10.18.

(27-Pentadecyl-29*H*,31*H*-tetrabenzo[*b*,*g*,*l*,*q*][5,10,15]-triazaporphine)magnesium (14). 1-Hexadecylmagnesium chloride (**9**) in dry diethyl ether solution (3 mL), prepared from 1-hexadecyl chloride (1 g, 3.8 mmol) and a slight excess of magnesium metal (0.1 g, 4.2 mmol), was added dropwise to a stirred suspension of phthalonitrile (**7**) (0.5 g, 4 mmol) in dry diethyl ether (2 mL), causing a reaction in which a purple color developed. The reaction was maintained at room temperature, under anhydrous conditions for 2 h. The solvent was then removed by passing a stream of dry argon through the reaction vessel for 15 min. Sufficient quinoline was added to dissolve the resultant brown solid and the temperature raised to 200 °C. Over a period of 2 h the reaction underwent a color change from a reddish-brown to a dark green. The reaction was allowed to stir for a further 22 h at 200 °C.

The resultant pigment was initially purified by elution through a silica column using THF as the eluant. A TLC analysis of the resultant material using a solvent system of hexane/pyridine (4:1) showed the presence of two different colored pigments. These two pigments, a green compound (R_f 0.8) which subsequently was found to be the required magnesium tetrabenzotriazaporphyrin, and a blue compound (R_f 0.2) which proved to be magnesium phthalocyanine, were separated by flash chromatography using a solvent system of hexane/pyridine (9:1). Recrystallization from THF/methanol (1:1) gave pure (20-pentadecyltetrabenzo[5,10,15]triazaporphyrin)magnesium (**14**) (65 mg, 9% yield) as green needle crystals: mp 252 °C; IR (KBr) 2946, 2863, 1494, 1338, 1102, 733 cm^{-1}; UV (THF) 668 (ϵ 117 000), 648 (ϵ 89 300), 618 (ϵ 22 000), 594 (ϵ 22 500), 446 (ϵ 34 500), 400 (ϵ 54 500); ^1H NMR (300 MHz, pyridine-d_5) 0.89 (3 H, t), 1.20–1.38 (20 H, m), 10.16 (2 H, m); MS m/z 746 (M^+, 100), 549 (83), 535 (64). Anal. Calcd for $C_{48}H_{47}N_7Mg$: C, 77.25; H, 6.35; N, 13.14. Found: C, 76.86; H, 6.19; N, 12.94.

2,9,16,23-Tetrakis(2,2-dimethylethyl)-27-phenyl-29*H*,31*H*-tetrabenzo[*b*,*g*,*l*,*q*][5,10,15]triazaporphine (15). Benzylmagnesium chloride (**10**) in dry diethyl ether solution (4 mL, 1 M) was added dropwise to a stirred solution of 4-*tert*-butylphthalonitrile (**6**) (0.6 g, 3.3 mmol) in diethyl ether (3 mL), causing a reaction in which a purple color developed. The reaction proceeded as for **13**, and the resultant pigment was purified by elution through a silica (flash chromatography grade) column, using hexane/toluene (7:3) as the eluant. This chromatographic procedure separated the required product from the tetra-*tert*-butylphthalocyanine (**4**) byproduct. Reprecipitation from a concentrated solution of toluene (4 mL) by methanol (40 mL) gave pure 2,9,16,23-tetra-*tert*-butyl-27-pentadecyltetrabenzo[5,10,15]triazaporphyrin (**15**) (90 mg, 12% yield) as a green amorphous powder: IR (KBr) 3280, 3062, 2962, 2910, 2863, 1624, 1493, 1032 cm^{-1}; UV (THF) 690 (ϵ 168 000), 648 (ϵ 104 000), 620 (ϵ 50 600), 564 (ϵ 30 000), 384 (ϵ 82 000); ^1H NMR (300 MHz, benzene-d_6) −0.45 to −0.27 (2 H, m), 1.35–1.75 (36 H, m), 7.00–8.23 (11 H, m), 9.60–10.12 (6 H, m); MS m/z 813 (M^+, 100). Anal. Calcd for $C_{55}H_{55}N_7$: C, 81.13; H, 6.81; N, 12.04. Found: C, 80.87; H, 6.37; N, 12.19.

(27-Phenyl-29*H*,31*H*-tetrabenzo[*b*,*g*,*l*,*q*][5,10,15]triazaporphine)magnesium (16). Benzylmagnesium chloride (**10**) in dry diethyl ether solution (5 mL, 1 M), was added dropwise to a stirred suspension of phthalonitrile (0.6 g, 4.7 mmol) in dry diethyl ether (2 mL), resulting in a reaction in which a purple color developed. The reaction proceded as for **14**, and the resultant pigment was initially purified by elution through a silica column using THF as the eluant. A TLC analysis of the resultant material using hexane/THF (5:1) showed the presence of two different colored pigments. These two pigments, a green compound (R_f 0.6) which subsequently was found to be the required magnesium tetrabenzotriazaporphyrin and a blue compound (R_f 0.2) which proved to be magnesium phthalocyanine, were separated by flash chromatography using a solvent system of hexane/THF (5:1). Recrystallization from THF/methanol (1:1) gave (27-pentadecyltetrabenzo[5,10,15]triazaporphyrin)magnesium (**16**) (110 mg, 15% yield) as green microcrystals: IR (KBr) 2955, 1595, 1490, 1338, 1122, 1040, 733 cm^{-1}; UV (THF) 670 (ϵ 157 000), 648 (ϵ 110 000), 618 (ϵ 22 800), 594 (ϵ 25 500), 444 (ϵ 27 800), 398 (ϵ 68 200); ^1H NMR (300 MHz, DMSO-d_6) 7.00 (2 H, d), 7.68 (2 H, t), 7.96–8.25 (7 H, m), 8.30 (4 H, m), 9.49 (4 H, m), 9.56 (2 H, d); MS m/z 611 (M^+, 100). Anal. Calcd for $C_{39}H_{21}N_7Mg$: C, 76.42; H, 3.46; N, 16.06. Found: C, 76.42; H, 3.58; N, 15.53.

2,11,20,29-Tetrakis(2,2-dimethylethyl)-34-pentadecyl-37*H*,39*H*-tetranaphtho[2,3-*b*:2′,3′-*g*:2″,3″-*l*-2‴,3‴-*q*]-[5,10,15]triazaporphine (21). 1-Hexadecylmagnesium chloride (**9**) in dry diethyl ether solution (5 mL), prepared from hexadecyl chloride (0.7 g, 2.9 mmol) and an excess of magnesium (0.1 g, 4.2 mmol), was added dropwise to a stirred solution of 6-*tert*-butyl-2,3-dicyanonaphthalene (**19**) (0.6 g, 2.7 mmol) in diethyl ether (3 mL), causing a reaction in which a purple color was developed. The reaction proceded as for **13**, and the resultant pigment was purified by elution through a silica (flash chromatography grade) column, using hexane/toluene (1:1) as the eluant. This chromatographic procedure separated a small portion of required product from the tetra-*tert*-butylnaphthalocyanine (**20**) byproduct, although total separation by this method was unsuccessful. Reprecipitation from a concentrated solution of toluene (1 mL) by methanol (5 mL) gave pure 2,11,20,29-tetra-*tert*-butyl-34-pentadecyltetranaphtho[5,10,15]triazaporphyrin (**21**) (18 mg, 3%

yield) as a green amorphous powder: IR (KBr) 3290, 3058, 2960, 2928, 2860, 1394, 1044 cm^{-1}; UV (THF) 778 (ϵ 132000), 746 (ϵ 98300), 674 (ϵ 31900), 430 (ϵ 40700), 374 (ϵ 60800), 346 (ϵ 62800); ^1H NMR (300 MHz, benzene-d_6) -4.30 to -2.40 (2 H, m), 0.89 (3 H, t), 1.18-1.85 (60 H, m), 2.00 (2 H, br s), 3.55 (2 H, br s), 7.35-8.62 (20 H, m); MS m/z 947 (M^+, 100), 950 (25). Anal. Calcd for $C_{80}H_{89}N_7$: C, 83.13; H, 8.32; N, 8.49. Found: C, 82.91; H, 8.04; N, 8.63.

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Isomeric Monoacetylmono(1-hydroxyethyl)deuteroporphyrins: Syntheses, Characterization, and Use for the Syntheses of Regioselectively Methyl- and Vinyl-Deuterated Hemins

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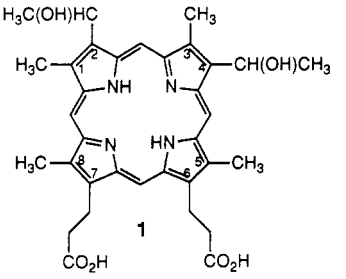
Treatment of hematoporphyrin IX dimethyl ester (**7**) with tetrapropylammonium perruthenate ($Pr^n_4N)(RuO_4$) and *N*-methylmorpholine *N*-oxide affords a high yield of the separable monoacetylmono(1-hydroxyethyl)-deuteroporphyrin isomers **5** and **6**. Proton NMR NOE experiments and chemical transformations involving specific individual deuteration at the 1- and 3-methyls and 2- and 4-vinyls are used to characterize the isomers.

Photodynamic therapy (PDT) is an experimental cancer treatment modality which selectively destroys cancer cells by interaction of light with a photosensitizing dye, presumably to form singlet oxygen.[5] Some porphyrins have been shown to be particularly effective sensitizers in this regard, and Photofrin II, a purified version of hematoporphyrin derivative which localizes in tumors, is currently in phase III clinical trials. The active constituent in Photofrin II appears to be an ether-ester linked oligmer containing between two and six hematoporphyrin (**1**) units.[6-8]



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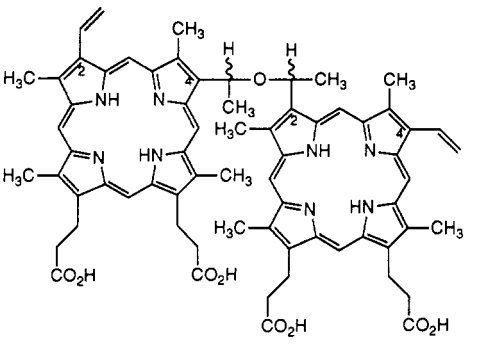
In our continuing efforts to characterize Photofrin II, and in the hope of preparing unique pure compounds contained in the active fraction of this drug, we have synthesized a number of dimers and trimers with both ether[9] and ester linkages.[10] In our animal tumor models, dimers with ester linkages were found to be biologically inactive,[10] while dimers (e.g. **2**) and trimers with ether linkages between positions 2 and 4 in **1** showed significant tumorcidal activity.[11] Our preliminary synthetic studies (Scheme I) utilized partial reduction of the acetyls in 2,4-diacetyldeuteroporphyrin IX dimethyl ester (**3**) and resulted in isolation of dimers (e.g. **4**) and trimers which were mixtures of regio- and stereoisomers at the 2- and 4-positions;[9-11] synthesis of a pure dimer or trimer, on the other hand, requires ready availability of large quantities of isomerically pure porphyrin monoacetylmono(1-hydroxyethyl)porphyrin isomers **5** and **6**.



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And other 2-, 4-connected ether positional isomers

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(5) Weishaupt, K. R.; Gomer, C. J.; Dougherty, T. J. *Cancer Res.* **1976**, *36*, 2326.
(6) Dougherty, T. J.; Potter, W. R.; Weishaupt, K. R. *Adv. Med. Biol.* **1984**, 301.
(7) Kessel, D.; Thompson, P.; Musselman, B.; Chang, C. K. *Cancer Res.* **1987**, *47*, 4642.
(8) Kessel, D. *Photochem. Photobiol.* **1986**, *44*, 193.
(9) Pandey, R. K.; Dougherty, T. J.; Smith, K. M. *Tetrahedron Lett.* **1988**, *29*, 4657.
(10) Pandey, R. K.; Dougherty, T. J. *Cancer Res.* **1989**, *49*, 2042.
(11) Pandey, R. K.; Majchrzycki, D. A.; Smith, K. M.; Dougherty, T. J. *SPIE Proc.* **1989**, *1065*, 164.

0022-3263/90/1955-2190$02.50/0