The Synthesis of Haematoporphyrin Derivative III
and other Novel Porphyrins

Sek Sau Yin, B.Sc.(Hons.)

A Thesis submitted for the Degree of
Doctor of Philosophy

in the
Department of Organic Chemistry
University of Adelaide
Australia

July 1990
CONTENTS

Abstract

Abbreviations

CHAPTER 1
1.1 General Introduction

1.2 References

CHAPTER 2
2.1 Introduction

2.2 Results and Discussion

2.2.1 Total Synthesis of Protoporphyrin III dimethyl ester (21a)

2.2.2 Conversion of Protoporphyrin III dimethyl ester (PP\textsubscript{III}dme) (21a) to Haematoporphyrin III dimethyl ester (HP\textsubscript{III}dme) (21a)

2.2.3 Total Synthesis of 3,7-Diacetyldeuteroporphyrin III dimethyl ester (31)

2.2.4.1 Spectral analysis of 3,7-Di(1-methoxyethyl)-deuteroporphyrin III dimethyl ester (34)

2.2.4.2 Spectral analysis of 3-(1-Hydroxyethyl)-7-(1-methoxyethyl)deuteroporphyrin III dimethyl ester (41)

2.2.5 HPD-III

2.3 Experimental

2.4 References
4.2.1.2 NMR analysis of the regiosomers of the diol derivatives (86), (87) and (88) 183

4.2.1.3 Pentane-1,5-diether-linked diporphyrin dimer (90) 189

4.2.1.4 Propane-1,3-diether-linked diporphyrin dimer (89) 194

4.2.1.5 Decane-1,10-diether-linked diporphyrin dimer (91) 196

4.2.2 The synthesis of a symmetric diporphyrin dimer linked by an ether- and ester-containing bridge (92) 197

4.2.3 1,3-Diaminopropene derivative (94) of 3-ethyl-8-vinyldeuteroporphyrin dimethyl ester 199

4.2.4 1,3-Diaminopropene-linked diporphyrin dimer (95) 201

4.2.5 Attempted synthesis of a diporphyrin dimer (97) linked by an amine- and amide-containing bridge 210

4.2.6 Propanolamine derivative (104) of 3-ethyl-8-vinyldeuteroporphyrin dimethyl ester 212

4.2.7 Attempted oxidation of the primary alcohol on the porphyrin sidechain 217

4.2.8 Jones oxidation of the propanolamine derivative (104a) 219

4.2.9 Attempted synthesis of a diporphyrin dimer with an amine- and amide-containing bridge (110) 222

4.3 Experimental 230

4.4 References 251

Appendix 256
ABSTRACT

The Synthesis of Haematoporphyrin Derivative III and other Novel Porphyrins

This thesis is divided into four chapters. Chapter 1, which provides an introduction to the work in Chapters 2 and 3, contains a brief account of haematoporphyrin derivative (HPD-IX), an antitumour drug which is currently undergoing final clinical trials in the United States for use in the photodynamic therapy of endobronchial, esophageal and bladder tumours.

Chapter 2 describes a study of the relationship between the regiochemistry of the haematoporphyrins and the biological activity of the material (HPD) derived from them. This involved first, the total synthesis of haematoporphyrin III by two literature routes, both via the copper-mediated cyclization of biladiene-ac salts, and then the preparation of haematoporphyrin derivative-III (HPD-III) by standard procedures, using haematoporphyrin IIII. Investigations of the literature steps in the total synthesis resulted in significant improvements in the yields in some cases. HPD-III was found (by HPLC, FAB m.s., NMR, visible spectroscopy) to be similar to HPD-IX in that HPD-III contained monomers as well as ether-, ester- and carbon-linked dimers and oligomers. However the proportion of dimeric/oligomeric material was significantly lower in HPD-III than in HPD-IX. In addition HPD-III was less soluble in water and less biologically active than HPD-IX. Reasons for these differences are discussed.
Chapter 3 describes the synthesis of four symmetrical amino-linked diporphyrin dimers with diacetyl-, diethyl-, divinyl and di(1-hydroxyethyl) terminal groups. Some of these dimers are amino analogues of the ether-linked material claimed to be in HPD-IX. Optimization studies for the hydrobromination (using saturated hydrobromic acid/dichloromethane) of ethyl- and acetyl-substituted vinyl-containing porphyrins, and the partial hydrobromination of protoporphyrin dimethyl ester, were undertaken. The amino-linked dimers were characterized by NMR, u.v./vis. absorption spectroscopy and FAB m.s. Tests of in vivo anticancer activity indicated that the amino-linked dimers were less active than the corresponding ether-linked dimers. A possible relationship between the nature of the linking group and the biological activity of the dimers was proposed.

The hydrobromination methodology established in Chapter 3 was used for a preliminary study of the synthesis of diporphyrin dimers with long linking groups. Compounds of this type are potential DNA intercalators. Chapter 4 details the synthesis and characterization of diporphyrin dimers linked by propane-1,3-diether, pentane-1,5-diether, decane-1,10-diether and propane-1,3-diamine bridges, as well as monomeric precursors to dimers with amine and amide-containing bridges. The synthesis of a dimer linked by a bridge which contained ether and ester groups was achieved but attempts to prepare and characterize dimers with amine- and amide-containing bridges were hampered by difficulties in obtaining informative FAB mass spectra.