PROTOPORPHYRIN-IX: SOME USEFUL SUBSTITUENT MANIPULATIONS

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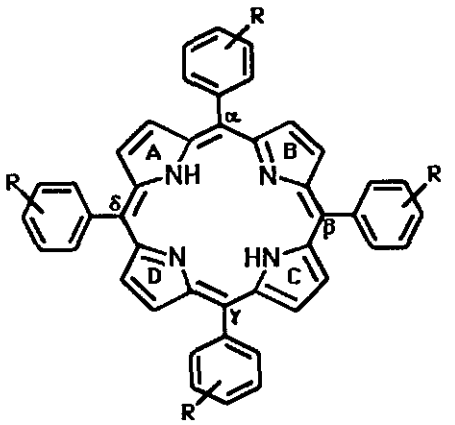
Abstract – Various substituent manipulations of the side chains in commercially available hemin (**3**) and its metal-free derivative, protoporphyrin-IX (**4**), are described, which illustrate the usefulness of these starting materials for preparation of a large number of theoretically, chemically, biologically, and spectroscopically useful porphyrins and hemes.

Introduction

Over the years, porphyrins have proven to be excellent substrates for testing important physical, chemical, biological, and medical hypotheses and principles. This has been aided by the unique properties exhibited by the porphyrin macrocycle, particularly with regard to chelation of chemically interesting metal ions which usually furnish the active, often catalytic, center of the chemical system. It cannot go unnoticed that all biologically significant systems using porphyrins or similar pyrrole-derived compounds require a chelated metal for their functional activity. Examples are the iron in hemes (hemoglobins, myoglobins, cytochromes, catalases, peroxidases, reductases), the magnesium in chlorophylls and bacteriochlorophylls, the cobalt in vitamin B12, and the nickel in Factor F430 from methanogenic bacteria

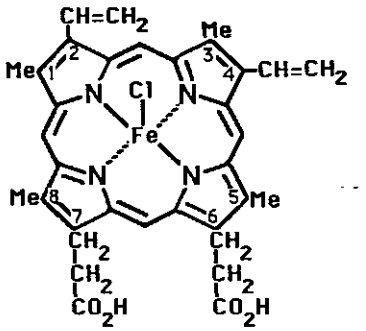
The biology practiced by these important pigments of life has spawned literally thousands of model studies in which ingenious chemists and biologists have attempted to mimic the awesome properties of the natural systems. For example, a major occupation of several prominent research groups is the imitation of cytochrome P450 activity; nature uses this system for detoxification through hydroxylation (or other monooxygenation), whereas the chemist of the 1980s is attempting to use analogues of the biological system for functionalization of petroleum hydrocarbons in a catalytic, recycling process.

With very few exceptions, the porphyrin of choice for the chemical studies has been tetraphenylporphyrin (1), prepared using the Adler modification[1] of the Rothemund reaction.[2] In this reaction, reasonable yields of tetra-arylporphyrins can be obtained simply by refluxing pyrrole and an aromatic aldehyde in propionic acid. The R group in the aryl aldehyde can be used as a handle for future manipulation, such as provision of water solubility, or for providing useful electronic activation or protection, or for building on steric bulk [as in the famous case of Collman's "picket fence" porphyrin (2)],[3] or the requisite ability for porphyrins to be active in micelle/vesicle systems.



(1) R = H

(2) R = o-NHCOC(Me)$_3$



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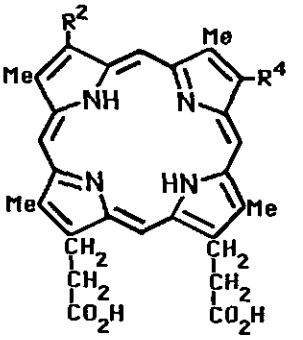
Structures show the Fischer system of nomenclature

It is the objective of this review to put the case for natural porphyrins, and to show how the cheap and readily accessible natural porphyrin, hemin (3), can be modified to make it available for many diverse uses. Indeed, may chemists, including our late mentor George Kenner, do not even regard tetraphenylporphyrin (1), with its four meso-substituents, to be a "real" porphyrin ! On the other hand, nature has made much use of slight modification of the hemin ligand, protoporphyrin-IX (4), or its biosynthetic precursors, to provide a host of biologically significant pigments. For example, the di-dehydro derivative (5) of coproporphyrin-III (6) has been shown to be present , as the S411 porphyrin, in meconium, while the prosthetic heme in the marine worm *Spirographis spallanzanii* is *Spirographis* hemin (7). Pemptoporphyrin (8) has been isolated from the feces of patients with metabolic disorders, while the Harderian gland behind the eyeballs of certain rodents produces harderoporphyrin (9), for some unknown reason. Most of these porphyrins, and various isomers and homologues, have been used for spectroscopic or structure/function studies in model or biological systems which use porphyrin compounds in their prosthetic groups. Such studies enable researchers to understand the way in which steric and electronic effects induced by individual substituents affect the overall function in the intact natural system.

Chemical Transformations of Hemin

Iron can be removed from commercial hemin (3) using any one of several methods.[4] The most useful of these appears to be the Grinstein method,[5] in which ferrous sulfate in methanol containing the hemin is treated with a stream of HCl gas; the ferrous sulfate causes reduction of the iron(III) to iron(II), which is then extruded by the acid. Iron(III) itself is very difficult to remove. Concomitant with removal of the metal, the propionic side chains are transformed into methyl esters which facilitates chromatographic purification of the product.



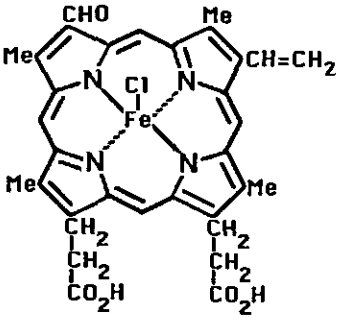
(4) $R^2 = R^4 = CH{=}CH_2$

(5) $R^2 = CH{=}CH.CO_2H$; $R^4 = CH_2CH_2CO_2H$

(6) $R^2 = R^4 = CH_2CH_2CO_2H$

(8) $R^2 = H$; $R^4 = CH{=}CH_2$

(9) $R^2 = CH{=}CH_2$; $R^4 = CH_2CH_2CO_2H$



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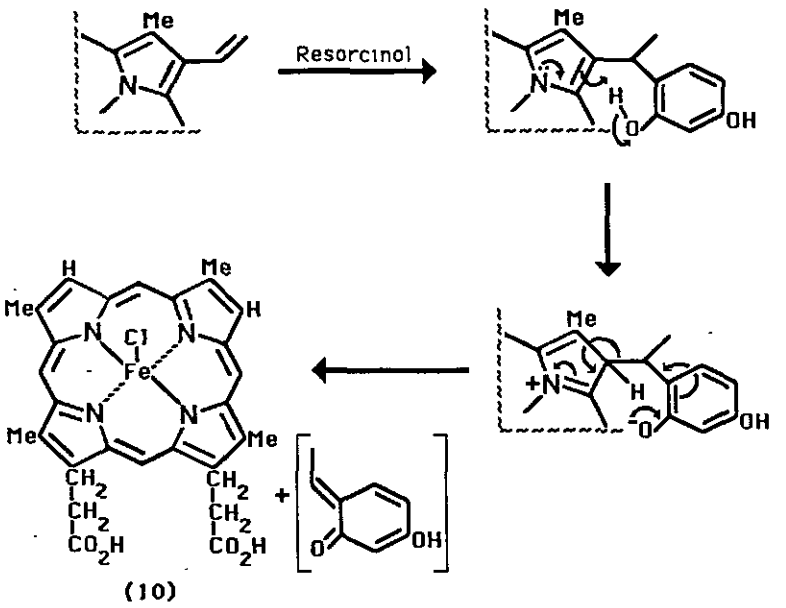
Reactions of the Vinyl Groups in Hemin and Protoporphyrin-IX

The most drastic reaction for the vinyl groups in hemin is their complete removal. This can be accomplished by use of the Schumm protiodevinylation reaction. In this reaction, hemin is heated briefly with resorcinol to afford a good yield of deuterohemin (10). Several mechanisms for the devinylation reaction have been proposed;[6-9] the original suggestion by Kenner et al.,[6] (based on isolation of an intermediate resorcinol adduct,) of initial "O-alkylation" was subsequently modified[7] to give a more likely mechanism, which is shown in Scheme 1.

Catalytic hydrogenation of protoporphyrin-IX dimethyl ester (11), usually in formic acid or as the zinc(II) complex (to avoid porphyrinogen formation) proceeds smoothly to afford mesoporphyrin-IX dimethyl ester (12). In the classical work which established to presence of vinyl groups in porphyrins, Fischer reacted the vinyl groups with diazoacetic ester to give the bis-substituted porphyrin (e.g. 13).[10]



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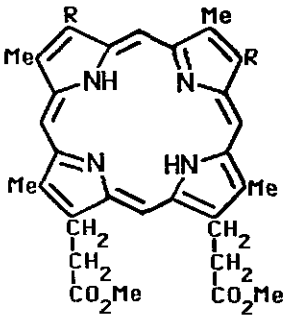
Scheme 1

In presence of acids, such as toluene p-sulfonic acid, the vinyl groups in protoporphyrin-IX undergo electrophilic deuteriation (along with the meso-positions) to give the corresponding derivative in which the vinyl methylene protons (and to a certain extent the vinyl methines) have undergone exchange.[11] The 2- and 4-unsubstituted positions in deuteroporphyrin-IX also undergo exchange under these conditions at about the same rate as the meso-positions.[11]



(11) R = CH=CH$_2$

(12) R = Et

(13) R = CH-CH$_2$ / CH / CO$_2$Et

(14) R = CH(OH)Me

(15) R = CO.Me

(16) R = CHO

(17) R = CH(OH)CH$_2$OH

(18) R = CH=CH.CO$_2$Me

(19) R = CH$_2$CH$_2$CO$_2$Me

(20) R = Me

(21) R = CH=N.OH

(22) R = CN

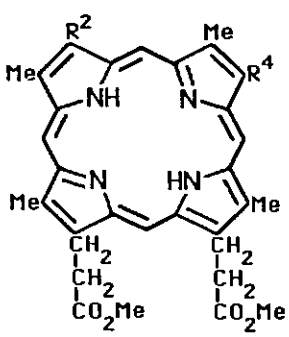
Markownikoff hydration of the protoporphyrin-IX vinyls can be readily accomplished using Fischer's method involving[12] reaction with HBr in acetic acid [giving the 2,4-bis-(1-bromoethyl) derivative], followed by hydration in the work-up to give hematoporphyrin-IX (**14**). The reaction can also be applied to mono-vinyl porphyrins and to chlorins, such as in the final hydration step in the synthesis of the bacteriopheophorbides -c and -d.[13] This hydration reaction, of course, affords enantiomers and/or

diastereomers which can usually be separated by HPLC. Reaction of the 2,4-bis-(1-bromoethyl-porphyrin with 4-carboxylthiazolidines gives the corresponding 2,4-di{α-[3-(4-carboxylthiazolidinyl)]-ethyl}-deuteroporphyrin-IX.[14] Further oxidation of the (1-hydroxyethyl) to acetyl can be accomplished with Jones' reagent, but, 2,4-diacetyldeuteroporphyrin-IX (**15**), for example, can be better prepared by other methods (vide infra). Dehydration of (1-hydroxyethyl) substituents to give vinyls can be readily performed by treatment with benzoyl chloride[15] or by heating in hot o-dichlorobenzene in the presence of toluene p-sulfonic acid.[16]

Using standard organic transformations, the vinyl groups in protoporphyrin-IX dimethyl ester (**11**) can be oxidatively cleaved to give 2,4-diformyldeuteroporphyrin-IX dimethyl ester (**16**). For this purpose, osmium tetroxide [giving the tetra-ol (**17**)] can be used, followed by periodate treatment.[17] The transformation can also be carried out directly with potassium permanganate.[18]

The useful formyl groups can be further elaborated, for example by treatment with methyl magnesium iodide to give (1-hydroxyethyl), or using the Knoevenagel[19] reaction, to give acrylates (**18**), which can be reduced to provide the propionates characteristic of coproporphyrin-III (**19**);[16] a Wittig reaction also allows the formyl groups to be transformed into vinyls.[20] The formyl groups can also be reduced catalytically[21] to give 2,4-dimethyldeuteroporphyrin-IX (**20**), or transformed via the bis-oxime (**21**), into the 2,4-dicyano derivative (**22**) which features two strongly electron-withdrawing groups in the A and B rings.[22] By controlling the stoichiometry, the osmium tetroxide reaction (vide supra) can be carried only to partial completion; thus, controlled oxidation of protoporphyrin-IX dimethyl ester (**11**) with one equivalent of osmium tetroxide gives[7] a mixture of the mono-glycol-mono-vinyl isomers (**23**) and (**24**), which can be separated chromatographically. Treatment with periodate then affords the pure monoformyl-mono-vinyl isomers (**25**) and (**26**), known as *Spirographis* and iso*Spirographis* porphyrin dimethyl esters, respectively. These same porphyrins can also be prepared by treatment of (**11**) with picryl azide.[23] Water soluble porphyrins can be prepared by treatment of (**11**) with various diamines;[24] the amines add to the vinyl groups as well as to the carboxylic ester functions.

The vinyl groups in protoporphyrin-IX dimethyl ester react with nitrosobenzenes to give Diels-Alder type adducts (e.g. **27**), and eventually formylporphyrins.[25] Similar [2+2] and [4+2] cycloadditions take place with many vinylporphyrins;[26,27] for example, reaction of (**11**) with tetracyanoethylene affords adducts (e.g. **28**), while electron-deficient alkynes produce similar compounds (e.g. **29**)

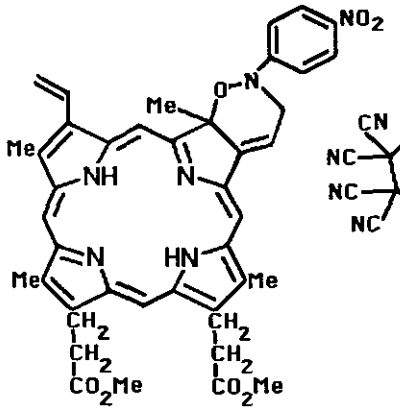


(**23**) R^2 = CH(OH)CH_2OH; R^4 = CH=CH_2

(**24**) R^2 = CH=CH_2; R^4 = CH(OH)CH_2OH

(**25**) R^2 = CHO; R^4 = CH=CH_2

(**26**) R^2 = CH=CH_2; R^4 = CHO



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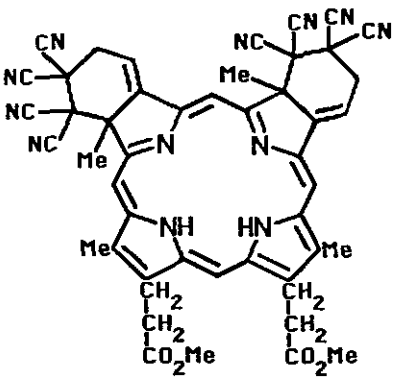

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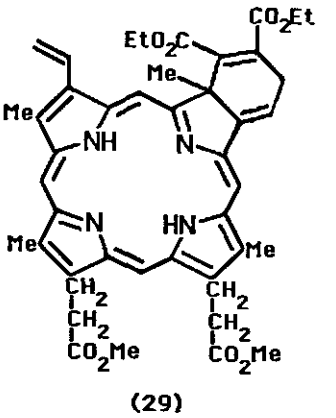

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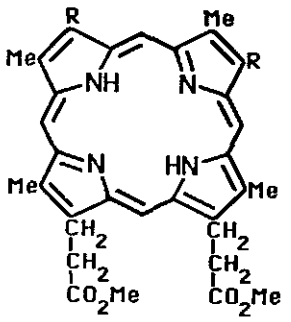
α–Hydroxyethyl groups, as found in hematoporphyrin-IX (**14**), are quite labile, and therefore cannot be used for vinyl protection. Their reactivity is the major reason for their use, in "hematoporphyrin derivative", for photoradiation therapy of tumors. However, β-hydroxyethyl groups are very resistant towards dehydration to produce vinyl groups. Anti-Markownikoff hydration of protoporphyrin-IX dimethyl ester (**11**) can be accomplished with diborane, but yields are poor. A more efficient route[16] involves treatment of, for example, protoporphyrin-IX dimethyl ester with 3 equivalents of thallium(III) trinitrate in methanol to give the bis-dimethyl acetal (**30**); this can be transformed into the bis-aldehyde (**31**) with aqueous acid, and then reduced with sodium borohydride to give the required vinyl-protected product (**32**) in good overall yield from (**11**). Conversion of the β-hydroxyethyl groups back to vinyl is brought about by chlorination with thionyl chloride to give (**33**) followed by dehydrohalogenation with base. Treatment of the diol (**32**) with thionyl bromide gives the bis-bromoethyl compound (**34**) which, after treatment with sodium cyanide in dimethylsulfoxide, gives the bis-cyanoethylporphyrin (**35**). Methanolysis with HCl/MeOH then affords a good overall yield of coproporphyrin-III tetramethyl ester (**19**).[16]



(**11**) R = $CH{=}CH_2$ (**32**) R = CH_2CH_2OH

(**19**) R = $CH_2CH_2CO_2Me$ (**33**) R = CH_2CH_2Cl

(**30**) R = $CH_2CH(OMe)_2$ (**34**) R = CH_2CH_2Br

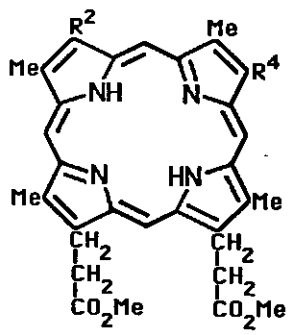
(**31**) R = CH_2CHO (**35**) R = CH_2CH_2CN

If the thallium(III) trinitrate reaction is carried out with only two equivalents of reagent (one equivalent accomplishing thallium chelation), the monoacetal mixture (**36**) and (**37**) is obtained. Hydrolysis and

reduction with borohydride gives the mono-hydroxyethyl-mono-vinyl mixture (**38**) and (**39**), which can be separated chromatographically. Protiodevinylation (resorcinol fusion) of the iron(III) complex, followed by demetalation, gives the pure individual monohydroxyethyl isomers (**40**) and (**41**) which, after chlorination (thionyl chloride) and base-treatment give pemptoporphyrin (**42**) and isopemptoporphyrin (**43**) dimethyl esters, in good overall yields.[7]

To the chagrin of several researchers, and the destruction of various elaborate synthetic routes, Vilsmeier formylation of copper(II) vinyl-porphyrins and -chlorins, (the standard method for meso-formylation),[28] takes place preferentially at the vinyl groups to give acrolein derivatives (e.g. **44**) rather than the meso-formyl product.[29] These acrolein derivatives, so far, have not found any useful applications.

One of the most interesting reactions of the vinyl groups in protoporphyrin-IX is the reaction with singlet oxygen in a Diels-Alder fashion to give the polar chlorin mixture of photoprotoporphyrin dimethyl ester (**45**) and isophotoprotoporphyrin dimethyl ester, its ring-B modified isomer.[30] This reaction was subsequently used by Inhoffen and co-workers[31] in an ingenious synthesis of *Spirographis* [(**25**) from (**45**)] and iso*Spirographis* porphyrin (**26**) esters, and in combination with several of the transformations above, by Dolphin and Sivasothy[32] in partial syntheses of the S411 porphyrin (**5**) and harderoporphyrin (**9**).



(**36**) $R^2 = CH{=}CH_2$; $R^4 = CH_2CH(OMe)_2$

(**37**) $R^2 = CH_2CH(OMe)_2$; $R^4 = CH{=}CH_2$

(**38**) $R^2 = CH{=}CH_2$; $R^4 = CH_2CH_2OH$

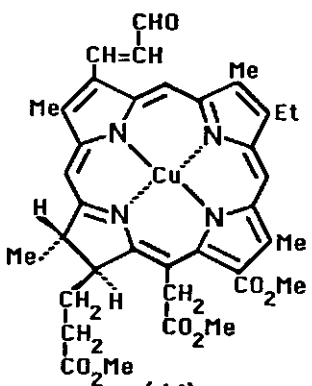
(**39**) $R^2 = CH_2CH_2OH$; $R^4 = CH{=}CH_2$

(**40**) $R^2 = H$; $R^4 = CH_2CH_2OH$

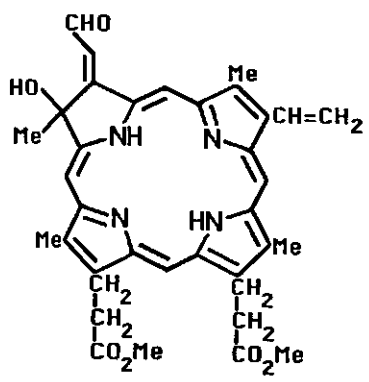
(**41**) $R^2 = CH_2CH_2OH$; $R^4 = H$

(**42**) $R^2 = H$; $R^4 = CH{=}CH_2$

(**43**) $R^2 = CH{=}CH_2$; $R^4 = H$



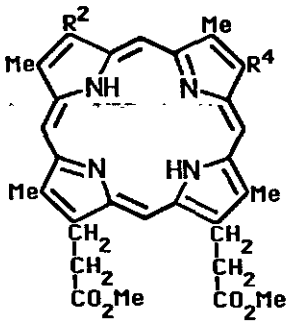
(**44**)

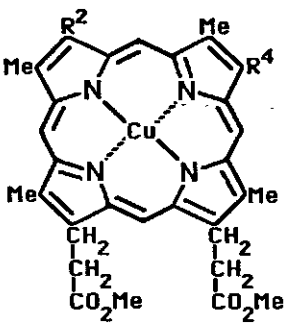


(**45**)

Reactions of the 2,4-Unsubstituted Positions in Deuteroporphyrin-IX

Deuteroporphyrin-IX dimethyl ester (**46**), as its iron(III) or copper(II) complex, can be acylated with relative ease at the 2- and 4-positions. With acetic anhydride and tin(IV) chloride (as a Friedel-Crafts catalyst), the diacetyl derivative (**15**) is obtained after demetalation, in high yield; acid chlorides can be used in place of the anhydrides but yields of product seem to be lower. If the copper(II) complex of deuteroporphyrin-IX dimethyl ester is treated briefly (for a few seconds) in benzene containing acetic anhydride and tin(IV) chloride, then a mixture containing mainly the 2- and 4-monoacetylporphyrin chelates (**47**) and (**48**) is obtained.[20,33] This mixture can be separated, either by thick layer chromatography, medium pressure chromatography, or more recently (on the 5 g scale) by preparative HPLC.[34] Separation of the metal free compounds (**49**) and (**50**) is more difficult. Surprisingly, in the mixture of (**47**) and (**48**), the 2-acetyl-isomer (**47**) seems to predominate slightly. Copper(II) acetylporphyrins can be de-acetylated (Scheme 2) by treatment with boron trifluoride etherate and ethane dithiol.[35,36]





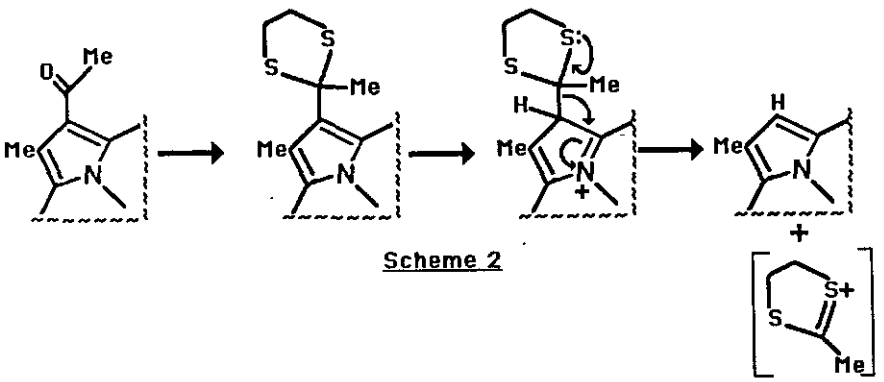
(**46**) $R^2 = R^4 = H$

(**47**) $R^2 = CO.Me$; $R^4 = H$

(**49**) $R^2 = CO.Me$; $R^4 = H$

(**48**) $R^2 = H$; $R^4 = CO.Me$

(**50**) $R^2 = H$; $R^4 = CO.Me$

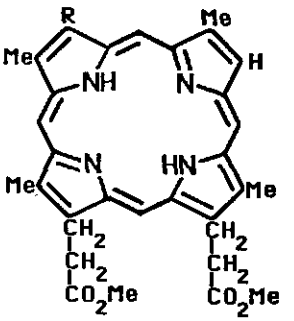


Scheme 2

With large quantities of the monoacetyldeuteroporphyrins (*49*) and (*50*) *being available, several interesting* series of transformations become available. For example, conversion of the acetylporphyrins to the

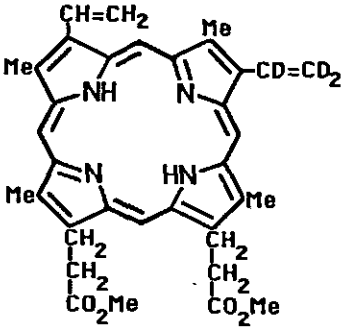
corresponding (1-hydroxyethyl) derivatives, followed by dehydration, affords pemptoporphyrin (42) and its isomer (43). Transformation of the mono-vinyl compound (43) into (2-hydroxyethyl) (thallium route) (i.e. 51), followed by acetylation and Friedel-Crafts acetylation gives (52) which can be deuteriated, reduced (sodium borodeuteride), and vinylated to give the regioselectively labeled vinyl compound (53).[20] Catalytic reduction of the isomerically pure vinylporphyrins (42) and (43) to give the ethyl derivatives [(54), (55)], followed by Friedel-Crafts acetylation (of the copper complex) and borohydride reduction, gives (56) and (57), which can then be dehydrated to give the vinyl-ethyl isomers (58) and (59).[37]

Treatment of the zinc(II) or copper(II) complexes of deuteroporphyrin-IX dimethyl ester with mercury(II) acetate, followed by chloride, gives[36] the bis-mercurichloride derivative (60). A small amount of trimercurated compounds (61) and (62) is also obtained.[38] Treatment of (60) with lithium palladium trichloride in acetonitrile, followed by methyl acrylate, gives the bis-acrylate (63) in good yield, along with small amounts of cyclized monoacrylates [e.g. (64) obtained from (61)].[38] The bis-acrylate (63), after demetalation, is the same (18) as that obtained from the Knoevenagel reaction of 2,4-diformyldeuteroporphyrin-IX dimethyl ester (16); thus, for example, catalytic hydrogenation gives coproporphyrin-III tetramethyl ester (19).



(43) R = $CH{=}CH_2$

(51) R = CH_2CH_2OH



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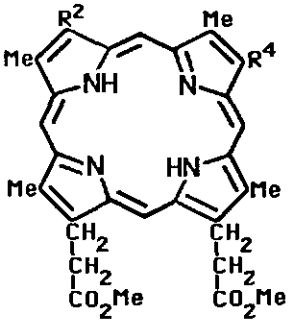


(42) R^2 = H; R^4 = $CH{=}CH_2$

(43) R^2 = $CH{=}CH_2$; R^4 = H

(52) R^2 = CH_2CH_2OAc; R^4 = CO.Me

(54) R^2 = H; R^4 = Et

(55) R^2 = Et; R^4 = H

(56) R^2 = CH(OH)Me; R^4 = Et

(57) R^2 = Et; R^4 = CH(OH)Me

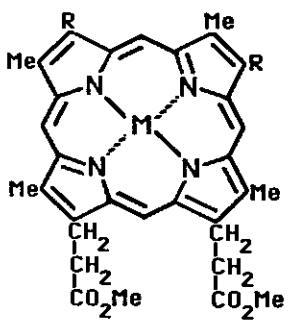
(58) R^2 = $CH{=}CH_2$; R^4 = Et

(59) R^2 = Et; R^4 = $CH{=}CH_2$

The bis-mercurated porphyrin (**60**) can be treated with sodium borodeuteride or DCl to give the deuteriated product (**65**),[36] or with iodine to give the bis-iodo compound (**66**) which is otherwise difficult to obtain. The corresponding bis-bromoporphyrin (**67**) can be obtained by treatment of deuteroporphyrin-IX dimethyl ester with pyridinium bromide perbromide.[39] Treatment of (**60**) with vinyl bromide and Wilkinson's rhodium catalyst gives a good yield of protoporphyrin-IX dimethyl ester (**11**), this being a useful two-step procedure[40] for regenerating protoporphyrin from deuteroporphyrin.

Mercuration of the zinc or copper complexes of the mono-acetyldeuteroporphyrins (**49**) or (**50**), gives (**68**) and (**69**) (zinc series), respectively, which give the monoacrylates (**70**) and (**71**), with lithium palladium trichloride and methyl acrylate.[36] Catalytic hydrogenation to give (**72**) and (**73**), followed by demetalation, borohydride reduction and dehydration, then gives harderoporphyrin and isoharderoporphyrin esters, (**74**) and (**75**), respectively. Deacetylation (vide supra) of (**72**) (copper complex) followed by mercuration and the palladium/olefin reaction, affords the S411 porphyrin trimethyl ester (**76**) after removal of the copper.[36]

Deuteroporphyrin-IX dimethyl ester (**46**) can be sulfonated with, for example, pyridinium N-sulfonic acid or oleum, to give (**77**).[41]



(**18**) R = CHO; M = 2H

(**19**) R = $CH_2CH_2CO_2Me$; M = 2H

(**60**) R = Hg-Cl; M = Zn or Cu

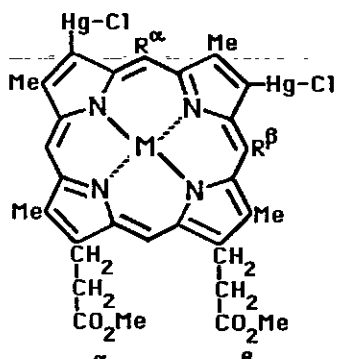
(**63**) R = $CH{=}CH.CO_2Me$; M = Zn or Cu

(**65**) R = D; M = 2H

(**66**) R = I; M = 2H

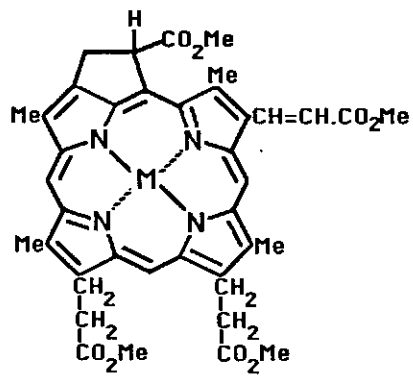
(**67**) R = Br; M = 2H

(**77**) R = SO_3H



(**61**) R^{α} = Hg-Cl; R^{β} = H

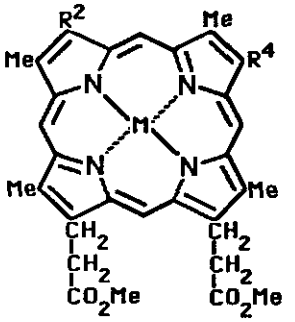
(**62**) R^{α} = H; R^{β} = Hg-Cl



(**64**)

Reactions of the Propionic Side Chains in Protoporphyrin-IX

The propionic side chains at the 6- and 7-positions in many natural porphyrins can readily be decarboxylated by dry pyrolysis,[42] to give the ethyl derivative. This was a standard reaction in Fischer chemistry, for example in the transformation of coproporphyrin-III (6) into etioporphyrin-III (78). A more efficient, but lengthier procedure, e.g. using mesoporphyrin-IX dimethyl ester (12) (Scheme 3), was subsequently developed by Baker and Corwin.[43]



(68) R^2 = CO.Me; R = Hg-Cl; M = Zn

(69) R^2 = Hg-Cl; R^4 = CO.Me; M = Zn

(70) R^2 = CO.Me; R^4 = CH=CH.CO_2Me; M = Zn

(71) R^2 = CH=CH.CO_2Me; R^4 = CO.Me; M = Zn

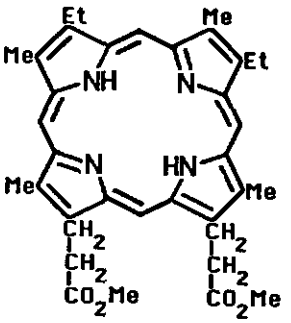
(72) R^2 = CO.Me; R^4 = $CH_2CH_2CO_2$Me; M = Zn

(73) R^2 = CH_2CH_2CO Me; R^4 = CO.Me; M = Zn

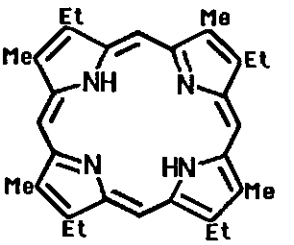
(74) R^2 = $CH=CH_2$; R^4 = $CH_2CH_2CO_2$Me; M = 2H

(75) R^2 = $CH_2CH_2CO_2$Me; R^4 = $CH=CH_2$; M = 2H

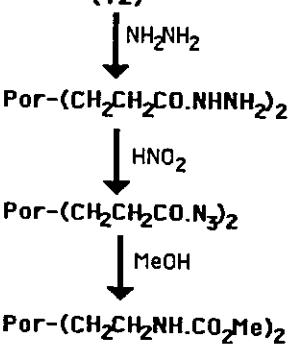
(76) R^2 = CH=CH.CO_2Me; R^4 = $CH_2CH_2CO_2$Me; M = 2H

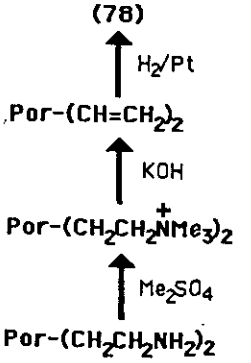


(12)



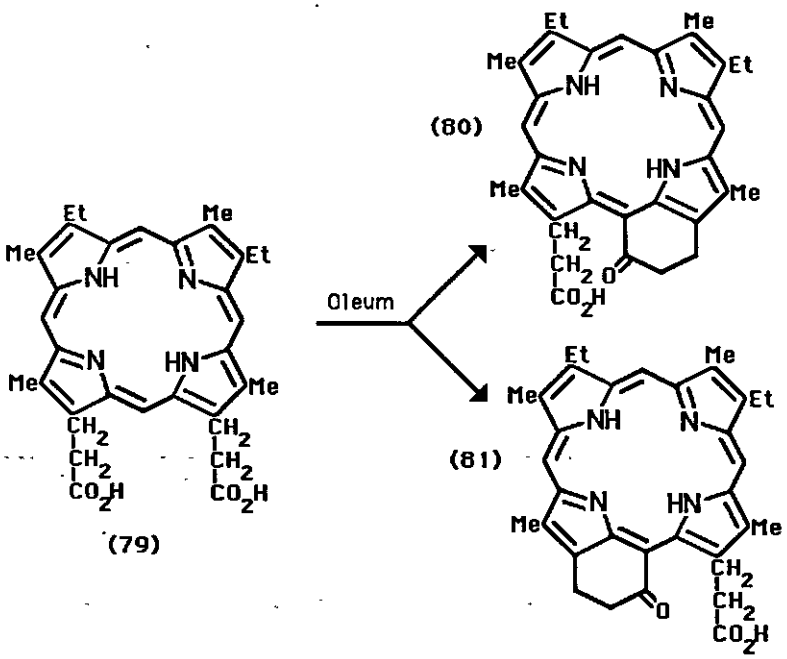
(78)



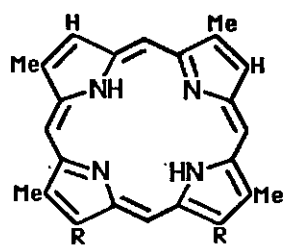


Scheme 3

The so-called "anhydro" reaction can be accomplished[44,45] with porphyrin or chlorin propionic acids or esters by treatment with oleum. Mesoporphyrin-IX (79), for example, gives a mixture of the two possible "anhydro"-isomers (80) and (81), and various further reactions can be carried out on these.[45] The anhydro-ring can also be re-opened by treatment with various acids.[44,45]



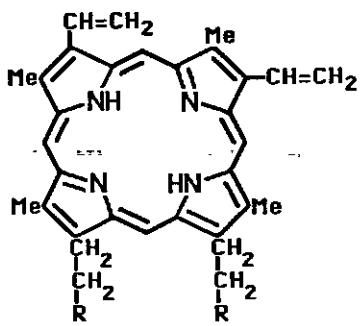
Treatment of mesoporphyrin-IX (12) or deuteroporphyrin-IX dimethyl esters (82) with lithium diethylamide, followed by phenyl selenyl bromide, gives[46,47] the bis-selenyl compound (e.g. 83). With hydrogen peroxide, a syn-elimination takes place to afford the bis-acrylate (84), which has been used in further deuteration reactions (vide infra).



(82) R = $CH_2CH_2CO_2Me$

(83) R = $CH(Se\text{-}Ph)\text{-}CH_2CO_2Me$

(84) R = $CH{=}CH.CO_2Me$



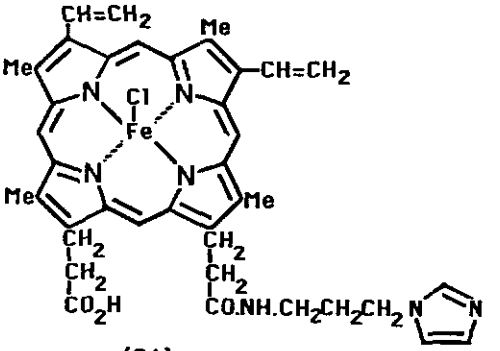
(11) R = CO_2Me (88) R = CH_2Br

(85) R = CH_2OH (89) R = CH_2CN

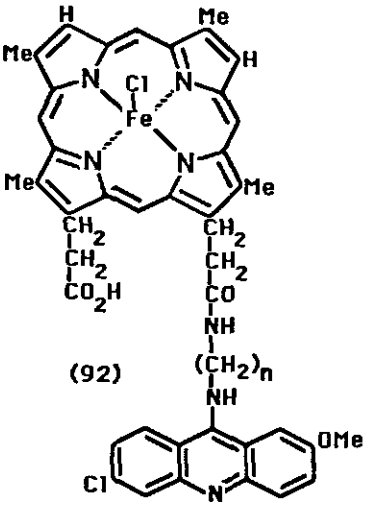
(86) R = CH_2OMes (90) R = CH_2CO_2Me

(87) R = CH_3

The propionic esters in mesoporphyrin-IX dimethyl ester (12)[48] or in protoporphyrin-IX dimethyl ester (11)[49] can be reduced to 3-hydroxypropyl (e.g. 85) using lithium aluminum hydride. Further reduction of the corresponding bis-mesylate (86) with the same reagent gives the bis-n-propyl derivative (87). With thionyl bromide, the diol (85) gives the bis-(3-bromopropyl) compound (88), and this can be made to react with cyanide to give (89). Methanolysis then gives (90), which has also been obtained by total synthesis.[50]



(91)



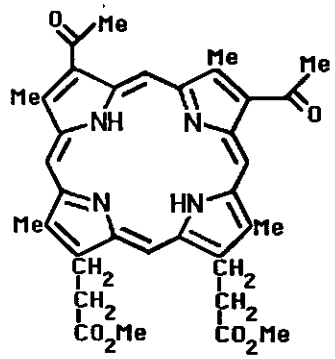
(92)

Esterification and transesterification of the propionic and other carboxylate side chains in porphyrins is a relatively trivial process which requires no further amplification here. However, some very interesting reactions of this type have been described; for example, attachment of aminoalkylimidazoles to hemin (3) leads to compounds, (e.g. 91) which are useful models for NMR studies of heme proteins.[51] Porphyrins dimers have been obtained using the possibility of amide or ester linkages,[52] and side chains which bear intercalators (e.g. 92) have been synthesized as models of the anti-cancer drug, bleomycin.[53]

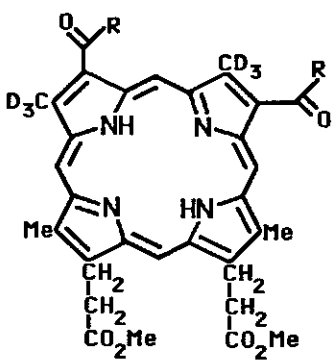
Reactions of the Methyls in Protoporphyrin-IX

The only chemical reaction of the methyls in protoporphyrin-IX to be reported so far involves electrophilic deuteriation. Thus, if (11) is heated in solvents containing MeOD and methoxide, exchange occurs[54,55] at the 1-, 3-, 5- and 8-methyls. Due to the electron-withdrawing effect of the vinyls on rings A and B, the 1- and 3-methyls are exchanged more than those at 5- and 8-. The differential reactivity (reactvity order 3- > 1-

> 5- > 8-) can be explained[55] on the basis of simple electronic effects. Some base-catalyzed deuteriation of the vinyl groups is also observed, indicating the the mechanism is not entirely inductive.

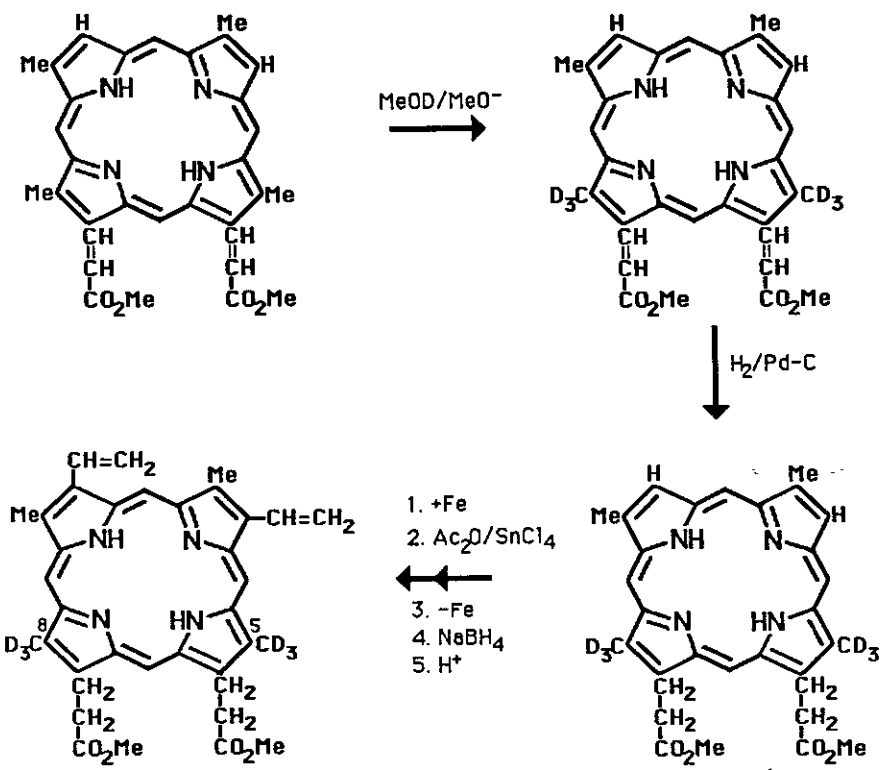


(15)



(93) R = CD_3

(94) R = CH_3



Scheme 4

If the methyl-bearing rings are also substituted with more strongly electron-withdrawing groups, e.g. acetyl groups, the porphyrin methyls and the acetyl methyls, for example, in 2,4-diacetyldeuteroporphyrin-IX dimethyl ester (**15**), are exchanged rapidly to give (**93**). The deuterium in the acetyl methyls can easily be removed in dilute acid,[34,56] but the porphyrin methyls are unaffected by this, allowing (**94**) to be isolated in high yield; as mentioned above, acetyl groups can be easily converted into vinyls, allowing syntheses of 1- and 3-methyl deuteriated samples of protoporphyrin-IX required for heme protein reconstitution reactions.[57] Acrylate groups, as vinylogous esters, e.g. in (**84**), can also be used for methyl deuteriation, and in this way (Scheme 4), 5- and 8-methyl deuteriated derivatives of protoporphyrin-IX can be synthesized.[34]

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