Aust. J. Chem., 1977, **30**, 217–20

The Chemistry of Pyrrolic Compounds. XXXIV* Vinylporphyrins from Derivatives of 2′-Hydroxyethylporphyrins

Peter S. Clezy and Christopher J. R. Fookes

Department of Organic Chemistry, University of New South Wales, P.O. Box 1, Kensington, N.S.W. 2033.

Abstract

The bromo, chloro and methanesulphonate derivatives of 2′-hydroxyethylporphyrins are readily converted in high yield into the corresponding vinylporphyrins by treatment with sodium hydroxide in refluxing aqueous pyridine.

Introduction

The vinyl group is found in many naturally occurring porphyrins and its generation during a porphyrin synthesis is, therefore, an operation with which chemists working in this field are frequently confronted. In general, vinylporphyrins have been formed by an elimination reaction involving one of three substituent types, namely the 1′-hydroxyethyl, the 2′-hydroxyethyl, the 2′-dimethylaminoethyl group.

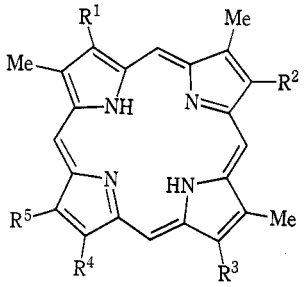
The use of the 2′-hydroxyethyl substituent as a precursor for the vinyl function was pioneered at Liverpool by Professor Kenner and his colleagues.[1] At an appropriate stage of the porphyrin synthesis, the alcoholic group was converted into the 2′-chloroethyl derivative; the generation of the vinyl function was then achieved by dehydrochlorination of the porphyrin zinc chelate with potassium t-butoxide. More recently 1,5-diazabicyclo[4,3,0]non-5-ene has been used as the base to carry out this elimination from a metal-free porphyrin.[2] However, we have found that both these procedures give disappointing results when applied to porphyrins substituted with electron-withdrawing substituents.[3] Other workers have shared this experience and have found it necessary to protect a formyl group as an acetal in order to achieve, in satisfactory yield, dehydrochlorination of a 2′-chloroethyl substituent in an aldehydic porphyrin.[4]

As part of a recent sequence leading to the synthesis of phaeophorbide c_2 methyl ester, the porphyrin (1a) was treated with sodium hydroxide in aqueous pyridine.[5] As a result, the desired hydrolysis of the ring ester was accomplished but in addition dehydrohalogenation of the chloroethyl side chains occurred. The fact that the latter

* Part XXXIII, *Aust. J. Chem.*, 1976, **29**, 2325.

[1] Carr, R. P., Jackson, A. H., Kenner, G. W., and Sach, G. S., *J. Chem. Soc. C*, 1971, 487.
[2] Battersby, A. R., Hodgson, G. L., Ihara, M., McDonald, E., and Saunders, J., *J. Chem. Soc., Perkin Trans. 1*, 1973, 2923.
[3] Clezy, P. S., and Diakiw, V., *Aust. J. Chem.*, 1975, **28**, 2703.
[4] Jackson, A. H., Kenner, G. W., and Wass, J., *J. Chem. Soc., Perkin Trans. 1*, 1974, 480.
[5] Clezy, P. S., and Fookes, C. J. R., *J. Chem. Soc., Chem. Commun.*, 1975, 707.

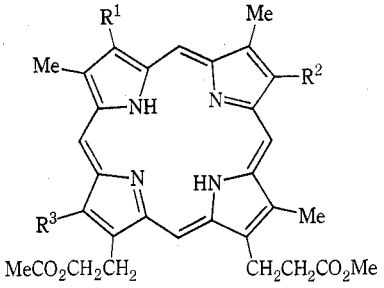
reaction was achieved both cleanly and in promising yield was a little unexpected in view of the difficulties outlined above. We now report that sodium hydroxide in aqueous pyridine can be used quite generally to obtain the vinyl group from derivatives of 2′-hydroxyethylporphyrins.



	R^1	R^2	R^3	R^4	R^5
(1a)	CH_2CH_2Cl	CH_2CH_2Cl	CO_2Et	CHO	Me
(1b)	CO_2Me	$CH{=}CH_2$	$CH_2CH_2CO_2Me$	$CH_2CH_2CO_2Me$	CHO
(1c)	CH_2CH_2OH	$COCH_3$	$CH_2CH_2CO_2Me$	$CH_2CH_2CO_2Me$	Me

Results and Discussion

The use of sodium hydroxide in aqueous pyridine has enabled us to improve significantly the yield (see Scheme 1) of vinylporphyrin generated from certain derivatives of 2′-hydroxyethyl porphyrins in sequences leading to *Spirographis* porphyrin [(2), (3), (4) → (8)], iso*Spirographis* porphyrin [(5) → (9)] and the porphyrin (1b) [(6) → (10)], an important intermediate in our projected synthesis of porphyrin *a*.[3]



	R^1	R^2	R^3		R^1	R^2	R^3	Yield (%)
(2)	$(CH_2)_2Cl$	Ac	Me					84
(3)	$(CH_2)_2Br$	Ac	Me	→ (8)	$CH{=}CH_2$	Ac	Me	75 (cf.[3] 37)
(4)	$(CH_2)_2OSO_2Me$	Ac	Me					83
(5)	$(CH_2)_2Cl$	CHO	Me	→ (9)	$CH_2{=}CH_2$	CHO	Me	62 (cf.[3] 27)
(6)	CO_2Me	Ac	$(CH_2)_2Br$	→ (10)	CO_2Me	Ac	$CH{=}CH_2$	78 (cf.[3] 57)
(7)	$(CH_2)_2Cl$	$CH{=}CH_2$	Me	→ (11)	$CH{=}CH_2$	$CH{=}CH_2$	Me	94

Scheme 1

The presence of an electronegative group is not essential for the success of the procedure as exemplified by the preparation of protoporphyrin IX dimethyl ester (11) from compound (7). In each case the structure of the product was confirmed by comparison (m.p.; m.m.p.; n.m.r.; t.l.c) with material synthesized independently.

Comparative experiments in which the vinylporphyrin (8) was prepared from the chloro (2), bromo (3) and methanesulphonate (4) derivatives of the 2′-hydroxyethylporphyrin (1c) indicated that the leaving group did not profoundly effect the outcome of the reaction. The simplest and most direct procedure, therefore, was to convert the porphyrin alcohol into the sulphonate derivative by reaction with methanesulphonyl chloride in pyridine and then to proceed directly to the elimination step by heating the resultant solution under reflux with aqueous sodium hydroxide.* Small amounts of 2′-hydroxyethylporphyrins (later fractions) and 2′-halogenoethylporphyrins (early fractions) were isolated at times during chromatographic purification of the vinylporphyrins. On such occasions the yield quoted in Scheme 1 could be improved by recycling these by-products.

We have found the reaction of sodium hydroxide in aqueous pyridine to be the most convenient and efficient procedure we have examined for the generation of the vinyl group from derivatives of 2′-hydroxyethylporphyrins. The facts that it is unnecessary to work with metal chelates or protect electronegative substituents are attractive features of the procedure.† A minor disadvantage of the use of aqueous pyridine is the need to re-esterify any ester group present in the porphyrin molecule.

Experimental

(*a*) General

All melting points were uncorrected and were determined on a Kofler micro-melting-point apparatus. Column chromatography was normally carried out on Merck silica gel H No. 60 with 'ethanol-free' chloroform as the eluent. This latter solvent was prepared by washing commercial chloroform with an equal volume of water and drying the organic phase over sodium sulphate. If necessary, solvent polarity was increased by washing subsequent portions of chloroform with the same lot of water. Solutions in water-immiscible solvents were dried over sodium sulphate. Pyridine (May & Baker) was dried over potassium hydroxide and distilled before use.

(*b*) Dehydrogenation Reactions and Related Procedures

(i) *General Procedure*

In a typical experiment (carried out under nitrogen), water (15 ml) was carefully added to a refluxing solution of the porphyrin (*c.* 200 mg) in pyridine (90 ml). After 5 min, sodium hydroxide (0·6 g) in water (20 ml) was added and the heating continued (1·5 h). At the end of the reaction, aqueous acetic acid (6 M) was added (to neutralize excess sodium hydroxide) followed by water (200 ml). The mixture was concentrated under reduced pressure, the product collected and the free acids esterified (methanolic sulphuric acid for side-chain acids; methanolic sulphuric acid followed by diazomethane if ring acids were present in addition to side-chain acids).

(ii) *8-Acetyl-13,17-di(2-methoxycarbonylethyl)-2,7,12,18-tetramethyl-3-vinyl-21*H,*23*H-*porphine* (*8*)

Method 1.—A solution of 8-acetyl-3-(2-chloroethyl)-13,17-di(2-methoxycarbonylethyl)-2,7,12,18-tetramethyl-21*H*,23*H*-porphine[3] (165 mg) in pyridine (90 ml) was refluxed under nitrogen for a few minutes and then treated with aqueous sodium hydroxide as described in the general procedure [(*b*)(i)]. The esterified product was purified by chromatography on silica (8 g) and recrystallization from chloroform–methanol to give the vinylporphyrin (130 mg) as red needles, m.p. 201–204° (lit.[3] 204–206°).

* Since the sulphonate was not isolated and was heated in a pyridine solution which contained chloride ions generated in the reaction between methanesulphonyl chloride and the porphyrin alcohol, it is possible that displacement of the sulphonate group by chloride occurred, at least in part, prior to the commencement of elimination.

† Very recent results have indicated that even higher yields of vinylformylporphyrins can be obtained if dehydrohalogenation is carried out with the formyl group protected as an acetal derivative.

Method 2.—Replacing the chloroethylporphyrin in method 1 by the bromoethyl analogue (209 mg) gave the vinylporphyrin (139 mg), m.p. 183°, solidifying, and melting again at 204–206°.

Method 3.—Methanesulphonyl chloride (100 μl) was added dropwise to a stirred solution of 8-acetyl-3-(2-hydroxyethyl)-13,17-di(2-methoxycarbonylethyl)-2,7,12,18-tetramethyl-21*H*,23*H*-porphine[3] (200 mg) in dry pyridine (20 ml). More pyridine (70 ml) was added after 30 min and the solution refluxed under nitrogen for 10 min. Aqueous sodium hydroxide was then added and the reaction continued as described in the general procedure [(*b*)(i)]. The product was purified as described under method 1 to give the vinylporphyrin (160 mg), m.p. 184°, solidifying and melting again at 204–206°.

The compounds prepared by methods 1–3 were identical with each other and with an authentic sample of this product.[3]

(iii) *8-Formyl-13,17-di(2-methoxycarbonylethyl)-2,7,12,18-tetramethyl-3-vinyl-21*H,*23*H-*porphine* (*iso*Spirographis *Porphyrin Dimethyl Ester*) (*9*)

A solution of 3-(2-chloroethyl)-8-formyl-13,17-di(2-methoxycarbonylethyl)-2,7,12,18-tetramethyl-21*H*,23*H*-porphine[3] (160 mg) in pyridine (90 ml) was refluxed under nitrogen for a few minutes and treated with aqueous sodium hydroxide as described in the general procedure [(*b*)(i)] except that in this case the reaction time was reduced to 25 min. After re-esterification, the product was purified by chromatography on silica (8 g) and recrystallization from chloroform–methanol to give the vinylporphyrin (94 mg) as short needles, m.p. 235–236° (lit.[3] 233–235°), identical with an authentic sample.[3]

(iv) *8-Acetyl-3-methoxycarbonyl-13,17-di(2-methoxycarbonylethyl)-2,7,12-trimethyl-18-vinyl-21*H,*23*H-*porphine* (*10*)

Method 1.—Methanesulphonyl chloride (200 μl) was added to a solution of 8-acetyl-18-(2-hydroxyethyl)-3-methoxycarbonyl-13,17-di(2-methoxycarbonylethyl)-2,7,12-trimethyl-21*H*,23*H*-porphine[3] (370 mg) in pyridine (40 ml) and the mixture left at room temperature for 30 min. Additional pyridine (80 ml) was added and the elimination reaction continued as described in the general procedure [(*b*)(i)]. The product was purified by chromatography on silica (20 g) and recrystallization from chloroform–methanol to give the vinylporphyrin (282 mg) as a mixture of large plates and woolly needles which both changed form at *c.* 170° and finally melted at 205–208° (lit.[3] 205–207°).

Method 2.—A solution of 8-acetyl-18-(2-bromoethyl)-3-methoxycarbonyl-13,17-di(2-methoxycarbonylethyl)-2,7,12-trimethyl-21*H*,23*H*-porphine[3] (533 mg) in pyridine (150 ml) was refluxed for 10 min under nitrogen and then treated with aqueous sodium hydroxide as described in the general procedure [(*b*)(i)]. The product was purified as described under method 1 to give the vinylporphyrin (372 mg).

The materials obtained by both methods were identical with an authentic sample of the compound.[3]

(v) *13,17-Di(2-methoxycarbonylethyl)-2,7,12,18-tetramethyl-3,8-divinyl-21*H,*23*H-*porphine* (*Protoporphyrin-IX Dimethyl Ester*) (*11*)

3-(2-Chloroethyl)-13,17-di(2-methoxycarbonylethyl)-2,7,12,18-tetramethyl-8-vinyl-21*H*,23*H*-porphine[3] (110 mg) was treated with aqueous sodium hydroxide in pyridine as described above [(*b*)(i)]. The product was esterified and purified by chromatography on silica (6 g) and by recrystallization from chloroform–methanol to give the divinylporphyrin (98 mg) as flat needles, m.p. 232–233° (lit.[1] 228–229°), identical with a sample independently synthesized.[3]

Acknowledgment

Financial support from the Australian Research Grants Committee is gratefully acknowledged.

Manuscript received 13 July 1976