Evidence for a Fast (Major) and Slow (Minor) Pathway in the Schumm Devinylation Reaction of Vinyl Porphyrins

Robert K. DiNello and David H. Dolphin*

Department of Chemistry, University of British Columbia, Vancouver, British Columbia V6T 1Y6

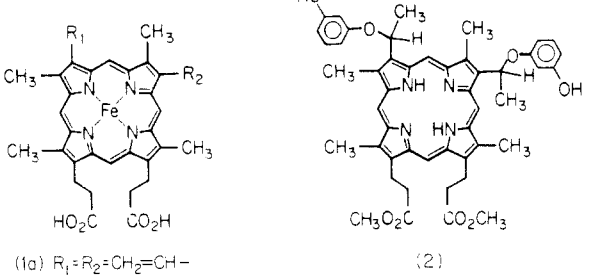
Received March 2, 1981

The devinylation of protohemin [Fe(III) protoporphyrin] in molten resorcinol is shown to proceed by two pathways. Two of the three possible intermediates in the minor (slow) pathway have been isolated and characterized as their dimethyl esters. In both, C-alkylation of resorcinol at the porphyrin C-1′ vinyl side chains has occurred. These intermediates are, however, converted into deuterohemin far too slowly for them to be on the major pathway from protohemin to deuterohemin. It is suggested that other intermediates, possibly in which O-alkylation of resorcinol has occurred, are intermediates in the major (fast) pathway from protohemin to deuterohemin.

Introduction

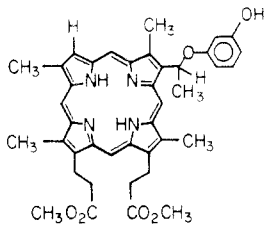
One of the most useful reactions in the chemistry of natural porphyrins is the devinylation of vinyl porphyrins in molten resorcinol such as the conversion of protoheme (**1a**) to deuteroheme (**1b**). The reaction is especially versatile in that 1′-hydroxyalkyl, formyl, and acetyl porphyrins have also been shown to lose these side chains under similar conditions. Devinylation of porphyrins in molten resorcinol, discovered by Schumm in 1928,[1] figured importantly in Fischer's synthesis of protohemin[2] and in the elucidation of the structure of heme *a*.[3] It is therefore surprising that only recently have attempts been made to elucidate the mechanism of this reaction, especially in the light of work which showed several hemins are present in crude resorcinol melts of protohemin.

In 1967, Burbidge et al.[4] isolated two porphyrins from crude melts of protohemin, which they identified as the O-alkylation products **2** and **3a,b**) from the reaction of

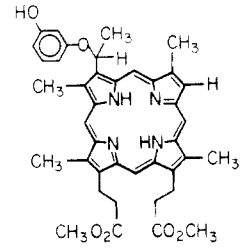


(1a) $R_1 = R_2 = CH_2{=}CH-$
(1b) $R_1 = R_2 = H$

(2)



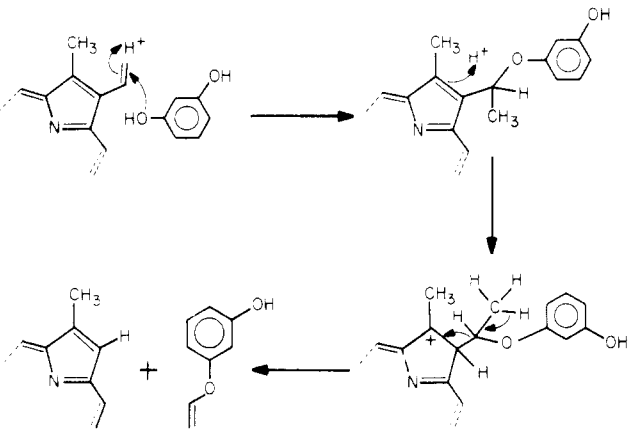
(3a)



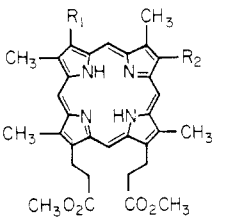
(3b)

protoporphyrin (**4**) and 2-(and 4-)vinyldeuteroporphyrin (**5a** and **5b**) with resorcinol, and suggested that the Schumm reaction proceeded as in Scheme I. In 1977, Bonnett et al.[5] showed this identification to be in error. These workers isolated two porphyrins from crude melts of protoporphyrin, both 1:1 adducts with resorcinol. Since

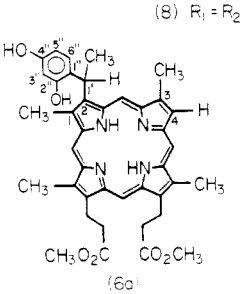
Scheme I



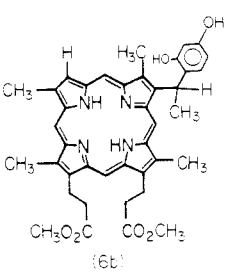
the mass spectra of the compounds could not distinguish whether C- or O-alkylation had occurred and as the compounds were not isolated in large enough amounts for adequate characterization, the devinylation of a model, 2-vinylheptaethylporphyrin, was studied. The mass spectrum of an intermediate isolated from devinylation reactions of 2-vinylheptaethylporphyrin showed that this compound formed a 1:1 adduct in which C-alkylation of resorcinol had occurred. The C-alkylated resorcinol adducts (**6a** and **6b**) of 2-(and 4-)vinyldeuteroporphyrin and



(4) $R_1 = R_2 = CH_2{=}CH-$
(5a) $R_1 = CH_2{=}CH-$; $R_2 = H$
(5b) $R_1 = H$; $R_2 = CH_2{=}CH-$
(8) $R_1 = R_2 = H$



(6a)



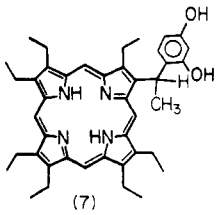
(6b)

that of 2-vinylheptaethylporphyrin (**7**) lost their resorcinyl side chains on heating in resorcinol, the first two compounds to give deuteroporphyrin (**8**) and the third, hep-

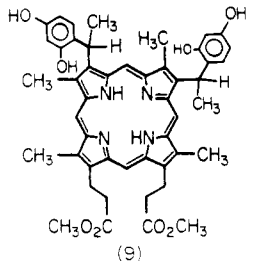
(1) O. Schumm, *Z. Physiol. Chem.*, **178**, 1 (1928).
(2) H. Fischer and H. Orth, "Die Chemie des Pyrrols", Vol. 1, Johnson Reprint Corporation, New York, 1968.
(3) G. S. Marks, D. K. Dougall, E. Bullock, and S. F. Macdonald, *J. Am. Chem. Soc.*, **82**, 3183 (1960).
(4) P. A. Burbidge, G. L. Collier, A. H. Jackson, and G. W. Kenner, *J. Chem. Soc. B*, 930 (1967).
(5) R. Bonnet, I. H. Campion-Smith, and A. J. Page, *J. Chem. Soc., Perkin Trans. 1*, 68 (1977).

0022-3263/81/1946-3498$01.25/0

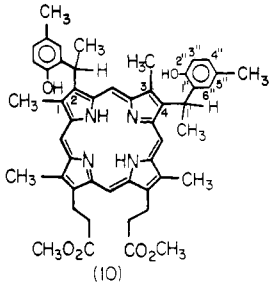
taethylporphyrin. The conclusion was that the devinylation reaction occurred by a pathway where C-alkylated resorcinol adducts were the intermediates in the major reaction pathway.



(7)



(9)



(10)

We became interested in the intermediates in the devinylation reaction as a means of synthesis of porphyrins in the IX series bearing bulky hydroxyalkyl side chains in the 2 and 4 positions. As had Burbidge et al., one of us mistakenly concluded that the 1:1 adducts of resorcinol and 2-(and 4-)vinyldeuteroporphyrin resulted from O-alkylation.[6] However, the proportion of the 1:1 adduct between resorcinol and 2-(and 4-)vinyldeuteroporphyrin was noted to rise rapidly to a maximum in resorcinol melts of protohemin and then remain constant, a behavior inconsistent with its being an intermediate in the devinylation reaction. In addition, protohemin was shown to form a 1:2 adduct with *p*-cresol whereas the devinylation reaction of porphyrins had previously been shown to occur only when the aromatic phenol contained the *m*-dihydroxybenzene skeleton. These observations suggested that a reinvestigation of the devinylation reaction was indicated.

Results and Discussion

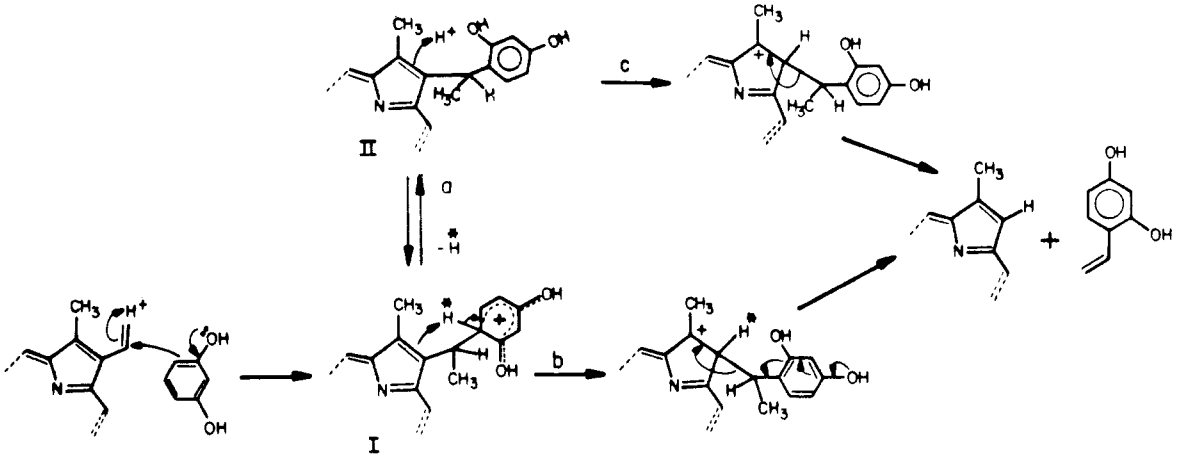
Thin-layer chromatographic studies (on polyamide, benzene–methanol–formic acid, 110:30:1 v/v/v, and methanol–acetic acid, 100:2 v/v) of the reaction of protohemin to form deuterohemin in resorcinol revealed the reaction to be complete within 15 min at 190 °C and 25 min at 145 °C. Longer reaction times did not increase the yield of deuterohemin, in agreement with previous studies. Clearly, any intermediate in the reaction pathway from protohemin to deuterohemin must react to form deuterohemin within 15 min at 190 °C and 25 min at 145 °C. Therefore, two of the three putative intermediates in the reaction pathway advocated by Bonnett et al.[5] (**9**) and an isomeric mixture (**6a** and **6b**) were synthesized as their dimethyl esters followed by metalation according to the ferrous sulfate–acetic acid method outlined by Falk.[7] The bis(resorcinylethyl)hemin [(**9**) as its Fe(III) complex] was shown, by silica gel TLC (chloroform–methanol–formic acid, 100:10:1 v/v/v, to form deuterohemin via the mono(resorcinylethyl)hemin isomers (**6a** and **6b**) [as the Fe(III) complexes]. However, even after a reaction time of 5 h at 190 °C in molten resorcinol, some of the mono(resorcinylethyl)hemins remained. Similarly, with a mixture of the mono(resorcinylethyl)hemins as starting material, deuterohemin was also produced in resorcinol at 190° C. Complete disappearance of the starting material, however, took in excess of 2.5 hours. Moreover, the yields of deuterohemin in these reactions were invariably lower than 10% and copious amounts of chloroform-insoluble material were obtained. The reaction of protohemin dimethyl ester to form deuterohemin dimethyl ester in resorcinol at 190 °C produces no chloroform-insoluble material and proceeds in moderate (50–55%) yield. The resorcinol adducts (**6a**, **6b**, and **9**; as their Fe(III) complexes) therefore cannot be intermediates on the major pathway from protohemin to deuterohemin.

Since the C-alkylated resorcinol adducts were not intermediates on the major pathway to deuterohemin, a further investigation of the devinylation reaction was undertaken. Since Bonnett et al.[5] reported that protoporporphyrin dimethyl ester also undergoes the same devinylation reaction as protohemin dimethyl ester, the behavior of this compound in molten resorcinol was studied. Complete disappearance of protoporphyrin dimethyl ester took in excess of 2.5 h at 190 °C in molten resorcinol and deuteroporphyrin dimethyl ester formation was not complete until 5 h had passed. Moreover, yields were again low. The yield of deuteroporphyrin dimethyl ester from 10 mg of protoporphyrin dimethyl ester was invariably less than 1 mg. Analysis of the reaction by silica gel TLC (chloroform–acetone, 30:1 v/v) showed the presence of two intermediates. That of greater mobility cochromatographed with a sample of the mixed isomeric mono(resorcinylethyl)porphyrins (**6a** and **6b**) which had previously been prepared from the corresponding hemin isolated from crude melts of protohemin. The intermediate of lower mobility was prepared in moderate (44%) yield by melting protoporphyrin dimethyl ester with resorcinol at 120 °C, a temperature at which deuteroporphyrin dimethyl ester is not formed. NMR spectroscopy and the mass spectrum of its acetylated derivative showed this compound to be the bis(resorcinol) adduct **9** of protoporphyrin. The NMR spectra of the acetylated derivatives of the mono- and bis(resorcinylethyl)porphyrins (**6a**, **6b**, and **9**) also showed unequivocally that C-1″ of resorcinol was linked to C-1′ of the porphyrin ethyl side chains (see structure **6a**). Both the mono- and bis(resorcinylethyl)porphyrins (**6a**, **6b**, and **9**) were slowly converted to deuteroporphyrin in low yield as was the case with their iron complexes and protoporphyrin bis(methyl ester).

Since C-alkylation of phenols is not limited to *m*-dihydroxybenzene derivatives, the reaction of protohemin in molten *p*-cresol was examined to ascertain whether the devinylation pathway involving C-alkylated intermediates was limited to *m*-dihydroxybenzene derivatives. A melt of protohemin in *p*-cresol at 145 °C for 3 h produced five porphyrin dimethyl esters after iron removal and esterification. Substantial protohemin was also recovered. Three of the compounds were shown to be di-*p*-cresol adducts of protoporphyrin bis(methyl ester) (**4**). C-Alkylation was confirmed in all three compounds by acetylation and mass spectrometry. The remaining two porphyrins were shown to be mono(*p*-cresol) adducts of 2-(and 4-)vinyldeuteroporphyrin bis(methyl esters) (**5a** and **5b**). C-Alkylation was confirmed for one of these compounds, but the amount of the second isolated was judged insufficient for acetylation. The amounts of these compounds isolated were insufficient in all cases to characterize the position of alkylation of *p*-cresol by NMR. Two of the three di-*p*-cresol adducts were, however, judged to be the two pairs of diasteriomers corresponding to **10** which has

(6) R. K. DiNello, Ph.D. Thesis, Harvard University, 1977.
(7) J. E. Falk, "Porphyrins and Metalloporphyrins", Elsevier, New York, 1964.

Scheme II



two asymmetric carbons. No deuteroporphyrin bis(methyl ester) was isolated from this reaction. The presence of devinylporphyrins in the reaction mixture, however, shows that the devinylation reaction pathway involving C-alkylated intermediates is not limited to *m*-dihydroxybenzene derivatives. The slow rate of the reaction, however, is additional evidence for two pathways in the devinylation of porphyrins and hemins.

The results described here are consistent with the following two pathways: (i) a fast, high-yield pathway limited to reaction of vinyl hemins with *m*-dihydroxybenzene derivatives; (ii), a slow, low-yield pathway involving C-alkylated phenols as intermediates where the *m*-dihydroxybenzene skeleton is not essential. Both porphyrins and hemins may react by pathway ii, but the devinylation reaction will proceed essentially *exclusively* by the much faster pathway i, when vinyl hemins are melted with *m*-dihydroxybenzene derivatives.

One cannot definitely exclude the C-alkylated systems as intermediates on the main pathway of the Schumm reaction solely on their slow conversion to products in molten resorcinol. It is possible that an initially formed C-alkylated intermediate (I, Scheme II) might partition in two ways. Route a (Scheme II) involving the loss of a proton from the pentadienyl cation would generate the isolated C-alkylated intermediate II. Reprotonation of II at the porphyrin (route c) or on the phenol (reverse a) would lead to devinylation. Both of these steps in weakly acidic resorcinol would be slow. On the other hand, route b (Scheme II) which involves an intramolecular proton transfer (H*, Scheme II) would explain the rapid formation of devinylated products via C-alkylation.

Experimental testing of this hypothesis is difficult. One might expect that treatment of the C-alkylated intermediates with a stronger acid than resorcinol might cause devinylation. In our hands this is not the case since treating a mixture of **6a,b** with varying concentrations of trifluoroacetic acid gave intractable tars but no devinylation. We suspect that the original suggestion[4] of O-alkylation may prove to be correct, but our early attempts to synthesize the O-alkylated intermediates have not been successful and the problem is still under investigation.

Experimental Section

General Procedures. Protohemin was obtained from Sigma Chemical Company, St. Louis, MO. Protoporphyrin was prepared as described by DiNello and Chang[8] Cheng Chin polyamide thin-layer sheets were obtained from Gallard Schlessinger Inc., Carle Place, NY, and 250-μM prescored silica gel G thin-layer plates from Analtech Inc., Newark, DE. Polyamide CC 6 <0.07 mm for column chromatography was obtained from Brinkmann instruments, Westbury, NY. Methanol was dried by distillation from calcium hydride. Protoporphyrin bis(methyl ester) was prepared from protoporphyrin as described by Caughey et al.[9] for protohemin, but with omission of ferrous sulfate. Deuterohemin bis(methyl ester) was prepared as described by Caughey et al.[9] All other chemicals were reagent or the best commercially available grade.

2-(and 4-)[1-(2,4-Dihydroxyphenyl)ethyl]deuteroporphyrin Bis(methyl ester) (6a,b) and Its Iron Complex. A. Protohemin (chloro iron(III) protoporphyrin) (1 g) and resorcinol (3 g) were mixed together in a 250-mL round-bottom flask and melted at 145–155 °C for 45 min under an air condenser. After cooling to room temperature, the mixture was triturated with ether and the solid (crude deuterohemin) was washed with ether until the filtrate was nearly colorless. The ether was removed from the filtrate in vacuo and the hemins contained therein were precipitated from the resultant viscous liquid by the addition of water. Chromatography of the crude deuterohemin on polyamide with benzene–methanol–formic acid (110:30:1 v/v/v) gave 470 mg (51%) of pure deuterohemin and 125 mg of a less mobile hemin later shown to be 2-(and 4-)[1-(2,4-dihydroxyphenyl)ethyl]-deuterohemin.

The ether-soluble fraction of the resorcinol melt material when chromatographed on polyamide with benzene–methanol–formic acid (110:50:1 v/v/v) gave an additional of 50 mg of 2-(and 4-)[1-(2,4-dihydroxyphenyl)ethyl]deuterohemin. In this case the desired hemin was the third most mobile of five hemins. The other minor products were not characterized.

The (resorcinylethyl)hemin (100 mg) when subjected to iron removal and esterification according to the method of Grinstein as outlined by Falk[7] gave 45 mg of the alkali-soluble porphyrin bis(methyl ester): ^{1}H NMR (100 MHz, acetone-d_6) δ 2.42 (d, J = 7 Hz, 3 H, ethyl CH_3, 3.24 (t, J = 7 Hz, 4 H, α-propionate CH_2), 3.62 (m, 18 H, 4 ring CH_3 and 2 ester CH_3), 4.32 (m, 4 H, β-propionate), 6.22 (q, J = 7 Hz, 1 H, ethyl CH), 6.47 (d, J = 2.5 Hz, 1 H, phenyl $H_{3''}$), 6.68 (dd, J_1 = 2.5, J_2 = 9 Hz, 1 H, phenyl $H_{5''}$), 6.92 (d, J = 9 Hz, 1 H, phenyl $H_{6''}$), 9.06 (s, 1 H, porphyrin ring β-H), 9.95, 10.00, 10.03, 10.08, 11.02, 11.18, 11.36, 11.38 (all s, 4 H, porphyrin meso H); mass spectrum, m/e 674 (87), 601 (33), 564 (98), 538 (100), 465 (100), 392 (100), 136 (98).

B. The corresponding hemin acid obtained from resorcinol melts of deuterohemin (20 mg) was esterified for 1 h in 5% sulfuric acid in methanol to give the bis(methyl ester) which was precipitated from chloroform, containing a little HCl gas, with petroleum ether (bp 30–60 °C) to give 18 mg of product. Absorption spectrum of pyridine hemochrome in 4 M pyridine–0.2 N KOH in water: λ_{max} 409 nm, 515.5, 546 (6.1:1:1.3).

2-(and 4-)[1-(2,4-Diacetoxyphenyl)ethyl]deuteroporphyrin Bis(methyl ester). Acetylation of 50 mg of the above porphyrin bis(methyl ester) (**6a,b**) by the procedure outlined in Falk[7] gave

(8) R. K. DiNello and C. K. Chang in "The Porphyrins", Vol. I, D. Dolphin, Ed., Academic Press, New York, 1978.

(9) W. S. Caughey, J. O. Alben, W. Y. Fujimoto, and J. L. York, *J. Org. Chem.*, 31, 2631 (1966).

45 mg of a second porphyrin of greatly increased mobility on silica gel (chloroform–acetone, 30:1 v/v). NMR and mass spectra of this compound were consistent with those expected from a mixture of the diacetylated isomers **6a** and **6b**: ^{1}H NMR (100 MHz, acetone-d_6) δ 1.18 (s, 1.5 H, acetate CH_3), 1.23 (s, 1.5 H, acetate CH_3), 2.24 (s, 3 H, acetate CH_3), 2.34 (d, J = 7 Hz, 3 H, ethyl CH_3), 3.22 (m, 4 H, β-propionate CH_2), 3.95 (m, 18 H, 4 ring CH_3 and two ester CH_3), 4.26 (t, J = 7 Hz, 4 H, α-propionate CH_2), 6.11 (q, J = 7 Hz, 1 H, ethyl CH), 6.93 (d, J = 2.5 Hz, 1 H, phenyl $H_{3''}$), 7.32 (dd, J_1 = 2.5, J_2 = 9 Hz, phenyl $H_{5''}$), 8.20 (d, J = 9 Hz, 1 H, phenyl $H_{6''}$), 9.08 (s, 1 H, porphyrin ring β-H), 10.00 (s, 1 H, meso H), 10.12 (s, 2 H, meso H), 10.16 (s, 1 H, meso H); mass spectrum, m/e 758 (59), 716 (80), 674 (52), 538 (100); λ_{max} ($CHCl_3$) (ϵ, mM) 400 nm (118), 498 (9.01), 531.5 (5.66), 566.5 (4.03), 620 (2.78). Anal. Calcd for $C_{44}H_{46}N_4O_8$: C, 69.64; H, 6.11; N, 7.38. Found: C, 69.51; H, 6.05; N, 7.28.

2,4-Bis[1-(2,4-dihydroxyphenyl)ethyl]deuteroporphyrin Bis(methyl ester) (9) and Its Iron(III) Complex. Protoporphyrin bis(methyl ester) (100 mg) and resorcinol (300 mg) were melted at 115–120 °C for 4 h. After cooling, the mixture was dissolved in minimal acetone, and chloroform (50 mL) was added. The solution was extracted three times with water, taken to dryness, and chromatographed on silica gel grade IV (100 g) with chloroform–acetone (2:1) as eluent. The major (less mobile) band gave 48.5 mg (35%) of the desired product which was precipitated from acetone with petroleum ether.

2,4-Bis[1-(2,4-dihydroxyphenyl)ethyl]deuteroporphyrin bis(methyl ester) (45 mg) was metalated according to the ferrous sulfate method outlined by Falk.[7] The product was extracted into chloroform and the chloroform layer washed three times with water, dried over sodium sulfate, and taken to dryness in vacuo. The hemin was then dissolved in minimal acetone and precipitated with petroleum ether. The yield was 24.6 mg (49%). The hemin chromatographed as a single spot on silica gel (chloroform–methanol–formic acid (100:10:1, v/v/v): λ_{max} (pyridine hemochrome in 4 M pyridine–0.2 N KOH in water) 412 nm, 515.5, 549 (6.8:1:1.5).

The metal-free product was directly acetylated and characterized as the tetraacetate as follows.

Acetylation of 250 mg of the above porphyrin bis(methyl ester) according to the method outlined in Falk[7] gave an acetylated porphyrin of much higher mobility on silica gel (chloroform–acetone, 30:1) than the starting material. The acetylated porphyrin was purified by chromatography on silica gel grade IV (100 g), using chloroform–acetone (30:1 v/v) as eluent, and precipitated from chloroform with petroleum ether (bp 30–60 °C). The yield was 16 mg (53%): ^{1}H NMR (100 MHz, acetone-d_6) δ 1.02, 1.12, 1.17, 1.36 (all s, 6 H, acetate CH_3), 2.26 (s, 6 H, acetate CH_3), 2.35 (d, J = 7 Hz, 6 H, ethyl CH_3), 3.28 (t, J = 7 Hz, 4 H, β-propionate CH_2), 3.60 (m, 18 H, 4 ring and 2 ester CH_3), 4.36 (m, 4 H, α-propionate CH_2), 6.10 (m, 2 H, ethyl CH), 6.90 (d, J = 2.5 Hz, 1 H, resorcinyl $H_{3''}$), 6.95 (d, J = 2.5 Hz, 1 H, resorcinyl $H_{3''}$), 7.35 (dd, J_1 = 2.5, J_2 = 9 Hz, 2 H, resorcinyl $H_{5''}$), 8.18 (d, J = 9 Hz, 1 H, resorcinyl $H_{6''}$), 8.22 (d, J = 9 Hz, 1 H, resorcinyl $H_{6''}$), 10.12 (s, 1 H, meso H), 10.16 (s, 1 H, meso H), 10.20 (s, 2 H, meso H); mass spectrum, m/e 978 (100), 936 (85), 894 (54), 757 (54), 715 (59), 538 (49). Anal. Calcd for $C_{56}H_{58}N_4O_{12}$: C, 68.70; H, 5.97; N, 5.72. Found: C, 68.95; H, 5.86; N, 5.65.

2,4-Bis[1-(2-hydroxy-5-methylphenyl)ethyl]deuteroporphyrin (Three Isomers) and 2-(and 4-)[1-(2-hydroxy-5-methylphenyl)ethyl]deuteroporphyrin Bis(methyl ester) (Two Isomers). Protohemin (500 mg) and p-cresol (2 g) were mixed and melted together for 3 h at 145 °C. The melt was cooled to room temperature, throughly mixed with 50 mL ether, and then filtered to remove any solid material. Petroleum ether (100 mL) was then added, the hemins forming an oil film on the sides of the flask. The liquid was decanted off and the hemins were dissolved in a minimum volume of pyridine. The pyridine solution was applied to a silica gel thick-layer plate and the plate dried overnight in vacuo. The dried preloaded silica gel was then scraped off the plate, slurried in methanol–acetic acid (100:2) and applied to a polyamide column (100 g) equilibrated in the same solvent. Development with the equilibration mixture yielded three hemin bands which were taken to near dryness, precipitated with water, and recovered by vacuum filtration. The yield of each hemin (in order of mobility) was as follows: band I, 75 mg; band II, 125 mg; and band III, 104 mg. The hemins (60 mg) corresponding to each band were demetalated and esterified according to the method of Grinstein.[7]

Band I gave a single porphyrin bis(methyl ester) (28 mg) whose mass and NMR spectra were consistent with its being a di-p-cresol adduct (vide infra). This compound was purified on silica gel grade IV (chloroform–acetone, 20:1). The mass spectrum of the acetylated derivative prepared according to the method given in Falk[7] indicated C-alkylation of both vinyl groups of protoporphyrin had occurred.

2,4-Bis[1-(2-hydroxy-5-methylphenyl)ethyl]deuteroporphyrin bis(methyl ester) (10) (isomer 1): ^{1}H NMR (100 MHz, acetone-d_6) δ 2.34, 2.38, 2.42 (d, s, s (superimposed), 12 H, ethyl CH_3 and phenyl CH_3), 3.24 (m, 4 H, β-propionate CH_2), 3.48, 3.58, 3.60, 3.65, 3.73, and 3.76 (all s, 18 H, ring and ester CH_3), 4.32 (m, 4 H, α-propionate CH_2), 6.04 (m, 2 H, ethyl CH), 6.66 (dd, J_1 = 8, J_2 = 3 Hz, 2 H, phenyl $H_{4''}$), 6.98 (d, J = 8 Hz, 2 H, phenyl $H_{3''}$), 7.94 (s, 1 H, phenyl $H_{6''}$), 10.10, 10.16, 10.26, and 10.34 (all s, 4 H, meso H); mass spectrum, m/e 806 (100), 698 (57), 672 (24), 538 (100); λ_{max} ($CHCl_3$) (ϵ, mM) 405 nm (183), 501.5 (13.1), 537 (9.14), 569 (6.25), 623 (3.52).

Acetylated derivative: ^{1}H NMR (100 MHz, acetone-d_6) δ 1.30, 1.42 (s, 6 H, acetate CH_3), 2.35 (d, J = 7 Hz, 6 H, ethyl CH_3), 2.54, 2.58 (s, 6 H, phenyl CH_3), 3.30 (t, J = 8 Hz, 4 H, β-propionate CH_2), 3.52, 3.60, 3.65 (s, 18 H, ring CH_3, ester CH_3), 4.40 (t, J = 8 Hz, 4 H, α-propionate CH_2), 6.08 (q, J = 7 Hz, 2 H, ethyl CH), 6.94 (dd, J_1 = 8, J_2 = 3 Hz, 2 H, phenyl $H_{4''}$), 7.22 (dd, J_1 = 8, J_2 < 1 Hz, 2 H, phenyl $H_{3''}$), 8.07 (dd, J_1 = 3, J_2 < 1 Hz, 2 H, phenyl $H_{6''}$), 10.10, 10.18, 10.22, 10.25 (all s, 4 H, meso H); mass spectrum, m/e 890 (100), 848 (37). Anal. Calcd for $C_{54}H_{58}N_4O_8$: C, 72.79; H, 6.56; N, 6.29. Found: C, 72.56; H, 6.51; N, 6.01.

Hemin band II gave two porphyrin bis(methyl esters) after iron removal, esterification, and chromatography on silica gel (chloroform–acetone, 20:1). The major (less mobile) band streaked ahead and behind during chromatography. A second chromatography failed to decrease the streaking and decreased the final yield to 21 mg. The acetylated derivative, however, ran as a single compact spot on silica gel (chloroform–ether, 40:1 v/v). The mass spectrum and NMR of the parent compound were again consistent with those of a di-p-cresol adduct. The mass spectrum of the acetylated derivative was consistent with C-alkylation of p-cresol by both protoporphyrin vinyl groups.

2,4-Bis[1-(2-hydroxy-5-methylphenyl)ethyl]deuteroporphyrin bis(methyl ester) (10) (isomer 2): ^{1}H NMR (100 MHz, acetone-d_6) δ 2.35, 2.38, 2.42 (d, s, s (superimposed), 12 H ethyl and phenyl CH_3), 3.28 (t, J = 8 Hz, 4 H, α-propionate CH_2), 3.54, 3.60, 3.62, 3.80 (s, 18 H, porphyrin ring and ester CH_3), 4.34 (t, J = 8 Hz, 4 H, β-propionate CH_2), 6.26 (m, 2 H, ethyl CH), 6.84 (dd, J_1 = 8, J_2 = 3 Hz, 2 H, phenyl $H_{3''}$), 7.06 (d, J = 8 Hz, 2 H, phenyl $H_{4''}$), 8.00 (s, 2 H, phenyl $H_{6''}$), 10.12, 10.20, 10.33, 10.44 (s, 4 H, meso H); mass spectrum m/e 806 (100), 672 (54), 538 (30). Acetylated derivative: mass spectrum, m/e 890 (100), 848 (17). Anal. Calcd for $C_{54}H_{58}N_4O_8$: C, 72.79; H, 6.56; N, 6.29. Found: C, 73.01; H, 6.87; N, 6.07.

The yield of the more mobile porphyrin from hemin band III (vide infra) was 5 mg. Half of this was acetylated according to the method outlined in Falk,[7] to give the diacetate.

2,4-Bis[1-(2-hydroxy-5-methylphenyl)ethyl]deuteroporphyrin bis(methyl ester) (10) (isomer 3): mass spectrum, m/e 806 (100), 698 (98), 672 (92), 538 (100); λ_{max} ($CHCl_3$) (ϵ, mM) 405.5 nm (132), 501 (9.79), 537.5 (6.91), 569 (4.94), 623 (2.62). **Acetylated derivative**: mass spectrum, m/e 890 (100), 848 (25), 806 (8), 672 (16), 538 (18). Anal. Calcd for $C_{54}H_{58}N_4O_8$: C, 72.79; H, 6.56; N, 6.29. Found: C, 72.91; H, 6.32; N, 6.02.

2-(and 4-)[1-(2-Hydroxy-5-methylphenyl)ethyl]deuteroporphyrin (Isomer 1). Only a small amount of the more mobile porphyrin bis(methyl ester) isolated from hemin band II was obtained after silica gel chromatography (vide supra). This compound was not acetylated but was analyzed by mass spectroscopy. The mass spectrum was consistent with that of a mono-p-cresol adduct of 2-(or 4-)vinyldeuteroporphyrin: mass spectrum, m/e 672 (81), 599 (50), 538 (100), 465 (100); λ_{max} ($CHCl_3$) (ϵ mM) 402 nm (115), 499.5 (8.18), 533.5 (5.21), 568 (4.05), 621.5 (2.29).

2-(and 4-)[1-(2-Hydroxy-5-methylphenyl)ethyl]deuteroporphyrin Bis(methyl ester) (Isomer 2). Hemin band III again

gave two porphyrin bis(methyl esters) after chromatography on silica gel (activity IV, chloroform–acetone, 20:1 v/v). The more mobile porphyrin proved to be a di-*p*-cresol adduct (vide supra). The less mobile porphyrin was chromatographed three times and still streaked ahead of and behind the main band after the third column. As a consequence, the yield was only 6 mg. The acetylated derivative again ran as a single compact spot, but it was necessary to chromatograph this compound on silica gel thin-layer plates (chloroform–acetone, 40:1) to remove a small amount of contaminating material. The mass spectra of the less mobile porphyrin dimethyl ester from hemin band III and its acetylated derivative again indicated C-alkylation of *p*-cresol by a single vinyl group of protoporphyrin had occurred; the other vinyl group had been lost: mass spectrum, *m/e* 672 (100), 599 (41), 538 (96), 465 (90); λ_{max} ($CHCl_3$) (ϵ mM) 402 nm (163), 498.5 (11.2), 533.5 (7.66), 568 (5.70), 621.5 (3.36). The acetylated derivative was prepared as above:[7] mass spectrum, *m/e* 714 (100), 672 (20), 538 (29). Anal. Calcd for $C_{43}H_{46}N_4O_6$: C, 72.25; H, 6.49; N, 7.84. Found: C, 71.87; H, 6.59; N, 7.99.

Acknowledgment. This work was supported by the United States National Institutes of Health (AM 17989) and by the Canadian Natural Science and Engineering Research Council. D.D. expresses his thanks to the Harvard Chemistry Department for their assistance in the preparation of this manuscript during his stay as a Visiting Professor, Fall 1980.

Registry No. 4, 553-12-8; **6a**, 77745-05-2; **6a** diacetate, 77745-06-3; **6b**, 77745-07-4; **6b** diacetate, 77773-67-2; **9**, 77773-68-3; **9** tetraacetate, 77745-09-6; **10** (isomer 1), 77745-08-5; **10** (isomer 1) diacetate, 77745-10-9; **10** (isomer 2), 77745-11-0; **10** (isomer 2) diacetate, 77773-69-4; 2-[1-(2,4-dihydroxyphenyl)ethyl]deuterohemin bis(methyl ester), 77745-14-3; 4-[1-(2,4-dihydroxyphenyl)ethyl]deuterohemin bis(methyl ester), 77745-15-4; 2-[1-(2,4-dihydroxyphenyl)ethyl]deuterohemin, 77745-16-5; 4-[1-(2,4-dihydroxyphenyl)ethyl]deuterohemin, 77745-17-6; 2,4-bis[1-(2,4-dihydroxyphenyl)ethyl]deuterohemin bis(methyl ester), 77745-18-7; 2-[1-(2-hydroxy-5-methylphenyl)ethyl]deuteroporphyrin bis(methyl ester), 77745-12-1; 4-[1-(2-hydroxy-5-methylphenyl)ethyl]deuteroporphyrin bis(methyl ester), 77773-70-7; protohemin, 15489-47-1; deuterohemin, 21007-21-6; resorcinol, 108-46-3; *p*-cresol, 106-44-5.

Dipolar Cycloaddition on the Transient Thiophene Sulfone: Isoxazoline and Isoxazolidine Derivatives

Armand Bened, Robert Durand, Daniel Pioch, and Patrick Geneste*

Laboratoire de Chimie Organique Physique Appliquée, Ecole Nationale Supérieure de Chimie de Montpellier, 34075 Montpellier, France

Jean Paul Declercq and Gabriel Germain

Laboratoire de Chimie Physique et Cristallographie, Université de Louvain-la-Neuve, Louvain-la-Neuve, Belgium

Joëlle Rambaud and Raymond Roques

Laboratoire de Cristallographie de l'Université Nationale de Côte d'Ivoire, Abidjan 04, Ivory Coast

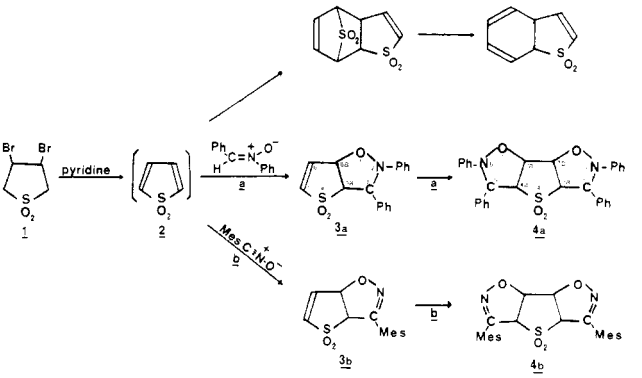
Received April 3, 1981

From the 3,4-dibromotetrahydrothiophene 1,1-dioxide under basic conditions and in the presence of 1,3 dipoles such as *N*,α-diphenylnitrone and/or mesitonitrile oxide are obtained isoxazoline and isoxazolidine derivatives of the transient thiophene sulfone as mono- or diadducts. Kinetic studies of the nitrone cycloaddition show a consecutive kinetic scheme of the addition and show that the monoadduct formation is 10^3 faster than that of the diadduct. NMR analysis (^1H and ^{13}C) and crystallographic studies show the formation of the adduct where the regioselectivity corresponds to the oxygen atom of the dipoles bonded to the carbon atom β to the sulfone group, the "endo" nature of the addition, and the anti situation of the two rings in the diadduct.

Substituted thiophene sulfones are reasonably well-characterized substances,[1,2] but the parent thiophene 1,1-dioxide is highly reactive and hence cannot be isolated.[3] In fact, the oxidations of thiophene by any reagents do not lead to specific products unless it is possible to form a dimer[4] or the sesquioxide.[5]

In continuation of our studies on oxidation[6] and 1,3-cycloaddition reactions[7] in the benzo[*b*]thiophene series,

Scheme I



we now report the intermediate formation of the transient sulfone of the thiophene by using different 1,3-dipoles under conditions that prevent the formation of other compounds. Oxidation of the thiophene molecule in the presence of a diene such as a quinone may lead to a

(1) W. L. Mock, *J. Am. Chem. Soc.*, **92**, 7610 (1970).
(2) D. N. Reinhoudt, P. Smael, W. J. M. Tilborg, and J. P. Visser, *Tetrahedron Lett.*, 3755 (1973).
(3) W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.*, **76**, 1932 (1954).
(4) W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.*, **76**, 1940 (1954).
(5) W. Davies, N. W. Gamble, and W. E. Savige, *J. Chem. Soc.*, 4678 (1952).
(6) P. Geneste, J. Grimaud, J. L. Olivé, and S. N. Ung, *Tetrahedron Lett.* 2345 (1975); *Bull. Soc. Chim. Fr.*, 271 (1977); P. Geneste, J. L. Olivé, and S. N. Ung, *J. Heterocycl. Chem.*, **14**, 449, 953 (1977).
(7) P. Geneste, R. Durand, and D. Pioch, *Tetrahedron Lett.*, 4845 (1979).

0022-3263/81/1946-3502$01.25/0