Tetrahedron Letters,Vol.31,No.2,pp 285-288,1990 0040-4039/90 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A SYNTHESIS OF PURPURIN DERIVATIVES SUBSTITUTED AT THE 6,16-*meso* POSITIONS.

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Abstract:

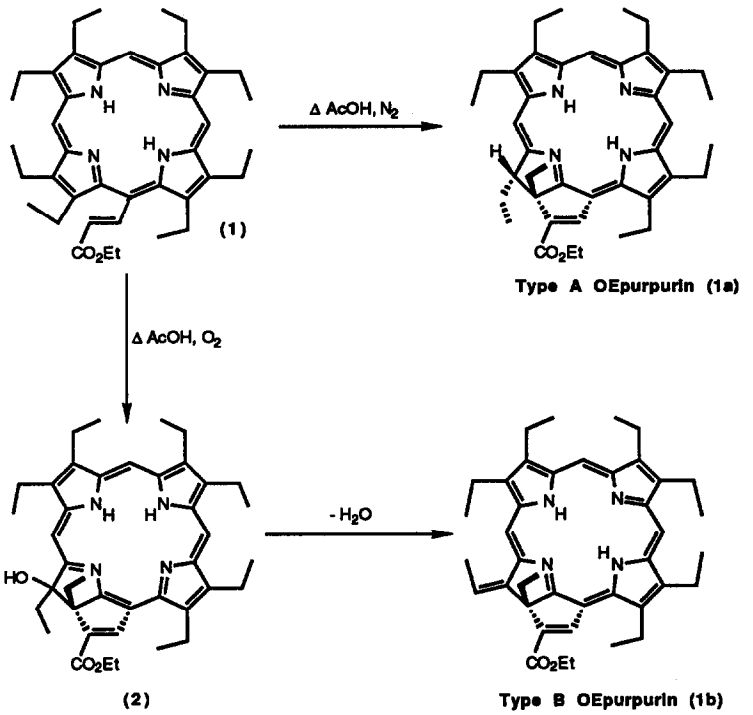
Purpurins bearing p-functionalised phenyl substituents in the 6,16-meso positions have been synthesised. Their formation in comparison to the purpurins derived from octaethylporphyrin (OEpurpurin) is discussed.

A class of hydroporphyrins called *purpurins* have recently received much attention as photosensitizing agents with particular interest in their application to photodynamic cancer therapy[1-8]. Their chromophores are directly influenced by extended conjugation via an annelated cyclopentenyl ring, which gives rise to major absorptions in the region 650 - 715nm, a region of the visible spectrum with excellent tissue penetrating properties. As part of our research into the reactions of purpurin derivatives substituted at the 6,16-*meso* positions a number of interesting observations have been made with respect to the mechanism of cyclization of the *meso*-(methoxycarbonyl)vinylporphyrins to give their respective purpurin derivatives. In this communication several aspects of the mechanism of cyclization are discussed.

In 1960 Woodward and co-workers[9] first described the synthesis of a 17,18-*trans*-purpurin (type A, Fig.1) from a *meso*-[β-(methoxycarbonyl)vinyl]porphyrin in their successful synthesis of chlorophyll. Cyclization of the porphyrin to its purpurin derivative was achieved by refluxing the porphyrin in glacial acetic acid under an atmosphere of nitrogen. In 1966 Fuhrhop and Witte[10] produced the first of the OEP series purpurins by refluxing a sterically crowded octaethyl-*meso*-[β-(2-methoxycarbonyl-2-carboxyl)vinyl]porphyrin in toluene under a nitrogen atmosphere to give an OEpurpurin of type A (**1a**). The mecanism of cyclization most probably involves attack onto the pyrrole ring by the radical formed *via* decarboxylation.

More recently Morgan and Tertel[11] have cyclized *meso*-[β-(ethoxycarbonyl)vinyl]octaethylporphyrin (**1**) (Scheme 1) under two different reaction conditions to give both type A (**1a**) and type B (**1b**) purpurins . It was noted that refluxing the meso substituted porphyrin in glacial acetic acid under a nitrogen atmosphere produced only purpurin of type A. However when oxygen was allowed into the system a 1 : 1 mixture of type A and B purpurins were recovered. It was proposed that in the presence of oxygen the less stable of the thermodynamic epimers may be trapped as its 2-hydroxy derivative (**2**) which under the reaction conditions

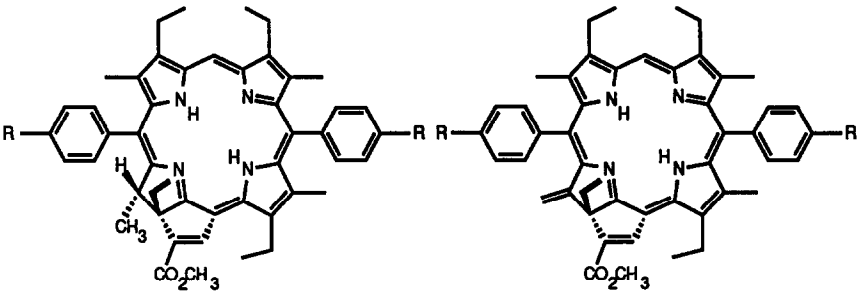
SCHEME 1



may dehydrate to the OEpurpurin of type B. This does not adequately explain the formation of the two products in equal yield, since it was demonstrated that the reaction was not under thermodynamic control, as interconversion of the two products did not occur under the reaction conditions. The product distribution then must reflect independent kinetically controlled pathways, which may involve a common intermediate.

In our laboratories many 6,16-di(p-functionalized phenyl)purpurin derivatives of type A and B (eg. (3) and (4), Fig.1) have been synthesised. The p-functionalized phenyl rings allows covalent attachment of the purpurin to other organic molecules, or incorporates water solubilizing groups. The purpurins are formed by cyclization of their respective *meso*-[β-(methoxycarbonyl)vinyl]porphyrin derivatives under specific reaction conditions. Purpurins of type A (3, R = CH_3)[13] are synthesised readily in high yield (77%) by refluxing the respective meso-substituted free base porphyrin[12] in a KOH / MeOH / CH_2Cl_2 solution in the **presence** of air. No trace of the type B purpurin (4) is observed as might be expected if the hydroxy-intermediate as proposed by Morgan dehydrates . Reaction under neutral (Δ toluene) or acidic conditions as used by Morgan *et al* (Δ glacial acetic acid, N_2) gives no purpurin formation. Conversely, treatment of (1) with KOH / MeOH / CH_2Cl_2 produces none of the purpurins (1a) or (1b) (Scheme 1). Under these conditions rapid hydrolysis of the ester results, giving the corresponding acid derivative which does not undergo cyclization to the acid purpurin.

FIGURE 1



Purpurin Type A R = CH_3 (3) Purpurin Type B R = CH_3 (4)

Purpurins of **both** types A and B (**3** and **4**, R = CH_3)[14] are formed by refluxing the respective free base porphyrin in KOH / MeOH / DMF or KSCN / DMF. The yield of each purpurin type is dependent on the temperature used, but generally both purpurin types are formed by this method. At reflux temperature, the major product is the Type B purpurin. At lower temperatures however, quite reasonable yields of the Type A are obtained with only small amounts of Type B being present. It is especially significant that the product distribution is independent of whether the reaction is carried out under nitrogen or in air. Under similar reaction conditions, type A purpurins are not converted to type B purpurins. These observations suggests that two different temperature dependent pathways exist for the formation of both purpurin types.

To investigate this idea further, cyclization of (**1**) was attempted in the presence of oxygen at different reaction temperatures. Reaction of (**1**) in refluxing benzene to which trifluoroacetic acid (3-5 molar excess) had been added produced no appreciable amounts of purpurin after 48hrs. Reaction of (**1**) in refluxing toluene under similar reaction conditions produced a 8 : 1 mixture of type A : B OEpurpurins. At higher temperatures, in refluxing xylene / TFA (24hrs), only OEpurpurin of type A is obtained in good yield. Thus it seems likely that the formation of type B OEpurpurins may be governed by either or both the temperature and the solubility of oxygen in the various solvents at these temperatures.

Thus on the basis of these observations it is clear that the mechanism of cyclization of the meso-substituted octaethylporphyrin is different to that of the meso-substituted biphenylporphyrins. Cyclization of the octaethyl porphyrin to produce OEpurpurins may proceed via a radical mechanism. Such a mechanism would explain why purpurins of type B are formed on the introduction of air into the reaction vessel. Cyclization of the meso-substituted diphenylporphyrins to their respective purpurins on the other hand, most probably involves a nucleophilic mechanism and so is unaffected by the presence of oxygen.

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(12) Methyl 3-{10'[5',15'-Bis(4"-methylphenyl)-2',8',12',18'-tetraethyl-3',7',13',17'-tetramethylporphyrinyl]}propenoate. **^{1}H N.M.R.** ($CDCl_3$) 300MHz: ∂ -1.54 (brs, 2H, NH.), 1.39 (t, 6h, 2 x CH_3.), 1.54 (t, 6H, 2 x CH_3.), 2.04 (s, 6H, 2 xCH_3.), 2.23 (s, 6H, 2 x CH_3.), 2.66 (s, 6H, $ArCH_3$.), 3.39(q, 4H, 2 x CH_2.), 3.69 (q, 4H, 2 x CH_2.), 3.93 (s, 3H, CO_2CH_3.), 6.07 (d, 1H, vinyl H_β.), 7.50 (d, 4H, ArH.), 7.89 (d, 4H, ArH.), 9.51 (s, 1H, meso-H.), 10.10 (d, 1H, vinyl H.). Anal.Calc.for $C_{50}H_{54}N_4O_2.H_2O$ **C**: 78.90. **H**: 7.42. **N**: 7.36. Found **C**: 79.06. **H**: 7.54. **N**: 7.08. UV / Vis (nm max) Benzene: 442 (125785), 528 (8200), 610 (8370).

(13) **Purpurin (3).^{1}H N.M.R.** ($CDCl_3$) 300MHz. ∂ -0.38 (t, 3H, CH_3 of 3-ethyl.),-0.08 (brs, 1H, NH.), 0.87 (brs,1H, NH.), 1.47 (t, 3H, CH_3.), 1.48 (d,3H, CH_3 of 2-methyl.), 1.59 (t, 3H,CH_3.), 1.63 (t, 3H, CH_3.), 1.25 (hidden m, 1H, CH of 2-ethyl.), 2.12 (s, 3H, CH_3.), 2.23 (s, 3H, CH_3.), 2.25 (s, 3H, CH_3.), 2.43 (m, 1H, CH of 2-ethyl.), 2.59 (s, 3H, $ArCH_3$.), 2.65 (s, 3H, $ArCH_3$.), 3.53 3.80 (m, 6H, 3 x CH_2.), 3.96 (s, 3H, CO_2CH_3.), 4.46 (q, 1H, 2-H.), 7.08 (d, 1H, ArH.), 7.23 (d, 1H, ArH.), 7.42 (d, 1H, ArH.), 7.52 (d, 2H, ArH.), 7.57 (d of d, 1H, ArH.), 7.96 (d of d, 1H, ArH.), 8.13 (d, 1H, ArH.), 9.47 (s, 2H, meso-H and isocyclic ring-H.). Anal.Calc.for $C_{50}H_{54}N_4O.H_2O$ **C**: 78.90. **H**: 7.42. **N**: 7.36. Found **C**: 78.45. **H**: 7.59. **N**: 6.96. UV / Vis (nm max) $CHCl_3$: 435 (132430), 508 (4845), 539 (6780), 579 (14050), 641 (6460), 697 (26490).

(14) **Purpurin (4) ^{1}H N.M.R.** ($CDCl_3$) 300MHz: ∂,-0.01 (brs, 1H, NH.), 0.08 (t, 3H, CH_3 of 3-ethyl.), 0.88 (brs,1H, NH.), 1.53 (t, 3H, CH_3.), 1.64 (t, 3H, CH_3.), 1.65 (t, 3H, CH_3.), 2.11 (s, 3H, CH_3.), 2.18 (m, 1H, CH of 2-ethyl.), 2.23 (s, 3H, CH_3.), 2.32 (s, 3H, CH_3.), 2.41 (m, 1H, CH of 2-ethyl.), 2.60 (s, 3H, $ArCH_3$.), 2.65 (s, 3H, $ArCH_3$.), 3.47 - 3.81 (m, 6H, 3 x CH_2.), 4.00 (s, 3H, CO_2CH_3.), 4.79 (s, 1H, vinyl-H.), 6.08 (s, 1H vinyl-H.), 7.31 (s, 2H, ArH.), 7.43 (d, 1H, ArH.), 7.52 (d, 1H, ArH.), 7.53 (d, 1H, ArH.), 7.59 (d of d, 1H, ArH.), 7.93 (d of d, 1H, ArH.), 8.07 (d, 1H, ArH.), 9.40 (s, 1H, isocyclic ring-H.), 9.48 (s,1H, meso-H.). Anal. Calc. for $C_{50}H_{52}N_4O_2.H_2O$ **C**: 79.12. **H**: 7.17. **N**: 7.37. Found **C**: 79.42. **H**: 7.13. **N**: 7.36. UV / Vis (nm max) Benzene: 362 (29270), 444 (165360), 548 (12380), 590 (17400), 652 (11290), 714 (38870).

(Received in UK 2 November 1989)