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An Efficient Approach to the Synthesis of Tetrahydroquinazoline and Cyclooctapyrimidine Derivatives of *meso*-Tetraphenylporphyrins

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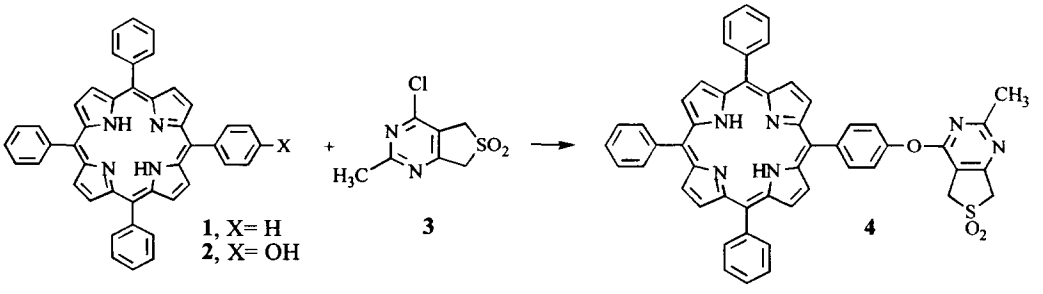
Abstract: Novel tetrahydroquinazoline and cyclooctapyrimidine derivatives of TPP were obtained by thermal extrusion of SO_2 from a porphyrin-pyrimidine fused 3-sulfolene in the presence of N-(4-nitrophenyl)maleimide. © 1997 Elsevier Science Ltd.

Porphyrins have been widely studied as sensitizers and are currently finding biomedical application in the treatment of malignant tumours (photodynamic therapy, PDT), plaque destruction, psoriatic lesions, and more recently in the treatment of viruses.[1]

Synthetic porphyrins are also receiving considerable interest as models of photosynthetic electron transfer reactions. Porphyrins linked to donor or acceptor moieties have been prepared in order to study electron transfer, singlet energy and triplet energy transfer.[2] All these processes are strongly dependent on the structure of the tetrapyrrolic system and a large number of studies has been based on derivatives of *meso*-tetraphenylporphyrin (TPP; **1**).

Recently we have described a new approach for the synthesis of pyrimidine fused 3-sulfolenes.[3] These sulfolenes were subsquently used as precursors to the corresponding *ortho*-quinodimethanes which were used in the synthesis of tetrahydroquinazolines. We now report the successful employment of that approach for the functionalization of *meso*-tetraphenylporphyrins. The synthetic pathway is outlined in schemes 1 and 2.

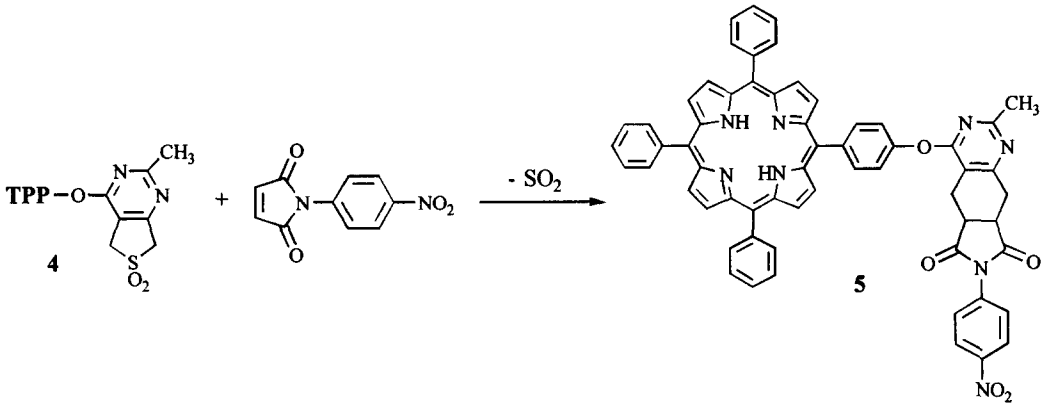


1, X= H
2, X= OH

3

4

Scheme 1



Scheme 2

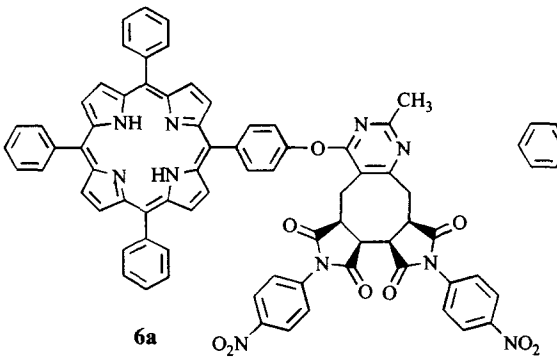
We have choosen *meso*-(*p*-hydroxyphenyl)triphenylporphyrin (TPPOH; **2**), which bears an hydroxy group in one of the phenyl rings, to be used as the nucleophile in the reaction with the chloropyrimidine **3**.

The porphyrin was synthesised from the crossed Rothemund reaction using pyrrole and the two appropriate benzaldehydes in refluxing acetic acid and nitrobenzene.[4] The chloropyrimidine **3** was obtained under the synthetic approach recently developed by us.[3b,3c] Treatment of TPPOH with 1.4 equivalents of 4-chloropyrimidine fused 3-sulfolene **3** in toluene, in the presence of four equivalents of sodium hydride, for 24 hours at 70° afforded, after column chromatography, the expected porphyrinpyrimidine fused 3-sulfolene **4** in 80% yield. The structure of this novel substituted "porphyrinpyrimidine" was confirmed by ^{1}H- and ^{13}C-NMR and mass spectrometry.[5] In particular the ^{1}H-NMR showed the presence of two singlets at δ 4.60 and 4.48 ppm, corresponding to the $CH_2SO_2CH_2$ protons, and a singlet at δ 2.71 ppm corresponding to the methyl group in the pyrimidine ring.

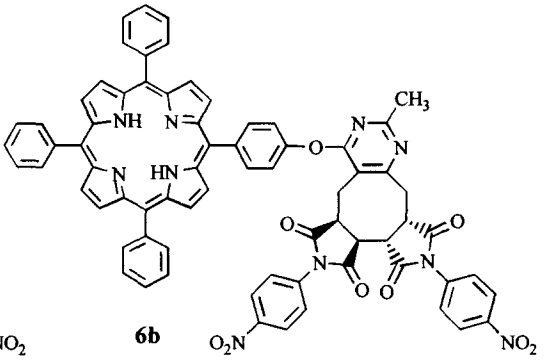
When a solution of porphyrin **4** and 1.1 equivalents of N-(*p*-nitrophenyl)maleimide in 1,2,4-trichlorobenzene was refluxed during 3 hours under nitrogen atmosphere, porphyrin **5** was obtained after the work up in 92% yield (scheme 2). The structure of the tetrahydroquinazoline-porphyrin **5** was established based on spectroscopic data, namely ^{1}H- and ^{13}C-NMR, MS, UV/Vis and elemental analysis.[6]

When the extrusion of SO_2 from porphyrin **4** was done in the presence of a large excess of N-(*p*-nitrophenyl)maleimide (9.4 equivalents) the expected porphyrin **5** (69% yield) was accompanied by two less polar minor compounds. Preparative TLC allowed the separation of these two minor compounds, the less polar one in 13 % yield and the more polar one in 7.4 % yield. These two compounds showed similar spectral characteristics, suggesting that they are diastereoisomers. Both compounds showed the same parent ion at m/z= 1185 in the MS spectrum (FAB^+) suggesting the introduction of two molecules of N-(*p*-nitrophenyl)maleimide per molecule of pyrimidine. The detailed analysis of the ^{1}H-NMR spectra of both compounds confirmed this fact. In addition to the porphyrin protons in the aromatic region, eight more protons were found due to the two *p*-nitrophenyl groups. Also, in the aliphatic region, in addition to the singlet at δ 2.50 (or δ 2.49 ppm, depending on the isomer) assigned to the methyl group, eight protons were found in the region between δ 2.60 and 4.50 ppm (or δ 2.60 - 4.30 ppm, other isomer) which is in agreement with the presence of two molecules of N-(*p*-nitrophenyl)maleimide. These results suggest that we have a pair of diastereoisomeric *cis* and *trans* "cyclooctapyrimidineporphyrins" **6a** and **6b**.[7] These results are in accordance with our previous studies on the

pyrimidine *o*-quinodimethanes.[3c,3d] Cyclooctapyrimidineporphyrins **6a** and **6b** were probably formed from **5** by a ring expansion reaction following the mechanism previously reported by us.[3c]



6a



6b

There are several examples of porphyrinic compounds with DNA cleavage activity prepared by alkylation of triaryl(*p*-hydroxyphenyl)porphyrins. Usually an heterocyclic moiety is covalently linked to the porphyrin through an ether function. An alkyl chain[8] or a sugar molecule[9] is normally used as a spacer. The synthetic route presented in this paper allows the introdution of pyrimidine moieties very close to the porphyrin nucleus, without the need of an extra spacer. The possibility of further transformation, with the introdution of a wide variety of substituents via Diels-Alder reactions, makes this route as a valuable method for the preparation of novel systems with potencial DNA cleavage activity. Work is in progress in our laboratory to extend these studies to other dienophiles and to other derivatives of TPP.

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5. Spectroscopic data for **4**: **m.p.** > 300 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ: -2.78 (s, 2H, NH), 2.71 (s, 3H, CH_3), 4.48 (s, 2H, SO_2CH_2), 4.60 (s, 2H, SO_2CH_2), 7.53-7.79 (m, 11H, phenyl-*m*- and *p*-H), 8.21-8.29 (m, 8H, phenyl-*o*-H), 8.86-8.90 (m, 8H, porphyrin β-H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ: 26.0, 53.7, 58.0, 109.3, 118.6, 119.7, 120.3, 120.4, 126.7, 127.8, 128.1, 131.2, 132.2, 134.6, 135.5, 140.0, 142.1, 151.5, 161.5, 164.9, 169.3; **MS** (FAB$^+$) 813 $(M+H)^+$, 749 $(M+H - SO_2)^+$; **UV-Vis** ($CHCl_3$) λ_{max} (log ε) 416 (5.50), 514 (4.27), 549 (3.91), 590 (3.74), 646 (3.67) nm.
6. Spectroscopic data for **5**: **m.p.** > 300 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ: -2.78 (s, 2H, NH), 2.66 (s, 3H, CH_3), 3.10-3.60 (m, 6H, CH_2, CH), 7.46-7.78 (m, 13 H, phenyl-*m*- and *p*-H and C_6H_4-NO_2), 8.21-8.30 (m, 10H, phenyl-*o*-H and C_6H_4-NO_2), 8.86-8.94 (m, 8H, porphyrin β-H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ: 21.0, 25.8, 31.3, 39.2, 39.2, 111.5, 119.0, 119.7, 120.2, 120.3, 124.3, 126.6, 126.7, 127.7, 130.8, 131.1, 134.5, 135.4, 137.0, 139.2, 142.1, 146.9, 152.4, 165.2, 165.5, 166.8, 176.6, 176.8; **MS** (FAB$^+$) 967 $(M+H)^+$; **UV-Vis** ($CHCl_3$) λ_{max} (log ε), 415 (5.50), 514 (4.29), 549 (3.94), 590 (3.76), 646 (3.67) nm; **Anal.**: Found (%): C, 75.10; H, 4.53; N, 11.00; Calcd. for $C_{61}H_{42}N_8O_5$. 0.5 H_2O: C, 75.02; H, 4.44; N, 11.48.
7. Compounds **6a** and **6b** could not be assigned unambiguously. Isomer with higher R_f (silica): **m.p.** > 300 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ: -2.78 (s, 2H, NH), 2.50 (s, 3H, CH_3), 2.60-4.50 (m, 8H, CH_2, CH), 7.54-7.78 (m, 15 H, phenyl-*m* and *p*-H and C_6H_4-NO_2), 8.21-8.43 (m, 12H, phenyl-*o*-H and C_6H_4-NO_2), 8.86-8.94 (m, 8H, porphyrin β-H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ: 26.1, 38.4, 40.0, 41.8, 42.1, 112.8, 118.8, 119.6, 120.3, 120.4, 124.4, 124.6, 126.7, 127.0, 127.8, 134.6, 135.5, 136.7, 137.8, 139.5, 142.1, 146.9, 147.3, 152.2, 164.2, 165.2, 165.7, 166.1, 174.8, 175.6, 176.8, 178.3; **UV-Vis** ($CHCl_3$) λ_{max} (log ε), 416 (5.60), 514 (4.38), 549 (4.02), 590 (3.84), 645 (3.75) nm; **MS** (FAB$^+$) 1185 $(M+H)^+$; **Anal.:** Found (%): C, 71.32; H, 4.37; N, 10.96; Calcd. for $C_{71}H_{48}N_{10}O_9.C_2H_5OH$: C, 71.21; H, 4.42; N, 11.38; Isomer with smaller R_f (silica): **m.p.** > 300 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ: -2.79 (s, 2H, NH), 2.49 (s, 3H, CH_3), 2.60-4.30 (m, 8H, CH_2, CH), 7.53-7.80 (m, 15 H, phenyl-*m*- and *p*-H and C_6H_4-NO_2), 8.20-8.44 (m, 12H, phenyl-*o*-H and C_6H_4-NO_2), 8.86-8.94 (m, 8H, porphyrin β-H); **UV-Vis** ($CHCl_3$) λ_{max} (log ε), 417 (5.47), 515 (4.11), 550 (3.76), 589 (3.58), 645 (3.47) nm; **MS** (FAB$^+$) 1185 $(M+H)^+$.
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