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Porphyrins Containing Aziridinyl-p-Benzoquinone Substituents

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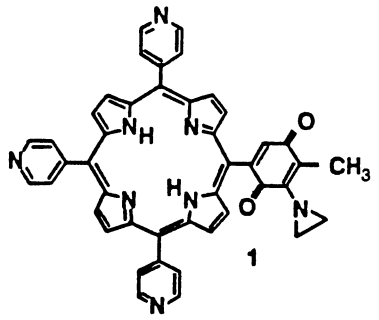
New porphyrins containing aziridinyl-p-benzoquinone meso-substituents were synthesized. They were designed to be specific DNA cross-linkers and alkylating agents.

Recent involvement of this laboratory in the synthesis of porphyrinyl-nucleosides[1-5] had among other goals to obtain the structures able to interact with DNA and be biologically active due to the participation of the porphyrin and nucleoside units. Following this line of interest we investigated the synthesis of porphyrins containing one or two aziridinyl-p-benzoquinone units as meso-substituents and in addition, the 4-pyridyl substituents which after N-methylation provide solubility in water.



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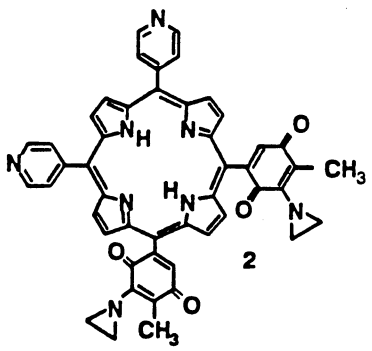

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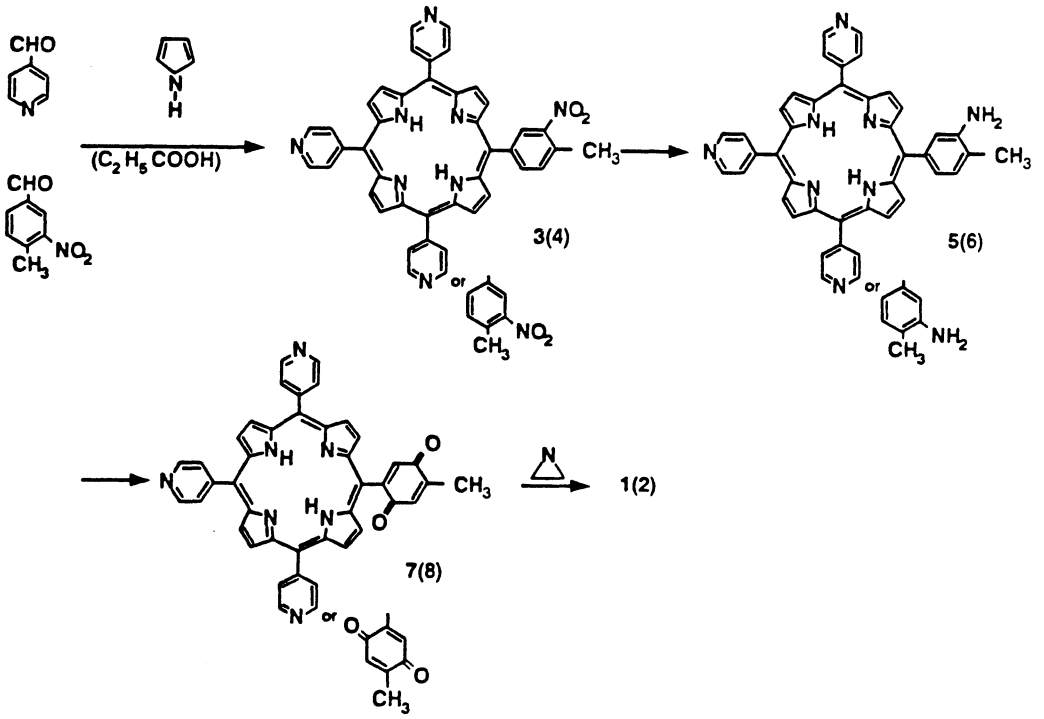
The title structures, meso-tri(4-pyridyl)-3-(1-aziridinyl)-4-methyl-2,5-benzoquinonyl porphyrin,1,and meso-di(4-pyridyl)-di[3-(1-aziridinyl)-4-methyl-2,5-benzoquinonyl]porphyrin, 2 were synthesized as shown in the Scheme. The latter porphyrin contains the aziridinyl-p-benzoquinone substituents in the 5,10-meso positions which would allow this porphyrin system to perform better as a DNA cross-linker than the 5,15-isomer. The p-benzoquinonyl substituents were obtained by oxidation of the aminophenyl substituents to which the starting nitrophenyl meso-substituents were reduced. The starting meso-tri-4-pyridyl-m-nitrotolylporphyrin 3, and meso-di-4-pyridyl-di(m-nitrophenylporphyrin) 4 were obtained by condensation of pyrrole, 4-pyridinecarboxaldehyde and 3-nitro-tolualdehyde[2,6,7] in the molar ratio 4:3:1. The latter aldehyde was obtained by oxidation of the respective alcohol with CrO_3 in pyridine.[8]

The porphyrins 3 and 4 were isolated from the reaction mixture as the third and second fraction respectively, eluted by $CHCl_3/CH_3OH$ 9:1 from a silica gel column;[9,10] respective yields, 3.5% and 7%.



Reduction of nitro groups carried out by $SnCl_2.2H_2O$ in conc. HCl at 65 °C[11] gave the meso-tri-4-pyridyl-m-aminophenylporphyrin 5, and meso-di-4-pyridyl-di(m-aminophenyl)porphyrin 6,[12,13] which were purified on a silica gel column with $CHCl_3$ as an eluent; yield of reduction, 42%. Next, the latter porphyrins were oxidized in methanol solution by aq. Fremy salt, with addition of KH_2PO_4,[14] to the respective quinonoporphyrins 7 and 8;[15,16] respective yields, 49% and 45%. In the final step, 7 and 8 were dissolved in dry methanol and stirred with freshly prepared aziridine[17] for 30 min. at 0 °C, then at room temperature for 1 h. The products 1 and 2[18,19] were purified by column chromatography and preparative TLC on Merck silica gel plates with $CHCl_3/CH_3OH$, 9:1, as an eluent; yield of the last step, 47%; overall yield of 1 and 2, based upon the starting m-nitro-p-tolylporphyrins 3 and 4 was, respectively, 9.7% and 7.9%. When a mixture of mono-m-nitrophenyl- and di-m-nitrophenyl-porphyrins, 3 and 4 was used as starting materials, the obtained mixture of final aziridinyl-quinonoporphyrins 1 and 2 was difficult to separate by preparative TLC due to small differences in their R_f values.

It is characteristic that the MS fragmentation by the magic bullet technique would show the aziridinyl-benzoquinone rings in 1 and 2 losing methyl groups and the respective appearance of m/z 690(25%) and 740(23%) ions, intensities referred to m/z 338. The ^1H NMR spectra of 1 and 2 showed a characteristic difference of aziridine methylene group singlets, 2.2 vs 2.3 ppm, which correspond to δ values observed by Islam and Skibo[14] for aziridinyl-quinone derivatives of benzimidazole. The appearance of these signals proves the attachment of the aziridine ring to the C-3 and not to the C-6 center of the quinone unit, since in the latter case doublets will appear. The location of the methyl group at the C-4 center favors the attachment of the aziridine ring in the final step of the synthesis to the C-3 center. Such an activation of aziridine attack on quinones by the adjacent methyl group has

already been documented.[14] The signals of strongly shielded porphyrin protons usually appearing in the -2.8 to -3.0 ppm range were shifted under the influence of the adjacent p-benzoquinone ring to δ = -1.4 which is consistent with the signals of quinonyl porphyrins reported by Sessler et al. [20-22]

For the synthesized aziridinyl-quinone porphyrins 1 and 2, one can expect a few modes of interaction with DNA. These expectations are based both on the presence of the pyridyl-porphyrin and aziridinyl-p-benzoquinone units. The intercalation of the former between the DNA nucleobase pairs[23,24] and their interaction with DNA[25] are already known phenomena. On the other hand, it is also known that aziridine is a good DNA alkylating agent since it reacts easily with nucleophiles, like those representing the guanosine N-7 centers in DNA,[26] to form open ring covalent adducts.[27,28] The attachment to aziridine of p-benzoquinone joined directly to porphine, would facilitate the opening of an aziridine ring by the change of electron distribution, especially when the non-aromatic quinone is reduced to an aromatic semiquinone or hydroquinone.[14,20] As a result of this, a porphyrin containing two aziridinyl-p-benzoquinone units is a potential DNA cross-linker[29,30] while the monosubstituted porphyrin should be able to create new functionalities located on a DNA strand; both activites disrupt the processes necessary for the transmission of genetic information and mutations.

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9) 3. MS, m/z: 676 $(M+1)^+$. ^{1}H NMR ($CDCl_3$), δ ppm: 9.12(d,4H,pr), 8.91(s,8H,β-pyr), 8.50(d,2H,py), 8.25(2H,d,py), 8.01(2H,d,py), 7.28, 7.55 and 7.75(m,3H,arom), 2.66(s,3H,CH_3), -2.97(s,2H,porph). UV-vis ($CHCl_3$), λ nm: 242, 416(S), 512, 545, 587, 642.
10) 4. MS, m/z: 739 $(M+1)^+$. ^{1}H NMR($CDCl_3$) δ ppm: 9.05(d,4H,py), 8.85 (s,8H,β-pyr), 8.45(d,2H,py), 8.20(d,2H,py), 7.95(dd,2H,arom), 7.72(d,2H,arom), 7.25(s,2H,arom), 2.55(bs,6H,CH_3), -2.90(s,2H,porph).
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12) 5. MS, m/z: 647$(M+1)^+$. ^{1}H NMR($CDCl_3$), δ ppm: 9.00(d,4H,py), 8.92(s,8H,β-pyr), 8.75(d,4H,py), 8.15(d,2H,py), 8.02(d,2H,py), 7.21, 7.52, 7.70 (m,3H,arom), -2.85(s,2H,porph). UV-vis($CHCl_3$), λ nm: 243, 298, 423(S), 518, 551, 593, 651.

13) 6. MS, m/z: 673$(M+1)^+$. ^{1}H NMR($CDCl_3$) δ ppm: 9.02(d,4H,py), 8.88(bs,8H,β-pyr), 8.75(d,2H,py), 8.20(d,2H,py), 7.51(s,2H,arom), 7.42(m,2H,arom), 7.21(m,2H,arom), 2.55(bs,6H,CH_3), -2.85(s,2H,porph).

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15) 7. MS, m/z: 662$(M+1)^+$. ^{1}H NMR($CDCl_3$) δ ppm: 9.01(d,4H,py), 8.75(s,8H,β-pyr), 8.62(d,4H,py), 8.15(d,2H,py), 8.01(d,2H,py), 6.85, 6.1(s,2H,quin), 2.51(s,3H,CH_3), -1.45(s,2H,porph). UV-vis($CHCl_3$) λ nm: 242, 305, 423(S), 518, 551, 591, 651.

16) 8. MS, m/z: 705$(M+1)^+$. ^{1}H NMR($CDCl_3$) δ ppm: 8.91(d,4H,py), 8.80(s,8H,β-pyr), 8.62(d,2H,py), 8.25(d,2H,py), 6.85(s,2H,quin), 6.15(s,2H,quin), 2.51(s,6H,CH_3), -1.50(s,2H,porph).

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18) 1. MS, m/z: 706$(M+2)^+$, 705$(M+1)^+$, 691 $(M+2)^+$-CH_3, 690$(M+1)^+$-CH_3. ^{1}H NMR($CDCl_3$) δ ppm: 8.95(d,4H,py), 8.75(bs,8H,β-pyr), 8.62(d,4H,py), 8.15(d,2H,py), 8.21(d,2H,py), 6.80(s,1H,quin), 2.52(s,3H,CH_3), 2.31(s,4H,azir), -1.45(s,2H,porph). UV-vis($CHCl_3$), λ nm: 241, 309, 419(S), 454, 516, 544, 598, 653.

19) 2. MS, m/z: 770$(M+1)^+$, 740$(M+1)^+$-2CH_3 ^{1}H NMR($CDCl_3$) δ ppm: 8.95(d,4H,py), 8.75(s,8H,β-pyr), 8.55(d,2H,py), 8.10(d,2H,py), 6.91(s,2H,quin), 2.52(s,6H,CH_3), 2.20(s,4H,azir), -1.45(s,2H,porph).

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