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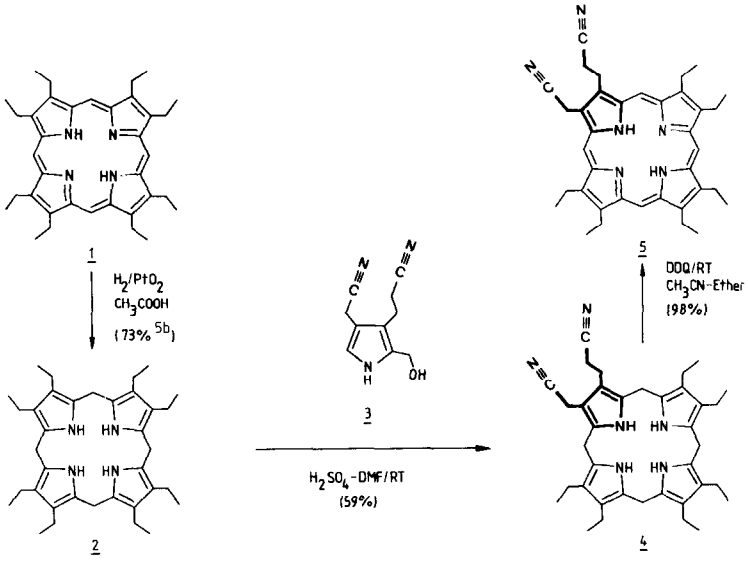
PORPHYRIN SYNTHESIS BY RING TRANSPLANTATION

Ulrich Kämpfen and Albert Eschenmoser*
Organisch-chemisches Laboratorium der Eidgenössischen Technischen Hochschule, CH-8092 Zürich, Switzerland

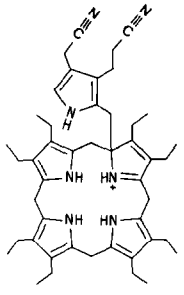
With best wishes to Harry Wasserman for his 65th birthday

Abstract: One of the four equivalent pyrrole rings of octaethyl porphyrinogen has been replaced by a foreign pyrrole ring in one operation and in (relatively) good yield.

Studies on the chemistry of α-amino nitriles and a search for structural relationships between this class of compounds and the biological cofactor molecules[1] have led us to investigate the chemistry of the octanitrile forms of uroporphyrinoids[2,3]. Concomitantly, a study of the model systems 4 and 5 has been initiated, because these dinitriles may facilitate the recognition of some of the anticipated features of the chemistry of the ensemble of two nitrile groups in such a constitutional environment; furthermore, it appeared to us that these two compounds might synthetically be quite close at hand. They are, and we describe here their preparation. The procedure embodies a type of porphyrin synthesis that we like to think of as being not only simple, but also - in a way - amusing.



When 2 mol-equivalents of octaethyl porphyrinogen 2[4] (prepared by catalytic hydrogenation[5] of octaethyl porphyrin 1[6]) are treated at room temperature with one equivalent of the hydroxymethylpyrrole derivative 3[2] in the presence of 4 mol-equivalents of sulfuric acid in a 4.1×10^{-3} M degassed DMF solution under exclusion of oxygen in the dark for 18 hours, a mixture is obtained from which after chromatography (silica G 60, CH_2Cl_2/ether 30:1) are isolated 1.10 equivalents of starting material 2 (54 %) and 0.66 equivalents of the transplantation product 4 (yield 66 % with ref. to 3, 59 % after crystallization). The dehydrogenation of the porphyrinogen 4 to the porphyrin 5 is essentially quantitative when 3.0 equivalents of DDQ are used in a 6.0×10^{-3} M degassed acetonitrile/ether (1:14) solution of 4 for 30 min at room temperature under exclusion of oxygen. Both 4 and 5 have been characterized by UV/VIS, IR, ^{1}H-NMR and mass spectroscopy as well as elemental analysis (see ref. 7 and for details ref. 8).



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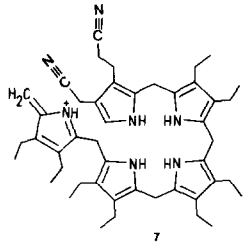

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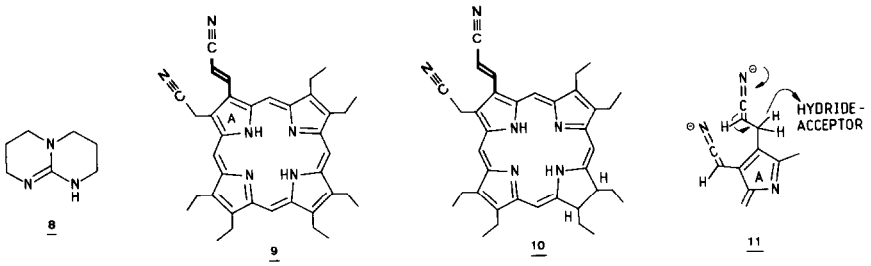
The ring transplantation 2 + 3 → 4 is a remarkably clean process; no other products apart from 4 and starting material 2 were isolated. The type of reactivity that is involved in the transplantation process is well known from the versatile non-enzymic[9], as well as enzymic[10] chemistry of uroporphyrinogen-type structures. The uncertainty lies not in the nature, but rather in the sequence (or sequences) of steps from which the transplantation product eventually emerges. The potential intermediates 6 and 7 indicate the perhaps most likely entry into the manifold of possible routes, but no experimental evidence has been collected to corroborate the occurrence of these specific intermediates or to find out by which sequence of steps the diethylpyrrole unit is cut off. Regardless of mechanistic details, the overall process is an illustration as well as an application of the (known[9]) extraordinary potential for self-assembly of the macrocyclic porphyrinogen structure. Further experimental

studies would be required to establish e.g. to what extent transplantation yields depend on relative nucleophilicities of the π systems of transplant- versus substrate-pyrrole rings, whether the approach would still prove useful in cases where the substrate is less symmetrical, and whether a porphyrin synthesis by meso carbon (instead of pyrrole ring) transplantation might also be preparatively feasible.



8 9 10 11

Among the chemical reactions which we observed for the porphyrin dinitrile 5 the following, however, was unexpected and is, therefore, included in this report.

When 5 (free of 4) was heated to 150° for 30 minutes in molten guanidine base 8[11] (approx. 80 equiv.) under strict exclusion of oxygen, a product mixture was obtained from which the didehydro derivative 9 was isolated as the main component by HPLC (Techsil 5 μ, methyl-t-butyl ether/pentane/methanol 1:10:0.3; yield 43 %)[12]. The acrylic side chain of this product seems to result from complex disproportionations since components with hydrogenated chromophore systems were found to be in the reaction mixture. Two were isolated in pure form, though in low yield, the porphyrinogen 4 (5 %, identified by HPLC, ^{1}H-NMR, UV and oxidation to the porphyrin) and the chlorin derivative 10 (4 %). For the latter, the location of the hydropyrrolic ring relative to the others rests on a ^{1}H-NMR-NOE analysis[13]. The di-anion 11, a presumably strong hydride donor, might be the acting species in the disproportionation; a hydride transfer would transform the di-carbanionic donor molecule into a highly stabilized mono-anion. The formation of the porphyrinogen under these conditions is remarkable.

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7. 4: Colorless needles, mp 176°, cryst. from CH_2Cl_2-hexane versus hexane by isothermal distillation; log ε (220 nm)=4.46 (CH_3CN), $\tilde{\nu}$(CN)=2245, 2260 cm^{-1} (KBr); δ(ppm)=2.55 and 2.83 (2t/J=6,8/2H each/CH_2-CH_2-CN), 3.46 (s/2H/CH_2-CN), 3.70/3.71/3.73/3.77 (4s/2H each/meso-CH_2), 6.66/7.28 (2s broad/1 NH each), 7.01 (s broad/2 NH)($CDCl_3$); m/e=576 (100 %/M^+).
5: Purple needles, mp 265°, cryst. from CH_2Cl_2-CH_3OH versus CH_3OH by isothermal destillation; λmax 401 (5.34), 503 (4.10), 539 (4.16), 565 (3.92), 576 (sh/3.74), 620 (3.16) (CH_2Cl_2); $\tilde{\nu}$(CN)=2245 (KBr); δ -3.74 (2 NH), 1.88-1.97 (m/18H/6 CH_2CH_3), 4.02 (q/J=7.6/4H) and 4.12-4.20 (m/8H/CH_2-CH_3), 3.31/4.45 (2t/J=7.4/2H each/CH_2-CH_2CN), 5.11 (s/2H/CH_2CN), 9.96/10.06/10.11/10.12 (4s/1H each/meso-CH)($CDCl_3$); m/e=570 (100 %/M^+).

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12. Purple plates, mp 303°, cryst. from CH_2Cl_2-CH_3OH; λmax 409 (5.31), 480 (sh/3.70), 508 (4.04), 545 (4.51), 572 (4.00), 627 (4.03)(CH_2Cl_2); δ 7.28/9.09 (2d/J=8.3/1H each/CH=CH-CN), 5.01 (s/2H/CH_2CN/exchangeable with D_2O), 10.07/10.08/10.12/11.02 (4s/1H each/meso-CH)(CD_2Cl_2); m/e=568 (100 %/M^+).

13. NOE-experiment: irradiation at 3.9-4.1 ppm (pyrrolic CH_2-CH_3) induces enhancements of all four meso proton signals: 9.13/9.15 (C-10 and C-15), 10.16 (C-20) and 10.79 (C-5)(DMSO); λmax 410 (5.27), 497 (4.05, 504 (sh/4.03), 534 (4.30), 602 (3.76), 627 (3.68), 658 (4.81)(CH_2Cl_2); m/e=570 (100 %/M^+).

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