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BIOMIMETIC ONE-STEP CYCLOOLIGOMERIZATION TO MESO-TETRAALKYLPORPHINS BY USE OF SCHIFF'S BASES

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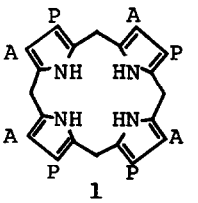
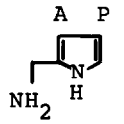
Biosynthesis of uroporphyrinogen III (1) from porphobilinogen (PBG, 2) involves a very interesting aspect that one of the PBG units is "switched" with respect to a head-to-tail oligomerization sequence.[1] The "switch" mechanisms[2] proposed by Corwin-Battersby[3] and Rimington-Johnson-Scott[4] both on the firm experimental grounds seem to be important, where the migration of the bond between pyrrole and C_1 unit proceeds to such a direction that the sequence of (at least) four substituents at the binding site is reinforced by the enzyme to be PAAP, although these postulate the different timing of the switch. The enzyme is supposed to have an active site residue(s) which can readily transfer a Schiff's base (C_1 unit), based on the Scott's results that the symmetrically tetra substituted labeled dipyrrylmethane without any aminomethyl group on its α-positions is incorporated into uro'gen III.[4a] Consideration of such the significance of the Schiff's base in the cyclooligomerization has given rise to an idea that joining pyrroles is made much easier by use of Schiff's bases, even when no switch is involved, thus providing a possibility of novel biomimetic one-step process of the cyclooligomerization of pyrroles to porphins.



1
uro'gen III



2
PBG

A = CH_2CO_2H
P = $CH_2CH_2CO_2H$

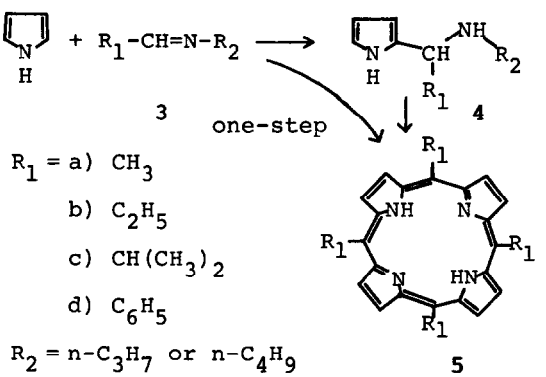
Now we wish to report a successful one-step preparation of porphins from pyrrole and a Schiff's base, by making full use of the idea; (1) aminomethylation

of pyrrole which mimics the suspected key process in enzymic "switch" and (2) the favorable amine-leaving from the resultant aminomethylated pyrrole, an event which readily occurs in usual cyclooligomerization of porphobilinogen.

The present one-step preparation is especially useful for the preparation of meso-tetraalkylporphins, which are hardly available from pyrrole and aliphatic aldehydes[5] via the one-step cyclooligomerization. Pyrroles whose β-H's are blocked with substituents are readily oligocyclized with aldehydes[6] but with much greater difficulties are afforded porphin or meso-tetraalkylporphins.

Thus, a solution of 1 mmol of pyrrole and 1 mmol of a Schiff's base (3a) in 5 ml of chloroform was allowed to stand for 6 days under the action of 20 mmol of methoxyacetic acid added to the mixture. After air-oxidation and the usual work-up,[6] the mixture was chromatographed on basic alumina (woelm, activity I) eluting with chloroform.[7] From a violet fraction was isolated pure meso-tetramethylporphin (5a, TMP 8.7 %) which exhibited satisfactory spectroscopic characteristics. TMP (5a): Nmr[8] ($CDCl_3$) δ 4.56 (12H, methyl), 9.42 (8H, β-H); UV[9] ($CHCl_3$) 418 (Soret), 486, 520, 554, 602, and 661 nm.

The yield of TMP [based on the Soret absorption] was 20 %. Therefore, the present route to TMP possesses a great synthetic advantage over the previous methods which employs acetaldehyde[5b] or its equivalence, since a very poor yield[5a] of 1 % had been the best among the reported yields of TMP.[5] The high yield in the present case probably originates in either the increased electrophilicity of the Schiff's base by protonation at nitrogen and/or better leaving of amine than hydroxyl. Results on one-step preparations of several meso-tetrasubstituted porphins together with isolated yields are shown in Table I.



Also noteworthy is that α-aminomethylpyrrole which is supposed to be the intermediate of the present one-step preparation, was isolated in a nearly quantitative yield, when the reaction between pyrrole and a Schiff's base (3a-c) was quenched after a short reaction period. The mixture was thus stirred for 10 to

Table I. One-Step Preparations of Porphins (5a-c)

Porphin	Precursor	Acid(eq.)/solvent	Time (day)	Yield[a] (%)
TMP (5a)	4a	$CH_3OCH_2CO_2H$ (20)/$CHCl_3$	6	22 (8.7)[b]
	pyrrole + 3a		6	20
TEP (5b)	pyrrole + 3b	CH_3I (2)/CH_3CO_2H[c]	6	9.3
TPP (5d)	pyrrole + 3d	CH_3CO_2H	24 hr	7 (5.6)[b]

[a]Based on the Soret. [b]Isolated yield. [c]Krol's method (ref.10).

Table II. α-Aminomethylation of Pyrrole by Schiff's Base

Schiff's base	Acid(eq.)/solvent	Temp. (°C)	Time (min)	Yield[a] (%)
3a	CH_3CO_2H (10)/CH_3Cl	0	10	4a (90)
3b	CH_3CO_2H (10)/CH_3Cl	0	25	4b (80)
3c	CH_3CO_2H[b]	25	30	4d (85)

[a]Preparative yields. [b]5 ml of acid was used as the solvent.

30 min in the presence of 10 equivalent amount of a weak acid (acetic or propionic acid), then almost pure (from nmr)[11] α-(N-propyl-1-aminoalkyl)pyrroles (4a-c) were isolated in practically quantitative yields (Table II). 2,4-Dimethylpyrrole too was successfully α-aminomethylated by use of this technique, so this provides a valuable and useful new route to the preparations of very labile α-aminomethylpyrroles. It, therefore, shows for the first time the effective function of the Schiff's base intermediate for the in vitro cyclooligomerization, suggesting their significant in vivo contribution as is proposed by Scott et al.[4a]

Further obvious extensions of the present work are in progress.

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11. α-(N-propyl-1-aminoethyl)pyrrole (6a): Nmr (CCl_4) δ 8.9 (broad, pyrrole NH), 6.5 (m, 1H, α-H), 5.9 (m, 2H, β-H), 3.9 (q, 1H, α-methin), 2.5 (t, 2H), 2.2 (S, NH), 1.2—1.6 (m, 2H), 1.35 (d, 3H), 0.9 (t, 3H). α-(N-propyl-1-amino-propyl)pyrrole (**6b**): Nmr (CCl_4) δ 9.8 (broad, pyrrole NH), 6.6 (m, 1H, α-H), 6.0 (m, 2H, β-H), 5.63 (q, 1H, α-methin), 2.93 (t, 2H), 2.0 (S, 3H), 1.4 (d, 3H), 1.0—1.5 (m, 2H), 0.75 (t, 3H). α-(1-N-butylamino-2-methylpropyl)pyrrole (6c): Nmr (CCl_4) δ 8.7 (broad, pyrrole NH), 6.6 (m, 1H, α-H), 5.9 (m, 2H, β-H), 3.4 (d, 1H, α-methin), 2.4 (t, 2H), 1.35 (S, 1H, NH), 1.0—1.8 (m, 5H), 0.9 (d, 6H), 0.8 (t, 3H).