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SYNTHESES OF 7,17-BIS(2-ETHOXYCARBONYLETHYL)-2,3,12,13-TETRAETHYL-8,18-DIMETHYLPORPHIN AND ITS DERIVATIVES

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Symmetric porphyrin, 7,17-bis(2-ethoxycarbonylethyl)-2,3,12,13-tetraethyl-8,18-dimethylporphin (6) was prepared by the a,c-biladiene route. Hydrolysis of 7,17-diethyl ester groups afforded 7,17-bis(carboxyethyl)porphyrin (7) and successive treatment of (7) with n-butylamine gave 7,17-bis[2-(N-n-butylcarbamoyl)ethyl]porphyrin (8). Reduction of (6) with $LiAlH_4$ gave 7,17-bis(2-hydroxyethyl)-porphyrin (9) and bromination of (9) with HBr yielded unstable 7,17-bis(2-bromoethyl)porphyrin (10).

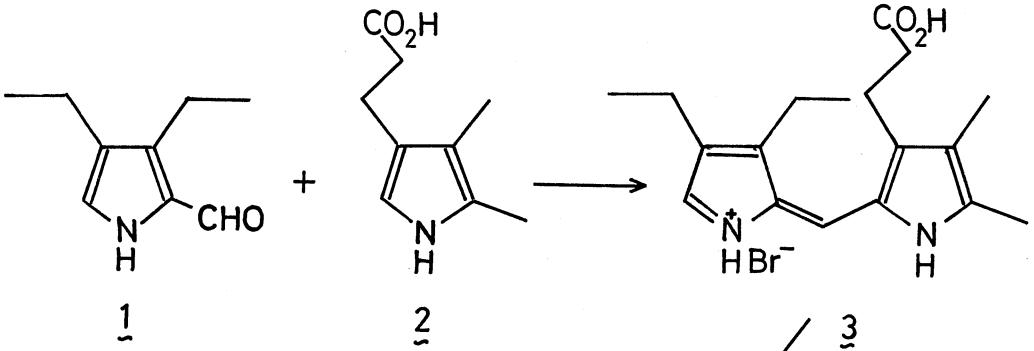
The chemical modification of the peripheral positions of porphyrins has been developed in order to elucidate the relationship between structure and function of the heme enzymes. Recent physicochemical studies on the synthetic metalloporphyrins have afforded a more elaborate insight into the close proximity of the iron porphyrin in heme protein. Fixation of axial ligands and formation of hydrophobic atmosphere around the central iron atom can be performed by substitution at the peripheral positions of porphyrin ligands.[1,2] We wish to report syntheses of symmetric porphyrin substituted with the carboxyethyl groups at the 7 and 17 positions *via* the a,c-biladiene[3] and its derivatives.

Dipyrromethene, 3'-(2-carboxyethyl)-3,4-diethyl-4',5'-dimethyl-2,2'-dipyrromethene hydrobromide (3) was prepared by condensation of 2,3-dimethyl-4-(2-carboxyethyl)pyrrole (2) and 3,4-diethyl-2-formylpyrrole (1) in ethanol - 48% hydrobromic acid (3/1, vol/vol). Recrystallization of the solid material from ethanol-petroleum ether (1/3, vol/vol) gave deep orange crystals in 66.2%, mp 127.8 ∿ 128.3°C; nmr τ($CDCl_3$) 8.81 (6H, t, 3,4-$CH_2\underline{CH_3}$), 7.98 (3H, s, 4'-$C\underline{H_3}$), 7.57 (2H,

t, 3'-$CH_2\underline{CH}_2CO_2H$), 7.36 (4H, q, 3,4-$C\underline{H}_2CH_3$), 7.35 (3H, s, 5'-$C\underline{H}_3$), 7.00 (2H, t, 3'-$C\underline{H}_2CH_2CO_2H$), 2.70 (1H, s, methine), 2.43 (1H, d, 5-proton), -2.85 (2H, broad, NH).

Treatment of (3) in glacial acetic acid with bromine afforded dibromodipyrromethene, 5-bromo-5'-bromomethyl-3,4-diethyl-3'-(2-carboxyethyl)-4'-methyl-2,2'-dipyrromethene hydrobromide (4) in 50% yield, (decomp. at 149°C); nmr τ(CD_3OD) 9.15 (3H, t, 3-$CH_2C\underline{H}_3$), 8.98 (3H, t, 4-$CH_2C\underline{H}_3$), 8.13 (3H, s, 4'-$C\underline{H}_3$), 7.10 ∿ 7.90 (8H, m, 3,4-$C\underline{H}_2CH_3$ and 3'-$C\underline{H}_2C\underline{H}_2CO_2H$), 5.57 (2H, s, 5'-$C\underline{H}_2Br$), 2.61 (1H, s, methine). Dipyrromethene (3) was coupled with dibromodipyrromethene (4) by using anhydrous stannic chloride. Recrystallization of thus obtained solid material from chloroform-ether gave brownish red crystals in 90% (decomp. 275°C). The nmr spectrum of 1-bromo-1,19-dideoxy-7,17-bis(2-ethoxycarbonylethyl)-2,3,12,13-tetraethyl-8,18,19-trimethylbiladiene a,c-dihydrobromide (5) shows the proton chemical shifts at τ($CDCl_3$), 9.32 (6H, t, 7,17-$CO_2CH_2C\underline{H}_3$), 8.8 (12H, m, 2,3,12,13-$CH_2C\underline{H}_3$), 8.13 (3H, s, 8-$C\underline{H}_3$), 7.99 (3H, s, 18-$C\underline{H}_3$), 6.9 ∿ 7.6 (16H, m, 2,3,12,13-$C\underline{H}_2CH_3$ and 7,17-$C\underline{H}_2C\underline{H}_2CO_2Et$), 7.32 (3H, s, 19-$C\underline{H}_3$), 5.96 (2H, q, 17-$CO_2C\underline{H}_2CH_3$), 5.88 (2H, q, 7-$CO_2C\underline{H}_2CH_3$), 4.75 (2H, s, 10-methylene), 2.73 (1H, s, 5-methine), 2.60 (1H, s, 15-methine). The a,c-biladiene (5) was cyclized in o-dichlorobenzene for 30 min,[3] and recrystallization of the red solid from methylene chloride-methanol gave purple crystals (6) in 56% yield, mp 212°C; nmr τ($CDCl_3$), 8.90 (6H, t, 7,17-$CO_2CH_2C\underline{H}_3$), 7.81 (6H, t, 2,12-$CH_2C\underline{H}_3$), 7.80 (6H, t, 3,13-$CH_2C\underline{H}_3$), 6.53 (4H, t, 7,17-$CH_2C\underline{H}_2CO_2$-Et), 6.45 (6H, s, 8,18-$C\underline{H}_3$), 6.00 (12H, m, 2,3,12,13-$C\underline{H}_2CH_3$ and 7,17-$CO_2C\underline{H}_2CH_3$), 5.75 (4H, t, 7,17-$C\underline{H}_2CH_2CO_2Et$), -0.03 (4H, s, mesoprotons). The nmr spectrum of porphyrin (6) shows two equivalent chemical shifts assigned to ethyl ester of propionic acid at 7,17-positions, methyl groups at 8,18, ethyl groups at 2,12 and another ethyl groups at 3,13. The visible spectrum of (6) indicates the characteristic ETIO-type absorptions at 400 nm (log ε 4.84), 499 (3.99), 533 (3.86), 567 (3.68) and 620 (3.50) in chloroform.

Hydrolysis of (6) in 25% HCl gave the diacid (7) mp 218°C. Crystallization of (7) from pyridine afforded the dipyridinium salt, of which pyridine molecules were removed by washing with methanol. After (7) was dissolved in thionyl chloride, the reaction mixture was evaporated to dryness. Treatment of the resulting acid chloride with n-butylamine gave the diamide (8) (decomp. at 214°C). Existence of n-butylamido groups were evidently indicated by the nmr chemical shifts due to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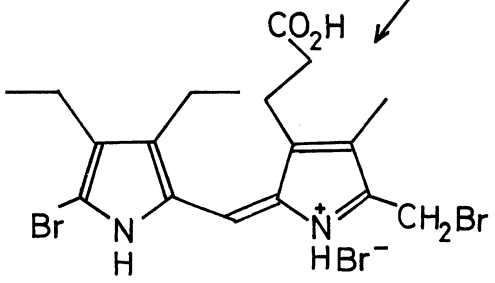
CHO
N
H
HBr⁻
1
2
3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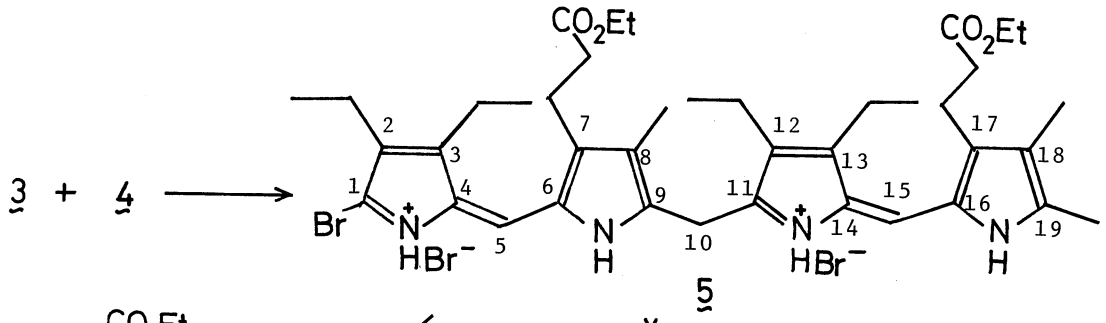
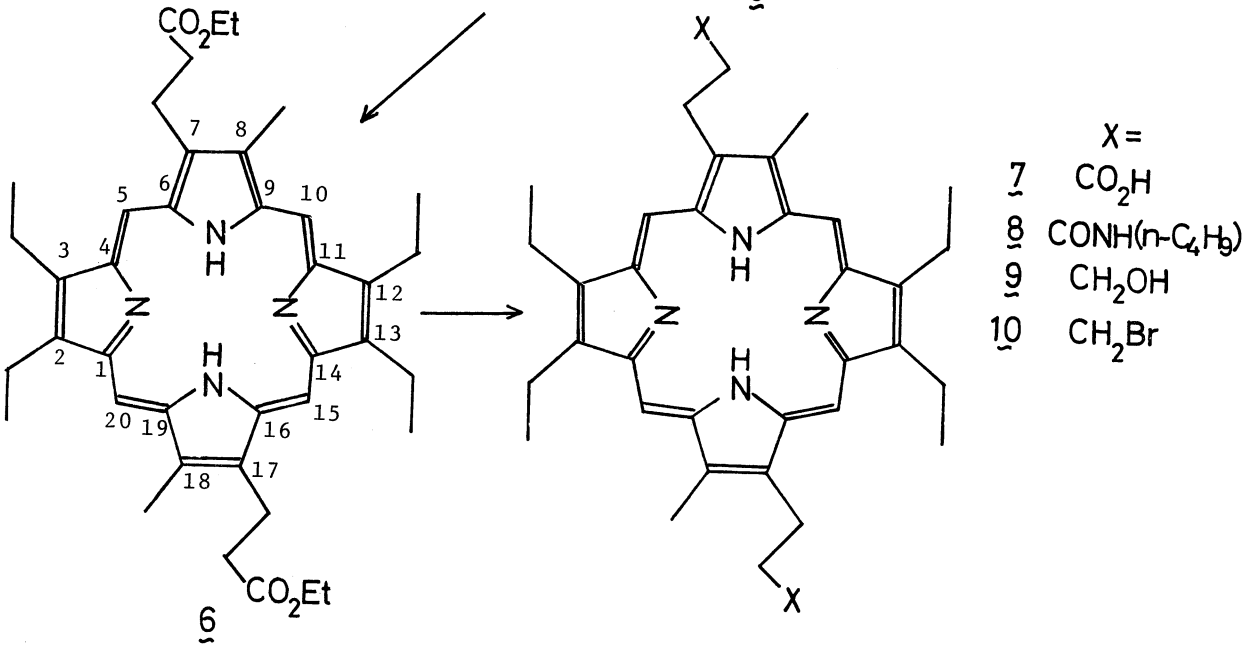
Br
CH2Br
HBr⁻
4


3 + 4
CO2Et
Br
HBr⁻
5


CO2Et
CO2Et
6
X
X =
7 CO2H
8 CONH(n-C4H9)
9 CH2OH
10 CH2Br

n-butyl groups at τ(CF_3CO_2D) 9.63 (6H, t, $NHCH_2CH_2CH_2\underline{CH_3}$), 8.97 (8H, m, $NHCH_2\underline{CH_2}$-$\underline{CH_2}CH_3$), and 6.91 (8H, m, $-CH_2\underline{CH_2}$-$CONH\underline{CH_2}CH_2CH_2CH_3$). Porphyrin dicarboxylic acid (7) was readily reduced to the porphyrin diol (9) in quantitative yield, (mp 230°C): nmr τ(pyridine-d^5), 8.10 (12H, t, 2,3,12,13-$CH_2\underline{CH_3}$), 7.50 (4H, quintet, 7,17-$CH_2\underline{CH_2}CH_2OH$), 6.20 (6H, s, 8,18-$\underline{CH_3}$), 5.8 (16H, m, 2,3,12,13-$\underline{CH_2}CH_3$, and 7,17-$\underline{CH_2}$-$CH_2\underline{CH_2}OH$), -0.50 (2H, s, mesoprotons), -0.70 (2H, s, mesoprotons). The foregoing porphyrin diol (9) was brominated by gentle heating the aqueous HBr solution of (9). The porphyrin dibromide (10) is very labile at room temperature. Therefore, (10) was characterized as zinc complex (11), nmr τ(pyridine-d^5), 8.00 (12H, t, 2,-3,12,13-$CH_2\underline{CH_3}$), 7.15 (4H, quintet, 7,17-$CH_2\underline{CH_2}CH_2Br$), 6.34 (6H, s, 8,18-$\underline{CH_3}$), 5.7 (16H, m, 2,3,12,13-$\underline{CH_2}CH_3$ and 7,17-$\underline{CH_2}CH_2\underline{CH_2}Br$), -0.55 (4H, d, mesoprotons).

Acknowledgment

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