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SYNTHETIC STUDIES OF PIGMENTS OF GREEN BACTERIA
I. Synthesis of Substituted Pyrroles

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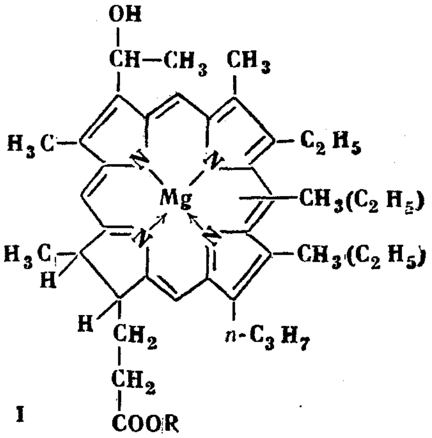
This paper deals with the preparation of a number of carbobenzoxypyrroles, intermediates in the synthesis of green bacterial pigments.

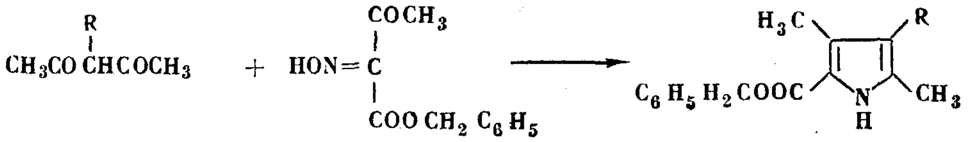
The molecule of the pigment of green bacteria I is known to consist of four different pyrroles. From the oxidation products of I methylethylmaleinimide, dihydrohematinic acid imide and also methyl-n-propylmaleinimide have been isolated [1]. This is the first case of the isolation of methyl-n-propylmaleinimide in the oxidation of natural porphyrins. Studies of the structure of I indicate that the n-propyl group is at position 6 in the porphyrin system [2].


I

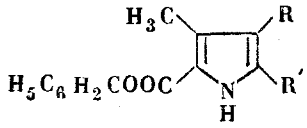
$R = C_{15}H_{25}$

This paper deals the the synthesis of substituted pyrroles which can be used to prepare substance I and related porphyrins.

Pyrroles of general formula IV (R=H, C_2H_5, n-C_3H_7, $CH_2CH_2COOCH_3$) were prepared by condensing acetylacetone (II, R=H) or its alkyl-substituted derivatives (II, R = C_2H_5; n-C_3H_7; $CH_2CH_2COOCH_3$) with benzylisonitrosoacetoacetate (III).


II III IV

By bromination, 2,4-dimethyl-5-carbobenzoxypyrrole (IV, R=H) was converted to 3-bromo-2,3-dimethyl-5-carbobenzoxypyrrole (IV, R=Br), and then into 3-bromo-2-bromomethyl-4-methyl-5-carbobenzoxypyrrole (V, R=Br, R'=CH_2Br)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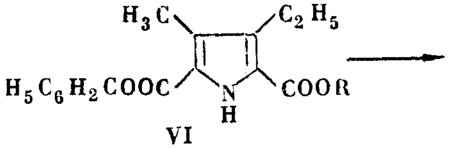
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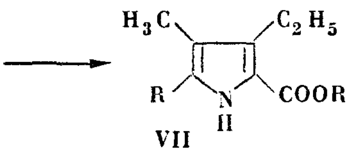
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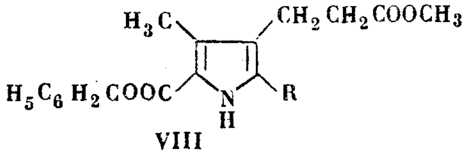

VIII

Reaction of 2, 3-dimethyl-3-ethyl-5-carbobenzoxypyrrole (IV), R=Et) with sulfuryl chloride converted it to a trichloro derivative, hydrolyzed to 3-methyl-4-ethyl-5-carboxy-2-carbobenzoxypyrrole (VI, R=H), esterified by diazomethane to 3-methyl-4-ethyl-5-carbomethoxy-2-carbobenzoxypyrrole (VI, R=Me). Hydrogenation with palladium-charcoal catalyst converted the benzyl ester to free acid (VII, R=Me; R'=COOH), decarboxylated to 3-methyl-4-ethyl-5-carbomethoxypyrrole (VII, R=Me; R'=H), and by transesterification the latter was converted to 3-methyl-4-ethyl-5-carbobenzoxypyrrole(VII, R=$CH_2C_6H_5$; R'=H). 2, 4-Dimethyl-3-(β-carbomethoxyethyl)-5-carbobenzoxypyrrole (IV, R=CH_2CH_2COOMe) was converted to 4-methyl-3-(β-carbomethoxyethyl)-2-carboxy-5-carbobenzoxypyrrole (VIII, R=COOH), and then into 4-methyl-3-(β-carbomethoxyethyl)-5-carbobenzoxypyrrole (VIII, R=H).

A method of synthesizing 2, 4-dimethyl-3-n-propyl-5- carbobenzoxypyrrole (IV, R=n—Pr) was worked out, and using it as a starting point, the following were prepared:

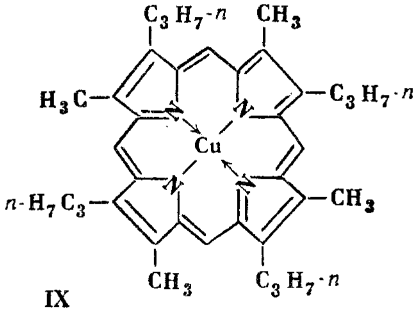
2-bromomethyl-4-methyl-3-n-propyl-5-carbobenzoxypyrrole (V, R=n —Pr; R'=CH_2Br),

4-methyl-3-n-propyl-2-acetoxymethyl-5-carbobenzoxypyrrole (V, R=n —Pr; R'=CH_2OCOMe),

4-methyl-3-n-propyl-2-carboxy-5-carbobenzosypyrrole (V, R=n —Pr; R'= COOH),

4-methyl-3-n-propyl-5-carbobenzoxypyrrole (V, R=n – Pr, R'=H).

4-Methyl-3-n-propyl-2-acetoxymethyl-5-carbobenzoxypyrrole (V, R=n —Pr, R'=CH_2OCOCH_3) was used to prepare tetramethyltetra-n-propylporphin.



IX

Just as the present work was concluded, there appeared a paper [3] describing a synthesis of a tetramethyltetra-n-propylporphin closely resembling the present one. However in the present work, much higher yields were obtained in some stages, e.g., in the preparation of 3-n-propylpentanedione-2, 4 (II, R=n —Pr), and of a pyrrole IV (R=n – Pr).

The copper complex of tetramethyltetra-n-propylporphin (IX) was also prepared with a view to establishing its structure. It was found that a type I isomer is mainly formed.

The individualities of the compounds prepared were confirmed by thin-layer chromatography on silicic acid, using a petrol ether-ether system (for IV, R=Br and n —Pr; V, R=Br, R' = CH_2Br and R= n —Pr, R' =CH_2Br; VI, R= H and Me; VII, R=Me, R' = COOH; R= Me, R' = H; R=$CH_2C_6H_5$, R' =H), or in chloroform on aluminum oxide (for V, R=n —Pr, R' =COOH; VIII, R' = H).

Experimental

3-Bromo-2, 4-dimethyl-5-carbobenzoxypyrrole (IV, R=Br). A solution of 4.75 g (0.03 mole) bromine in 10 ml carbon tetrachloride was quickly poured into a solution of 6.8 g (0.03 mole) 2, 4-dimethyl-5-carbobenzoxypyrrole (IV, R=H) in 50 ml carbon tetrachloride at 40-50°, the whole cooled, and left at 0-5° for 30 min. The precipitate was filtered off, washed with petrol ether (twice with 10 ml portions) and recrystallized from 200 ml n-octane. Yield 6.6 g (72.2%) colorless needles mp 138.5-139°. Found: C 54.46; H 4.61; Br 25.77; N 4.84%. Calculated for $C_{14}H_{14}BrNO_2$: C 54.54; H 4.58; Br 25.92; N 4.54%.

3-Bromo-2-bromomethyl-4-methyl-5-carbobenzoxypyrrole (V, R= Br; R' =CH_2Br). A solution of 2.1 g (13 mole) bromine in 14 ml carbon tetrachloride was added dropwise, but rapidly, to a solution of 4.0 g (13 mole) IV (R = Br)) in 36 ml carbon tetrachloride held at 40-50°. The precipitate was filtered off, washed with carbon tetrachloride (twice with 10 ml portions), and then recrystallized from 250 ml n-octane. It was dried in a vacuum desiccator. Yield 4.14 g (82.5%), colorless crystals with a blueish reflex, darkening in air, mp 161-161.5°. Found: C 43.31; H 3.51; Br 41.58; N 3.50%. Calculated for $C_{14}H_{13}Br_2NO_2$: C 43.42; H 3.38; Br 41.29; N 3.62%.

3-Methyl-4-ethyl-5-carboxy-2-carbobenzoxypyrrole (VI, R=H). 22.7 g (168 mmole) sulfuryl chloride was added dropwise to a solution of 14.25 g (55 mmole) 2, 4-dimethyl-3-ethyl-5-carbobenzoxypyrrole (IV, R=Et) in 300 ml dry ether cooled to 0-4°, and then left at the latter temperature for 8 hr. Then the reaction products were washed with ice water until the reaction was slightly acid. The ether was evaporated under reduced pressure, and a solution of sodium acetate added to the residue (40 g in 650 ml water), after which the whole was boiled for 15 min. The crystals which separated after cooling were separated off, recrystallized from 10 ml ethanol, and then dried in a vacuum desiccator. Yield 9.28 g (58.5%), colorless crystalline compound, mp 169.5-170°. Found: C 66.81; H 5.94; N 4.75%. Calculated for $C_{16}H_{17}NO_4$: C 66.88; H 5.96; N 4.87%.

3-Methyl-4-ethyl-5-carbomethoxy-2-carbobenzoxypyrrole (VI, R=Me). An ethereal solution of diazomethane, prepared from 4.4 g nitrosomethylurea, was added to a suspension of 4.2 g (15 mmole) VI (R=H) in 10 ml ether. The reaction mixture was left an hour, filtered, and the solvent evaporated under reduced pressure. The residue was recrystallized from 120 ml petrol ether. Yield 3.5 g (79.5%), colorless crystals, mp 76.5-77°. Found: C 67.73; H 6.44; N 4.92%. Calculated for $C_{17}H_{19}NO_4$: C 67.76; H 6.36; N 4.65%.

3-Methyl-4-ethyl-5-carbomethoxy-2-carboxypyrrole (VII, R=Me, R'=COOH). 1.5 g catalyst (nickel on chromium oxide) was added to a solution of 2.0 g (6.6 mmole) VI (R=Me) in 90 ml methanol, and the whole stirred for 30 min. The catalyst was separated off, washed with methanol, then 1.5 g of palladium on activated charcoal catalyst added. When hydrogenation was complete, the catalyst was separated off, washed with methanol, and the catalyst removed under reduced pressure. The residue was recrystallized from 20 ml methanol, yield 1.20 g (85.5%), colorless crystalline compound, mp 217.5-218.5°. Found: C 56.61; H 6.00; N 6.41%. Calculated for $C_{10}H_{13}NO_4$: C 56.85; H 6.20; N 6.63%.

3-Methyl-4-ethyl-5-carbomethoxypyrrole (VII, R=Me; R'=H). 1.89 g (9 mmole) VI (R=Me; R'=COOH) was heated in a stream of nitrogen at 200-250°, till evolution of carbon dioxide ceased. The residue was vacuum distilled, yield 1.05 g (70.5%). Colorless crystalline substance, sublimed readily, turned yellow in air, soluble in organic solvents, insoluble in water. Bp 88-89° (0.3 mm), mp 60-60.5°. Found: C 64.80; H 8.04; N 8.38%. Calculated for $C_9H_{13}NO_2$: C 64.66; H 7.85; N 8.38%.

3-Methyl-4-ethyl-5-carbobenzosypyrrole (VII, R=$CH_2C_6H_5$; R'=H). 0.02 g sodium metal was added to a solution of 0.91 g (5.4 mmole) VII (R=Me; R'=H) in 10 ml benzyl alcohol. The reaction mixture was heated to 100°, and held there for an hour. The alcohol formed during the course of the reaction, and the unchanged benzyl alcohol were distilled off under reduced pressure. The residue was dissolved in 10 ml ether, the ether solution washed with water until neutral, the solvent evaporated under reduced pressure, and the residue vacuum-distilled. Bp 100-110° (0.12-0.15 mm). On cooling the mass crystallized, the colorless crystals were separated off, and washed with petrol ether. Yield 0.46 g (34.8%). Mp 46.5-47°. Found: C 74.30; H 7.01; N 5.62%. Calculated for $C_{15}H_{17}NO_2$: C 74.08; H 7.05; N 5.75%.

4-Methyl-3-(β-carbomethoxyethyl)-2-carboxy-5-carbobenzoxypyrrole (VIII, R=COOH). 20.8 g (154 mmole) sulfuryl chloride was added dropwise to a suspension of 15.0 g (48 mmole) 2, 4-dimethyl-3-(β-carbomethoxyethyl)-5-carbobenzoxypyrrole (IV, R=CH_2CH_2COOMe) in 300 ml ether at 1-4°, and the whole left for 12 hr. The ethereal solution was washed with water (5 times with 50 ml portions), the solvent evaporated under reduced pressure, a solution of 80 g sodium acetate in 1300 ml water added to the residue, and the whole refluxed for 20 min, filtered hot and cooled. A resinous precipitate was formed, which was triturated with ether, and recrystallized from 80 ml 60% methanol. Yield 2.94 g (17.9%), mp 141.5-142.5°. Found: C 62.71; H 5.53; N 4.28%. Calculated for $C_{18}H_{19}NO_6$: C 62.62; H 5.54; N 4.06%.

4-Methyl-3-(β-carbomethoxyethyl)-5-carbobenzoxypyrrole (VIII, R=H). 2.94 g (8.5 mmole) VIII (R=COOH) was heated in a current of nitrogen at 160-170°, till evolution of carbon dioxide ceased, and the residue was then distilled, to give a cut of slightly yellow oily liquid, bp 224-225° (0.32 mm), yield 1.66 g (65.4%). Found: C 67.77; H 6.33; N 4.86%. Calculated for $C_{17}H_{19}NO_4$: C 67.76; H 6.36; N 4.65%.

3-n-Propylpentanedione-2,4 (II, R=n-Pr). 12 g (0.087 mole) calcined potash was added to a solution of 8.7 g (0.087 mole) acetylacetone and 16.9 g (0.01 mole) n-propyl iodide in 35 ml dry acetone, and the mixture refluxed for 24 hr. The precipitate was removed, and the solvent evaporated under reduced pressure, after which the residue was vacuum-distilled, to give 11.8 g (96%)* bp 58-60° (1 mm), d_4^{20} 0.94878, n_D^{20} 1.450. Found: C67.40; H 10.20%; MR_D 39.32. Calculated for $C_8H_{14}O_2$: C 67.57; H 9.92%; MR_D 39.17 (for the keto form).

2, 4-Dimethyl-3-n-propyl-5-carbobenzoxypyrrole (IV, R=n-Pr). A solution of 14.55 g (0.21 mole) sodium nitrite in 30 ml water was added to a solution of 40.50 g (0.20 mole) benzyl acetoacetate in 85 ml glacial acetic acid, the temperature not being allowed to exceed 10°, and the mixture was left for 12 hr at 18-20°.

The solution of isonitrosobenzylacetoacetate was added to a well-stirred mixture of 29.87 g (0.20 mole) 3-n-propylpentanedione-2,4, 35 g zinc dust, and 91 ml glacial acetic acid at 60-65°, the whole heated for 30 min on a steam bath, and poured on to 500 g crushed ice. The precipitate was separated off, recrystallized from 12 ml methanol, and

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* If propyl bromide is used for alkylation of acetylacetone, the yield drops to 45% [3].

dried in a vacuum desiccator. Yield 23.12 g (40.5%) mp 79.5-80.5° (the literature [3] gives 30% yield mp 76-78°). Found: C 75.25; H 7.69; N 5.46%. Calculated for $C_{17}H_{21}NO_2$: C 75.25; H 7.80; N 5.16%.

4-Methyl-3-n-propyl-2-carboxy-5-carbobenzoxypyrrole (V, R=n–Pr; R'=COOH). 8.05 g sulfuryl chloride was added dropwise to a solution of 5.0 g (18 mmole) IV (R=n–Pr) in 100 ml ether at 0-4°, and the whole left for 12 hr. The ether solution was then washed with ice water (5 times with about 30 ml portions), after which the ether was removed under reduced pressure, a hot solution of 40 g sodium acetate in 650 ml water added to the oily residue, and the mixture boiled for 15 min, filtered, and the precipitate which separated after cooling was filtered off and recrystallized from 20 ml methanol. Yield 1.88 g (33.8%), mp 143-144.5° (decomp). Found: C 67.72; H 6.36; N 4.68%. Calculated for $C_{17}H_{19}NO_4$: C 67.76; H 6.36; N 4.65%.

4-Methyl-3-n-propyl-5-carbobenzoxypyrrole (V, R=n–Pr, R'=H). 0.88 g (2.9 mmole) V (R=n–Pr; R'=COOH) was heated, in a stream of nitrogen, at 150-160° till evolution of carbon dioxide ceased, and then distilled to give a cut bp 116-118° (0.15 mm), a colorless liquid which crystallized on standing. Yield 0.44 g (58.5%), mp 35.5-35.6°. Found: C 74.92; H 7.68; N 5.37%. Calculated for $C_{16}H_{19}NO_2$: C 74.67; H 7.44; N 5.44%.

2-Bromomethyl-4-methyl-3-n-propyl-5-carbobenzoxypyrrole (V, R=n–Pr; R'=CH_2Br). A solution of 2.36 g (15 mmole) bromine in 180 ml ether was quickly added to a solution of 4.0 g (15 mmole) 2, 4-dimethyl-3-n-propyl-5-carbobenzoxypyrrole (IV, R=n–Pr) in 200 ml ether, and the mixture left for 1 hr 30 min at 20°, after which it was concentrated under reduced pressure to 1/3rd of its initial volume. The precipitate was separated off, washed with 10 ml dry ether, recrystallized from 150 ml n-octane, and dried in a vacuum desiccator. Yield 2.22 g (42.9%), mp 123.5-124.5°. Found: C 58.46; H 5.57; Br 22.6; N 4.25%. Calculated for $C_{17}H_{20}BrNO_2$: C 58.30; H 5.76; Br 22.82; N 4.00%.

2-Acetoxymethyl-3-n-propyl-4-methyl-5-carbobenzoxypyrrole (V, R=n–Pr; R'=CH_2OCOMe). Oxidation of 4.2 g (16 mmole) IV (R=n–Pr) with lead tetraacetate in glacial acetic acid, under conditions similar to those already given in the literature [3], gave 1.95 g (38%) V (R=n–Pr; R'=CH_2OCOMe), mp 119.5-120.6° (from petrol ether). Found: C 69.53; H 6.94; N 4.20%. Calculated for $C_{19}H_{23}NO_4$: C 69.28; H 7.04; N 4.25%.

Tetramethyltetra-n-propylporphin was obtained from 0.85 g (2.6 mmole) V (R=n–Pr, R'=CH_2OCOMe) in a way similar to that described in the literature [3], followed by purification on an alumina column and recrystallization from chloroform-methanol. Mp 198-200°, spectrum in benzene: I, 625; II, 570; III, 532; IV, 499 mμ, (I < II < III < IV). Found: C 80.67; H 8.49; N 10.17%. Calculated for $C_{36}H_{46}N_4$: C 80.85; H 8.67; N 10.48%.

Tetramethyltetra-n-propylporphin copper complex (IX). A saturated solution of copper acetate in acetic acid was added to 34.6 mg tetramethyltetra-n-propylporphin. After heating for a short time the precipitate formed was separated off, and purified by precipitation from chloroform with methanol. Yield 28 mg (73%), mp 209.5-211.5° (softens at 202°). Spectrum in chloroform: I, 564, II, 527 mμ (I > II). Found: C 72.60; H 7.50; N 9.55%. Calculated for $C_{36}H_{44}CuN_4$: C 72.51; H 7.44; N 9.40%.

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