SYNTHETIC STUDIES IN THE FIELD OF CHLOROBIUM CHLOROPHYLL

III*. SYNTHESIS OF UNSYMMETRICAL DIPYRROLYLMETHANEMONOCARBOXYLIC ACIDS

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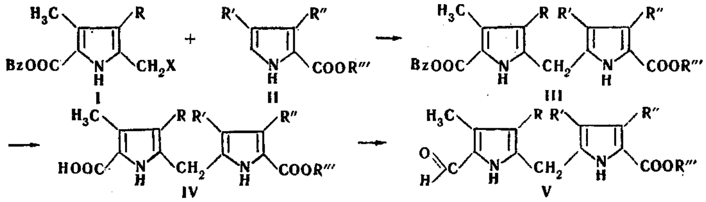
By the condensation of α-halogenomethyl derivatives of pyrroles with α-unsubstituted pyrroles the synthesis of the following unsymmetrical dipyrrolylmethanes has been effected: 5-benzyloxycarbonyl-5'-ethoxycarbonyl-3,3'-di(β-methoxycarbonylethyl)-4,4'-dimethyl-2,2'-dipyrrolylmethane (IIIa), 5-benzyloxycarbonyl-5'-ethoxycarbonyl-3-(β-methoxycarbonylethyl)-4,4'-dimethyl-3'-n-propyl-2,2'-dipyrrolylmethane (IIIb), 3-acetyl-5-benzyloxycarbonyl-4'-ethyl-5'-methoxycarbonyl-3',4-dimethyl-2,2'-dipyrrolylmethane (IIIc), and 3-bromo-5-benzyloxycarbonyl-4'-ethyl-5'-methoxycarbonyl-3',4-dimethyl-2,2'-dipyrrolylmethane (IIId). Hydrogenation of the unsymmetrical dipyrrolylmethanes IIIa, b, c, and d has given the corresponding monocarboxylic acids IVa, b, c, and d. The formylation of the dipyrrolylmethanemonocarboxylic acid IVa has given 5'-ethoxycarbonyl-5-formyl-3,3'-di(β-methoxycarbonylethyl)-4,4'-dimethyl-2,2'-dipyrrolylmethane (V).

The present paper is a continuation of reports on the preparation of unsymmetrical dipyrrolylmethanes that are intermediate in the synthesis of the pigment of photosynthesizing bacteria – chlorobium chlorophyll [1]. In performing the directed stepwise synthesis of porphyrins, the condensation of dipyrrolylmethane-α-monocarboxylic acids and α-monoformyl-substituted dipyrrolylmethanes is used.

To obtain dipyrrolylmethanemonocarboxylic acids we have effected the synthesis of a number of unsymmetrical α-alkoxycarbonyl-α'-benzyloxycarbonyldipyrrolylmethanes (IIIa, b, c, d), which were converted quantitatively by hydrogenation in the presence of palladium into the dipyrrolylmethane-α-monocarboxylic acids IVa, b, c, d. The unsymmetrical dipyrrolylmethanes were synthesized by condensing the α-halogenomethylpyrroles Ia, b, c with the α-unsubstituted pyrroles IIa, b, c, in chloroform, benzene and dimethylformamide.

The initial halogen-substituted pyrroles were obtained either by chlorination with sulfuryl chloride in acetic acid (Ib) or by bromination in ether (Ia) or in carbon tetrachloride (Ic). The α-unsubstituted pyrroles IIa, b, c were obtained by the decarboxylation of the corresponding carboxylic acids.



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*For communication II, see [1].

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TABLE 1

I	R	X	II	R′	R″	R‴	III	R	R′	R″	R‴
a	$(CH_2)_2COOCH_3$	Br	a	$(CH_2)_2COOCH_3$	CH_3	C_2H_5	a	$(CH_2)_2COOCH_3$	$(CH_2)_2COOCH_3$	CH_3	C_2H_5
b	$COCH_3$	Cl	b	$n\text{-}C_3H_7$	CH_3	C_2H_5	b	$(CH_2)_2COOCH_3$	$n\text{-}C_3H_7$	CH_3	C_2H_5
c	Br	Br	c	CH_3	C_2H_5	CH_3	c	$COCH_3$	CH_3	C_2H_5	CH_3
								Br	CH_3	C_2H_5	CH_3

IV	R	R′	R″	R‴	V	R	R′	R″	R‴
a	$(CH_2)_2COOCH_3$	$(CH_2)_2COOCH_3$	CH_3	C_2H_5		$(CH_2)_2COOCH_3$	$(CH_2)_2COOCH_3$	CH_3	C_2H_5
b	$(CH_2)_2COOCH_3$	$n\text{-}C_3H_7$	CH_3	C_2H_5					
c	$COCH_3$	CH_3	C_2H_5	CH_3					
d	Br	CH_3	C_2H_5	CH_3					

The unsymmetrical nature of the structure of the dipyrrolylmethanes IIIa, b, c, d was confirmed by comparing their physicochemical constants with those of the corresponding symmetrical dipyrrolylmethanes: IIIa, b with 5,5'-dibenzyloxycarbonyl-3,3'-di(β-methoxycarbonylethyl)-4,4'-dimethyl-2,2'-dipyrrolylmethane, IIIc with 5,5'-dibenzyloxycarbonyl-4,4'-diethyl-4,4'-dimethyl-2,2'-dipyrrolylmethane, and IIId with 3,3'-diacetyl-5,5'-dibenzyloxycarbonyl-3,3'-dibromo-2,2'-dipyrrolylmethane.*

5-Ethoxycarbonyl-5'-formyl-3,3'-di(β-methoxycarbonylethyl)-4,4'-dimethyl-2,2'-dipyrrolylmethane (V) was synthesized by the formylation of the monocarboxylic acid IVa with phosphorus oxychloride and dimethylformamide.

The individuality of the compounds obtained was confirmed by thin-layer chromatography on silica in the petroleum ether–diethyl ether system (for IIIa and IVa-d) and on alumina of activity grade 2-5 in the petroleum ether–diethyl ether system (for Ib, IIIc, d).

EXPERIMENTAL

2-Ethoxycarbonyl-3-methyl-4-n-propylpyrrole (IIb). 2-Carboxy-5-ethoxycarbonyl-4-methyl-3-n-propylpyrrole (1.3 g; 4.0 mmoles) was heated at 215-220°C in a current of nitrogen until the evolution of carbon dioxide ceased. The residue was distilled; bp 90-92°C (0.3 mm). Colorless liquid crystallizing on standing. Yield 0.60 g (56%), mp 43-44°C. Found, %: C 67.6; H 8.6; N 7.1. Calculated for $C_{11}H_{17}NO_2$, %: C 67.7; H 8.8; N 7.2.

5-Benzyloxycarbonyl-5'-ethoxycarbonyl-3,3'-di(β-methoxycarbonylethyl)-4,4'-dimethyl-2,2'-dipyrrolylmethane (IIIa). A solution of 0.72 g (2.0 mmoles) of 2-benzyloxycarbonyl-5-bromomethyl-4-(β-methoxycarbonylethyl)-3-methylpyrrole (Ia) in 30 ml of chloroform was added to a solution of 0.5 g (2.1 mmoles) of 2-ethoxycarbonyl-4-(β-methoxycarbonylethyl)-3-methylpyrrole (IIa) in 10 ml of chloroform. The reaction mixture was heated for 30 min and then the solvent was distilled off in vacuum and the residual oil was separated in a column of alumina of activity grade 5. Elution was performed with ether. The solvent was driven off, and the residue was dissolved in 5 ml of methanol and precipitated with water. This was filtered off and crystallized from 10 ml of isopropanol. Yield 0.85 g (79%), mp 87-88°C. Found, %: C 65.2; H 6.8; N 5.3. Calculated for $C_{30}H_{36}N_2O_8$, %: C 65.2; H 6.6; N 5.1.

5-Carboxy-5'-ethoxycarbonyl-3,3'-di(β-methoxycarbonylethyl)-4,4'-dimethyl-2,2'-dipyrrolylmethane (IVa). A solution of 0.3 g (0.54 mmoles) of IIIa in 25 ml of absolute methanol was treated with palladium on activated carbon and hydrogenation was carried out until the absorption of hydrogen ceased. The catalyst was separated off and washed wtih methanol. The solvent was driven off in a current of nitrogen, and the residue was crystallized from 10 ml of methanol. Yield 0.23 g (92%), mp 174-175°C. Found, %: C 59.9; H 6.9; N 6.4. Calculated for $C_{23}H_{30}N_2O_8$, %: C 59.7; H 6.5; N 6.0.

5-Ethoxycarbonyl-5'-formyl-3,3'-di(β-methoxycarbonylethyl)-4,4'-dimethyl-2,2'-dipyrrolylmethane (V). A suspension of 0.25 g (0.54 mmole) of IVa in 5 ml of dichloroethane was treated with 0.094 g (1.3 mmole) of dimethylformamide and 0.202 g (0.81 mmole) of phosphorus oxychloride, and the mixture was heated to 80°C and left for 10 hr. The solvent was driven off and the residue was triturated with water. The aqueous solution was neutralized with 50% sodium acetate solution and brought to pH 9 with 20% sodium bicarbonate solution. The precipitate that deposited was separated off and crystallized from 2 ml of ethanol. Yield 0.063 g (25%), mp 115-115.5°C. Found, %: C 61.6; H 6.8; N 6.3. Calculated for $C_{23}H_{30}N_2O_7$, %: C 61.9; H 6.8; N 6.3.

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*As in Russian original – Publisher.

5-Benzyloxycarbonyl-5'-ethoxycarbonyl-3-(β-ethoxycarbonylethyl)-4,4'-dimethyl-3'-n-propyl-2,2'-dipyrrolylmethane (IIIb). At 60-65°C, 1.22 g (3.1 mmoles) of Ia was added in small portions to a solution of 0.6 g (3.1 mmoles) of IIb in 6 ml of benzene, and the mixture was heated at 60-65°C for 1 hr. The solvent was driven off in vacuum and the residue was triturated with a small amount of petroleum ether and crystallized from n-octane. Yield 0.43 g (27%), mp 82-84°C. Found, %: C 68.2; H 7.1; N 5.0. Calculated for $C_{29}H_{36}N_2O_6$, %: C 68.5; H 7.1; N 5.5.

5-Carboxy-5'ethoxycarbonyl-3-(β-methoxycarbonylethyl)-4,4'-dimethyl-3'-n-propyl-2,2'-dipyrrolylmethane (IV b). A nickel-on-chromium-oxide catalyst was added to a solution of 0.4 g (0.78 mmole) of IIIb in 15 ml of ethyl acetate, and the mixture was stirred for 40 min. Then the catalyst was separated off, a palladium-on-activated-carbon catalyst was added to the solution, and hydrogenation was carried out until the absorption of hydrogen ceased. The second catalyst was separated off and washed with ethyl acetate, and the solvent was evaporated in vacuum. The residue was crystallized from methanol. Yield 0.24 g (73%), mp 166-168°C (decomp.). Found, %: C 63.5; H 7.1; N 6.8. Calculated for $C_{22}H_{30}N_2O_6$, %: C 63.1; H 7.2; N 6.7.

3-Acetyl-5-benzyloxycarbonyl-4'-ethyl-5'-methoxycarbonyl-3',4-dimethyl-2,2'-dipyrrolylmethane (IIIc). Over 45 min, 0.68 g (2.1 mmoles) of 4-acetyl-2-benzyloxycarbonyl-5-chloromethyl-3-methylpyrrole (Ib) was added to a solution of 0.37 g (2.2 mmoles) of 3-ethyl-2-methoxycarbonyl-4-methylpyrrole (IIIc) in 5 ml of dimethylformamide at 110-115°C, and the mixture was heated for 2 hr at the same temperature. Then it was poured into 20 ml of water and extracted with 50 ml of ether. The solvent was driven off and the residue was triturated with 50 ml of petroleum ether. The precipitate that deposited was separated off and crystallized from n-octane. Yield 0.25 g (26%), mp 142-143°C. Found, %: C 68.8; H 6.6; N 6.4. Calculated for $C_{25}H_{28}N_2O_5$, %: C 68.7; H 6.5; N 6.3.

3-Acetyl-5-carboxy-4'-ethyl-5'-methoxycarbonyl-3,4'-dimethyl-2,2'-dipyrrolylmethane (IVc). Palladium on activated carbon was added to a solution of 0.45 g (1.02 mmole) of IIIc in 40 ml of ethyl acetate and hydrogenation was carried out until the absorption of hydrogen ceased. The catalyst was separated off and washed with ethyl acetate. The solvent was driven off, and the residue was crystallized from methanol. Yield 0.24 g (67%), mp 201-202°C (decomp.). Found, %:C 62.4; H 6.8; N 8.1. Calculated for $C_{18}H_{22}N_2O_5$, %: C 62.4; H 6.4; N 8.1.

5-Benzyloxycarbonyl-3-bromo-4'-ethyl-5'-methoxycarbonyl-3',4-dimethyl-2,2'-dipyrrolylmethane (IIId). Over 3 hr 30 min 2.22 g (5.7 mmoles) of 2-benzyloxycarbonyl-4-bromo-5-bromomethyl-3-methylpyrrole (Ic) was added to a solution of 0.96 g (5.7 mmoles) of IIc in 25 ml of dry benzene at 60-65°C, and the mixture was then left at 0°C for 12 hr. The crystals that had deposited were separated off, washed with 30 ml of petroleum ether and 20 ml of methanol, and crystallized from methanol. Yield 0.74 g (27%), mp 177-178°C. Found, %: C 58.4; H 5.3; Br 16.8; N 5.7. Calculated for $C_{23}H_{25}BrN_2O_4$, %: C 58.3; H 5.3; Br 16.9; N 5.9.

3-Bromo-5-carboxy-4'-ethyl-5'-methoxycarbonyl-3',4-dimethyl-2,2'-dipyrrolylmethane (IVd) was obtained similarly to IVb by the hydrogenation of 0.5 g (1.1 mmole) of IIId in 60 ml of ethyl acetate. Yield 0.39 g (95%), mp 250-252°C (decomp). Found, %: Br 20.6; N 7.5. Calculated for $C_{16}H_{19}BrN_2O_4$, %: Br 20.8; N 7.3.

LITERATURE CITED

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