The Reactions of Methyl β-(Substituted-2-pyrrolyl)-propionate and Ethyl β, β-Bis(substituted-2-pyrrolyl)-propionate with Some Formylating Reagents*

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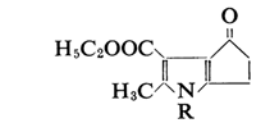
In a preceding paper[1] we reported on an attempt to obtain cyclopenteno(b)pyrrole derivatives, the skeletal structure of which is present in chlorophyll-a and -b. The Friedel-Crafts cyclization of β-(3-ethoxycarbonyl-2-methyl-5-pyrrolyl)-propionyl chloride (Ia) failed to yield 3-ethoxycarbonyl-2-methyl-1, 4, 5, 6-tetrahydrocyclopenta(b)pyrrol-4-one (IIa) and this reaction gave an undesired product III, though in it β-(1, 2-dimethyl-3-ethoxycarbonyl-5-pyrrolyl)-propionyl chloride (Ib) afforded 1, 2-dimethyl-3-ethoxycarbonyl-4, 5, 6-trihydrocyclopenta(b)pyrrol-4-one (IIb).



(IIa) : R=H
(IIb) : R=CH_3

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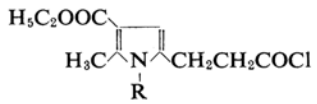

(Ia) : R=H
(Ib) : R=CH_3

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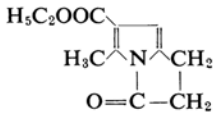

(III)

As an alternative method of synthesizing a compound with a cyclopenteno(b)pyrrole ring, we propose to condense the active α-methylene group of the side chain of VIII or XII with a formyl group at the neighboring β-position of the pyrrole ring. The formylation of α, α', β'-trisubstituted pyrroles with such formylating reagents as (a) dimethylformamide and phosphorus oxychloride, (b) dichloromethyl ethyl ether and stannic chloride, or (c) dichloromethyl ethyl ether and boron trifluoride-etherate, is reported in this paper. As is shown in Fig. 1, these formylating reagents gave incoherent results. The formylating reagents a and b gave the normally formylated products V or VII respectively as the result of the reaction with ethyl 2, 5-dimethyl-3-pyrrolecarboxylate (IV)[2] or methyl β-(1, 2-dimethyl-3-ethoxycarbonyl-5-pyrrolyl)-propionate (VI),[1] but the reactions of these compounds with c resulted in the recovery of the starting materials. From methyl β-(3-ethoxycarbonyl-2-methyl-5-pyrrolyl)-propionate (VIII),[3] two different products were obtained. One is the normally formylated product IX, resulting from the reaction with a or b; the other is bis(4-ethoxy carbonyl-2-methoxycarbonylethyl-5-methyl-3-pyrrolyl)-carbinol (X), resulting from the reaction with c. From ethyl β, β-bis(4-ethoxycarbonyl-5-methyl-2-pyrrolyl)-propionate (XII)[4] two kinds of products were also derived; one is the normally formylated product XIII, resulting from the reaction with a, while the other is a compound, $C_{22}H_{28}N_2O_7$, the product of the reaction with a or b. The structures of all the normally formylated products, V, VII, IX and XIII, have been concluded to be as shown in Fig. 1 on the basis of the results of their elementary analyses, infrared spectra, the formation of 2, 4-dinitrophenylhydrazones, and elementary analyses of the 2, 4-dinitrophenylhydrazones. Moreover, the structure of the carbinol X has been assumed to be as given in the formula on the basis of the results of elementary analysis, the measurement of the molecular weight, and the infrared spectrum. Furthermore, the carbinol X gave a 2, 4-dinitrophenylhydrazone as the result of the reaction with 2, 4-dinitrophenylhydrazine in an acidic medium; this 2, 4-dinitrophenylhydrazone

* Studies of Pyrroles, Part IX. Part VIII : H. Shinohara and E. Imoto, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **83**, 945 (1962).

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1) H. Shinohara, G. Shichijo and E. Imoto, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **83**, 615 (1962).

2) G. Korschun, *Ber.*, **37**, 2196 (1904).

3) A. Treibs and K. H. Michl, *Ann.*, **589**, 163 (1954).

4) H. Shinohara, H. Shiba, M. Sawada and E. Imoto, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **83**, 618 (1962).

TABLE I.

Starting compound	Method*	Reaction temp., °C	Reaction time, min.	Resulting compound	Yield %
IV[2]	a	50—55	30	V	84**
IV[2]	b	0	15	V	40
VI[1]	a	Room temp.	30	VII	90
VI[1]	b	0	10	VII	14
VIII[3]	a	30	30	IX	56
VIII[3]	b	0	10	IX	4.5

* The procedures are shown in the synthesis of XIII and compound $C_{22}H_{28}N_2O_7$.
** This compound has been prepared by Fischer et al.[6] by the Gattermann formylation of IV with hydrogen cyanide and hydrogen chloride in yield of 75%.

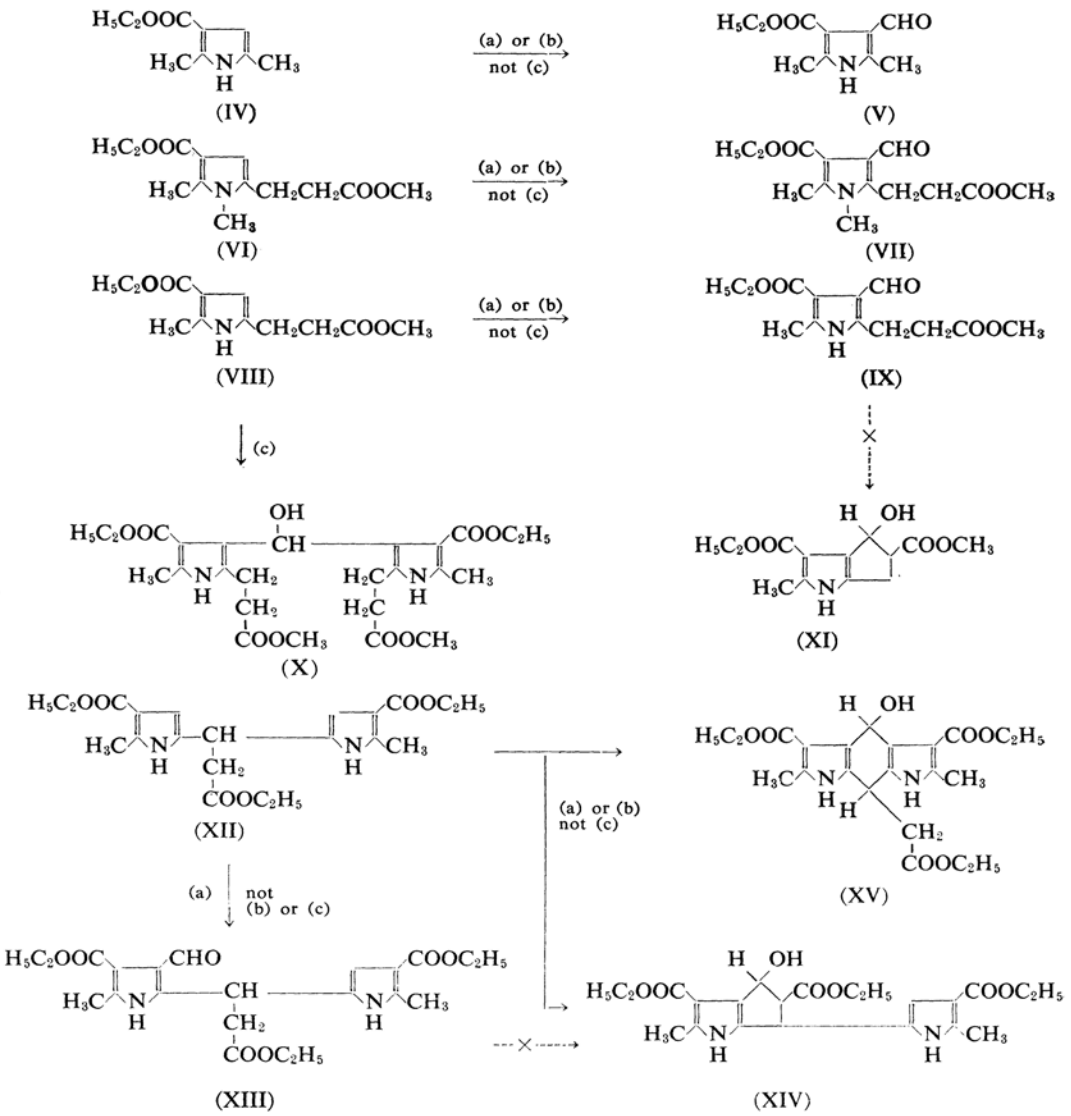

Fig. 1.

was identical with that derived from IX. This fact is also an evidence of the structure of X.

The compound $C_{22}H_{28}N_2O_7$ is an isomer of XIII, but it has no formyl group attached to the carbon atom or to the nitrogen atom of the pyrrole ring. Therefore, the structure of the compound $C_{22}H_{28}N_2O_7$ may be either XIV or XV.

The infrared spectrum definitely shows the presence of a hydroxyl group at 3500 cm^{-1} and the compound $C_{22}H_{28}N_2O_7$ has a band at 3000 cm^{-1} which should be assigned[5] to a stretching vibration of the C–H bond in the pyrrole ring. The compound $C_{22}H_{28}N_2O_7$ seems to have the structure formulated as XIV, because in the structure XV there is no hydrogen atom attached to the pyrrole nucleus. However, the NMR spectra of the compound $C_{22}H_{28}N_2O_7$ do not show a signal due to protons of the pyrrole ring. Attempts to derive XV from XIII in the presence of an acid as a catalyzer have also been unsuccessful, as have attempts to derive XIV from XIII in the presence of sodium methoxide as a catalyzer. From the results previously obtained, it is impossible to determine which structure should be assigned to the compound $C_{22}H_{28}N_2O_7$.

TABLE II.

Compound		M. p. °C	Analyses % Nitrogen Calcd.	Found
$C_{10}H_{13}NO_3$	(V)	149—151	7.74	7.76
$C_{14}H_{19}NO_5$	(VII)	86—87	4.98	5.03
$C_{13}H_{17}NO_5$	(IX)	113.5—114.5	5.24	5.38

2, 4-Dinitrophenylhydrazone of IX was prepared by the usual method. M. p. 202—205°C (decomp.)
Found: N, 15.68. Calcd. for $C_{19}H_{21}N_5O_8$: N, 15.44%.

Experimental

Bis(4-ethoxycarbonyl-2-methoxycarbonylethyl-5-methyl-3-pyrrolyl)-carbinol (X).—To a cold mixture of 1 g. of VIII[3] and 4 g. of dichloromethyl ethyl ether, there was added 3 ml. of borontrifluoride-etherate under ice cooling. The reaction mixture was warmed to 49—50°C and stirred at this temperatue for 30 min., diluted with iced water, and neutralized to Congo red with a saturated solution of sodium acetate in order to precipitate crystals. These crystals were collected by filtration, washed with cold water, and recrystallized from aqueous ethanol repeatedly to give colorless needles with a m. p. of 150—151.5°C in a yield of 350 mg. (33%).
Found: C, 59.29; H, 6.66; mol. wt. (Rast), 508. Calcd. for $C_{25}H_{34}N_2O_9$: C, 59.30; H, 6.72%; mol. wt., 506.

Reaction with 2, 4-Dinitrophenylhydrazine. — A solution of 100 mg. of X was mixed with an acidic solution of 2, 4-dinitrophenylhydrazine, warmed for a short time, and allowed to stand in order to precipitate crystals, which were then recrystallized from ethanol. The m. p., 202—204°C (decomp.), was undepressed on admixture with 2, 4-dinitrophenylhydrazone of IX.

Found: N, 15.71. Calcd. for $C_{19}H_{21}N_5O_8$: N, 15.44%.

Ethyl β-(4-Ethoxycarbonyl-3-formyl-5-methyl-2-pyrrolyl)-β-(4-ethoxycarbonyl-5-methyl-2-pyrrolyl)-propionate (XIII). — To a cold solution of 3 g. of XII[4] in 3.1 g. of dimethylformamide, 2.3 g. of phosphorus oxychloride was added drop by drop at room temperature. The reaction mixture was stirred for 60 hr. at room temperature in order to precipitate a solid material stained by a resinous material, diluted with 70 ml. of a saturated solution of sodium acetate, and stirred for a further two days. After the aqueous layer of the reaction mixture had been removed by decantation, the solid material was repeatedly washed with water and then with a small amount of ethanol to remove the resinous material; then the material was collected by filtration, washed with water, and treated with boiling benzene. The insoluble part in benzene was recrystallized from ethanol to obtain the desired product, XIII, in a yield of 200 mg. (6.3%), m. p. 186—188°C (decomp.).
Found: C, 61.14; H, 6.57; N, 6.62. Calcd. for $C_{22}H_{28}N_2O_7$: C, 61.11; H, 6.49; N, 6.49%. 2, 4-Dinitrophenylhydrazone of XIII, m. p. 187～188°C.
Found: N, 13.78. Calcd. for $C_{28}H_{31}N_6O_{10}$: N, 13.67%.

The Compound $C_{22}H_{28}N_2O_7$ XIV or XV.—a) In to a mixture of 4 g. of XII[4] and 1.5 g. of dimethyl formamide, 1.53 g. of phosphorus oxychloride was gradually stirred at 40°C. After the addition, the reaction mixture was warmed to 60°C, kept at this temperature for 15 min., mixed with iced water, and then neutralized to Congo red with a saturated solution of sodium acetate. The precipitate thereby yielded was collected by filtration, washed with cold water, and recrystallized from aqueous ethanol. Yield, 1.2 g. Pale yellow crystals, m. p. 217—219°C (decomp.).

b) To a cold mixture of 1 g. of XII and 16 g. of dichloromethyl ethyl ether, 2 ml. of stannic chloride was added at once under ice cooling. After having been stirred for 10 min., the reaction mixture was poured into iced hydrochloric acid. Since the oily product which separated solidified slowly, it was collected by filtration, washed with cold water, and dissolved in warm ethanol. After the ethanolic solution had been treated with norite, it was diluted with water to reprecipitate the product. The product was then washed with a few drops of ethanol and repeatedly recrystallized from aqueous ethanol to obtain pale yellow crystals of the compound $C_{22}H_{28}N_2O_7$. M. p. 215—217°C (decomp.), undepressed with the sample obtained above at a) on admixture. Yield, 50 mg.
Found: C, 60.94; H, 6.50; N, 6.56. Calcd. for $C_{22}H_{28}N_2O_7$: C, 61.11; H, 6.49; N, 6.49%.

An Attempt to Cyclize Methyl β-(4-Ethoxycarbonyl-3-formyl-5-methyl-2-pyrrolyl)-propionate (VII) into 3-Ethoxycarbonyl-5-methoxycarbonyl-2-methyl-1, 4, 5, 6-tetrahydrocyclopenta(b)pyrrol-4-ol (XI).—a) To 100 ml. of an ethereal solution of sodium ethoxide prepared from 50 mg. of sodium 500 mg. of VII was added; the mixture was then refluxed for 5 hr. After the ether had been evaporated, the residue was dissolved in water and filtered.

5) A. R. Katrifzky, *Quart. Rev.*, **13**, 353 (1959).
6) H. Fischer and W. Zerweck, *Ber.*, **55**, 1942 (1922).

The filtrate was acidified to obtain a solid material. The solid material was washed with iced water and recrystallized from aqueous ethanol to obtain 180 mg. of β-(3-ethoxycarbonyl-4-formyl-2-methyl-5-pyrrolyl)-propionic acid, m. p. 166—167°C, which is soluble in an aqueous solution of sodium bicarbonate.

Found: N, 5.40. Calcd. for $C_{12}H_{15}NO_5$: N, 5.54%.

b) A mixture of 500 mg. of VII, 0.5 ml. of triethylamine, and 10 ml. of absolute ethanol was refluxed for 3 hr. and then poured into iced water to precipitate crystals. The crystals were collected by filtration, washed with water, and recrystallized from water to recover the starting material (about 500 mg.) with a m. p. of 113—114°C. Similarly, the reaction of VII with dispersed sodium in benzene at the refluxing temperature or with hydrogen chloride in absolute ethanol under reflux also resulted in the recovery of the starting material.

Attempts to Cyclize XIII into XIV.—a) To 80 ml. of an ethereal solution of sodium ethoxide prepared from 50 mg. of sodium, 300 mg. of XIII was added; the mixture was then refluxed for 3 hr. After it had evaporated, the residue was treated with iced hydrochloric acid and filtered. The solid material was washed with iced water and recrystallized from ethanol to recover the starting material.

b) The reaction of XIII with hydrogen chloride in absolute ethanol at reflux also resulted in the recover of the starting material.

Infrared Spectra. — These were recorded with a Hitachi EPI-2 spectrophotometer; the measurements were made on pressed disks of potassium bromide.

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