Ochotensine and Related Compounds. II. (1)
A Synthesis of Iso-ochotensine. (Studies on the Syntheses of Heterocyclic Compounds. CCLXXV (2))

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In order to examine the total syntheses of ochotensine (I) and ochotensimine (II), one of the isomers, iso-ochotensine (III), was synthesized as a preliminary experiment. Namely, Wittig reaction of VI, followed by treatment with sodium bicarbonate solution, gave the expected compound, 7-ethoxycarbonyl-3-ethoxycarbonyloxy-2-methoxy-13-methylene-10,11-methylenedioxyochotensinan (VII) which was reduced with lithium aluminum hydride to give III. This was also obtained by methylation of 3-hydroxy-2-methoxy-13-methylene-10,11-methylenedioxyochotensinan (VIII).

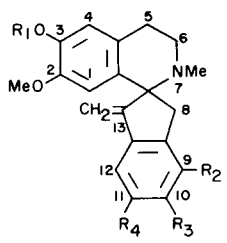
In a previous paper (1) an interesting synthetic route was carried out successfully for the purpose of accomplishing the total syntheses of ochotensine (I) and ochotensimine (II), which were isolated from *Corydalis ochotensis Turcz.* (3). We now wish to report the synthesis of the ochotensine type compound (III) which is one position isomer of ochotensine.

Phenolic cyclization (4) of 3-hydroxy-4-methoxyphenethylamine with 3,4-methylenedioxyphenylpyruvic acid gave 1,2,3,4-tetrahydro-6-hydroxy-1-(3,4-methylenedioxybenzyl)-7-methoxyisoquinoline-1-carboxylic acid. Ethoxycarbonylation followed by cyclization with polyphosphoric acid ester, gave the compound (V) (1) having a spiro ring similar to ochotensine (I).

A Wittig reaction (5) of 7-ethoxycarbonyloxy-3-hydroxy-2-methoxy-10,11-methylenedioxyochotensinan-13-one (V) (1) was attempted in order to convert the ketonic carbonyl group at the C_{13}-position into the methylene group, but this was unsuccessful. Therefore, attempts to synthesize compound VI, which was protected by an ethoxycarbonyl group, were investigated. After the cyclization of IV, the reaction mixture was treated with saturated sodium carbonate solution (1), giving V, but the treatment of the reaction product with saturated sodium bicarbonate solution afforded the expected 7-ethoxycarbonyl-3-ethoxycarbonyloxy derivative (VI).

Wittig reaction of VI with methylene triphenylphosphorane in dry ether gave a mixture of V, VII, and VIII, from which V and VII were extracted with ether. Fractional recrystallization from ether gave compound VII in 55% yield and the compound V in 0.5% yield, respectively.

Chart 1

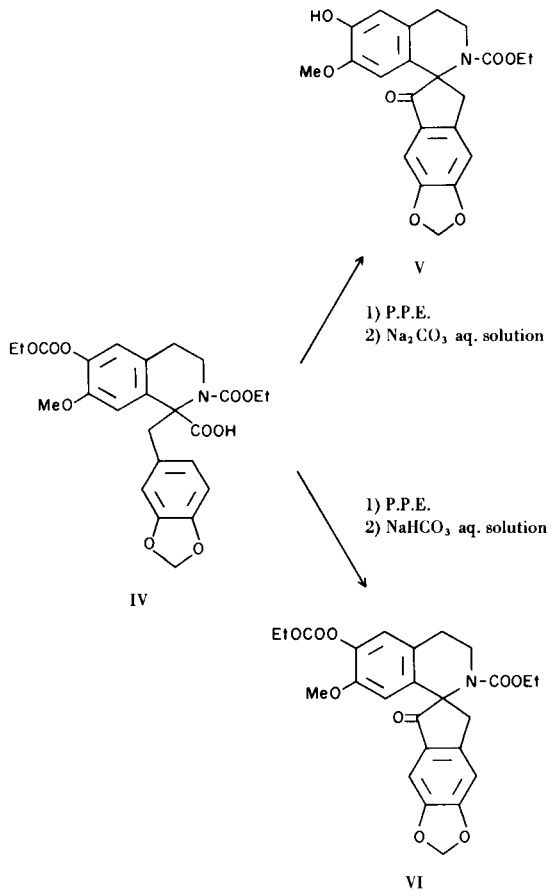


I : $R_1 = R_4 = H$, $R_2 + R_3 = OCH_2O$
II : $R_1 = Me$, $R_2 + R_3 = OCH_2O$, $R_4 = H$
III : $R_1 = R_2 = H$, $R_3 + R_4 = OCH_2O$

Recrystallization of V from acetone gave colorless plates, m.p. 171-172° [lit. (1), m.p. 171-172°], which were identical with an authentic sample by mixed melting point and spectral (ir and nmr) data.

Recrystallization of VII from acetone gave colorless prisms, m.p. 190°, whose ir spectrum (chloroform) showed an absorption band of an ester carbonyl group at 1757 cm^{-1} (6) and the deformation vibration of terminal methylene CH is observed at 870 cm^{-1}. A broad absorption at 1660-1685 cm^{-1} is attributable to the *N*-ethoxycarbonyl and terminal methylene groups which overlap each other. Furthermore, the nmr spectrum (deuteriochloroform) showed two singlets (2H) at 4.15 and 4.12 τ, and confirmed the presence of a terminal methylene group.

Chart 2

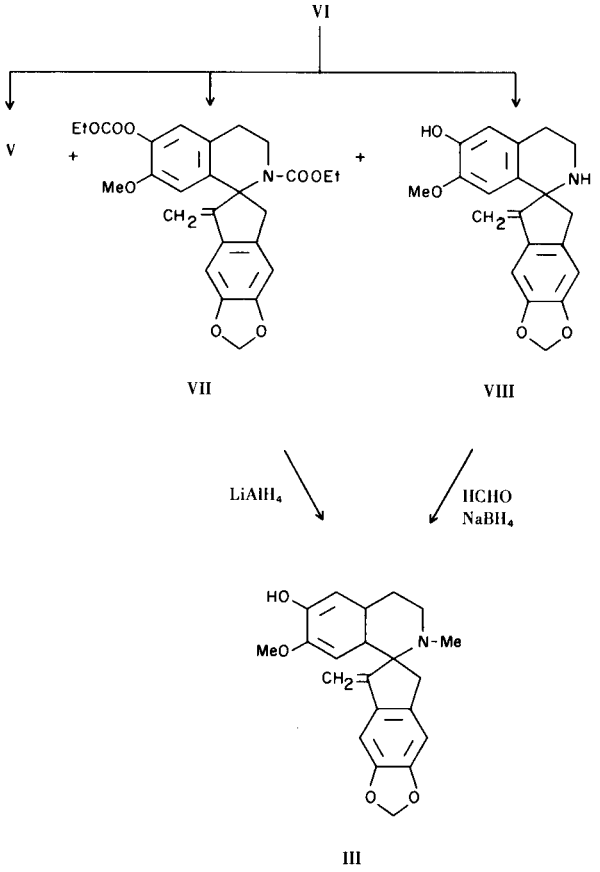


The ether insoluble part from the above Wittig reaction was extracted with chloroform giving compound VIII as a syrup whose thin layer chromatography showed one spot. The ir spectrum (chloroform) showed a broad absorption attributable to both hydroxyl and amino groups at 3490 and 3350-3300 cm^{-1}, respectively, and the characteristic bands due to the terminal methylene group were observed at 1755 cm^{-1} (overtone of 880 cm^{-1} was due to the deformation vibration CH) and 1670 cm^{-1}. In its nmr spectrum no signals of ethyl groups attributable to the ester and carbamoyl groups were observed, but the pattern of aromatic protons was closely similar to that of VII.

Reduction of VII with lithium aluminum hydride in tetrahydrofuran gave the expected iso-ochotensine (III), which was also obtained by the Eschweiler-Clarke reaction of VIII with formalin and sodium borohydride.

The ir spectrum (chloroform) of III showed a hydroxyl group at 3500 cm^{-1}, *N*-methyl at 2800 cm^{-1}, and a terminal methylene group at 1742 cm^{-1} (overtone of 870 cm^{-1} was due to the deformation vibration, CH). The nmr spectrum (deuteriochloroform) showed the following resonances; *N*-methyl group as a singlet (3H) at 7.41 τ, methoxyl group as a singlet (3H) at 6.53 τ, terminal methylene group (2H) as a pair of doublets at 5.05 and 4.22 τ with J = 2.7 cps, methylenedioxy group (2H) at 4.13 τ, three aromatic protons (3H; C_1-H, C_4-H, and C_9-H) as singlets at 3.32, 3.36, 3.41 τ and one aromatic proton of C_{12}-position as a singlet at 2.5 τ.

Chart 3



These results confirmed the synthesis of iso-ochotensine and indicated a possible synthetic route to ochotensine (I).

EXPERIMENTAL

Infrared spectra were measured with a Type EPI-3 Hitachi recording spectrophotometer, and nmr spectra were run on a Hitachi H-60 spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal reference.

7-Ethoxycarbonyl-3-ethoxycarbonyloxy-2-methoxy-10,11-methylenedioxyochotensinan-13-one (VI).

To a suspension of 1.2 g. of 2-ethoxycarbonyl-6-ethoxycarbonyloxy-1,2,3,4-tetrahydro-7-methoxy-1-(3,4-methylenedioxybenzyl)-isoquinoline-1-carboxylic acid (1) in 20 ml. of dry chloroform was added 10 g. of polyphosphoric acid ester and the mixture was refluxed at 65° for 5 hours. After removal of the solvent,

saturated aqueous sodium bicarbonate solution was added to the above residue. The mixture after standing overnight was extracted with chloroform. The extract was washed with aqueous sodium bicarbonate solution and water, dried over sodium sulfate and evaporated to dryness to give 717 mg. of the crude compound (VI), whose recrystallization from acetone-petroleum ether afforded colorless needles, m.p. 142°. Infrared (chloroform); ν (C=O) 1758 (ester), (C=O) 1740-1690 cm^{-1} (ketone and *N*-ethoxycarbonyl); nmr (deuteriochloroform) τ 8.62, 8.83 (6H, two triplets, J = 7 cps, 2 x OCH_2CH_3), 6.16 (3H, singlet, OCH_3), 5.66, 5.72 (4H, two quartets, J = 7 cps, 2 x OCH_2CH_3), 4.18 (2H, singlet, OCH_2O), 2.89, 3.21, 3.52, 3.79 (4H, four singlets, aromatic protons).

Anal. Calcd. for $C_{25}H_{25}NO_9$: C, 62.11; H, 5.21; N, 2.90. Found: C, 61.77; H, 5.40; N, 3.03.

7-Ethoxycarbonyl-3-ethoxycarbonyloxy-2-methoxy-13-methylene-10,11-methylenedioxyochotensinan (VII) and 3-hydroxy-2-methoxy-13-methylene-10,11-methylenedioxyochotensinan (VIII).

To a solution of 1 g. of compound VI in 40 ml. of dry ether was added dropwise 20 ml. of an ethereal solution of methylene triphenylphosphorane (5) [prepared by dropwise addition of 14.5 g. of bromobenzene into a mixture of 1.4 g. of lithium and 140 ml. of dry ether, followed by addition of 14.3 g. of triphenylphosphonium methyl bromide] while shaking. After continued shaking for 1 hour, the mixture was heated at 65° for 3 hours. The ether was removed and the resultant residue was mixed with saturated aqueous sodium bicarbonate solution and allowed to stand overnight. The solution was extracted with ether, the extract was washed with saturated sodium bicarbonate solution followed by sodium chloride solution, dried over sodium sulfate and evaporated to give a residue, whose fractional recrystallization from ether afforded 30 mg. of V and 550 mg. of VII. Recrystallization of V from acetone gave colorless plates, m.p. 171-172° [lit. (1), m.p. 171-172°], whose ir and nmr spectra were identical with those of an authentic sample. Recrystallization of VII from ether gave colorless prisms, m.p. 190°. Infrared (chloroform): ν (C=O) 1757 (ester), (C=C and C=O) 1660-1685 (terminal methylene and *N*-ethoxycarbonyl); nmr (deuteriochloroform) τ 8.53, 8.66 (6H, two triplets, J = 7 cps, 2 x OCH_2CH_3), 6.28 (3H, singlet, OCH_3), 5.73, 5.92 (4H, two quartets, J = 7 cps, 2 x OCH_2CH_3), 4.15, 4.21 (2H, two singlets, J = 2.6 cps, C = CH_2), 4.00 (2H, singlet, OCH_2O), 3.11, 3.25, 3.30 (3H, three singlets, aromatic protons), 2.51 (1H, singlet, C_{12}-aromatic proton).

Anal. Calcd. for $C_{26}H_{27}NO_8 \cdot \frac{1}{2}H_2O$ (7): C, 63.67; H, 5.75; N, 2.86. Found: C, 63.87; H, 5.38; N, 2.55.

The solution from which the above two compounds (V and VI) were extracted was again extracted with chloroform. The extract was treated as before to give 50 mg. of VIII as a syrup, which could not be crystallized and therefore was used in the following reaction without purification. Nmr (deuteriochloroform) τ 6.20 (3H, singlet, OCH_3), 4.05, 4.12 (2H, two singlets, C=CH_2), 4.01 (2H, singlet, OCH_2O), 3.33, 3.38, 3.42 (3H, three singlets, aromatic protons), 2.50 (1H, singlet, C_{12}-aromatic proton).

3-Hydroxy-2-methoxy-13-methylene-10,11-methylenedioxy-7-methylochotensinan (III).

(a) Lithium Aluminum Hydride Reduction of VII.

To a stirred suspension of 100 mg. of lithium aluminum hydride in 70 ml. of dry tetrahydrofuran was added dropwise a solution of 120 mg. of VII in 50 ml. of dry tetrahydrofuran (0.5 hour). After being refluxed with stirring for 2 hours, the reaction mixture was decomposed with wet ether followed by 5 ml. of water, filtered through celite, and the filtrate was evaporated and extracted with chloroform. The extract was washed with water, dried over potassium carbonate and evaporated to dryness to give 70 mg. of III. After purification by silica gel chromatography using the solvent chloroform:acetone:methanol, 50:40:3, as an eluant, evaporation of the above eluate gave a syrup, whose methiodide was recrystallized from methanol-ether to give colorless crystals, m.p. 198-200°.

Anal. Calcd. for $C_{22}H_{24}INO_4$: C, 53.56; H, 4.87; N, 2.84. Found: C, 53.72; H, 5.03; N, 3.05.

(b) Methylation of VIII.

To a stirred solution of 40 mg. of VIII and 100 mg. of 38% formalin in 30 ml. of methanol was added 100 mg. of sodium borohydride and stirring was continued for 1.5 hours. After removal of methanol, 50 ml. of 5% sodium hydroxide solution was added to the residue and the solution was washed with chloroform. Crystalline ammonium chloride was added to *p*H 8 and the ammoniacal solution was extracted with chloroform. The extract was washed with water, dried over potassium carbonate and evaporated to give 20 mg. of III. Infrared and nmr spectra were identical with those of the sample prepared by method (a) and there was no mixed melting point depression of the methiodides.

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(6) In this region an overtone of the terminal methylene group was included.

(7) This was dried over phosphorus pentoxide at 70° for 48 hours under reduced pressure.

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