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Studies on the Syntheses of Spiro-dienone Compounds. VI.[1] A New Synthesis of *dl*-Pronuciferine.[2]

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dl-Pronuciferine has been synthesized *via* photochemical cyclization of 8-bromo-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-hydroxybenzyl)-2-methylisoquinoline.

Keywords——proaporphine alkaloids; *dl*-pronuciferine; photochemical cyclization; spiro-dienone; a new synthesis

In our previous papers,[4,5] it was reported that the photolysis of 2-bromo-N-ethyl-4′-hydroxybenzanilide (I) in aqueous sodium hydroxide gave 2′-ethylspiro[cyclohexa-2,5-diene-1,1′-isoindoline]-3′,4-dione (II) directly and that the photolysis of I in the presence of sodium borohydride gave 2′-ethyl-4-hydroxyspiro[cyclohexa-2,5-diene-1,1′-isoindolin]-3′-one (III), which was oxidized with manganese dioxide in chloroform to give the desired spiro-dienone (II) in high yield. Now we extend this photochemical cyclization reaction to the synthesis of proaporphine alkaloids, containing the spiro-dienone system. The present paper deals with a new synthesis of *dl*-pronuciferine (IX),[6] one of proaporphine alkaloids, *via* photochemical cyclization.

8-Bromo-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-2-methyl-6,7-dimethoxyisoquinoline (VII) was prepared as follows. Fusion of 3-bromo-4,5-dimethoxyphenethylamine[7] with methyl *p*-hydroxyphenylacetate[8] in the presence of pyridine at 180° for 3 hr gave the amide (IV) in 70% yield. The amide (IV) was converted into the ester (V) by condensation with ethyl chloroformate in pyridine in 90% yield. Bishler-Napieralski reaction of V with a mixture of phosphorous oxychloride and phosphorous pentoxide in benzene, followed by reduction with sodium borohydride in methanol, gave the crude tetrahydroisoquinoline (VI). Treatment of VI with 37% formaline solution, followed by reduction with sodium borohydride, gave the desired starting material (VII)[9] in 70% yield from V.

Irradiation of the N-methyltetrahydroisoquinoline (VII) in aqueous sodium hydroxide in the presence of sodium borohydride with a 100 W high pressure mercury lamp untill the starting material was not recognized on the thin-layer chromatography (TLC) (*ca.* 2 hr) gave the crude spiro-dienol (VIII) in 40% yield. The oxidation of VIII with manganese dioxide in chloroform for 15 hr at room temperature gave *dl*-pronuciferine (IX) in 20% yield from VII. The infrared (IR) spectrum shows the presence of a typical dienone system (1660 and

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9) The structure of VII was confirmed by the following data: Catalytic hydrogenation of VII with Raney Ni in potassium hydroxide-methanol gave 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-hydroxybenzyl)-2-methylisoquinoline whose NMR spectrum showed a band at δ 5.97 (singlet) due to a C_8–H.

1620 cm^{-1}). The ultraviolet (UV) spectrum shows two absorption bands at 230 and 280 nm due to a dienone system. This product (IX) was identical with the natural product.

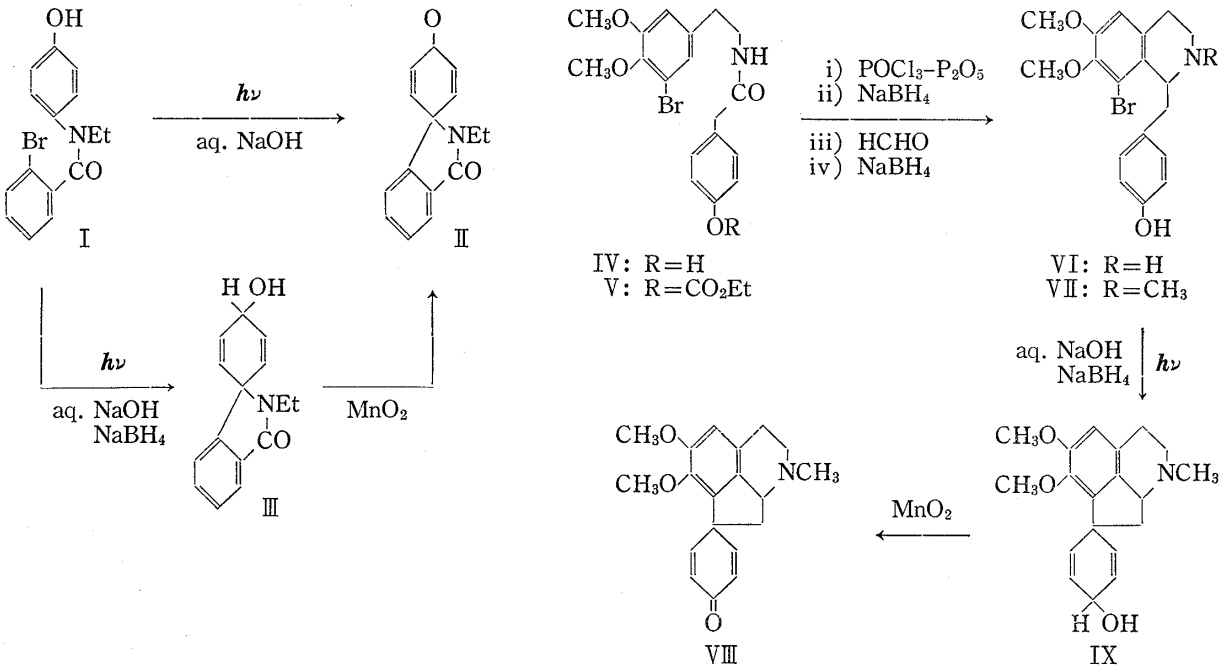

Chart 4

Experimental

All melting points are uncorrected. Spectra were recorded as follows: nuclear magnetic resonance (NMR) on a Hitachi R-20 (60 MHz) spectrometer, using tetramethylsilane as the internal reference; IR on a Hitachi EPI-G3 spectrometer; UV on a Hitachi 124 spectrometer; mass on a Hitachi RMU-60 spectrometer. Eikosha PIH-100 from Eikosha Co., Osaka, was used as light source for the photoreaction.

N-(3-Bromo-4,5-dimethoxyphenethyl)-2-(4-hydroxyphenyl)acetamide (IV)——A mixture of 4.0 g of 3-bromo-4,5-dimethoxyphenethylamine, 6.0 g of methyl *p*-hydroxyphenylacetate and 0.5 g of pyridine was heated for 3 hr at 180°. The mixture was diluted with $CHCl_3$ and the solution was washed with 3% HCl, saturated brine, dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by chromatography on silica gel (Mallinckrodt) with $CHCl_3$. Recrystallization of the product from acetone–ether gave 7.0 g (70%) of IV as colorless crystals, mp 123—124°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3400 (NH), 1650 (CONH). *Anal.* Calcd. for $C_{18}H_{20}BrNO_4$: C, 54.83; H, 5.11; N, 3.53. Found: C, 54.57; H, 5.04; N, 3.44.

N-(3-Bromo-4,5-dimethoxyphenethyl)-2-(4-ethoxycarbonylphenyl)acetamide (V)——To an ice-H_2O cooling solution of 1.0 g of IV in 5.0 ml of pyridine was added 1.5 ml of ethyl chloroformate with stirring and the mixture was warmed at 60° for 2 hr. After cooling, the mixture was diluted with $CHCl_3$ and the solution was washed with 3% HCl, saturated brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a colorless solid, which was recrystallized from ether to yield 1.0 g (90%) of V as colorless crystals, mp 93—94°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1750 (CO), 1655 (CONH). *Anal.* Calcd. for $C_{21}H_{24}BrNO_6$: C, 54.08; H, 5.18; N, 3.00. Found: C, 54.27; H, 5.27; N, 2.87.

8-Bromo-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-hydroxybenzyl)-2-methylisoquinoline (VII)——A mixture of 1.0 g of V, 5.0 g of phosphorous pentoxide, 10 ml of phosphorous oxychloride and 25 ml of benzene was refluxed for 3 hr. After the solvent was decanted, the residue was washed with benzene and poured into ice-H_2O gradually. The resulting mixture was basified with dil. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated brine and dried over anhydrous Na_2SO_4. After the solvent was evaporated under reduced pressure, the residue [1.0 g, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (CO), 1670 (C=N)] was dissolved in 50 ml of MeOH. To this stirred solution was added 2.5 g of sodium borohydride in small portions under ice-H_2O cooling. The reaction mixture was stirred for 3 hr at room temperature, poured into 120 ml of ether and extracted with 3% HCl. The HCl extract was basified with dil. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated brine, dried over anhydrous Na_2SO_4 and evaporated to give 750 mg of VI. This crude (VI) was dissolved in a solution of 2.0 ml of formaline and 20 ml of MeOH and allowed to stand overnight. To this stirred mixture was added 3.0 g of sodium borohydride in small portions

under ice-H_2O cooling and the mixture was stirred for 1.5 hr at room temperature. After the mixture was acidified with AcOH, then basified with dil. NH_4OH, the solution was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 750 mg of crude product (VII). Chromatography of the crude VII on silica gel (Mallinckrodt) with $CHCl_3$ gave 570 mg (70%) of VII as colorless crystals, mp 169—170° (from acetone–ether). MS *m/e*: 393, 391 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3350 (OH). NMR ($CDCl_3$) δ: 2.38 (3H, s, NCH_3), 3.85 (6H, s, $2\times OCH_3$), 5.41 (1H, s, C_5–H), 6.30—7.25 (4H, AA′BB′ type, *p*-hydroxyphenyl). *Anal.* Calcd. for $C_{19}H_{22}BrNO_3$: C, 58.17; H, 5.65; N, 3.57. Found: C, 58.32; H, 5.80; N, 3.53.

***dl*-Pronuciferine (IX)**——A water cooled mixture of 300 mg of VII, 100 mg of NaOH, 100 mg of sodium borohydride and 100 ml of H_2O was irradiated for 2 hr. The reaction mixture was acidified with AcOH, then basified with dil. NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 264 mg of crude product (VIII). Chromatography of the crude VIII on silica gel (Mallinckrodt) with $CHCl_3$ gave 100 mg (40%) of VIII as brown solid, that darkened in an air atmosphere. MS *m/e*: 315 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH). This product was used in the next step without further purification. A mixture of 100 mg of VIII, 2.0 g of manganese dioxide and 10 ml of $CHCl_3$ was stirred for 10 hr at room temperature. The reaction mixture was filtered and the residue was washed with $CHCl_3$ repeatedly. The filtrate and washings were combined and condenced under reduced pressure. The residue was purified by preparative TLC on silica gel (Merck, GF_{254}) with $CHCl_3$ to give 48 mg (20% yield from VII) of *dl*-pronuciferine as a colorless oil. MS *m/e*: 313 (M^+), 282, 268. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 (CO), 1620 (C=C). UV λ_{max}^{EtOH} nm (log ε): 230 (4.35), 280 (3.73). NMR ($CDCl_3$) δ: 2.44 (3H, s, NCH_3), 3.59 and 3.80 (6H, s, $2\times OCH_3$), 6.20—6.45 and 6.80—6.90 (4H, AA′BB′ type, dienone), 6.67 (1H, s, C_3–H). The picrolonate of IX was recrystallized from acetone–ether to give yellow crystals, mp 224—225° (dec.). *Anal.* Calcd. for $C_{29}H_{29}N_5O_8$: C, 60.51; H, 5.08; Found: C, 60.04; H, 5.03.

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