Studies on the Syntheses of Heterocyclic Compounds. Part DXCVII (1). A Synthesis of Dienone Analogs by Electrolytic Oxidation

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Electrolytic coupling reaction of laudanosine (I) gave the O-methylflavinantine (II). *N*-Ethoxycarbonylated dihydrostilbene (IVa) gave a rearranged dienone (Va) and *N*-trifluoroacetylated dihydrostilbene (IVb) contrastively gave an unrearranged dienone (Vb).

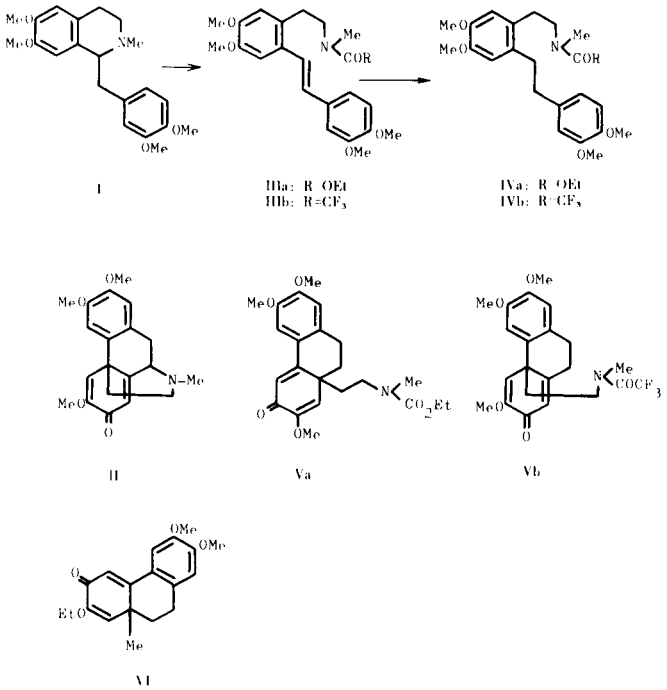
Recently, the application of an intramolecular anodic cyclization to the alkaloid synthesis has been successfully described by two groups (3-4). We here wish to report the application of this method to the synthesis of the potential alkaloids of hasubanan (5) and protostephanine (6).

Firstly we have re-examined a synthesis of *O*-methylflavinantine (II) by electrolytic oxidation of laudanosine (I) according to Tobinaga's method (4) although Miller had already synthesized the alkaloid under different conditions (5). Thus we could improve its yield in the *O*-methylflavinantine synthesis (II) by modified procedure.

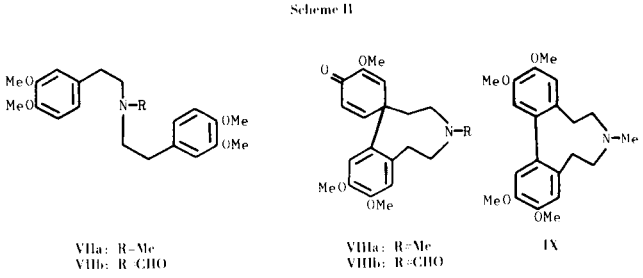
Secondly, the amides (IVa,b), which could be available from laudanosine (I) as shown in Scheme I, were oxidized. Oxidation of the amide (IVa) gave a rearranged dienone (Va) in 87% yield, whose spectra were similar to those of (VII), reported by Miller and Stermitz (3): (Va), λ max 354, 290, 263, 240 nm: nmr (δ): 5.70, 7.05 (each 1H, s, olefinic protons); (VI), λ max 353, 289, 264, 238 nm; nmr (δ): 6.60, 7.08 (each 1H, s). Interestingly, the amide (IVb) gave an expected dienone (Vb) in 75% yield. These results showed that the protective group on nitrogen atom played an important role in electrolytic oxidation.

Finally, we have investigated the anodic cyclization of compounds (VIIa,b) which would be expected to give the precurcer of protostephanine-type compound (IX) as shown in Scheme II, but the cyclization did not occur, the starting materials being recovered in both cases.

Scheme I



Scheme II



EXPERIMENTAL

Melting points are uncorrected and were determined on a Yanagimoto microapparatus (MP-S2). Ir spectra were measured with a Jasco IRA-I and uv spectra with a Hitachi H-60 spectrometer. Nmr spectra were recorded on a Hitachi H-60 spectrometer using TMS as an internal standard. The mass spectra were taken with a Hitachi RMU-7 spectrophotometer.

General Electrolysis Procedure.

Preparative oxidations were conducted in an opened one-compartment cell in conjunction with a Yanagimoto Model VE-3 potentiostat. The anode was platinum sheet (total area 60 cm^2) and a platinum spiral was used as the cathode. A Horiba Model

2531-25A calomel reference electrode was used; all potentials are given *vs* this reference. The compounds which would be oxidized (*ca.* 500 mg.) were dissolved in acetonitrile (100 ml.) containing fluoroboric acid (0.2 *M*). This solution was oxidized at a platinum anode in a one-compartment cell. The potential was maintained at 1.0-1.3 V, with initial currents generally 100 mA. The cell content was stirred magnetically at room temperature. The reaction was followed by tlc and the current dropping. After neutralization of the reaction mixture, the solvent was removed and extracted with chloroform. The extract was washed with water and dried over sodium sulfate. Evaporation of the solvent gave the crude product, which was purified by column chromatography on silica gel.

(±)-*O*-Methylflavinantine (II).

Oxidation of 0.5 g. (1.4 mmoles) of I was carried out at 1.2 V in the manner described above to give 0.5 g. of a brownish oil, which was purified by column chromatography on silica gel with 850 ml. of chloroform to give 0.4 g. (84%) of II as a pale yellow viscous oil, whose spectral data were identical with those of authentic sample (7); ν max (chloroform): 1670, 1645, 1622 cm^{-1}; nmr (deuteriochloroform): δ 2.46 (3H, s), 3.79 (3H, s) 3.84 (3H, s), 3.87 (3H, s), 6.29 (1H, s), 6.37 (1H, s), 6.62 (1H, s) 6.81 (1H, s); mass (*m/e*), 341 (M^+).

2′-(β-*N*-Ethoxycarbonyl-*N*-methyl)aminoethyl-3,3′,4,4′-tetramethoxystilbene (IIIa).

To a mixture of 5.0 g. (14 mmoles) of laudanosine (I) and 3.25 g. (20 mmoles) of ethyl chlorocarbonate in 50 ml. of chloroform a solution of 2.76 g. (60 mmoles) of potassium hydroxide in 30 ml. of water was dropwise added at 0-5°, and the mixture was stirred for 1 hour at room temperature. The organic layer was separated and the alkaline layer was extracted twice with chloroform. The combined organic layer was washed successively with 10% hydrochloric acid and water, dried over sodium sulfate, and concentrated *in vacuo* to afford 4.8 g. of crystals, which were recrystallized from benzene to give 4.2 g. (70.0%) of IIIa as colorless prisms, m.p. 157-159°; λ max (ethanol): 335, 297 nm; ν max (chloroform): 1680 cm^{-1}; nmr (chloroform): δ 1.20 (3H, t, J = 7.5 Hz), 2.85 (3H, s), 2.88 (12H, br s), 3.95 (2H, q, J = 7.5 Hz), 6.65-7.30 (7H, m).

Anal. Calcd. for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.28; N, 3.26. Found: C, 67.45; H, 7.19; N, 3.36.

2′-(β-*N*-Methyl-*N*-trifluoroacetyl)aminoethyl-3,3′,4,4′-tetramethoxystilbene (IIIb).

A mixture of 2.3 g. (6.4 mmoles) of laudanosine (I) and 10.0 g. (47.6 mmoles) of trifluoroacetic anhydride in a sealed tube was heated at 160° for 3 hours. Evaporation of an excess of trifluoroacetic anhydride gave brownish crystals, which were dissolved in 20 ml. of chloroform. The extract was washed successively with water, 5% sodium hydrogen carbonate and water, dried over sodium sulfate, and concentrated *in vacuo* to afford 2.5 g. (85.6%) of IIIb as an amorphous material, nmr (deuteriochloroform): δ 3.05 (3H, br s), 3.71-3.89 (12H, m), 6,37-6.98 (7H, m).

Anal. Calcd. for $C_{23}H_{26}NO_5F_3 \cdot 1/2\,H_2O$: C, 59.73; H, 5.88; N, 3.02. Found: C, 60,25; H, 5.72; N, 2.81.

2′-(β-*N*-Ethoxycarbonyl-*N*-methyl)aminoethyl-3,3′,4,4′-tetramethoxydihydrostilbene (IVa).

To a solution of 2.0 g. (4.7 mmoles) of IIIa in 50 ml. of ethanol and 10 ml. of acetic acid, 100 mg. of 10% palladium on charcoal was added. The mixture was stirred in a current of hydrogen at room temperature. After a calculated amount of hydrogen had been absorbed, the reaction mixture was worked up as usual and purified by recrystallization from benzene to give 1.9 g. (95%) of IVa as colorless needles, m.p. 105°; λ max (ethanol): 283 nm; ν max (nujol) 1690 cm^{-1}; nmr (deuteriochloroform): δ 1.20 (3H, t, J = 7.5 Hz), 2.85 (3H, s), 3.82 (12H, s), 4.05 (2H, q, J = 7.5 Hz), 6.58-6.70 (5H, m).

Anal. Calcd. for $C_{24}H_{33}NO_6$: C, 66.80; H, 7.71; N, 3.25. Found: C, 66.69; H, 7.71; N, 3.25.

2′-(β-*N*-Methyl-*N*-trifluoroacetyl)aminoethyl-3,3′,4,4′-tetramethoxydihydrostilbene (IVb).

To a solution of 2.0 g. (4.4 mmoles) of IIIb in 50 ml. of ethanol, 100 mg. of 10% palladium on charcoal was added. The reaction mixture was treated as usual to afford an amorphous material, which was purified by preparative tlc to give 1.8 g. (90%) of IVb as pale yellow crystals, m.p. 79-81°; λ max (ethanol): 284 nm; ν max (nujol) 1690 cm^{-1}; nmr (deuteriochloroform): δ 3.08 (3H, br s), 3.85 (12H, br s), 6.25-6.95 (5H, m).

Anal. Calcd. for $C_{23}H_{28}NO_5F_3$: C, 60.06; H, 6.19; N, 3.07. Found: C, 59.96; H, 5.68; N, 3.02.

Anodic Oxidation of IVa.

Oxidation of 0.5 g. (1.2 mmoles) of IVa was carried out at 1.0 V in the manner described above to give 1.8 g. of a brownish oil, which was purified by column chromatography on silica gel with 1500 ml. of chloroform to give 0.42 g. (87%) of Va as colorless crystals, m.p. 150-152°; λ max (ethanol): 354, 290, 263, 240 nm; ν max (chloroform): 1695, 1670, 1642, 1620 cm^{-1}; nmr (deuteriochloroform): δ 1.13 (3H, t, J = 7.5 Hz), 2.65 (3H, s), 3.75 (3H, s), 3.90 (3H, s), 4.00 (2H, q, J = 7.5 Hz), 5.70 (1H, s), 6.67 (2H, br s), 7.05 (1H, s); mass (*m/e*) 415 (M^+).

Anal. Calcd. for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.09; H, 7.04; N, 3.37.

Anodic Oxidation of IVb.

Oxidation of 0.5 g. (1.1 mmoles) of IVb was carried out at 1.3 V in the manner described above to give 1.0 g. of a brownish oil, which was purified by column chromatography on silica gel with 630 ml. of chloroform and further purified by preparative tlc on silica gel to give 0.36 g. (75%) of Vb as yellow needles, m.p. 129-132° dec.; λ max (ethanol): 284, 240 nm; ν max (chloroform): 1698, 1670, 1620 cm^{-1}; nmr (deuteriochloroform): δ 3.18 (3H, br s), 3.70-3.88 (9H, m), 6.18 (1H, br s), 6.45 (1H, s), 6.60-6.95 (2H, m); mass (*m/e*) 439 (M^+).

Anal. Calcd. for $C_{22}H_{24}NO_5F_3 \cdot 1/2\,H_2O$: C, 58.29; H, 5.61; N, 3.12. Found: C, 57.89; H, 5.65; N, 3.12.

Bis-(3,4-dimethoxy-*N*-methyl-β-phenethyl)amine (VIIa).

A mixture of 4.5 g. (17.2 mmoles) of bis-(3,4-dimethoxy-β-phenethyl)amine hydrochloride and 3.0 g. (100 mmoles) of formalin and 30 ml. of methanol was stirred for 1 hour, to which 3.0 g. (80 mmoles) of sodium borohydride was added and stirred for 1 hour under ice-water cooling. The reaction mixture was refluxed for 30 minutes, concentrated *in vacuo*, and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to afford 4.0 g. (97%) of VIIa as a pale yellow viscous oil; ν max (neat): 2820, 1590 cm^{-1}; nmr (deuteriochloroform): δ 2.36 (3H, s), 2.69 (8H, s), 3.80 (12H, s), 6.70 (6H, s), whose picrate showed m.p. 155-157°.

Anal. Calcd. for $C_{28}H_{32}N_4O_{12}$: C, 54.54; H, 5.23; N, 9.09. Found: C, 55.28; H, 5.66; N, 9.34.

Bis-(3,4-dimethoxy-*N*-formyl-β-phenethyl)amine (VIIb).

A mixture of 2.0 g. (7.6 mmoles) of bis-(3,4-dimethoxy-β-phenethyl)amine hydrochloride and 2.0 g. (13.5 mmoles) of ethyl orthoformate was heated on a water-bath at 85° for 15 hours. The crystals separated from the reaction mixture was collected and recrystallized from ethanol to afford 1.8 g. (93.3%) of VIIb as colorless leaflets, m.p. 102-103° [Lit. (8) 102.5-103.5°]; νmax (chloroform): 1650 cm^{-1}; nmr (deuteriochloroform): δ 2.74 (4H, q, J = 8.0 Hz), 3.19-3.63 (4H, m), 3,80 (12H, s), 6.25-6.80 (6H, m), 7.78 (1H, s).

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