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Synthesis of Aminoisoquinolines and Related Compounds. IX.[1] Synthesis of *dl*-O-Methylcaseadine

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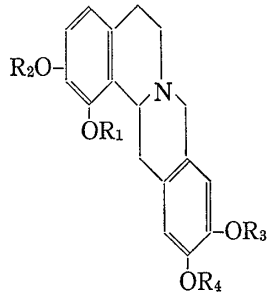
The Mannich reaction of tetrahydroisoquinolines (IVa, b) with 36% formalin in acetic acid gave respectively protoberberines (Va, b) and each compounds were converted to tetramethoxyprotoberberines (Ic, d). Ic was identified by the infrared and nuclear magnetic resonance spectral comparisons with caseadine methyl ether derived from natural caseamine or caseadine. Hydrochloric acid catalyzed condensation of 7,8-disubstituted tetrahydroisoquinoline (VIII) with 36% formalin gave the same compound (Ic).

Caseamine, $C_{19}H_{21}O_4N$ and caseadine, $C_{20}H_{23}O_4N$ were isolated from *Corydalis caseana* A. Gray and chemical and spectral investigation led to the proposed structure (Ia and Ib), which were protoberberines with an unusual 1,2-dioxygenated pattern, by R.H.F. Manske and his co-worlers.[3]



Ia: $R_1+R_2=R_3+R_4=H+Me$
Ib: $R_1=H$, $R_2=R_3=R_4=Me$
Ic: $R_1=R_2=R_3=R_4=Me$

Chart 1

Manske reported[3b] that methylation of both caseamine and caseadine gave the same tetramethoxyprotoberberine (Ic), melted at 186° and that the infrared (IR), the ultraviolet (UV), and the mass spectra of Ic suggested a protoberberine skeletone. Moreover, Ic was not identical with any of the known tetramethoxyprotoberberine recorded in the literature.[4] On the base of above facts and biogenetic consideration, Manske indicated that Ic was a protoberberine with a novel substitution pattern.

In this paper, the authors wish to report the synthesis of *dl*-O-methylcaseadine in order to examine the structure of Ia and Ib.[5]

A mixture of 3,4-dihydroisoquinolines (IIIa, b), prepared from the Bischler-Napieralski reaction of the amide (II),[6a] was reduced with sodium borohydride in methanol to give a mixture of tetrahydroisoquinolines (IVa, b), which showed two spots on thin-layer chromatogram of silica gel. Accordingly, the mixture was chromatographed on silica gel eluted with benzene-methanol and separated into each components with a ratio of 1:4=IVa:IVb.

1) Part VIII: S. Ishiwata and K. Itakura, *Chem. Pharm. Bull.* (Tokyo), **18**, 1841 (1970).
2) Location: *No. 600, Kashiwagi-4-chome, Shinjuku-ku, Tokyo.*
3) *a*) R.H.F. Manske and M.R. Miller, *Canad. J. Research* (*B*), **16**, 153 (1938); *b*) C.-Y.Chen, D.B. MacLean, and R.H.F. Manske, *Tetrahedron Letters*, **1968**, 349.
4) *a*) R.H.F. Manske and W.R. Ashford, "The Alkaloids," IV, R.H.F. Manske. Ed. Academic Press, New York, 1954, p. 77; *b*) H.G. Biot, "Ergebnisse der Alkaloid-chemie bis 1960," Akademi-Verlag, Berline, 1961, p. 330.
5) In the couse of our works, CaVa and his co-workers reported the synthesis of *dl*-O-methylcaseadine *via* Reissert compound. M.P. Cava, M.V. Lakshmikantham, and M.J. Mitchell, *J. Org. Chem.*, **34**, 2665 (1969).
6) *a*) S. Ishiwata and K. Itakura, *Chem. Pharm. Bull.* (Tokyo), **18**, 1224 (1970); *b*) *Idem, ibid.*, **18**, 896 (1970).

The Mannich reaction of IVb with 36% formaldehyde solution in acetic acid afforded the protoberberine (Vb), which was hydrolyzed to the amino derivative (VIb) with 10% ethanolic potassium hydroxide solution in the presence of nitrogen gas. Deamination of VIb by the usual method gave Id, which was identified by the IR spectral comparison with the authentic sample, *dl*-xylopine.[6b]

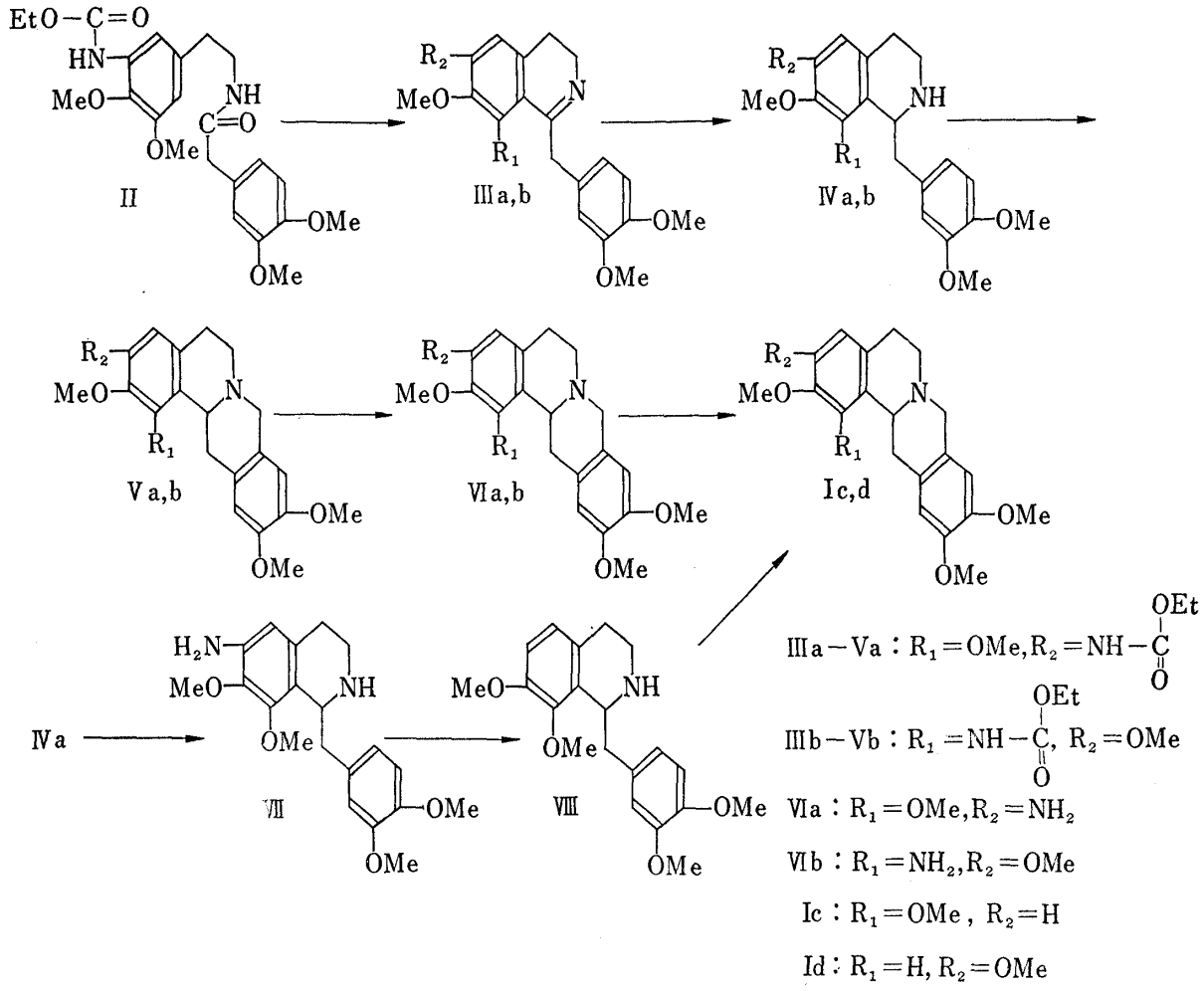


Chart 2

In the same way, the Mannich reaction of IVa gave the protoberberine (Va), which was converted to VIa, and successively VIa was deaminated to the tetramethoxyprotoberberine (Ic), melted at 169° (Lit.[5] 165°). The IR and nuclear magnetic resonance (NMR)[7] spectra of the synthesized sample were superimposable with those of O-methylcaseadine prepared from caseadine. Moreover, the mass spectrum[7] of our sample was very similar to that[8] of caseadine methyl ether as illustrated in Chart 3.

On the other hand, hydrolysis of IVa under the same conditions as the case of Vb gave the aminotetrahydroisoquinoline (VII), which was selectively deaminated in hypophosphorous acid[9] to the 7,8-disubstituted isoquinoline (VIII).[5] Hydrochloric acid catalyzed reaction of VIII with 36% formaldehyde solution in ethanol gave a tetramethoxyprotoberberine, which was identified by the IR spectral comparison with Ic.

7) NMR spectra were measured by JNM-4H 100 spectrophotometer at 100 Mc in deuteriochloroform and tetramethylsilane was used as internal reference. The mass spectrum was measured by Hitachi RMU-6 mass spectrometer.
8) C.-Y. Chen and D.B. MacLean, *Can. J. Chem.*, **46**, 2501 (1968).
9) N. Kornblum and D.C. Iffland, *J. Am. Chem. Soc.*, **71**, 2137 (1949).

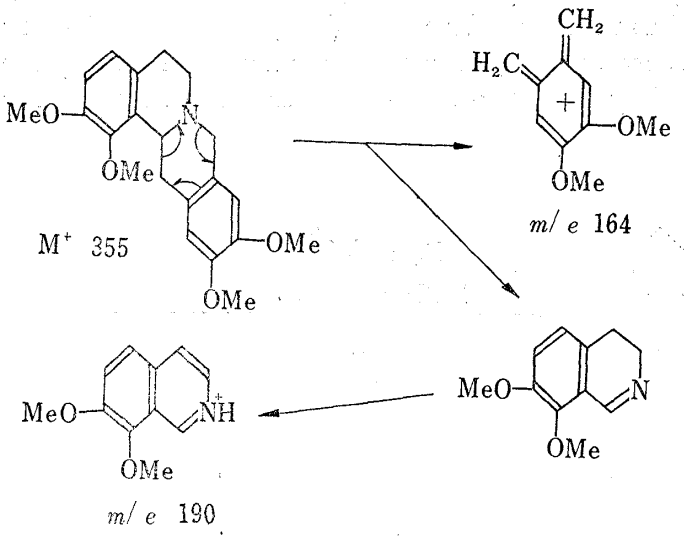


Chart 3

The mass spectrum of *dl*-O-methylcaseadine

In the IR spectra, both VIb and Id had Bohlmann bands, absorption at 2750—2760 cm^{-1}, showing the presence of *trans*-quinolizine skeletone, but Vb, Va, VIa, Ic had not Bohlmann bands.

The details of the streochemistry of the quinolizine ring in synthesized protoberberines are being in progress.

Experimental[10]

A Mixture of 6-Ethoxycarbamido-7,8-dimethoxy (IVa)- and 8-Ethoxycarbamido-6,7-dimethoxy (IVb)-1,2,3,4-tetrahydro-1-(3,4-dimethoxybenzyl) isoquinolines——A mixture of 0.5 g of the amide (II) and 10 ml of $POCl_3$ was refluxed for 1.5 hr in 70 ml of anhyd. benzene and the solvent and excess of the reagent were removed under reduced pressure to give a yellow oily residue. The residue was washed with *n*-hexane for several times and treated with $NaBH_4$ (4 g) in 50 ml of MeOH for 1 hr at room temperature with stirring. The reaction mixture was poured into 300 ml of ether and the basic product was extracted with 3% aq. HCl from the ethereal solution. The aqueous acidic solution was basified with conc. NH_4OH and the product was taken up in benzene, and the extract was washed with water, dried over K_2CO_3 and evaporated to yield 2.5 g of pale yellow oil. This oily product was chromatographed on silica gel (50 g) eluted with benzene–MeOH (50:1) to be separated into two components. The first eluted product was IVa (0.4 g): IR cm^{-1} ($CHCl_3$): ν_{NH} 3400, $\nu_{C=O}$ 1730. NMR (τ): 8.68 (3H, triplet, J=7 cps, O–$CH_2\underline{CH_3}$), 6.15—6.07 (12H, 4×O–$\underline{CH_3}$), 5.75 (2H, quartet, J=7 cps, O–$\underline{CH_2}CH_3$), 3.15 (3H, multiplet, aromatic H), 2.34 (1H, singlet, C_5–H). Picrate: Recrystallized from EtOH as yellow needles, mp 109—110° (decomp.). *Anal.* Calcd. for $C_{23}H_{30}O_6N_2 \cdot C_6H_3O_7N_3 \cdot H_2O$[11]: C, 52.09; H, 5.13; N, 10.48. Found: C, 52.31; H, 5.10; N, 10.10.

The secound was IVb (1.6 g): IR cm^{-1} ($CHCl_3$): ν_{NH} 3400, $\nu_{C=O}$ 1730. NMR (τ): 8.70 (3H, triplet, J=7 cps, O–$CH_2\underline{CH_3}$), 6.15—6.10 (12H, 4×O–$\underline{CH_3}$), 5.75 (2H, quartet, J=7 cps, O–$\underline{CH_2}CH_3$), 3.32—3.15 (4H, multiplet, aromatic H). Picrolonate: Recrystallized from EtOH, as yellow needles, mp 152—155° (decomp.). *Anal.* Calcd. for $C_{23}H_{30}O_6N_2 \cdot C_{10}H_8O_5N_4 \cdot H_2O$: C, 55.61; H, 5.66; N, 11.79. Found: C, 55.40; H, 5.37; N, 12.19.

1-Ethoxycarbamido-2,3,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*, *g*]quinolizine (Vb)——A mixture of 0.5 g of IVb, 5 ml of formalin, and 5 ml of AcOH was refluxed for 3 hr and the reaction mixture was evaporated to give a yellow residue, which was dissolved in $CHCl_3$. The extract was washed with successively 10% NH_4OH and water, dried over K_2CO_3, and evaporated to afford a yellow oil, which was purified by chromatography on silica gel (10 g) eluted with $CHCl_3$–MeOH (100:1) to yield 0.3 g of colorless oily product. IR cm^{-1} ($CHCl_3$): ν_{NH} 3400, $\nu_{C=O}$ 1734. NMR (τ): 8.75 (3H, triplet, J=7 cps, O–$CH_2\underline{CH_3}$), 6.20—6.17 (12H, 4×O–$\underline{CH_3}$), 5.80 (2H, quartet, J=7 cps, O–$\underline{CH_2}CH_3$), 3.42 (2H, $C_{9,12}$–H), 3.35 (1H, singlet, C_4–H). Methiodide: Recrystallized from EtOH, as colorless powder, mp 205—208° (decomp.). *Anal.* Calcd. for $C_{24}H_{30}O_6N_2 \cdot CH_3I$: C, 51.35; H, 5.69; N, 4.79. Found: C, 50.84; H, 5.62; N, 4.79.

1-Amino-2,3,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (VIb)——A mixture of 0.2 g of Vb and 10% EtOH–KOH solution was refluxed for 1.5 hr in the presence of N_2. The residue left after evaporation of the solvent was treated with conc.HCl and this acidic solution was basified again with conc.NH_4OH and the amino compound was extracted with $CHCl_3$. The extract was dried over K_2CO_3 and evaporated to afford a pale yellow solid, which was recrystallized from MeOH to yield 0.1 g of colorless needles, mp 197—199°. *Anal.* Calcd. for $C_{21}H_{26}O_4N_2$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.67; H, 6.96; N, 7.54. IR cm^{-1} ($CHCl_3$): ν_{NH_2} 3360, 3440, Bohlmann bands 2750. NMR (τ): 6.20—6.18 (12H, 4×O–$\underline{CH_3}$), 3.81 (1H, singlet, C_4–H), 3.39 (2H, $C_{9,12}$–H).

Deamination of VIb——To a stirred mixture of 0.1 g of VIb, 2 ml of AcOH, and 3 ml of 10% aq. H_2SO_4, was added a slight excess of $NaNO_2$ in 0.5 ml of water at 5° and the reaction mixture was stirred further for 30 min at 0—5°. To this mixture, was added 2 g of 50% aq.H_3PO_2 over period of 5 min and the mixture

10) All melting points were not corrected.

11) This product was dried over P_2O_5 at 90° (5 mmHg) for 5 hr.

was kept in an ice box for 12 hr. After basification of this mixture with conc.NH_4OH, the product was taken up in $CHCl_3$ and the extract was dried over K_2CO_3, and evaporated to give 60 mg of pale yellow solid, whose IR spectrum was superimposable with that of authentic sample.

3-Ethoxycarbamido-1,2,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*, *g*]quinolizine (Va)——Prepared from IVa (0.5 g), formalin (5 ml), and AcOH (5 ml) by the same method. Recrystallization of the product from EtOH yielded 0.25 g of colorless needles, mp 163—165°. *Anal.* Calcd. for $C_{24}H_{30}O_6N_2$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.80; H, 6.70; N, 6.13. IR cm^{-1} ($CHCl_3$): ν_{NH} 3400, $\nu_{C=O}$ 1733. NMR (τ): 8.75 (3H, triplet, $J=7$ cps, O-$CH_2C\underline{H}_3$), 5.75 (2H, quartet, $J=7$ cps, O-$C\underline{H}_2CH_3$), 6.17—6.10 (12H, $4\times$O-$C\underline{H}_3$), 3.40 (2H, $C_{9,12}$-$\underline{H}$), 2.30 (1H, singlet, C_4-$\underline{H}$).

3-Amino-1,2,10,11-tetramethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (VIa)——Prepared from Va (0.2 g) by the same method as described for VIb. Recrystallization of the product from EtOH gave 0.1 g of colorless leafles, mp 155—157°. *Anal.* Calcd. for $C_{21}H_{26}O_4N_2$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.78; H, 6.86; N, 7.77. IR cm^{-1} ($CHCl_3$): ν_{HN_2} 3370, 3430. NMR (τ): 6.18—6.14 (12H, $4\times$O-$C\underline{H}_3$), 3.70 (1H, singlet, C_4-$\underline{H}$), 3.38 (2H, $C_{9,12}$-$\underline{H}$).

1,2,10,11-Tetramethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (Ic)——Prepared from VIa (50 mg) by the same method as described for deamination of VIb. Recrystallization of the product from EtOH afforded 25 mg of colorless prisms, mp 167—169°. *Anal.* Calcd. for $C_{21}H_{25}O_4N$: C, 70.96; H, 7.09; N, 3.84. Found: C, 70.46; H, 7.17; N, 3.70. NMR (τ): 6.15—6.13 (12H, $4\times$O-$C\underline{H}_3$), 3.82 (2H, singlet, $C_{9,12}$-$\underline{H}$), 3.13 (2H, singlet, $C_{3,4}$-$\underline{H}$).

1,2,3,4-Tetrahydro-7,8-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline (VIII)——Hydrolysis of IVa (200 mg) under the same conditions as described for Vb gave a reddish brown oil, which was purified by chromatography on alumina to yield 130 mg of VII, as a pale yellow oily product. IR cm^{-1} ($CHCl_3$): ν_{NH_2}, ν_{NH} 3450—3350. This product was used for the next step without further purification. To a stirred mixture of 100 mg of VII in 2.5 g of 50% aq.H_3PO_2, was added a slight excess of $NaNO_2$ at 5° and the reaction mixture was stirred further for 30 min at 0—5°, and kept in an ice box for 12 hr. The reaction mixture was basified with conc.NH_4OH and the product was extracted with benzene and the extract was washed with water, dried over K_2CO_3, and evaporated to yield 60 mg of yellow oil. Oxalate: Recrystallized from EtOH, as colorless needles, mp 181—183° (decomp.). *Anal.* Calcd. for $C_{20}H_{25}O_4N\cdot C_2H_2O_4$: C, 60.96; H, 6.28; N, 3.23. Found: C, 61.02; H, 6.25; N, 3.64.

Acid Catalyzed Condensation of VIII with Formalin——A mixture of 30 mg of VIII, 0.1 ml of formalin, and 0.1 ml of conc.HCl was refluxed in 5 ml of EtOH for 3 hr. Evaporation of the solvent and the reagent gave a yellow residue, which was basified with 10% NH_4OH, and the product was extracted with $CHCl_3$. The extract was washed with water, dried over K_2CO_3, and evaporated to give a brown solid, which was recrystallized from EtOH to yield 15 mg of colorless prisms, mp 166—168°. The IR spectrum of this compound was superimposable with that of Ic.

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