Synthesis of Analogs of Ochotensine and Ochotensimine

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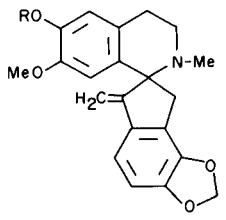
The isolation of the pair of related alkaloids ochotensine (I) and ochotensimine (II) from *Corydalis Ochotensis* TURCZ, was reported by Manske (2) almost thirty years ago. Only recently, however, where the structure of these alkaloids determined by chemical and spectroscopic methods (3) and by X-ray crystallographic analysis (4). Very recently, when this work was nearing completion, a total synthesis of one of these alkaloids, ochotensimine (II) was reported (5).

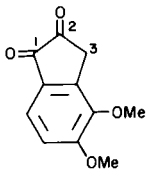
We now wish to report syntheses of analogs V and VI of ochotensine and ochotensimine respectively in which two methoxyl groups are substituted for the methylenedioxy group present in the alkaloids. In contrast with the recently reported synthesis (5), the phenolic group corresponding to that in ochotensine is preserved. It is therefore anticipated that the synthetic route described herein will serve, as intended, as a model for the synthesis of both alkaloids; a synthesis of ochotensine has not been reported. We also anticipate using the analogs (V and VI), which are much more readily available than the scarce naturally occurring alkaloids or synthetic alkaloids, as models for degradation studies. Such studies are a necessary prelude to an investigation of the biogenesis of these structurally unique alkaloids (3b).

A Pictet-Spengler condensation between the dimethoxyindanedione (III) (6) and 3-hydroxy-4-methoxyphenethylamine (IV) (7) in ethanolic hydrochloric acid afforded the hydrochloride of VII. The salt crystallized from the reaction mixture in 59% yield and no effort has been made to recover more from the mother liquors. The ultraviolet, infrared and nuclear magnetic resonance spectra of VII and all succeeding compounds were consistent with the assigned structures (see Experimental). The spectral properties of VII and its successors rule out the positional isomer that would result by involvement of the ketone in position 1 of III as the condensation product.

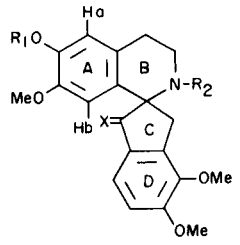
Heating of the free amine (VII) in an aqueous mixture of formic acid and formaldehyde converted it in 84% yield to the corresponding *N*-methylamine (VIII). A Wittig reaction carried out on the tetrahydropyranyl derivative of VIII, chromatography of the crude product on silica gel and acid hydrolysis afforded, in 52% yield, the analog (V) of ochotensine. Methylation of the phenolic group of VIII with diazomethane followed by a Wittig reaction and chromatography of the crude product gave, in 73% yield, the analog (VI) of ochotensimine. This compound was also obtained by treating V with diazomethane.



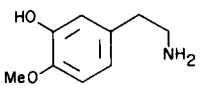
I R = H
II R = Me



III



V R_1 = H; R_2 = Me; X = CH_2
VI R_1 = R_2 = Me; X = CH_2
VII R_1 = R_2 = H; X = O
VIII R_1 = H; R_2 = Me; X = O



IV

The ultraviolet, infrared red and N.M.R. spectra of V and VI were consistent with published data (3b) for ochotensine and ochotensimine, the similarities between the N.M.R. spectra being particularly striking. In the spectrum of V, the two protons on ring D appeared as a pair of doublets (1H each) of an AB system (J = 8Hz) at 7.33 δ and 6.88 δ. Singlets (1H each) were found at 6.58 δ (Ha) and 6.29 δ (Hb) while singlets due to = CH_2 appeared at 5.66 δ and 4.93 δ. Singlets (3H each) due to methoxyl groups were located at 3.90 δ and 3.87 δ (ring D) and at 3.61 δ (ring A) and there was a singlet (3H) at 2.15 δ due to N-CH_3. The spectrum of VI was essentially identical with that of V but with an additional singlet

(311) superimposed on the singlet already at 3.87 δ due to additional methoxyl group.

EXPERIMENTAL

N.M.R. spectra were determined in deuteriochloroform and chemical shifts in ppm, are relative to tetramethylsilane as internal standard. U. V. spectra were determined in 95% ethanol. Petroleum ether refers to the fraction with b.p. 30-60°.

Condensation Product (VII).

A mixture of 3.50 g. of the hydrochloride of IV, 3.50 g. of III, 98 ml. of ethanol and 42 ml. of concentrated hydrochloric acid was brought to reflux over a period of 15 minutes then allowed to reflux for 40 minutes. On cooling the resulting solution to 0°, 3.95 g. (59%) of the hydrochloride of VII crystallized, m.p. 260-261° dec.; U. V. λ max 232 (ε, 24,300), 290 mμ (ε, 20,300); infrared cm^{-1} (Nujol), 3435 (phenol), 2750-2300 (ammonium bands), 1710 (ketone).

Anal. Calcd. for $C_{20}H_{22}ClNO_5$: C, 61.30; H, 5.66; Cl, 9.05; N, 3.58. Found: C, 61.52; H, 5.98; Cl, 9.00; N, 3.49.

A solution of 2.20 g. of the hydrochloride in 75 ml. of 2 *N* ammonium hydroxide was extracted with chloroform and the extract was evaporated *in vacuo*. The residue, on crystallization from methanol-ether yielded 1.85 g. of the free amine VII, m.p. 167°; U. V. λ max 229 (ε, 26,200), 287 mμ (ε, 21,600); infrared cm^{-1} (chloroform) 3535 (phenol), 3270 (NH), 1710 (ketone); N.M.R. 3.53 δ (3H, s; OMe on ring A), 3.90 δ (3H, s; OMe on ring D), 3.99 δ (3H, s; OME on ring D), 4.09 δ (1H, s; NH), 6.08 δ (1H, s; Hb shielded by ketone), 6.60 δ (1H, s; Ha), 7.06 δ (1H, d, J = 8Hz; on ring D), 7.65 δ (1H, d, J = 8Hz; on ring D), 2.50-3.50 δ (6H, complex; remaining methylenes).

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.52; H, 5.91; N, 3.74.

N-Methylamine (VIII).

A solution of 1.75 g. of VII in 9 ml. each of 88% formic acid and 37% formaldehyde was refluxed for 11 hours. After the addition of 60 ml. of water, the cooled solution was adjusted to *p*H 7.0 with concentrated ammonium hydroxide. The resulting precipitate was crystallized from methanol-water then from ethanol-petroleum ether. The yield of crystalline VIII was 1.52 g. (84%), m.p. 169-171°; U. V. identical with VII; infrared cm^{-1} (chloroform), 3525 (phenol), 2790 (N-CH_3), 1705 (ketone); N.M.R. similar to VII but it lacked the NH signal at 4.09 δ and had a singlet (3H) at 2.30 δ due to N-CH_3.

Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.16; H, 6.18; N, 3.78.

Analog (V) of Ochotensine.

The tetrahydropyranyl derivative of VIII (530 mg. prepared by standard procedure) was subjected to a Wittig reaction exactly as previously described (8). The crude product was applied to a column of silica gel (25 g.) and, after development with ether-petroleum ether (1:1), the tetrahydropyranyl derivative of V (349 mg.) was eluted with ether-petroleum ether (4:1). A solution of 150 mg. of the derivative in 1.5 ml. each of ethanol and 5*N* hydrochloric acid was left at room temperature for 4 hours. Chloroform (20 ml.) was added and the solution was washed with 2*N* ammonium hydroxide and water then evaporated *in vacuo*. The residue, on crystallization from ether-petroleum ether afforded 116 mg. (52%) of V, m.p. 139-140°; U. V. λ max 225 (ε, 26,700), 276 (ε, 14,400), 305 (sh) mμ (ε, 3,400); infrared cm^{-1} (chloroform), 3525 (phenol), 2780 (N-CH_3), 1600 and 1630 (C=C); N.M.R. see above.

Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81; M. W., 367.5. Found: C, 72.04; H, 6.71; N, 3.69; M. W., 367 (mass spectrum).

Analog (VI) of Ochotensimine.

The phenol VIII (406 mg.) in 10 ml. of ethanol was treated with an excess of an ethereal solution of diazomethane and left at 4° for 15 hours then for one hour at room temperature. The resulting oil was subjected to a Wittig reaction and the product purified by chromatography as described above. Thereby, 290 mg. (73%) of VI was obtained as a crystalline compound which melted below room temperature, U. V. λ max 225 (ε, 27,400), 275 (ε, 14,800), 305(sh) mμ (ε, 3,600); infrared cm^{-1} (chloroform) 2790 (N-CH_3), 1610 and 1635 (C=C); NMR, see above.

Anal. Calcd. for $C_{23}H_{27}NO_4$: M. W., 381.5: Found 381 (mass spectrum).

The hydrochloride melted at 210-215° dec.; U. V. λ max 228 (ε, 26,600), 278 (ε, 16,200), 305(sh) mμ (ε, 5,800); infrared cm^{-1} (Nujol) 2700-2200 (ammonium bands), 880 (=CH_2).

Anal. Calcd. for $C_{23}H_{28}ClNO_4$: C, 66.10; H, 6.75; Cl, 8.48; N, 3.35. Found: C, 66.18; H, 7.02; Cl, 8.67; N, 3.54.

Conversion of V to VI.

A solution of 6.15 mg. of V in 0.5 ml. of methanol was treated with 0.5 ml. of an ethereal solution (1*M*) of diazomethane and left at room temperature for 3.5 hours. The product was not separated from VI by thin layer chromatography in the following solvent systems: benzene-methanol (95:5), chloroform-methanol (95:5) and ethylene dichloride-methanol (95:5). The infrared and U. V. spectra were identical with those of VI.

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