

## Studies on Orchidaceae Alkaloids

XI.\* Three 1-Phenyl-1,2,3,4-tetrahydroisoquinolines  
from *Cryptostylis fulva* Schltr.

KURT LEANDER, BJÖRN LÜNING and ENE RUUSA

*Department of Organic Chemistry, University of Stockholm, S-113 27 Stockholm, Sweden*

Three 1-phenyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines have been isolated from *Cryptostylis fulva* Schltr. The three alkaloids differ in the substitution pattern of the 1-phenyl group, being 3,4-methylenedioxy, 3,4-dimethoxy, and 3,4,5-trimethoxy, respectively. Their structures were assigned by spectral methods and by synthesis.

The occurrence of 1-(3,4-methylenedioxyphenyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I) in *Cryptostylis fulva* Schltr. was reported in a preliminary paper.<sup>2</sup> We here present a full report on the structural elucidation of I (Cryptostyline I) and two further alkaloids (Cryptostyline II and Cryptostyline III) isolated from the same species (*cf.* Fig. 1).

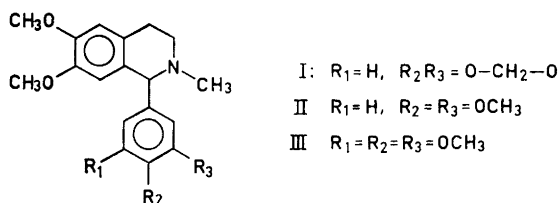
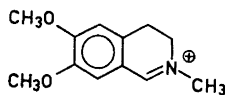


Fig. 1.

I crystallized spontaneously from the alkaloid fraction isolated from the plant, and two further alkaloids (II and III) were shown to be present in the mother liquor. II and III were isolated by preparative GLC after firstly removing I (which has the same GLC retention time as II) by chromatography on neutral alumina.

\* For Paper X in this series, see Ref. 1.



$m/e$  206

Fig. 2.

The NMR spectrum of I ( $C_{19}H_{21}NO_4$ ) shows the presence of two *O*-methyl groups ( $\tau$  6.15, 6.37) and one methylenedioxy bridge ( $\tau$  4.05) attached to aromatic systems, as well as one *N*-methyl group ( $\tau$  7.75) and five aromatic protons ( $\tau$  3.20, 3.35, 3.75). One of the carbon atoms attached to nitrogen is tertiary, and is further linked to one or two phenyl groups. The hydrogen atom bound to this carbon gives a singlet at  $\tau$  5.87 in I, shifted to  $\tau$  4.08 in the methiodide. There remain two carbon atoms and four strongly coupled deshielded hydrogen atoms in the molecule to be accounted for. This implies that I is a 1-phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline bearing two methoxyl groups and one methylenedioxy bridge. The base peak in the mass spectrum,  $m/e$  206 (*cf.* Fig. 2) indicates that the methoxyl groups are attached to the isoquinoline nucleus and the methylenedioxy bridge to the 1-phenyl group.

The mass spectra of II ( $C_{20}H_{25}NO_4$ ) and III ( $C_{21}H_{27}NO_5$ ) both show the same base peak as that of I,  $m/e$  206 (*cf.* Fig. 2), and this indicates that the structural differences are found in the 1-phenyl group. The NMR spectra show the presence of four methoxyl groups in II and five methoxyl groups in III, implying that II is a 1-dimethoxyphenyl-2-methyl-dimethoxy-1,2,3,4-tetrahydroisoquinoline and III a 1-trimethoxyphenyl-2-methyl-dimethoxy-1,2,3,4-tetrahydroisoquinoline. The positions of the oxygen functions were assumed, on biogenetic grounds, to be identical with those of the benzyl-isoquinoline alkaloids. The actual positions of the substituents were proved by syntheses.

In the syntheses, the appropriate *N*-(3,4-dimethoxyphenethyl)benzamide was cyclized by a Bischler-Napieralsky reaction, and the imine obtained was quaternized with methyl iodide. The bright yellow immonium salt was reduced catalytically (Adams catalyst, 25°) or with sodium borohydride to the 1,2,3,4-tetrahydroisoquinoline derivative. 1-(3,4-Methylenedioxyphenyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIII) was found to be identical with the racemate of I (UV, IR, NMR, MS, m.p.) 1-(3,4-dimethoxyphenyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (X) and 1-(3,4,5-trimethoxyphenyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XII) showed NMR, UV, and mass spectra identical with those of II and III, respectively.

## EXPERIMENTAL

All melting points are corrected. Mass spectra were measured on an LKB 9000 spectrometer, and with a double focussing Atlas SM 1 mass spectrograph. IR spectra were recorded on a Perkin Elmer 257 instrument, the UV spectra (in ethanol) on a Beckman DK2 instrument, and the NMR spectra on a Varian A60-A spectrometer. Elemental analyses were carried out by Dr. A. Bernhardt, Mülheim (Ruhr).

*Isolation of alkaloids.* Fresh plants of *Cryptostylis fulva* Schltr.\* (750 g) were extracted with methanol (4 l). The extract was concentrated to 200 ml, acidified with hydrochloric acid and washed with ether (5×100 ml). The aqueous layer was made alkaline with sodium hydroxide and extracted with ether (3×150 ml). The ether solution was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated to 4 ml and filtered through neutral alumina (10×2.5 cm) using ether as eluent. Evaporation to dryness, *in vacuo*, of the eluate and crystallization of the residue from ether afforded I (0.5 g) as white needles. The mother liquor was then chromatographed on neutral alumina (30×1.5 cm) using ether as eluent. The first fraction collected contained pure I. Further elution with ether afforded a second alkaloid fraction, which could be separated into two components II (20 mg) and III (10 mg) by preparative GLC: Column 20%, SE-52 on Chromosorb AW DMCS, 60/80 mesh; 4 mm×2.0 m; gas flow rate 35 ml/min. Retention times at 265°: 21 min (II) and 26 min (III). Retention time of I under the same conditions was 20 min.

*Characterization of I.* Fine needles from ether, m.p. 101–102°;  $[\alpha]_D^{20} + 56^\circ$  (c 2.7, chloroform). (Found: C 69.6; H 6.66; N 4.30; O 19.4. Calc. for C<sub>16</sub>H<sub>21</sub>NO<sub>4</sub>: C 69.7; H 6.47; N 4.28; O 19.5). UV spectrum:  $\lambda_{\max}$  286.5 m $\mu$  ( $\epsilon$  7800),  $\lambda_{\text{inf}}$  235 m $\mu$  ( $\epsilon$  12600). NMR spectrum\*\* (CDCl<sub>3</sub>):  $\tau$  3.20 (s, 3H),  $\tau$  3.35 (s, 1H),  $\tau$  3.75 (s, 1H),  $\tau$  4.05 (s, 2H),  $\tau$  5.87 (broad s, 1H),  $\tau$  6.15 (s, 3H),  $\tau$  6.37 (s, 3H),  $\tau$  6.5–7.8 (m, 4H),  $\tau$  7.75 (s, 3H). Pertinent mass spectra peaks *m/e* (rel. intensity): 327 (22), 326 (15), 206 (100), 190 (6).

After boiling an ethereal solution of I for 10 min the less soluble racemate, m.p. 116–117°, can be isolated in the form of rhomboid crystals.

*Methiodide of I.* Colourless needles from acetone, m.p. 239–241°. (Found: C 51.1; H 5.36; N 2.96; O 13.7; I 27.2. Calc. for C<sub>20</sub>H<sub>26</sub>INO<sub>4</sub>: C 51.2; H 5.16; N 2.99; O 13.6; I 27.0). NMR spectrum (DMSO-*d*<sub>6</sub>):  $\tau$  2.95 (s, 4H),  $\tau$  3.58 (s, 1H),  $\tau$  3.82 (s, 2H),  $\tau$  4.08 (s, 1H),  $\tau$  6.15 (s, 3H),  $\tau$  6.39 (s, 3H),  $\tau$  6.77 (s, 3H),  $\tau$  7.08 (s, 3H),  $\tau$  6.0–8.0 (m, 4H).

*Characterization of II.* Needles from ether, m.p. 117–118°;  $[\alpha]_D^{25} + 58^\circ$  (c 0.28, chloroform). (Found: M<sup>+</sup> 343.177. Calc. for C<sub>20</sub>H<sub>25</sub>NO<sub>4</sub>: 343.178. <sup>12</sup>C=12.00000). UV spectrum:  $\lambda_{\max}$  281 m $\mu$  ( $\epsilon$  6000),  $\lambda_{\text{inf}}$  228 m $\mu$  ( $\epsilon$  16000). NMR spectrum (CDCl<sub>3</sub>):  $\tau$  3.10–3.25 (m, 3H),  $\tau$  3.38 (s, 1H),  $\tau$  3.82 (s, 1H),  $\tau$  5.88 (s, 1H),  $\tau$  6.12 (s, 3H),  $\tau$  6.15 (s, 3H),  $\tau$  6.18 (s, 3H),  $\tau$  6.40 (s, 3H),  $\tau$  6.7–7.7 (m, 4H),  $\tau$  7.77 (s, 3H). Pertinent mass spectra peaks *m/e* (rel. intensity): 343 (36), 342 (26), 269 (20), 206 (100).

*Characterization of III.* Needles from ether, m.p. 126–129°;  $[\alpha]_D^{25} + 51^\circ$  (c 0.15, chloroform). (Found: M<sup>+</sup> 373.181. Calc. for C<sub>21</sub>H<sub>27</sub>NO<sub>5</sub>: 373.189. <sup>12</sup>C=12.00000.) UV spectrum:  $\lambda_{\max}$  281 m $\mu$  ( $\epsilon$  3700). NMR spectrum (CDCl<sub>3</sub>):  $\tau$  3.38 (s, 1H),  $\tau$  3.45 (s, 2H),  $\tau$  3.77 (s, 1H),  $\tau$  5.92 (s, 1H),  $\tau$  6.04–6.24 (unresolved band, 12H),  $\tau$  6.38 (s, 3H),  $\tau$  6.5–7.7 (m, 4H),  $\tau$  7.73 (s, 3H). Pertinent mass spectra peaks *m/e* (rel. intensity): 373 (53), 372 (22), 299 (15), 206 (100), 190 (16).

*N-(3,4-Dimethoxyphenethyl)-3,4-methylenedioxybenzamide (V).* To a suspension of homoveratrylamine (9.1 g; 0.050 mole) in 1 M aqueous potassium hydroxide (100 ml) piperonyloyl chloride (9.7 g; 0.053 mole) dissolved in ether (70 ml) was added dropwise with shaking over a period of 20 min. After evaporation of the ether, the mixture was extracted with chloroform (2×100 ml). The chloroform solution was washed successively with 1 M potassium hydroxide (50 ml) and 1 M hydrochloric acid (50 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness, leaving V as a white crystalline residue. Recrystallization from methanol yielded 14.8 g (0.045 mole, 90%) of the amide, m.p. 113–114°. (Found: C 65.4; H 5.97; N 4.22; O 24.1. Calc. for C<sub>18</sub>H<sub>19</sub>NO<sub>5</sub>: C 65.6; H 5.81; N 4.25; O 24.3).

*1-(3,4-Methylenedioxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (VI).* A solution of V (4.0 g, 0.012 mole) and phosphorus oxychloride (8 ml) in xylene (50 ml) was re-

\* Collected at 1300 m alt. around Bupu Village, Wampit, Territory of New Guinea.

\*\* Cf. Fig. 1 in Ref. 2.

fluxed for 30 min. After evaporation to dryness, the residue was partitioned between 2 M aqueous sodium hydroxide (25 ml) and chloroform (50 ml). The chloroform solution was washed with water (20 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to 10 ml. This solution was filtered through neutral alumina ( $15 \times 3$  cm) using chloroform as eluent. After evaporation, the residue was crystallized from ether. Recrystallization from acetone yielded 2.0 g (0.0061 mole, 51 %) of VI, m.p. 109–110°. (Found: C 69.3; H 5.63; N 4.52; O 20.4. Calc. for  $\text{C}_{18}\text{H}_{17}\text{NO}_4$ : C 69.4; H 5.51; N 4.50; O 20.6). UV spectrum:  $\lambda_{\text{max}}$  233  $\mu$  ( $\epsilon$  31 400), 305  $\mu$  ( $\epsilon$  13 100).

*1-(3,4-Methylenedioxyphenyl)-2-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium iodide* (VII). To a solution of VI in acetone an excess of methyl iodide was added. Within 30 min the yellow methiodide VII, m.p. 208–209°, was formed in quantitative yield. (Found: C 50.1; H 4.78; I 28.1; N 3.02; O 13.9. Calc. for  $\text{C}_{19}\text{H}_{20}\text{INO}_4$ : C 50.3; H 4.45; I 28.0; N 3.09; O 14.1). UV spectrum:  $\lambda_{\text{max}}$  251  $\mu$  ( $\epsilon$  17 200), 315  $\mu$  ( $\epsilon$  10 200), 367  $\mu$  ( $\epsilon$  12 500).

*1-(3,4-Methylenedioxyphenyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (VIII). The methiodide VII (215 mg) was dissolved in 15 ml methanol-water (1:1). Sodium borohydride (50 mg) was added with stirring and the yellow colour disappeared immediately. The reaction mixture was extracted with chloroform ( $3 \times 20$  ml) which was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated, yielding VIII (95 %) as a crystalline residue. Two recrystallizations from ether gave pure VIII, m.p. 117–118°. (Found: C 69.6; H 6.52; N 4.36; O 19.6. Calc. for  $\text{C}_{19}\text{H}_{21}\text{NO}_4$ : C 69.7; H 6.47; N 4.28; O 19.6). The NMR, UV and mass spectra of I and VIII are identical.

*1-(3,4-Dimethoxyphenyl)-2-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium iodide* (IX). *1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline* (0.55 g; prepared as VI above, having properties identical with those given for this compound by Müller *et al.*<sup>3</sup>) was treated with methyl iodide in acetone to give IX as yellow crystals, m.p. 211–213° (Müller *et al.*<sup>3</sup> reported m.p. 242°). (Found: C 51.2; H 5.38; I 26.9; N 2.86; O 13.6. Calc. for  $\text{C}_{20}\text{H}_{22}\text{INO}_4$ : C 51.2; H 5.16; I 27.0; N 2.99; O 13.6). UV spectrum:  $\lambda_{\text{max}}$  250  $\mu$  ( $\epsilon$  20 700), 312  $\mu$  ( $\epsilon$  11 700), 365  $\mu$  ( $\epsilon$  14 800).

*1-(3,4-Dimethoxyphenyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (X). The immonium salt IX (200 mg) was reduced with sodium borohydride as described above for VII, giving a quantitative yield of X. Recrystallization from ether gave colourless needles, m.p. 103–104° (Müller *et al.*<sup>3</sup> reported 94° for the monohydrate). (Found: C 70.1; H 7.44; N 3.93; O 18.7. Calc. for  $\text{C}_{20}\text{H}_{25}\text{NO}_4$ : C 70.0; H 7.34; N 4.08; O 18.6). NMR, UV, and mass spectra of X and II are identical.

*1-(3,4,5-Trimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline* (XI). *N-(3,4-Dimethoxyphenethyl)-3,4,5-trimethoxybenzamide*<sup>4</sup> was cyclized in the same way as V above to give an 80 % yield of XI, m.p. 159–160°. (Found: C 67.1; H 6.33; N 4.02; O 22.2. Calc. for  $\text{C}_{20}\text{H}_{23}\text{NO}_5$ : C 67.2; H 6.46; N 3.91; O 22.4). This compound has been prepared previously by Slotta and Haberland<sup>4</sup> as a monohydrate, m.p. 160°, and by Shroff *et al.*<sup>5</sup> who reported m.p. 159° although the analyses were unsatisfactory.

*1-(3,4,5-Trimethoxyphenyl)-2-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium iodide* (XII). An excess of methyl iodide was added to an acetone solution of XI (100 mg) and XII was formed as yellow crystals in quantitative yield, m.p. 193–196°. (Found: C 50.4; H 5.12; I 25.4; N 2.74; O 16.2. Calc. for  $\text{C}_{21}\text{H}_{26}\text{INO}_5$ : C 50.5; H 5.25; I 25.4; N 2.80; O 16.0). UV spectrum:  $\lambda_{\text{max}}$  248  $\mu$  ( $\epsilon$  20 600), 310  $\mu$  ( $\epsilon$  11 200), 364  $\mu$  ( $\epsilon$  13 400).

*1-(3,4,5-Trimethoxyphenyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (XIII). The immonium iodide XII (250 mg) was reduced with sodium borohydride in the same way as VII, giving, after two recrystallizations from ethanol, an 82 % yield of XIII, m.p. 141–142°. (Found: C 67.6; H 7.24; N 3.89; O 21.4. Calc. for  $\text{C}_{21}\text{H}_{27}\text{NO}_5$ : C 67.5; H 7.29; N 3.75; O 21.4). NMR, UV, and mass spectra of XIII and III are identical.

We wish to thank Dr. R. Ryhage for measuring the mass spectra. We thank Mr. J. Womersley and Mrs. A. Millar for the facilities put at our disposal and invaluable help in collecting the plant material. This work has been supported by grants from the *Swedish Natural Science Research Council*.

## REFERENCES

1. Lüning, B. and Tränkner, H. *Acta Chem. Scand.* **22** (1968) 2324.
2. Leander, K. and Lüning, B. *Tetrahedron Letters* **1968** 1393.
3. Müller, A., El-Sawy, M. M., Mészáros, M. and Ruff, F. *Acta Chim. Acad. Sci. Hung.* **52** (1967) 261.
4. Slotta, K. H. and Haberland, G. *Angew. Chem.* **46** (1933) 766.
5. Shroff, H.D., Diwadkar, A.B. and Kulkarni, A.B. *Indian J. Chem.* **2** (1964) 190.

Received June 17, 1968.