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Revision of the Structures of Linaresine and Dihydrolinaresine

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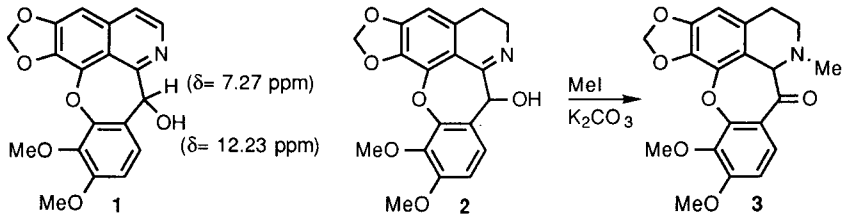
Abstract: The alkaloids linaresine and dihydrolinaresine have the structures of the known benzoyl isoquinolines rugosinone (**4**) and dihydrorugosinone (**5**). Copyright © 1996 Elsevier Science Ltd

The alkaloids linaresine and dihydrolinaresine isolated from *Berberis valdiviana*,[1] were originally assigned the α-hydroxycularine structures **1** and **2** on the basis of spectroscopic evidence and the chemical transformation of **2** into **3**. The substitution patterns of **1** and **2** are anomalous with respect to those of natural cularines, and the plant sources of linaresine and dihydrolinaresine are very different from those of cularine alkaloids.[2] In keeping with these singularities, it was hypothesized[1] that linaresine and dihydrolinaresine both originate biogenetically from protoberberines unlike the usual cularines.



We recently[3] described the total synthesis of compound **1** and found that its spectra differ significantly from those of the natural alkaloid,[4] the structure of which therefore cannot be **1**. Close inspection of the ^{1}HNMR spectrum of linaresine in CD_3CN suggested the possibility that the signal at 7.27 ppm might belong to an aromatic proton rather than to a benzylic one, and that the signal at 12.23 ppm might be due to a phenolic proton.

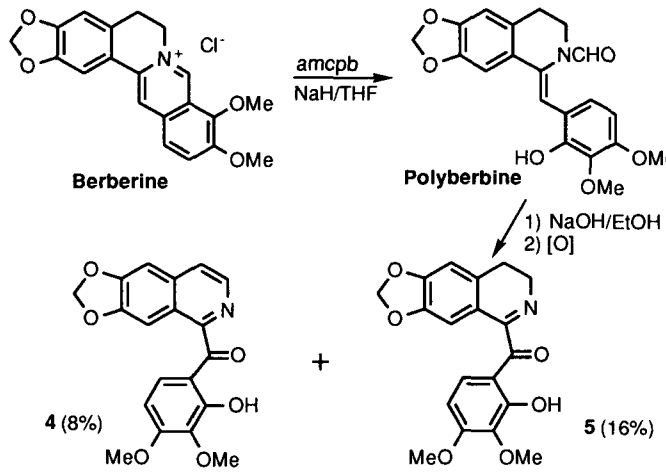
We accordingly hypothesized that linaresine might have a benzoyl isoquinoline structure like **4**,[5] and that dihydrolinaresine might have structure **5**.[7] The formation of a hydrogen bond between the phenol and the nearby carbonyl in **4** would explain the downfield shift of the phenolic signal; and structure **4** is furthermore in keeping with the NOEs obtained with linaresine, which interrelate most of the protons in the molecule.[1]

To investigate our hypothesis we synthesized compounds **4** and **5** starting from commercially available berberine chloride, treatment of which with mcpba in dry THF in the presence of NaH at rt gave the known polyberbine.[6] Basic hydrolysis of polyberbine (NaOH/EtOH, reflux, 3h) led to the corresponding enamine,

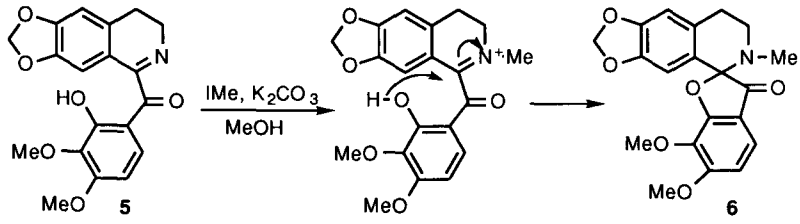
which underwent ready oxidation in CH_2Cl_2 solution to afford a mixture of **4** and **5** in 8% and 16% yields respectively.

The ^1H NMR spectrum of **4** in CD_3CN, and its MS and UV spectra, were identical to those of linaresine.[4] Its IR spectrum was very different from the IR spectrum of linaresine, but the latter was recorded in very dilute $CHCl_3$ solution, and most of its bands are due to the solvent. Exactly analogous considerations held for compound **5** and dihydrolinaresine.

Finally, a sample of **5** was allowed to react with MeI in MeOH in the presence of K_2CO_3. The ^1H NMR, MS, UV and IR spectra of the product are identical to those reported for the methylated derivative of dihydrolinaresine (**3**).



However, ^{13}C and DEPT experiments showed the presence of four aromatic C-H (105.4, 106.9, 108.5 and 120.7) and a low-field quaternary aliphatic carbon (104.6), which is incompatible with the cularine structure **3** but is compatible with the spiro-isoquinoline structure **6**. Compound **6** would be obtained from the dehydroderivative **5** through N-methylation followed by intramolecular attack by the hydroxyl group.



In conclusion, we have shown that the previously published structures of the alkaloids linaresine and dihydrolinaresine are wrong, and that these alkaloids are in fact the known benzoyl isoquinolines rugosinone (**4**) and dihydrorugosinone (**5**).

EXPERIMENTAL

^1H and ^{13}C nmr spectra were recorded at 250.13 and 62.83 MHz respectively on a Bruker WM-250 spectrometer; the solvent for nmr spectra was $CDCl_3$ unless otherwise stated, and chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane. Mass spectra were recorded at an ionization voltage of 70 eV. Melting points are uncorrected.

Preparation of Polyberbine from berberine chloride.[6] To a suspensión of berberine chloride (100 mg, 0.26 mmol, purchased from Aldrich) in 5 ml of anhydrous THF under Ar, were sequentially added 80% NaH (16 mg, 0.52 mmol) and 70% mcpba (100 mg, 0.40 mmol). After being stirred for 1h at rt, the reaction was worked up by addition of 2 ml of MeOH and evaporation of all the volatiles. The remaining residue was dissolved in CH_2Cl_2 (15 ml) and washed with $NaHCO_3$ saturated solution (2x10 ml), H_2O (20 ml) and brine (10 ml), and dried (Na_2SO_4). The crude so obtained (aprox. 100 mg) was chromatographied on a SiO_2 column (2.5:1, EtOAc:hexane) affording 40 mg (40%) of polyberbine as an amorphous solid. ^1H NMR (ppm): 8.11 (s, 1H, NCHO), 7.26 (s, 1H), 7.00 (d, J= 8.9, 1H, Ar-H), 6.84 (s, 1H), 6.59 (s, 1H), 6.46 (d, J= 8.9, 1H, Ar-H), 6.12 (s broad, 1H, OH), 5.96 (s, 2H, O-CH_2-O), 3.94 (t, J= 6.2, 2H, CH_2), 3.90 (s, 3H, OMe), 3.85 (s, 3H, OMe), 2.85 (t, J= 6.2, 2H, CH_2).

Obtention of rugosinone (4) and dihydrorugosinone (5) . Polyberbine (100 mg, 0.27 mmol) was dissolved in 50 ml of EtOH. To this solution were added 2.5 ml of 50% NaOH and the resulting mixture was heated to reflux until tlc (SiO_2, 95:5, CH_2Cl_2:MeOH) showed no starting material remaining but a new, slower moving spot. Evaporation to dryness left a residue which was dissolved in CH_2Cl_2 (20 ml) and washed with NH_4Cl sat. sol. (10ml), H_2O (10 ml) and brine (10 ml), and dried (Na_2SO_4). The solvent is concentrated to an approx. volume of 10 ml and left opened to the air for 12h. After that time, tlc showed a complex mixture with two majors spots and no sign of the former slow moving spot. Preparative tlc (50:50, EtOAc:hexane) afforded two products (Rf= 0.45 and 0.30); the less polar one was identified as rugosinone (**4**, 8 mg, 8%), mp 219-221ºC (lit 223-224ºC).[5] ^1H NMR (ppm): 12.40 (s, 1H, OH), 8.43 (d, J= 5.5, 1H, Ar-H), 7.62 (d, J= 5.5, 1H, Ar-H), 7.38 (s, 1H, Ar-H), 7.20 (d, J= 9.1, 1H, Ar-H), 7.15 (s, 1H, Ar-H), 6.41 (d, J= 9.1, 1H, Ar-H), 6.11 (s, 2H, O-CH_2-O), 3.95 (s, 3H, OMe), 3.91 (s, 3H, OMe). The more polar one was identified as dihydrorugosinone (**5**, 16 mg, 16%), mp 178-180ºC (lit 172-174ºC).[7] ^1H NMR (ppm): 7.40 (d, J= 9.0, 1H, Ar-H), 6.72 (s, 1H, Ar-H), 6.60 (s, 1H, Ar-H), 6.40 (d, J= 9.0, 1H, Ar-H), 5.90 (s, 2H, O-CH_2-O), 3.92 (s, 6H, 2xOMe), 3.82 (t, J= 6.0, 2H, CH_2N), 2.81 (t, J= 6.0, 2H, Ar-CH_2).

Methylation of 5. Obtention of 7,8-dihydro-6',7'-dimethoxy-6-methyl spiro[1,3-dioxolo[4,5-g]isoquinoline-5(6H),2'-[2H]benzofuran]-3'-one (6). Dihydrorugosinone (**5**, 15 mg, 0.042 mmol) was dissolved in 1.5 ml of MeOH (HPLC grade) and to this solution were added 1.5 ml (24 mmol) of MeI and roughly 40 mg of solid anhydrous Na_2CO_3. The mixture was heated at 55ºC for 1h, and then all the volatiles were evaporated. The solid residue was washed with CH_2Cl_2 (2x10 ml) and the liquid decanted. Evaporation of the solvent left 13 mg of crude which after chromatography on a SiO_2 column (1:1, EtOAc:hexane) afforded 8 mg (51%) of **6** as a yellowish solid, mp 155-157ºC. IR (KBr): 2935, 2836, 1713, 1602, 1498, 1441. ^1H NMR (ppm): 7.49 (d, J= 8.6, 1H, Ar-H), 6.70 (d, J= 8.6, 1H, Ar-H), 6.59 (s, 1H,

Ar-H), 6.29 (s, 1H, Ar-H), 5.87-5.85 (2xs, 2x1H, O-CH_2-O), 3.98 (s, 3H, OMe), 3.95 (s, 3H, OMe), 3.30-3.17 (m, 2H, CH_2), 2.93 (dd, J= 3.9 and J= 10.1, 1H, CH), 2.68 (d, J= 13.7, 1H, CH), 2.40 (s, 3H, NMe). ^{13}C NMR (ppm): 198.6 (CO), 164.5 (C), 161.0 (C), 148.8 (C), 146.8 (C), 134.0 (C), 130.5 (C), 125.5 (C), 120.7 (CH), 117.0 (C), 108.5 (CH), 106.9 (CH), 105.4 (CH), 104.6 (C), 101.5 (CH_2), 61.2 (OMe), 57.0 (OMe), 47.7 (CH_2), 38.4 (NMe), 29.2 (CH_2). MS, m/e (%): 369 (M^+, 45), 354 (23), 340 (100), 324 (21), 190 (26). UV (MeOH): 296, 234, 208. HRMS Calc for $C_{20}H_{19}NO_6$, 369.1212; found 369.1215.

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