LABRANDINE: A NEW PENTACYCLIC PROAPORPHINE ALKALOID FROM ROEMERIA HYBRIDA

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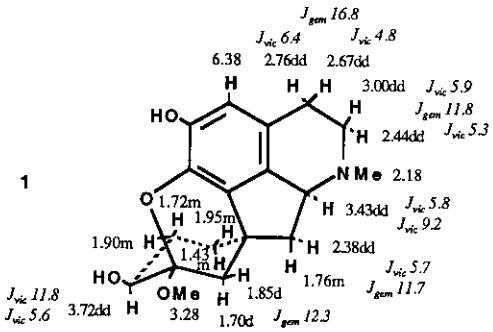
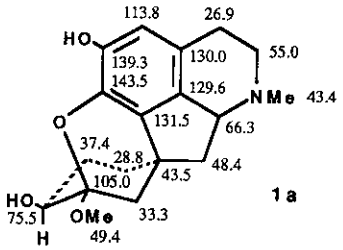
Abstract- The pentacyclic phenolic proaporphine (-)-labrandine (1) has been isolated from Turkish Roemeria hybrida (L.) DC. (Papaveraceae). O-Methylation furnished (-)-misramine (2) which is also present in the plant. Acetylation of 1 afforded (-)-2,10-diacetyllabrandine (3), and selective deacetylation of the latter provided (-)-10-acetyllabrandine (4).

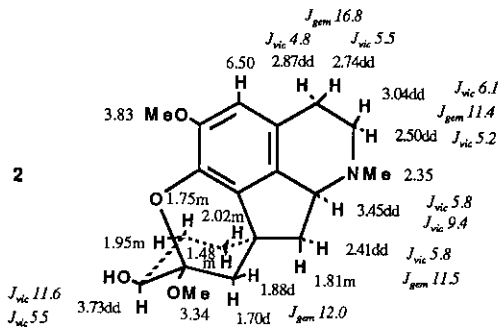
The proaporphine alkaloids are of more than passing interest since some of them have demonstrated antidepressive, hypotensive, local anesthetic and analgesic activity.[1-3] Our previous studies on Turkish Roemeria hybrida (L.) DC. (Papaveraceae) have shown this annual to be a rich repository of novel proaporphines along with some already known alkaloids of that group.[4] Presently, a further investigation of R. hybrida has afforded the amorphous phenolic proaporphine (-)-labrandine (1), $C_{18}H_{23}NO_4$. This alkaloid is a further example of the unusual pentacyclic proaporphine skeleton represented so far only by the prototype (-)-misramine (2) which was originally found in Egyptian R. hybrida.[5]

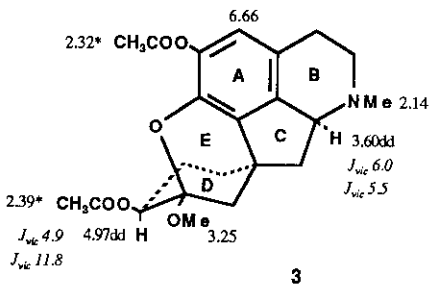
The presence of only one aromatic singlet at δ 6.38, an aliphatic methoxyl at δ 3.28, a relatively upfield N-methyl resonance at δ 2.18 and a complex pattern of aliphatic protons were characteristic features of the 360 MHz ^1H nmr spectrum of (-)-labrandine which has been summarized around expression 1. Complete chemical shift assignments of aliphatic protons were made possible through spin-decoupling and carbon-hydrogen correlated nmr experiments. The ^{13}C nmr spectral assignments are shown around expression 1a.

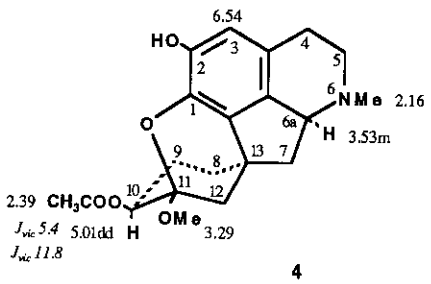
The mass spectral fragmentation pattern was reminiscent of that for (-)-misramine (2).[5] The molecular ion (m/z 317) was 89% of the base peak (m/z 316). As expected, the uv spectrum displayed a distinct bathochromic shift upon addition of alkali, indicating the phenolic nature of the alkaloid.











Acetylation of (-)-lahrandine (1) with acetic anhydride in pyridine afforded (-)-2,10-diacetyl-labrandine (3), $C_{22}H_{27}NO_6$, whose nmr spectrum displayed two acetyl methyl singlets at δ 2.32 and 2.39. The chemical shift of H-10 fell at δ 4.97 as compared to δ 3.72 in the parent alkaloid. The aromatic H-3 singlet was also shifted downfield upon acetylation by about 0.3 ppm since that proton is now ortho to an acetoxyl function. The mass spectrum displayed molecular ion m/z 401 (21%). An acetyl fragment was readily expelled to produce the m/z 358 (28%) ion.

Interestingly, routine addition of alkali to a methanolic solution of diacetate 3 during measurement of uv absorption resulted in a bathochromic shift after about five seconds, pointing to the generation of a phenolic species. Experiments were, therefore, conducted to define further the behavior of (-)-2,10-diacetyllabrandine (3) with alkali.

When diacetate 3 was treated with 1N NaOH for 15 minutes at room temperature, facile deacetylation furnished the parent compound 1. Selective deacetylation was next attempted using a less basic reagent. Reaction of 3 with 5% aqueous Na_2CO_3 for 15 minutes at room temperature provided a product in high yield distinctly different by tlc from either 1 or 3. The mass spectrum of this new compound displayed molecular ion m/z 359, indicating a monoacetylated derivative of (-)-labrandine. The ^1H nmr spectral results are presented around expression 4. It will be noted that the chemical shift of H-10 (δ 5.01) is very close to the corresponding value for the diacetyl derivative 3 (δ 4.97), indicating that deacetylation had taken place selectively at the alternate C-2 site. These results are consonant with the finding that our new product, namely (-)-10-acetyllabrandine (4), $C_{20}H_{25}NO_5$, displayed a bathochromic shift in its uv spectrum upon addition of base due to its phenolic character.

Diazomethane O-methylation of (-)-labrandine (1) furnished, as expected, the known (-)-misramine (2) which is also present in the plant. In previous work on (-)-misramine, chemical shifts were reported in C_6D_6, a solvent which certainly provides better resolution of the aliphatic proton resonances.[5] However, in the present study, ^1H nmr chemical shifts for (-)-misramine in $CDCl_3$ are reported around structure 2 to facilitate future comparisons.

The possible biogenesis of (-)-labrandine (1) would parallel that already discussed for its analog (-)-misramine (2).[5]

EXPERIMENTAL

Optical rotations are at 25° C. ^1H And ^{13}C nmr spectra were recorded at 360 and 90.56 MHz, respectively, in $CDCl_3$ solution. Column chromatography was on Merck Kieselgel 60, 70-230 mesh; and tlc was on Merck silica gel glass plates, 0.25 mm in thickness.

Plant Collection and Extraction, and Alkaloid Isolation. R. hybrida was collected near Kula, along the Izmir-Uşak highway, on April 22, 1988. The plant was identified by Dr. M. Ali Önür of Ege University. A voucher specimen, No. 1091, was deposited in the herbarium of the Pharmacognosy Department, Ege University. The air-dried powdered plant (8.8 kg) was extracted for 5 days with cold EtOH (250 l) to furnish 915 g of crude extract. This was acidified with 5% HCl and filtered. The acid soln was basified with NH_4OH and extracted with $CHCl_3$ to give 25 g of crude alkaloids. Preliminary separation of the alkaloids was achieved on a chromatographic column. Elution was with $CHCl_3$ gradually enriched with MeOH; one l fractions were collected. Fraction No. 33, eluted with 5% MeOH, and fraction No. 44, eluted with 7.5% MeOH, were further fractionated by additional column chromatography. Final purification was by tlc. Thus, fraction No. 33 afforded (-)-misramine (2) (7 mg), and fraction No. 44 furnished (-)-labrandine (1) (375 mg).

(-)-Labrandine (1). Amorphous, uv λ max MeOH 215, 229sh, 286 nm (log ε 4.24, 3.96, 3.45); λ max MeOH+OH^- 221, 247, 300 nm (log ε 4.27, 3.88, 3.62); ir ν max $CHCl_3$ 3670, 3550, 3010, 2995, 2930, 2830, 1490, 1435, 1350, 1320, 1275, 1255, 1210 cm^{-1}; eims m/z (%) 317 (M^+, 89), 316 (100), 303 (18), 302 (90), 300 (19), 299 (29), 298 (60), 285 (16), 284 (80), 274 (43), 256 (70), 242 (21), 241 (19), 230 (16), 216 (34), 215 (16); high res. eims M^+ calc'd for $C_{18}H_{23}NO_4$ 317.1627, found. 317.1619; [α]D -120° (c 0.22, MeOH) and -145° (c 0.12, $CHCl_3$).

(-)-2,10-Diacetyllabrandine (3). (-)-Labrandine (21 mg) was treated with pyridine (0.3 ml) and acetic anhydride (1 ml) overnight. Work-up afforded amorphous 3 (19 mg); uv λ max MeOH 210, 224sh, 281 nm (log ε 4.26, 3.97, 3.24); λ max MeOH+OH^- 213, 248, 300 nm (log ε 4.33, 3.69, 3.50); ir ν max $CHCl_3$ 2980, 2920, 2820, 1755, 1730, 1600, 1485, 1420, 1350, 1320, 1210 cm^{-1}; eims m/z (%) 401 (M^+, 21), 400 (18), 358 (28), 342 (70), 341 (25), 340 (23), 326 (23), 300 (47), 299 (21), 298 (73), 284 (32), 257 (21), 256 (100), 238 (18), 216 (14); [α]D -120° (c 0.12, MeOH).

(-)-10-Acetyllabrandine (4). Diacetate 3 (9 mg) in MeOH (5 ml) was treated with 5% aq Na_2CO_3 (0.5 ml). The mixture was kept at room temp for 15 min. Following acidification with 1N HCl, the MeOH was evaporated. Basification with NH_4OH was succeeded by extraction with $CHCl_3$. Solvent evaporation and tlc gave amorphous 4 (8 mg); uv λ max MeOH 212, 227sh, 286 nm (log ε 4.25, 3.76, 3.26); λ max MeOH+OH^- 216, 248, 300 nm (log ε 4.29, 3.66, 3.41); ir ν max $CHCl_3$ 3540, 3000, 2985, 2920, 1720, 1585, 1480, 1420, 1350, 1320, 1220 cm^{-1}; eims m/z (%) 359 (M^+, 10), 358 (12), 316 (10), 301 (12), 300 (63), 299 (48), 298 (51), 285 (18), 284 (100), 256 (46), 241 (12), 216 (27); [α]D -106° (c 0.18, MeOH).

Conversion of (-)-Labrandine (1) to (-)-Misramine (2). Alkaloid 1 (19 mg) in MeOH (2 ml) was treated with ethereal CH_2N_2 at room temp for 15 h. Work-up led to 16.5 mg of amorphous material identical with 2 (nmr, ms, uv, tlc, optical rotation).

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