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A NEW CLASS OF ISOQUINOLINE ALKALOIDS: THE PROAPORPHINE-TRYPTAMINE DIMERS

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Abstract: The previously isolated Roemeria hybrida (Papaveraceae) alkaloids (-)-roehybridine and (-)-roemeridine are the first proaporphine-tryptamine dimers, and possess structures 1 and 2, respectively.

Roemeria hybrida (L.) DC. (Papaveraceae) was first investigated by a Russian team in the 1950's, as a consequence of which the alkaloid (-)-roemeridine, $C_{31}H_{39}N_3O_5$, m.p. 236-237° C (MeOH), was isolated but its structure not determined.[2] Work on R. hybrida was resumed in the 1970's in Czechoslovakia when (-)-roemeridine was reisolated, and the isomeric (-)-roehybridine, m.p. 210-211° C (MeOH) was also obtained.[3] Spectral data were duly reported, but the structures still remained unknown. (-)-Roemeridine is readily soluble in MeOH and less so in $CHCl_3$, whereas (-)-roehybridine is poorly soluble in MeOH and easily soluble in $CHCl_3$.[3]

We have now reisolated these alkaloids from R. hybrida of Turkish origin, and have determined that (-)-roehybridine is represented by structure 1 and (-)-roemeridine by 2.

Our previous studies on R. hybrida had established this annual as a rich source of proaporphines.[4] Since both (-)-roemeridine and (-)-roehybridine possess three nitrogen atoms, it was logical to assume that we were dealing with proaporphine-tryptamine dimers, with the proaporphine accounting for one of the nitrogens and the tryptamine moiety for the remaining two. Significantly, the mass spectrum of (-)-roehybridine (1) displayed molecular ion m/z 533 and base peak m/z 244, $C_{14}H_{16}N_2O_2$, due to the β-carboline type ion 3.

The 360 MHz ^1H spectrum of (-)-roehybridine in $CDCl_3$ has been summarized around expression 1. Most prominent are the three aromatic singlets at δ 6.97, 6.93 and 6.52 assigned to H-5', H-2' and H-3, respectively; and the five methyl singlets at δ 3.94, 3.93, 3.85, 3.38 and 2.46, corresponding to the 4'-OMe, 3'-OMe, 2-OMe, 9-OMe and 6-NMe, respectively. A broad exchangeable proton appears at δ 8.48 and can be assigned to 1'-NH.

Among the aliphatic protons, the equatorial H-9 (δ 3.45) appears furthest downfield and was shown to be geminal to the axial 9-OMe by mutual NOE's. The H-6a signal is at δ 3.35 and overlaps with that for H-7α. The clear doublet of doublets at δ 1.54 for H-7β indicates a trans relationship to H-6a ($J_{6a,7\beta}$ = 10.3 Hz), and a gem relationship to H-7α ($J_{7\alpha,7\beta}$ = 10.8 Hz).

The seven aliphatic protons of ring D can be divided into two spin systems. Long range W couplings between H-9eq (δ 3.45) and H-11eq (δ 1.70), as well as between H-8eq (δ 2.04) and H-12eq (δ 1.40) established that ring D is in a chair conformation and that the hydrogens in question are equatorial. It follows that the 9-OMe group (δ 3.38) is axial.

A 4% NOE of the H-8eq signal (δ 2.04) was observed upon irradiation of H-7α (δ 3.35). Similarly, the H-12eq signal (δ 1.40) was enhanced when H-7β (δ 1.54) was saturated. In turn, irradiation of the H-8eq (δ 2.04) signal effected an enhancement of the 9-OMe (δ 3.38). This is another indication that the aliphatic methoxyl on ring D is at C-9 and is axially oriented as shown in expression 1.

The stereochemistry at the C-10 spiro center was defined through further NMR NOE measurements. Irradiation of either the H-11ax (δ 2.23) or the 9-OMe (δ 3.38) signals led to enhancements of the broad 1'-NH signal (δ 8.48).

A ^{13}C NMR spectrum was obtained which confirmed the novel carbon skeleton of (-)-roehybridine. Of particular interest was the quaternary spiro C-10 resonance which was at δ 54.3, while that for the spiro C-12a appeared at δ 45.3. One-bond carbon-proton couplings were observed using an XH correlated two-dimensional sequence. Quaternary carbons were identified through two and three-bond couplings analyzed by a COLOC experiment.[5]

Turning now to (-)-roemeridine (2), it was clear that the mass spectral, UV and IR data were close to those for (-)-roehybridine (1). The telling differences were in the aliphatic region of the NMR spectra. ^{1}H NMR spectra (500 MHz) were obtained in $CDCl_3$ as well as in CD_3OD. The results in $CDCl_3$ are given around expression 2, and in CD_3OD around 2A.

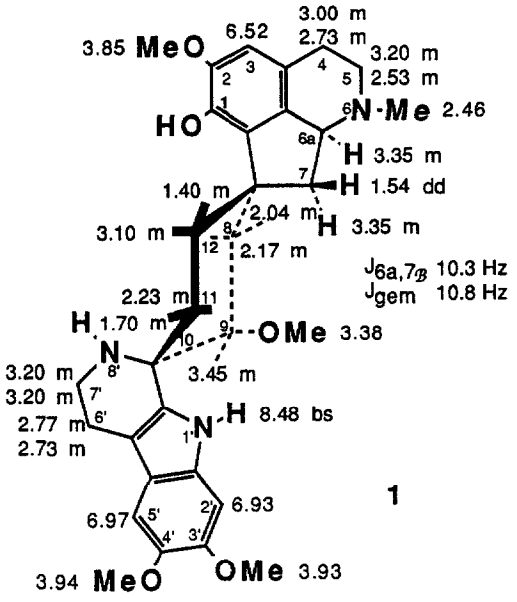
In CD_3OD, the aromatic singlets at δ 7.23, 6.93 and 6.63 were assigned to H-2', H-5' and H-3, respectively. The resonances for the 3'-OMe, 2-OMe, 4'-OMe, 11-OMe and 6-NMe groups were found at δ 3.88, 3.88, 3.84, 3.25 and 2.35, in that order. The 1'-NH could not be observed but was evident as a broad singlet at δ 8.66 in $CDCl_3$.

The assignments of the protons for ring D in (-)-roemeridine (2) proved more challenging than for 1 due to slight motion within that ring, with a resulting broadening of the resonances. In particular, the ring D methoxyl singlet changed from a narrow resonance in the case of (-)-roehybridine (1) to a short broad peak at δ 3.25 (CD_3OD) in (-)-roemeridine (2A), while it was not possible to observe small, long range, W couplings. However, the couplings for H-11 (δ 3.66) in CD_3OD showed this hydrogen to be equatorial, with J values of 5.8 Hz with respect to H-12ax (δ 2.07) and 3.2 Hz with respect to H-12eq (δ 2.01).

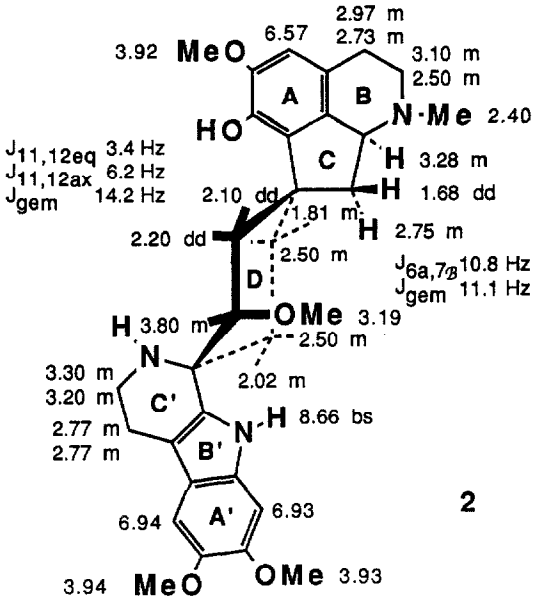
NMR NOE measurements for 2 were run in $CDCl_3$ as well as in CD_3OD, and the results proved complementary. In $CDCl_3$, irradiation of 1'-NH (δ 8.66) induced enhancement of 11-OMe (δ 3.19). In CD_3OD, the corresponding 11-OMe signal, now at δ 3.25, was enhanced by irradiation of H-7β (δ 1.54). Also, the NOE between H-11 and H-12eq was almost identical to that between H-11 and H-12ax, indicating the axial disposition of the 11-OMe group.

The ^{13}C NMR spectrum of (-)-roemeridine in CD_3OD showed close agreement with that for (-)-roehybridine; and again XH correlated and COLOC experiments were employed.

The presence in R. hybrida of diastereomeric proaporphines such as (-)-roemerialinone and (-)-isoroemerialinone has already been demonstrated.[4] It appears, therefore, as if this


3.00 m
2.73 m
3.85 MeO
6.52
3.20 m
2.53 m
HO
N-Me 2.46
H 3.35 m
H 1.54 dd
1.40 m
2.04 m
H 3.35 m
3.10 m
2.17 m
J6a,7β 10.3 Hz
Jgem 10.8 Hz
2.23 m
H 1.70 m
OMe 3.38
3.20 m
3.20 m
3.45 m
2.77 m
2.73 m
N-H 8.48 bs
6.97
6.93
3.94 MeO
OMe 3.93

1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6.57
3.10 m
2.50 m
A
B
HO
N-Me 2.40
J11,12eq 3.4 Hz
J11,12ax 6.2 Hz
Jgem 14.2 Hz
C
H 3.28 m
2.10 dd
H 1.68 dd
1.81 m
H 2.75 m
2.20 dd
2.50 m
J6a,7β 10.8 Hz
Jgem 11.1 Hz
D
H 3.80 m
OMe 3.19
2.50 m
3.30 m
3.20 m
C'
2.02 m
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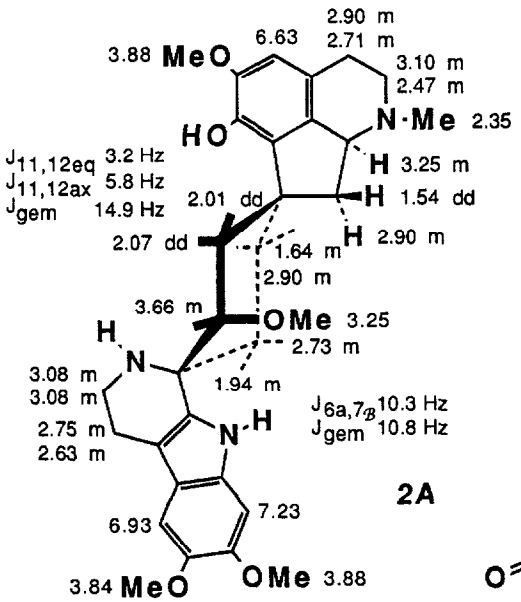
2.77 m
B'
N-H 8.66 bs
6.94
A'
6.93
3.94 MeO
OMe 3.93

2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6.63
3.10 m
2.47 m
HO
N-Me 2.35
J11,12eq 3.2 Hz
J11,12ax 5.8 Hz
Jgem 14.9 Hz
H 3.25 m
2.01 dd
H 1.54 dd
2.07 dd
1.64 m
H 2.90 m
2.90 m
3.66 m
OMe 3.25
2.73 m
3.08 m
3.08 m
1.94 m
J6a,7β 10.3 Hz
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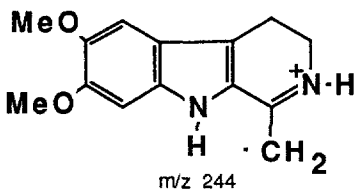
2.75 m
2.63 m
7.23
6.93
3.84 MeO
OMe 3.88

2A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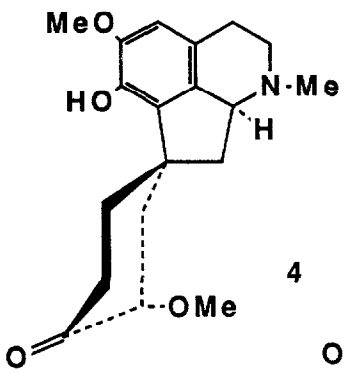
N
H
CH2
m/z 244

3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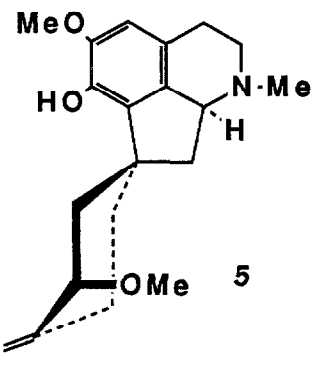
HO
N-Me
H
OMe
O

4


MeO
HO
N-Me
H
OMe
O

5

plant can also produce a diastereomeric pair of ketonic reduced proaporphines, 4 and 5, which can undergo in vivo Pictet-Spengler condensation with a tryptamine analog to afford alkaloids 1 and 2. In support of this thesis is the fact that simple tricyclic alkaloids derived from tryptamine via Pictet-Spengler condensation are known to occur among the Papaveraceae.[6]

The absolute configuration at C-6a for proaporphines from R. hybrida is known to be S.[4] It follows that (-)-roehybridine (1) and (-)-roemeridine (2) must also incorporate that stereochemistry.

EXPERIMENTAL

R. hybrida (10 kg) was collected near Uşak. The powdered plant was extracted with cold EtOH. Acid-base separation provided 50 g of crude alkaloids. This was fractionated first on a silica gel column, and then by TLC on silica gel to afford 1 (1 g) and 2 (2 g).

(-)-Roehybridine (1): $[\alpha]_D$ -16° (c 0.056, MeOH). Principal NOE's in $CDCl_3$ 1'-NH to H-2' 10%, H-2' to 1'-NH 9%, 3'-OMe to H-2' 26%, 4'-OMe to H-5' 25%, H-5' to 4'-OMe 30%, H-5' to H-6' 5%, H-6' to H-5' 10%, H-9 to H-8eq 4%, H-9 to H-8ax 5%, H-8eq to 9-OMe 6%, H-11ax to 1'-NH 2%, 9-OMe to 1'-NH 2%, H-7α to H-8eq 4%, H-7β to H-12eq 3%, H-4 to H-3 7%, 2-OMe to H-3 24%, H-3 to 2-OMe 11%.

(-)-Roemeridine (2): $[\alpha]_D$ -21° (c 0.075, MeOH). Principal NOE's in $CDCl_3$ 1'-NH to H-2' 7%, H-2' to 3'-OMe 32%, 3'-OMe to H-2' 26%, 4'-OMe to H-5' 26%, H-5' to 4'-OMe 34%, H-6' to H-5' 5%, H-6a to H-7α 4%, H-7α to H-6a 3%, H-6a to 6-NMe 4%, 6-NMe to H-6a 7%, H-4 to H-3 5%, H-3 to 2-OMe 22%, 2-OMe to H-3 26%, 1'-NH to 11-OMe 2%; NOE's in CD_3OD H-2' to 3'-OMe 13%, 3'-OMe to H-2' 23%, H-5' to 4'-OMe 12%, 4'-OMe to H-5' 18%, H-6' to H-5' 3%, H-11 to 11-OMe 3%, 11-OMe to H-11 13%, H-11 to H-12ax 3%, H-11 to H-12eq 3%, H-11 to H-7' 3%, H-9ax to H-8eq 4%, H-7β to 11-OMe 5%, 6-NMe to H-7β 5%, 6-NMe to H-6a 9%, 6-NMe to H-5 8%, H-6a to 6-NMe 3%, H-5 to 6-NMe 3%, H-4 to H-3 2%, H-3 to 2-OMe 12%, 2-OMe to H-3 14%.

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