THE STEREOCHEMISTRY AT C-13 FOR THE PROAPORPHINE-BENZYLISOQUINOLINE ALKALOIDS

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Abstract —— Berberis actinacantha Mart. ex Schult. (Berberidaceae) has yielded
the new proaporphine-benzylisoquinolines (+)-epiberbivaldine (13) and (+)-
rupancamine (15). The first of these dimers belongs to the epi stereochemical
series, while the second incorporates the normal stereochemistry at C-13.

Proaporphine-benzylisoquinoline dimers have been found only among the Berberidaceae.[1] They originate biogenetically from intramolecular oxidative coupling of the bisbenzylisoquinoline (+)-berbamunine (1) or one of its close relatives.[2] Proaporphine-benzylisoquinolines may be subdivided into two classes. The more common and hitherto the more prevalent class is represented by the alkaloid (+)-pakistanamine (2) and its analogs (+)-valdiberine (3), (+)-berbivaldine (4), (+)-valdivianine (5) and (+)-patagonine (6) which incorporate the "normal" stereochemistry at the spiro C-13 center. When treated with acid, these alkaloids rearranged to aporphine-benzylisoquinoline dimers 7-11, respectively, substituted at C-1,2,9,10 on the aporphine moiety.[2,3]

The less common variety of proaporphine-benzylisoquinolines included, up to the present study, only (+)-epivaldiberine (12) which rearranged to an analog of the C-1,2,10,11-substituted aporphine-benzylisoquinoline 14. Valdiberine and epivaldiberine were both found in Berberis valdiviana. But whereas 15 mg of (+)-valdiberine (3) were obtained from 10 kg of the plant, only 1 mg of the diastereomeric (+)-epivaldiberine (12) could be found.[3] Although never specifically so stated, one was thus left with the lingering impression that proaporphine-benzylisoquinolines of the normal series were more common and prevalent than those of the epi series.

The stereochemistry at C-13 of (+)-pakistanamine (2) and its analogs of the normal series was originally determined by a detailed NMR NOEDS study on 2. But the stereochemistry of (+)-epivaldiberine (12) was deduced indirectly mainly through its rearrangement product (analog of 14),

since insufficient amounts were available for NOEDS.[3] Presently, we have found that B. actina-
cantha Mart. ex Schult. (7.28 kg) produces an array of proaporphine-benzylisoquinolines includ-
ing (+)-pakistanamine (2) (5 mg), (+)-berbivaldine (4) (4 mg) and (+)-patagonine (6) (60 mg).[4]

The most significant product found, however, was the new amorphous dimer (+)-epiberbivaldine (13),
$C_{36}H_{38}N_2O_6$, ν max $CHCl_3$ 1645, 1675, 3555 cm^{-1}, diastereomeric with (+)-berbivaldine (4), and
obtained in the relatively generous amount of 45 mg. The 360 MHz $CDCl_3$ NMR spectrum has been sum-
marized around expression 13. The ring D vinylic doublet at δ 6.36 is diagnostic of the epi series,
and so is the well defined A_2B_2 system at δ 6.89 d and 6.99 d due to the protons of ring C'.[3]

Since, for the first time, we had on hand a dimer of the epi series in sufficient amounts, the
alkaloid was subjected to an NMR NOEDS analysis[5] to confirm independently the stereochemistry at
C-13.[6] The results are presented around expression 13-NOE. A telling feature is the 13.8% NOE
of H-12 (δ 6.36) upon irradiation of H-6a (δ 3.34), so that these hydrogens must be proximate.

The mass spectrum of (+)-epiberbivaldine (13) includes molecular ion m/z 594 (19), and base ion
m/z 192 representing rings A' and B' of the tetrahydrobenzylisoquinoline moiety.[7]

Final proof of structure was supplied by the acid catalyzed rearrangement of (+)-epiberbivaldine
(13) to the amorphous (-)-aporphine-benzylisoquinoline 14, $C_{36}H_{38}N_2O_6$.[8] The 200 MHz NMR $CDCl_3$
spectrum is quoted around expression 14. Significantly, the downfield aromatic absorption near
δ 8.1 due to H-11 of an aporphine is missing since that site is substituted.

Another new proaporphine-benzylisoquinoline dimer we subsequently obtained from the same source
is the amorphous and monophenolic (+)-rupancamine (15), $C_{37}H_{40}N_2O_6$, ν max $CHCl_3$ 1645, 1670, 3550
cm^{-1}.[9] This normal alkaloid was present in lesser amount (23 mg) than epiberbivaldine (13) (45 mg).
In the 200 MHz $CDCl_3$ spectrum (expression 15), the ring D vinylic doublet is relatively upfield at
δ 5.92, in accord with the normal stereochemistry.[3] Furthermore, the A_2B_2 system representing the
ring C' protons falls between δ 6.94 and 7.00, and is less well delineated than in epiberbivaldine.
The mass spectrum shows molecular ion m/z 608 (6), and base peak m/z 192.[9]

To complete the structure elucidation, rupancamine was rearranged to amorphous aporphine-benzyl-
isoquinoline (+)-16, $C_{37}H_{40}N_2O_6$, whose NMR spectrum (200 MHz, $CDCl_3$) included a singlet at δ 8.10
representing H-11.[10]

The isolation of relatively large amounts of epiberbivaldine, accompanied by other proaporphine-
benzylisoquinolines of the alternate normal stereochemistry, indicates that both series may exist
in a plant in abundance. The amounts present probably depend upon the different enzymes respons-
ible for the intramolecular oxidative coupling of the bisbenzylisoquinoline precursor(s).
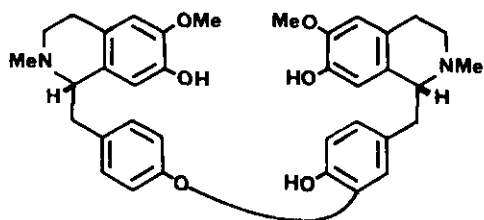
1
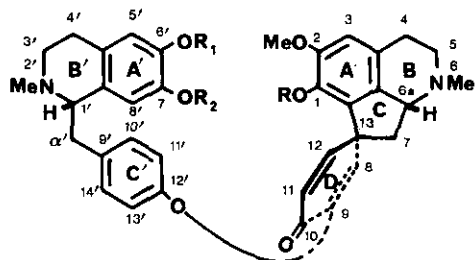
2 R=R₁=R₂=Me   **3** R=R₂=H, R₁=Me

4 R=R₁=H, R₂=Me   **5** R=H, R₁=R₂=Me

6 R=R₁=Me, R₂=H
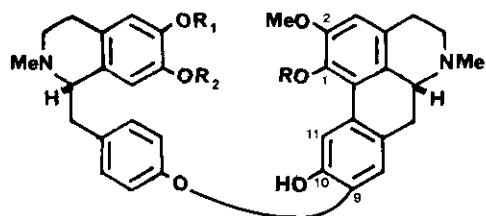
7 R=R₁=R₂=Me   **8** R=R₂=H, R₁=Me

9 R=R₁=H, R₂=Me   **10** R=H, R₁=R₂=Me

11 R=R₁=Me, R₂=H

12

$J_{6a,7\beta}$ 6.2 Hz
$J_{6a,7\alpha}$ 10.4 Hz
$J_{7\alpha,\beta}$ 11.9 Hz

13

13-NOE

14

6.55* OH
2.56: MeN 3.40
H OMe
5.78
6.82d J_o 8.7 Hz
6.84d
6.82d
J_o 8.7 Hz 6.64 d

6.57* MeO
3.84 2.48:
HO NMe
H
7.13 d
J_o 8.1 Hz
6.97 d

15

6.63* OH
MeN 3.21
2.54 H OMe
5.77
7.00 d J_o 8.9 Hz
6.94 d
7.00 d
J_o 8.9 Hz 6.94 d

3.81 MeO 6.56*
3.64 NMe
MeO 2.37
J_m 2.6 Hz
7.03 dd
J_o 9.8 Hz 5.92 d
6.36 d J_m 2.6 Hz
O

16

6.63: OH
2.55* MeN 3.64
H OMe
6.05
7.10 d
J_a 8.7 Hz
6.99 d
7.10 d
J_o 8.7 Hz
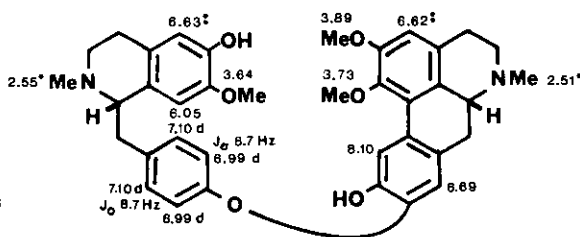6.99 d

3.89 MeO 6.62:
MeO NMe 2.51*
3.73
8.10
HO 6.69
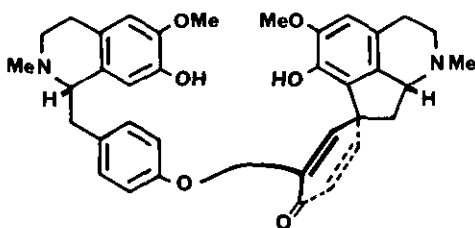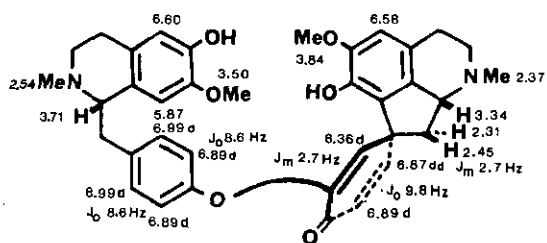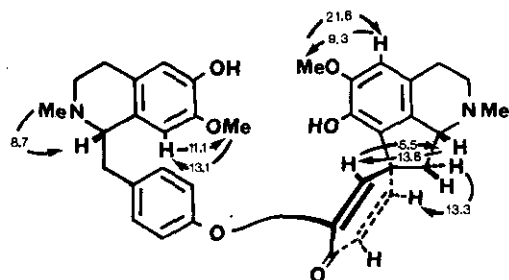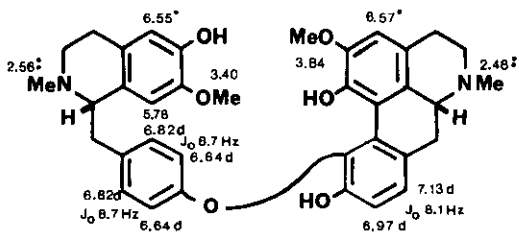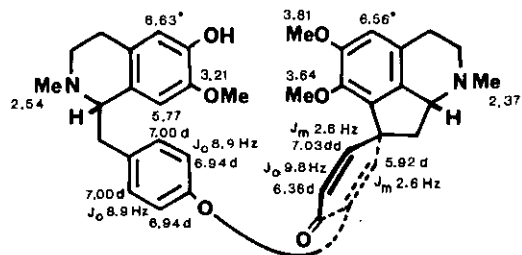
Chemical shifts with
identical superscripts
are interchangeable.

REFERENCES AND FOOTNOTES

1. For a recent listing of the aporphine- and proaporphine-benzylisoquinoline dimers, together with their spectral characteristics, see H. Guinaudeau, M. Leboeuf and A. Cavé, *J. Nat. Prod.*, in press.

2. M. Shamma, J.L. Moniot, S.Y. Yao, G.A. Miana and M. Ikram, *J. Am. Chem. Soc.*, 1973, **95**, 5742.

3. H. Guinaudeau, V. Elango, M. Shamma and V. Fajardo, *J. Chem. Soc.*, *Chem. Commun.*, 1982, 1122.

4. B. actinacantha was collected in Cerro Lo Curro, Santiago. The powdered plant was first defatted with petroleum ether. Extraction was with cold ethanol. The extracts were fractionated using 3N HCl and then dil. ammonium hydroxide. They were finally subjected to extensive column chromatography on silica gel, and thin layer chromatography on preprepared Merck Silica Gel G glass plates.

5. L.D. Hall and J.K.M. Sanders, *J. Am. Chem. Soc.*, 1980, **102**, 5703.

6. Proaporphine- as well as aporphine-benzylisoquinoline dimers derived from two coclaurine units always possess the C-6a(R) and C-1'(S) absolute configuration. See refs. 2 and 3 above.

7. (+)-Epiberbivaldine (13), $[\alpha]_D^{25}$ +45.7° (c 0.12, CHCl$_3$); λ max MeOH 233, 286 nm (log ϵ 4.47, 3.98); m/z 595 (M + 1)$^+$ (7), 594 (M)$^+$ (19), 593 (M – 1)$^+$ (15), 403 (3), 402 (3), 297 (2),

295 (3), 294 (3), 293 (2), 193 (13), 192 (100), 191 (36), 190 (14), 177 (11), 176 (7), 175 (7), 175 (5), 174 (12), 168 (6), 162 (3), 161 (3), 148 (6), 146 (4), 145 (5), 132 (2), 107 (2).

8. (+)-Epiberbivaldine (13) was treated with 1N HCl at 90° C for 2 h. The product, dimer (-)-14, exhibited $[\alpha]_D^{25}$ -77.7° (c 0.09, CHCl$_3$); λ max MeOH 222 sh, 273, 295 sh, 309 sh nm (log ε 4.55, 4.13, 3.98, 3.93); m/z 594 (M)$^+$ (0.1), 593 (M - 1)$^+$ (0.2), 403 (3), 402 (1), 297 (4), 296 (7), 295 (9), 281 (2), 280 (4), 279 (2), 278 (3), 265 (3), 264 (3), 263 (2), 251 (2), 250 (2), 236 (2), 207 (2), 206 (2), 193 (14), 192 (100), 191 (11), 190 (14), 189 (6), 188 (6), 178 (3), 177 (15), 163 (2), 162 (4), 161 (3), 160 (3), 151 (1), 150 (2), 149 (3), 148 (5).

9. (+)-Rupancamine (15), $[\alpha]_D^{25}$ +116.9° (c 0.12, CHCl$_3$); λ max MeOH 231, 285 nm (log ε 4.27, 3.49); m/z 609 (M + 1)$^+$ (2), 608 (M)$^+$ (6), 607 (M - 1)$^+$ (5), 417 (2), 416 (3), 415 (3), 310 (1), 309 (1), 294 (1), 293 (1), 280 (1), 266 (1), 236 (1), 206 (2), 204 (1), 193 (14), 192 (100), 191 (4), 190 (7), 178 (2), 177 (12), 176 (2), 163 (2), 162 (2), 161 (2), 160 (2), 149 (2), 148 (3), 146 (3), 145 (3), 132 (3), 131 (2), 107 (2).

10. Conditions for the acid rearrangement of 15 are identical to those described in ref. 8 above. Dimer (+)-16 exhibited $[\alpha]_D^{25}$ +42.5° (c 0.08, CHCl$_3$); λ max MeOH 229 sh, 277, 302 nm (log ε 4.87, 4.49, 4.33); m/z 608 (M)$^+$ (0.2), 607 (M - 1)$^+$ (0.3), 606 (0.2), 417 (4), 416 (6), 415 (3), 309 (1), 207 (3), 206 (9), 193 (14), 192 (100), 191 (6), 190 (8), 189 (3), 188 (3), 178 (2), 177 (9), 176 (1), 175 (1), 163 (1), 162 (2), 161 (2), 150 (2), 149 (2), 148 (3), 147 (2), 145 (2), 132 (4), 131 (3), 102 (2).

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