CHENABINE AND JHELUMINE: SECOBISBENZYLISOQUINOLINES OR SIMPLE ISOQUINOLINE-BENZYLISOQUINOLINE DIMERS?

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Abstract: *(+)-Chenabine (6) and (+)-jhelumine (7) are the first dimeric alkaloids incorporating a benzylisoquinoline bonded through a diaryl ether bridge to a simple isoquinoline. They may be formed in vivo either through cleavage of a bisbenzylisoquinoline precursor, or by oxidative coupling of the simple isoquinoline corypalline (11) with an analog of the new alkaloid (+)-karakoramine (4).*

One of the main catabolic pathways available to the bisbenzylisoquionlines in nature involves oxidative cleavage at the benzylic C-1 to C-α bond of one of the two tetrahydrobenzylisoquinoline units. This oxidation occurs preferentially at the tetrahydrobenzylisoquinoline which is unsubstituted at C-8, since the adjacent C-1 center is less sterically hindered. The resulting secobisbenzylisoquinolines are lactam aldehydes as exemplified by the alkaloids (-)-baluchistanamine (1),[2] (-)-revolutinone (2),[3] and (-)-punjabine (3).[4] Occassionally, the aldehyde function may suffer oxidation or reduction, so that secobisbenzylisoquinolines may also be lactam alcohols, lactam carboxylic acids or lactam methyl esters.[5]

In a continuing chemical study of the flora of Pakistan, we had occassion to investigate the contents of Berberis lycium Royle (Berberidaceae), from which a small sample of the new alkaloid (+)-karakoramine, $C_{25}H_{27}O_5N$, was obtained as an amorphous material.[6] The spectral profile of karakoramine is in agreement with structure 4. The UV spectrum shows a maximum at 283 nm, typical of tetrahydrobenzylisoquinolines (Table). The CD curve, with a positive tail at 212 nm, is diagnostic of the S absolute configuration. In accord with this stereochemical assignment, the alkaloid shows a positive specific rotation, $[\alpha]_D^{25}$ +71° (c 0.17, MeOH).[7]

The 200 MHz NMR spectrum ($CDCl_3$) has been summarized around expression 4. The A_2B_2 doublet of doublets appears at δ 6.92 and 7.06 (J = 8.5 Hz). These shifts are in agreement with the corresponding values for the known dimer (+)-berbamunine (5) which are at δ 6.82 and 7.03 (J = 8.5 Hz). The main feature of the mass spectrum (Table) is base peak m/z 192 representing rings A and B of the molecule.

(+)-Karakoramine (4) is the first known benzylisoquinoline derivative resulting from *in vivo* oxidation of a bisbenzylisoquinoline possessing only one diaryl linkage; as such, it lacks the lactam moiety. Its precursor may well be (+)-berbamunine (5) which we have also found in the plant.

The next new alkaloid isolated from *B. lycium* was the monophenolic (+)-chenabine (6), $C_{37}H_{40}O_7N_2$, whose IR spectrum ($CHCl_3$) shows a conjugated aldehyde carbonyl at 1680 cm^{-1}, but no lactam absorption. The UV spectrum (Table) displays a substantial bathochromic shift as well as a hyperchromic effect in base, reflecting the fact that the phenolic function lies para to the aldehyde group. The 360 MHz NMR spectrum ($CDCl_3$) is described around expression 6. Noteworthy are the upfield C-7' methoxyl singlet at δ 3.25 and the upfield H-8 singlet at δ 5.23 consonant with a conformation in which the phenolic function is hydrogen bonded to the nitrogen as indicated in expression 6a.[8] The 7'-methoxyl is shielded by ring A, while H-8 is in the shielding region of ring C. In CD_3OD solution, intramolecular hydrogen bonding is minimized, so that the 7'-methoxyl signal falls at δ 3.48 and that for H-8 is at 5.75.

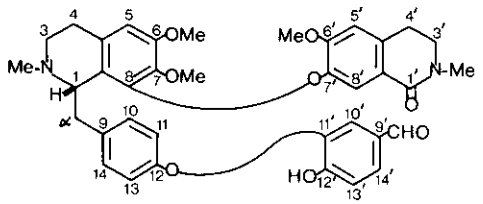
Since NMR NOE measurements are ideally suited to the structural elucidation of dimeric isoquinoline bases,[9] this analytical method was applied to chenabine (6). The results corroborate the structural assignment, and are summarized around expression 6a. Irradiation of H-8 (δ 5.23) leads to a 1.8% enhancement of the H-1 signal (δ 3.52), as well as to a 2.2% enhancement of the δ 6.77 broad singlet which represents H-10 and 14 as well as H-11 and 13. Furthermore, irradiation of the 7'-methoxyl absorption (δ 3.25) results in 1.7% and 0.7% enhancements of the H-8 (δ 5.23) and H-10,11,13,14 signals, respectively.

The mass spectrum of chenabine (6) (Table) shows molecular ion m/z 624 which was also confirmed by CI as well as FAB mass spectroscopy. The rest of the spectrum reflects cleavage at the C-1 to C-α benzylic bond with formation of peaks m/z 397 (a) (base) and 227 (b).

Acetylation of 6 with acetic anhydride in pyridine led to O-acetylchenabine, $C_{39}H_{42}O_8N_2$ whose mass spectrum (Table) still showed base peak m/z 397 congruent with placement of the phenolic function in 6 in the lower half of the molecule.

The CD spectrum of chenabine (6) (Table) has a positive tail beyond 217 nm due to the S configuration at C-1. The positive sign of the specific rotation, $[\alpha]_D^{25}$ +40° (c 0.18 MeOH) also confirms this stereochemical assignment.[7]

The third new alkaloid obtained from *B. lycium* is the diphenolic (+)-jhelumine (7), $C_{36}H_{38}O_7N_2$, which is more polar than chenabine. The IR spectrum again shows an aldehyde carbonyl absorption at 1680 cm^{-1}. The UV spectra in neutral and basic solutions are generally similar to those for chenabine (Table). The NMR spectrum (360 MHz) as shown in expression 7 is nearly identical with that of



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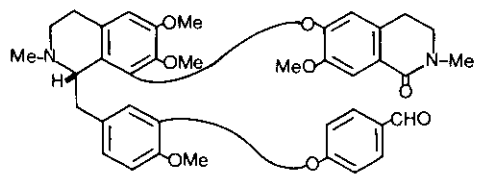

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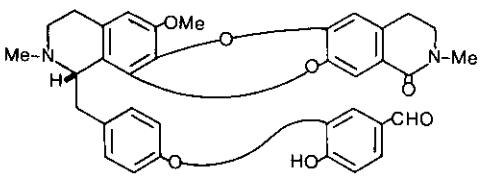

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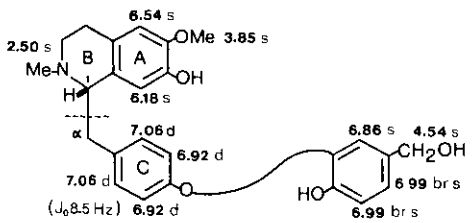

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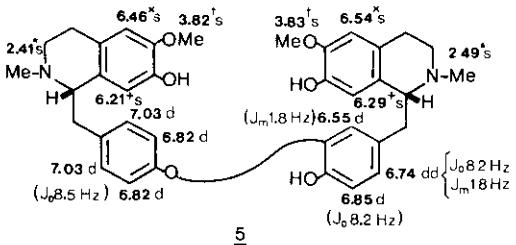

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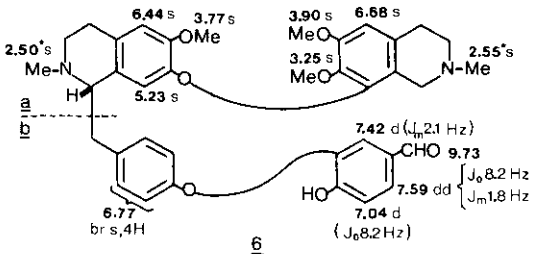

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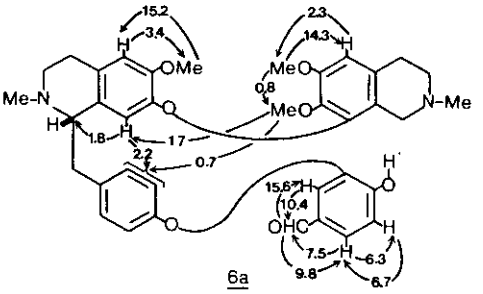
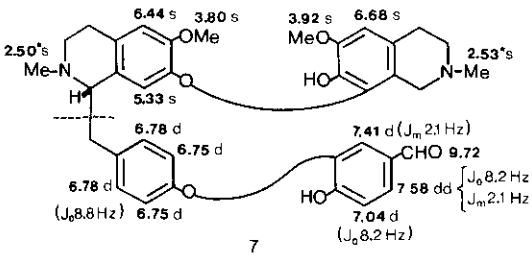


6a



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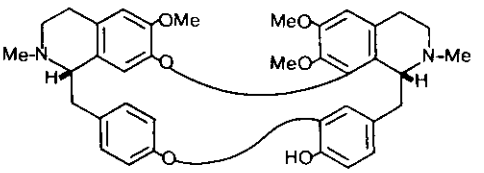

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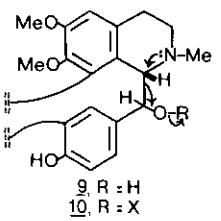
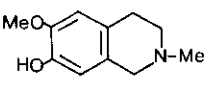


9, R = H
10, R = X



11

Chemical shifts with identical superscripts are interchangeable.

6, except for the absence of the δ 3.25 methoxyl resonance. The mass spectrum (Table) has peak m/z 610 (M^+). Cleavage at the benzylic C-1 to C-α bond gives base peak 383 (a) and peak 227 (b). Jhelumine has a CD curve with a positive tail beyond 217 nm (Table), and a positive rotation, $[\alpha]_D^{25}$ +28° (c 0.6, MeOH), mirroring the fact that structures 6 and 7 possess the identical configuration.[10]

Chenabine (6) and jhelumine (7) raise an interesting problem in biogenesis. Two pathways are possible for their formation. It may be that they originate from cleavage of a bisbenzylisoquinoline possessing two diaryl ether bridges such as the commonly occurring (+)-berbamine (8) or one of its analogs. In such a sequence, the bisbenzylisoquinoline would first undergo benzylic oxidation at C-α to yield alcohol 9. If leaving group X now replaces the alcoholic hydrogen, the alkaloid can undergo benzylic cleavage as indicated in expression 10 to yield an aldehydo iminium salt. This material can then suffer reduction at the iminium center to provide chenabine or jhelumine. Such a cleavage of benzylisoquinoline has never been formally demonstrated, but it should nevertheless be considered a possibility.[11] One factor mitigating against this sequence, however, is that the original bisbenzylisoquinoline would have to undergo oxidation at the more hindered, and hence the less reactive benzylic site.

An alternate and equally plausible biogenetic route would start with the aldehyde analog of karakoramine (as in 4, but with CH_2OH replaced by CHO) which can be considered to be the direct product of in vivo benzylic oxidation of a bisbenzylisoquinoline incorporating only one diaryl bridge. Phenolic oxidative coupling of this phenolic aldehyde with the simple isoquinoline corypalline (11) can lead to jhelumine (7), whose O-methylation would furnish chenabine (6). Partial support for this route comes from the finding that karakoramine (4) is present in the plant. If this route obtains, chenabine and jhelumine could be considered the first examples of simple isoquinoline-benzylisoquinoline dimers.

TABLE: Spectral Characteristics of New Alkaloids[12]

(+)-Karakoramine (4): λ max (MeOH) 208, 226 sh, 283 nm (log ε 4.56, 4.30, 3.75); ms m/z 420 $(M - 1)^+$ (0.2), 403 (0.4), 192 (100); CD Δε(nm) (MeOH) +2(285), 0(265), +7.4(230), +6(222), +14(212).

(+)-Chenabine (6): λ max (MeOH) 209, 227 sh, 281, 326 nm (log ε 4.72, 4.49, 4.08, 3.87); λ max ($MeOH,OH^-$) 211, 283, 342 nm (log ε 4.83, 3.91, 4.28); ms m/z 624 (M^+) (0.2), 397 (100), 365 (17), 227 (4), 222 (2), 206 (4); CD Δε(nm) (MeOH) 0(310), +4(287), 0(270), +8.3(236), 0(217), +10(210).

(+)-Chenabine Acetate Ester: NMR 360 MHz ($CDCl_3$) δ 2.26 (3H, s, $COCH_3$), 2.42 and 2.46 (2 x 3H, 2s, 2 NCH_3), 3.68, 3.81 and 3.92 (3 x 3H, 3s, 7'-OCH_3, 6-OCH_3 and 6'-OCH_3, respectively), 6.21, 6.54 and 6.66 (3 x 1H, 3s, H-8, H-5 and H-5', respectively), 6.82 and 7.02 (4H, dd, J_o 8.5 Hz, H-10,11,

13,14), 7.30 (1H, d, J_o 8.2 Hz, H-13'), 7.33 (1H, d, J_m 2.0 Hz, H-10'), 7.60 (1H, dd, J_o 8.2 Hz, J_m 2.0 Hz, H-14'), 9.87 (1H, s, CHO); ms m/z 666 (M^+) (0.3) 624 (0.2), 623 (0.4), 397 (100), 269 (0.2).

(+)-Jhelumine (7): λ max (MeOH) 211, 227 sh, 281, 326 nm (log ε 4.72, 4.56, 4.17, 3.89); λ max (MeOH-OH^-) 214, 233 sh, 287, 341 nm (log ε 4.78, 4.47, 4.07, 4.31); ms m/z 610 (M^+) (0.1), 609 (0.4), 608 (0.5), 383 (100), 227 (4), 192 (26); CD Δε(nm) (MeOH) 0(310), +2.3(286), 0(270), +5.3 (235), 0(217), +7(210).

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References and Footnotes

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6. Ten kg (dry) of B. lycium collected in the Murree Hills of northern Pakistan yielded 2 mg of 4, 15 mg of 5, 36 mg of 6, and 11 mg of 7.
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8. Similar intramolecular hydrogen bonding has been observed with the bisbenzylisoquinoline thalibrunine, see J. Wu, J. L. Beal and R. W. Doskotch, J. Org. Chem., 45, 208 (1980).
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10. It will be noted that baluchistanamine (1), revolutinone (2) and punjabine (3) are levorotatory while karakoramine (4), chenabine (6) and jhelumine (7) are dextrorotatory, even though they all incorporate the identical absolute configuration. This apparent delinquency in the optical data is due to substitution at C-8 in species 1-3, which forces the lower pendant aromatic rings to lie on the same side as the basic nitrogen, with a resulting change in the sign of the specific rotation. The same phenomenon is observed with simple monomeric tetrahydrobenzylisoquinolines, see D. R. Dalton, M. P. Cava and K. T. Buck, Tetrahedron Lett., 2687 (1965); J. Fridrichsons and A. Mc.L. Mathieson, Tetrahedron, 24, 5785 (1968); and M. Shamma and J. L. Moniot, Isoquinoline Alkaloids Research, 1972-1977, Plenum Press, New York (1978), pp. 51-52.
11. An equivalent free radical mechanism could also apply.
12. All compounds are amorphous. TLC R_f values in $CHCl_3$-MeOH-NH_4OH (90:10:1 v/v) on Merck Silica Gel F-254 glass plates are for karakoramine 0.22, for chenabine 0.46, and for jhelumine 0.29.

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