Gandharamine: A New Benzylisoquinoline Alkaloid from Berberis baluchistanica

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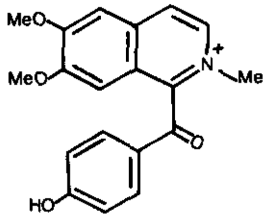
Gandharamine (1) is a new quaternary oxobenzylisoquinolinium alkaloid found in Berberis baluchistanica Ahrendt (Berberidaceae), as well as in Thalictrum fendleri Engelm. ex Gray (Ranunculaceae). Its synthesis from dihydrobenzylisoquinoline 4 has been achieved. The only known naturally occurring close analog of gandharamine is N-methylpapaveraldine (7).

Berberis baluchistanica Ahrendt (Berberidaceae), native to Pakistan, has proven a rich repository of novel tertiary isoquinoline alkaloids including the proaporphine-benzylisoquinoline pakistanamine,[3] the aporphine-benzylisoquinoline pakistanine,[3,4] and the isoquinolone-benzylisoquinoline baluchistanamine.[5] Presently, investigation of the polar quaternary alkaloid fraction from 15 kg of dried plant material has yielded 17 mg of the new amorphous and optically inactive oxobenzylisoquinoline alkaloid gandharamine (1) chloride, $C_{19}H_{18}O_4NCl$, λ_{max}^{EtOH} 255, 316 and 365 nm (log ε 4.07, 3.65 and 3.73), λ_{min}^{EtOH} 278 and 335 nm (log ε 3.43 and 3.62), λ_{max}^{EtOH,H^+} 253 and 313 nm (log ε 3.98 and 3.72), λ_{min}^{EtOH,H^+} 273 nm (log ε 3.96). The alkaloid is phenolic since the uv spectrum in base shows a bathochromic shift, $\lambda_{max}^{EtOH,OH^-}$ 253, 323sh and 365 nm (log ε 4.09, 3.63 and 3.89), $\lambda_{min}^{EtOH,OH^-}$ 278 nm (log ε 3.43).

The nmr spectrum in TFA-d includes three singlets at δ3.96, 4.27 and 4.32, which can be assigned to one N-methylimino and two aromatic methoxyl groups, respectively. H-3 and H-4 appear as a doublet of doublets at δ8.29 and 8.34 (J = 6.8 Hz), while the remaining six aromatic protons are represented by a broad singlet centered at δ7.21 and a sharp singlet at 7.63. The mass spectrum exhibits peaks m/e 324 (M^+, $C_{19}H_{18}NO_4$) (1.6), 323 $(M - 1)^+$ (7.4), and 44 (100).

Sodium borohydride in methanol reduction of gandharamine chloride at room temperature overnight afforded the amorphous diastereomeric alcohols 2a and 2b, $C_{19}H_{23}O_4N$, in a 1:3 ratio. The mass spectra of both alcohols show an $(M - H_2O)^+$ peak m/e 311, and a base peak m/e 206. The respective nmr spectra in $CDCl_3$ have been summarized in expressions 2a and 2b.

Acetylation of the major alcohol 2b with acetic anhydride in pyridine overnight furnished diacetate 3, $C_{23}H_{27}O_6N$. The $CDCl_3$ nmr downfield shift of the ring C protons of 3 relative to



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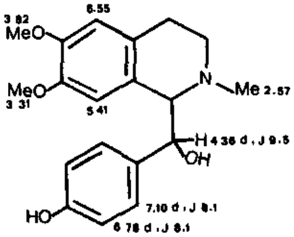
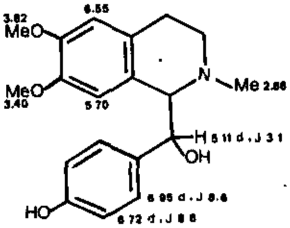
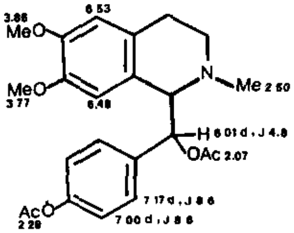


2a



2b



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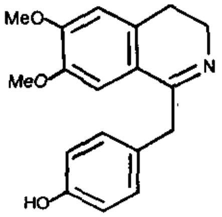

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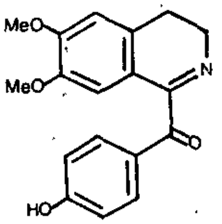

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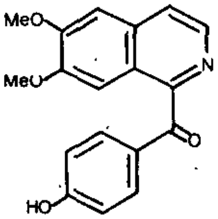

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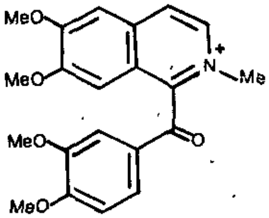

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those of alcohol 2b locates the phenolic group of gandharamine (1) at C-4' rather than in ring A.

The structural assignment for gandharamine was confirmed by its synthesis from the known dihydrobenzylisoquinoline 4.[6] Oxidation of an ethanolic solution of this imine by bubbling a stream of air for three days[7] provided a 24% yield of the imino ketone 5, $C_{18}H_{17}O_4N$, mp 142-144° C (CH_2Cl_2), $\nu_{max}^{CHCl_3}$ 1600, 1660 and 3450 cm^{-1}, which was dehydrogenated using Pd/C in refluxing xylene overnight to furnish amorphous benzylisoquinoline 6 (66%), $C_{18}H_{15}O_4N$, $\nu_{max}^{CHCl_3}$ 1660 and 1690 cm^{-1}.[8] N-Methylation of 6 with methyl iodide in refluxing acetonitrile overnight afforded yellow needles of gandharamine (1) iodide, 75%, $C_{19}H_{18}O_4NI$, mp 185-186° C (methanol-ether).[9] Conversion to the amorphous chloride salt was achieved by passing a solution of the iodide in 1:1 methanol-acetone through an Amberlite CG-400 chloride anion exchange column. The chloride salt proved to be identical with gandharamine chloride obtained from the plant isolation sequence.

In some early isolation work in our laboratory carried out in the 1960's,[10] a quaternary alkaloidal chloride salt was obtained from *Thalictrum fendleri* Engelm. *ex* Gray (Ranunculaceae), native to Utah, which was not fully characterized at the time due to paucity of material. We have now found that the *T. fendleri* alkaloid is identical in terms of nmr and uv spectra, as well as tlc R_f values, with gandharamine chloride.

It is interesting to note that gandharamine (**1**) is the first known naturally occurring quaternary oxobenzylisoquinolinium salt belonging to the coclaurine series. Its sole counterpart in the reticuline series is N-methylpapaveraldine (**7**) found in *Stephania sasakii* Hayata (Menispermaceae).[11]

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References and Footnotes

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8. The $CDCl_3$ nmr spectrum of benzylisoquinoline **6** exhibits δ3.96 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 6.73 (d, 2H, J = 8.5 Hz, H-3' and 5'), 7.16 and 7.52 (2s, 2H, H-5 and 8), 7.73 (d, 2H, J = 8.5 Hz, H-2' and 6'), 7.73 (d, 1H, J = 4.3 Hz, H-4), and 8.45 (d, 1H, J = 4.3 Hz, H-3).
9. Gandharamine iodide shows ms m/e 323 $(M - 1)^+$ (3.5), and 142 (base); ν_{max}^{KBr} 1590, 1645, 3070 and 3380 cm^{-1}; nmr (DMSO-d_6) δ 3.71 (s, 3H, NCH_3), 4.07 (s, 3H, C-7 OCH_3), 4.14 (s, 3H, C-6 OCH_3), 6.87 and 7.87 (2s, 2H, H-5 and 8), 6.94 (d, 2H, J = 8.6 Hz, H-3' and 5'), 7.80 (br d, 2H, H-2' and 6'), 8.43 (d, 2H, J = 6.9 Hz, H-4) and 8.68 (d, 2H, J = 6.9 Hz, H-3).
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12. NMR spectra are at 200 MHz (FT) with TMS as internal standard. All tlc was on Merck silica gel F-254 glass plates. TLC R_f values are as follows: Gandharamine (**1**) chloride 0.48 (chloroform-methanol-HCl_g (50:50:trace), gandharamine iodide 0.28 (*n*-butyl alcohol—acetic acid-water 60:10:27), minor alcohol **2a** 0.58 (diethylamine-chloroform 10:90), major alcohol **2b** 0.52 (diethylamine-chloroform 10:90), diacetate **3** 0.40 (methanol-chloroform 2:98).

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