CHITRALINE AND 1-O-METHYLPAKISTANINE, TWO APORPHINE-BENZYLISOQUINOLINE ALKALOIDS†

S. Fazal Hussain,[1] Lajber Khan[1] and Maurice Shamma*,

Department of Chemistry, The Pennsylvania State University,

University Park, Pennsylvania 16802

†Dedicated to Professor Tetsuji Kametani

Berberis orthobotrys has yielded the new alkaloid chitraline (2) which is the first known naturally occurring analog of pakistanine (1). Another alkaloid present is 1-O-methylpakistanine (4) which had been previously derived in vitro from pakistanamine (5) through an acid catalyzed dienone-phenol rearrangement. Known alkaloids also present in the plant are pakistanamine (5) and pakistanine (1).

At the initiation of the present work, the alkaloid pakistanine (1), present in Berberis baluchistanica Ahrendt (Berberidaceae), was the only aporphine-benzylisoquinoline dimer known to be derived biogenetically from the condensation of two coclaurine-type units.[2] In an effort to find other alkaloids of this specific class, six kilograms of the roots of Berberis orthobotrys Bienert ex Aitch. were collected in the mountainous region of Chitral, in northwestern Pakistan. The resulting five kilograms of dried roots were extracted with cold ethanol. Solvent evaporation followed by acid extraction and basification yielded 36 g of a crude alkaloidal fraction.

Chromatography of a small sample of this fraction on Merck silica gel F-254 thin layer plates using the developing system $CHCl_3$-$HN(Et)_2$ (90:10), and the iodoplatinate spray reagent[3] for visualization, showed a number of spots, a few of which turned green after about 6-10 hours. This behavior is characteristic of aporphines or aporphine dimers possessing a phenolic function at the aporphine C-1 position.[4]

A clearly defined spot with R_f 0.27 was quickly identified as being due to pakistanine (1), but another spot, R_f 0.10, appeared to represent a new phenolic aporphine-benzylisoquinoline dimer.

In order to isolate the alkaloid with R_f 0.10, a 9 g portion of the crude alkaloidal fraction was repeatedly subjected to thin layer chromatography using the system described above. Twenty milligrams of the new amorphous aporphine-benzylisoquinoline dimer chitraline (2) were thus obtained, $C_{36}H_{38}N_2O_6$, $[\alpha]_D^{25}$ +136° (MeOH, c = 0.172). The mass spectral breakdown pattern with m/e 593 $(M - 1)^+$, 401 (M - a - H), 192 (base, a) and 177 (a - CH_3) is strongly suggestive

of an aporphine-benzylisoquinoline of the pakistanine series possessing three phenolic functions, one of which is located in ring A of the benzylisoquinoline moiety.

The uv spectrum of chitraline (2), λ_{max}^{MeOH} 220sh, 268sh, 278, 292sh and 304 nm (log ε 4.51, 4.03, 4.10, 3.94 and 3.96) is closely related to that of pakistanine (1),[2] again denoting an overall similar oxygenation pattern for the two alkaloids.

Inspection of the nmr spectrum of chitraline (2) (Table) confirmed the kinship between compounds 1 and 2; the one obvious difference being the presence in the chitraline spectrum of only two methoxyl singlets instead of the three found in pakistanine (Table).

Acetylation of chitraline (2) with acetic anhydride in pyridine at room temperature affords 1,10,7'-tri-O-acetylchitraline (3), $C_{42}H_{44}N_2O_9$, m/e 719 $(M - 1)^+$, 677, 486, 485, 444, 443, 401, 234 (base), 192 and 177; $\nu_{max}^{CHCl_3}$ 1760 cm^{-1}; R_f 0.54. The most salient feature of the nmr spectrum of 3 is the chemical shift of the H-8' proton singlet which appears at δ6.53, downfield from the corresponding shift of δ6.37 for chitraline (2) (Table), due to acetylation of the neighboring C-7' phenolic function. Furthermore, the upfield shift of H-11 from δ8.12 to 7.69 upon acetylation of chitraline (2) to the triacetate 3 compares favorably with a similar shift from δ8.13 to 7.73 following conversion of pakistanine (1) to its di-O-acetyl derivative.[2] It follows that chitraline, just like pakistanine, incorporates phenolic groups at C-1 and C-10.

The CD curve of chitraline (2) in methanol shows $\Delta\varepsilon_{nm}$ $+12.29_{310}$, $+14.04_{272}$, -52.68_{244} and $+35.12_{215}$. These values are comparable to those of pakistanine (1), $\Delta\varepsilon_{nm}$ $+17.62_{310}$, $+32.04_{274}$, -52.86_{244} and $+80.10_{212}$, so that both compounds must possess the identical absolute configuration.

In addition to pakistanine (1) and chitraline (2), a spot with R_f 0.47 was present upon thin layer chromatography of the crude alkaloidal fraction, and was quickly recognized to be due to 1-O-methylpakistanine (4). This compound had previously been prepared in vitro by the acid catalyzed dienone-phenol rearrangement of the proaporphine-benzylisoquinoline alkaloid pakistanamine (5), and both the natural and the semi-synthetic materials were found to exhibit identical nmr spectra (Table) and tlc R_f values.[2]

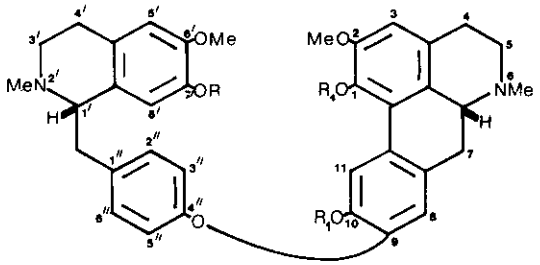
Pakistanamine (5), R_f 0.57, is abundant in B. baluchistanica[2] and is also the main alkaloid in B. orthobotrys. The fact that chitraline (2) is present in B. orthobotrys in addition to 1-O-methylpakistanine (4), while the only proaporphine-benzylisoquinoline found is pakistanamine (5), lends support for the belief that chitraline and by extension 1-O-methylpakistanine are true alkaloids rather than artefacts produced through a dienone-phenol rearrangement during the acidic treatment of the plant extract. More significantly, ethanol extraction of the alkaloids of B. calliobotrys Bienert ex Aitch., which also grows in Chitral, without the use of acid at any stage, showed the presence of pakistanamine (5) and pakistanine (1), thus demonstrating that the dienone-phenol rearrangement is a natural process.[5,6]

TABLE

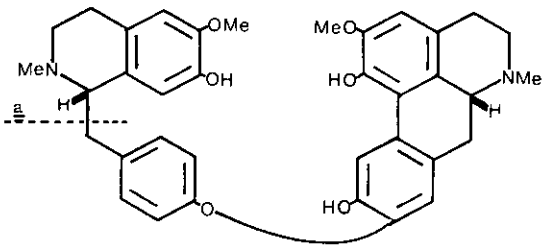
NMR Resonances at 200 MHz (FT) in $CDCl_3$ with TMS as Internal Standard

	N-2'	N-6	C-2	C-6'	C-7'	H-8'	H-3	H-5'	H-8	H-11	H-2'',6''	H-3'',5''
	Methylimino		Methoxyl			Aromatic Proton						
Pakistanine (1)	δ2.51	2.55	3.85	3.92	3.64	6.13	6.57	6.57	6.72	8.13	7.10d	6.98d
Chitraline (2)	2.50	2.51	3.86	3.92	-	6.37	6.54	6.57	6.75	8.12	7.01d	6.96d
1,10,7'-Tri-O-acetylchitraline (3)	2.50	2.50	3.80	3.84	-	6.53	6.65	6.67	6.82	7.69	7.11d	6.94d
1-O-Methyl-pakistanine (4)	2.50	2.55	3.84	3.89	3.64	6.11	6.57	6.61	6.70	8.11	7.10d	6.99d

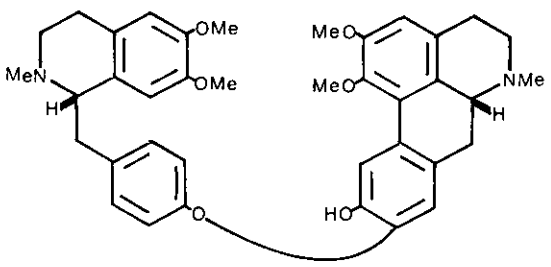
Chemical shift assignments for H-3 and H-5' are interchangeable. For compound 3, acetoxyl singlets at δ2.21, 2.28 and 2.33. Compound 4, C-1 methoxyl singlet at δ3.72. $J_{2'',3''}$ and $J_{5'',6''}$ are equal to about 8.7 Hz for each compound in the Table.



1, R = Me, R_1 = H
2, R = R_1 = H
3, R = R_1 = Ac



Mass spectral breakdown for chitraline (2)



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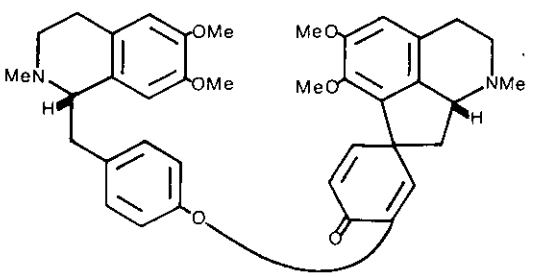

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References and Footnotes

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