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THE ABSOLUTE CONFIGURATION OF BERBERASTINE AND THALIDASTINE

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Optical resolution of (±)-tetrahydrojatrorrhizine using (-)-O,O-di-p-toluoyl-d-tartaric acid gave rise to (+)-tetrahydrojatrorrhizine (6) of high optical purity and of known absolute configuration. Oxidation of this enantiomer with lead tetraacetate, followed by acid hydrolysis, furnished alcohols 10 and 11 in a 2:1 ratio, whose relative stereochemistry was established from their nmr spectra. Iodine oxidation of the major alcohol 10 led to protoberberinium salt 14 which was found to be dextrorotatory. Since berberastine (1) and thalidastine (2) are also dextrorotatory, they must possess the same absolute configuration as 14.

The quaternary salts berberastine (1)[2] and thalidastine (2)[3] occupy a unique position within the ambit of the protoberberine alkaloids. They are the only members of this group to be hydroxylated at C-5, and their chirality has remained hitherto unknown. The problem of establishing their absolute configuration is magnified by the fact that both compounds were isolated several years ago, that they were obtained in small quantities, and more importantly that they tend to dehydrate on long standing to the corresponding ring B aromatic dehydroprotoberberinium salts, so that neither alkaloid was presently available for further investigation. What was known, however, was that both berberastine (1) iodide and thalidastine (2) chloride are dextrorotatory, the former exhibiting $[\alpha]_D$ +107° (c 0.06, 90% EtOH), and the latter $[\alpha]_D^{25}$ +138° (MeOH).

A possible scheme for the elucidation of the stereochemical problem suggested itself from the twin facts that we have found that Berberis baluchistanica Ahrendt (Berberidaceae) is a rich source of the phenolic protoberberinium salt jatrorrhizine (3),[4] while Umezawa and coworkers have established that lead tetraacetate oxidation of the tetrahydroisoquinoline 4, which incorporates a phenolic group at a position corresponding to that in jatrorrhizine (3), leads to benzylic acetoxylation with formation of compound 5.[5]

Reduction of jatrorrhizine (3) chloride with sodium borohydride provided (±)-tetrahydrojatrorrhizine which was resolved using (-)-O,O-di-p-toluoyl-d-tartaric acid in ethanol. (+)-Tetrahydrojatrorrhizine (6) was thus obtained, $C_{20}H_{23}NO_4$, mp 205-206° C decomp ($CHCl_3$-MeOH), $[\alpha]_D^{25}$ +294° (c 0.3, $CHCl_3$). The specific rotation of this enantiomer reflects its high degree of optical purity, since it is known that naturally occurring berbine alkaloids of established absolute configuration and with similar oxygenation pattern have specific rotations of about the same magnitude, although usually of different sign.[6] To cite a few examples, stepholidine (7), $[\alpha]_D$ -311° (EtOH); kikemanine (8), $[\alpha]_D$ -287° ($CHCl_3$); and tetrahydropalmatine (9), $[\alpha]_D$ -280°.[7] Furthermore, an nmr spectral study of the complexation of the acetate esters of racemic and

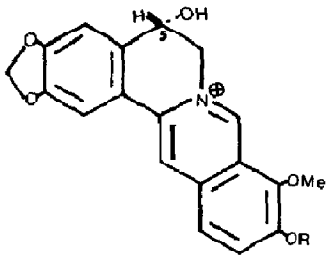
optically active tetrahydrojatrorrhizine, $C_{22}H_{25}NO_5$, mp 143-145° C (MeOH) and 178-179° C decomp. (MeOH), respectively, with the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium III indicated that 6 was of greater than 95% optical purity.[8]

By analogy with the conversion of the simple tetrahydroisoquinoline 4 to the acetoxy derivative 5 cited above, oxidation of (+)-tetrahydrojatrorrhizine (6) with lead tetraacetate in glacial acetic acid led to a mixture of diastereomeric C-5 monoacetates. Hydrolysis of this mixture using 10% hydrochloric acid afforded alcohols 10 and 11, $C_{20}H_{23}NO_5$, which could readily be separated by tlc, and were present in a 2:1 ratio. The nmr spectrum of the major alcohol 10, mp 188-189° C decomp. (MeOH), shows a broad apparent doublet for H-5 at δ4.51 (J = 8.5 Hz), and a singlet at δ6.93 representing H-4. The minor alcohol 11, mp 183-186° C decomp. (MeOH), on the other hand, exhibits an nmr spectrum whose H-5 peak appears as a quartet centered relatively downfield at δ4.86 (J = 7.0 Hz and J' = 4.8 Hz), while the H-4 singlet is found also downfield at δ7.13. The reason for these downfield shifts is that in structure 11 H-5 is proximate to the pair of non-bonded electrons on the nitrogen, and H-4 is similarly close to the pair of electrons on the quasi-equatorial alcoholic oxygen at C-5. It is relevant to point out that exactly the same spacial and nmr spectral relationships obtain within the aporphines hydroxylated at the corresponding C-4 site, one example of which has been summarized in expressions 12 and 13 below.[9] In the case of the C-4 hydroxylated aporphines, the stereochemical assignments have been further confirmed by an x-ray crystallographic analysis.[10,11]

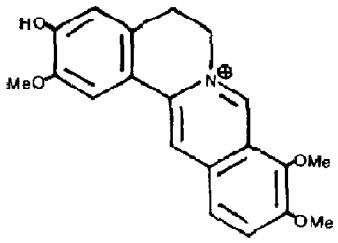
With both the relative and absolute stereochemistry of alcohols 10 and 11 firmly established, the major alcohol 10 was oxidized with iodine in ethanol. The resulting alcoholic quaternary protoberberinium salt 14, $C_{20}H_{20}NO_5I$, mp 230-232° C decomp. (MeOH), was found to be dextrorotatory $[\alpha]_D^{25}$ +152° (c 0.25, MeOH). It must, therefore, possess the same absolute configuration as berberastine and thalidastine which can now be represented by stereostructures 1 and 2, respectively.

Interesting conclusions can be drawn from the above results. The chirality of 1 and 2 corresponds to that for the simple phenethylamine alkaloids hydroxylated at the β position such as R-(-)-noradrenaline (15) also known as (-)-arterenol,[12] (-)-ubine (16),[13] (-)-normacromerine (17),[14] and (-)-longimammine (18).[13,15]

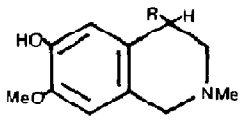
In a series of *in vivo* experiments with labeled precursors, it has been previously shown that berberastine (1) is not derived from berberine and that the C-5 benzylic hydroxyl group is generated at an early stage of biosynthesis, preceding formation of the benzylisoquinoline nucleus.[16] It therefore appears as if (-)-noradrenaline (15) or a close congener must be involved in the biogenesis of the berbines berberastine (1) and thalidastine (2), and that the integrity of the asymmetric center due to the presence of the benzylic alcohol group is maintained throughout. These conclusions stand in stark contrast to the situation prevailing among the naturally occurring C-4 hydroxylated aporphines, the majority of which possess the opposite stereochemistry at that center.[17] The exact reason for this difference in stereochemistry between berbines and aporphines possessing a benzylic hydroxyl group in ring B is presently unclear.



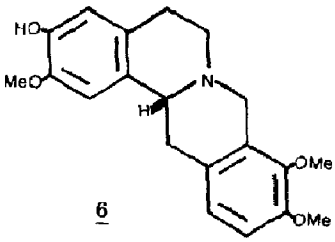
1, R = Me
2, R = H



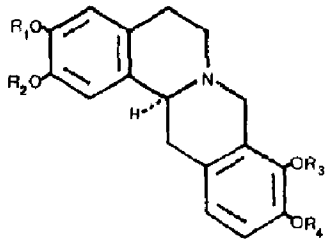
3



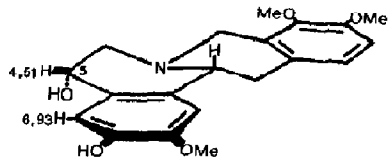
4, R = H
5, R = OAc



6



7, $R_1 = R_3 = Me$; $R_2 = R_4 = H$
8, $R_1 = R_2 = R_3 = Me$; $R_4 = H$
9, $R_1 = R_2 = R_3 = R_4 = Me$



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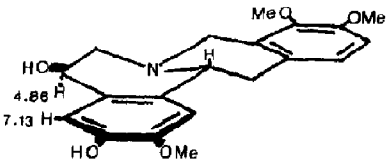

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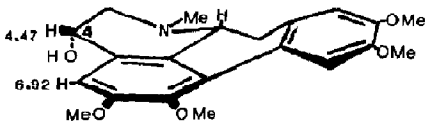
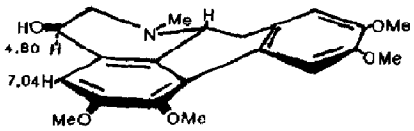


12



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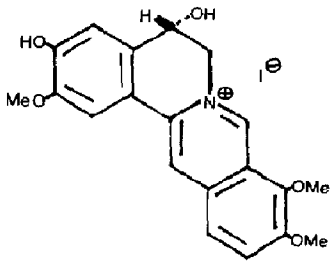
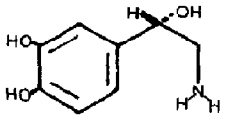


14



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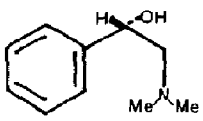
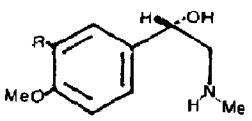


16



17, R = OMe
18, R = H

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References and Footnotes

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