

A CONVENIENT METHOD FOR THE DETERMINATION OF THE ATTACHED POSITION
OF DIPHENYL ETHER LINKAGE IN BISBENZYLISOQUINOLINE ALKALOIDS¹

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The cleavage reaction of the diphenyl ether linkage with sodium in liquid ammonia was first applied to bisbenzylisoquinoline alkaloids by Tomita and his collaborators,² and this technique has played a great role for the structure elucidation of the alkaloids of this series. However, the attached position of the diphenyl ether linkage of oxyacanthine-berbamine series alkaloids, C₅ or C₈ [see (I)], can not be determined by this method, and the available chemical method for solving this problem is costly in both time and material. We now wish to report a convenient new method to this end.

Oxyacanthine (II, R=H; 1 g), the structure of which has completely been established,³ was methylated with diazomethane. The O-methylated base was dissolved in 20 ml of 3% DCl in D₂O and the solution was heated at 120° in a sealed tube for 144 hr. After cooling, the solution was made alkaline with sodium hydroxide and extracted with ether. The ether extract was evaporated after drying over anhydrous MgSO₄ and the residue in benzene was filtered through an alumina column to give deuterated O-methyloxyacanthine as an oil. In the n.m.r. spectrum of this substance, the decrease of the signal area corresponding to 3H protons in the aromatic proton region was found by comparison with the spectrum of O-methyloxyacanthine itself.

Deuterated O-methyloxyacanthine (0.733 g) in ether was then subjected to the diphenyl ether fission reaction in the usual manner.³ To a solution of the resulting phenolic base in ethanol was added a solution of oxalic acid in ethanol. The precipitated oxalate (0.208 g) was collected by filtration, purified by recrystallization and then made free to give 0.148 g of S-[5-D]-

armepavine, mp 142.5–143° (III). The n.m.r. spectra⁴ of deuterated armepavine and armepavine itself were shown in Figure 1. Since the assignments of all aromatic protons in armepavine have been established,⁵ it is obvious that only one proton at the C₅ position in the compound (III) is deuterated.

The filtrate from filtration of the armepavine oxalate was made alkaline and the free base (0.248 g) in chloroform was purified by chromatography on an alumina column to give 0.09 g of oily R-[5,3'-D₂]-4'-O-methyl-N-methyl coclaurine (IV). In Figure 2 were shown the n.m.r. spectra of the compound (IV) and of authentic R-4'-O-methyl-N-methyl coclaurine whose aromatic proton signals have already been assigned.⁵ A detailed comparison of these spectra reveals that two aromatic protons at C₅ and C_{3'}, in the compound (IV) are deuterated.

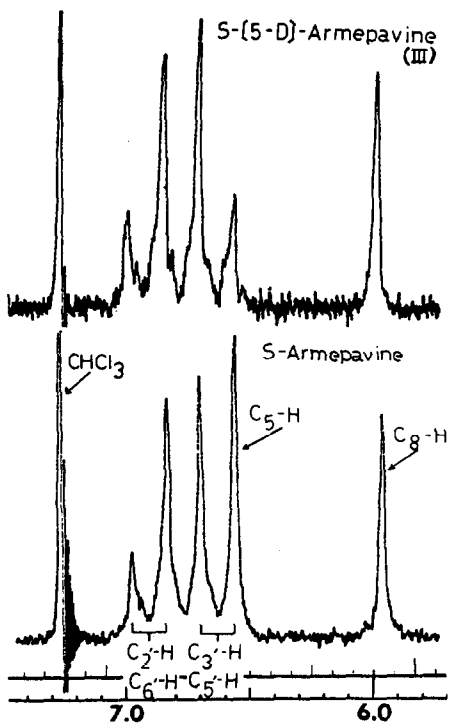


Figure 1

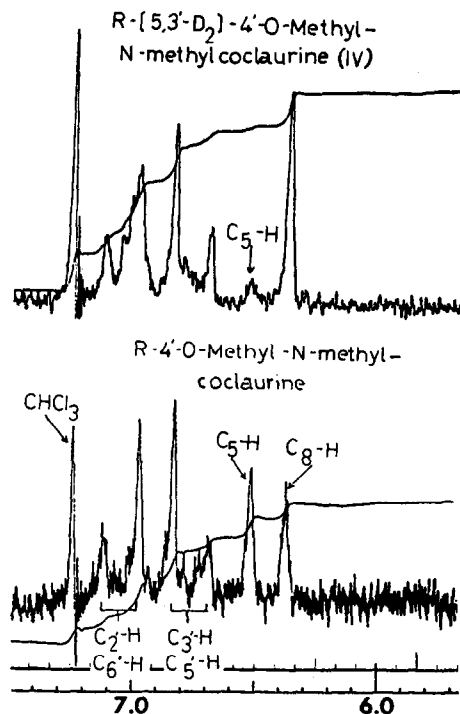
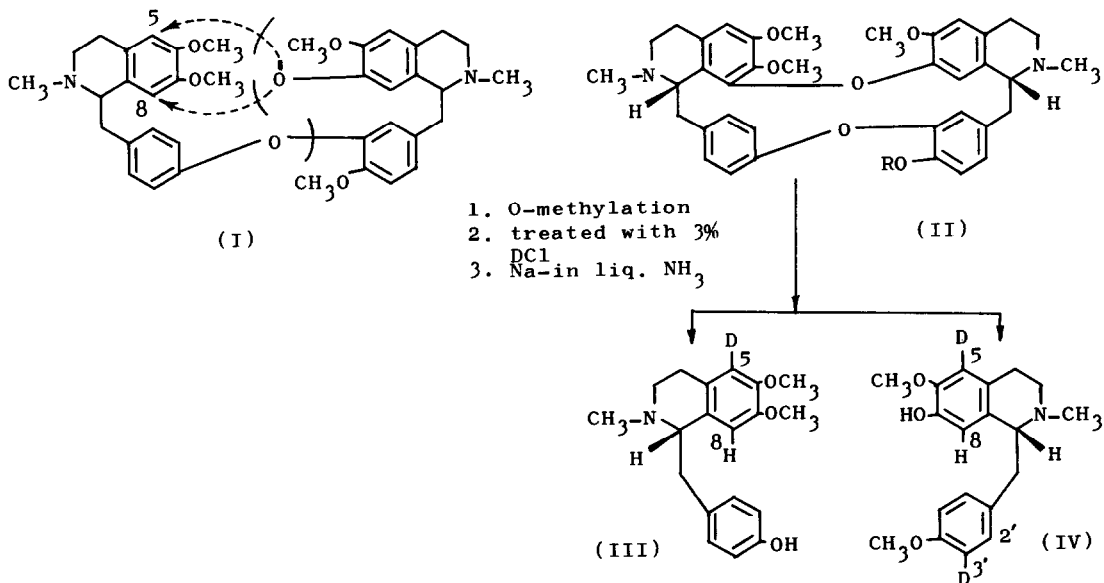


Figure 2

From the above experimental results, it is clear that only protons ortho to methoxyl groups of O-methoxyacanthine were deuterated under the exchange reaction condition employed here and that diphehyl ether linkage is attached at the C₈ of the left half tetrahydroisoquinoline moiety of the oxyacanthine molecule.



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