

THE USE OF THE INTRAMOLECULAR NUCLEAR  
OVERHAUSER EFFECT TO ESTABLISH THE POSITIONS  
OF SUBSTITUENTS IN THE AROMATIC NUCLEI  
OF THE ALKALOIDS MAJORIDINE AND O-ACETYL-  
N-METHYLLOCHNERINE

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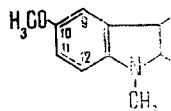
The determination of the positions of substituting groups in the aromatic nuclei of the indoline and indole alkaloids is usually performed by UV spectroscopy [1-14] and in some cases by oxidizing the alkaloids to the corresponding N-oxalylanthranilic acids [15]. Although UV spectroscopy is the simplest and most accessible method, in its use the differences in the maxima of the absorption bands in the substituted molecules of hexahydrocarbazoles [1] and indoles [14] are small. Furthermore, there is information that the number of absorption-band maxima in the indole alkaloids varies according to the position of the substituents, especially  $\text{OCH}_3$  and  $\text{OH}$ . For example, in the UV spectrum of the indole alkaloid lochnerine [11] with a  $\text{OCH}_3$  group in position 10 of the aromatic nucleus, there are two maxima - 225 and 280 nm ( $\log \epsilon$  4.45, 3.92) - and in the spectra of gardnutine and hydroxygardnutine [13], which contain a  $\text{OCH}_3$  group in position 11, there are four maxima - at 223, 260, 295, and 302 nm ( $\log \epsilon$  4.64, 3.64, 3.73, 3.63) and 223, 260, 295, and 301 nm ( $\log \epsilon$  4.61, 3.69, 3.79, 3.70), respectively.

Since the indole moiety of the alkaloids gardnutine and hydroxygardnutine is not conjugated with the chromophoric group, and their other chromophores are similar to those of lochnerine, it is difficult to explain the appearance of two new maxima in the UV spectrum of gardnutine and hydroxygardnutine only by a difference in the position of the methoxy group.

In the present paper we give the results of the use of the intramolecular nuclear Overhauser effect (NOE) to determine the position of the substituents ( $\text{OCH}_3$ ) in the aromatic nuclei of the N-methylindoline alkaloid majoridine and in O-acetyl-N-methyllochnerine [8, 9].

The great possibilities of NOE measurements for structural and stereochemical purposes have been shown previously [16, 17]. In particular, we have used this method to determine the positions of the methoxy groups in the aromatic nuclei of the hydroxyindole alkaloids majdine and isomajdine [18].

The experiments on the measurement of the NOE of majoridine and of O-acetyl-N-methyllochnerine were performed on a Varian HA-100D spectrometer ( $\text{CDCl}_3$ , internal standard HMDS). The three aromatic protons of majoridine give a spectrum of the ABC type, the chemical shifts (CSs) and spin-spin coupling constants of which can be determined approximately from the experimental spectrum (Fig. 1). If the  $\text{OCH}_3$  group is located at  $\text{C}_{10}$



the following assignments of the signals of the protons can be made: doublet with  $\tau$  3.53 ppm,  $J_{\text{ortho}}^{11,12} = 8.5$  Hz -  $\text{C}_{12}$ -H; quadruplet with  $\tau$  3.36 ppm,  $J_{\text{ortho}}^{11,12} = 8.5$  Hz and  $J_{\text{meta}}^{9,11} = 2.3$  Hz -  $\text{C}_{11}$ -H; doublet with  $\tau$  3.16 ppm,  $J_{\text{meta}}^{11,9} = 2.3$  Hz -  $\text{C}_9$ -H. Obviously,  $J_{\text{para}}^{9,12} \approx 0$ .

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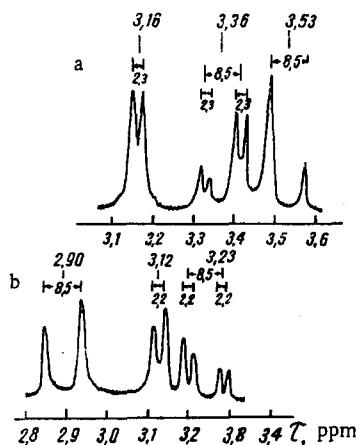


Fig. 1. Signals of the aromatic protons of majoridine (a) and of O-acetyl-N-methyllochnerine (b).

However, an alternative assignment of these signals is possible if the  $\text{OCH}_3$  group is located at  $\text{C}_{11}$ , in which case  $\tau$  3.53 ppm corresponds to  $\text{C}_9\text{-H}$ ,  $\tau$  3.36 ppm to  $\text{C}_{10}\text{-H}$ , and  $\tau$  3.16 ppm to  $\text{C}_{12}\text{-H}$ . Consequently, it is difficult from the CSs alone to make an unambiguous choice between  $\text{C}_{10}\text{-OCH}_3$  and  $\text{C}_{11}\text{-OCH}_3$  in majoridine. Hence, starting from the correlation found between the value of the NOE and the  $\text{CH}_3\text{-H}$  distance [16], it might be expected that in majoridine a NOE will be observed between the signals of the  $\text{N-CH}_3$  group (7.33 ppm) and one of the doublets at  $\text{C}_{12}\text{-H}$  (in the case of  $\text{C}_{10}\text{-OCH}_3$ , with the doublet at  $\tau$  3.53 ppm,  $J=8.5$  Hz, and in the case of  $\text{C}_{11}\text{-OCH}_3$  with the doublet at  $\tau$  3.16 ppm,  $J=2.3$  Hz). The experiment showed that on saturation of the  $\text{N-CH}_3$  signal ( $\nu_{\text{irr}}=267$  Hz) the integral intensity of the strong-field doublet with  $\tau$  3.53 ppm,  $J=8.5$  Hz, increased by  $18 \pm 2\%$ ; i.e., the NOE is 18%; the intensities of the remaining signals of the aromatic protons did not change. These results unambiguously show the correctness of the assignment of the  $\text{OCH}_3$  group to  $\text{C}_{10}$  in majoridine: if it ( $\text{OCH}_3$ ) were present at  $\text{C}_{11}$ , a NOE should have been observed between the  $\text{N-CH}_3$  group and the weak-field doublet at  $\tau$  3.16 ppm,  $J=2.3$  Hz.

The chemical shifts of the aromatic protons of O-acetyl-N-methyllochnerine differ substantially from the chemical shifts of these signals of majoridine (Fig. 1), which can naturally be explained by a difference in the  $\pi$ -electron density of the charges on the carbon atoms in the indole  $\text{N-CH}_3$  and the indoline  $\text{N-CH}_3$  systems, on the one hand, and the corresponding contribution of the ring currents of the five-membered ring to the shielding constants of the aromatic protons of the O-acetyl-N-methyllochnerine, on the other hand [19]. Just as in the case of majoridine, from the CSs of the aromatic protons of O-acetyl-N-methyllochnerine it is impossible to deduce whether the  $\text{OCH}_3$  group is attached to  $\text{C}_{10}$  or  $\text{C}_{11}$ .

However, when the  $\text{N-CH}_3$  signal was saturated ( $\nu_{\text{irr}}=346$  Hz), a NOE (13%) of the weak-field doublet with  $\tau$  2.90 ppm,  $J=8.5$  Hz, was observed, which, as in the case of majoridine, unambiguously shows the location of the  $\text{OCH}_3$  group in O-acetyl-N-methyllochnerine at  $\text{C}_{10}$ . Thus, the method of measuring the intramolecular NOE is a convenient and unambiguous one for determining the positions of substituents in the aromatic nuclei of the N-methylindoline and N-methylindole alkaloids.

## SUMMARY

The use of the NOE method has permitted the unambiguous determination of the position of the  $\text{OCH}_3$  groups at  $\text{C}_{10}$  in the aromatic nuclei of majoridine and of O-acetyl-N-methyllochnerine and has thereby shown the possibility of using this method for determining the position of substituents in the benzene rings of the N-methylindoline and indole alkaloids.

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