PROOF OF THE POSITION OF THE METHOXY GROUPS IN THE AROMATIC NUCLEUS OF MAJDINE AND ISOMAJDINE BY MEANS OF THE INTRAMOLECULAR NUCLEAR OVERHAUSER EFFECT

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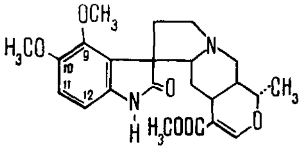
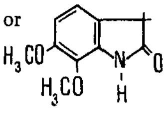
Previously, on the basis of an analysis of the NMR spectra of the hydroxyindole alkaloids majdine (I) and isomajdine (II), two possible structures (Ia or Ib) were put forward which differed in the positions of the aromatic OCH_3 groups – at C_9 and C_{10} or at C_{11} and C_{12} [1].



Ia

or



Ib

Ognyanov et al. [2, 3] came to an analogous conclusion for the alkaloids A-4 and A-5 isolated from Vinca herbacea W.K., which proved to be identical with majdine and isomajdine, respectively. These authors, by reducing majdine in dioxane in the presence of $LiAlH_4$, obtained 2-dihydroxy-2-dihydromajdinol (III), in the NMR spectrum of which the signals of the aromatic protons gave two doublets at δ 6.38 and 6.79 ppm, $J = 8.0$ Hz. In acetylated (III), i.e., in N_a,O-diacetyldihydromajdinol (IV) the signals of these protons were found at 6.92 and 7.12 ppm, $J = 9.0$ Hz, respectively, and, therefore, the relative chemical shifts (CS) $\Delta\delta_1 = \Delta\delta_{IV} - \Delta\delta_{III} = 0.54$ ppm and $\Delta\delta_2 = 0.33$ ppm, respectively. Considering these shifts of the aromatic protons to be small and taking into account the fact that their CS's in (IV) are comparable with the signals of the protons at C_{14} (C_9) and C_{15} (C_{10}) in alkaloids of the indole series, they decided in favor of the location of the OCH_3 groups in (I) and (II) at C_{11} and C_{12}. It must be mentioned that although in the majority of cases the N-acylation of indole, indoline, and hydroxyindole alkaloids leads to a considerable paramagnetic shift with $\Delta\delta = 0.75$–1.73 ppm of the aromatic protons at C_{12} [4-8], nevertheless, there are cases in which this shift may be small. For example, in the acetylation of the hydroxyindole alkaloid vinerine* the relative CS for C_{12}–H is only 0.47 ppm, i.e., smaller than $\Delta\delta$ in (IV). Thus, the value of 0.54 ppm of the relative CS of the aromatic proton during the acylation of N–H in (III), which also depends on the orientation of the C=O group of the N-acyl residue [9], still does not prove the position of the OCH_3 groups at C_{11}–C_{12} in (I) and (II).

In order to prove the substitution of the methoxy groups in the aromatic nucleus of majdine and isomajdine unambiguously, we have used the method of measuring the intramolecular nuclear Overhauser effect (NOE). This method has been widely and successfully used recently in the solution of structural and, in particular, stereochemical problems of the spirobenzylisoquinoline [10-12], hasubanane [13, 14], and other alkaloids [15]. Bell and Saunders [11], generalizing experimental results on the NOE for various compounds, have established that the value of the NOE correlates with the distance between the H–H and CH_3–H nuclei. Consequently, it could be expected that if a methoxy group were located at C_{12} in (I) and

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*Details will be published later in Khim. Prirodn. Soedin.

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(II) a NOE should be observed between the N−H and the OCH_3 signals. Otherwise, a NOE could be detected between the signals of the N−H proton and one of the doublets of the aromatic protons.

The NOE for isomajdine was measured on a Varian-HA-100D instrument ($CDCl_3$; internal standard HMDS), since the signals from the two aromatic OCH_3 groups in it are separated, while in majdine they give a single six-proton singlet. The experiment showed that when the signal of one of the OCH_3 groups of isomajdine was saturated at 3.81 ppm ($\nu_{obs} = 381$ Hz), the integral intensity of the N−H proton at δ 8.76 ppm increased by 15%, and when the signal of the second OCH_3 group with $\nu = 378$ Hz was irradiated, the integral intensity of the doublet at δ 6.47 ppm, J = 8.0 Hz, increased by 27%.

Consequently, the experimental observation of a NOE (15%) between the signals of the OCH_3 protons and the N−H unambiguously shows that the methoxy groups in (I) and (II) are located at C_{11} and C_{12}. Furthermore, the results of the measurement of the NOE permit the following assignments of the signals of the OCH_3 and the aromatic protons in isomajdine: δ 3.81 ppm, the OCH_3 at C_{12}; δ 3.78 ppm, the OCH_3 at C_{11}; doublet with δ 6.47 ppm, J = 8.0 Hz, C_{10}−H; and doublet with δ 6.86 ppm, J = 8.0 Hz, C_9−H.

SUMMARY

On the basis of measurements of the NOE, the position of the aromatic methoxy groups in majdine and isomajdine at C_{11} and C_{12} has been shown unambiguously, and an assignment has been made of the aromatic protons at C_9 and C_{10}.

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