A STUDY OF THE STEREOCHEMISTRY OF THE ALKALOIDS CODONOPSINE AND CODONOPSININE BY THE NMR-SPECTROSCOPIC METHOD

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Structures for the new alkaloids codonopsine (I) and codonopsinine (III) isolated from Codonopsis clematidea have been proposed previously [1, 2] on the basis of chemical reactions and spectral characteristics (Fig. 1).

In order to establish the spatial structue of these alkaloids, we have studied the NMR spectra of the bases and their acetyl derivatives (II and IV) (see Fig. 1 and Table 1).

The NMR spectrum of (I) (Fig. 1, I) clearly shows the signals of all the methyl protons: singlets at 6.26 and 6.36 ppm (each 3H – two aromatic $-OCH_3$ groups), singlet at 7.82 ppm ($-N-CH_3$), and doublet at 8.72 ppm [3H, J = 6.5 Hz ($-CH-CH_3$)]. Three aromatic protons give a signal in the 2.7-3.3 ppm region and the signals of two hydroxylic protons are found at 3.5 ppm in the form of a broadened singlet. This assignment was confirmed by the spectrum of (I) recorded with the heating of the sample. In this case, the signal at 3.5 ppm underwent a diamagnetic shift.

The signals of the four methine protons of the N-methylpyrrolidine ring in the spectrum of (I) were found in the 5.3-6.3 ppm region, while the signal of one of them was superposed on the signals of the protons of the methoxy group. Consequently, we performed the asignment of these signals in the spectrum

TABLE 1. Chemical Shifts (ppm) and Spin–Spin Coupling Constants (J, Hz) of the Alkaloids Codonopsine (I) and Codonopsinine (III) and Their Acetyl Derivates (II) and (IV)

Substance	Sol-vent	H_1	H_2	H_3	H_4	OCH_3	OCH_3	NCH_3	$C-CH_3$	$\overset{O}{/\!/}OC_a-CH_3$	$\overset{O}{/\!/}OC_b-CH_3$	Ph–H	OH	$J_{H_1H_2}$	$J_{H_2H_3}$	$J_{H_3H_4}$
I	C_5D_5N	6,36 (q)*	5,71 t	5,46 q	6,06 (6,06) d	6,26 s	6,36 s	7,82 s	8,72 (d) J=6,5	—	—	2,7–3,3 m	3,50 bs	3,8	3,8	6,1
II	CCl_4	6,73 q	5,37 t	5,11 q	6,46 d	6,20 s	6,25 s	7,93 d or 8,03	8,84 (d) J=7,5	6,93 s	7,93 s	3,2 m	—	2,2	2,2	6,1
III	C_5D_5N	6,33 q	5,69 t	5,46 q	6,04 d	—	6,33 s	7,80 s	8,70 d J=6,5	—	—	2,54 dd 3,18 J=8,5	3,65 ws	3,8	3,8	6,1
IV	CCl_4	6,69 q	5,32 t	5,04 q	6,39 d	—	6,20 s	7,90 s	8,78 d J=7,5	7,88 s	7,99 s	2,77 (dd) 3,19 J=8,5	—	2,2	2,2	6,1

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*s – singlet; d – doublet; t – triplet; q – quartet; dd – doublet of doublets; bs – broadened singlet; ws – wide signal; m – multiplet.

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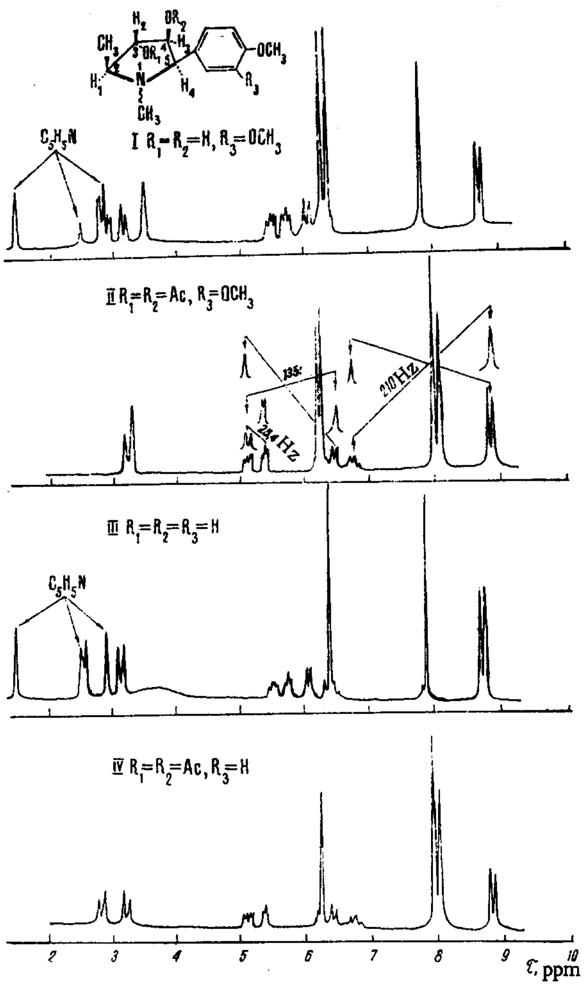

Fig. 1. NMR spectra of codonopsine in [D]pyridine (I), of codonopsine acetate in CCl_4 (II), of codonopsinine in [D]pyridine (III), and of codonopsinine acetate in CCl_4 (IV).

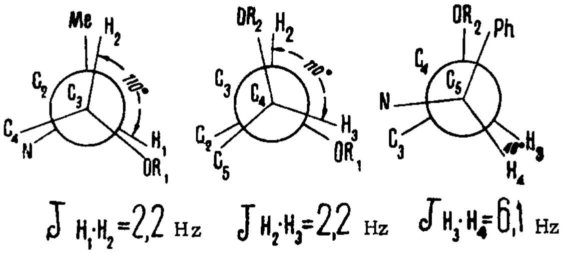

Fig. 2. Newman projections of the molecule of (II).

of the acetyl derivative of codonopsine (see Fig. 1, II), in which the signals of all the four methines were clearly separated.

Under double resonance conditions with the saturation of the doublet with τ 8.84 ppm in the spectrum of (II), the complex quartet (octet) at 6.73 ppm with $^3J_1 = 7.5$ Hz and $^3J_2 = 2.2$ Hz was converted into a broadened singlet and, conversely, on saturation of the quartet at 6.73 ppm the doublet at 8.84 ppm was converted into a singlet; i.e., the quartet at 6.73 ppm relates to the H_1C-CH_3 proton. The double-resonance method also showed that the doublet at 6.46 ppm with $^3J = 6.1$ Hz interacts with the weak-field quartet at 5.11 ppm with $^3J_1 = 6.1$ Hz and $^3J_2 = 2.2$ Hz; and the triplet at 5.37 ppm with $^3J_1 = {}^3J_2 = 2.2$ Hz with the quartet at 5.11 and 6.73 ppm.

Thus, the results of double resonance show that the weak-field quartet at 5.11 ppm with $^3J_1 = 6.1$ Hz and $^3J_2 = 2.2$ Hz is due to H_3 interacting with a high vicinal spin–spin coupling constant with H_4 at 6.46 ppm and with a small constant with H_2 at 5.37 ppm; i.e., the following assignment of the chemical shifts (CSs) and the spin–spin coupling constants of the signals of the protons follow unambiguously: H_1 – 6.73 ppm; H_2 – 5.73 ppm; H_3 – 5.11 ppm; H_4 – 6.46 ppm; $^3J_{H_1H_2} = 2.2$ Hz; $^3J_{H_2H_3} = 2.2$ Hz; and $^3J_{H_3H_4} = 6.1$ Hz. Analogous results were obtained in an analysis of the spectrum of (IV). By a correlation of the experimental values of the constants with the corresponding dihedral angles according to Karplus [3] for (II) and (IV) we found the following approximate values of the angles: $\varphi_1\ (\widehat{H_1H_2}) \sim 110^\circ$, $\varphi_2\ (\widehat{H_2H_3}) \sim 110^\circ$ and $\varphi_3\ (\widehat{H_3H_4}) \sim 40^\circ$. Consequently, the $-OCOCH_3$ group and also the H_1 and H_2 and the H_2 and H_3 protons are in the partially eclipsed (transoid) conformation, and the H_3 and H_4 protons in the skew (gauche) conformation (Fig. 2, Newman projections).

On considering spatial models of the molecule of (II) and the values of the spin–spin coupling constants obtained for the H_1, H_2, H_3, and H_4 protons, it can be seen that the N-methylpyrrolidine ring A has the half-chair conformation with the relative* mutual positions and orientations of the protons and groups according to the formula given (see Fig. 1): H_1 and H_3 – α-pseudoequatorial, H_2 and Ph – β-pseudoequatorial and $C-CH_3$ – β-pseudoaxial, $-OC_3OCH_3$ – α-pseudoaxial, $-OC_4OCH_3$ – β-pseudoaxial, and H_4 – α-pseudoaxial. It is apparently difficult to determine unambiguously the orientation of the $N-CH_3$ group and, correspondingly, that of the lone pair of electrons of the nitrogen on the basis of the results of NMR spectroscopy.

EXPERIMENTAL

The spectra were obtained on a JNM-4H-100 spectrometer with a working frequency of 100 MHz. The experiments on double proton–proton resonance with field and frequency sweeps were performed on

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*Relative to $C-CH_3$, the configuration of which is taken as β.

on the spectrometer mentioned, fitted with a double-resonance unit. The values of ν_1 and ν_2 were measured with a recording frequency-meter to an accuracy of 0.1 Hz.

The chemical shifts were determined with an accuracy of 0.01 ppm. The NMR spectra of codonopsine (I) and codonopsinine (III) were taken in deuteropyridine ($c \sim 10\%$) and those of their acetyl derivatives (II) and (IV) in carbon tetrachloride. The internal standard was TMS, the signals of the protons of which were taken as 10 (τ scale).

SUMMARY

The spatial structures of codonopsine and codonopsinine have been determined by high-resolution NMR spectroscopy.

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