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STEREOCHEMISTRY OF THE ALKALOIDS CODONOPSINE AND CODONOPSININE

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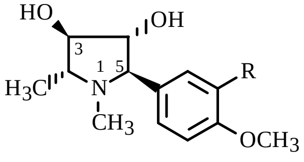
The isolation of the alkaloids codonopsine (**1**) and codonopsinine (**2**) from the aerial part of *Codonopsis clematidea* (harebell, Campanulaceae) has been previously reported [1]. Based on spectral data (IR, UV, NMR, and mass spectroscopy) and chemical transformations (Hofmann degradation, $KMnO_4$ and periodic-acid oxidation), the structures for **1** and **2** were established as 1,2-dimethyl-3,4-dihydroxy-5-(3,4-dimethoxyphenyl)pyrrolidine and 1,2-dimethyl-3,4-dihydroxy-5-(4-methoxyphenyl)pyrrolidine, respectively [2, 3]. Later double-resonance PMR spectroscopy was used in an attempt to determine the relative configuration of the substituents on the N-methylpyrrolidine ring [4].



1, 2

1: R = OCH_3
2: R = H

The methyl iodide of codonopsine (**3**) was prepared and its x-ray crystal structure was solved in order to solve unambiguously these issues.

The results of the x-ray structure analysis (XSA) confirm the proposed chemical formulas for **1** and **2** [2, 3] but necessitate a correction in the stereochemistry of the N-methylpyrrolidine ring. Figure 1 shows the corrected structural formulas for **1** and **2** and the molecular structure of codonopsine methyl iodide (**3**).

It can be seen that the C2 methyl and the C4 hydroxyl have the α-configuration; the C3 hydroxyl and the C5 substituted aromatic ring, the β-configuration. The N-methylpyrrolidine ring adopts the 5α-envelope conformation. Atom C5 deviates from the plane of the other four atoms (coplanar within ±0.027 Å) by 0.625 Å. For this reason, only C4 and C5 can have substituents that are pseudo-axial or -equatorial relative to the plane of the four atoms. The C4 hydroxyl and C5 aromatic ring are pseudo-equatorial. The planar (±0.01 Å) substituted aromatic ring is twisted relative to the plane of the pyrrolidine ring by 74.2°.

The absolute configuration of **3** was also established from the XSA. According to the Flack parameter [5] [0.00(4)], the absolute configuration of the chiral centers corresponds with that shown in Fig. 1. Therefore, all asymmetric centers (C2, C3, C4, and C5) have the *R*-configuration.

The crystal packing of **3** indicates that I...H–O and O...H–O H-bonds are present. The parameters for the I...H–O1 bond are: I...O1 3.45, I...H–O1 2.66 Å and I...H–O1 172.1°. Molecules transformed by 2_1 symmetry form an infinite chain along the *a* axis owing to a branched H-bond (O1′...H–O2 and O2′...H–O2). The parameters of this bond are: 2.90, 2.22, 161.3 and 2.92, 2.40, 131.6.

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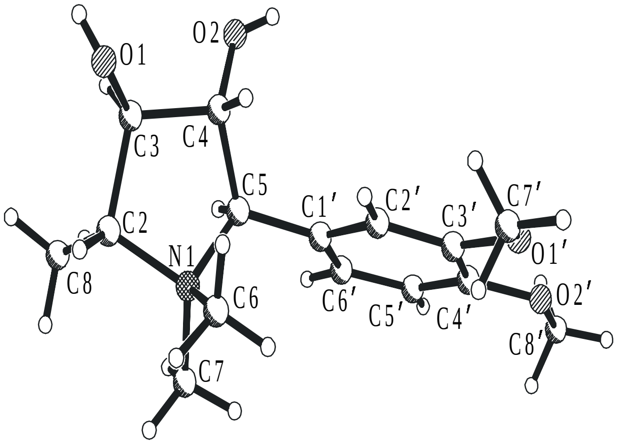

Fig. 1. Conformation and atomic numbering in **3**.

In conclusion, it should be noted that **2** has a N-containing ring similar to codonopsine (according to PMR spectroscopy they are stereochemically identical) and differs only by the presence of a second OCH_3 group on the aromatic ring. Therefore, the absolute configuration of codonopsine probably corresponds with that of codonopsinine.

Thus, the alkaloids codonopsine and codonopsinine have structures and absolute configurations N-methyl-2(*R*)-α-methyl-3(*R*)-β-hydroxy-4(*R*)-α-hydroxy-5(*R*)-β-(3,4-dimethoxyphenyl)pyrrolidine and N-methyl-2(*R*)-α-methyl-3(*R*)-β-hydroxy-4(*R*)-α-hydroxy-5(*R*)-β-(4-methoxyphenyl)pyrrolidine.

Single crystals of codonopsine methyl iodide ($C_{15}H_{24}NO_4I$, mp 207-208°C) were obtained from methanol. The crystals were transparent elongated prisms. Unit-cell constants and intensities of reflections were measured on a STOE Stadi-4 four-circle diffractometer ($\theta/2\theta$-scanning) using Mo Kα-radiation (graphite monochromator): $a = 7.805(2)$, $b = 13.592(3)$, $c = 16.667(3)$ Å, V = 1768.1(6) Å^3, $\rho = 1.537$ g/cm^3, space group $P2_12_12_1$, Z = 4. Absorption corrections were not applied.

The structure of **3** was solved by direct methods using the SHELXS-97 programs. The structure was refined using the SHELXL-97 programs. Nonhydrogen atoms were refined by anisotropic full-matrix least-squares methods (over F^2). The positions of H atoms were found geometrically and refined isotropically with fixed thermal parameters $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others and U_{eq} is the equivalent isotropic thermal parameter of the corresponding C atoms. H-atoms of hydroxyls were found from a difference electron-density synthesis and refined isotropically. The final agreement factor $R_1 = 0.0369$, $wR_2 = 0.0798$ for 2164 reflections with $I > 2\sigma(I)$ and $R_1 = 0.0416$ and $wR_2 = 0.0862$ for the whole data set (2439).

The data from the XSA were deposited as a CIF file in the Cambridge Structural Database (CCDC 249723).

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