

# ALKALOIDS OF *Stephania delavayi*

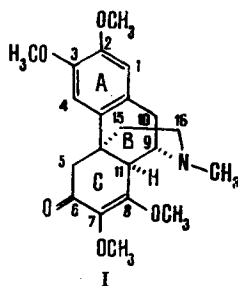
## IV. ISOSTEPHODELINE

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UDC 547.944/945

From the roots of *Stephania delavayi* (Menispermaceae) collected in the Transcaucasus, by chromatography on alumina followed by crystallization from benzene with the addition of ether, we have isolated a new base having the composition  $C_{21}H_{27}O_5N$ , mp 184-185°C,  $[\alpha]_D^{20} +160^\circ$  (c 2; ethanol), which we have called isostephodeline.

A study of the alkaloid has shown that it has the structure (I):



The Hofmann degradation of isostephodeline followed by acetolysis gave a nitrogen-free product which, in view of its small amount, was characterized only by the UV spectrum which was similar to the spectra of diacetoxydimethoxyphenanthrenes [1]. The latter fact showed the possibility that the structure of the alkaloid was based on a morphinan or hasubanan skeleton.

The presence of a benzene nucleus and of an  $\alpha,\beta$ -unsaturated ketone in the isostephodeline molecule follows from its IR and UV spectra ( $\nu^{CHCl_3}$  1661, 1615, 1522  $cm^{-1}$ , Fig. 1;  $\lambda_{max}^{ethanol}$  226, 275 nm;  $\log \epsilon$  3.78, 3.79). The UV spectrum of the substance is the result of the superposition of the absorption of the chromophoric groups mentioned; similar characteristics of the absorption in the UV region are possessed by the alkaloids delavayine, 16-oxodelavayine, and stephodeline [2-4], each of which also contains a benzene nucleus and an  $\alpha,\beta$ -unsaturated keto group not conjugated with one another.

The presence of four methoxy groups and an N-methyl group was established from the features of the NMR spectrum (Fig. 2, Table 1). Two methoxy groups are attached to a benzene nucleus which has two protons in the para positions with respect to one another. When the three-proton singlets at 3.72 and 3.74 ppm were irradiated, an increase in the intensities of the signals of the aromatic protons was observed (6.45 ppm by 20%; 6.56 ppm by 15%). There was no intramolecular nuclear Overhauser effect (NOE) between the two remaining methoxy groups, which permits them to be regarded as olefinic; in these circumstances, the  $C_8-OCH_3$  signal is in the weak field (3.88 ppm) and the  $C_7-OCH_3$  signal in the strong field (3.26 ppm).

In the NMR spectrum, the protons at  $C_5$  give two doublets with a spin-spin coupling constant of 17 Hz, which is characteristic for methylene groups having a  $\pi$ -electronic system in the  $\alpha$  position [2]. The distance between the  $C_4-H$  and  $C_5-H_\alpha$  signals in the spectrum of (I) is about 1.9 Å; in complete correspondence with this a NOE is observed between these protons (irradiation of the doublet at 3.05 ppm leads to

All-Union Scientific-Research Institute of Medicinal Plants. Translated from *Khimiya Prirodnykh Soedinenii*, No. 2, pp. 188-193, March-April, 1975. Original article submitted December 7, 1973.

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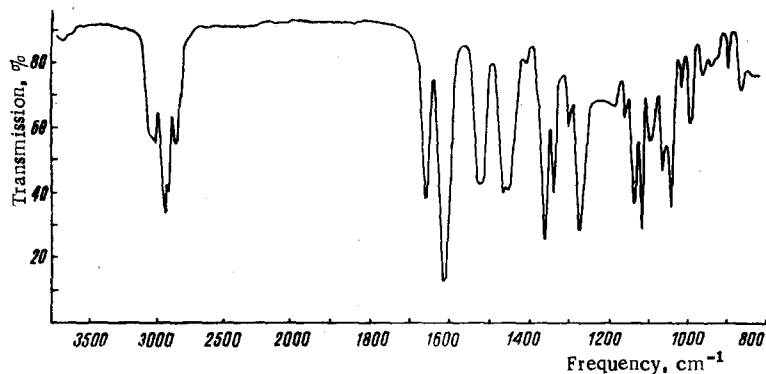


Fig. 1. IR spectrum of isostephodoline in  $\text{CHCl}_3$ .

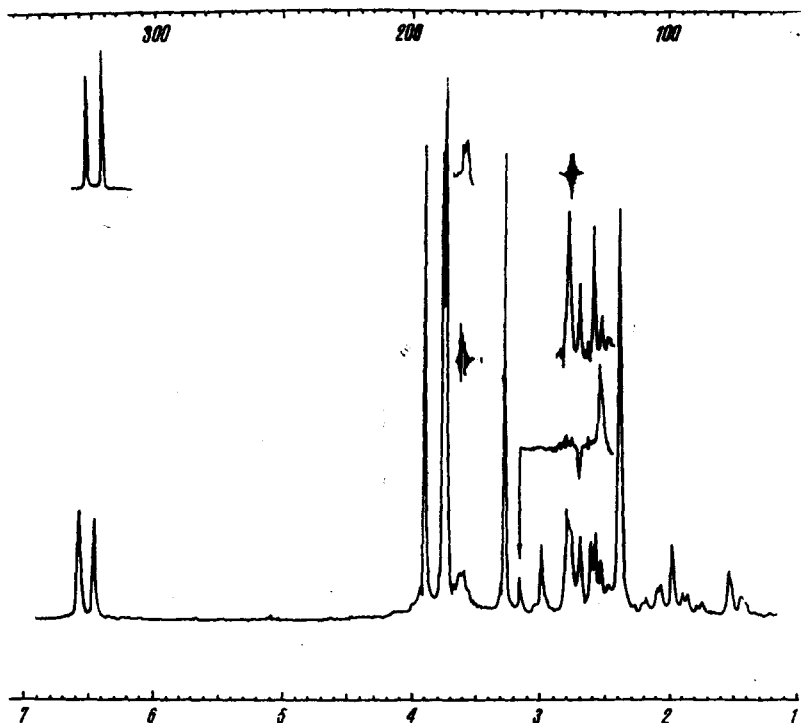
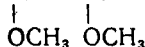


Fig. 2. NMR spectrum of isostephodoline in  $\text{CDCl}_3$  (Varian HA-100D,  $20^\circ\text{C}$ , 0 - HMDS). Above the main spectrum are shown the fragments of the INDOR and double-resonance spectra.

an increase in the intensity of the signal at 6.56 ppm by 23%). A different arrangement of the  $\alpha,\beta$ -unsaturated keto group ( $-\text{C}_6 = \text{C}_7 - \text{C}_8 = \text{O}$ ) is excluded on the basis of the values of the chemical shifts of the protons at  $\text{C}_5$  [2].



The structure of ring B was also established from NMR spectra (see Table 1); the bond between the protons at  $\text{C}_9$ ,  $\text{C}_{10}$ , and  $\text{C}_{11}$  was confirmed by double resonance (Fig. 2). The coupling constant between  $\text{C}_9\text{-H}$  and  $\text{C}_{10}\text{-H}_\alpha$  was determined from the INDOR spectra on the components of the doublet from  $\text{C}_{11}\text{-H}$ .

Confirmation of the correctness of the assignment of the broadened two-proton signal with its center at 2.78 ppm to the hydrogen atoms at  $\text{C}_{10}$  is the detection by means of double resonance of allyl interaction between  $\text{H}-\text{C}_{10}-\text{H}$  and  $\text{C}_1\text{-H}$ : On irradiation of the signal at 2.78 ppm the peak intensity of the singlet at 6.45 ppm rose and its half-width decreased from 2.4 to 1.6 Hz (Fig. 2).

In the range from 1.4 to 2.5 ppm, the spectrum of a solution of isostephodoline in  $\text{CDCl}_3$  has a four-proton multiplet an analysis of which according to first-order rules proved impossible. However, by using as solvent a mixture of benzene- $\text{d}_6$  and pyridine- $\text{d}_5$  (5 : 1) it was possible to simplify the spectrum somewhat

TABLE 1. Features of the NMR Spectra of Isostephodeline (20°C, 0 - HMDS, Varian HA-100D)

Protons	$\delta$ , ppm; J, Hz, multiplicity	
	CDCl <sub>3</sub>	benzene-d <sub>6</sub> + pyridine-d <sub>5</sub> (5:1)
C <sub>1</sub> -H	6,45 s	6,31 s
C <sub>4</sub> -H	6,56 s	6,60 s
C <sub>7</sub> -OCH <sub>3</sub>	3,26 s	3,22 s
C <sub>8</sub> -OCH <sub>3</sub>	3,88 s	3,51 s
C <sub>2</sub> -OCH <sub>3</sub> ; C <sub>3</sub> -OCH <sub>3</sub>	3,72 s, 3,74 s	3,29 s, 3,40 s
N-CH <sub>3</sub>	2,36 s	2,17 s
C <sub>5</sub> -H <sub>a</sub>	3,05; d, J <sub>5a,5e</sub> = 17	2,87; d, J <sub>5a,5e</sub> = 17
C <sub>5</sub> -H <sub>e</sub>	2,62; d, J <sub>5a,5e</sub> = 17	2,23; d, J <sub>5a,5e</sub> = 17
C <sub>9</sub> -H	3,58, J <sub>9,11</sub> = 3,1	3,73; J <sub>9,11</sub> = 3,1
	J <sub>9,10a</sub> = 5,6; J <sub>9,10e</sub> = 0	J <sub>9,10a</sub> = 5,6; J <sub>9,10e</sub> = 0
C <sub>10</sub> -H <sub>a</sub>	2,78; J <sub>10a,9</sub> = 5,6	2,79; J <sub>10a,9</sub> = 5,6
C <sub>10</sub> -H <sub>e</sub>	2,78; J <sub>10e,9</sub> = 0	2,79; J <sub>10e,9</sub> = 0
C <sub>11</sub> -H	2,56; J <sub>11,9</sub> = 3,1	2,53; J <sub>11,9</sub> = 3,1
C <sub>15</sub> -H <sub>a</sub>	1,4-2,5 m	1,64; J <sub>15a,15e</sub> = 11,5
C <sub>15</sub> -H <sub>e</sub>		1,22; J <sub>15a,16a</sub> = 5,0
C <sub>16</sub> -H <sub>a</sub>		2,00; J <sub>15e,16a</sub> = 3,0
C <sub>16</sub> -H <sub>e</sub>		2,22; J <sub>15e,16e</sub> = 1,3
		J <sub>16a,16e</sub> = 12,0

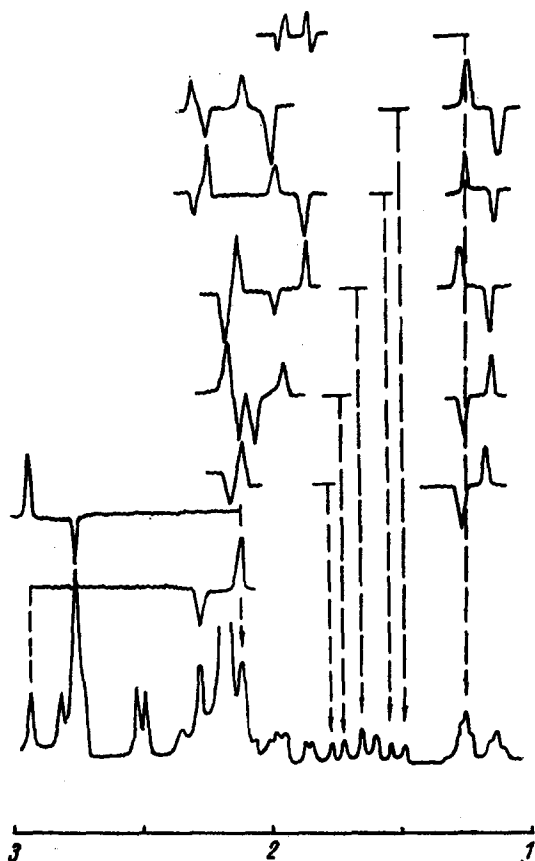


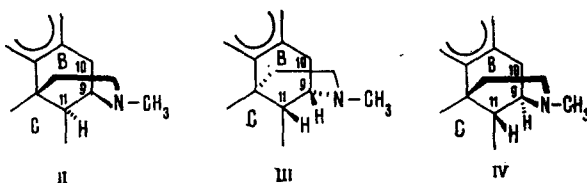
Fig. 3. NMR spectrum of isostephodeline in a mixture of benzene-d<sub>6</sub> and pyridine-d<sub>5</sub> (5:1) in the range from 1 to 3 ppm (0 - HMDS, 20°C). Fragments of the INDOR spectra are shown above the main spectrum.

TABLE 2. Calculated Spin-Spin Coupling Constants of the Protons at C<sub>9</sub>, C<sub>10</sub>, and C<sub>11</sub> for Different Variants of the Relative Configurations of Stephodeline and Isostephodeline

Variant	φ <sub>9,10a</sub>	φ <sub>9,10e</sub>	φ <sub>9,11</sub>	J <sub>9,10a</sub>	J <sub>9,10e</sub>	J <sub>9,11</sub>
	deg			Hz		
I	42	84	54	4,3	0	2,5
II	36	78	66	5,2	0	1,0
III	42	84	66	4,3	0	1,0
IV	36	78	60	5,2	0	1,7

In our preceding investigation [4], we did not determine the nature of the coupling of rings B and C in stephodeline, and therefore we shall here discuss the stereochemistry of this alkaloid, as well.

For both compounds there are four possible variants of the relative configuration (I-IV):



The values of the dihedral angles  $\varphi$  between the protons measured on Dreiding models for all the variants, and the values of the spin-spin coupling constants calculated by means of the Karplus equation for carbon atoms in the  $sp^3$  state ( $J = 4.22 - 0.5 \cos \varphi + 4.5 \cos 2\varphi$ ) [4] are given in Table 2.

For stephodeline,  $J_{9,10a} = 6.0$ ;  $J_{9,10e} = 0$ ;  $J_{9,11} = 1.5$  Hz, and for isostephodeline  $J_{9,10a} = 5.6$ ;  $J_{9,10e} = 0$ ;  $J_{9,11} = 3.1$  Hz. On comparing the experimental values of the constants with those calculated, and taking into account the fact that the Karplus equation, as a rule, gives somewhat low values, it may be assumed that variant (I) is more suitable for isostephodeline and (II) for stephodeline.

The following facts also lead to this conclusion. The signal of the C<sub>7</sub> methyl group in the spectrum of isostephodeline has an anomalously low position (3.26 ppm), which is readily explained on the basis of a cis linkage of rings B and C (variants (I) and (IV)), since in this case the C<sub>7</sub>-methoxyl falls into the region of the screening influence of the benzene nucleus. In the spectrum of stephodeline, the signal from C<sub>7</sub>-OCH<sub>3</sub> occupies the usual position, 3.64 ppm, which agrees with the trans linkage of rings B and C (variants (II) and (III)). In structures (II) and (III) C<sub>10</sub>-H<sub>e</sub> is present in the cis position with respect to the nitrogen atom, which leads to some downfield shift of its signal in comparison with C<sub>10</sub>-H<sub>a</sub> [6]. In variants (I) and (IV) the same situation is observed, but the oxygen atom of the C<sub>8</sub>-methoxyl proves to be close to C<sub>10</sub>-H<sub>a</sub>, as a result of which both protons become equivalent and give a single signal which is split only as the result of the interaction of C<sub>10</sub>-H<sub>a</sub> and C<sub>9</sub>-H (the latter takes place in the spectrum of isostephodeline).

The facts given above permit us to consider that isostephodeline and stephodeline have the most probable relative configuration (I) and (II), respectively.

#### EXPERIMENTAL METHOD

**Isostephodeline (I).** The combined alkaloids isolated by the dichloroethane method (73 g) were dissolved in 5% sulfuric acid. The sulfuric acid solutions were made alkaline with ammonia, and the precipitate that deposited was filtered off. The aqueous-ammoniacal mother liquor was extracted with benzene, the benzene extract was evaporated, and the concentrate was deposited on a column of alumina. When the fraction of alkaloids obtained by elution with benzene was crystallized from benzene with the addition of diethyl ether, a base was obtained with mp 184-185°C;  $[\alpha]_D +160^\circ$  (c 2; ethanol).

Found %: C 67.41; 67.35; H 7.45; 7.30; N 3.63; 3.70; C<sub>21</sub>H<sub>27</sub>O<sub>5</sub>N. Calculated %: C 67.56; H 7.23; N 3.75. Mol. wt. 373 (mass spectrometrically).

and by the INDOR method (Fig. 3) to determine the chemical shifts and spin-spin coupling constants of the four-proton system (see Table 1). The values of the parameters obtained leave no doubt

of the fact that they belong to the protons of a N-CH<sub>2</sub>-CH<sub>2</sub>-C grouping.

Thus, the functions of all the hydrogen atoms have been shown to be determined. Taking into account the empirical formula of the substance, structure (I) can be proposed as the only possible one for isostephodeline. Consequently, isostephodeline is a spatial isomer of the alkaloid stephodeline which we have isolated previously [4] from the same plant.

Methodide of (I). A solution of 0.05 g of (I) in 3 ml of methanol was treated with 0.3 ml of methyl iodide. The mixture was heated in the water bath under reflux for half an hour. After evaporation of the solvent, 0.06 g of technical methodide was obtained.

The Des-base (I). A mixture of 0.06 g of the methodide of (I) and a solution of 0.14 g of caustic potash in 3 ml of methanol was heated on the water bath under reflux for 4 h. Then the solvent was evaporated off. The reaction product was dissolved in water, and the solution was made acid to pH 4.0 with 20% sulfuric acid and it was then extracted with ether and the extract was made alkaline with 25% ammonia solution. Then it was extracted with chloroform, and evaporation of the chloroform yielded 0.04 g of the des-base.

Acetolysis of the Des-base of (I). To 0.04 g of the des-base of (I) were added 0.5 ml of acetic anhydride and 0.05 g of anhydrous sodium acetate. The mixture was heated under reflux in a sand bath at 160-175°C. The cooled reaction mixture was diluted with water, acidified with sulfuric acid, and extracted with ether. The ethereal extract was washed several times with water, dried over sodium sulfate, and evaporated to give 0.013 g of nitrogen-free product.

#### SUMMARY

The structure of the new alkaloid isostephodeline isolated from the roots of Stephania delavayi Diels has been established. The most probable relative configurations of isostephodeline and of the stephodeline isolated previously have been proposed.

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