THE STRUCTURE OF DELAVAYINE – AN ALKALOID FROM Stephania delovayi

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UDC 547.944/945

We have previously [1] reported the isolation from the herb Stephania delovayi* of the alkaloid delavayine having the composition $C_{20}H_{23}O_5N$, mp 149-150°C (ethanol), $[\alpha]_D - 240°$ (chloroform). As was observed, the IR spectrum of (I) has the absorption bands of an α,β-unsaturated ketone (1670 cm^{-1}) and of C = C bonds (1608 cm^{-1}) (Fig. 1). The UV spectrum of the substance $(\lambda_{max}^{ethanol}$ 238, 268 nm, log ε 3.59, 3.97) also indicates the presence of a system of conjugated double bonds in the molecule of (I). According to the NMR spectrum (Fig. 2, Table 1), delavayine includes a $N-CH_3$ group, two methoxy groups, and a

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* As in Russian original; the previous paper gives the name of this herb as Stephania delavayi – Translator.

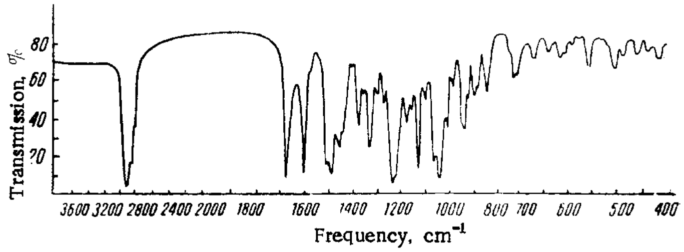

Fig. 1. IR spectrum of delavayine (mull in paraffin oil, UR-10).

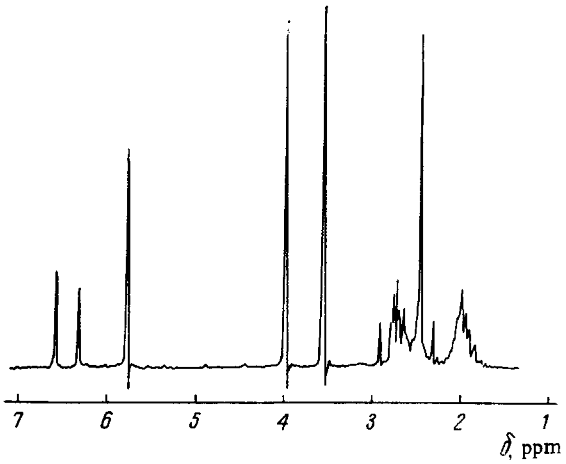

Fig. 2. NMR spectrum of delavayine [in CCl_4, 0–TMS, HA-100 D (100 MHz)].

All-Union Scientific-Research Institute of Medicinal Plants. Translated from Khimiay Prirodnykh Soedinenii, No. 6, pp. 784-790, November-December, 1971. Original article submitted June 19, 1971.

TABLE 1. NMR Spectra of Delavayine and Its Derivatives*

Compound	Solvent	$O-CH_2-O$	C_1-H	C_4-H	C_6-H	C_7-H	$H-C_5-H$	OCH_3	$N-CH_3$	$H-C_{10}-H$ $H-C_{15}-H$	$H-C_9-H$ $H-C_{15}-H$
Delavayine (I)	$CDCl_3$	5,84, us	6,41,s	6,64,s	—	—	2,46, d; 16 Hz 3,00, d; 16 Hz	4,06 3,60	2,49	2,6–2,9 m	1,9–2,2 m
	CCl_4	5,78, s	6,33,s	6,58,s	—	—	2,40, d; 16 Hz 2,81, d; 16 Hz	3,99 3,57	2,45	2,4–2,8 m	1,8–2,2 m
The des-base of delavayine (II)	CCl_4	5,86, us	6,36,s	6,65,s	—	—	2,89, s; 2H	3,71 3,31 3,17	2,04 (6 H)	—	—
	Deuteropyridine	5,95, s	6,62,s	7,00,s	—	—	3,06, d 13,0Hz 3,22, d 13,0Hz	3,93 3,51 3,33	2,04 (6H)	—	—
6-Acetoxy-8-methoxy-2,3-methylenedioxyphenanthrene (III)	$CDCl_3$	5,98, s	7,0', s	7,76, s	C_5-H 7,68 2,0, d	6,65 2,0, d	—	3,95	$\overset{O}{\overset{\Vert}{OC}}-CH_3$ 2,35	C_9-H $C_{10}-H$ 7,91 (d; 9,0); 8,0 (d; 9,0)	
6,8-Dimethoxy-2,3-methylenedioxyphenanthrene (IV)	CCl_4	6,04, s	7,09,s	7,78,s	C_5-H 7,24 2,0, d	6,45 2,0,d	—	3,99 3,96	—	C_9-H $C_{10}-H$ 7,36 (d; 8,8) 7,91 (d; 8,8)	
Alcohols of delavayine crystalline (VIIa)	$CDCl_3$	5,86, s	6,48,s	6,75,s	4.28 $T_1J_1+J_2 = 9$ Hz	— —	2,12, q; 13Hz; 4Hz 2,58, q; 13Hz; 5Hz	3,81 3,61	2,48	—	—
amorphous (VIIb)	$CDCl_3$	5,88, us	6,47,s	6,75,s	3,88 q; 8,0; 6,0	—	—	3,77 3,47	—	—	—
	Deuteropyridine	5,93, us	6,60,s	7,01,s	4,34 q, 8,0; 5,8	—	2,34, q; 13,0; 5,8 2,66, q; 13,0; 8,0	3,85 3,62	2,60	—	—

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* HA-100D (100 MHz); 0 – TMS; s – singlet, d – doublet, t – triplet, q – quartet, us – feebly resolved signal appearing in the form of a singlet, m – multiplet.

methylenedioxy group attached to an aromatic ring. Substance (I) also contains a methylene group in the α position to a carbonyl group and attached to a quaternary carbon atom, since on deuteration in an alkaline medium the protons of the methylene group are replaced by deuterium and the corresponding quadruplet is absent in the spectrum of the deuteration product.

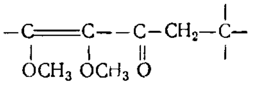
In the Hofmann degradation of delavayine with subsequent acetolysis of the methine base (II), we obtained the substituted phenanthrene (III). On the basis of the NMR spectra of delavayine and the product of its deuteration, and also the results of the Hofmann degradation, substance (I) was assigned to the group of hasubanan alkaloids. Two possible structural formulas were proposed for it: Ia and Ib.

The further investigation of (I) has confirmed that it is based on the hasubanan nucleus: the spectrum of the base lacks a signal in the 3-4 ppm region from a proton at C_9, which is found in the spectra of the morphinan alkaloids [2, 3]. In addition to this, we have found that the positions of the substituents must be corrected.

The hydrolysis of the methylenedioxy group in (I) gave the corresponding dihydroxy derivative (V). The absorption of the carbonyl of an ester grouping (1775-1780 cm^{-1}) in the acetylation product (VI) shows the phenolic nature of the hydroxyls, from which it follows that the methylenedioxy group is aromatic.

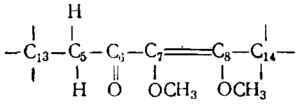
A study of the NMR spectra of the substituted phenanthrene (II) and of the dimethoxymethylenephenanthrene (IV) obtained in the saponification of (III) with subsequent methylation, showed that they each contain six aromatic protons in three pairs, respectively, in the ortho, meta, and para positions with respect to one another. These facts show that the methylenedioxy group is located at C_2 and C_3.

The reduction of (I) with sodium tetrahydroborate gave two epimeric alcohols: a crystalline alcohol (VIIa) and an amorphous alcohol (VIIb) the IR spectra of which lacked the band of a carbonyl and showed the absorption of a hydroxy group (VIIa – 3180 cm^{-1}; VIIb – 3370 cm^{-1}). In (VIIa) the hydroxy group is pseudoaxial and in (VIIb) pseudoequatorial, as follows from the values of the spin–spin coupling constants of the proton geminal to the hydroxyl with the protons of the neighboring methylene group. On passing from (I) to (VIIa and VIIb), the two singlets in the weak field (6.41 and 6.64 ppm) do not undergo a diamagnetic shift, which permits their assignment to the para protons of an aromatic nucleus. At the same time, the signals of one of the methoxy groups (4.06 ppm) shifts upfield by 0.25 and 0.29 ppm in (VIIa) and (VIIb) as compared with (I). This signal must be ascribed to a methoxyl in the β position to a carbonyl group, since it is known [4] that in such systems an effective positive π-electronic charge is concentrated on the β-carbon atom, leading to some downfield displacement of the signals of the protons of the β substituents. Thus, the information obtained shows that the molecule of delavayine contains the structural fragment *a*:



$$-\underset{OCH_3}{\overset{}{C}}=\underset{OCH_3}{C}-\underset{\|\atop O}{C}-CH_2-\underset{|}{\overset{|}{C}}-$$

The Hofmann degradation of delavayine methiodide in methanol formed the des-base (II). The molecule of (II) contains an unconjugated keto group (1735 cm^{-1}), an isolated double bond (1658 cm^{-1}), a methoxy group on a double bond, and two aliphatic methoxyls (see Table 1). The absence of the signals of olefinic protons in the NMR spectrum of (II) confirms the hasubanan skeleton of delavayine. The degradation of hasubanonine methiodide takes place similarly [5]. The nature of the Hofmann cleavage of delavayine methiodide shows the position of the fragment in ring C of delavayine:

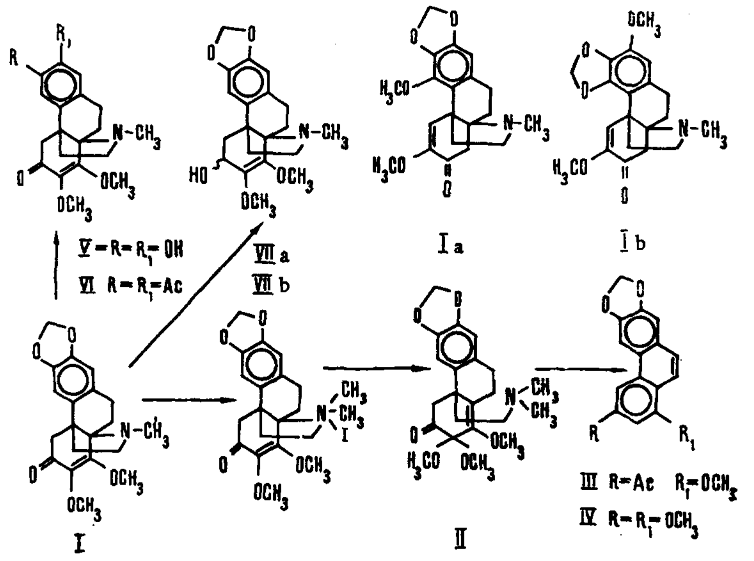


$$-\underset{|}{\overset{|}{C_{13}}}-\underset{H}{\overset{H}{C_5}}-\underset{\|\atop O}{C_6}-\underset{OCH_3}{C_7}=\underset{OCH_3}{C_8}-\underset{|}{\overset{|}{C_{14}}}-$$

On the basis of the facts given, the only possible structure for delavayine is structure (I) (below).

The results of a study of long-range spin–spin coupling in delavayine by means of double resonance and the measurement of the intramolecular nuclear Overhauser effect (NOE) confirmed the conclusions drawn above.

The spectrum of (I) has two four-proton multiplets with centers at 2.0 and 2.65 ppm. It is obvious that the multiplet in the stronger field relates to the methylene protons in positions 9 and 15; the deshielding influence of the benzene ring in the one case and of the nitrogen atom in the other case leads to downfield shifts of the signals of the methylene groups in positions 10 and 16. Long-range spin–spin coupling must arise between the aromatic proton at C_1 and the protons of the C_{10} methylene group. In actual fact, one of the signals of the aromatic protons (6.41 ppm) is somewhat broadened; on irradiation of the multiplet with its center at 2.65 ppm, the broadening diminishes. A NOE (about 15%) is observed between C_1–H and H–C_{10}–H, which also confirms the conclusions drawn. A NOE is observed qualitatively between H–C_{15}–H and C_4–H (irradiation of the multiplet at 2.00 ppm). In addition, on irradiation of the multiplet with its center at 2.65 ppm the intensity of the signal from the C_4 hydrogen atom increases by about 12%. The protons of the methylene groups in positions 10 and 16 are too remote from the C_4 hydrogen for a NOE to be caused. However, in the same region there is the doublet of one of the protons of a methylene group in the α position with respect to a carbonyl. In the case of structure (I), one of the protons at C_5 is sufficiently close to the C_4 hydrogen for a NOE to arise.



Scheme of the transformations of delavayine

EXPERIMENTAL

Combined Alkaloids. The dry comminuted herb Stephania delovayi was moistened with 10% ammonia and exhaustively extracted with dichloroethane. The alkaloids were isolated from the extract with 10% sulfuric acid. The sulfuric acid solutions were made alkaline with ammonia, and the mixture of bases was extracted with chloroform. This extract was dried and evaporated to give 55 g of the mixture of alkaloids. Yield 0.55%.

Delavayine (I). The mixture of alkaloids (5 g) was transferred to a column of alumina (activity grade II), and eluted with ether–methanol (99 : 1). Evaporation of the first portions of eluate gave 1 g of a substance which, after crystallization from ethanol, had mp 140-150°C, $[\alpha]_D$ −240° (c 1; chloroform).

Found %: C 67.06, 67.31; H 6.67, 6.68; N 3.97, 3.93; OCH_3 17.30, 17.60, mol. wt. 364 (Rast). $C_{20}H_{23}O_5N$. Calculated %: C 67.05, H 6.70; N 3.91; OCH_3 17.36. Mol. wt. 357. The test for a methylenedioxy group with phloroglucinol and sulfuric acid was positive.

[D]Delavayine. Delavayine (0.15 g) was added to a solution of 0.3 g of metallic sodium in 3 ml of [D]methanol, 0.6 ml of [D]water was added, and the mixture was boiled for 30 min. The solvents were evaporated off to dryness and the residue was treated with 5 ml of [D]methanol and 0.5 ml of [D]water, and the resulting solution was heated for another 30 min and was then evaporated to dryness. The dry residue was dissolved in [D]water and extracted with ether, and the extract was carefully washed free from alkali, dried, and distilled. A crystalline substance was obtained, the NMR spectrum of which confirmed that deuteration had been successful.

Delavayine Methiodide. A solution of 1 g of delavayine in 5 ml of methanol was treated with 1.5 ml of methyl iodide, and the mixture was heated in the boiling water bath for 3 h. The precipitate that deposited was filtered off and crystallized from methanol; mp 190–192°C.

Found %: N 3.13, 3.02; I 26.80. $C_{20}H_{23}O_5N \cdot CH_3I$. Calculated %: N 2.80; I 25.45.

The Des-base of Delavayine (II). A suspension of 0.98 g of delavayine methiodide in 3 ml of methanol was treated with a solution of 2.5 g of caustic potash in 4 ml of methanol. The mixture was heated in the boiling water bath for 3 h, and then the solvent was evaporated off, and the residue was dissolved in water and extracted with ether. The operations of drying, distilling off the solvent, and crystallization from ether twice yielded 0.52 g of the des-base with mp 118-120°C.

Acetoxymethylenedioxyphenanthrene (III). A mixture of 0.5 g of the des-base of delavayine, 0.6 g of acetic anhydride, and 0.6 g of anhydrous sodium acetate was heated under reflux in a sand bath at 160-175°C for 1.5 h. The cooled reaction mixture was diluted with water, acidified with sulfuric acid, and extracted with ether. The ethereal extract was washed with water several times, dried with sodium sulfate, and evaporated. The resinous residue was crystallized from methanol and then from acetone and was washed with ether. A nitrogen-free product with mp 169-170°C (0.18 g) was obtained.

Found %: C 69.63, 69.53; H 4.70, 4.75; OCH_3 11.24, 11.90. $C_{18}H_{14}O_5$. Calculated %: C 69.67; H 4.51; OCH_3 10.00.

The Dimethoxymethylenedioxyphenanthrene (IV). A solution of 0.15 g of the nitrogen-free product in 50 ml of methanol was treated with 4.2 g of previously ground caustic potash, and the mixture was shaken until the alkali had dissolved completely and was then heated in the water bath in an atmosphere of nitrogen for 1 h. The hydrolysis product was methylated by the addition of 1.7 ml of dimethyl sulfate to the reaction mixture. The resulting mixture was shaken for 1.5 h and was then heated in the water bath for 2 h. The solvent was distilled off, the residue was dissolved in water, and the solution was acidified and extracted with chloroform, after which the extract was dried and distilled. The dry residue was crystallized from benzene, giving a substance with mp 181-182°C.

Found %: C 71.78, 71.60; H 5.08, 4.91. $C_{17}O_{14}O$. Calculated %: C 72.35; H 4.96.

Demethylenedelavayine (V). A solution of 2 g of delavayine in a mixture of 30 ml of concentrated sulfuric acid and 45 ml of water was treated with a solution of 2 g of phloroglucinol in the same mixture of sulfuric acid and water. The reaction mixture was heated in the water bath at 80-90°C for 3 h. The cooled solution was filtered from the precipitate that had deposited, the filtrate was made alkaline with ammonia, and the saponification product was extracted with ether and then with chloroform. Crystallization from a mixture of ethanol and ether gave 0.2 g of a substance with mp 212-213°C. Its IR spectrum showed absorption bands at 3500 and 3300 cm^{-1} (OH groups).

Diacetyldemethylenedelavayine (VI). A solution of 0.08 g of demethylenedelavayine in 1.5 ml of pyridine was treated with 0.5 ml of acetic anhydride. The mixture was shaken for 4 h, the solvent was distilled off, the residue was dissolved in water, the reaction product was extracted with chloroform, and the extract was purified on alumina. It yielded 0.07 g of a noncrystallizing substance the IR spectrum of which lacked the absorption band of OH groups.

Reduction of Delavayine (VIIa, VIIb). With warming, 0.85 g of delavayine was dissolved in a mixture of 40 ml of methanol and 30 ml of water, and the solution was treated with 0.6 g of sodium tetrahydroborate added in portions. The reaction mixture was heated in the water bath for about 14 h. The alcohol was evaporated off, the residue was diluted with water and made alkaline with ammonia, and the alkaloids were extracted with chloroform. This gave a mixture of two substances, one of which it was possible to separate by crystallization from acetone and ethanol. This substance had mp 114°C, $[\alpha]_D$ 127.2° (c 0.55; chloroform). The other substance, which was amorphous, was purified on a column of alumina (activity grade II), $[\alpha]_D$ −303.8° (c 0.79; chloroform).

CONCLUSIONS

The definitive structure of delevayine – an alkaloid isolated earlier from the herb Stephania delovayi – has been established.

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