PRODUCTS OF THE REDUCTION OF REGELAMINE AND IOLANTAMINE AND THE STUDY OF THEIR HIGH-RESOLUTION MASS SPECTRA

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UDC 547.944.6 + 543.51

Regelamine and iolantamine—alkaloids from Colchicum kesselringii—have the structures of 11,12-dihydroxy-2-methoxyhexahydro-1,12-epoxyhomoproaporphine (I, Scheme 1) and 1-hydroxy-2-methoxy-9,10-dihydrohomoproaporphine (II) [1-3], respectively. For a strict proof of the function of the inert (bridge) oxygen atom and of the position of linkage of rings E and D in the regelamine molecule we have reduced it with metallic sodium in ethanol. Two crystalline reaction products were isolated: 1-hydroxy-1,12-deoxyregelamine (III) and 1-hydroxy-1,12:12-dideoxyregelamine (IV).

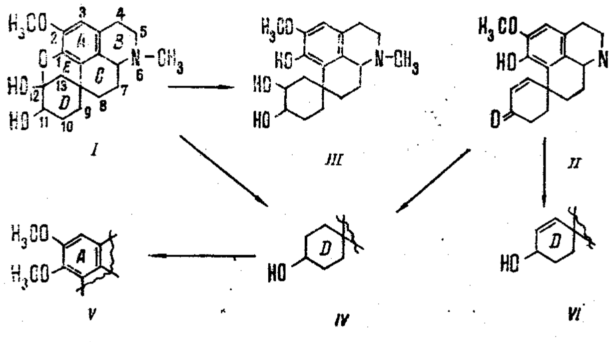
The methylation of compound (IV) gave 1-methoxy-1,12:12-dideoxyregelamine (V). The reduction of iolantamine (II) with sodium tetrahydroborate gave iolantaminol (VI). Hydrogenation of iolantamine with the aid of Raney nickel led to tetrahydroiolantamine, identical with compound (IV).

The structures of the compounds mentioned were determined by the investigation of their UV, IR, and NMR spectra and by mass-spectrometric analysis.

In the mass spectrum of regelamine peaks of ions with m/e 331 (M^+), 330, 228, 270, 244, 242, and 205 are intense, and those with m/e 284, 272, and 256 and a number of others are less intense. The structures of these ions (their compositions were determined by high-resolution mass spectra) are given in Scheme 2.

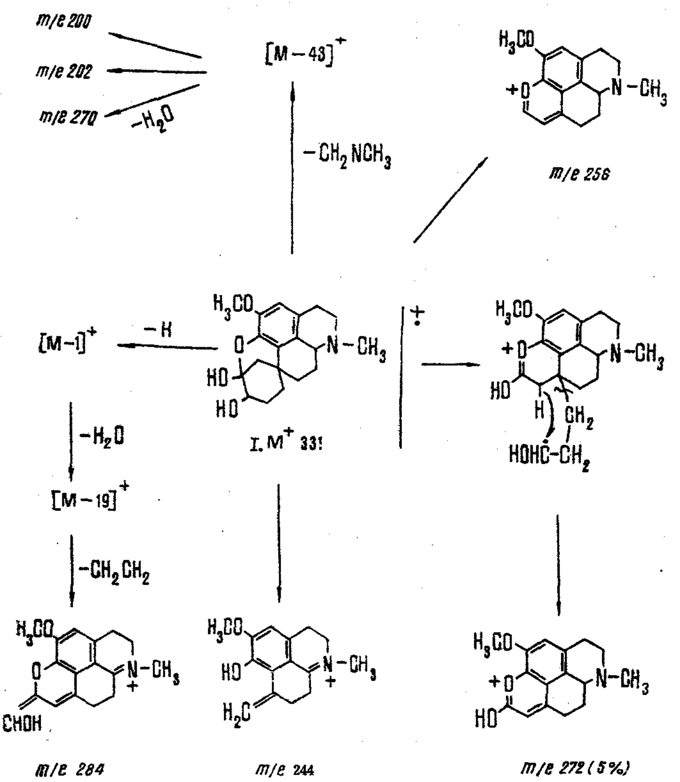
The ion with m/e 270 (M−61) is formed from the ion with m/e 288 by the elimination of water. The mass spectra of regelamine also has the peak of an ion with m/e 312 (M−19) formed analogously from the $(M-1)^+$ ion.

Ions with m/e 244.1341, with the composition $C_{15}H_{18}NO_2$, and m/e 256.1330, with the composition $C_{16}H_{18}NO_2$, show the position of the spiro center and of the oxygen bridge forming the six-membered ring E. The elimination of groups of atoms containing two oxygen atoms ($C_3H_7O_2$ and $C_4H_7O_2$) in the formation of the ions with m/e 256 and 244, respectively, is possible only with the decomposition of rings D and D, E. A detailed consideration of all the pathways of this decomposition and a comparison of them with results published previously [4] completely confirm the linkages of the A, C, D, and E rings in structure (I). Ions with m/e 272.1281, with the composition $C_{16}H_{18}NO_3$, confirm the presence of two alcoholic hydroxy groups in regelamine. The formation of ions with m/e 272 and 284 is in full harmony with the decomposition of α-diols [5].



Scheme 1

V. I. Lenin Tashkent State University. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 328-334, May-June, 1976. Original article submitted July 28, 1975.



Scheme 2

The formation of these ions by Scheme 2 is confirmed by the production of the spectra of metastable transitions by the direct analysis of the daughter ions (DADI). Information on the metastable ions is given below (m_0 is the mass of the initial ion, m_1 the mass of the ion formed, V_1/V_0 the ratio of the values of the deviating voltage, experimental, and $[V_1/V_0]_T$ the same ratio, calculated):

m_0	m_1	V_1/V_0	$[V_1/V_0]_T$	Δm
331	288	0.871	0.870	43
331	272	0.822	0.821	59
331	256	0.774	0.773	75
331	244	0.734	0.737	87
331	242	0.730	0.731	89
331	230	0.694	0.694	101
330	312	0.944	0.945	18
312	284	0.911	0.910	28
288	270	0.937	0.938	18
288	202	0.701	0.701	78

The formation of an ion with m/e 244 directly from the molecular ion was shown by the defocusing method. The ratio of the values of the accelerating voltages $E_1/E_0 = 1.359$ (calculated 1.356).

The peaks of the ions in the mass spectrum of dihydroregelamine (III) are shifted by two mass units in the direction of larger masses as compared with the spectrum of regelamine. This confirms that the reduction took place at the bond of the oxygen bridge with the C_{12} atom. The reduction of the same ring at the bond with the C_1 atom is excluded, since it should lead to the splitting out of water and the formation of a compound with a mass number of 315.

The structure of the second reduction product follows directly from a comparison of the molecular masses of the substances: (I), 331; (III), 333; and (IV), 317. The formation of substances (III) and (IV) on reduction at one and the same reaction center, C_{12}, is also confirmed by the identical peaks of ions formed in the decomposition of rings [for example, the ions $(M-29)^+$ and $(M-43)^+$].

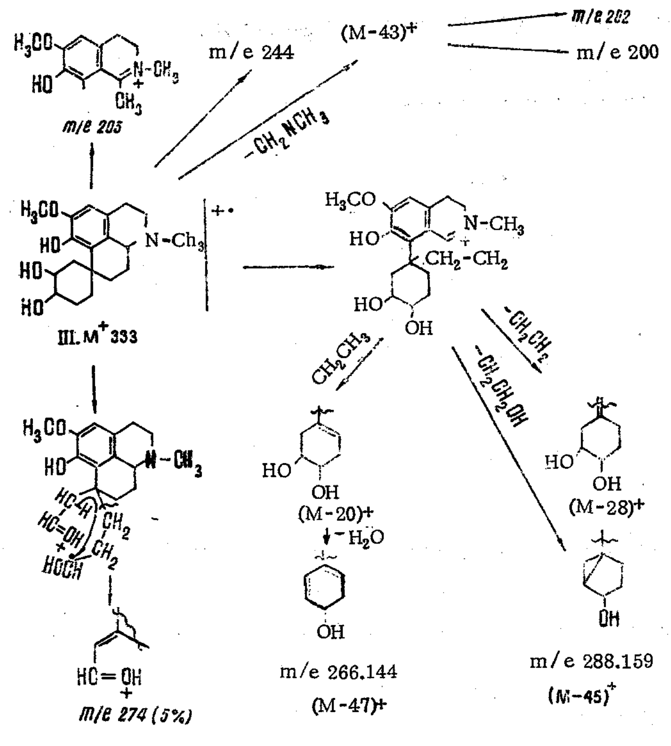
The fragmentation of substances (III), (IV), and (VI) is shown in Schemes 3 and 4. The peaks of the ions in the same spectrum of compound (V), containing ring A, are shifted by 14 amu in the direction of larger masses as compared with the corresponding peaks in the spectrum of (IV).

Information on the relative intensities of the ions in the mass spectra of substances (I), (III), (IV), (V), and (VI) is given in Table 1.

TABLE 1

Substance	M	M−1	M−17	M−19	M−28	M−29	M−43	M−45	M−47	M−61	200	202	205	242	244	256
I	43	100	4	7	—	—	45	7	5	7	8	27	15	18	32	4
III	60	100	2	2	9	8	45	7	6	7	2	3	19	2	4	—
IV	65	100	1	3	8	8	55	7	6	8	5	12	68	4	11	—
V	60	100	11	1	9	9	54	7	8	9	8	10	40	8	15	—
VI	45	100	11	10	60	15	25	51	17	13	(214) 7	(216) 5	(219) 15	(256) 18	(258) 22	

m/e, Relative intensity, %



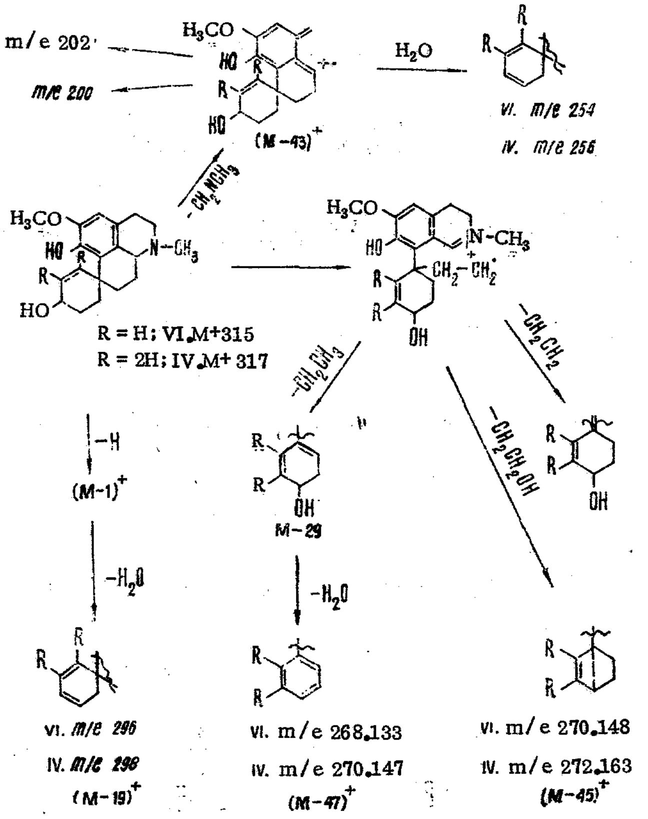
Scheme 3

In the mass spectrum of regelamine there are no peaks of the ions $(M-28)^+$ and $(M-29)^+$, but there is the peak of an ion $(M-19)^+$, which is formed from the ion $(M-1)^+$. In its turn, the ion $(M-19)^+$ decomposes with the elimination of ethylene, forming an ion $(M-47)^+$, as is confirmed by the method of the direct analysis of daughter ions (see above).

In the mass spectra of substances not containing the oxygen bridge and ring E (III, IV, and VI) there are the peaks of the ions $(M-28)^+$ and $(M-29)^+$. The ion $(M-45)^+$ is formed directly from the molecular ion by the elimination of a CH_2CH_2OH group. This is confirmed by a metastable transition in the case of (III). The ion $(M-47)^+$ in (III), (IV), and (VI) is formed from the ion $(M-29)^+$ by the elimination of water. This change is also confirmed by a metastable transition:

m_0	m_1	V_1/V_0	$[V_1/V_0]_T$	Δm
333	305	0.915	0.916	28
333	304	0.913	0.913	29
333	290	0.868	0.871	43
333	288	0.864	0.865	45
333	274	0.820	0.823	59
333	302	0.907	0.907	31
333	244	0.729	0.733	89
333	230	0.690	0.681	103
304	286	0.942	0.940	18

The formation of the ion $(M-47)^+$ from the ion $(M-29)^+$ is observed in the spectrum of iolantaminol (VI). The ion $(M-47)^+$ is formed only from the ion $(M-29)^+$ by the elimination of water. The formation of the ion $(M-47)^+$ from the ion $(M-19)^+$ containing conjugated double bonds in ring D is impossible (see Scheme 4). The ion $(M-47)^+$ in the mass spectra of the products of the reduction of (III, IV, and VI) is formed from the ion $(M-29)^+$, and in regelamine and kesselridine, which contain the oxygen bridge and ring E, it is formed from the ion $(M-19)^+$.



Scheme 4

In dihydroregelamine (III) there is the peak of an ion with m/e 274 showing the position of the alcoholic hydroxy group. We have observed decomposition with the formation of such an ion previously in the case of kesselridine [4].

EXPERIMENTAL

The mass spectra were taken on an MAT-311 instrument and an ionizing voltage of 70 V in the range of temperatures of evaporation of the samples of 80-100°C, the UV spectra were taken on an SF-4A spectrometer (in methanol), the IR spectra on a UR-10 double-beam spectrometer, and the NMR spectra on a Varian XL-100 spectrometer (in deuterochloroform).

The individuality of the substances obtained and their R_f values were determined by paper chromatography using "Filtrak" No. 2 paper (fast, 120-125 g/cm^3) with the solvent system n-butanol–5% acetic acid (50:50).

Reduction of Regelamine. With vigorous stirring and cooling, 4 g of metallic sodium were slowly added to a solution of 500 mg of regelamine in 80 ml of abs. ethanol. After the end of the reaction, the solvent was distilled off and the residue was dissolved in water. To eliminate the unchanged regelamine (R_f 0.50), the resulting alkaline solution was extracted with chloroform. The aqueous solution was acidified with hydrochloric acid to pH 1 and was again made alkaline, with ammonia to pH 8, and carefully extracted with chloroform. The chloroform extract was found to contain two substances, with R_f 0.43 and 0.67.

When the chloroform solution of the mixture was extracted with 3% caustic soda solution, the compound with R_f 0.43 passed into the alkaline solution.

1-Hydroxy-1,12-Deoxyregelamine (III). The alkaline extract containing the compound with R_f 0.43 was acidified with hydrochloric acid to pH 1, made alkaline again, the ammonia to pH 8, and extracted with chloroform. The dry residue obtained after the distillation of the solvent was purified by passage through a small layer of alumina (elution with chloroform) and was crystallized from acetone. A substance $C_{19}H_{27}O_4N$ (mass spectrometrically), mp 185-187°C, M$^+$ 333.192, R_f 0.43, was isolated.

UV spectrum: λ_{max} 213 and 287 nm. IR spectrum, ν_{max}, cm^{-1}: 1600 (–CH=CH–); 3100-3500 (OH).

NMR spectrum (δ, ppm): 6.40 (1 H, ar), 3.76 (3 H, s, OCH_3, ar), 2.35 (3 H, s, N–CH_3).

1-Hydroxy-1,12:12-Dideoxyregelamine (IV). The chloroform solution after extraction with alkali was dried with sodium sulfate, the solvent was distilled off, and the residue was treated with acetone. A white crystalline substance deposited with the formula $C_{19}H_{27}O_3N$ (mass spectrometrically), mp 175–177°C, M^+ 317.1972, R_f 0.67. UV spectrum: λ_{max} 215 and 287 nm. IR spectrum, ν_{max}, cm^{-1}: 1600 (ar. –C = C–), 3100–3400 (OH). NMR spectrum, (δ, ppm): 6.38 (1 H, s, arom.), 5.38 (1 H, s, OH phenolic), 3.76 (3 H, s, OCH_3, arom.), and 2.35 (3 H, s, N–CH_3).

Iolantaminol (VI). In portions, 210 mg of sodium tetrahydroborate was added to a solution of 70 mg of iolantamine in 3 ml of methanol, and the mixture was left at room temperature to the following day. Then the solvent was distilled off and the residue was treated with water and extracted withe acetone.

This gave a light yellow amorphous powder with R_f 0.47 having the composition $C_{19}H_{25}O_3N$ (mass spectrometrically); M^+ 315.182.

IR spectrum, cm^{-1}: 1600 (ar. –C = C–), 3400–3500 (OH).

NMR spectrum, ppm: 6.38 (1 H, ar.), 5.65, 5.40 (olefinic protons), 3.72 (3 H, s, OCH_3), and 2.34 (3 H, s, N–CH_3).

Tetrahydroiolantamine (IV). A solution of 60 mg of iolantamine in 5 ml of methanol was reduced with hydrogen in the presence of freshly prepared Raney nickel catalyst. After the end of the reaction the catalyst was filtered off and the solvent was distilled off. The dry residue was treated with acetone. This yielded white crystals with mp 173–175°C, R_f 0.67. According to its spectral characteristics and R_f value, the substance isolated was 1-hydroxy-1,12:12-dideoxyregelamine.

SUMMARY

On the basis of a mass-spectrometric analysis of regelamine and the products of its reductive decomposition information has been obtained which confirms the position of the hemiacetal group and its structure as a whole, which is also confirmed by the results of the mass spectroscopy of the products of the reduction of iolantamine.

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