THE STRUCTURE OF LAPACONIDINE

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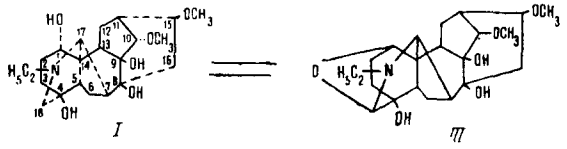
From the combined chloroformic alkaloids of Aconitum leucostomum we have previously isolated a new base – lapaconidine (I), $C_{22}H_{35}O_6N$ [1]. The NMR spectrum of the alkaloid contained the signals of one N-ethyl and two methoxy groups. Acetylation showed the presence of four hydroxy groups. Consequently, the developed formula of the compound is $C_{18}H_{20}(OH)_4(OCH_3)_2(N-C_2H_5)$. On comparing the developed formulas of lappaconine [2, 3] and of lapaconidine it can be seen that they differ by the numbers of hydroxy and methoxy groups, the total number of substituents in the two compounds being the same. The methylation of (I) with methyl iodide in the presence of sodium hydride gave tetramethyllapaconidine (II), $C_{26}H_{43}O_6N$, which proved to be identical with the product of the methylation of lappaconine obtained under the same conditions. It remained to determine the mutual positions of the substituents in lapaconidine.

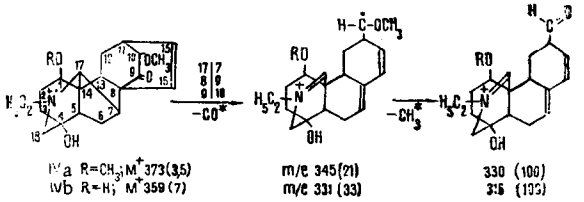
In the mass spectrum of lapaconidine, the maximum peak is that of the ion M−17. This shows that there is a hydroxy group at C-1 [4]. This was confirmed by the oxidation of (I) with potassium permanganate according to Marion [5]. The oxidation product (III) has the composition $C_{22}H_{33}O_6N$; i.e., it differed from the initial alkaloid by two hydrogen atoms. The Adams hydrogenation of (III) gave the initial lapaconidine. It is known that if there is an α-OH group at C-1 in the Aconitum alkaloids, instead of an oxo derivative an internal ether of a carbinolamine ether is also shown by the peak of the ion M−56 (100%) in the mass spectrum of (III) due to the ejection of an acrolein molecule from ring A [6]. This transition is confirmed by a metastable peak.

We have shown previously [2] that, on being heated with 50% sulfuric acid, lappaconine gives a product for which, on the basis of IR, UV, and NMR spectra, structure (IVa) was proposed. The reaction of lapaconidine with sulfuric acid led to an analogous compound $C_{21}H_{29}O_4N$ (IVb), as was shown by the similarity of the NMR, IR, and mass spectra of the two products. This induced us to make a more detailed study of the structures of (IVa) and (IVb), in the first place to prove the structure of (IVa) proposed previously and, in the second place, to determine the mutual positions of the four substituents in lapaconidine.



I III

The main route of fragmentation under the conditions of mass spectrometry agrees with structure (IV).



IVa R=CH$_3$; M$^+$ 373 (3.5)
IVb R=H; M$^+$ 359 (7)
m/e 345 (21)
m/e 331 (33)
330 (100)
316 (100)

Because of the formation of a stable system, the molecules undergo no appreciable further degradation after the ejection of carbon monoxide and a methyl radical. Compounds (IVa) and (IVb) show weak peaks of ions with m/e 312 (1.5%) and 298 (1.7%), respectively.

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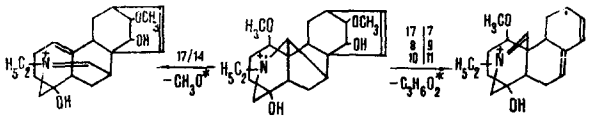
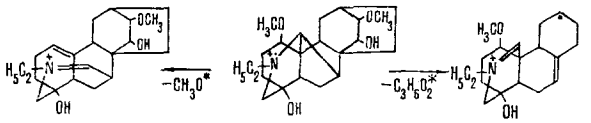
The reduction of (IVa) with sodium amalgam in absolute ethanol led to a crystalline product $C_{22}H_{33}O_4N$ (V) whose IR spectrum lacked the absorption band of a carbonyl group. The appearance of an additional hydroxy group was shown by the preparation of the diacetate (V). In the mass spectrum of (V) the maximum peak is that with m/e 301, and the next in intensity is the peak of the ion with m/e 344. The loss of 74 mass units is connected with the departure of a fragment including carbon atoms C-9 and C-10. The mass spectrum of the OD analog of (V) confirms this fragmentation route.

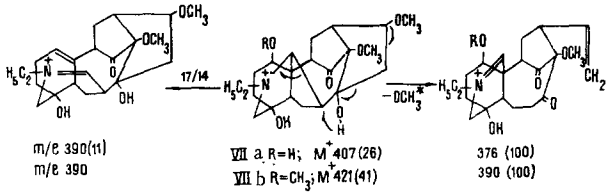


The Adams hydrogenation of (IVa) gave a crystalline tetrahydro derivative, $C_{22}H_{35}O_4N$ (VI). Its IR spectrum lacked the absorption both of a carbonyl group and of a double bond. In the mass spectrum of this compound the maximum peak with m/e 346 arises in the expulsion of a methoxy radical from C-1, and the fragmentation due to the appearance of a fragment with m/e 303 is again of secondary importance.



Additional information on the presence in lapaconidine of a diol system at C-8 and C-9 and also of a methoxy group at C-15 was obtained by the oxidation of lapaconidine with chromium trioxide in acetone. The IR spectrum of the reaction product (VIIa) had the absorption band of a carbonyl group at 1745 cm^{-1} (cyclopentanone). According to spectroscopy, this compound is similar to (VIIb) obtained analogously from lappaconine [2]. The fragmentation of (VIIa) under the conditions of mass spectrometry differed from that of the initial (I). While in the case of (I) there was a peak of the M−17 ion and no peak of the M−31 ion, in (VIIa) the M−31 peak became the maximum peak, while M−17 amounted to 11%. In the mass spectrum of (VIIb) the maximum peak was again that of the ion M−31.

Taking what has been said into account, the route of the decomposition of these compounds on mass spectrometry can be represented by the following scheme:



The information given enables the mutual position of five of the substituents in lapaconidine to be determined and, consequently, only one possible position remains for the fourth hydroxy group – C-4. As a result of the correlation that we have made between lapaconidine and lappaconine, for which the absolute configuration has been established [7], a similar configuration is proposed for lapaconidine.

EXPERIMENTAL

The mass spectra were recorded on an MKh-1303 instrument fitted with a system for direct introduction into the ion source, and the NMR spectra on a JNM-4H-100/100 MHz instrument in chloroform with HMDS as internal standard. (The values are given in the δ scale.) The uniformity of the products was checked by chromatography in a thin layer of type ShSK silica gel in the benzene–methanol (4 : 1) system.

Isolation of Lapaconidine. The combined chloroformic alkaloids of A. leucostomum (5 g) were separated into eight fractions according to their basicities. Fraction 5 (2.3 g), on treatment with benzene,* gave lapaconidine benzoate* with mp 118-120°C. Yield 1.4 g. After recrystallization from benzene–meth-

*As in Russian original – Publisher.

anol and drying in vacuum, mp 206-207°C, $[\alpha]_D^{20}$ + 120° (c 2.2; $CHCl_3$). NMR spectrum: 1.07 ppm (triplet, $N-CH_2-CH_3$); 3.27 and 3.36 ppm (singlets, two OCH_3 groups). Mol. wt. 409.

Lapaconidine Tetraacetate. A mixture of 0.1 g of lapaconidine, 5 ml of acetic anhydride, and 0.05 g of p-toluenesulfonic acid was heated in the water bath for 1 h. After the usual working up, a crystalline acetate with mp 195-197°C (ether–methanol) was obtained. NMR spectrum: 1.02 ppm (triplet, $N-CH_2-CH_3$); 1.86, 1.95, 1.98, and 2.02 (singlets, four $OCOCH_3$ groups). IR spectrum: 1730 cm^{-1} (ester carbonyl).

Methylation of (I). A mixture of 60 mg of the base and 40 mg of sodium hydride in 15 ml of dry dioxane was stirred for 30 min, and then 2 ml of methyl iodide was added. The resulting mixture was stirred for 6 h, being heated periodically to 50-60°C. The precipitate was separated off, and the mother solution was evaporated. The residue was dissolved in 5% sulfuric acid, and the solution was made alkaline with sodium carbonate with cooling and extracted with chloroform. The tetramethyllapaconidine was purified on a column of alumina, being eluted with ether. Yield 45 mg, mp of (II) 69-71°C (from hexane). The IR spectrum lacked absorption bands of hydroxy groups. Mol. wt. 465.

Methylation of Lappaconine. The trimethyllappaconine obtained by the method described above had mp 69-71°C (from hexane) and was shown to be identical with (II) by a mixed melting point and by IR and mass spectra.

Anhydrohydroxylapaconidine (III). Solutions of 0.15 g of lapaconidine in 40 ml of acetone–water (4 : 1) and of 0.15 g of potassium permanganate in 50 ml of acetone–water (1 : 1) were shaken together for 5 min. The excess of potassium permanganate was decomposed with sodium sulfite. After the manganese dioxide had been separated off, the acetone was distilled off. The reaction product was extracted with chloroform and purified on a column of alumina, being eluted with benzene–methanol (100 : 1). Yield 75 mg, mp 233-234°C (hexane–acetone). Mol. wt. 407.

Hydrogenation of (III). The hydrogenation of 25 mg of (III) was performed by Adams' method in 8 ml of methanol, giving lapaconidine with mp 206-207°C.

Reaction of Lapaconidine with Sulfuric Acid. A solution of 0.5 g of (I) in 15 ml of 50% sulfuric acid was heated in the water bath for 2 h. With cooling, the acid solution was made alkaline with sodium carbonate, and it was extracted with ether. The solvent was distilled off and 0.3 g of the initial lapaconidine was separated off. The mother solution (0.19 g) after evaporation was chromatographed on a column of alumina, elution being performed with ether. This gave 0.12 g of a crystalline product (IVb) with mp 170-172°C (ethyl acetate–ether). Mol. wt. 359. IR spectrum: 1720, 1730 cm^{-1} (carbonyl group). NMR spectrum, ppm: 1.01 (three-proton triplet, $N-CH_2-CH_3$); 3.45 (three-proton singlet, OCH_3), 5.42 (one-proton doublet); 6.45 (one-proton triplet).

Reduction of (IVa) with Sodium Amalgam. A mixture of 0.12 g of (IVa) and 3.5 g of sodium amalgam in 7 ml of absolute ethanol was stirred at room temperature for 10 h. The ethanolic solution was separated from the mercury and evaporated. The residue was chromatographed on alumina. Elution with benzene gave 50 mg of a crystalline product (V), mp 117-118°C (ether–methanol), and elution with benzene–methanol (100 : 1) gave 35 mg of the initial (IVa). IR spectrum of (V), cm^{-1}: 3520 and 3450 (OH), 3057 (double bond). Mol. wt. 375.

Diacetate of (V). A solution of 40 mg of (V) in 4 ml of acetyl chloride was left at room temperature for 8 days. Then the acetyl chloride was evaporated off, the residue was dissolved in water, with cooling the solution was made alkaline with sodium carbonate, and it was extracted with chloroform. This gave the diacetate of (V) in the form of an oil. NMR spectrum: 1.01 ppm (triplet, $N-CH_2-CH_3$), 1.90 and 1.98 (three-proton singlets, 2 $OCOCH_3$), 3.15 and 3.20 (three-proton singlets, 2 OCH_3), 5.57 (one-proton doublet), 6.41 (one-proton triplet).

Hydrogenation of (IVa). The Adams hydrogenation of 100 mg of (IVa) in 10 ml of ethanol gave a precipitate of the crystalline tetrahydro derivative (VI) with mp 180-182°C (ether–ethanol). Mol. wt. 377. IR spectrum: 3525 and 3460 cm^{-1} (OH).

Oxidation of Lapaconidine with Chromium Trioxide. With cooling, a solution of 0.1 g of (I) in 5 ml of acetone was mixed with 0.1 g of chromium trioxide in 5 ml of acetone and left at room temperature for 48 h. Then the acetone was distilled off, the residue was dissolved in 10% sulfuric acid, and the excess of chromium trioxide was decomposed with sodium sulfite. The solution was made alkaline with sodium carbonate and extracted with chloroform. The residue after the solvent had been distilled off was treated with

benzene, and 0.06 g of the initial (I) was separated off. The material from the mother solution (0.035 g) was chromatographed on alumina and eluted with ether. This gave dehydrolapaconidine with mp 230-232°C (ether–methanol). IR spectrum: 1743 cm^{-1} (cyclopentanone). Mol. wt. 407.

SUMMARY

1. The structure of the new alkaloid lapaconidine has been established.

2. The structure proposed previously for the product of the reaction of lappaconine with sulfuric acid has been confirmed on the basis of chemical and spectral studies.

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