Ajanin Triacetate (IV). A solution of 130 mg of ajanin in 7 ml of acetyl chloride was kept for 3 h, after which it was evaporated in vacuum. The residue was separated on a column of silica gel. Elution with benzene and with benzene–acetone (20:1) yielded compound (IV) with the composition $C_{21}H_{26}O_8$, mp 182-183°C (ether).

Oxidation of Ajanin. Solutions of 300 mg of ajanin in 3 ml of ethanol and 400 mg of periodic acid in 2 ml of water were mixed. After four days, the mixture was treated with ethyl acetate. Separation on a column yielded substances with mp 179-181°C and 206-207°C.

Anhydroajanin (V). A solution of 200 mg of ajanin in 10 ml of ethanol containing 0.5 ml of concentrated H_2SO_4 was kept at 70°C for 7 h. The excess of acid was neutralized with sodium bicarbonate to a weakly acid reaction, and the mixture was shaken with chloroform. Separation of the chloroform extract on a column of silica gel with a mixture of benzene and acetone (40:1) yielded a product with the composition $C_{15}H_{18}O_4$, mp 220-221°C (benzene).

SUMMARY

The new sesquiterpene lactone ajanin has been isolated from the epigeal part of the plant Ajania fastigiata (Winkl.) Poljak. It has been shown that it has the structure of 3,4,8α-trihydroxy-5α,6β,7α(H)-guaia-1(10),11(13)-dien-6,12-olide.

LITERATURE CITED

1. M. I. Yusupov, Sh. Z. Kasymov, G. P. Sidyakin, and U. Rakhmankulov, Khim. Prir. Soedin., 579 (1979).
2. M. A. Irwin and T. A. Geissman, Phytochemistry, 12, 863 (1973).
3. E. L. Jackson, Organic Reactions, 2, 341 (1944).
4. H. Furukawa, K.-H. Lee, T. Shingu, R. Neck, and C. Piantadosi, J. Org. Chem., 38, No. 9, 1722 (1973).
5. K. Vokac, Z. Samek, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 37, 1346 (1972).

STRUCTURE AND CONFIGURATION OF A NEW DITERPENOID LACTONE FROM Lagochilus hirsutissimus

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The epigeal part of the plant Lagochilus hirsutissimus has yielded a new diterpenoid lactone – lagohirsidin, $C_{22}H_{34}O_5$, mp 144-145°C, $[\alpha]_D^{22}$ − 17.5° (c 1; ethanol). Reduction with $LiAlH_4$ has yielded a diol $C_{22}H_{38}O_5$, mp 165-166°C $[\alpha]_D^{20}$ −1.2 (c 0.6; ethanol). Acid hydrolysis of the diol has led to the formation of lagochilin, $C_{20}H_{36}O_5$, mp 167-168°C, $[\alpha]_D^{20}$ −3.9° (c 1; ethanol). The synthesis of lagohirsidin from lagochilin has been effected.

The plant Lagochilus hirsutissimus, family Labiatae, contains lagochilin and tanning substances [1]. From the epigeal part of this plant we have isolated a new crystalline substance, $C_{22}H_{34}O_5$, with mp 144-145°C, $[\alpha]_D^{22}$ −17.53°, which we have called lagohirsidin (I).

Lagohirsidin possesses a neutral character and it is readily soluble in methanol, chloroform, acetone, and benzene, sparingly soluble in ether, carbon tetrachloride, and petroleum ether, and insoluble in water.

On being heated with aqueous alkali, (I) passed into solution and on subsequent acidification it was liberated in the unchanged state, which indicates that it belongs to the class of lactones. The presence of a lactone group was also shown by absorption at 1800 cm^{-1}

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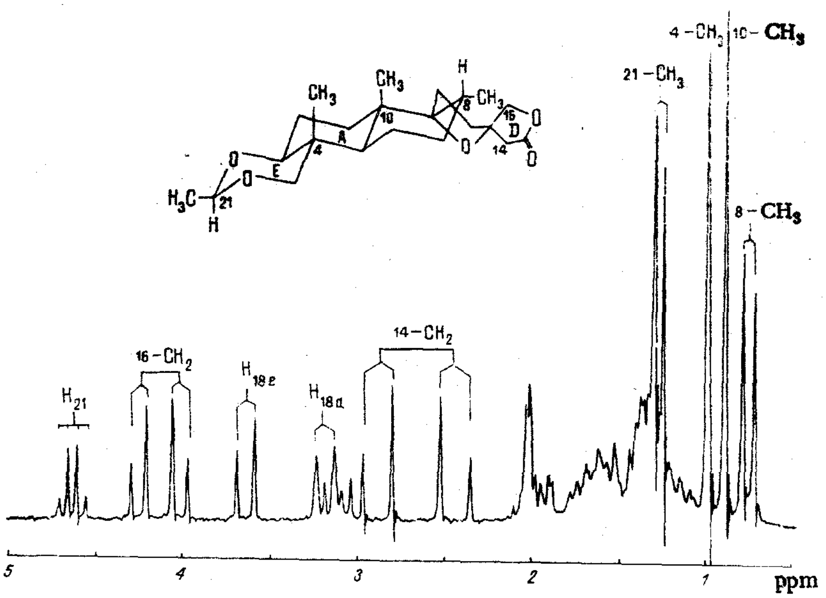


Fig. 1. PMR spectrum of lagohirsidin.

in the IR spectrum of (I). Such a high value of the absorption of a carbonyl group is characteristic for highly strained five-membered lactones.

When (I) was reduced with lithium tetrahydroaluminate, a diol (II) was formed, and the acid hydrolysis of this led to lagochilin (III). Consequently, (I) contains the lagochilin skeleton.

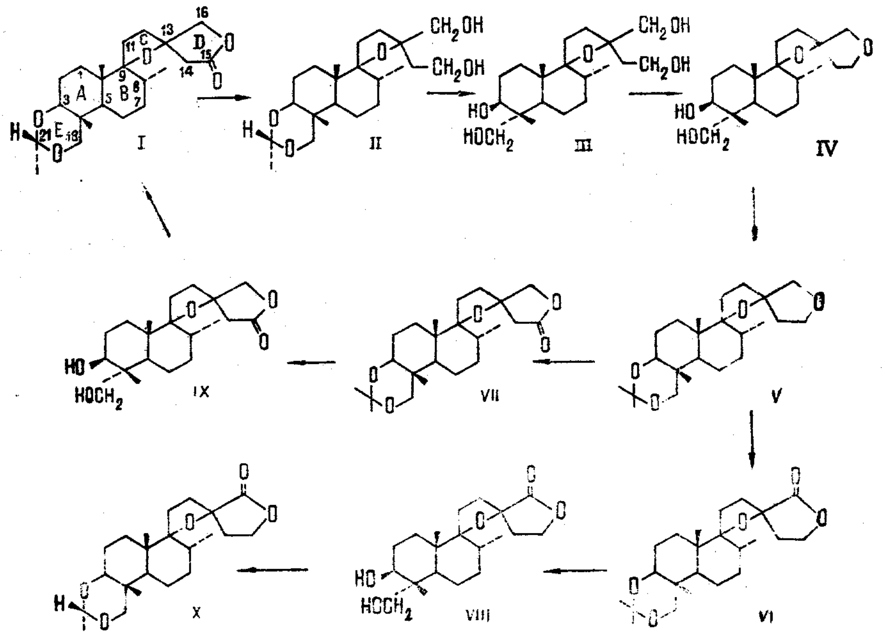
To elucidate the structure of (I) we studied its mass and PMR spectra. The mass spectrum of (I) contained the peak of the molecular ion with m/e 378 in low intensity, and peaks with m/e 334, 194, 181, and 168, which indicates the presence of lactone and furan groups. Similar fragmentation is characteristic for diterpenoids of the 9,13-epoxylabdane series [2, 3].

In the PMR spectrum of (I) (Fig. 1) there are the signals of three methyl groups at C-4, C-10, and C-8 in the strong-field region at 0.99, 0.90, and 0.78 ppm (doublet, J = 6 Hz) [4]. At 1.27 ppm there is a strong doublet with a constant J = 5 Hz of another methyl group. It was established by the double-resonance method that the splitting of this signal was due to spin–spin coupling with a methine proton the signal of which is located at 4.63 ppm in the form of a quartet. The values of the chemical shifts and the absence of additional splittings of the signals show the presence of an ethylenedioxy fragment in the molecule.

The protons of the main skeleton of the molecule of (I) resonate in the 1.0-2.1 ppm region.

Two doublets at 2.88 and 2.4 ppm form an AB system with a constant J = 17.0 Hz. The size of the constant permits us to assign these signals to a geminal pair of protons adjacent to the carbonyl of the lactone ring. The other pair of geminal protons of the lactone ring gives an AB system of signals at 4.24 and 4.02 ppm with J = 8.7 Hz. The signals of an oxymethylene group at C-18 also form an AB system of doublets at 3.65 and 3.2 ppm with a geminal coupling constant J = 10.5 Hz. The components of a proton signal at 3.20 ppm are broadened in comparison with the signal of its geminal partner. It was established by the double-resonance method that the broadening was due to the spin–spin coupling with the methyl group at C-4 (0.99 ppm). Consequently, this proton is oriented axially, since only in that case would it be possible to observe long-range spin–spin coupling by the "zig–zag" rule with the axial methyl group at C-4 [5]. At 3.12 ppm is the signal of the proton at C-3 in the form of a doublet of doublets (5.6 and 9.2 Hz), which shows the axial orientation of this proton.

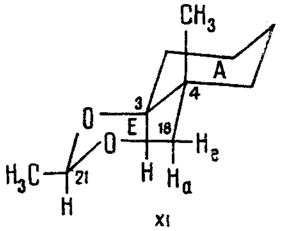
To determine the positions of the lactone and ethylenedioxy groups, compound (I) was synthesized from lagochilin. The structure and configuration of lagochilin itself have been established by physicochemical methods, and also by x-ray structural analyses [2, 4, 6, 7].



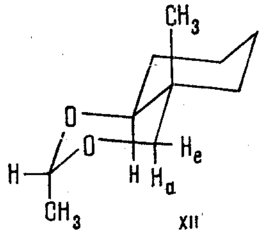
For the synthesis of (I), lagochilin (III) was converted into anhydrolagochilin (IV) the isopropylidene derivative of which (V) was oxidized with potassium permanganate in a weakly acid medium in acetone solution. This formed a mixture of two isomeric oxy products (VI and VII). On hydrolysis, the oxy products gave substances (VIII) and (IX). On treatment with acetaldehyde, compound (IX) formed (I), identical with the natural compound in all its indices. When (VIII) was treated with acetaldehyde, it formed (X), the structure of which was established by a study of its mass and PMR spectra. In all its physicochemical constants, compound (X) was identical with the compound obtained by oxidizing the ethylenedioxy derivative of lasiocoryin [6].

The configurations of rings E and D of the lagohirsidin molecule were determined from PMR spectra using experiments to measure the nuclear Overhauser effect (NOE).

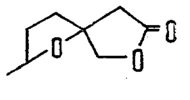
As has been shown above, the proton at C-3 and the methyl group at C-4 are oriented 1,2-diaxially. Consequently, the 1,3-dioxane ring E is trans-linked with ring A. The configuration of the methyl group at C-21 was determined from NOE experiments [8].



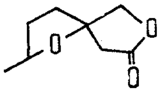
XI



XII



XIII



XIV

The essence of the experiments consisted in the fact that with the two alternative cases (XI) and (XII), when the methyl group at C-21 was irradiated the intensities of the $H-C_3$ and H_e-C_{18} signals should rise to different extents. By acting on the methyl group (1.27 ppm) with a perturbing field H_2 it was established that the intensities of the $H-C_3$, H_a-C_{18}, and H_e-C_{18} signals rose by 11.5, 10.2, and 15.7%, respectively. Such a uniform increase in the intensities of the signals is apparently due to the equatorial orientation of the CH_3-C_{21} group (since the distances from it to the H_e-C_{18} and H_a-C_{18} atoms are practically identical) and also by the possible irradiation of the neighboring protons resonating in the region into which CH_3 groups fall. Additional experiments were carried out to eliminate the ambiguity. In the case of (XI), H-C_3, H_a-C_{18}, and H-C_{21} are oriented 1,3-diaxially and should give appreciable NOEs on mutual irradiation. When H-C_{21} was irradiated, the H-C_3 and H_a-C_{18} signals increased their intensities by 12.2 and 6.9%; when the H_a-C_{18} and H-C_3 protons were irradiated, the intensity of the H-C_{21} signal rose by 10.0 and 21.1%, respectively. The existence of a well-defined NOE in this series of experiments on nonoverlapping signals showed the axial orientation of H-C_{21} and, consequently, the equatorial orientation of the methyl group (XI).

The orientation of the lactone ring relative to the remainder of the molecule of (I) was determined by the NOE method. Two cases are possible theoretically: (XIII) and (XIV).

On the basis of x-ray structural results for the lagochilin (III) molecule [6, 7], we considered that the configuration of the bonds at C_9 and the equatorial orientation of the methyl group at C-8 in the molecule of (I) were known. In this case, the methyl group at C-8 is sterically close either to the O-CH_2 protons of the lactone ring (XIII) or to the methylene protons adjacent to the carbonyl group (XIV). Under the action of a perturbing field on the methyl group at C-8 (0.78 ppm), the signals at 2.88 and 2.40 ppm increased their intensities by 6.9 and 7.5%, while the other pair of signals of lactone ring protons (4.24 and 4.02 ppm) did not increase the intensities of their signals. Consequently, fragment (XIV) corresponds to the (I) molecule.

The configuration of lagohirsidin established on the basis of PMR results is in harmony with x-ray structural information obtained previously about lagochilin [6, 7].

EXPERIMENTAL

IR spectra were recorded on a UR-10 spectrophotometer, PMR spectra on a Varian XL-100-15 spectrometer in $CDCl_3$ solution, and mass spectra on a MAT-311 instrument. Specific rotations were determined on a Carl Zeiss Polamat S instrument (GDR).

For thin-layer chromatography (TLC) we used silica gel LS 5/40 μ. The revealing agent was concentrated H_2SO_4 with 1% of vanillin.

Isolation and Separation of the Lactone. The air-dry and comminuted epigeal parts of *L. hirsutissimus* were extracted with methanol (5 × 15 liters). The extract was concentrated, diluted with water (1:1), and extracted with diethyl ether. Elimination of the solvent yielded 22 g of combined substances which were chromatographed on alumina (activity grade III, neutral) with elution by benzene containing gradually increasing amounts of methanol. Fractions with a volume of 150 to 200 ml were collected. Fractions 1-15 contained carbohydrates, flavonoids, sterols, etc.

Fractions 16-34 (3.35 g) were rechromatographed on a column of type LS 100/160 μ silica gel. They were eluted with benzene—ether (95:5).

Fractions 1-20 yielded 0.3 g of lagohirsidin, $C_{22}H_{34}O_5$ (M^+ 378), mp 144-145°C (ether), $[\alpha]_D^{21}$ −17.53° (c 1; ethanol). Yield 0.075% on the dry raw material.

Reduction of Lagohirsidin (I). A solution of 0.15 g of substance (I) in 30 ml of anhydrous tetrahydrofuran was added to a suspension of 0.3 g of lithium tetrahydroaluminate in 50 ml of tetrahydrofuran. The mixture was boiled for 1 h and then the usual working up gave 0.1 g of the diol (II), $C_{22}H_{38}O_5$, mp 165-166°C (ether), $[\alpha]_D^{20}$ −1.2° (c 0.6; ethanol).

Hydrolysis of the Diol (II). A solution of 0.1 g of the diol (II) in 5 ml of a 5% solution of HCl was heated on the water bath for 30 min. After the usual working up, 0.06 g of lagochilin (III), $C_{20}H_{36}O_5$ was obtained with mp 167-168°C (acetone), $[\alpha]_D^{20}$ −3.9° (c 1; ethanol).

Synthesis of Lagochilin. Anhydrolagochilin (IV) was obtained from lagochilin by a method described by Abramov [9], $C_{20}H_{34}O_4$, mp 97-98°C (ether), $[\alpha]_D^{20}$ −3.3° (c 1; ethanol).

Isopropylideneanhydrolagochilin (V). A solution of 3 g of (IV) in 50 ml of acetone was treated with 0.6 g of $CuSO_4$ (anhydrous) and the mixture was stirred for 6 h. Then it was filtered and the solvent was distilled off, giving 2.5 g of $C_{23}H_{38}O_4$, mp 132-133°C (acetone), $[\alpha]_D^{20}$ −11.8° (c 1; ethanol).

Oxidation of Isopropylideneanhydrolagochilin (V). A solution of 2.5 g (V) in 80 ml of acetone was treated with 10 g of $KMnO_4$ and the mixture was stirred for 18 h with the dropwise addition of concentrated HNO_3 (approximately 3 ml). The excess $KMnO_4$ was decomposed with oxalic acid. The solution was filtered and the solvent was distilled off. The residue (2g) was separated on a column of silica gel of type LS 100/250 μ. Elution was carried out with mixtures of hexane and ether containing increasing proportions of the latter. This gave 0.3 g of the ketone (VI), $C_{23}H_{36}O_5$, mp 169-170°C (hexane—ether), $[\alpha]_D^{21}$ −14.8° (c 1; ethanol), and 0.2 g of the ketone (VII), $C_{23}H_{36}O_5$, mp 107-108°C (hexane—ether), $[\alpha]_D^{22}$ −18.5° (c 1; ethanol).

Hydrolysis of the Ketone (VI). A solution of 0.3 g of the ketone (VI) in 5 ml of ethanol was treated with 5 ml of 10% HCl solution and the mixture was heated on the water bath for 30 min. After the usual working up, 0.2 g of $C_{20}H_{32}O_5$ (VIII) was obtained with mp 187-188°C (ether), $[\alpha]_D^{21}$ −2.6° (c 1; ethanol).

Hydrolysis of the Ketone (VII). Similarly, 0.2 g of the ketone (VII) yielded 0.16 g of $C_{20}H_{32}O_5$ (IX) with mp 142-143°C (ether), $[\alpha]_D^{21}$ −2.0° (c 1; ethanol).

Ethylenedioxy Derivative of the Ketone (VIII). A solution of 0.1 g of (VIII) in 5 ml of acetaldehyde was treated with 0.1 ml of concentrated H_2SO_4 and the mixture was stirred for 30 min. Then it was neutralized with gaseous ammonia. The mixture was filtered, the solvent was distilled off, and the residue was passed through a column of silica gel with elution by means of benzene—ether (95:5). This gave 0.08 g of $C_{22}H_{34}O_5$ (X) (M^+, mp 186-187°C (ether), $[\alpha]_D^{22}$ −0.8° (c 1; ethanol).

Ethylenedioxy Derivative of the Ketone (IX). Similarly, 0.1 g of (IX) and 5 ml of acetaldehyde gave 0.08 g of $C_{22}H_{34}O_5$ (I) (M^+ 378), mp 144-145°C (ether), $[\alpha]_D^{22}$ −17.53° (c 1; ethanol).

SUMMARY

A new diterpenoid lactone which has been called lagohirsidin has been isolated from the plant Lagochilus hirsutissimus and has been characterized.

On the basis of chemical transformations and spectral characteristics, a structure and configuration has been proposed for it.

LITERATURE CITED

1. Sh. T. Sharipova, O. S. Otroshchenko, and A. S. Sadykov, Nauchn. Tr. Tashk. Gos. Univ., 419, 215 (1972).
2. D. E. A. Rivett, Chemsa, 2, No. 1, 7 (1976).
3. G. Enzell and R. Ryhage, Arkhiv. Kemi, 23, 367 (1965).
4. O. S. Chizhov, A. V. Kessenikh, I. P. Yakovlev, B. M. Zolotarev, and A. V. Petukhov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 1983 (1970).
5. S. Sternhell, Quart. Rev., 23, 237 (1969).
6. G. Gafner, G. J. Kruger, and D. E. A. Rivett, Chem. Commun., 249 (1974).
7. L. G. Vorontsova, O. S. Chizhov, B. L. Tarnopol'skii, and V. I. Andrianov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 2, 338 (1975).
8. G. E. Bachers and T. Shaefer, Chem. Revs., 71, 617 (1971).
9. M. M. Abramov, Dokl. Akad. Nauk UzbSSR, No. 3, 41 (1958).