STRUCTURE AND STEREOCHEMISTRY OF LAPIDIN

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The roots of *Ferula lapidosa* Eug.Korov. have yielded lapidin, $C_{20}H_{30}O_4$, mp 80-81°C (hexane), $[\alpha]D^{20}$ +166° (c 1.5; chloroform) — an ester of a new carotane alcohol lapidol and angelic acid. A structure and absolute configuration has been suggested for it on the basis of chemical transformations and spectral characteristics.

Chimgin, ferolin, and chimganidin have previously been isolated from the roots of *Ferula lapidosa* Eug. Korov. collected in the Susamyr valley in Kirghizia [1].

Studying the ester composition of the roots of *F. lapidosa* from the Chigirik Pass, we have isolated a new compound of neutral nature with the composition $C_{20}H_{30}O_4$, M^+ 334, and have called it lapidin (I).

Lapidin is readily soluble in all organic solvents and is insoluble in water. Its IR spectrum has the absorption bands of an ester carbonyl (1710 cm^{-1}), of a hydroxy group (3350 cm^{-1}), and of a carbonyl group present in a seven-membered ring in conjugation with a double bond (1640 cm^{-1}). The latter is confirmed by the presence in the UV spectrum of the maximum characteristic for an α,β-unsaturated ketone with λ_{max} 230 nm (log ε 4.08).

The mass spectrum of lapidin is the usual one for esters of sesquiterpene alcohols [2] and has the peaks of ions with m/e 334 (M^+), 291 $(M - C_3H_7)^+$, 251 $(M - C_5H_7O)^+$, 234 $(M - C_5H_8O_2)^+$, 216 $(M - C_5H_8O_2 - H_2O)^+$, 191 $(M - C_5H_8O_2 - C_3H_7)^+$, 173 $(M - C_5H_8O_2 - C_3H_7 - H_2O)^+$.

The alkaline hydrolysis of lapidin with 5% aqueous alcoholic sodium hydroxide gave a sesquiterpene alcohol $C_{15}H_{24}O_3$ (M^+ 252), which has been called lapidol (II). From the acid part of the hydrolysate an equimolecular amount of angelic acid was isolated, this being identified by comparison with a known sample in relation to melting point and IR spectrum.

Thus, lapidin is the monoester of lapidol and angelic acid.

The mass spectra of lapidin (I) and lapidol (II) show intense peaks of the $(M^+ - 43)$ ions due to the elimination of an isopropyl group. The PMR spectra of both compounds (Table 1) contain the signals of two methyl groups in the form of doublets with SSCCs of 6 Hz and of a methyl group at a double bond.

With the composition $C_{15}H_{24}O_3$ and the presence of a double bond, a carbonyl group, and an isopropyl group, lapidol must have the bicyclic carotane (daucane) skeleton, as is confirmed by the formation of daucalene (III) by the dehydrogenation of (I) with palladium.

Of the three oxygen atoms present in the lapidol molecule, one forms the keto group and the two others are included in hydroxy groups.

The PMR spectrum of lapidol shows the signal of only one gem-hydroxylic proton (m, 4.48 ppm), and, therefore, one of the two hydroxy groups present is secondary and the other is tertiary.

The position of the substituents mentioned and of the double bond were determined on the basis of chemical transformations (scheme) and spectral characteristics.

In the carotane skeleton, three positions are possible for a tertiary hydroxy group, C_4, C_5, and C_{11}, the last of which is excluded because of the multiplicity of the signals of the methyl groups at C_{11}.

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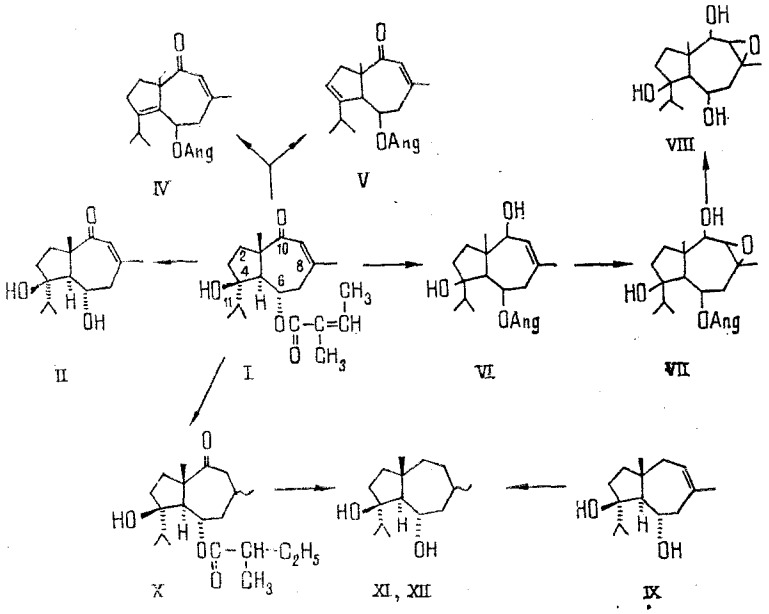

The dehydration of lapidin with thionyl chloride in pyridine gave two anhydro derivatives, A (IV) and B (V), with the same composition $C_{20}H_{28}O_3$ (M^+ 316) the IR spectra of which included no absorption band of hydroxy groups.

The PMR spectrum of the anhydro derivative A was very similar to the spectrum of the initial compound, the only difference being that the signal of the gem-acyl proton had been converted from a multiplet to a quartet with J_1 = 8 Hz, J_2 = 5 Hz, and appeared in a weaker field (5.74 ppm).

In the PMR spectrum of (V), unlike that of (IV), the signals of another olefinic proton appeared in the weak field at 5.39 ppm in the form of a broadened singlet, and the gem-acyl proton had the form of a multiplet at 5.30 ppm.

On comparing the multiplicities and chemical shifts of the signals of the gem-acyl protons in the spectra of the anhydro derivatives A and B and taking into account the appearance of an additional signal of an olefinic proton in the latter, it may be concluded that the tertiary and secondary hydroxyl groups are present in the 1,3 position in relation to one another. This is possible if the tertiary hydroxy group is attached to C_4 and the secondary to C_6.

The UV spectrum of lapidol, like that of lapidin, has the absorption maximum of an α,β-unsaturated ketone with λ_{max} 241 nm.

The appearance of the signals of the protons of a methyl group at a double bond and of an olefinic proton in a somewhat weaker field than usual shows that the carbonyl group is conjugated with a double bond, and the absorption band of a carbonyl group at 1640 cm^{-1} that is present in the IR spectrum of (II) is due to its location in a seven-membered ring.

Thus, if the double bond is located at C_8—C_9, the carbonyl group must be present at C_{10}. The position of the double bond at C_7—C_8 and of the ketone groups at C_6 does not agree with the multiplicity of the signal of the gem-hydroxylic proton. In the PMR spectra of lapidol and of lapidin and its derivatives the latter appears in the form of a multiplet or a sextet, which excludes the presence of the secondary hydroxy group at C_{10}.

The reduction of lapidin with sodium tetrahydroborate led to the formation of dihydrolapidin, $C_{20}H_{32}O_4$ (VI), in the IR spectrum of which the absorption band of the carbonyl group had disappeared, while the PMR spectrum showed a diamagnetic shift of the signals of the angular methyl group, of the methyl at the double bond, and of the olefinic and gem-acyl protons, which explains the proposed position of the carbonyl at C_{10}.

Under the action of perphthalic acid on dihydrolapidin, epoxydihydrolapidin, $C_{20}H_{32}O_5$ (VII), was formed. Its PMR spectrum is characterized by the appearance of the signal of an epoxide proton (2.80 ppm, d, J = 5 Hz), and by the presence of the signals of gem-hydroxylic (3.33 ppm, J = 5 Hz), and gem-acyl (5.17 ppm, sex, ^3J = 10.5, 10.5, 5.0) protons.

TABLE 1. Values of the Chemical Shifts (ppm), Spin–Spin Coupling Constants (Hz), and Multiplicities of the Signals of the Protons of Lapidin and Its Derivatives

Compound	C_1–CH_3	C_5–CH_3	C_{11}–$2CH_3$	C_6–H	C_7–H	C_{15}–H	C_{16}–H	C_{21}–H
Lapidin	1,32s	1,95 br.s	0,82 0,88 d(6)	5,59 m	2,95 q	5,89 br.s		
Lapidol	1,24s	1,93 br.s	0,89d (6)	4,28 m	2 72 q	5,69 br.s		
Dihydrolapidin	1,04s	1,75 br.s	0,83 d(6)	5,04 sex (10,5; 10,5; 5,0)	—	5,37 br.s	3,96 br.s	
Epoxydihydro-lapidin	1,20s	1,44 s	0 81 0,89d (6)	5,17 sex (10,5; 10,5; 5,0)	—	2,80d (5)	3,33d (5)	
Epoxydihydro-lapidol	1,28s	1,43 s	0,83 1,00d (6)	4,35 m		3,10d (5)	3,73t (5;5)	
Anhydrolapidin A	1,28s	1,94 s	0,88d (6)	5,74 q (8;5)		5,92 br. s		
Anhydrolapidin B	1.14s	1,95 s	0.84 1,02d (6)	5,30 m		5,92 br.s		5,39 br.s

Note. s — singlet; d — doublet; t — triplet; q — quartet; br. s — broadened singlet; sex — sextet; m — multiplet. The spectra were taken in deuterochloroform; 0 — HMDS; δ scale.

It must be mentioned that on passing from lapidin to dihydrolapidin and to epoxydihydrolapidin, the signal of the gem-acyl proton was converted from a multiplet into a well-resolved sextet with ^3J = 10.5, 10.5, 5.0 Hz. Such a pattern is characteristic for esters of the carotane alcohol jaschkeanadiol (ferutinol) [3, 4].

The alkaline hydrolysis of (VII) gave epoxydihydrolapidol, $C_{15}H_{26}O_4$ (VIII). The PMR spectrum of (VIII) taken in deuteropyridine shows the following signals: of an isopropyl group (0.83, 1.00 ppm, d, J = = 6 Hz, 3 H each), of an angular methyl group (1.28 ppm, s, 3 H), of a methyl and an epoxide ring (1.43 ppm, s, 3 H), of an epoxide proton (3.10, d, J = 3 Hz), and of two gem-hydroxylic protons (3.73 ppm, t, $J_1 = J_2$ = 5 Hz, and 4.35 ppm, m). In addition, doublets were present from two secondary hydroxyl groups at 5.7 and 6.67 ppm with J = 5 Hz and a singlet from a tertiary hydroxy group at 4.16 ppm.

Thus, the PMR spectra are in full agreement with the structural formula (VIII) for epoxydihydrolapidin.

The chemical and spectral characteristics given permit the most probable structures (II) and (I), respectively, to be suggested for lapidol and lapidin (see scheme).

A comparison of the results obtained with literature information shows that lapidol differs from the known carotane alcohol jaschkeanadiol (IX) only by the presence of a carbonyl group in the cyclopentane ring.

For jaschkeanadiol, Indian workers have proposed an absolute configuration and have established the trans-linkage of the cyclopentane ring with the cycloheptane ring, and they have also shown that the hydroxy and isopropyl groups occupy the most favorable pseudoaxial positions.

In the PMR spectra of lapidol derivatives, as in the spectra of esters of jaschkeanadiol, the gem-acyl proton at C_6 appears in the form of a sextet with the same spin–spin coupling constants (10.5, 10.5, and 5.0) or in the form of a multiplet. This shows the similarity of the configurations of the C_5 and C_6 asymmetric centers and the same trans-linkage of the rings in the compounds being compared.

Taking into account what has been said above, to establish the absolute configuration of lapidol it was desirable to perform a direct passage to jashchkeanadiol, i.e., to reduce the carbonyl group. The direct reduction of the carbonyl group in lapidin and lapidol is complicated by the presence of a double bond conjugated with it.

The hydrogenation of lapidin (see scheme) in the presence of a platinum catalyst in ethanol gave a mixture of two isomeric tetrahydro derivatives (X) with the composition $C_{20}H_{34}O_4$, M^+ 338. The PMR spectra of (X) has no signals of olefinic protons, which shows the saturation of the double bonds at C_8–C_9 and also in the angelic acid residue.

The Huang–Minlon reduction of (X) took place with the simultaneous splitting out of the acyl residue and, as a result, two isomeric deoxotetrahydrolapidols with the composition $C_{15}H_{28}O_2$, M^+ 240, were formed (XI and XII). Their IR spectra contained no absorption band of a carbonyl or ester group, and their PMR spectra differed mainly in the chemical shift of the angular methyl group (1.07 and 0.93).

These compounds (XI and XII), according to mixed-melting points and IR spectra, were absolutely identical with the two isomers obtained in the catalytic hydrogenation of jaschkeanadiol (ferutinol).

It follows from this that in lapidin and lapidol the configurations of all the asymmetric centers and the linkage of the rings are the same as in jaschkeanadiol. i.e., the hydroxy group at C_6 and the isopropyl group at C_4 have the α orientation.

Thus, for lapidol and lapidin we propose the absolute configurations (II) and (I), respectively.

EXPERIMENTAL

UV spectra were taken on a Hitachi spectrophotometer (in ethanol), IR spectra on a UR-10 instrument (tablets with KBr, film), mass spectra on a MKh-1303 mass spectrometer, and PMR spectra on a JNM-4H-100 MHz in deuteropyridine or deuterochloroform. The chemical shifts are given in the δ scale (HMDS — 0).

The course of the reactions and the purities of the substances were monitored by TLC on Silufol R plates in the hexane–ethyl acetate (2:1) system with a 1% solution of vanillin in concentrated sulfuric acid as the visualizing agent.

Isolation of Lapidin (I). An ethanolic extract of 2 kg of dried and comminuted roots was concentrated, diluted with water (1:2), and treated with ether. The ethereal extract was repeatedly treated with a 1% solution of caustic soda and was washed with water and dried. After the solvent had been distilled, 266 g of combined neutral components was obtained. Of this material, 48 g was chromatographed on a column of silica gel (100 × 4.5 cm), the substances being eluted with hexane (3 liters) and then with hexane–ethyl acetate (4:1), with the collection of 250 ml fractions. Fractions 17-25 were combined and the solvent was distilled off. The residue was crystallized from hexane. This gave 0.35 g of a substance with mp 80-81°C $[\alpha]_D^{20}$ +166° (c 1.5; chloroform), R_f 0.46.

Hydrolysis of Lapidin (I). A solution of 400 mg of lapidin in 25 ml of methanol was treated dropwise with a 5% aqueous solution of sodium hydroxide until a turbidity appeared, and the mixture was then heated in the water bath for 3 h. The metanol was distilled off in vacuum, and the mixture was diluted with water, and treated with ether. The ethereal extract was washed, dried, and evaporated. The oily residue was chromatographed on silica gel (80 × 1.4 cm) the substances being eluted with the hexane–ethyl acetate (3:1) system. This gave 80 mg of a yellowish oil $C_{15}H_{24}O_3$ (II) $[\alpha]_D^{20}$ +123° (c 1.2; chloroform), R_f 0.7. The mother solution was acidified with 5% sulfuric acid and treated with ether. Concentration of the ethereal solution yielded an acid with the composition $C_5H_8O_2$, mp 43-44°C, identical with angelic acid.

Dihydrolapidin (VI). With cooling and stirring, 500 mg of $NaBH_4$ was added in portions to a solution of 500 mg of lapidin on 50 ml of methanol. The methanol was distilled off in vacuum to small volume, and the reaction mixture was diluted with water. The reaction product was extracted with ether. The residue after the elimination of the solvent was chromatographed on a column of silica gel (80 × 1.3 cm; hexane–ethyl acetate (2:1) system). This gave 360 mg of a white amorphous substance with R_f 0.3.

Epoxydihydrolapidin (VII). An ethereal solution of perphthalic acid was added to a solution of 360 mg of dihydrolapidin in ether, and the mixture was left at room temperature for 30 min. Then it was diluted with water and extracted with ether. The ethereal layer was washed with a 5% solution of sodium carbonate and with water. The solvent was distilled off and the residue was chromatographed on a column of silica gel (50 × 1.8 cm), the substances being eluted with hexane–ethyl acetate (3:1). This gave 300 mg of a compound with the composition $C_{20}H_{32}O_5$, $[\alpha]_D^{20}$ +92° (c 1.0; chloroform), R_f 0.25.

Epoxydihydrolapidol (VIII). Epoxydihydrolapidin (300 mg) was hydrolyzed with a 2% aqueous alcoholic solution of caustic potash for 30 min. The usual working up of the reac-

tion mixture yielded 200 mg of a compound with the composition $C_{15}H_{26}O_4$, $[\alpha]_D^{20}$ + 72° (c 1.1; ethanol), R_f 0.15, mp 163-164°C (hexane–ethyl acetate (2:1)).

Dehydration of Lapidin. With stirring, 1.5 ml of freshly distilled thionyl chloride was added to a solution of 300 mg of lapidin in 10 ml of dry pyridine cooled to below 0°C. Then the reaction mixture was left at 15-17°C for 10 min and it was poured in portions into ice water. The reaction product was extracted with ether. The residue after the solvent has been distilled off was deposited on a column of silica gel (40 × 1.3 cm). The substances were eluted with hexane–ethyl acetate (50:1). This gave two compounds, (IV) and (V), each with the composition $C_{20}H_{28}O_2$, having mp 50-51°C and 58-59°C; R_f 0.53 and 0.48, respectively (hexane–ethyl acetate (4:1)).

Dehydrogenation of Lapidin. A mixture of 300 mg of the substance with 300 mg of 10% Pd/$CaCO_3$ was heated at 240-250°C for 3 h. The reaction product was extracted with petroleum ether and the extract was washed with phosphoric acid and with water and was dried and concentrated. The oily product was chromatographed on Al_2O_3. This gave 50 mg of daucalene (III) with a characteristic naphthalene-like odor, mp 59-60°C, mp of the picrate 89-90°C.

Hydrogenation of Lapidin. The hydrogenation of 700 mg of the substance was performed in 30 ml of ethanol in the presence of 100 mg of PtO_2 for 2 h. The solution was filtered off, and the residue after the distillation of the solvent was chromatographed on silica gel (hexane–ethyl acetate (4:1)). This gave 290 mg of tetrahydrolapidin, $C_{20}H_{34}O_4$ (X), mp 80-81°C (heptane).

Huang-Minlon Reduction of Tetrahydrolapidin. A mixture of 230 mg of the compound, 25 ml of diethyleneglycol, 250 mg of caustic potash, and 1.5 ml of hydrazine was heated in the water bath for 1 h. The high-boiling products were distilled off, and the temperature of the reaction mixture was raised to 190-210°C and was kept there for 16 h. Then the mixture was cooled, diluted with water, and treated with ethyl acetate. This gave two substances (XI) and (XII) with the composition $C_{15}H_{28}O_2$, mp 91-92°C (heptane), $[\alpha]_D^{20}$ + 28° (1.4; chloroform) and 85-86° (heptane), $[\alpha]_D^{20}$ +40° (c 1.5; chloroform), R_f 0.46 and 0.4, respectively.

Hydrogenation of Ferutinol. The hydrogenation of 200 mg of ferutinol was carried out in 20 ml of ethanol in the presence of a platinum catalyst (30 mg). After the usual working up and chromatography on silica gel, two substances were obtained (XI) and (XII), $C_{15}H_{28}O_2$, with mp 91-92°C (heptane), $[\alpha]_D^{20}$ +26.6° (c 1.5; chloroform), and 85-86°C (heptane), $[\alpha]_D^{20}$ +40° (c 1.5; chloroform), R_f 0.46 and 0.4, respectively.

SUMMARY

From the roots of *Ferula lapidosa* has been isolated an ester of a new carotane alcohol, lapidol, and angelic acid. On the basis of chemical transformations and spectral characteristics, a structure and absolute configuration have been suggested for lapidin.

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