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STRUCTURES OF ANGRENDIOL, FEROLIN, AND CHIMGANIDIN

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We have previously reported the isolation from the roots of *Ferula pallida* Eug. Kor. and *Ferula tschimganica* Lipsky of two new esters, which were called ferolin (I) and chimganidin (II) [1, 2]. On saponification, both substances were cleaved, forming a sesquiterpene diol with the composition $C_{15}H_{26}O_2$, identical with angrendiol (III) described previously [3] and one mole of an acid - p-hydroxybenzoic acid (IV) from (I) and vanillic acid (V) from (II). Consequently, ferolin and chimganidin are monoesters of the acids mentioned and of the same diol. N. P. Kir'yalov has previously isolated angrendiol in the free state from the resins of a number of species of *Ferula* and has shown that it has a bicyclic carbon skeleton with one double bond and two secondary hydroxy groups [3], but the question of its structure has remained open.

In the present paper we give the results of a determination of the structure of the diol itself and of the positions of the acid residues in the substances that we have isolated. The UV spectrum of (III) has a maximum at 210 nm (3.18), which is characteristic for nonconjugated dienic compounds [4], and its IR spectrum has adsorption bands at 3430 cm^{-1} (hydroxy group) and 1660 cm^{-1} and its IR spectrum has adsorption bands at 3430 cm^{-1} (hydroxy group) and 1660 cm^{-1} (double bond).

In the PMR spectrum of angrendiol (III) (Fig. 1), a six-proton singlet with its center at 1.01 ppm, consisting of two doublets, is due to the methyl of an isopropyl group. Two three-proton singlets at 1.58 and 1.37 ppm are due to methyl groups at a double bond and a hydroxy group, respectively. A proton geminal to a hydroxy group appears in the spectrum in the form of a quartet at 4.16 ppm with $^3J = 11.4$ and 5.3 Hz.

When (III) was acetylated with acetic anhydride in pyridine, a diacetyl derivative was obtained with the composition $C_{19}H_{30}O_4$ (VI) the IR spectrum of which lacked the absorption band of hydroxy groups, while in the PMR spectrum, in addition to the disappearance of the two-proton broadened singlet at 3.10 ppm due to two hydroxy groups, a paramagnetic shift of the signals of the proton in the geminal position to a hydroxy group ($\Delta\delta = 1.20$ ppm) and of the tertiary methyl group at the other hydroxyl ($\Delta\delta \approx 0.1$ ppm) was observed.

These results show that in actual fact one of the hydroxy groups is secondary and the other is tertiary, being present in the geminal position to a methyl group.

As can be seen from Fig. 1, in the region of olefinic protons there are three doublet signals at 4.62, 4.89, and 5.11 ppm, the lines of which are appreciably broadened. These signals are not present in the spectrum of the tetrahydroderivative (VII), with the composition $C_{19}H_{34}O_4$, obtained by the hydrogenation of angrendiol diacetate over platinum in acetic acid, i.e., (III) has not one but two double bonds.

The presence of an isopropyl group and two methyl groups and of two double bonds shows that, with the composition $C_{15}H_{26}O_2$, angrendiol probably has the monocyclic structure of germacrane.

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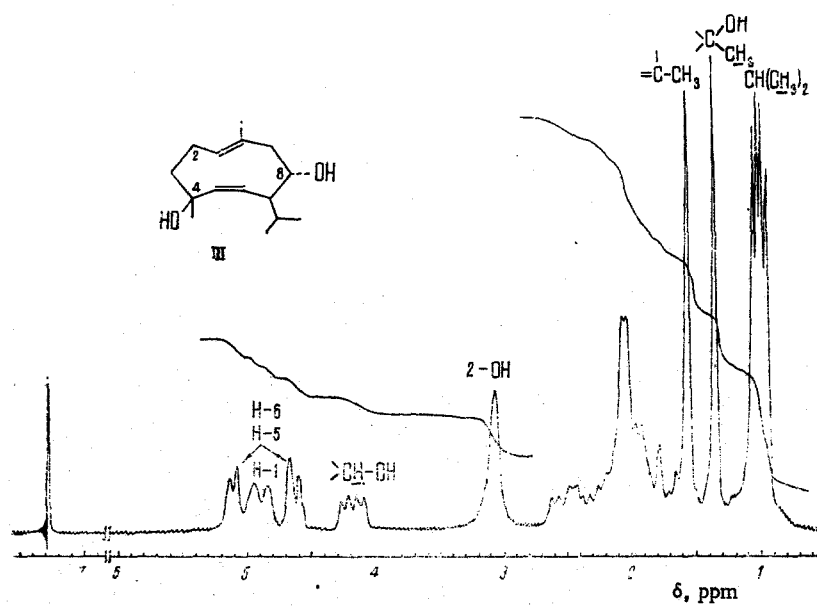


Fig. 1. PMR spectrum of angrendiol in CDCl₃.

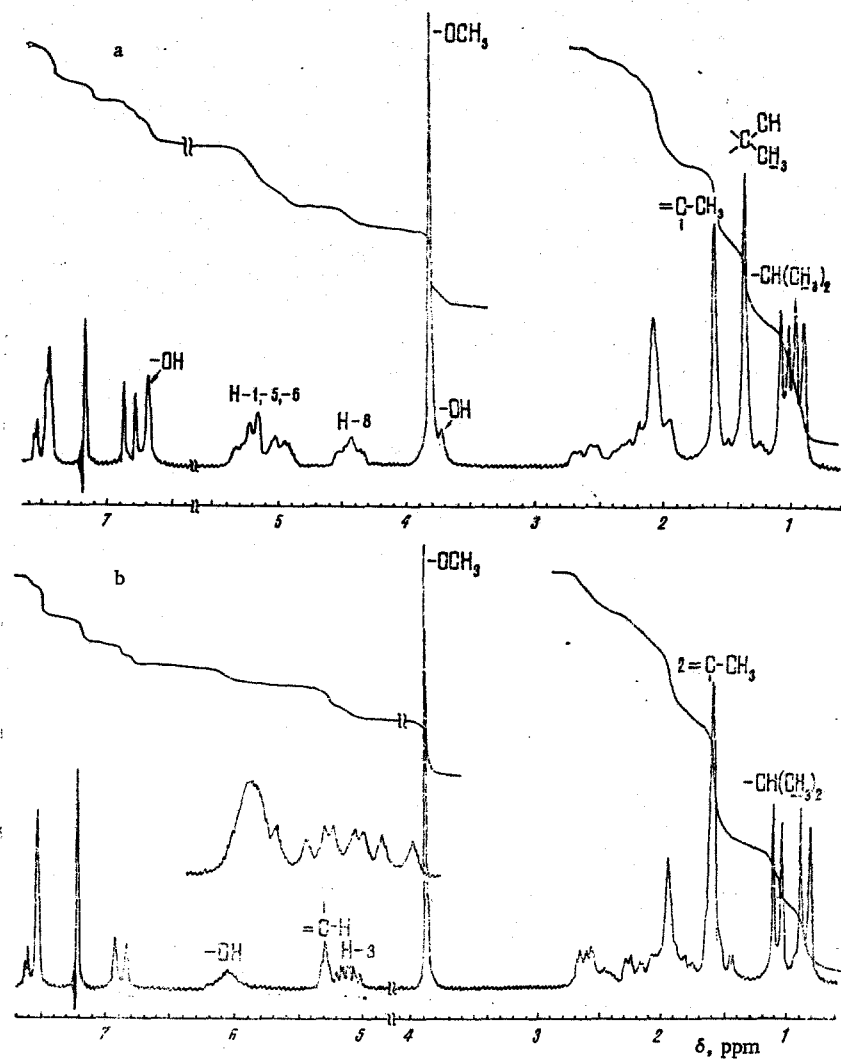
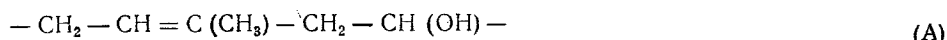


Fig. 2. PMR spectra of chimganidin (a) and of its cyclization product (b) in CDCl₃.

The position of the hydroxy groups and the double bonds were established on the basis of the following spectral and chemical facts. The study of the double resonance spectra of (III) showed that the quartet nature of the splitting of the signal at 4.16 ppm $\begin{matrix} | \\ \text{H}-\text{C}-\text{OH} \\ | \end{matrix}$ is due to the vicinal interaction of the proton geminal to the secondary hydroxy group with two hydrogen atoms of a neighboring group to which a quartet with broadened components at 2.56 ppm and a triplet at 1.79 ppm belong. Another conclusion from this is that the latter interact vicinally with the proton mentioned.

The first structure of the signal of the olefinic proton at 4.89 ppm (quartet with $^3J = 8.7$ and 2.5 Hz) is shown in the triple resonance spectrum when the methyl group on the double bond (1.58 ppm) and one of the methylene protons mentioned above (2.56 ppm) are subjected simultaneously to irradiation with a strong radio frequency field. The situation mentioned is possible only if the olefinic proton under consideration undergoes not only vicinal interaction with the two neighboring methylene protons but also the allyl or spatial action of the irradiated groups. On the basis of the facts given above, it may be assumed that the structure of (III) includes the fragment (A):



It is known that germacrane derivatives containing double bonds or an oxide group undergo cyclization under the influence of electrophilic reagents with the formation of compounds of the eudesmane and guaiane types [5-7]. The cyclization of chinganidin (II), which we performed in the presence of sulfuric acid, gave a product with the composition $\text{C}_{23}\text{H}_{30}\text{O}_4$ (VIII), mp 152-153°C (M^+ 370). When (VIII) was dehydrogenated with selenium at 200-220°C we obtained guaizaulene (IX) (blue oil, picrate with mp 120-121°C).

A comparison of the spectra of (II)* and (VIII) (Fig. 2, a,b) has shown that in the latter there is a six-proton signal at 1.60 ppm from two vinyl methylene groups and a broadened singlet at 5.33 ppm of only one olefinic proton. In addition, the signal of a proton geminal to an acyl group appears at 5.15 ppm in the form of a sextet with $^3J = 5.6, 8.8,$ and 10.3 Hz.

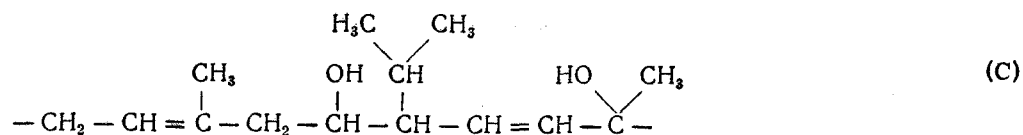
It follows from these facts that the dehydration of the tertiary hydroxy group, is accompanied by the subsequent cross-linking of the germacrane ring (II) to form a guaiane ring (VIII), and in the vicinal position to the secondary hydroxy group there is, in addition to the above-mentioned two methyl groups, a methine proton at C_7 , i.e., $\begin{matrix} | \\ -\text{CH}_2-\text{CH}-\text{CH}- \\ | \\ \text{OH} \end{matrix}$. In view of the chemical transformations noted and the results of double and triple resonance in relation to the determination of the structure of fragment A in the angreniol molecule, it may be concluded that one double bond is located at C_1-C_{10} and the secondary hydroxy group at C_8 .

The second double bond is disubstituted and its olefinic protons (doublets at 4.62 and 5.11 ppm) interact vicinally with one another (established by the INDOR method) with $^3J = 6.7$ Hz, which is characteristic for a cisoid vinyl group [11]. A considerable narrowing of the lines of these doublets and an increase in their intensities was found when the methyl at the tertiary hydroxy group was irradiated (1.37 ppm). On the other hand, in the PMR spectrum of (VI) such signals are present in a weaker field at 5.08 and 5.52 ppm [relative to the spectrum of (III)], i.e., $\Delta\delta = 0.46$ and 0.41 ppm. These three factors show that the other fragment (B) of the molecule of (III) forms a cis-vinyl group located adjacent to the tertiary hydroxyl and to a carbon atom bearing a methyl group:



Fragments A and B, the presence of which has been shown above, must be connected with one another by a tertiary carbon atom to which an isopropyl group is attached.

* The anomalous nature of the H-8 chemical shift (4.48 ppm) in the spectrum of (II) is due to the steric factor.

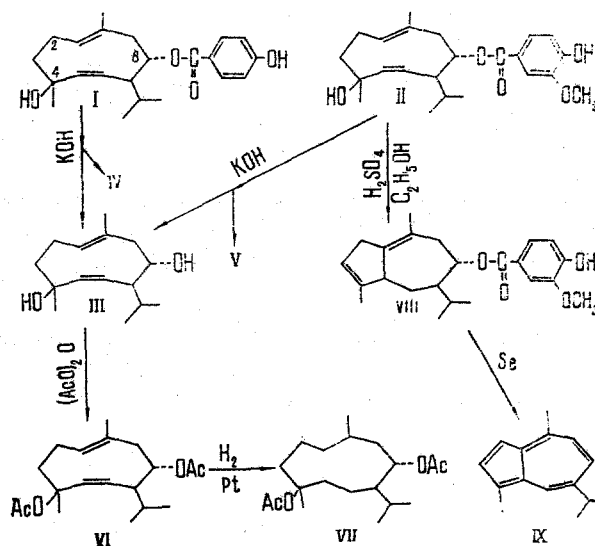


With the composition $\text{C}_{15}\text{H}_{26}\text{O}_2$ for angrendiol, which permits another methylene group, C can be closed only to form the germacrane structure (III).

It has been reported previously that on pyrolysis 1(10), 4(5)- and 1(10),5(6)-diene derivatives of germacrane undergo a Cope rearrangement and form elemene derivatives [8-10]. By pyrolyzing angrendiol we obtained two substances with the composition $\text{C}_{15}\text{H}_{26}\text{O}_2$ (M^+ 238). The IR spectra of both these substances had absorption bands at $3300\text{--}3600\text{ cm}^{-1}$ ($-\text{OH}$), 1640 and 890 cm^{-1} ($> \text{C}=\text{CH}_2$), and 910 cm^{-1} ($-\text{CH}=\text{CH}_2$), and the PMR spectra showed signals from the protons of isopropyl, quaternary methyl, vinyl methyl, and two exomethylene groups, characterizing the presence of an elemene nucleus. The formation of an elemene derivative by the pyrolysis of (III) confirms that angrendiol has a germacrane ring, and the disubstituted bond is in the $\text{C}_5\text{--C}_6$ position.

It must be mentioned that in the spectrum of angrendiol the vicinal SSCC between the H-6, H-7, and H-8 protons is less than 1 Hz, i.e., the dihedral angle between them is close to 90° , and the other two constants, $^3J = 11.4$ and 5.3 Hz, found for H-8 show the pseudoequatorial orientation of the secondary group.

Thus, angrendiol has the structure of 4,8-dihydroxygermacr-1(10), 5(6)-diene and ferolin and chimganidin are its monoesters with parahydroxybenzoic and vanillic acids at the secondary hydroxy group. The transformations of angrendiol and its esters described above can be represented in the following form:



EXPERIMENTAL

The IR spectra were taken on a UR-10 instrument (tablets with KBr), the mass spectra on a MKh-1303 instrument, the UV spectra on a Hitachi EPS-3T spectrophotometer (in ethanol), and the PMR spectra on a JNM-4-100 spectrometer in CDCl_3 solution, 0 - HMDS. The R_f values were obtained on "Silufol-R" plates in the hexane-ethyl acetate (4:1) system with a 1% solution of vanillin in concentrated sulfuric acid as the revealing agent. The results of the elementary analyses corresponded to the calculated figures.

Isolation of Chimganin and Chimgin. A methanolic extract of the roots of *Ferula pallida*, after concentration, was diluted with water and extracted with ether. The ethereal extract was treated successively with 5% sodium carbonate solution and 1% potassium hydroxide solution. The caustic alkali solution was washed with ether, acidified with 5% sulfuric acid, and extracted with ether. The solvent was distilled off, and 30 g of the combined phenolic compounds was transferred to a column (90 x 6 cm) of silica gel and was chromatographed with petroleum ether-diethyl ether (4:1), 200-ml fractions being collected. Fractions IV-XII yielded 13 g of *l*-chimganin, $\text{C}_{18}\text{H}_{24}\text{O}_4$, mp $85\text{--}86^\circ\text{C}$, $[\alpha]_D^{25} -41.7^\circ$ (c 1.56; ethanol), and fractions XIV-XVI yielded 10.5 g of *l*-chimgin, $\text{C}_{17}\text{H}_{22}\text{O}_3$, mp 155°C . Fractions XVIII-XXV contained a mixture of ferolin and chimganidin (4.7 g).

Isolation of Chimganidin and Ferolin. The mixture of ferolin and chimganidin was transferred to a column (60 × 4.5 cm) of silica gel and was chromatographed in chloroform, 100-ml fractions being collected. Fractions IV-XVI yielded chimganidin C₂₃H₃₂O₅ (II), mp 140-141°C, and (XIX)-(XXVI) yielded ferolin, C₂₂H₃₀O₄ (I), mp 189-190.5°C.

Hydrolysis of Ferolin (I). A solution of 0.2 g of the substance in 5 ml of 5% aqueous caustic potash was heated in the water bath for 4 h and was then diluted with water and treated with ether. The ethereal solution was washed with water and the solvent was distilled off. Crystals deposited with the composition C₁₅H₁₆O₂ (III), mp 135-136°C (from ether), [α]_D - 86.1° (c 0.9; ethanol).

The aqueous solution after extraction with ether was acidified with 10% sulfuric acid and was reextracted with ether. After elimination of the solvent, crystals with mp 210-211°C and the composition C₇H₆O₃ (IV) were obtained. This substance was identified as p-hydroxybenzoic acid.

Hydrolysis of Chimganidin (II). The hydrolysis of 0.2 g of (II) was carried out under the conditions described above. This gave angrendiol (III) and vanillic acid, C₈H₈O₄, mp 205-206°C (V).

Acetylation of Angrendiol. Angrendiol (0.15 g) was acetylated with acetic anhydride (3 ml) in pyridine (2 ml). The acetyl derivative of was isolated by the usual method and was crystallized from ether: C₁₉H₃₀O₄ (VI), M⁺ 322, mp 91-92°C.

Hydrogenation of Angrendiol Diacetate. Angrendiol diacetate (0.12 g) was hydrogenated in the presence of PtO₂ in acetic acid, 2 moles of hydrogen being absorbed. The catalyst was separated off, and the solution was diluted with water and treated with ether (3 × 50 ml). The residue after the elimination of the solvent was crystallized from ether, mp 113-115°C, C₁₉H₃₄O₄ (VII), M⁺ 326.

Cyclization of Chimganidin. A solution of 0.25 g of chimganidin in 20 ml of 10% ethanolic sulfuric acid was left at room temperature for 30 min. Then the reaction mixture was diluted with water and treated with ether. The ethereal extract was washed with water and the ether was distilled off. This gave a substance with the composition C₂₃H₃₀O₄ (VIII), mp 152-153°C (from ether).

Selenium Dehydrogenation of Substance (VIII). A mixture of 0.15 g of the substance and 0.5 g of selenium was heated with an air condenser at 200-220°C for 4 h. The dehydrogenation product (IX) was passed through a column of alumina (20 × 1 cm), being eluted with petroleum ether. A blue oil was obtained the picrate of which melted at 120-121°C.

Pyrolysis of Angrendiol. Angrendiol (0.3 g) was heated in a sealed tube at 120-140°C for 3 h. The pyrolysis product was transferred to a column of silica gel (30 × 1 cm) and was eluted with hexane-ethyl acetate (9:1). Fractions IX-XII yielded a substance with the composition C₁₅H₂₆O₂, R_f 0.45, and XIX-XXIII a substance C₁₅H₂₆O₂ with mp 83-84°C.

SUMMARY

On the basis of the results of a study of the products of chemical transformations and spectra, the structure of angrendiol has been established as 4,8-dihydroxygermacra-1(10), 5(6)-diene. It has been shown that ferolin and chimganidin are monoesters of angrendiol with parahydroxybenzoic and vanillic acids, respectively, at the secondary hydroxy group.

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