THE STRUCTURE OF TEUCRIN A

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It has been reported previously [1] that a number of bitter-tasting substances which have been given the general name of teucrin have been isolated from Teucrium chamaedrys L., family Labiatae. It has been shown that the main substance of an acetone extract of the plant – teucrin A – is a norditerpenoid $C_{19}H_{20}O_6$, containing a furan nucleus, a hydroxy group, and two γ-lactone rings, one of which is α,β-unsaturated. The present paper gives chemical and physical facts confirming structure (I) for this compound. The dehydrogenation of teucrin A with selenium gave a mixture of 1,2-dimethyl- and 1,2,5-trimethylnaphthalenes, which shows the presence in the compound of a decalin skeleton with hydrocarbon substituents in positions 1, 2, and 5.

In the NMR spectrum of teucrin A (Fig. 1a) the signals of two α protons (7.61 and 7.83 ppm) and one β proton (6.53 ppm) of a furan nucleus can be seen, which shows β substitution in the furan ring. At 5.75 ppm (J 8.5 Hz) there is the signal of the H_{12} proton, present on the same atom as oxygen and interacting with the two vicinal protons at C_{11}. The signals of the latter appear in the form of a doublet in the 2.6-ppm region (J 8.5 Hz), as has been confirmed by double resonance. No other protons belonging to this part of the molecule are shown. These facts give grounds for considering that the remaining two bonds of the furolactone grouping of teucrin are attached to the C_9 center as in the case of picropolin [2] or crotonin [3].

The only methyl group of this diterpenoid is secondary (1.2 ppm, J 7 Hz) and, according to the results of dehydrogenation, it must be located in the C_8 position. Since teucrin A is not oxidized by chromium trioxide and is acetylated only on being heated with acetyl chloride in dimethylaniline, it could be assumed that its hydroxy group is tertiary. However, the NMR spectrum has the signal of a proton geminal to a hydroxyl (4.21 ppm, $W_{1/2}$ = 9 Hz) which is shifted in teucrin A acetate to 5.8 ppm. This shows that the hydroxyl is secondary and occupies the axial position which explains the difficulty in acetylating it. Double resonance with saturation of the H_8 signal in the spectrum of substance (II) (Fig. 1b) confirms that the proton at the hydroxy group interacts with the vicinal H_8 proton at the secondary methyl group. Consequently, the hydroxy group can be only at C_7, since the second possibile position for it (C_1) is excluded.

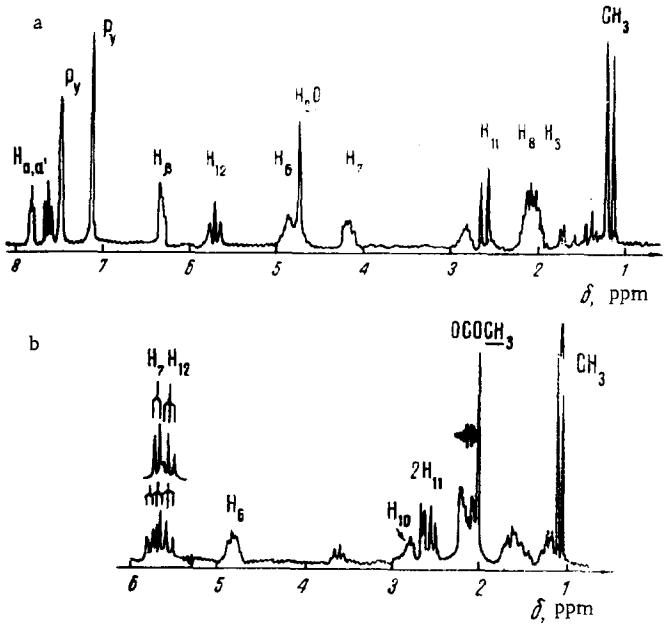

Fig. 1. NMR spectra of teucrin A (deuteropyridine) (a) and its acetate (deuterochloroform) (b).

The hydrogenation of teucrin A confirms this position of the functional groups. When it was saturated with hydrogen in the presence of $Pd/BaSO_4$ in ethanol, hydrogenolysis took place with the participation of the oxygen at C_{12} and the formation of a new γ-lactone (III), together with a certain amount of a substance (IV) retain-

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ing the furan ring. A proof of this translactonization with the formation of a hydroxyl-free compound is the shift in the H_7 signal from 4.21 ppm in the spectrum of teucrin A to 4.70 ppm in the spectrum of the lactone (III).

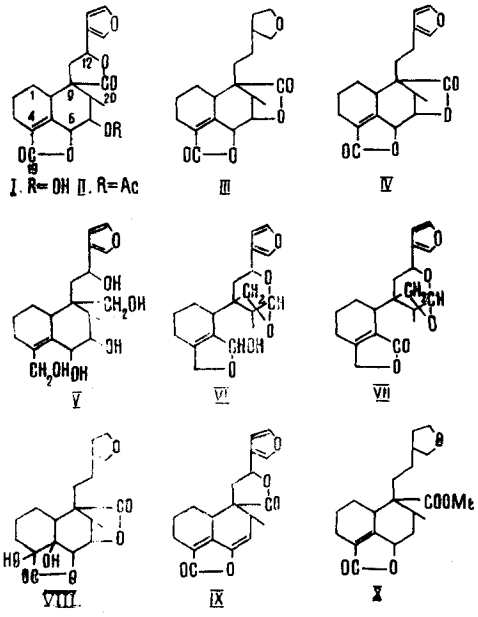
The reduction of teucrin A with lithium tetrahydroaluminate in tetrahydrofuran gave a pentaol (V) which, in contrast to teucrin A, was oxidized by one mole of sodium periodate in aqueous methanol with the formation of a product (VI) containing no carbonyl group and being readily converted on oxidation with manganese dioxide into the unsaturated lactone (VII). This is possible only if there is a pair of vicinal hydroxyls in the pentaol (V) and the others are present in a convenient position for the formation of acetals with the aldehyde groups obtained after oxidation. It follows from this that the second α,β-unsaturated lactone ring in teucrin A must be arranged in such a way that the alcoholic oxygen of the lactone capable of forming a hydroxyl on reduction is located at C_6. Then the carbonyl lactone can be only at C_{19}, as shown in formula (I).

The presence in the UV spectra of (I), (III), and (IV) of an absorption maximum at 220 nm (ε 18,000) shows that in each of the molecules there is a double bond conjugated with the lactone carbonyl. Their NMR spectra lacked the signals of olefinic protons, with the exception of the furan protons, which permits the conclusion that this bond is tetrasubstituted. This is confirmed by its stability on hydrogenation over catalysts under the usual conditions. Furthermore, the IR spectra have, in addition to the maximum in the 1745-1755-cm^{-1} region, a band of medium intensity at 1695 cm^{-1} which is characteristic for unsaturated γ-lactones with such a double bond – for instance, the eremophilenolides [4]. In the spectrum of the diol (VIII) obtained by the hydroxylation of the dilactone (III) with osmium tetroxide the band under consideration has disappeared, and the carbonyl maximum has shifted to the usual position for a saturated lactone (1770 cm^{-1}).

With the arrangement of the oxygen functions in the molecule of teucrin A shown above, the double bond can occupy only the 4,5 position. This is in harmony with the results of the dehydration of teucrin A under the conditions of acetylation. When it was heated with acetic anhydride and sodium acetate, a dienic enol-lactone (IX) with double linear conjugation of the carbonyl (281 nm) like the ginkgolides [5] was formed.

In the IR spectrum of compound (IX), as in the acetate (II), the band of a saturated γ-lactone is present at 1775 cm^{-1}, instead of 1760 cm^{-1}, in teucrin A. This hypsochromic shift of the band is due to the presence in the initial diterpenoid of a hydrogen bond between the hydroxy group and the lactone carbonyl.

The hydrogenation of the dienic lactone (IX), taking place with the absorption of four molecular equivalents of hydrogen, and subsequent methylation of the acid with diazomethane gave the methyl ester (X), containing, according to IR and UV spectrometry, the initial α,β-unsaturated lactone ring.



Thus, teucrin A belongs to a new type of compounds – 18-norditerpenoids – and has the structure shown by formula (I).

EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrometer in chloroform; the UV spectra on a Specord UV VIS instrument in ethanol; and the NMR spectra on a Varian HA-100 instrument (with HMDS as internal standard); the values of $[\alpha]_D$ were determined in a Zeiss instrument in chloroform, and the melting points on a Kofler block. Silica gel in fixed and nonfixed layers was used as adsorbent for TLC. The analyses of all the compounds corresponded to the calculated figures.

Dehydrogenation of Teucrin A. First, 1 g of substance (I) was saturated with hydrogen in the presence of platinum oxide in acetic acid. The residue after working up was ground with 2 g of selenium, and the mixture was heated at 250-300°C for 30 h. The comminuted mass was extracted with ether, and the evaporated extract was chromatographed on alumina (activity grade II). Petroleum ether eluted 50 mg of a hydrocarbon fraction. UV spectrum (in hexane), λ_{max} in cm^{-1}, (ε): 225 (51,000), 229 (64,000), 275 (2330), 287 (2500), 292 (2400), 298 (2000), 308 (1000), 323 (760). 1,2-Dimethylnaphthalene and 1,2,5-trimethylnaphthalene (the main component) were identified in the presence of markers by the GLC method (LKhM-8M instrument, flame-ionization detector, stainless-steel column, rate of flow of helium 45 ml/min, temperature 180°C, 15% of Reoplex-40° on Chromaton N-AW DMC).

Oxidation of Teucrin A. A solution of 100 mg of the substance in 0.5 ml of pyridine was added to the complex obtained from 200 mg of chromium trioxide in pyridine. The mixture was left at room temperature for 24 h and then, after the usual working up, 90 mg of a substance identical with the starting material was obtained.

The Acetate (II). A solution of 200 mg of substance (I) in 4 ml of dimethylaniline was treated dropwise with 2 ml of acetyl chloride, and the mixture was heated at 100°C under reflux for 4 h. Then it was diluted with water, acidified with sulfuric acid, and extracted several times with chloroform. The extracts were washed with dilute acid and then with water to neutrality, and were dried and evaporated, giving 250 mg of crude substance. After chromatography on silica gel in chloroform, 170 mg of a crystalline substance with the composition $C_{21}H_{22}O_7$ deposited, and this was recrystallized from a mixture of chloroform and ether; mp 174-176°C, M^+ 386 (mass spectrum). IR spectrum, cm^{-1}: 1775, 1765, 1740, 1700, 1240, 1600, 1505, 880. The action on teucrin A of acetic anhydride in pyridine caused no change even in the course of several days.

The Pentaol (V). A solution of 1 g of teucrin A in tetrahydrofuran was added dropwise over 15 h to a boiling solution of 700 mg of lithium tetrahydroaluminate in tetrahydrofuran. After cooling, the excess of reagent was decomposed, and the reaction mixture was acidified with sulfuric acid to pH 3 and was extracted with butanol. The butanolic extracts were washed with water to neutrality, dried with sodium sulfate, and evaporated in vacuum. The residue was chromatographed on 10 g of silica gel. A mixture of chloroform and 5% of methanol eluted 850 mg of a liquid with the composition $C_{19}H_{28}O_6$, which set to a vitreous mass with $[\alpha]_D$ +24° (c 4.2; pyridine). IR spectrum (KBr), cm^{-1}: 3400 (strong), 1600, 1508, 1030, 880.

Oxidation of the Pentaol (V). With cooling, 250 mg of sodium periodate in the minimum amount of aqueous methanol was added to 320 mg of substance (V) in a mixture of 3 ml of water and 1 ml of methanol. The mixture was left in the cold for 1 h and it was then diluted with water and extracted with chloroform. Evaporation of the chloroform in vacuum at room temperature left 280 mg of an amorphous mass consisting, according to TLC, of a practically pure substance. When it was subjected to chromatographic purification on silica gel (8 g), it underwent pronounced decomposition with the formation of less polar products, as a result of which only 100 mg of pure (VI) with the composition $C_{19}H_{24}O_5$, M^+ 332 (mass spectrum), was isolated. IR spectrum cm^{-1}: 3620, 3440 (hydroxyl), 1595, 1508, 880 (furan), 1028 (very strong).

Oxidation of Compound (VI). A mixture of 50 mg of the substance and 800 mg of active manganese dioxide was shaken in acetone for 8 h. Then the solid matter was filtered off and the acetone was distilled off. The residue was chromatographed on 2 g of silica gel in chloroform. This gave 25 mg of a carbonyl-containing compound, $C_{19}H_{22}O_5$ (VII). UV spectrum: λ_{max} 203 nm (ε 13,000). IR spectrum, cm^{-1}: 1765 and 1685 (α,β-unsaturated γ-lactone), 1600, 1507, 880 (furan), 1020 cm^{-1}.

Production of the Diol (VIII). A pyridine solution of 250 mg of OsO_4 was added to 300 mg of substance (III) in 3 ml of pyridine. The mixture was left at room temperature for 40 h. Then it was diluted with water, acidified with hydrochloric acid, and extracted with chloroform. To decompose the osmate complex, a current of hydrogen sulfide was passed through the chloroform solution for 2 h. The precipitate was filtered off, and the filtrate was washed successively with sodium bicarbonate solution, ferric chloride solution, and water, and was dried and evaporated. The residue was chromatographed on 8 g of silica gel. A

mixture of chloroform and 2% of methanol eluted 250 mg of a colorless substance with the composition $C_{19}H_{26}O_7$. After crystallization from chloroform containing ether, mp 202-205°C. Transparent in UV light. IR spectrum (KBr), cm^{-1}: 3500-3300 (hydroxyls), 1785, 1770 (γ-lactones), 1170 and 1085.

Dehydration of Teucrin A. A mixture of 300 mg of the substance, 6 ml of acetic anhydride, and 800 mg of fused sodium acetate was boiled under reflux for 5 h. The cooled solution was diluted with water and extracted with chloroform, and the extracts were washed with sodium bicarbonate solution and with water and were evaporated. The residue was chromatographed on silica gel in chloroform, giving 250 mg of a compound $C_{19}H_{18}O_5$ (IX). After crystallization from chloroform containing ether, mp 198-200°C, $[\alpha]_D$ +18° (c 3.4; chloroform). UV spectrum: λ_{max} 281 nm (ε 17,000), 210 nm (ε 8000). IR spectrum, cm^{-1}: 1775 (saturated γ-lactone), 1765 (unsaturated enol-lactone), 1670, 1595, 1505, 1162, 800 cm^{-1}.

Hydrogenation of the Diene (IX). The hydrogenation of 170 mg of the substance was performed in 5 ml of acetic acid in the presence of 70 mg of $Pd/BaSO_4$ (4%). Under normal conditions, 44 ml of hydrogen was absorbed, which corresponds to 3.8 molecular equivalents. After the usual working up, 130 mg of an acid was obtained, and this was methylated with diazomethane. Chromatography on silica gel gave 100 mg of the ester (X) in the form of a viscous liquid with the composition $C_{20}H_{28}O_5$. UV spectrum: λ_{max} 223 nm (ε 13,000). IR spectrum, cm^{-1}: 1750 and 1695 (unsaturated γ-lactone), 1725 (methyl ester), 1235, 1240, 1040.

SUMMARY

The structure of a new 18-norditerpenoid – teucrin A, isolated from the plant Teucrium chamaedrys L. – has been demonstrated. It has been shown that it belongs to the furolactones with a rearranged labdane skeleton.

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