ANIONOTROPIC REARRANGEMENT IN A SERIES OF DERIVATIVES OF TEUCRIN A

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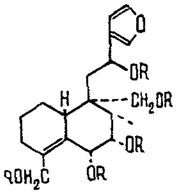
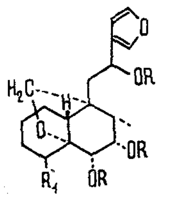
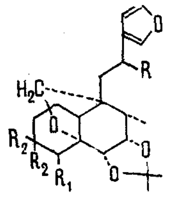
Previously, in order to prove the structure of teucrin A, and norditerpenoid from *Teucrium chamaedrys* L., we described some of its chemical reactions, including the preparation of a pentaol (I) by reduction with lithium tetrahydroaluminate [1]. It was subsequently observed that the pentaol (I) readily loses a molecule of water in the presence of catalytic amounts of mineral acid, undergoing a rearrangement leading to a compound with an exocyclic double bond (II). In this paper we give the results of the study of the structure of this substance and the determination of the paths by which it is formed.

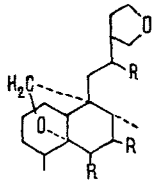
According to elementary analysis and mass spectrometry, compound (II) has the empirical formula $C_{19}H_{26}O_5$, i.e., it differs from the pentaol (I) by one molecule of water. In contrast to the pentaol, it contains an exocyclic double bond (880, 1650 cm^{-1}), three hydroxy groups, and one ether oxygen.

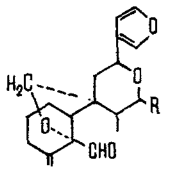
In addition to the doublet of a secondary methyl group and the signals of furan protons at 4.88 and 5.17 ppm, the NMR spectrum of (II) (Table 1) has two doublets of vinyl protons at 3.19 and 4.0 ppm — the signals of the AB system of geminal protons $-CH_2-O-$ (J = 7.5 Hz). A doublet at 3.59 ppm (J = 5.0 Hz) and a triplet at 3.79 ppm ($J_1 + J_2$ = 10.0 Hz) are assigned to protons geminal to hydroxy groups.

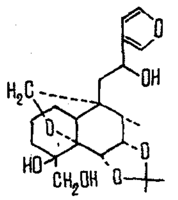

I, VI


II, V, VII


III, IV, XIII, XIV


VIII, IX


X, XI


XII

I. R = H, II. R = H; $R_1 = CH_2$, III. R = OH; $R_1 = CH_2$; R_2 = H, IV. R = O; $R_1 = CH_2$; R_2 = H
V. $R = CH_3CO$; $R_1 = CH_2$, VI. $R = CH_3CO$, VII. R = H; $R_1 = CH_3$, VIII. R = OH, IX. R = O
X. R = OH, XI. R = O, XIII. R = OH; R_1 = O; R_2 = H, XIV. R = OH; R_1 = O; R_2 = D.

The arrangement of the hydroxy groups given in formula (II) agrees with the formation from it of an acetonide (III), its ready oxidation by sodium periodate, and also the formation of the ketone (IV) by the oxidation of the acetonide (III). Compound (IV) contains an α-keto furan system with characteristic IR and UV spectra (3150, 1680, 1645, 1565, 1514, 878 cm^{-1}; 210.5, 255 nm) similar to the sciadinone system [2]. This is also confirmed by an analysis of the PMR spectrum of the triacetate (V) obtained by the acetylation of compound (II) and containing no hydroxy groups. In contrast to the spectrum of (II), in the 2-ppm region there are three singlets of acetate methyls, and the signals of the protons geminal to acetate groups are shifted (∼1.5 ppm) downfield. In comparison with the PMR spectrum of

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TABLE 1. Chemical Shifts (ppm) and Spin–Spin Coupling Constants (Hz) of the Protons of Some Derivatives of Teucrin A

Compound	H_6	H_7	H_{12}	H_{14}, H_{15}, H_{16}	H_{17}	H_{19}	H_{20}	Notes
I* In $CDCl_3$	5,25 m	5,11 dd $J_1+J_2=4,0$	5,89 dd $J_1+J_2=12,0$	6,28; 7,23; 7,35	3,92/4,27 AB J=12,5	4,60/4,76 AB J=12,0	1,08 d J=7,0	1,9–2,0– acetate methyls
II* In $(CD_3)_2SO$	3,59 d J=5,0	3,79 t $J_1+J_2=10,0$	4,65	6,37; 7,44	3,19/4,40 AB J=7,5	4,88/5,17 AB J=2,0	0,93 d J=7,0	1,18; 1,36 s — acetonide methyls
III† In $CHCl_3$	—	—	—	5,98; 7,10	3,14/3,80 AB J=8,0	4,68/4,94 AB J=1,5	0,96 d J=6,0	[3,7–4,1] — multiplet of of H_6, H_7, and H_{12} signals
V* In $CDCl_3$	5,07 d J=5,0	5,46 t $J_1+J_2=10,0$	5,98 m	6,36; 7,37; 7,42	3,48/4,25 AB J=8,0	4,91/4,97 AB J=1,5	0,88 d J=7,0	1,88; 2,02; 2,07s – acetate methyls
VIII† In $CHCl_3$	—	—	—	—	—	1,07 d J=7,0	0,95 d J=7,0	[2,8– 4,0] — multiplet of H_6, H_7, H_{12}, H_{14}, H_{15}, H_{16}, and H_{17} protons
X† In CCl_4	8,90 s	5,10 d J=1,0	4,15	6,12; 7,10	3,25/4,15 AB J=8,0	4,70/4,82	1,03 d J=7,0	

s) singlet; d) doublet; t) triplet; dd) doublet of doublets; m) multiplet.

*Spectra taken at a frequency of 100 MHz.

†Spectra taken at a frequency of 60 MHz.

the pentaacetate (VI) [1], here the signal of the H_6 proton appears as a sharp doublet (5.07 ppm, J = 5.5 Hz), which confirms the presence of a neighboring completely-substituted carbon atom.

The hydrogenation of (II) over $Pd/BaSO_4$ in ethanol took place with the adsorption of 2.5 equivalents of hydrogen and led to a mixture of substances (VII) and (VIII). The PMR spectrum of (VIII) lacked the signals of vinyl protons, and an additional doublet of a secondary methyl group appeared in the strong field.

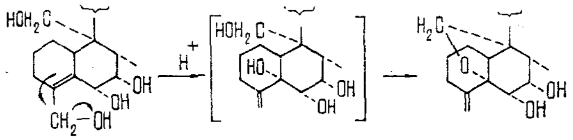
The oxidation of compound (VIII) with chromium trioxide in pyridine formed the trione (IX), readily undergoing enolization. The IR and UV spectra confirmed the presence in (IX) of an α-diketonic grouping in a six-membered ring [3] (1760, 1710, 1675, 1640 cm^{-1}; 277 nm).

The oxidation of compound (II) with sodium periodate gave the aldehyde (X) (1630, 2810 cm^{-1}; 8.90 ppm, singlet), which contained a semiacetal group, since it was oxidized by chromium trioxide in pyridine to a lactone (XI) (1748, 1730, 2830 cm^{-1}).

It follows from what has been said, in the first place, that in the pentaol (I) a system including an allyl primary alcohol group undergoes rearrangement. Furthermore, any alternative structure of the compound obtained can include only two tetragonal completely substituted carbon atoms and they must be centers connecting the carbon and oxygen atoms of a $-CH_2-O-$ bridge. In view of the PMR spectra of the compounds (II) and (V), however, (see the signals of the H_6 and H_{17} protons), it must be assumed that the oxygen atom is located at C_5 and the $-CH_2-$ group at C_9.

A confirmation of the fact that the exocyclic double bond is formed by the C_4 and C_{19} carbon atoms is based on the production of the ketone (XIII) (1715 cm^{-1}) by the successive oxidation of the acetonide (III) with osmium tetroxide and sodium periodate. In this compound there is a completely substituted carbon atom in the α position to the ketone group, since the ketone (XIII) replaces only two hydrogen atoms by deuterium.

Thus, all the information given serves as a proof of the fact that compound (II) is the product of the anionotropic rearrangement of the pentaol (I) and of the cyclization of the intermediate alcohol (XV) taking place successively.



I XV II

EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrometer in KBr; the UV spectra on a Specord UV-Vis; the PMR spectra on Varian HA-100 and on RS-60 instruments (with HMDS as internal standard); and the mass spectra on an MKh-1303 instrument at 140°C with an ionization energy of 70 eV. The values of $[\alpha]_D$ were determined on a "Zeiss" instrument and the melting points on a Kofler block.

The analyses of all the compounds corresponded to the calculated figures.

Preparation of Compound (II). A solution of 200 mg of the pentaol (I) in 2 ml of methanol was treated with a few drops of 50% sulfuric acid and was then left at room temperature for 2 h. After this, it was diluted with water and extracted with chloroform. The residue after evaporation of the solvent was chromatographed on silica gel. A mixture of chloroform and 3% of methanol eluted 120 mg of crystalline (II). After recrystallization from methanol—chloroform—ether, mp 189-192°C, $[\alpha]_D^{20}$ −37.5° (c 3.75; pyridine); composition $C_{19}H_{26}O_5$, M^+ 334. IR spectrum, cm^{-1}; 3450, 3150, 3050, 1650, 1600, 1508, 880. UV spectrum, λ_{max}: 2105 nm (ε 7500).

Preparation of the Acetonide (III). A mixture consisting of 100 mg of compound (II) in 15 ml of dry acetone and 5 g of anhydrous copper sulfate was allowed to stand at room temperature for 48 h. After this, the solution was filtered and evaporated. The 95 mg of residue was crystallized from chloroform with ether; mp 196-198°C, composition $C_{22}H_{30}O_5$. IR spectrum, cm^{-1}: 3450, 3150, 1645, 1600, 1502, 1265, 1380, 880.

Oxidation of the Acetonide (III). The acetonide (III) (50 mg) was oxidized in the usual way with chromium trioxide in pyridine for two hours. The usual working up gave 40 mg of a crystallizing oil; after crystallization from ether from petroleum ether, mp 143-145°C; composition $C_{22}H_{28}O_5$. IR spectrum, cm^{-1}: 3150, 3060, 1680, 1645, 1565, 1514, 878 cm^{-1}. UV spectrum, λ_{max}, nm: 210.5 (ε 8000), 255 (ε 3660).

Acetylation of Compound (II). Compound (II) (70 mg) was acetylated in the usual way at room temperature with acetic anhydride in pyridine for 48 h. After the working up of the reaction mixture and chromatography of silica gel, benzene containing 3% of acetone eluted 50 mg of the acetate (V), mp 168-170°C (chloroform/ether), $C_{25}H_{32}O_8$. IR spectrum (CCl_4), cm^{-1}: 1745, 1657, 1600, 1508, 1240, 880.

Hydrogenation of Compound (II). In the presence of 30 mg of 4% $Pd/BaSO_4$, 120 mg of substance (II) was saturated with hydrogen. Under normal conditions, 19 ml of hydrogen was absorbed in 7 h, which corresponds to 2.5 equivalents. The usual working up gave 120 mg of a mixture, and after chromatography on silica gel chloroform with 2% of methanol eluted successively:

40 mg of a crystalline compound (VII) with mp 150-152°C (diethyl ether/petroleum ether), $C_{19}H_{28}O_5$, M^+ 336. IR spectrum, cm^{-1}: 3400, 1600, 1500, 880; and

70 mg of an amorphous compound (VIII), $C_{19}H_{32}O_5$. IR spectrum ($CHCl_3$), cm^{-1}: 3500, 1010, 980.

Oxidation of Compound (VIII). Substance (VIII) (50 mg) was oxidized with chromium trioxide in pyridine for 1.5 h. After working up and chromatography on silica gel in chloroform, 25 mg of substance (IX) was obtained in the form of an amorphous mass. IR spectrum ($CHCl_3$), cm^{-1}: 1760, 1710, 1675, 1640. UV spectrum, λ_{max}: 277 nm (ε 1200). It gave a green coloration with an ethanolic solution of $FeCl_3$.

Oxidation of Compound (II) with Sodium Periodate and Preparation of the Ketone (XI). A mixture consisting of 100 mg of substance (II) and 80 mg of sodium periodate in 2 ml of water and 2 ml of methanol was left for 2 h. Then it was diluted with water and extracted with ether and the extract was evaporated. This gave 100 mg of the amorphous aldehyde (X), $C_{19}H_{24}O_5$. IR spectrum (CCl_4) cm^{-1}: 3620, 3450, 3040, 2810, 1730, 1645, 1600, 1505, 880. UV spectrum, λ_{max}, nm: 204 (ε 6000).

Of this aldehyde (X), 40 mg was oxidized with chromium trioxide in pyridine for two hours. After working up and chromatography on silica gel in chloroform, the amorphous lactone (XI) (20 mg) was isolated. IR spectrum (CCl_4), cm^{-1}: 3050, 2820, 1748, 1730, 1650, 1600, 1508, 1030, 880.

Oxidation of the Acetonide (III) with Osmium Tetroxide. A pyridine solution of 200 mg of osmium tetroxide was added to a solution of 200 mg of the acetonide (III) in 2 ml of pyridine. The mixture was left at room temperature for 48 h and was then diluted with chloroform (30 ml) and was washed with a dilute solution of hydrochloric acid and with water. A current of hydrogen sulfide was passed through the chloroform solution for 8 h. Then it was washed with water, dried, and evaporated.

The residue (170 mg) after chromatography in chloroform yielded 70 mg of crystalline (XII), mp 197-199°C (chloroform), $C_{22}H_{32}O_7$. IR spectrum, cm^{-1}: 3400, 1600, 1500, 1005, 878. UV spectrum, λ_{max}, nm: 212 (ε 6500). In addition, on chromatography 80 mg of a solid amorphous osmate was obtained.

Preparation of the Ketone (XIII). Compound (XII) (35 mg) was oxidized with sodium periodate by the method described above for 14 h. After the usual working up, 30 mg of the ketone (XIII) was obtained with mp 181-185°C (chloroform/ether), $C_{21}H_{28}O_6$. IR spectrum, cm^{-1}: 3400, 1715, 1600, 1505, 880. Mass spectrum: 361 ($M^+ - 15$).

Preparation of the Ketone (XIII). To 0.5 ml of absolute dioxane were added 0.2 ml of deuterium oxide and 10 mg of metallic sodium, and then 15 mg of the ketone (XIII) in 0.5 ml of dioxane. The mixture was boiled under reflux for 15 min and was evaporated. The residue was treated with 0.5 ml of dioxane and 0.2 ml of deuterium oxide. The experiment was repeated three times. The residue after evaporation was dissolved in 1 ml of deuterium oxide and was extracted with chloroform. The extract was acidified with dilute hydrochloric acid, washed with water, dried, and evaporated. This gave 12 mg of substance (XIV) $C_{21}H_{26}D_2O_6$. Mass spectrum: 363 ($M^+ - 15$).

SUMMARY

Under the action of catalytic amounts of mineral acid, the pentaol obtained by the reduction of the norditerpenoid teucrin A with lithium tetrahydroaluminate undergoes an anionotropic rearrangement with the subsequent elimination of a molecule of water.

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TRITERPENOIDS FROM THE LEAVES OF *Betula costata*

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Triterpenoids with a dammarane structure have been found in the leaves of various species of birch. Fischer and Seiler have isolated two previously unknown triterpenes — betulafolienetriol and betulafolienetetraol — from the leaves of the European species of birch *Betula alba* [1, 2] and have established their structure. Later, Japanese chemists showed the presence of new triterpenoids in the leaves of *Betula platyphylla* [3, 4].

Our aim was to search for sources rich in polycyclic alcohols of the dammarane series, which have been proposed for use as the starting material in the synthesis of glycosides [5]. We investigated the leaves of the far-eastern species *Betula costata*, since the presence of betulafolienetriol in them was known [6].

According to TLC, in the unsaponifiable part of an ethereal extract of the leaves of *Betula costata* (collected at the beginning of June, 1973, by G. P. Gorov) contained five triterpenes. We have isolated four individual substances — A, B, C, and D — so names in order of increasing polarity — and have determined their structures.

Triterpene A(I), $C_{30}H_{52}O_3$; the IR spectrum ($CHCl_3$) shows hydroxyl absorption at 3560 and 3620 cm^{-1}. Its PMR spectrum ($CDCl_3$) has the signals of the protons of eight tertiary methyl groups with δ (ppm) 0.77 (3H, s), 0.80 (3H, s), 0.88 (3H, s), 0.90 (3H, s), 1.0 (3H, s), 1.11 (3H, s), 1.57 (3H, s), 1.63 (3H, s) and the signal of a vinyl proton at C-24 with δ 5.09 ppm (1H, triplet), and also the signal of a C-3 proton at δ 3.32 ppm (1H, triplet, $J_{3,2} = J_{3,2} < 4$ Hz). The value of the constant shows the α configuration of the OH group at C-3. No signals of protons were observed in the 3.80-3.90 region, which permitted us to assume that there was no hydroxyl at C-12.

The mass spectrum of (I) contained the peak of the molecular ion M^+ 460, the peak of a tetracyclic fragment with m/e 333 and a peak with m/e 360. The absence of a hydroxyl at C-12 is responsible for the appearance of strong peaks of the side chain with m/e 128 and 110 as the result of cleavage between the fully substituted C-17 and C-20 atoms, since these peaks are the main ones in the mass spectrum of (I) taken at a low voltage (12 V).

Thus, for the triterpene acetate, A (I), the structure of dammar-24-ene-3α,17α,20-triol is proposed.

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