STRUCTURE OF THE SESQUITERPENE HYDROXYACID FROM ARTEMISIA VACHANICA KRASCH.

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We have isolated an optically active crystalline substance (I) with the composition $C_{15}H_{24}O_3$ from the leaves and flower heads of Artemisia vachanica Krasch. The substance is readily soluble in alcohol and chloroform, less readily in ethyl acetate and ether, and very sparingly in benzene and water [1]. The IR spectrum has an absorption maximum at 216 mμ (ε 3.60). IR spectrum: 1631 (C=C bond), 1702 (carboxyl C=O), 2631, 2825, 2964 (carboxyl OH), 3444 cm^{-1} (free OH group).

The presence of a carboxyl group is also confirmed by the solubility of the substance in caustic and carbonate alkalis giving solutions from which it is recovered unchanged on acidification. Two mobile hydrogen atoms have been found by the Tschugaeff-Zerewitinoff method.

Treatment of (I) with diazomethane gave a methyl ester of composition $C_{16}H_{26}O_3$ (III). The IR spectra of this ester had the following absorption bands: 3444 (OH groups), 1728 (–O–C=O group), and 1629 cm^{-1} (C=C bond).

It follows from the information given that the substance isolated is a sesquiterpene hydroxyacid; we have called it vachanic acid.

Hydrogenation of vachanic acid in the presence of Raney Ni or Pt catalysts (derived from PtO_2) gave a dihydro derivative with the composition $C_{15}H_{26}O_3$, mp 163-165°, (II). IR spectra of dihydrovachanic acid: 1711 (carboxyl C=O), 2955 (carboxyl OH), and 3420 cm^{-1} (free OH group). Thus, vachanic acid contains one double bond. The acid is not acetylated by acetic anhydride, which shows that the free OH group is very probably tertiary. This nature of the hydroxyl group is confirmed by the elimination of the OH group when vachanic acid is treated with sulfuric acid to form an anhydro derivative with the composition $C_{15}H_{22}O_2$.

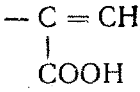
Dihydrovachanic acid was subjected to dehydrogenation over selenium. After appropriate purification and distillation over sodium, the reaction products gave two fractions: 1) with n_D^{20} 1.5110, d_4^{20} 0.9080, and 2) with n_D^{20} 1.5720.

The NMR spectrum of Fraction 1 gave signals of CH_3 and CH_2 groups present in an open chain and CH_3-CH_2 and CH_3 groups adjacent to an aromatic ring (this fraction formed almost no picrate), while the NMR spectrum of Fraction 2 gave signals only of CH_3 and CH_3-CH_2 groups adjacent to an aromatic ring. Fraction 2 gave a picrate with the composition $C_{13}H_{14} \cdot C_6H_3N_3O_7$, identical with the picrate of 1-methyl-7-ethylnaphthalene from tauremisin.

The dehydration of vachanic acid itself gave similar results.

The formation of 1-methyl-7-ethylnaphthalene from this acid is a proof of the presence in it of a carbon skeleton similar to that of santonin, alantolactone, and tauremisin [2, 3, 4], i.e., vachanic acid belongs to the sesquiterpenoids of the selinane type [5]. In addition, the production of 1-methyl-7-ethylnaphthalene shows that the carboxyl group is present at C_{11}.

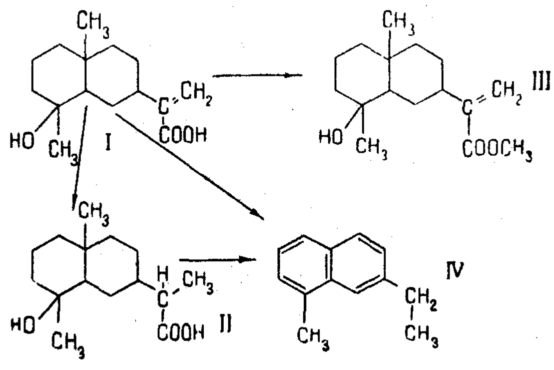
In the NMR spectra of vachanic acid (I), the singlet at 0.93 ppm corresponds to a quaternary methyl group, and the singlet of the same intensity at 1.21 ppm to a methyl group on a carbon atom to which, it must be assumed, the OH group is also attached.

Signals from the protons of the ring methylenes are located in the 1.3-2 ppm region. A series of peaks in the 2.3-2.9 ppm region with an intensity of 2 proton units corresponds to the protons of a tertiary hydroxyl group present, in all probability, on C_4. Isolated signals at 5.56 ppm and 6.45 ppm correspond to protons at a double bond. The displacement between the proton signals is caused by the different positions of the vinyl group hydrogen atoms in relation to the carboxyl group, whose proton gives a signal in the 9.6 ppm region. Consequently, the vinyl protons are located in a  $-\underset{\underset{\displaystyle COOH}{|}}{C}=CH_2$ group (figure, a).

As may be expected, the spectrum of dihydrovachanic acid lacks signals in the vinyl proton region.

In addition, there is a doublet with an intensity of 3 proton units at 1.25 ppm which, apparently, corresponds to a methyl group at C_{11} (Figure, b).

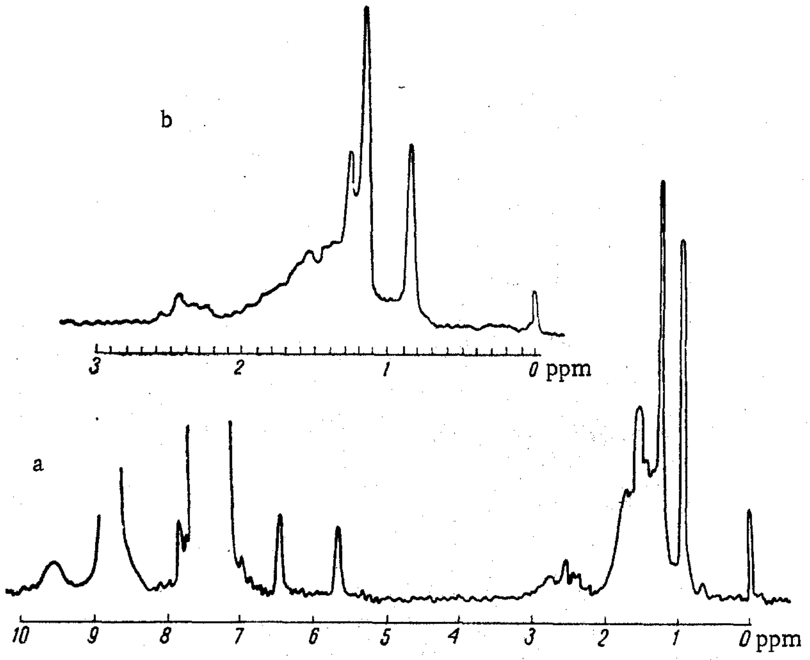
On these grounds, we propose Formula I as the most probable structure for vachanic acid:



Experimental

Vachanic acid (I). Five kg of a mixture of the leaves, flower heads, and thin green sprigs of Artemisia vachanica Krasch. collected in the flower-budding phase on the 8th August 1962 close to the town of Khorog, Tajik SSR, was extracted three times with hot (80°) water for 1 hour. The aqueous extract was shaken with three 500-ml portions of chloroform. The residue remaining after the chloroform had been distilled off crystallized completely on standing. The crystals were washed with small portions of ether and were recrystallized three times with ethyl acetate. Mp 173-175°, $[\alpha]_D^{20}$ 35.09° (c 0.9; alcohol). Yield 0.16%.

Found, %: C 71.79, 71.72; H 9.59, 9.68; H 0.79, 0.76; mol. wt. 258. Calculated for $C_{15}H_{24}O_3$, %: C 71.42; H 9.52; 2H• 0.80, mol. wt. 252.



NMR spectra of (a) vachanic acid, and (b) dihydrovachanic acid.

Dihydrovachanic acid (II). A solution of 0.86 g of vachanic acid in 70 ml of absolute alcohol was hydrogenated with hydrogen in the presence of a Raney Ni catalyst. Hydrogenation took place rapidly, and only 1 mole of hydrogen was absorbed. The residue after the removal of the catalyst and the solvent was triturated with ether. On standing, small crystals with mp 163-165° (from a mixture of alcohol and ether) were deposited.

Found, %: C 71.31, 71.02; H 10.03, 10.03. Calculated for $C_{15}H_{26}O_3$, %: C 70.87; H 10.23.

The same results were obtained when vachanic acid was hydrogenated in the presence of a Pt catalyst derived from PtO_2 (Adams' catalyst).

Methyl ester of vachanic acid (III). A solution of 0.5 g of vachanic acid in 500 ml of ether was treated with an ethereal solution of diazomethane until a yellow coloration appeared; an excess of diazomethane was added and the mixture was left overnight; the excess of diazomethane was then decomposed with water, and the ethereal layer was washed twice. Evaporation of the ether gave a slightly yellowish vitreous mass which, after distillation under vacuum, became colorless; it was impossible to crystallize it.

Found, %: C 72.48, 72.20; H 9.89, 9.89. Calculated for $C_{16}H_{26}O_3$, %: C 72.17; H 9.77.

Anhydrovachanic acid. A mixture of 1 g vachanic acid and 60 ml 50% sulfuric acid was heated on a water bath at 50° for 8 hr, with periodic shaking. After the reaction mixture had been cooled and diluted with 250 ml of water, the reaction product was extracted five times with ether. The ethereal extract was washed five times with 5% $NaHCO_3$ solution and then four times with 5% NaOH solution. The bicarbonate layer was acidified with 10% hydrochloric acid to an acid reaction to litmus, and was extracted with ether. The ethereal extract was washed twice with water. The elimination of the ether gave about 0.4 g of crystals with mp 173-175° (from ethyl acetate); a mixture with vachanic acid had mp 173-175°; the IR spectrum was identical with the spectrum of vachanic acid.

The alkaline solution was acidified with 10% hydrochloric acid to an acid reaction to congo red and was extracted with ether. The extract was washed three times with 5% $NaHCO_3$ solution and then with water. Elimination of the ether gave a glassy product which could not be crystallized. Yield 0.0942 g.

Found, %: C 76.65, 76.97; H 9.57, 9.40. Calculated for $C_{15}H_{22}O_2$, %: C 76.92; H 9.40.

Dehydrogenation of dihydrovachanic acid. A mixture of 5 g of dihydrovachanic acid and 5 g of selenium was heated in a liquid metal bath for 12 hours at 290-300°. The reaction product was extracted with petroleum ether, the solvent was eliminated, and the residue was distilled under vacuum (2 mm). This gave three fractions: 1) a yellowish mobile liquid, bp 110-115°, n_D^{20} 1.5160 – 1.5 ml; 2) a yellowish mobile liquid, bp 115-125°, n_D^{20} 1.5300 – 1 ml; 3) a viscous liquid with a faint pink-purple color, bp 125-140°, n_D^{20} 1.5520 – 2 ml.

Fractions 1 and 2 were combined and were redistilled under vacuum over Na. The distillate consisted of 0.6 g of a colorless mobile liquid with d_4^{20} 0.9080 and n_D^{20} 1.5110.

Found, %: C 88.70, 88.68; H 11.29, 11.56.

The NMR spectrum showed signals for a considerable number of CH_3 and CH_2 groups present in an open chain and also those of a small number of CH_3 and $CH_3{-}CH_2$ groups adjacent to an aromatic ring.

Fraction 3 was also redistilled over Na. It gave 0.25 g of a viscous liquid with n_D^{20} 1.5720.

Found, %: C 91.80, 91.94; H 9.01, 9.15. Calculated for $C_{13}H_{14}$, %: 91.76; H 8.23.

The NMR spectrum of this fraction showed signals of CH_3 and $CH_3{-}CH_2$ groups adjacent to an aromatic ring. Thus, the third fraction consisted mainly of a methylethylnaphthalene.

Picrate of 1-methyl-7-ethylnaphthalene. A solution of 0.25 g of the fraction with n_D^{20} 1.5720 in 2 ml of absolute alcohol was mixed with a hot solution of 0.25 g of picric acid in 5 ml of absolute alcohol. Needle-like orange crystals with mp 94-95° (from alcohol) were deposited.

Found, %: C 56.91, 56.93; H 4.45, 4.57. Calculated for $C_{13}H_{14} \cdot C_6H_3N_3O_7$, %: C 57.14; H 4.26.

A test for a depression of the melting point with the picrate of 1-methyl-7-ethylnaphthalene obtained from tetrahydrotauremisin was negative.

Dehydrogenation of vachanic acid. A mixture of the acid and selenium (5 g each) was heated in a liquid metal bath at 290-310° for 12 hours. The reaction product was extracted with petroleum ether, the solvent was partially evaporated, and the solution was then chromatographed on alumina (activity grade I; 30 g); petroleum ether eluted about 2 ml of a yellow-green liquid which was rechromatographed on alumina of the same activity (20 g) and was distilled under vacuum (2 mm). This gave about 1 ml of a yellowish liquid with n_D^{20} 1.5620. Redistillation gave three fractions: 1) a yellowish mobile liquid with n_D^{20} 1.5450 – 0.02 g; 2) a yellowish mobile liquid with n_D^{20} 1.5620 – 0.45 g; 3) a yellowish viscous liquid with n_D^{20} 1.5760 – 0.1268 g.

By the method described above, the combined second and third fractions gave the picrate of 1-methyl-7-ethylnaphthalene.

Summary

From the leaves and flower heads of Artemisia vachanica Krasch. we have isolated a new sesquiterpene hydroxyacid of the composition $C_{15}H_{24}O_3$, which has been called vachanic acid and for which structural formula I is proposed as the most probable.

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