THE STRUCTURE OF ACROPTILIN – A SESQUITERPENE LACTONE FROM Acroptilon repens

R. I. Evstratova, E. Ya. Kiseleva,
V. I. Sheichenko, and K. S. Rybalko

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Acroptilon repens L. (DC) has been repeatedly studied chemically. However, the literature information on its composition is extremely contradictory. According to A. Orekhov [1], the epigeal part of this plant contains alkaloids; G. Lazurevskii and A. Sadykov did not confirm this; other workers [2] found about 4% of glucoalkaloids in the epigeal part of this plant.

From the leaves and flower heads of A. repens collected in the Caucasus we have isolated two new sesquiterpene lactones possessing pharmacological activity: acroptilin and repin [3].

In the present paper we describe the results of a chemical study of acroptilin, which has the composition $C_{21}H_{24}O_9$, mp 196-198°C (from ethanol), $[\alpha]_D^{20}+92.3°$ (c 0.68; ethanol). The IR spectrum (Fig. 1) has absorption bands at 3470 cm^{-1} (OH group) and 1743 cm^{-1} (C=O), and weak bands at 1665 and 1630 cm^{-1} (C=C).

The NMR spectrum of acroptilin (Fig. 2, a) has the signals of two exocyclic methylenes; one of them is conjugated with the lactone carbonyl (doublets at 6.26 and 5.84 ppm, J=3.5 Hz); the signals of the second are located in a stronger field (doublets at 5.14 and 5.24 ppm with a coupling constant of the protons with one another of 1.5 Hz); a singlet at 1.75 ppm of three proton units corresponds to a methyl group, probably adjacent to a hydroxyl or on a double bond. It has been established by the double-resonance method that a multiplet (1H) at 4.35 ppm corresponds to a gem-hydroxy proton, a quartet at 5.05 ppm to a lactone proton, and a doublet in the 6.94 ppm region to a hydroxy proton.

Acroptilin dissolves readily in ethanol and pyridine, is almost insoluble in chloroform, and dissolves in alkalis on heating, with saponification, consuming 3 moles of caustic soda. The hydrolysis of acroptilin takes place in the cold giving two substances according to the concentration of the alkali and the duration of the process. From the products of the saponification of acroptilin with a 4% aqueous solution of KOH the following two substances have been obtained: a hydroxy lactone A, with the composition $C_{15}H_{18}O_5$; ν_{max} 3370 cm^{-1} (OH), 1770 cm^{-1} (γ-lactone), 1648 cm^{-1} (C=C), and a hydroxy lactone B, with the composition $C_{19}H_{22}O_8$; ν_{max} 3550 cm^{-1} (OH), 3440 cm^{-1} (OH), 1775 cm^{-1} (γ-lactone), and 1660 and 1650 cm^{-1} (C=C).

In the NMR spectrum of hydroxy lactone A (Fig. 2, b), the signals of an exocyclic methylene group conjugated with the lactone carbonyl undergo pronounced changes (triplets at 6.25 and 6.45 ppm), which shows the β position of the acyl group in acroptilin with respect to an exocyclic methylene; the signal of the methyl group in the 1.75 ppm region also disappears, while the signals of the second exocyclic methylene group are retained. In the NMR spectrum of hydroxy lactone B (Fig. 2, c), the signals of the exocyclic methylenes change similarly, but the signals of the methyl protons do not.

Hydroxy lactone B gives an acetyl derivative with the composition $C_{21}H_{24}O_9$, mp 167-169°C, ν_{max} 3510 cm^{-1} (OH), 1780 cm^{-1} (γ-lactone), 1740 and 1240-1270 cm^{-1} ($OCOCH_3$), and 1650 cm^{-1} (C=C).

Acetic acid, identified by paper chromatography and by NMR spectroscopy, was isolated from the acid fractions from the hydrolysis of acroptilin.

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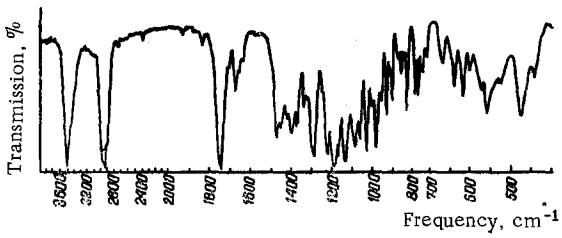

Fig. 1. IR spectrum of acroptilin (UR-10 instrument, KBr prism, paraffin oil).

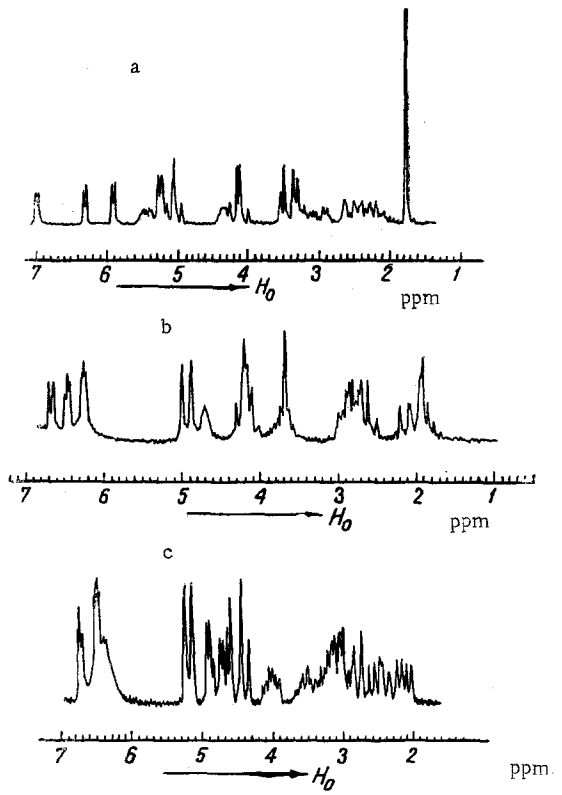

Fig. 2. NMR spectra of acroptilin (100 MHz, pyridine) (a), the hydroxy lactone A (100 MHz, $CDCl_3$) (b), and the hydroxy lactone B (100 MHz, pyridine) (c).

When acroptilin was hydrogenated over PtO_2 in ethanol, 2 moles of hydrogen was consumed, but the reaction product could not be crystallized. When acroptilin was hydrogenated in acetic acid, 3 moles of hydrogen was consumed with the formation of a hexahydro derivative of the composition $C_{21}H_{30}O_9$; ν_{max} 3420-3530 cm^{-1} (OH) and 1770-1740 cm^{-1} (C=O). Hexahydroacroptilin was reduced with lithium tetrahydroaluminate. The resulting product was dehydrogenated over selenium at 280-315°C for 30 min. From the reaction products chamazulene with mp 128-129.5°C, identified through its trinitrobenzene derivative, was isolated.

The facts given permit the conclusion that acroptilin is a sesquiterpene lactone of the guaiane or germacrane type and contains two acyl residues, an OH group, and two exocyclic methylenes, one of which is conjugated with the carbonyl group. The study of the structure of acroptilin is continuing.

EXPERIMENTAL

Isolation of Acroptilin. The leaves, flower heads, and green parts of the stems of A. repens collected in May in the Caucasus were steeped in hot water (80-85°C) for 30 min four times. The total lactones were extracted from the cooled aqueous extract with chloroform, and the chloroform extract was evaporated to dryness. The residue was treated with ethanol and ether (1:5). The microcrystalline precipitate that deposited was filtered off and was washed on the filter with ether twice. This gave the white microcrystalline combined lactones, with mp 143-160°C. Yield 0.18%. In a thin layer of Al_2O_3 (activity grade IV) in the benzene–methanol (9:1) system, using a 0.5% solution of $KMnO_4$ in 0.5% H_2SO_4 as the revealing agent, two spots were found with R_f 0.54 and 0.44. After four recrystallizations from ethanol, colorless crystals were obtained in the form of needles with mp 196-198°C giving on TLC in the same system a single spot with R_f 0.44. IR spectrum, ν_{max}, cm^{-1}: 3470, 1743, 1665.

Found %: C 59.75; 60.24; H 5.78; 5.67; mol. wt. 400.44,* 444 (Rast). $C_{21}H_{24}O_9$. Calculated %: C 60.0; H 5.71, mol. wt. 420.

Hydrolysis of Acroptilin. A mixture of 1.0 g of acroptilin and 50 ml of 4% KOH solution was left at room temperature for 19 h, and was then acidified with 10% H_2SO_4 to pH 1 and extracted with ethyl acetate. The ethyl acetate extract was washed with 5% $NaHCO_3$ solution and with water. The solvent was eliminated to give colorless crystals of hydroxy lactone A, with the composition $C_{15}H_{18}O_5$, mp 162-164°C (from ethyl acetate), which was dried under vacuum over P_2O_5 with heating by ethanol vapor for 3 h. The analytical results for this and the subsequent substances corresponded to the calculated figures.

The mother liquors from the recrystallization were dissolved in a mixture of benzene and ethanol (9:1) and purified on a column containing 10 g of neutral Al_2O_3 (activity grade IV), being eluted with benzene, benzene–ethanol, and ethanol. The benzene fractions deposited colorless needles of the hydroxy lactone B, with the composition $C_{19}H_{22}O_8$, mp 184-186°C (decomp., from ethyl acetate).

* As in Russian original – Publisher.

The bicarbonate extract was acidified with 10% HCl to pH 1 and was extracted with ether. Then the ether was evaporated off at room temperature. The residue consisted of a colorless liquid with a characteristic odor which was identified as acetic acid by its NMR spectrum and by descending paper chromatography in the butan-1-ol–1.5 N ammonia (1:1) system in the presence of markers (the spots were revealed with a 0.1% ethanolic solution of bromthymol blue) [4].

Hydrogenation of Acroptilin in Ethanol. The hydrogenation of 1.0 g of acroptilin in 173 ml of ethanol was performed in the presence of 0.05 g of PtO_2 until the absorption of hydrogen ceased. The amount absorbed was 2 moles. The catalyst was filtered off, and the ethanol was evaporated off to give a colorless liquid which could not be crystallized. IR spectrum, ν_{max}, cm^{-1}: 3460, 1780, 1660 cm^{-1}.

Hydrogenation of Acroptilin in Acetic Acid; Preparation of Hexahydroacroptilin. The hydrogenation of 1.25 g of acroptilin in 50 ml of acetic acid was performed in the presence of 0.25 g of PtO_2 until the absorption of hydrogen ceased. The reaction was complete after 2 h, 2 moles of hydrogen having been absorbed. The reaction mixture was diluted with water (1:5) and neutralized with Na_2CO_3, and the reaction product was extracted with chloroform. The chloroform extract was washed with water to neutrality, and the solvent was evaporated off. The residue crystallized from ethanolic solution. Composition $C_{21}H_{30}O_9$, mp 105°C (Kofler), mol. wt. 426.

Reduction of Hexahydroacroptilin with $LiAlH_4$; Preparation of the Glycol. A solution of 2.2 g of hexahydroacroptilin in 200 ml of dry benzene was treated dropwise with a solution of 3.4 g of $LiAlH_4$ in 200 ml of dry benzene. The reaction mixture was boiled on the water bath for 4 h. After 12 h, the residues of unchanged $LiAlH_4$ were destroyed – first with moist benzene and then with a small amount of water. Elimination of the solvent gave a slightly yellowish viscous liquid with the composition $C_{15}H_{28}O_5$; IR spectrum, ν_{max}, cm^{-1}: 3580-3280, 2380.

Dehydrogenation of the Product of the Reduction of Hexahydroacroptilin. A mixture of 0.3 g of the glycol and 0.3 g of selenium was heated at 280-315°C for 30 min. The reaction product was extracted with petroleum ether. The residue consisted of a blue oil (azulene). This was dissolved in 1 ml of absolute ethanol and the solution was mixed with an equal amount of a hot ethanolic solution of trinitrobenzene. Long, thin, black crystals deposited with mp 128-129.5°C (after drying in a vacuum desiccator over H_2SO_4).

SUMMARY

A new sesquiterpene lactone – acroptilin – isolated from Acroptilon repens L. (DC) has been assigned to the sesquiterpene lactones of the guaiane or germacrane type, and it contains two acyl residues, a OH group, and two exocyclic methylenes, one of which is conjugated with the carbonyl.

LITERATURE CITED

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