SESQUITERPENE LACTONES FROM Artemisia caucasica

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From the epigeal green part of Artemisia caucasica Willd (-A. Grossheimii-Krasch, ex-Poljak) (Caucasian wormwood) collected in the Krasnodar region in May, 1970 we have isolated two sesquiterpene lactones by aqueous extraction.

One of them, which we have called grossmisin, $C_{15}H_{18}O_4 \cdot H_2O$, melts at 120-135°C and then crystallizes again and remelts at 156-158°C (from ethanol), $[\alpha]_D^{20}$ + 115.26° (c 1.2; ethanol). Its IR spectrum, ν_{max}, cm^{-1}: 3500 (OH), 3300-3040 (H_2O), 1760 (γ-lactone), 1683 (α,β-cyclopentenone), 1635 and 1610 (double bonds in conjugation). Its UV spectrum has a strong absorption maximum at 256 nm [log ε 4.09 (α,β-cyclopentadienone)].

The NMR spectrum of grossmisin (Fig. 1) has the signals of the protons of a secondary methyl group – doublet at 1.25 ppm; of the protons of two methyl groups on a double bond – singlets at 2.25 and 2.38 ppm; of a vinyl proton – doublet (1H) at 6.12 ppm; a lactone proton – triplet at 3.85 ppm; and a proton geminal to a hydroxyl – sextet at 3.70 ppm.

When this substance was dehydrogenated over selenium, chamazulene was formed. By comparing the observations made with literature information we came to the conclusion that grossmisin possesses the same structural formula as austricin (deacetylmatricarin) – a sesquiterpene lactone from Artemisia austriaca Jacq. et al. [1-5] – but grossmisin is not identical with austricin. Their IR spectra differ. The NMR spectrum of grossmisin is very similar to that of austricin but differs from the position of the signal of the methyl group at C_{11}.

With acetic anhydride, grossmisin gave an acetate $C_{17}H_{20}O_5$ with mp 190-191.5°C (from ethanol), $[\alpha]_D^{20}$ + 97.9 (c 1.3; ethanol). IR spectrum, ν_{max}, cm^{-1}: 1780 (γ-lactone), 1740 ($OCOCH_3$), 1680 (α,β-cyclopentenone), 1640 and 1610 (C = C); UV spectrum: λ_{max} 255 nm (log ε 4.172).

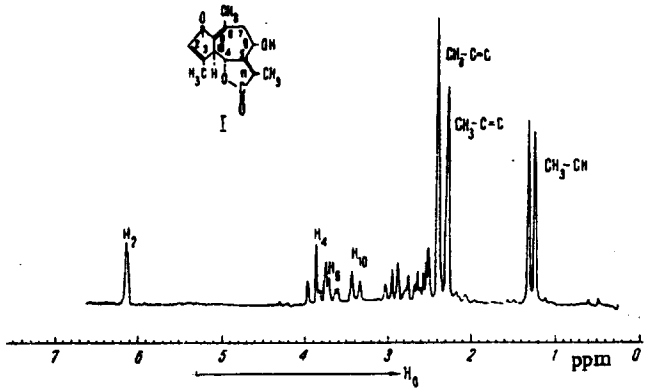

Fig. 1. NMR spectrum of grossmisin (deuterochloroform, 100 MHz).

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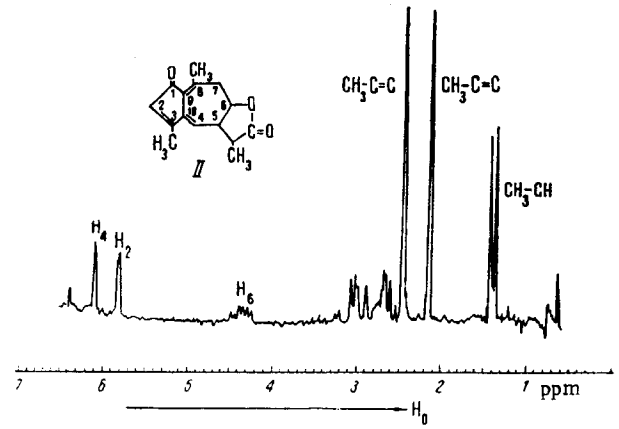

Fig. 2. NMR spectrum of anhydrogrossmisin (deuterochloroform, 100 MHz).

Acetylgrossmisin has the same melting point as acetylaustricin (matricarin); however, a mixture of these compounds showed a melting point depression of 19°C. The NMR spectrum of acetylgrossmisin again differs from the NMR spectrum of acetylaustricin only by the position of the signal of a methyl group. This permits the assumption that grossmisin is the stereoisomer of austricin at C_{11}; i.e., grossmisin (I) has the same spatial arrangement at C_4, C_5, C_{10}, and C_{11} as 6-hydroxyachillin [5-8].

When grossmisin was heated with a 0.1% solution of $Ca(OH)_2$ or a 3% solution of K_2CO_3 with subsequent acidification, dehydration took place with the formation of a substance having the composition $C_{15}H_{16}O_3$, mp 184-186°C (from ethanol), IR spectrum, ν_{max}, cm^{-1}: 1780 (γ-lactone), 1690 (α,β-cyclopentenone), 1625 and 1600 (C = C in conjugation). The UV spectrum had two absorption maxima: λ_{maxI} 243 nm (log ε 4.279), and λ_{maxII} 258 nm (log ε 4.273). The NMR spectrum of anhydrogrossmisin (Fig. 2) has the signal of a lactone proton – multiplet with a center at 4.4 ppm – and in addition, another signal of a vinyl proton – singlet at 6.15 ppm. The NMR spectrum of the anhydro derivative showed a reorientation of the lactone ring and the dehydration of the hydroxy group formed by the hydrolysis of the lactone ring. Hence, the structure of the anhydro derivative is shown by formula (II).

As is well known, on treatment with $Ca(OH)_2$ and H_2SO_4, austricin likewise gives anhydroaustricin with mp 207-208°C (from ethanol) [3, 4]. The NMR spectra of anhydroaustricin and anhydrogrossmisin differ only in the position of the signal of a methyl group. Thus, the structure of anhydroaustricin proposed previously [9] requires reconsideration. Anhydroaustricin is stereoisomeric with anhydrogrossmisin and has the structure (II).

Chromatography of the resin from the mother liquor after the isolation of grossmisin gave a second lactone, with the composition $C_{15}H_{18}O_5$, mp 234-236°C (decomp., from ethanol), $[\alpha]_D^{20} \pm 0°$. IR spectrum: ν_{max} 3500 cm^{-1} (OH), 1770 cm^{-1} (γ-lactone). UV spectrum: λ_{max} 208 nm (log ε 4.01). The NMR spectrum has two singlets in the 1.20 and 1.60 ppm region, $2CH_3-C-O$, two doublets of 1H each at 3.25 and 3.50 ppm, a quartet at 4.45 ppm of a lactone proton, and a doublet at 2.75 ppm (1H).

From its constants and spectra, this lactone is identical with rutifolin, a sesquiterpene lactone from Artemisia rutifolia [10].

EXPERIMENTAL

The IR spectra (mulls in paraffin oil) were taken on a UR-10 spectrophotometer, the NMR spectra on a JNM-4H-100 MHz spectrometer, and the UV spectra (solutions in 96% ethanol) on a "Hitachi" EPS-3T spectrophotometer. The analyses of all the compounds corresponded to the calculated values.

Isolation of Grossmisin and Rutifolin. The herb Artemisia caucasica collected on May 23, 1970 in the budding phase (Gelendzhik region, Krasnodar territory) (1 kg) was steeped in hot water (80°C) for 30 min. The extraction with water was repeated three times. The aqueous extract was treated with chloroform, and the chloroform extract was evaporated. The resulting resin was treated with ether. A faintly colored precipitate deposited with a yield of 1.5 g. After three recrystallizations from ethanol and drying

over $CaCl_2$, the substance melted at 120-135°C in a capillary and then it crystallized again and remelted at 156-158°C, $[\alpha]_D^{20}$ + 115.26° (c 1.2; in ethanol).

Found %: C 64.50; 64.57; H 7.29; 7.19. $C_{15}H_{18}O_4 \cdot H_2O$. Calculated %: C 64.27; H 7.19.

On drying over P_2O_5 at 75°C/5 mm Hg, this substance slowly lost its water of hydration, and the anhydrous form had mp 157-159°C.

Found %: C 68.57; H 6.95. Calculated %: C 68.68; H 6.92.

The mother liquor after the isolation of the grossmisin was chromatographed on neutral alumina (activity grade IV) in a ratio of 1 : 30. Ethereal fractions 9-12 (50 ml each) gave an additional amount of grossmisin in the form of colorless crystals; ethereal fractions 18-20 yielded colorless crystals with the composition $C_{15}H_{18}O_5$, mp 234-236°C (from acetone and from ethanol). $[\alpha]_D^{20}$ ±0° (in pyridine).

Acetylgrossmisin. A mixture of 0.5 g of grossmisin (hydrate), 5 ml of acetic anhydride, and 10 ml of pyridine was heated at 60°C for 1 h. After cooling, it was diluted with water and the reaction product was extracted with chloroform. The extract was washed with 10% hydrochloric acid solution and then with water. The solvent was driven off, giving crystals with mp 187-202°C. The product was purified by chromatography on neutral alumina (activity grade IV) in a ratio of 1 : 30, elution being performed with ether. Fraction 5 deposited colorless crystals in the form of prisms with the composition $C_{17}H_{20}O_5$, mp 190-191.5°C (from ethanol), $[\alpha]_D^{20}$ + 97.9 (c 1.3; ethanol). A mixture of the substance obtained with acetylaustricin had mp 160-179°C.

Anhydrogrossmisin. A mixture of 0.5 g of grossmisin (hydrate), 0.5 g of $Ca(OH)_2$, and 500 ml of distilled water was boiled for 15 min, and the filtrate was acidified with 10% H_2SO_4 solution to pH 1. The reaction product was extracted with chloroform, which was then washed with 5% K_2CO_3 solution and with water; after the elimination of the solvent yellowish crystals were obtained, and on recrystallization these formed colorless plates with the composition $C_{15}H_{16}O_3$, mp 184-186°C (from ethanol).

CONCLUSIONS

1. Two sesquiterpene lactones have been isolated from the epigeal green part of Artemisia caucasica Willd.: one with the composition $C_{15}H_{18}O_5 \cdot H_2O$, which has been called grossmisin, and one with the composition $C_{15}H_{18}O_5$, identified as rutifolin. Structure (I) has been proposed for grossmisin.

2. The structure of anhydroaustricin has been reviewed. Structure (II) is proposed for it.

LITERATURE CITED

1. K. S. Rybalko and P. S. Massagetov, Med. Prom. SSSR, 1961, No. 11, 25.
2. W. Herz and K. Ueda, J. Amer. Chem. Soc., 83, No. 5, 1138 (1961).
3. K. S. Rybalko, N. N. Ban'kovskaya, and R. I. Evstratova, Med. Prom. SSSR, 1962, No. 3, 13.
4. Tr. VILAR [Proceedings of the All-Union Scientific-Research Institute for Medicinal and Aromatic Plants], 15, 203 (1969).
5. E. H. White and R. E. K. Winter, Tetrahedron Lett., 1963, No. 3, 137.
6. E. H. White and J. N. Marx, J. Amer. Chem. Soc., 89, No. 21, 5511 (1967).
7. E. H. White, S. Eguchi, and J. N. Marx, Tetrahedron, 25, No. 10, 2099 (1969).
8. D. H. R. Barton, Helv. Chim. Acta, 42, 2604 (1959).
9. K. S. Rybalko, Zh. Obshch. Khim., 33, No. 8, 2734 (1963).
10. I. Evstratova and P. V. Chugunov, Khim. Prirodn. Soedin., 5, 445 (1969).