# STRUCTURE OF THE SESQUITERPENE LACTONE STIZOLICIN

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From the epigeal green part of Stizolophus coronopifolius (Lam.) Cass., collected in the Caucasus, we [1] have isolated a new sesquiterpene lactone, "Stizolicin," with the composition $C_{20}H_{26}O_7$, mp 152-153.5°C (from ethanol), $[\alpha]_D^{25}$ − 32.4° (c 2.19, ethanol). We have also isolated this substance from the epigeal part of Stizolophus balsamita, where it is present together with stizolin (I). The IR spectrum of stizolicin has absorption bands at ($cm^{-1}$) 3455 and 3480 (OH), 1762 and 1670 ($\alpha$-methylene $\gamma$-lactone), 1720 and 1240 (C=O), and 1650 (C=C).

The hydrogenation of the lactone over a Raney Ni catalyst gave a tetrahydro derivative with the composition $C_{20}H_{30}O_7$, mp 163-167°C (decomp.), $\nu_{max}$ ($cm^{-1}$) 3470 and 3550 (OH), 1756 ($\gamma$-lactone), and 1720 (C=O); diacetyltetrahydrostizolicin formed a vitreous product with the composition $C_{24}H_{34}O_9$, $\nu_{max}$ ($cm^{-1}$) 1780 ($\gamma$-lactone) and 1740-1750 (OCO).

On hydrogenation over a Pt catalyst (according to Adams) in ethanol, 2.5 mole of hydrogen was consumed. The reaction products yielded a hexahydro derivative with the composition $C_{20}H_{30}O_6$ in the form of a vitreous product with $\nu_{max}$ ($cm^{-1}$) 3490-3530 (OH), 1775 ($\gamma$-lactone), and 1730 (C=O). These results permit us to consider that stizolicin contains two hydroxyls, one of which is readily reduced [2, 3].

Stizolicin is saponified in the presence of caustic soda, 2 moles of alkali being consumed (it contains two saponifiable groups), but it was impossible to isolate the hydrolysis products (a resinous product was obtained in extremely low yield). When tetrahydrostizolicin was saponified in the presence of $K_2CO_3$ at 60-70°C for 2 h, we obtained a hydroxylactone with the composition $C_{15}H_{22}O_4$ in the form of a vitreous product with $\nu_{max}$ ($cm^{-1}$) 3470-3500 (OH) and 1770-1760 ($\gamma$-lactone). This shows that stizolicin contains a five-carbon acyl residue.

The NMR spectrum of stizolicin (Fig. 1) is extremely close to that of stizolin (Fig. 2). Like that of stizolin, it contains the following proton signals: methyl on an epoxide ring and an epoxide proton (singlet at 1.20 ppm and doublet at 2.88 ppm), a methyl on a double bond (singlet at 1.70 ppm), an exocyclic methylene group conjugated with a lactone carbonyl (doublet at 5.96 and 6.38 ppm), J = 4 and 3.5 Hz, and vinyl and lactone protons (quartets at 5.35 ppm and 4.58 ppm) [4].

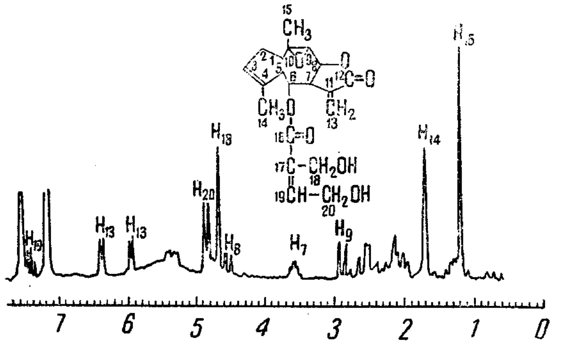

Fig. 1. NMR spectrum of stizolicin ($[D_5]$-pyridine, 100 MHz).

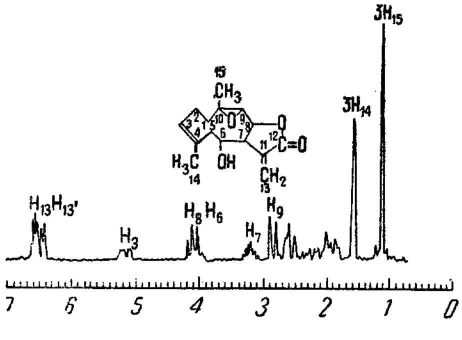

Fig. 2. NMR spectrum of stizolin ($[D_5]$-pyridine, 100 MHz).

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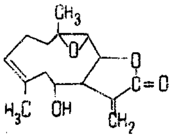
In contrast to the spectrum of stizolin, the NMR spectrum of stizolicin has a triplet of one proton unit at 7.45 ppm (J = 12 Hz), the vinyl proton of an acyl residue, and a doublet at 4.84 ppm (J = 6 Hz) and a singlet at 4.70 ppm (each of two proton units) characterizing the protons of hydroxymethylene groups on a double bond [5].

On dehydrogenation over Se, stizolicin, like stizolin, forms chamazulene.

According to the results obtained, we propose structure II as the most probable for stizolicin.



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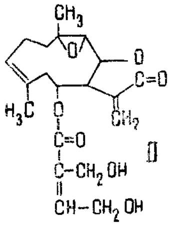

II

## EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrophotometer. The analytical results for all the compounds corresponded to the calculated figures.

Isolation of Stizolicin. A mixture of the leaves, flower heads, and thin stems of *Stizolophus coronopifolius* (Lam.) Cass. collected on July 5, 1968 in Azerbaidzhan on the Dzheiranchel mountain plateau was steeped in hot water (80-85°C) for 30 min four times. The lactones were extracted from the aqueous solution with chloroform, the chloroform was evaporated off, and the residue was treated with a small amount of ethanol and an excess of ether. The light, cream-colored crystals that deposited were washed with ether, mp 130-140°C. On TLC in neutral $Al_2O_3$ (activity grade IV) in a benzene–ethanol (9 : 1) system, two spots with $R_f$ 0.34 and 0.46 were revealed by a 0.5% solution of $KMnO_4$ in 0.5% $H_2SO_4$.

After four recrystallizations from ethanol, colorless crystals with mp 152-153.5°C were obtained; on TLC in the same system, one spot was obtained with $R_f$ 0.34; $[\alpha]_D^{25}$ − 32.4° (c 2.19 ethanol). Found %: C 63.40, 63.36; H 7.12, 7.15. $C_{20}H_{26}O_7$. Calculated %: C 63.48; H 6.93.

Saponification of Stizolicin. A mixture of 0.0921 g of stizolicin, 10 ml of ethanol, and 10 ml of 0.1 N NaOH solution was heated in a water bath for 20 min. After cooling, the excess alkali was back-titrated with 0.1 N HCl solution (with phenolphthalein as indicator). The consumption of 0.1 N NaOH was 5.0 ml, which corresponds to 2 g-eq of alkali.

Hydrogenation of Stizolicin. Production of Hexahydrostizolicin. To a solution of 2.9785 g of stizolicin in 150 ml of ethanol was added 0.1 g of $PtO_2$, and then hydrogenation was carried out until the absorption of hydrogen ceased, when 2.5 moles had been absorbed. The catalyst was filtered off, and the ethanol was evaporated off. This gave a vitreous product showing, on TLC, spots with $R_f$ 0.75 and 0 (ether system). The reaction product was chromatographed on neutral $Al_2O_3$ (activity grade IV) in a ratio of 1 : 30. Ether eluted a vitreous product with $R_f$ 0.78 having the composition $C_{20}H_{30}O_6$.

Hydrogenation of Stizolicin over Ni. Preparation of Tetrahydrostizolicin. Raney Ni catalyst was added to a solution of 2.9909 g of stizolicin in 150 ml of ethanol, and hydrogenation was carried out until the absorption of hydrogen ceased, when two moles had been absorbed. The catalyst was filtered off, and the ethanol was evaporated off to give a paraffin-waxlike mass which was washed several times with ethyl acetate and then gave a single spot on TLC with $R_f$ 0.68 (ether system). The substance was recrystallized from benzene–ethanol (1 : 1). Colorless crystals with mp 163-167°C (decomp.) having the composition $C_{20}H_{30}O_7$ deposited.

Preparation of Diacetyltetrahydrostizolicin. A solution of 0.1 g of tetrahydrostizolicin in 2 ml of pyridine was treated with 1 ml of acetic anhydride. The mixture was left at room temperature for 12 hr, and then diluted with water. The reaction product was extracted with chloroform, and the chloroform extract was washed with 3% HCl solution and then with water to neutrality. After the solvent had been driven off, a liquid product with the composition $C_{24}H_{34}O_9$ was obtained which gave a single spot on TLC with $R_f$ 0.75 (ether system).

Saponification of Tetrahydrostizolicin. A mixture of 0.3 g of tetrahydrostizolicin, 10 ml of ethanol, 7.5 ml of water, and 0.25 g of $K_2CO_3$ was heated in a water bath at 60–70°C for 2 hr, and then diluted with water. The reaction product was extracted with chloroform,and the chloroform extract was washed with 0.5% HCl solution and with water to neutrality. After the solvent had been driven off, a vitreous product was obtained with $R_f$ 0.78 on TLC (ether system) and having the composition $C_{15}H_{22}O_4$.

Dehydrogenation of Stizolicin. Production of Chamazulene. A mixture of 2.0 g of stizolicin and 1.8 g of selenium was heated at 335–345°C for 7 min. The reaction product was extracted with petroleum ether and chromatographed on a column of neutral $Al_2O_3$ (activity grade II). The petroleum ether eluate yielded 0.05 g of a blue oil which, according to TLC (petroleum ether system) was identical with chamazulene.

## CONCLUSIONS

1. A new sesquiterpene lactone, "stizolicin," has been isolated from Stizolophus coronopifolius (Lam.) Cass.

2. Structure II has been proposed as the most probable for stizolicin on the basis of chemical reactions and spectral characteristics.

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