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NEW FLAVONOID COMPOUNDS FROM GALEOPSIS LADANUM

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By recrystallizing the total flavonoids of Galeopsis ladanum L. (red hempnettle) [1] from methanol we have isolated a glycoside fraction the acid hydrolysis of which under mild conditions (1% hydrochloric acid, 95° C, 1 hr) has given one and under more severe conditions (10% sulfuric acid, 95° C, 8 hr) two substances of a flavonoid nature. With magnesium and hydrochloric acid, both substances form an orange pigment soluble in octanol. Consequently, they are aglycones.

Aglycone (I) is a bright yellow crystalline substance with mp 310–313° C (ethanol—water) and R_f 0.72 [butanol—acetic acid—water (4 : 1 : 2)], 0.32 (40% acetic acid) and 0.60 [benzene—ethyl acetate—acetic acid—formamide (24.5 : : 73.5 : 2 : 1)]. According to its IR spectrum, this flavonoid has a free hydroxy group (3400 cm^{-1}), methoxy groups (2850 and 2980 cm^{-1}), the carbonyl group of a γ-pyrone participating in the formation of a hydrogen bond with neighboring hydroxy groups (1665 cm^{-1}), and also substitution of the hydrogen atoms of benzene rings in positions 1, 2, 3, 4, and 5 (880 cm^{-1}) and 1 and 4 (845 cm^{-1}) [2, 3]. The UV spectrum exhibits maxima at 335, 282, and 255 and a shoulder at 300 mμ. The distance between the main maxima (335 and 282 mμ) is 53 mμ, which is characteristic for flavones [4]. However, the low intensity of the long-wave maximum (about 10%) gives grounds for assuming that the aglycone (I) is a flavone in which hydroxy groups are either not present in the B ring or are substituted. Spectroscopic investigations in the UV region with diagnostic reagents showed the presence of only one free hydroxy group at C_5 in the aglycone (I) from the bathochromic shift of the maximum of the long-wave band (20 mμ) of the complex of the flavonoid with zirconyl nitrate [5]. The low value of this shift may be due to the steric influence of substituents present in position 6.

Aglycone (II) is a yellow crystalline substance with mp 190–192° C, R_f in the systems given above 0.60, 0.20, and 0.50, respectively and λ_{max} 342 and 285 mμ. The maximum of the long-wave band has a considerably greater intensity than that of the short-wave band, which is generally observed for flavone compounds with a hydroxy group in position 4'. By means of a spectroscopic study with diagnostic reagents, the aglycone (II) was found from the bathochromic shift of 30 mμ with sodium ethoxide to contain a 4'-hydroxy group in addition to a 5-hydroxy group.

Both substances were rapidly decomposed on being heated with sodium acetate in an aqueous medium. Such properties are probably explained by the presence in the molecules of 5,6-dihydroxy groupings, which are readily oxidized in a weakly alkaline medium.

The demethylation of the substances led to the formation of scutellarein (mp 345° C, decomp., λ_{max} 338 and 285 mμ, R_f in the above-mentioned systems 0.70, 0.30, and 0.60, respectively) with free hydroxy groups in positions 5, 6, 7, and 4'. Consequently in the aglycone (I) the 7- and 4'-hydroxy groups are methylated and in the aglycone (II) only the 7-hydroxy group.

Thus, on the basis of chemical and spectroscopic investigations substance (I) has been characterized as 5,6-dihydroxy-7,4'-dimethoxyflavone and substance (II) as 5,6,4'-trihydroxy-7-methoxyflavone. These substances proved to be new, and we have called them, respectively, ladanein and ladanetin.

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STIZOLIN—A NEW SESQUITERPENE LACTONE FROM STIZOLOPHUS BALSAMITA

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From the leaves of Stizolophus balsamita (Lam.) Cass. ex Takht. family Compositae, collected on June 28, 1967, in the region of the Kurdai Mountains (Kazakhstan), we have isolated a new sesquiterpene lactone—stizolin $C_{15}H_{20}O_4$ with mp 184.5–186.5° C (decomp.; from benzene) $[\alpha]_D^{20}$ −30.46° (c 2.68; chloroform). Its IR spectrum has absorption bands at 3560 cm^{-1} (OH group) and 1757 and 1650 cm^{-1} (carbonyl of an α-methylene-γ-lactone ring). Stizolin contains one OH group (determined by the Chugaev-Tserevitinov [Zeriwitinoff] method); on oxidation with chromic anhydride in pyridine, dehydrostizolin $C_{15}H_{18}O_4$ was obtained with mp 219–221° C (decomp.; from ethanol); ν_{max} 1775 cm^{-1} (C=O of a γ-lactone), 1712 cm^{-1} (C=O) and 1665 cm^{-1} (C=C).

On hydrogenation of a Pt catalyst (according to Adams) in glacial acetic acid, 2 moles of hydrogen were consumed and a tetrahydro derivative $C_{15}H_{24}O_4$ was formed with mp 180–182° C (from ethanol), ν_{max} 3542 cm^{-1} (OH), 1785 cm^{-1} (γ-lactone); acetyltetrahydrostizolin $C_{17}H_{26}O_5$ with mp 169–170.5° C (from ethanol), ν_{max} 1780 cm^{-1} (γ-lactone), and 1725 and 1255 cm^{-1} ($OCOCH_3$). The oxidation of tetrahydrostizolin with chromic anhydride in 90% acetic acid led to the formation of dehydrotetrahydrostizolin $C_{15}H_{22}O_4$ with mp 199–201.5° C (from ethanol), ν_{max} 1785 cm^{-1} (γ-lactone), 1707 cm^{-1} (C=O). These results show that the OH group in stizolin is secondary.

Stizolin does not form derivatives for a keto group and therefore the fourth carbon atom is present either in the form of an epoxide or as part of a furan ring.

When stizolin was hydrogenated over a Pt catalyst (according to Adams) in ethanol, one mole of hydrogen was absorbed and dihydrostizolin $C_{15}H_{22}O_4$ was formed with mp 198–200° C (from ethanol), ν_{max} 3550 cm^{-1} (OH) and 1757 cm^{-1} (γ-lactone); acetyldihydrostizolin $C_{17}H_{24}O_5$ with mp 180–183° C (from ethanol), ν_{max} 1770 cm^{-1} (γ-lactone), 1735 and 1250 cm^{-1} ($OCOCH_3$). Dihydrostizolin was reduced with lithium aluminum hydride, giving a liquid glycol $C_{15}H_{28}O_4$; ν_{max} 3360–3440 cm^{-1} (OH) and 1655 cm^{-1} (C=C) which was dehydrogenated in the presence of selenium at 290–310° C for 30 min. From the reaction products were isolated chamazulene (identified by thin-layer chromatography) and linderazulene (identified through the trinitrobenzoate $C_{15}H_{14}O \cdot C_6H_3N_3O_6$) with mp 154–156.5° C (from ethanol).

It is known that azulenes are formed not only by the dehydrogenation of sesquiterpenoids of the azulene series but also by the dehydrogenation of sesquiterpenoids of the germacrane type. With the composition $C_{15}H_{20}O_4$ and two double bonds, a bicyclic structure for stizolin is excluded. Consequently, it is a monocyclic compound, and the formation of linderazulene shows that it belongs to the sesquiterpene lactones of the germacrane type with the lactone ring at C_7—C_8 and the double bond at C_1—C_{10} or at C_4—C_5.

The NMR spectrum of stizolin has two singlets: one at 1.20 ppm (CH_3 attached to an epoxide) and the other at 1.65 ppm (CH_3 on a double bond); there are also signals of an epoxide proton (doublet at 2.86 ppm), a lactone proton (triplet at 4.10 ppm), and a proton present in the geminal position with respect to a hydroxyl at 4.05 ppm; in the 5.1–5.5 ppm region are signals of vinyl and hydroxyl protons, and in the 6.4 and 6.6 ppm regions signals of an exocyclic methylene group.

The NMR spectrum of tetrahydrostizolin shows two CH_3 groups attached to CH (doublet at 1.06 ppm and 1.50 ppm) and a CH_3 group attached to an epoxide (singlet at 1.43 ppm). The signal of the epoxide proton is found in the 3.01 ppm region (doublet), the lactone proton has remained in the form of a proton at 3.89 ppm, and the proton in the geminal position to the hydroxyl is expressed in the form of a multiplet at 4.09 ppm and the hydroxyl proton in the form of a signal at 4.98 ppm.