STRUCTURE OF LIGNAN GLYCOSIDES FROM THE ROOTS OF ACANTHOPANAX

CHEMISTRY

1965

SovietRxiv

Abstract

Full Text

UDC 547.918

CHEMISTRY

L. A. ELYAKOVA, A. K. DZIZENKO, G. B. ELYAKOV

STRUCTURE OF LIGNAN GLYCOSIDES FROM THE ROOTS OF ACANTHOPANAX

(Presented by Academician M. M. Shemyakin, 26 IV 1965)

Chemical investigation of various plants of the family Araliaceae, many of which are used as valuable medicinal agents, has shown that the substances responsible for the physiological activity of the plants studied to date are glycosides of pentacyclic and tetracyclic triterpenoids ([1-3]). Acanthopanax (*Acanthopanax sessiliflorum*) is a plant also belonging to the family Araliaceae; the extract of its roots possesses physiological activity ([4]), but chemically this plant had not previously been investigated.

In a communication ([5]) the isolation from a methanolic extract of the roots of acanthopanax of four individual glycosides, named acanthosides A, B, C, and D, was described. On the basis of analytical and spectroscopic data it was shown that these substances cannot be assigned to the triterpene glycosides and have genins of aromatic nature. From the same data it followed that acanthosides A and C, and acanthosides B and D, in pairs have closely related or even identical genins in structure. The present work gives data on the structure of acanthosides B and D.

Table 1

Substance	M.p., °C	$[\alpha]_D^{20}$	Found, % C	Found, % H	Found, % OCH_3	Found, % $COOCH_3$	Empirical formula	Mol. wt. found	Mol. wt. calculated	Calculated, % C	Calculated, % H	Calculated, % OCH_3	Calculated, % $COOCH_3$
Acanthoside D	245–247	−33.0	54.52	6.06	16.21	5.89	$C_{34}H_{46}O_{18}$	767	742	54.98	5.79	16.71	—
Acetate of acanthoside D	110–112	−27.0	55.95	5.72	15.80	45.6	$C_{50}H_{62}O_{26}$	1001	1079	55.65	5.79	11.50	43.9

Substance	M.p., °C	$[\alpha]_D^{20}$	Found, % C	Found, % H	Found, % OCH_3	Found, % $COOCH_3$	Empirical formula	Mol. wt. found	Mol. wt. calculated	Calculated, % C	Calculated, % H	Calculated, % OCH_3	Calculated, % $COOCH_3$
Acanthoside B	150	−36.0	57.53	6.51	16.8	20.6	–	$C_{28}H_{36}O_{13}$	580	57.93	6.2	21.4	–
Acetate of acanthoside B	105		57.77	5.96	6.00	36.1		$C_{38}H_{46}O_{18}$	790	57.72	5.83	15.7	37.8
Progenin of acanthoside D	150	−35.5	57.48	6.28	6.71	19.5	—	$C_{28}H_{36}O_{13}$	580	57.93	6.2	21.4	–
Genin of acanthosides B and D	170–172	−21.5	63.89	6.52				$C_{22}H_{26}O_8$	418	63.15	6.26	29.67	–

Acanthosides B and D have the empirical formulas $C_{28}H_{36}O_{13}$ and $C_{34}H_{46}O_{18}$, respectively. On acetylation under ordinary conditions, acanthoside B forms a crystalline pentaacetate, and acanthoside D a crystalline octaacetate; their melting points and analytical data are given in Table 1. Both glycosides are cleaved both by acid and by alkaline hydrolysis, and in the hydrolysates only glucose is detected chromatographically. Cleavage can also be carried out in the presence of emulsin. This indicates that both substances are β-*d*-glucosides. Methanolysis of completely methylated acanthosides B and D according to Kuhn led to tetramethylglucose, identified chromatographically in the reaction mixture.

After preparative hydrolysis of acanthoside D in the presence of 0.5% oxalic acid, from the reaction mixture, by adsorption chromatography on SiO_2, a genin with the empirical formula $C_{22}H_{26}O_8$ and a progenin were isolated.

$C_{28}H_{36}O_{13}$. The latter, in terms of the value of R_f on chromatograms in a thin fixed layer of SiO_2, melting point, specific rotation, and analytical data (Table 1), proved to be completely identical with acanthoside B. Consequently,

structural formula of syringaresinol with methoxy and hydroxy substituents and numbered bicyclic ring

Figure 1: structural formula of syringaresinol with methoxy and hydroxy substituents and numbered bicyclic ring

three stereochemical formulas labeled I, II, and III

Figure 2: three stereochemical formulas labeled I, II, and III

acanthosides B and D are, respectively, mono- and diglucosides of the same genin, $C_{22}H_{26}O_8$.

The genin of acanthosides B and D is a crystalline substance with mp 170-172°, giving a positive Moile reaction ([6]) (pyrogallol grouping) and, according to analysis of the initial glycosides, containing 4 methoxyl groups (Table 1). Its UV spectrum has two maxima: $\lambda_{\max}^{\mathrm{EtOH}}$ 234, 271 mμ ($\lg \varepsilon$ 4.2; 3.6); the general appearance of the spectrum indicates the presence of two isolated benzene nuclei. Similar spectra are possessed by lignans of the 2,6-diphenyl-3,7-dioxabicyclo-[3,3,0]-octane series, in particular syringaresinol, the optically inactive form of which was synthesized by Freudenberg. (±)-Syringaresinol $C_{22}H_{26}O_8$. Mp 170-172° ([7]).

Diglucoside of the dextrorotatory form of syringaresinol—liriodendrin $C_{34}H_{46}O_{18}$, mp 270°—was isolated by E. Dickey ([8]) from *Liriodendron tulipifera*. By enzymatic hydrolysis of liriodendrin in the presence of emulsin, E. Dickey succeeded in obtaining (+)-syringaresinol, named lirioresinol C, $[\alpha]_D^{20} + 48.9$.

Comparison of the IR spectra of synthetic (±)-syringaresinol, lirioresinol C ([8]), and the genin of acanthosides B and D showed their complete identity. A mixed sample with lirioresinol C showed no depression of the melting point, and the R_f values on thin-layer chromatograms were identical.* Taking into account the levorotation of the genin of acanthosides B and D, it can thus be asserted that they are mono- and di-β-*d*-glucopyranosides of (−)-syringaresinol. It should be noted that neither (−)-syringaresinol itself nor its glycosides had, prior to the present work, been isolated from natural material. The reduced value of the specific rotation of the genin of acanthosides B and D in comparison with lirioresinol C is apparently explained by an admixture of the dextrorotatory form.

The stereochemistry of lignans of the 2,6-diphenyl-3,7-dioxabicyclo-[3,3,0]-octane series has been studied by a number of authors ([9],[10]). It was shown that the hydrogens at carbon atoms 1 and 5 are always in the cis position; therefore only three racemates are possible, corresponding to formulas I, II, and III.

Freudenberg and Sitku established the absolute configuration of certain lignans

Fig. 1. NMR spectra: (+)-syringaresinol (lirioresinol C) (1), (−)-syringaresinol (genin of acanthosides B and D) (2)

Figure 3: Fig. 1. NMR spectra: (+)-syringaresinol (lirioresinol C) (1), (−)-syringaresinol (genin of acanthosides B and D) (2)

Fig. 2. NMR spectra: (+)-episyringaresinol (lirioresinol A) (1), (−)-episyringaresinol, obtained on hydrolysis of acanthoside D under the conditions of experiment 3 (2)

Figure 4: Fig. 2. NMR spectra: (+)-episyringaresinol (lirioresinol A) (1), (−)-episyringaresinol, obtained on hydrolysis of acanthoside D under the conditions of experiment 3 (2)

of the pinoresinol series ([10]). In accordance with the nomenclature of these authors, when R = syringyl, formula I belongs to (±)-syringaresinol, II to (±)-episyringaresinol, and III to (±)-diasyringaresinol. Investigation of synthetic (±)-syringaresinol by NMR spectroscopy confirmed that it indeed has structure I ([11]).

The dextrorotatory form of episyringaresinol—lirioresinol A—was isolated by Dickey during acid hydrolysis of liriodendrin ([8]). Carrying out the hydrolysis of acanthoside D under more severe conditions (1% HCl), we obtained a substance with mp 177°, $[\alpha]_D^{20} - 90^\circ$, differing in R_f on thin-layer chromatograms from (−)-syringaresinol. For a definitive solution of the question of the configuration of both substances, their NMR spectra were taken, as well as the spectra of lirioresinols A and C. It then turned out (Fig. 1) that

* Samples of liriodendrin and lirioresinols A, B, and C were kindly provided by E. Dickey at our request.

the NMR spectra of our (−)-syringaresinol and lirioresinol C are identical. The narrow unsplit line at 3.8 ppm indicates a symmetrical arrangement of the 4 methoxyl groups in the benzene rings. Both benzene rings are in the equatorial position, as indicated by

Fig. 1. NMR spectra: (+)-syringaresinol (lirioresinol C) (1), (−)-syringaresinol (genin of acanthosides B and D) (2)

a constant spin-spin coupling (I_{12} and I_{56} = 5 Hz) at 4.7 ppm, indicating the trans arrangement of the protons at C_1, C_2, and C_5, C_6, respectively. The same follows from comparison with the spectrum presented

Fig. 2. NMR spectra: (+)-episyringaresinol (lirioresinol A) (1), (−)-episyringaresinol, obtained on hydrolysis of acanthoside D under the conditions of experiment 3 (2)

of ([11]) (+)-pinoresinol, the absolute configuration of which (cis-equatorial arrangement of the benzene rings) has been strictly proved ([10]).

The NMR spectra of the substance obtained on hydrolysis of acanthoside with 1% HCl and of lirioresinol A are also identical (Fig. 2). The doublet at 4.86 ppm corresponds to the axial proton at C_2. This is indicated by the constant spin-spin coupling (I_{12} = 5 Hz), corresponding to the trans arrangement of the protons at C_1 and C_2. Consequently, the benzene ring at C_2 is located equatorially. The proton signal at C_6 is shifted into the strong-field region (4.44 ppm), and the spin-spin coupling constant (I_{56} = 7 Hz) indicates an equatorial arrangement of the proton at C_6.

Thus, the second benzene ring at C_6 is in the axial position and, as a whole, both substances have the trans configuration of the benzene rings relative to the dioxabicyclooctane ring, i.e., they are, respectively, the (−)- and (+)-forms of episyringaresinol.

Since enzymatic hydrolysis of acanthosides B and D leads

to (−)-syringaresinol, while the epi form is obtained under more severe hydrolysis conditions; evidently, the native genin of acantosides B and D is (−)-syringaresinol. On the basis of the data presented, the complete structure of acantosides B and D may be represented by formulas IV and V,

IV: $R_1 = H$; $R_2 = \beta$-*d*-glucopyranose —acantoside B;
V: $R_1 = R_2 = \beta$-*d*-glucopyranose —acantoside D.

Experimental Part

All melting points were determined on a heating stage (Boetius) and are uncorrected. Specific rotation was determined on a Hilger M-412 polarimeter. Preparative chromatography was carried out on KSK silica gel, 100–200 mesh. UV spectra were recorded on an SF-4m spectrophotometer. NMR spectra were recorded on an INM-C-60 spectrometer in $CDCl_3$. IR spectra were recorded in KBr on a UR-10 spectrophotometer by M. Yu. Nefedova. Analyses were performed in the microanalysis laboratory of our institute by L. I. Glebko and Zh. I. Ul' kina.

1. **Methylation and hydrolysis of methylated acantosides.** A solution of 50 mg of acantoside, 500 mg of BaO, and catalytic amounts of $Ba(OH)_2$ in 2 ml of dimethylformamide and 3–4 ml of methyl iodide is heated in a sealed ampoule for 9 h at 80–90°. Completeness of methylation is monitored by chromatography in a thin, unfixed layer of Al_2O_3 in the toluene–ethanol (9:1) system. The contents of the ampoule are poured into saturated $Na_2S_2O_3$ solution, filtered, and the filtrate is extracted with chloroform. The chloroform extracts are combined, washed with water, and evaporated. The methylated acantosides (60 mg) are hydrolyzed with a mixture of $HClO_4$–methanol (1:10) in a sealed ampoule for 5 h at 80–90°. The reaction mixture is poured into an equal volume of water, boiled for 2 h with a reflux condenser, and neutralized with Dowex 1 × 4

anion exchanger (HCO_3^-). The anion exchanger is filtered off, the filtrate is evaporated and analyzed chromatographically on Goznak factory paper, grade "M," in the methyl ethyl ketone–25% ammonia (to saturation) system. As a result, by comparison with authentic samples of methylated monosaccharides, only 2,3,4,6-tetramethylglucose is identified.

2. **Hydrolysis of acantoside D in the presence of oxalic acid. (−)-Syringaresinol.** 250 mg of acantoside D in 5 ml of 0.5% oxalic acid is heated for 2 h in a sealed ampoule at 70°. The contents of the ampoule are extracted with chloroform; the chloroform extract is washed with water and evaporated. The residue is chromatographed on a column of SiO_2, eluting with the chloroform–ethyl acetate (1:1) system. (−)-Syringaresinol (30 mg) and the genin of acantoside D (50 mg) are isolated. They are recrystallized from acetone and methanol, respectively.

3. **Hydrolysis of acantoside D in the presence of HCl. (−)-Episyringaresinol.** 100 mg of acantoside D in 3 ml of 1% HCl solution is boiled with a reflux condenser for 15 min. The reaction mixture is extracted with sulfuric ether; the extracts are combined, washed with water, and evaporated. The crystals that precipitate are recrystallized from sulfuric ether.

Far Eastern Institute of Biologically Active Substances
Siberian Branch of the Academy of Sciences of the USSR

Received
10 IV 1965

Cited Literature

1. G. B. Elyakov, L. I. Strigina et al., *Tetrahedron Letters*, **48**, 3591 (1964).

2. N. K. Kochetkov, A. Ya. Khorlin et al., *ZhOKh*, **31**, 658 (1961).

3. G. B. Elyakov, A. Ya. Khorlin et al., *Izv. AN SSSR, OKhN*, 1962, No. 9, 1605.

4. A. V. Zvereva, Khabarovsk Medical Institute, Materials of the XXI Scientific Session, Khabarovsk, 1964, p. 122.

5. L. A. Elyakova, G. B. Elyakov, *Izv. AN SSSR, Ser. Khim.*, 1965, No. 3, 555.

6. C. Mäule, *Beitr. wiss. Bot.*, **4**, 166 (1900).

7. K. Freudenberg, H. Dietrich, *Chem. Ber.*, **86**, 4 (1953).

8. E. E. Dickey, *J. Org. Chem.*, **23**, 179 (1958).

9. H. Erdtman, J. Gripenberg, *Acta chem. scand.*, **1**, 71 (1947).

10. K. Freudenberg, G. S. Sidhu, *Chem. Ber.*, **94**, 851 (1961).

11. C. H. Ludwig, B. Nist, J. McCarthy, *J. Am. Chem. Soc.*, **86**, 1193 (1964).

12. W. A. Jones, M. Beroza, E. D. Becker, *J. Org. Chem.*, **27**, 3232 (1962).

Note: Figure translations are in progress. See original paper for figures.