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Review Article

ELUCIDATION OF STRUCTURES OF NEW ELLAGITANNINS FROM PLANTS OF EUPHORBIACEOUS

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Abstract
A chemical investigation of tannins in three Euphorbia species (*E. himufusa., E. franchetii B. Fedtsch., E.canescens L.*) has led to the isolation and characterization of five new hydrolyzable tannins thogather with thirty known compounds. The structures of these tannins were established on the basis of spectroscopic and chemical evidence.

Keywords: ellagitannins, galloyl group, hexahydroxydiphenoyl group, valoneoyl group; ^{13}C NMR spectroscopy; Q-TOF LC-MS.

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INTRODUCTION

The natural compounds are widely distributed in the plant kingdom. Among of plant origin compounds polyphenols are attracted much attention because their therapeutic effects and lower toxicity, different biologically effects.

Therefore, the plant search containing polyphenols, development of methods for their isolation, to establish their chemical structure and biological activity of study depending on the chemical structure in order to create new and effective drugs is an important and urgent problem of modern bioorganic chemistry.

Ellagitannins – are the most abundant plant polyphenols among hydrolysable tannins. They are ellagic acid esters with sugars. To date, isolated and established the structure of more than 700 individual compounds. Ellagitannins possess a wide spectrum of biological activity, the most important of which are antiviral, antitumor and immunomodulatory activity.

Currently, carryinf out researches out on the isolation of plant tannins, obtaining their derivatives, revealing structure activity relationship (SAR), the investigation of the mechanism of antiviral activity, synthesizing gallo- and ellagotannins, which are a priority for research.

Recent advances in the field of NMR spectroscopy and mass spectrometry allowed to identify tannins with different degree of galloyl and their molecular weight in complex mixture [1-4]. In addition, these methods are ideally match for the characterization of oligomers and considered the best methods for the analysis of heterogeneity structural tannins [5-13].

MATERIALS AND METHODS

General

Ellagitannins separated by column chromatography on silica gel (LS 100/40, Czechoslovakia). TLC was performed on precoated on Silufol UV-254 plated, with benzene–acetone (9:4, v/v). The up-ground parts of plant material Euphorbiaceous (Spurge) collected at the end of vegetative period were air-dried and blended. For the extraction of plant materials used solvents produced by «Himreaktivkomplekt» (Uzbekistan) and «Реахим» (Russia). Optical activity was measured on Photoelectrocolorimeter FEC-56m. UV spectra of ellagitannins were recorded in ethanol on EPS-3T (Hitachi, Japan). 13C NMR spectra was recorded obtained on a Bruker 400 (Germany) spectrometer (400 MHz), using acetone-d_6 as solvent and tetramethylsilane (TMS) as internal standard, and the chemical shifts reported in δ (ppm) units relative to 0. LC-MS was performed on a Q-TOF Agilent Technologies mass spectrometer (USA) 6520B series, in the negative ion mode.condition: electrospray ionization source (ESI-), gas spray: 5 l/min, temperature of gas 300^{0}C, the capillary voltage was 20 V, the 125V, mass: MS 100–2000 m/z, Targeted MS/MS 25–2000 m/z, collision energy – 65. Ionization method: negative. Samples fractionated on Agilent Technologies 1200 series, on column Zorbax SB C18, 3µm, 0.5x150 mm. Mobile phase: A - 0.1% solution of formic acid, B - acetonitrile + 0.1% formic acid. A - the negative full or selected ion monitoring (SIM) scan type. Compounds were also monitored simultaneously using the dual-wavelength absorbance detector at 280 nm. Compounds were separated using the Aqua C18 column as for HPLC. Elution was performed on the instrument Agilent Technologies 1260 series Cap Pump at a flow rate of 15 µl/min. The gradient concentration of solution B - in minutes: 0% - 5 min, 25% - 20 min, 50% - 35-40 min, 0% - 43 min. The solutions were degassed on the Agilent Technologies 1260 µ-degasser instrument. Samples were applied on column (1 µl) by Agilent Technologies WPS.

Isolation of tannins

Air-dried aerial parts of plants of *E. himufusa, E. franchetii B. Fedtsch., E.canescens L.,* collected different region Republic of Uzbekistan, were cut into small pieces and extracted with chloroform to remove lipophilic substances. Subsequently, plant materials were extracted with 70% aqueous acetone. Then, aqueous acetone extract was evaporated under vacuum; the aqueous layer was successively partitioned with ethyl acetate. By adding hexane to concentrated ethyl acetate portion (4x1, v/v), obtained sum of polyphenols with yield 2.1–6.2%.

Polyphenols were subjected to column chromatography on silica gel, eluted with chloroform-methanol solution (17:3;

17:4; 17:5) and obtained three fractions. From fraction 1 were isolated known phenolic acids.

The fraction 2 and 3 were shown to contain flavonols and tannins by paper chromatography (PC) (n-buthanol-acetic acid-water, 4:1:5; n-buthanol-acetic acid-water, 40:12:28, system -1).

After rechromatography of fraction 3 on silica gel with different solutions were isolated tannins. The structures of tannins were determined by physical-chemical methods. From all studied plants were more than 30 phenolic compounds, 5 of them were fond as new compounds.

1-O-galloyl-6-O-bis-galloyl-2,4-valoneoyl-β-D-glucose – isolated from *Euphorbia himufusa*, 0.45 g of white amorphous powder. $C_{48}O_{31}H_{34}$, $[\alpha]_D$ $+70^0$ (c = 0,5 MeOH), R_f 0.48 (system 1). UV spectrum λ_{max} (EtOH, nm) nm (lgε): 216 (5.22), 270 (4.86) MS *m/z*: 1106 $[M-H]^-$; ^{13}C-NMR (100 MHz, acetone-d_6 + D_2O, ppm): galloyl group: 119.88 (C-1), 110.20 (C-2), 145.82 (C-3), 139.61 (C-4), 145.8 (C-5), 110.20 (C-6), 167.23 (C-7); bisgalloyl group: 120.44 (C-1, C-1 '), 110.15 (C-2, C-2'), 145.54 (C-3, C-3 '), 139.22 (C-4, C-4'), 145.51 (C-5, C-5'), 110.10 (C-6, C-6'), 168.70, 166.40 (C-7, C-7''); valoneoyl group: 114.30 (C-1), 126.44 (C-2), 106.80 (C-3), 145.14 (C-4), 136.10 (C-5), 144.44 (C-6), 169.10 (C- 7), 118.85 (C-1 '), 128.09 (C-2'), 110.58 (C-3 '), 148.84 (C-4'), 135.64 (C-5 '), 147.03 (C-6') , 168.32 (C-7''), 112.22 (C-1''), 138.65 (C-2''), 130.44 (C-3''), 141.17 (C-4''), 143.55 (C-5''), 110.15 (C-6''), 163.36 (C-7''); glucose: 92.37 (C-1), 76.78 (C-2), 76.99 (C-3), 76.99 (C-4), 73.49 (C-5), 63.34 (C-6).

1-O-galloyl-4,6-hexahydroxydiphenoyl-2,3-valoneoyl-β-D-glucose – brown amorphous powder, isolated from *Euphorbia canescens* L, 0.38 g, $C_{48}O_{31}H_{32}$, $[\alpha]_D$ $+68^0$ (c = 0.5, MeOH), R_f 0.60 (system 1). UV spectrum (λ_{max}, EtOH, nm, lgε): 214 (5.60) 240 (5.26). MS *m/z*: 1104 $[M-H]^-$; ^{13}C-NMR (100 MHz, acetone-d_6, ppm): galloyl group: 121.30 (C-1), 110.34 (C-2), 144.45 (C-3), 139.87 (C-4), 144.75 (C-5), 110.44 (C-6), 169.10 (C-7); hexahydroxydiphenoyl group: 114.57, 114.92 (C-1, C-1`), 125.87, 126.00 (C-2, C-2`), 107.69 (C-3, C-3`), 145.17 (C-4, C-4`), 136.43 (C-5, C-5`), 144.20, 144.30 (C-6, C-6`), 169.29, 169.56 (C-7, C-7`); valoneoyl group: 115.98, 116.05, 116.68 (C-1, C-1`, C-1``), 126.53, 126.72, 137.41 (C-2, C-2`, C-2``), 108.11, 108.42 , 140,49 (C-3, C-3`, C-3``), 144.25, 146.66, 141.47 (C-4, C-4`, C-4``), 136.57, 136.66, 143.12 (C -5, C-5`, C-5``), 149.60, 145.70, 111.41 (C-6, C-6`, C-6``), 168.56, 169.10, 167.87 (C-7, C-7 `, C-7``); glucose: 92.3 (C-1), 76.7 (C-2), 76.9 (C-3), 69.6 (C-4), 73.3 (C-5), 63.3 (C-6).

1-O-galloyl-2,3-hexahydroxydiphenoyl-4,6-valoneoyl-β-D-glucose, isolated from *Euphorbia Franchetii B.Fedtsch*, 0.35 g of yellow amorphous powder, $C_{48}O_{31}H_{32}$, $[\alpha]_D$ + 66.2^0 (c 0.5, MeOH); UV spectrum (λ_{max}, EtOH, nm): 220, 280; MS *m/z*: 1104 $[M-H]^-$; ^{13}C-NMR (100 MHz, acetone-d_6, ppm): galloyl group: 125.9 (C-1), 110.9 (C-2), 145.8 (C-3), 136.0 (C-4), 145.8 (C-5), 110.9 (C-6), 167.0 (C-7); hexahydroxydiphenoyl group: 119.0 (C-1), 124.8 (C-2), 111.4 (C-3), 144.7 (C-4), 136.65 (C-5), 144.7 (C -6), 167.0 (C- 7), 119.0 (C-1`), 144.7 (C-2 '), 136.5 (C-3'), 144.7 (C-4 '), 111.4 (C-5'), 124.8 (C-6 ') , 167.0 (C-7 '); valoneoyl group: 119.0 (C-1), 124.8 (C-2), 111.4 (C-3), 144.7 (C-4), 136.5 (C-5), 114.7 (C-6), 167.0 (C-7), 119.5 (C-1 '), 123.1 (C-2'), 113.0 (C-3'), 143.5 (C-4'), 138.1 (C-5'), 143.0 (C-6'), 167.0 (C-7 '), 114.8 (C-1"), 138.9 (C-2"), 134.6 (C-3"), 136.6 (C-4"), 138.9 (C-5"), 111.0 (C-6"), 172.0 (C-7'); glucose: 94.2 (C-1), 70.9 (C-2), 65.3 (C-3), 67.2 (C-4), 64.3 (C -5), 65.4 (C-6).

1,4-di-O-galloyl-β-D-xylose – isolated from *Euphorbia franchetii B.Fedtsch*, 0.23 g of white amorphous powder, $C_{19}O_{13}H_{18}$, $[\alpha]_D$ - 40^0 (c 1.0, MeOH); UV spectrum (MeOH, λ_{max}, nm): 214, 286; MS *m/z*: 454 $[M-H]^-$; ^{13}C-NMR (100 MHz, acetone-d_6, ppm): galloyl group: 125.9 (C-1), 110.9 (C-2), 145.8 (C-3), 136.0 (C-4), 145.8 (C-5), 110.9 (C-6), 167.0 (C-7), xylose: 93.6 (C-1), 70.9 (C-2), 61.6 (C-3), 77.0 (C-4), 87.5 (C-5).

1,4,6-tri-O-galloyl-2,3-valoneoyl-β-D-glucose – isolated from *Euphorbia canescens* L., 0.40 g of brown amorphous powder, $C_{48}O_{31}H_{34}$, $[\alpha]_D$ - 26^0 (c 0.5, MeOH); UV spectrum (MeOH, λ_{max}, nm): 225, 290; MS *m/z*: 1106 $[M-H]^-$, ^{13}C-NMR (100 MHz, acetone-d_6+D_2O, ppm): galloyl group: 125.9 (C-1), 110.9 (C-2), 145.8 (C-3), 136.0 (C-4), 145.8 (C-5), 110.9 (C-6), 167.0 (C-7); valoneoyl group: 119.0 (C-1), 124.8 (C-2), 111.4 (C-3), 144.7 (C-4), 136.5 (C-5), 144.7 (C-6), 167.0 (C- 7), 119.5 (C-1`), 123.1 (C-2 '), 113.0 (C-3`), 146.5 (C-4`), 138.1 (C-5`), 143.0 (C-6`) , 167.0 (C-7`), 114.8 (C-1``), 138.9 (C-2``), 134.6 (C-3``), 136.6 (C-4``), 138.9 (C-5``), 111.0 (C-6``), 172.0 (C-7``); glucose: 94.2 (C-1), 70.9 (C-2), 65.3 (C-3), 67.2 (C-4), 64.3 (C-5), 65.4 (C-6).

Acid hydrolysis

A solution of compounds (5 mg) in 5% H_2SO_4 (2 ml) was heated in boiling water bath for 9 hours. After cooling, the reaction mixture was extracted with EtOAc. The hydrolysis products were identified by preparative PC and TLC.

Partial hydrolysis of tannins

A solution of compounds (70 mg) in acetone (10 ml) and H_2O (50 ml) was heated at 90 ^{0}C for 24 h. The resulting hydrolysis products were controlled by TLC each hour.

Methylation of tannins, followed by alkaline methanolysis

A mixture of compounds (5 mg), K_2CO_3 (100 mg), $(CH_3)_2SO_4$ (0,1 ml), in acetone (2 ml) was stirred overnight at room temperature and then heated at reflux for 3 h. After removal of K_2CO_3 by centrifugation followed evaporation of the solvent, the residue was directly subjected to methanolysis with 1% NaOMe in MeOH (1ml) at room temperature overnight. After acidification with AcOH and evaporation of the solvent, the residue was submitted to preparative TLC.

RESULTS AND DISCUSSION

Recently, researches carried out by scientists of Bioorganic Chemistry of the Academy of Sciences of Uzbekistan, have shown prosperity of use of natural phenolic compounds as an antiviral, antioxidant, anti-tumor agents [14-20]. It was found that these compounds have high biological activity, which manifests itself in suppressing the activity of various viral infections, redox enzymes and etc. Also, it was shown that natural polyphenols have anti-HIV activity [21].

Based on these research results, we studied polyphenols of three plants belonging to Euphorbia family [22-24]. More than 30 individual compounds were isolated from these plants, determined their chemical structures and biological activities. It was revealed that some of isolated compounds found as a new, not previously noted compound in the literature. On the basis obtained physic-chemical and spectral date were characterized chemical structures of compounds.

By the known method [22], air-dried up-ground parts of plants extracted with chloroform, aqueous acetone, ether and ethyl acetate. By using column chromatography, from ethyl acetate extraction were isolated 5 new compounds.

To determine the monomer composition and chemical structure of compound-1 were carried out chemical transformations according to Scheme 1. In products of acid hydrolysis with 5% H2SO4 detected glucose (I), gallic (II) and valoneic acid (III). Methylation of compound with dimethyl sulfate and anhydrous K2CO3 resulted in the formation permethylate, upon methanolysis with sodium methoxide formed methyl tri-O-methylgallate (IV) (TLC, Rf 0.75, solvent system 1: benzene-acetone 4:1) and trimethyl-octa-O-methylvaloneate (V) (TLC, Rf 0.27, system 1). The partial hydrolysis of compond-1 (heating in water at 900C) resulted in formation 1-O-galloyl-β-D-glucose (VI), 6-O-bisgalloyl-β-D-glucose (VII) and 2,4-valoneoyl -β-D-glucose (VIII).

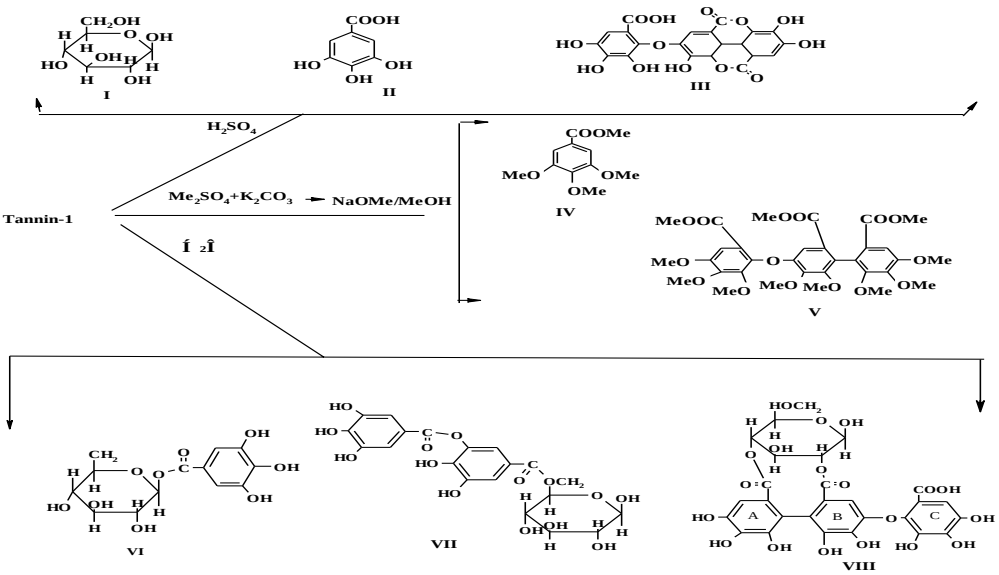
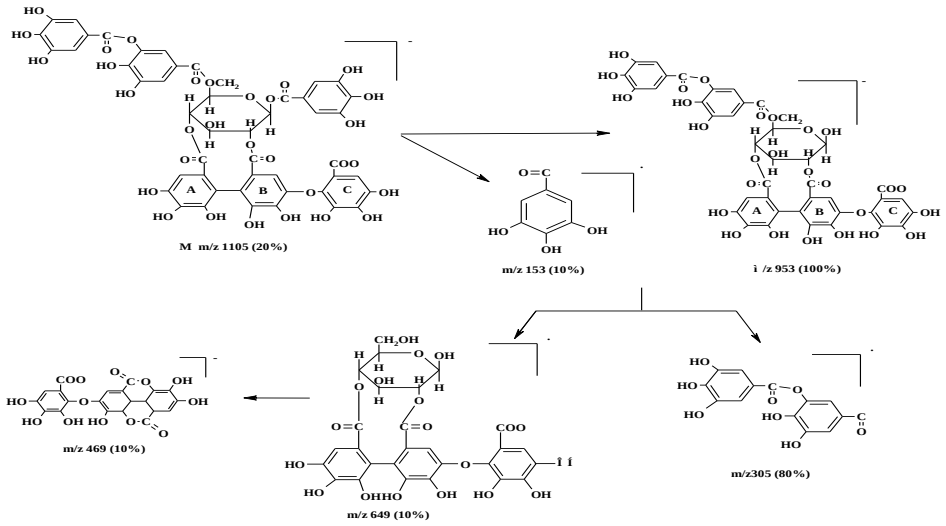


Figure 1. Chemical transformations of compound-1

In the ^{13}C NMR spectrum of the compound-1, in the complete suppression of spin-spin coupling with protons detected signals specific to glucose, gallic and valoneic acids [25-30]. Intensive signal at 92.37 ppm, corresponding to the anomeric center of glucose molecule has β-configuration [28-30]. Chemical shifting at 92.37, 76.78, 76.89, 63.34 ppm corresponding to the atoms C-1, C-2, C-4 and C-6 of sugar residue indicates the acylation of the carbohydrate residues at these positions. In the ^{13}C NMR spectrum present the signals of three residues of gallic acid: the signals of carbon atoms of carbonyl groups appear at 167.23, 168.70, 166.40 ppm and signals of carbon atoms of trigalloyl group observed at 119.88, 120.44, 120.44 ppm. Signals of C-2, C-6 and C-3, C-5 carbon atoms give relative signals and intensities at 110.20, 110.15 and 110.20, 110.10 ppm, also at 145.82, 145.54 and 145.80, 145.51 ppm, respectively. The carbon atom C-4 of this residue overlapped and as a result of the diamagnetic shift resonates at 139.61 and 139.22 ppm. In the spectrum also observed signals of 21 carbon atoms valoneoyl group. The resonance signals of C-1, C-1` and C-1`` carbon atoms of valoneoyl group observed at 114.30, 118.85 and 112.22 ppm, respectively. Intense signals at 144-145 ppm refer to the C-4 and C-6 carbon atoms of valoneoyl group. The chemical shifts of C-3, C-3`, and C-3`` carbons observed at 106.80, 110.58 and 130.44 ppm. Analysis of the ^{13}C-NMR spectra shows that the chemical shifts of valoneoyl group coincide with the literature data [26-30]. Signals of C-7, C-7`and C-7`` carbon atoms in carbonyl groups give intensive signals at 169.1, 168.32 and 163.36 ppm.

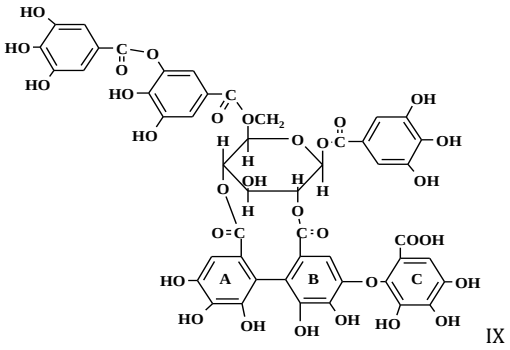
The UV spectrum of the compound-1 has the absorptions characteristic for phenolic compounds (λ_{max} 216, 270 nm).

These data are confirmed by the mass spectrometry defragmentation of compound-1, obtained on the instrument LC-MS Q-TOF in negative ionization mode. As can be seen from the scheme, the molecular ion compound-1 at *m/z* 1105 split into two fragments at *m/z* 953 and 153. This indicates that the breaking the ester bond between glucose and galloyl group, which is consistent with the literature data [35-36]. Secondary ion at *m/z* 953 further cleaved into fragments at *m/z* 649 and 305. The presence of intense ion signal at *m/z* 469 in the mass spectrum fragmentation, formed as a result of split of the ion at *m/z* 649 indicates containing valoneoyl group of compound-1.



Scheme 2. Possible ways of fragmentation compound-1

On the base of analyzing the chemicals products and spectral dates and their comparison with the literature data the structure of compond-1 established (IX) as 1-O-galloyl-6-O-bis-galloyl-2,4-valoneoyl-β-D-glucose.



IX

The structure of the compound-2 also determined on the base the analysis of chemical reactions and spectral data (^{13}C-NMR and mass spectra). The results of the study of chemical reaction products are shown in Scheme 3.

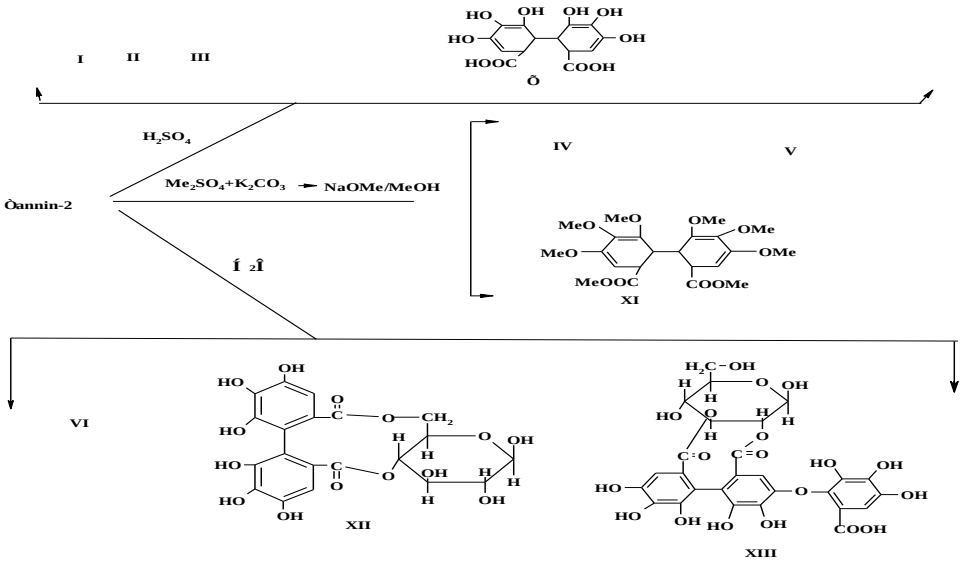


Figure 3. The chemical conversion of compound-2

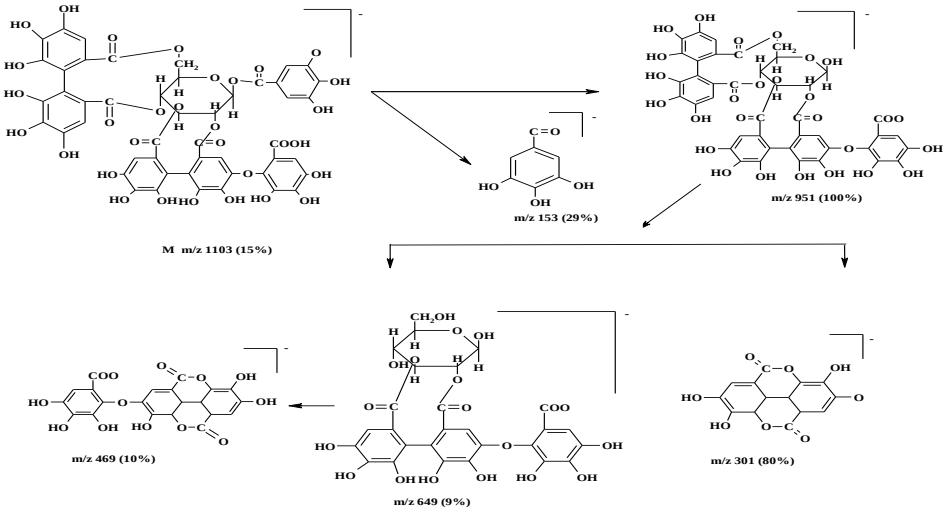
In the acid hydrolysis products of tannin-2 unlike compound-1 was found ellagic acid (X) except of glucose (I), gallic acid (II), dilaktone of valoneic acid (III). Methylation of compound with dimethyl sulfate and anhydrous K_2CO_3 resulted in the formation of permetilate, after alkaline hydrolysis with methanolic solution of sodium methoxide yielded methyl tri-O-methylgallate (IV) (TLC, R_f 0.75, solvent system 1), trimethyl octa-O-methylvaloneate (V) (TLC, R_f 0.27, system 1), di-methyl hexamethoxydiphenate (XI) (TLC, R_f 0.36, system 1). The partial hydrolysis of compound-2 lead to produce 1-O-galloyl-β-D-glucose (VI), 4,6-hexahydroxydiphenoyl-β-D-glucose (XII) and 2,3-O-valoneoyl-β-D- glucose (XIII).

In the UV spectrum of compound-2 observed absorption maxima at 218 and 275 nm, which is typical for ellagitannins.

In the ^{13}C-NMR spectrum of the compound-2 except compound-1 (IX), along with resonance signals of glucose, gallic and valoneic acids observed signals specific to residual hexahydroxydiphenoyl group. The chemical shifts of carbon atoms C-1, C-3, C-5 (92.3, 76.9, 73.3 ppm, respectively) glucose confirm that the anomeric center has β-configuration. The chemical shifts of the atoms C-1, C-2, C-3, C-4 and C-6 glucose at 92.3, 76.7, 76.9, 69.6, and 63.3 ppm respectively, confirm that their OH groups have galloyl groups. The similar chemical shifts of the signals of carbon atoms, gallic and valoneic acids were observed in the spectrum of compound-1. The spectrum also has the signals of 14 carbon atoms of hexahydroxydiphenoyl group. The substituted carbon atom C-4, C-4`, C-5, C-5`, and C-6, C-6`resonate at 145.17, 136.43 and 144.20-144.30 ppm, respectively. Unsubstituted carbon atoms C-3 and C-3` of hexahydroxydiphenoyl group observed at 107.69 ppm. Signals of carbon atoms C-7 and C-7`of carbonyl groups detected at 169.29 and 169.56 ppm.

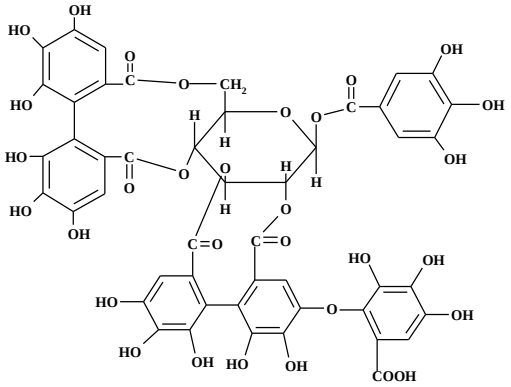
Analysis of the ^{13}C NMR spectra shows that chemical shifts valoneic acid coincide with literature data [26-30].

Mass spectrometric studies compound-2 was also carried out on a mass spectrometer Q-TOF LC-MS in negative ionization mode. The results are shown in Figure 4. As seen in scheme-4, molecular ion of tannin-2 at *m/z* 1103 splits into two fragments at *m/z* 951 and 153. This indicates breaking of the ester bond between glucose and galloyl group, which is consistent with published data [35-36]. Secondary ion at *m/z* 951 further cleaved into fragments at *m/z* 649 and 301. The presence in the mass spectrum a fragmentation with intense ion signal at *m/z* 469, formed by the fragmentation of the secondary ion at *m/z* 649 indicates that the compound-2 contains valoneoyl group, corresponding to the molecular formula $C_{21}O_{13}H_{10}$.

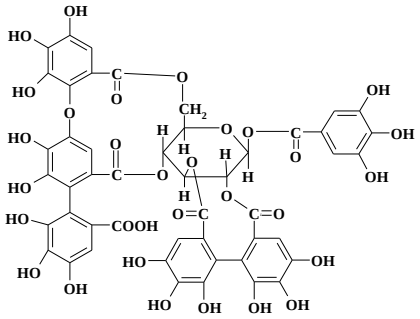


Scheme-4. Possible ways of fragmentation compound-2

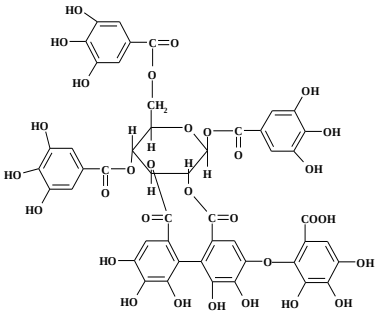
Summarizing spectrum data and chemical defragmentation, as well as determining the molecular weight and by comparing all obtained results with literature data the chemical structure of compound-2 (XIV) established as 1-O-galloyl-4,6-hexahydroxydiphenoyl-2,3-valoneoyl-β-D-glucose.



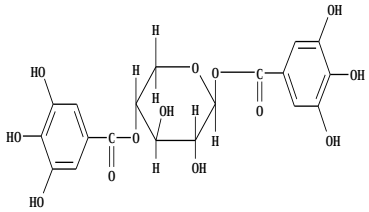
(XIV)Similarly, were established other structures of new ellagitannins (XV-XVII) isolated from plants of the *Euphorbia* family.



XV. *1-O-galloyl-2,3-hexahydroxydiphenoyl-4,6-valoneoyl-β-D-glucose (E. Franchetii B. Fedtsch).*



XVI. *1,4,6-tri-O-galloyl-2,3-valoneoyl-β-D-glucose (Euphorbia canescens* L)



XVII. *1,4-di-O-galloyl-β-D-xylose* (*Euphorbia franchetii B.Fedtsch)*

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