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OLIGOMERIC PROANTHOCYANIDIN GLYCOSIDES OF *Clementsia semenovii*

K. N. Matamarova,[2] Z. A. Kuliev,[1] A. D. Vdovin,[1] N. D. Abdullaev,[1] and B. M. Murzubraimov[2]

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Five new proanthocyanidins have been isolated from the roots of Clementsia semenovii *A. Bor. The structures of two of these compounds have been established by various chemical and physical methods: 7-O-[6-O-galloyl-β-D-Glcp* $\xrightarrow{6}$ *O-β-D-Glcp* $\xrightarrow{6}$ *O-β-D-Glcp* $\xrightarrow{6}$ *O-β-D-Glcp]-(+)-gallocatechin-(4α—8)-(+)-gallocatechin-(4α—8)-(−)-epigallocatechin-(4β—8)-(−)-epigallocatechin-(4β—8)-(-) -epigallocatechin-(4β—8)-(+)-catechin — CS-1 and 3-O-galloyl-7-O-(β-D-Glcp* $\xrightarrow{6}$ *O-β-D-Glcp)-(−)-epigallocatechin-(4β—8)-[3-O-galloyl-(−)-epigallocatechin]-(4β—8)-[3-O-galloyl-(−)-epigallocatechin]-(4β—8)-[3-O-galloyl-5-O-(6-O-galloyl-O-β-D-Glcp)]-(−)-epicatechin — CS-2.*

Among plants producing proanthocyanidins, those of the genus *Rhodiola*, belonging to the family Grassulaceae, stand out [1]. They are represented by 50 species, and more than 50 natural compounds have been isolated from various organs of the various species. The object of our investigations was the plant *Clementsia semenovii* (fam. Grassulaceae) growing in the mountain ranges of northern Kyrgystan [1]. *Clementsia semenovii* was previously called *Rhodiola semenovii* [1, 2], but was later singled out as a separate genus - *Clementsia* [3]. Four catechins and seven proanthocyanidins have been isolated from *C. semenovii* [4—7]. By chromatography on a column of microcrystalline cellulose and rechromatography on Sephadex LH-20, five new compounds have now been isolated from the butanolic fraction of an aqueous alcoholic extract of the roots of this plant gathered in the flowering and budding phase. The present paper describes the determination of the structures of two of the compounds that we have isolated.

The first compound, which we have called proanthocyanidin CS-1, has the elementary composition $C_{121}H_{118}O_{65}$, with a molecular mass of 2602. UV, IR, and NMR spectroscopy showed that this oligomeric glycosylated proanthocyanidin consists of (+)-catechin, (+)-gallocatechin, and (−)-epigallocatechin.

We used chemical methods of investigation to determine the monomeric composition and establish the structure of CS-1. In order to find which fragments the catechin blocks consist of, we performed an alkaline fusion and obtained phloroglucinol (**1**) and protocatechuic and gallic acids (**2** and **3**). For determining its monomeric structure we subjected the compound to acid hydrolysis, and in the hydrolysate we identified (+)-catechin (**4**), delphinidin (**5**), *D*-glucose (**6**), and glucose acylated with gallic acid in the sixth position (**6a**) [8]. To determine the terminal fragments of the molecule we used cleavage with thiophenol. Under the action of the latter on CS-1, its "lower" half formed (+)-catechin (**4**) and its "upper" half a mixture of two thioethers (**7** and **9**). Catalytic reduction of the thioethers with Raney nickel formed (+)-gallocatechin (**8**) and (−)-epigallocatechin (**10**) (Scheme 1).

To elucidate the position, the size of the oxide rings, and the type of bonds of the sugar residues we used Hakomori methylation [9] followed by methanolysis of the resulting permethylates. The methylation product proved to be 2,3,4-tri-O-methyl-*D*-glucopyranose.

The further study of the structure of CS-1 involved ^{13}C NMR spectroscopy. In the interpretation of the spectrum we gave a complete assignment of the resonance lines of (+)-catechin, (+)-gallocatechin, and (−)-epigallocatechin and of the glucose and gallic acid residues (Table 1).

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1) Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (371) 120 64 75; 2) Osh State University, Osh, fax (33 222) 2 23 73. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 756—763, November-December, 1998. Original article submitted May 11, 1998.

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TABLE 1. Chemical Shifts (ppm) of the Signals of the Carbon Atoms in the ^{13}C NMR Spectrum of Proanthocyanidin CS-1

Carbon atom	Fragments of CS-1					
	a	b	c	d	galloyl	glucose
C-2	84.4	84.4	77.1; 77.8	81.4		
C-3	73.6	73.6	72.7	68.4		
C-4	39.7	39.7	36.0	30.0		
C-6	98.9[o]	98.9[o]	98.9[o]	98.9[o]		
C-8	97.5[o]	108.0	108.0	108.0		
C-10	100.9[a]	102.6[a]	104.1[a]	105.0[a]		
C-5,7,9	155.9[x]	157.7[x]	157.1[x]	157.1[x]		
C-1′	132.3	132.3	132.3	132.3	122.8	102.6[a]
C-2′	108.0	108.0	108.0	116.4	111.6	74.5, 75.6
C-3′	147.0	147.0	147.0	147.0	147.0	78.8
C-4′	134.5	134.5	134.5	147.0	140.3	72.7
C-5′	147.0	147.0	147.0	117.0	147.0	77.1, 77.8
C-6′	108.0	108.0	108.0	120.7	111.6	64.8*, 63.5**
-COO					167, 169.4	

Signals labeled with the same letter may be interchanged.
* Glycosylation in position 6. ** Galloylation in position 6.

In addition, on the basis of the chemical shifts, we deduced the spatial orientations of the substituents of the catechin and gallocatechin blocks.

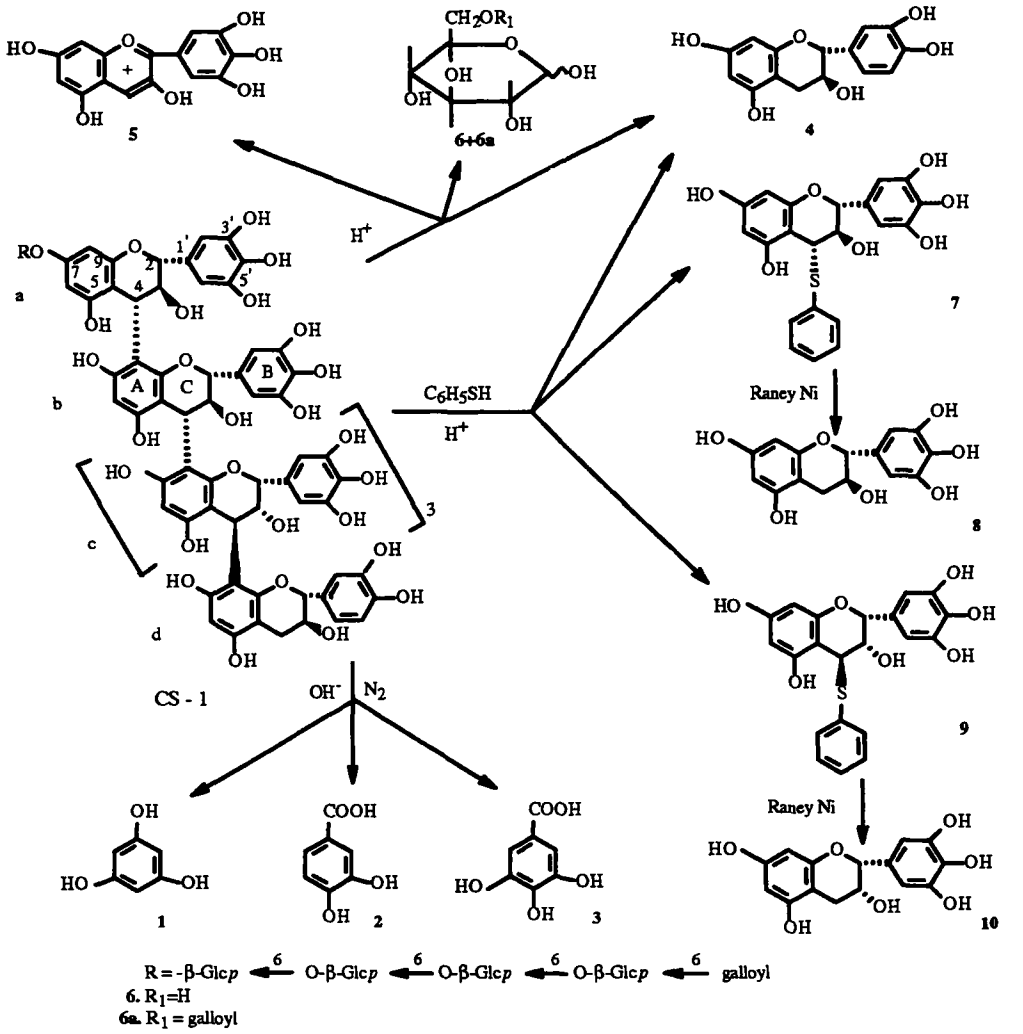
Signals at 155.9—157.1 ppm related to the oxygen-substituted carbon atoms C-5, -7, and -9 of ring *A*, their signals being located in relatively weak fields, while signals with chemical shifts of between 97.5 and 98.9 ppm belonged to the unsubstituted C-6 and C-8 atoms of ring *A* [11].

The presence of a catechin block was shown by a characteristic combination of the signals of the C-2′, C-5′, and C-6′ atoms of ring *B* at 116.4, 117.0, and 120.7 ppm [12, 17]. A distinguishing feature of the gallocatechin system is the signal of the C-4′ carbon atom at 134.5 ppm and also a combined signal of C-2′ and C-6′ at 108.0 ppm [11, 19]. The spectrum included the signals of a sugar residue with a galloylated hydroxy group at C-6. The C-1, C-3, and C-5 signals of glucose at 102.6, 78.8, and 77.1 ppm, respectively, showed that the glucan consists of β-*D*-glucopyranose residues. The chemical shifts given above and the chemical shift of the C-6 atoms of the glucose residues at 64.8 ppm showed that the glucose residues were linked to one another by (1—6)-β- bonds and to the aglycon by a β-glucosidic bond [14, 15, 21]. This was also confirmed by enzymatic hydrolysis with β-glucosidase. The acylation of a terminal glucose residue in the sixth position was shown by a signal of the C-6 atom of glucose with a chemical shift of 63.5 ppm and by the presence of signals characteristic for gallic acid.

The results of gentle acid and thiolytic cleavage showed the absence of a sugar residue in the "lower" (+)-catechin block; consequently, if the stereochemical hindrance in the "middle" blocks of the proanthocyanidin is taken into account, it may be assumed that the "upper " gallocatechin block is glycosylated.

The interflavan bonds in CS-1 are of the C-4—C-8 type, as is shown by the chemical shifts of the C-10 atoms (100.9—105.0 ppm) [16, 11]. The chemical shifts of the C-2 carbon atoms at 84.4 and 77.1—77.8 ppm show the 2,3-*trans*- and 2,3-*cis*- configurations of the asymmetric centers of the catechin systems [17, 18].

In CS-1, the "upper" position is occupied by gallocatechin, the chemical shifts of its aromatic carbon atoms being close to those observed in flavan-3-ols, while the chemical shifts of the atoms of the pyran ring (ring *C* in the Scheme 1) C-2, C-3, and C-4 at 84.4, 73.6, and 39.7 ppm correspond to the values for nongalloylated proanthocyanidins with the 2,3-*trans*-3,4-*cis*-configuration. The "lower" position is occupied by (+)-catechin the signals of the carbon atoms C-2, C-3, and C-4 of the pyran nucleus of which appear at 81.4, 68.4, and 30. 0 ppm. The "middle" position is occupied by (−)-epigallocatechin and (+)-gallocatechin. The carbon atoms of the (+)-gallocatechin are characterized by signals at 84.4, 73.6, and 39.7 ppm for C-2, C-3, and C-4, respectively, and those of the (−)-epigallocatechin by signals at (ppm) 77.1 and 77.8 for C-2, 72.7 for C-3, and 36.0 for C-4 [13, 18, 19].



Scheme 1

Thus, according to its UV and IR spectra and on the basis of an accurate assignment of the signals in the ^{13}C NMR spectrum it may be concluded that proanthocyanidin CS-1 has the structure and configuration of 7-O-[6-O-galloyl-β-*D*-Glc*p* $\xrightarrow{6}$ O-β-*D*-Glc*p* $\xrightarrow{6}$ O-β-*D*-Glc*p* $\xrightarrow{6}$ O-β-*D*-Glc*p*]-(+)-gallocatechin-(4α—8)-(+)-gallocatechin-(4α—8)-(−)-epigallocatechin-(4β—8)-(−)-epigallocatechin-(4β—8)-(-)-epigallocatechin-(4β—8)-(+)-catechin.

We called the second compound proanthocyanidin CS-2. It had the elementary composition $C_{113}H_{101}O_{61}$, with a molecular mass of 2433. According to its UV and IR spectra, compound CS-2 is a glycosylated proanthocyanidin.

Analysis of its ^{13}C NMR spectrum showed that CS-2 consists of (−)-epicatechin and (−)-epigallocatechin systems and glucose and gallic acid residues (Table 2). Resonance signals in the 154.2—156.9 ppm region related to the C-5, C-7, and C-9 carbon atoms of the phloroglucinol nucleus of ring *A*. Signals of the unsubstituted carbon atoms of this ring appeared in the region of 94.7 ppm [11].

The chemical shifts of the resonance signals of the carbon atoms of ring *B* gave the combination of C-2′, C-5′, and C-6′ signals — 116.6, 116.6, and 120.0 ppm — that is characteristic for (−)-epicatechin . The appearance of signals at 107.8 ppm (C-2′, C-6′), and 133.9 ppm (C-4′) showed the presence of epicatechin blocks [10].

As an analysis of the spectrum showed, the epicatechin and epigallocatechin blocks are galloylated in the C-3 position [17]. The attachment of gallic acid in the C-3 position leads to a regular upfield shift of the C-4 signal; in this case, C-4 of the "lower" block resonated in the 25.6 ppm region and the corresponding atoms of the upper blocks at 34.5 ppm. The absence of a downfield displacement of the signals of the C-2 carbon atoms (81—85.8 ppm) and their appearance at 74.0—76.4 ppm permitted the assumption that the C-2 and C-3 asymmetric centers have the 2,3-*cis*- configuration.

TABLE 2. Chemical Shifts (ppm) of the Signals of the Carbon Atoms in the ^{13}C NMR Spectrum of Proanthocyanidin CS-2

Carbon atom	Fragments of CS-2						
	a	b	c	galloyl	glucose	galloyl	glucose
C-2	74.0	74.0	76.4				
C-3	74.0	74.0	69.2				
C-4	34.5	34.5	25.6				
C-6	94.7	94.7	94.7				
C-8	94.7	107.8	107.8				
C-10	101.6[a]	101.6[a]	101.6[a]				
C-5,7,9		154.2-156.9					
C-1′	132.2	132.2	132.2	121.1	104.8[a]	104.8[a]	104.8[a]
C-2′	107.8	107.8	116.6	111.2	74.0	74.0	74.0
C-3′	146.5	146.5	146.5	146.5	76.4	76.4	76.4
C-4′	133.9	133.9	146.5	140.7	71.1°	69.9°	69.2°
C-5′	146.5	146.5	116.6	146.5	74.0	76.4	74.0
C-6′	107.8	107.8	120.0	111.2	66.8*	60.4	62.8**
-COO⁻				162.5, 165.9			

Signals labeled with the same letter may be interchanged.

*Glycosylation in position 6.

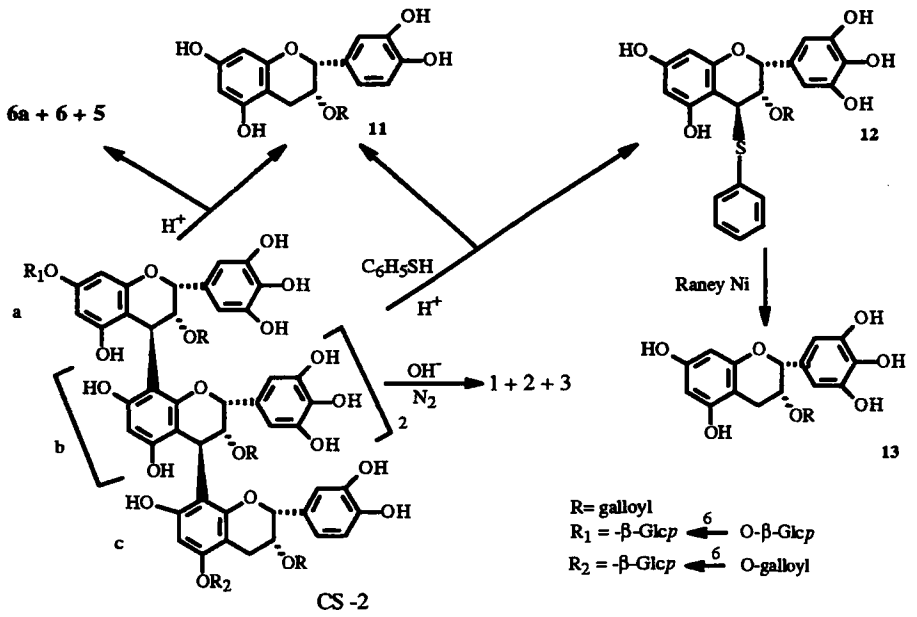
**Galloylation in position 6.

The interflavan bonds in CS-2 are of the C-4—C-8 type, as was shown by the chemical shifts of the C-10 atoms, of 101.6 and 104.8 ppm [16, 11].

In the interpretation of the carbohydrate parts of CS-2 it was established that they consist of fragments formed by (1—6)-bound β-*D*-glucopyranose (**6**) and of a monoester — β-*D*-glucopyranose galloylated in the C-6 position (**6a**). This conclusion was based on the chemical shifts of the C-1′, C-3′, and C-5′ atoms of glucose (101.6—104.8, 76.4, 74.0—76.4 ppm), which are characteristic for β-*D*-glucopyranose, and the presence of the signals of three C-6′ atoms of glucose at 60.4, 66.8, and 62.8 ppm corresponding to free glucose and to glucose glycosylated and esterified in the sixth position [14, 15, 21]. The spectrum shows signals of gallic acid. In catechin glycosides the carbohydrate component is generally attached to the aglycon in the C-7 and C-5 positions of the catechin systems. Since attachments to the "middle" blocks is sterically hindered, it is most likely that the carbohydrate moieties are attached to C-5 of the "lower" and C-7 of the "upper" blocks of the catechin systems of the proanthocyanidin.

The results of spectral methods have been confirmed by the chemical investigations. Thus, the degradation products from the alkaline fusion of CS-2 included phloroglucinol (**1**) and protocatechuic and gallic acids (**2** and **3**). Acid hydrolysis gave (−)-epicatechin gallate (**11**), delphinidin (**5**), glucose (**6**), and a monogalloylglucose (**6a**). As a result of mild thiolytic cleavage the "lower" block yielded (−)-epicatechin gallate (**11**) and a thioether (**12**). The thioether was subjected to reductive cleavage over Raney nickel and gave a substance identified as (−)-epigallocatechin gallate (**13**). Methylation followed by hydrolysis of the permethylate gave 2,3,4-tri-O-methyl-*D*-glucopyranose and 2,3,4,6-tetra-O-methyl-*D*-glucopyranose (Scheme 2).

Thus, on the basis of physicochemical methods of investigation we came to the conclusion that proanthocyanidin CS-2 has the structure and configuration of 3-O-galloyl-7-O-(β-*D*-Glc*p* $\xrightarrow{6}$ O-β-*D*-Glc*p*)-(−)-epigallocatechin-(4β—8)-[3-O-galloyl-(−)-epigallocatechin]-(4β—8)-[3-O-galloyl-(−)-epigallocatechin]-(4β—8)-[3-O-galloyl-5-O-(6-O-galloyl-O-β-*D*-Glc*p*)]-(−)-epicatechin.



Scheme 2

EXPERIMENTAL

General Observations. The UV spectra of the proanthocyanidins and their derivatives were taken in alcoholic soluiton on a Lambda-16 UV/VIS spectrometer, IR spectra on a Perkin-Elmer System 2000 FT-IR Fourier- spectrometer in tablets with potassium bromide. ^{13}C NMR spectra were obtained on a Tesla BS-567 A instrument (25 MHz for ^{13}C) in CD_3OD solution with TMS as internal standard, δ-scale. The concentration of the substances was in the range of 15—20%. Carbon spectra were obtained under conditions of complete suppression of spin-spin coupling with protons. Molecular masses were determined on a MOM 3170 ultracentrifuge and by gel filtration on a calibrated column of Sephadex LH-20. To check the homogeneity of the substances we used PC and TLC on Silufol UV-254 plates, with the following solvent systems: 1) chloroform—butan-1-ol—acetone—formic acid—water (3.5:13:10:10:8); 2) butan-1-ol—acetic acid—water (4:1:5); 3) chloroform—butan-1-ol—acetone—formic acid—water (3.5:12:20:10:8); 4) isoamyl alcohol—36% HCl—water (5:11:1); 5) butan-1-ol—acetic acid—water (40:12:8).

The elementary analyses of all the compounds corresponded to the calculated figures.

Extraction and Isolation of the Proanthocyanidins. Comminuted air-dry roots of *C. semenovii* (6 kg) were extracted six times with 35% ethanol. The resulting extracts were combined and evaporated in vacuum at 40—50°C. The concentrated extract (3 liters) was diluted with water (1:3) and was treated successively with diethyl ether, ethyl acetate, and *n*-butanol. This gave 157.5, 52.5, and 222 g of the corresponding dry fractions. After this treatment, the aqueous extract was evaporated on the water bath and the residue was ground to a powder. The yield of light brown amorphous powder was 1660 g.

Separation of the Proanthocyanidins. The butanolic extract (100 g) was mixed with cellulose (100 g) and transferred to a column of microcrystalline cellulose (5 × 170 cm, 1100 g). Elution was performed with methanol—chloroform (1:9)—(9:1), pure methanol, and methanol—water (9:1)—(7:3), with the collection of 50-ml fractions. Similar fractions were combined. Eluates containing identical substances were rechromatographed on a column of Sephadex LH-20 (5 × 160 cm). Elution was performed with water—methanol (2:3)—(1:4), with the collection of 20-ml fractions. The homogeneity of the fractions was checked by TLC.

Proanthocyanidin CS-1. 0.941 g, $C_{121}H_{118}O_{65}$, M 2602. UV spectrum: λ_{max} 210, 245, 276 nm; λ_{min} 255 nm. IR spectrum, ν_{max} 3210, 1695, 1615, 1539, 1513, 1448, 1338, 1215, 1100, 1029, 824, 805, 774, 734 cm^{-1}. For the ^{13}C NMR spectrum, see Table 1.

Proanthocyanidin CS-2. 1.119 g, $C_{113}H_{101}O_{61}$, M 2433. UV spectrum: λ_{max} 209, 246, 274, 305 nm; λ_{min} 256 nm.

IR spectrum: ν_{max} 3358, 1698, 1617, 1542, 1518, 1457, 1340, 1231, 1111, 1031, 829, 806, 775, 737 cm^{-1}. For the ^{13}C NMR spectrum, see Table 2.

Alkaline Cleavage of CS-1. With the slow passage of a current of nitrogen, a reaction mixture consisting of 50 mg of the substance and 5 ml of 50% KOH was heated in a bath with a temperature of 155—160°C and then the temperature was raised over 5 min to 230°C. The reaction mixture was rapidly cooled, and it was then acidified, diluted with water and extracted with ethyl acetate. The extract was dried, the solvent was distilled off, and the residue was chromatographed on polyamide. As a result, we detected and identified three compounds — phloroglucinol (**1**) and protocatechuic and gallic acids (**2** and **3**).

The alkaline cleavage of CS-2 was conducted by the method described above and gave the same three substances — phloroglucinol (**1**) and protocatechuic and gallic acids (**2** and **3**).

Acid Cleavage of CS-1. A solution of 60 mg of the substance in 2 ml of ethanol was treated with 1 ml of 2 N hydrochloric acid and heated in the water bath under reflux in a current of nitrogen for 2 h. The reaction mixture (colored crimson) was diluted with water and extracted with ethyl acetate (3 × 2 ml). The extract was washed and dried, and the solvent was distilled off. The residue was chromatographed on a column of Sephadex LH-20, with elution by 60% ethanol. The following compounds were isolated and identified: (+)-catechin (**4**), $C_{15}H_{14}O_6$, mp 178—180°C, $[\alpha]_D^{22}$+21° (*c* 0.51; acetone—water (1:1)); delphinidin (**5**), R_f 0.36 (2 N HCl), λ_{max} 554 nm (0.1% HCl in ethanol); *D*-glucose (**6**) (butan-1-ol—pyridine—water (6:4:3) system, R_f 0.50, spot reagent aniline phthalate); and glucose 6-O-gallate (**6a**), $C_{13}H_{16}O_{10}$, mp 137—138°C, $[\alpha]_D^{23}$ +22° (*c* 0.032; acetone).

The acid cleavage of CS-2 was conducted by the method described above and it led to the detection of (−)-epicatechin gallate (**11**), mp 253—255°C, $[\alpha]_D^{22}$ −176° (*c* 0.015; methanol); a monogalloylglucose (**6a**), $C_{13}H_{16}O_{10}$, M 332, mp 135—137°C, $[\alpha]_D^{24}$ +26.5° (*c* 0.21; acetone); *D*-glucose (**6**); and delphinidin (**5**).

Thiolytic Cleavage of CS-1. A mixture of 350 mg of CS-1 and 4 ml of thiophenol was treated with 2 ml of acetic acid and 10 ml of ethanol, and the resulting reaction mixture was left at room temperature for 48 h. Then it was concentrated and the oily residue formed was chromatographed on Sephadex LH-20 (1 × 20 cm) with elution by ethanol. This gave 19 mg of (+)-catechin (**4**) and 143 mg of an amorphous substance — a mixture of the two thioethers (**7** and **9**).

Cleavage of the Thioethers (7 and 9). The thioethers (143 mg) were mixed with 4 ml of ethanol—acetic acid (9:1). Raney nickel catalyst was added to the reaction mixture and it was kept at 50°C for 3 h, after which it was filtered and the filtrate was chromatographed on a column of Sephadex LH-20, with elution by 80% ethanol. Two compounds were obtained: 26 mg of (+)-gallocatechin (**7**), $C_{15}H_{14}O_7$, M 306, mp 186—188°C, $[\alpha]_D^{24}$ +15°C (*c* 0.1; ethanol), and 39 mg of (−)-epigallocatechin (**9**), $C_{15}H_{14}O_7$, M 306, mp 216—218°C, $[\alpha]_D^{24}$ −55° (*c* 0.33; methanol).

Thiolytic Cleavage of CS-2. Compound CS-2 was cleaved and the reaction product was purified by the method described above. This gave (−)-epicatechin gallate (**11**). Catalytic cleavage of the thioether (**12**) gave (−)-epigallocatechin gallate (**13**), mp 210—211°C, $[\alpha]_D^{22}$ −132° (*c* 0.38; methanol—water).

Methylation of CS-1. A solution of 0.119 g of CS-1 in 10 ml of dimethyl sulfoxide was treated with 0.1 g of sodium hydride, and the mixture was stirred at room temperature for 1 h. Then 5 ml of methyl iodide was added in drops and stirring was continued for another 4 h, after which the reaction mixture was poured into ice water (30 ml) and extracted with chloroform. The extract was treated with sodium thiosulfate, washed with water, and dried with anhydrous sodium sulfate. The residue was methylated similarly another five times. The reaction product was separated by column chromatography, and 0.066 g of amorphous permethylate was obtained.

Hydrolysis of the Permethylate of CS-1. The permethylate (0.066 g) was dissolved in 5 ml of aqueous methanol (1:1) containing 5% of sulfuric acid, and the reaction mixture was heated in the water bath for 8 h. Then it was neutralized, filtered, and evaporated to dryness. The residue was purified on a chromatographic column, giving 0.013 g of a methylated carbohydrate which was identified by GLC and TLC as 2,3,4-tri-O-methyl-*D*-glucopyranose.

Methylation of CS-2. The reaction was performed by the method described above. The compounds obtained were identified as 2,3,4-tri-O-methyl-*D*-glucopyranose and 2,3,4,6-tetra-O-methyl-*D*-glucopyranose.

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