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OBTAINING AND INVESTIGATION OF SUPRAMOLECULAR INCLUSION COMPLEX OF 2-DEOXY-20-HYDROXYECDYSONE WITH γ-CYCLODEXTRINE BY NMR SPECTROSCOPY METHOD

Abstract. For the first time, 2-deoxy-20-hydroxyecdysone (2-deoxyecdysterone) has been isolated from the above-ground part of *Silenefruticulosa* (Pall.) Schischk (*Caryophyllaceae* Juss. family). The formation of complex of phytoecdysteroids with γ-cyclodextrin has been studied with the help of NMR spectroscopy. Due to changing the chemical shifts of the substrate and receptor protons, it has been revealed that 2-deoxy-20-hydroxyecdysone interacts with γ-cyclodextrin to form a supramolecular inclusion complex of the stoichiometric composition of 1:1 with the entry of the fragment A of the substrate molecule into the inner cavity of the receptor.

Keywords: *Silenefruticulosa* (Pall.) Schischk, 2-deoxy-20-hydroxyecdysone, cyclodextrin, inclusion complexes, NMR spectroscopy.

Introduction. At the present stage of development of supramolecular chemistry, the most promising and intensively developing direction is the preparation and investigation of inclusion complexes of steroid compounds with cyclodextrins (CDs) [1-3]. The increased interest in CDs is due to their cyclic structure and the ability to form supramolecular host-guest inclusion complexes (receptor-substrate) due to the internal hydrophobic cavity. The supramolecular inclusion complexes of CDs with biologically active compounds make it possible to increase the solubility of the latter in water, reduce toxicity, allow liquid substances to be converted into solid substances, increase the stability of the substances to oxidation and hydrolysis [4-6]. Therefore, the preparation of inclusion complexes of phytoecdysteroids of ecdysterone and 2-desoxyecdysone that are promising synthons for regioselective modifications with CDs are in great demand [7-10].

Selection as a substrate of supramolecular self-assembly of 2-deoxy-20-hydroxyecdysone (3β, 14α, 20R, 22R, 25-pentahydroxy-5β(H)-cholest-7-en-6-one, 2-deoxyecdysterone) **1**is due to the wide range of biological activity of the latter. Compound **1** in small doses exhibits hormonal activity for insects in *invivo* tests [11] and was previously first isolated from the *Jacuslalandei* crayfish [12] and the *Blechnumminus* fern [13]. The compound **1** was also isolated from the Kazakh plant *Silenefruticulosa* (Pall.) Schischkhar vested in flowering phase [14,15].

EXPERIMENTAL PART

The reversed-phase high-performance liquid chromatography method was carried out on a HEWLETT PAKKARD Agilent 1100 Series instrument, an analytical column 4.6 × 150 mm, Zorbax SB-C_18; mobile phase: 10% isopropyl alcohol, UV detection at a length of 254 nm, a column temperature of 20º, a flow rate of the eluent of 0.75 ml/min, and a sample volume of 20 μl.

^{1}H and ^{13}C NMR spectra were recorded on the JeolJNM-ECA 400 spectrometers (399.78 and 100.53 MHz on ^{1}H and ^{13}C nuclei, respectively) in a solution of DMSO-d_6 and BrukerAvance DRX-500 (500 and 125 MHz on ^{1}H and ^{13}C nuclei, respectively) for solutions in $CDCl_3$. Chemical shifts are measured relative to the residual signals of protons or carbon atoms DMSO-d_6 and $CDCl_3$. The mass spectra were obtained on an LCQ Fleet mass spectrometer (ThermoElectron Corporation, USA) under the conditions of chemical ionization at atmospheric pressure. Positive ion spectra were analyzed using the Xcalibur program. TLC was performed on Kieselgel 60 F254chromatographic plates. Column chromatography was carried out on Kieselgel 60 (VWR, Art. 7734)silica gel.

γ-CD was used by Fluka's production facilities with a purity of 99%.

The melting point of the inclusion complex was determined on a Boetius instrument. The course of the reaction and the purity of the obtained compounds were monitored by thin-layer chromatography on Sorbfil plates in the ethanol-chloroform system (2:8). The plates were developed with a mixture of H_2SO_4: vanillin.

Isolation of the ecdysteroid-containing fraction of *Silenefruticulosa* (Pall.) Schischk. Airborne aerial parts of *Silenefruticulosa* (Pall.) Schischk sem. of *Caryophyllaceae* Juss. family (6 kg, collected on August 20, 2015 during the flowering phase in the Karaganda region of the Ulytau district of the Republic of Kazakhstan) was extracted four times with 70% aqueous ethanol by heating in a water bath. The resulting ethanol extract was treated with a 2:1 mixture of petroleum ether and ethyl acetate to remove non-polar components, the remaining water soluble portion was extracted with isobutanol. Isobutanol extracts were combined, and then isobutanol was distilled off to dryness in vacuo. There was obtained the sum of ecdysteroids with concomitant substances in the form of a thick green syrupy mass in the amount of 504 g.

Chromatographic separation of the ecdysteroid-containing fraction. The extract (16.3 g) was dissolved in a mixture of chloroform-methanol (150 ml, 1:1) in an ultrasonic bath. The resulting solution with a small suspension of insoluble substance was mixed with silica gel and the solvent was evaporated. The residue was applied to a silica gel column, eluting with a chloroform-methanol (50: 1 → 1: 1) mixture. The eluate from the column in 30 ml portions was collected in separate tubes (the first 19 tubes were discarded as substance-free), which were pooled into 8 fractions based on TLC analysis.

Acetylation of F-5 fraction. A solution of the F-5 oil (235 mg) and DMAP (9.4 mg) in pyridine (5 ml) and Ac_2O (2.5 ml) was held at 40-45^{0}C for 5 hours.

The solvent was then evaporated in vacuum; the residue was applied to a SiO_2-containing column. Elution was carried out with a mixture of $CHCl_3$-MeOH (100: 1 → 30: 1). 123.14 mg of (22R)-2β,22-diacetoxy-5β-cholest-7-en-6-one-14α,25-diol was obtained as an oil.^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.66 (3H, s, CH_3-18), 0.93 (3H, d, J=6.7, CH_3-21), 0.97 (3H (2H, s, CH_3-19), 1.21 (3H, s, CH_3-26), 1.23 (3H, s, CH_3-27), 2.04 (3H, s, CH_3-COO-2), 2.05 (3H, s, CH_3 -OCO-20), 2.35 (1H, dd, J = 12.6, 3.9, H-5), 3.09 (1H, m, H-9), 4.87 (1H, d, J=10.1, H-22), 5.05 (1H, br. s, H-3), 5.84 (1H, d, J=1.9, H-7). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 13.39, 15.69, 20.50, 21.36, 21.91, 23.94, 25.36, 25.43, 28.93, 29.48, 29.89, 30.78, 31.90, 36.38, 39.01, 40.34, 47.31, 51.64, 67.66, 70.72, 77.20, 84.70, 121.28, 164.44, 170.46, 170.98, 203.01. MS (APCI$^+$) *m/z* (%): 532.8 ([M]$^+$, 15), 515.1 ([M-H_2O+H]$^+$, 100), 497.2 ([M-2H_2O+H]$^+$, 46), 473.3 ([M-AcOH+H]$^+$, 64), 455.6 ([M-H_2O-AcOH+H]$^+$, 95).

Acetylation of F-7 fraction. A solution of the F-7oil (240 mg) and DMAP (9.4 mg) in pyridine (5 ml) and Ac_2O (2.5 ml) was held at 40-45°C for 5 hours. The solvent was then evaporated in vacuum; the residue was applied to a SiO_2-containing column. Elution was carried out with a mixture of $CHCl_3$-MeOH (100: 1 → 30: 1). 31.2 mg of (22R)-2β,22-diacetoxy-5β-cholest-7-en-6-one-14α,20,25-triol was obtained. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.86 (3H, s, 3H, CH_3-18), 0.98 (3H, s, CH_3-19), 1.21 (3H, s, CH_3-26), 1.23 (3H, s, CH_3-27), 1.27 (3H, s, CH_3-21), 2.06 (3H, s, CH_3-COO-2), 2.12 (3H, s, CH_3-COO -20), 2.32-2.43 (1H, m, H-5), 3.11 (1H, s, H-9), 4.80 - 4.90 (1H, m, H-22), 5.08 (1H, br. s, H-3), 5.86 (1H, d, J=2.1, H-7). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 17.46, 20.53, 21.14, 21.38, 23.92, 24.75, 25.35, 28.87, 29.12, 29.68, 30.01, 31.27, 31.72, 36.42, 40.24, 47.69, 49.49, 51.70, 67.59, 70.60, 77.21, 79.54, 84.87, 121.56, 164.32, 170.46, 172.48, 202.87. MS (APCI$^+$) *m/z* (%): 549.1 ([M+H]$^+$, 41), 531.6 ([M-H_2O+H]$^+$, 100), 513.1 ([M-2H_2O+H]$^+$, 36), 471.4 ([M-H_2O-AcOH+H]$^+$, 8), 453.4 ([M-2H_2O-AcOH+H]$^+$, 26).

Preparation of compound 1 from diacetate. 40 mg of potassium bicarbonate in 3 ml of water was added to a solution of 31.2 mg of diacetate in 4 ml of methanoland left at 40°C for one hour. The reaction mixture was diluted with water, neutralized with acetic acid and extracted with ether. The ether was distilled off; the residue was chromatographed on a thin layer of silica gel in chloroform-methanol (9:1). 12 mg of **1** with m.p. 250-252°C (from acetone-hexane) was obtained. The yield is 38.4%.

The inclusion complex 1 with γ-CD was obtained by the interaction of equimolecular quantities of solutions of **1** and γ-CD. 0.032 g (0.025 mmol) of γ-CD dissolved in 4 ml of distilled water was added to 0.022 g (0.025 mmol)of **1** dissolved in 3 ml of absolute ethanol. The solution was stirred with a magnetic stirrer at 50°C for 8 hours. The precipitate formed was filtered off, washed with ethanol and dried in a vacuum oven at 40°C. The inclusion complex of **1**-γ-CD was obtained as a white powder, melting with decomposition at 350^{0}C.

RESULTS AND DISCUSSION

At the obtaining **1** in the first stage the yield of extractives extracted by 70% aqueous ethyl alcohol was studied, and then, the reverse-phase high-performance liquid chromatography method was used to analyze the extract of the aerial part for the content of phytoecdysteroids.

Before it was revealed that the above-ground parts of *Silenefruticulosa* (Pall.) Schischkcontain ecdysterone as the main ecdysteroid (content 2.4 g/kg of dry weight), as well as 2-deoxyecdysone (0.45 g/kg) and **1** (0.11 g/kg) as minor representatives of this class of polyhydroxysteroids [14].

For the preparative isolation of the above-mentioned compounds, the air dried plant was subjected to extraction with aqueous ethyl alcohol and the resulting extract was then purified from non-polar components by washing with a mixture of petroleum ether and ethyl acetate. Purification from water-soluble impurities was carried out by the extraction of ecdysteroidfraction dissolved in water withisobutanol. The resulting ecdysteroid mixture was applied to a silica gel column, eluting with a step gradient of chloroform with ethanol. The eluate from the column was combined into 8 fractions based on the TLC analysis. ^{1}H NMR and mass spectra were recordedfor all F-1-F-8 fractions, on the basis of which the F-1-F-4 and F-6 fractions were excluded from further consideration as steroid-free. Fraction F-8 contained an individual compound 20-hydroxyecdysone, the structure of which was identified by the NMR spectroscopy method.

Further work with F-5 and F-7 fractions suggested their additional purification, but repeated chromatography on silica gel using other solvents did not yield the desired results. The solution of the problem was the acetylation of F-5 and F-7 fractions, followed by the isolation of 2-deoxyecdysoneand **1** acetates, respectively, identified by NMR and mass spectrometry. Deacetylation of the resulting compounds was carried out with potassium bicarbonate according to the procedure [16].

It is known that the sizes, shape and geometric complementarity of the interacting components play an important role in supramolecular chemistry, therefore, γ-CD was chosen as the most suitable for obtaining the inclusion complex **1**, the most suitable according to the above-mentioned criteria. [17] Currently, NMR spectroscopy is one of the most informative research methods of structure and intermolecular interactions in inclusion complexes of steroid compounds [3, 18]; therefore this method of investigation was chosen for the study of the supramolecule **1** with γ-CD.

The supramolecular inclusion complex **1** with γ-CD was obtained by the interaction of equimolecular amounts of the substrate with the receptor in an alcoholic solution upon heating.

DMSO-d_6 proved to be the most suitable solvent for NMR spectroscopic studies of inclusion complexes**1** with γ-CD; therefore, NMR spectraof**1** and its complexes with γ-CD were obtained in this solvent. Previously, NMR spectra of **1** were identified in deuterated pyridine and methanol [13], so the results of the

Chemical shifts of ^{1}H and ^{13}C NMRof 1 and γ-CD in the free state (δ_o) and in the inclusion complex (δ)

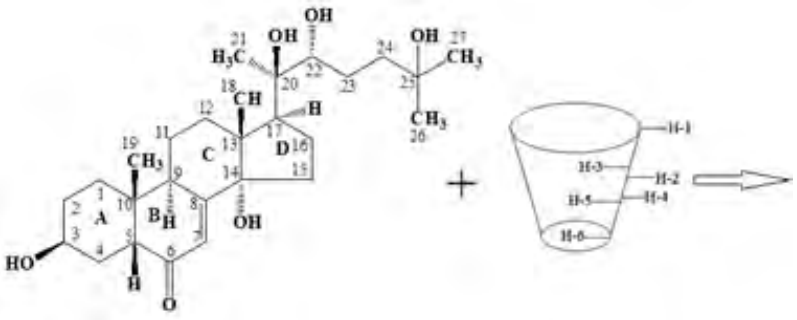
C Atom	CH_xGroup	$\delta_0(^{13}C)$, ppm	$\delta(^{1}H)$, ppm	$\delta(^{1}H)$, ppm	$\Delta\delta(^{1}H)=\delta(^{1}H)-\delta_0(^{1}H)$, ppm
1					
1	$-CH_2-$	28.56			
2	$-CH_2-$	28.56			
3	>CH-OH	63.15			
4	$-CH_2-$	29.51			
5	>CH-	51.40			
6	>C=O	210.97	–	–	–
7	-CH=C<	120.85	5.58 s	5.57 s	–0.01
8	>C=C<	166.19	–	–	
9	>CH-	36.10	3.06 m	3.04 m	–0.02
10	>C<	36.56	–	–	–
11	$-CH_2-$	21.49			
12	$-CH_2-$	31.30			
13	>C<	48.56	–	–	–
14	>C<	83.63	–	–	–
15	$-CH_2-$	32,56			
16	$-CH_2-$	21.49			
17	>CH-	49.21	2.22 m	2.21 m	–0.01
18	$-CH_3$	17.68	0.71 s	0.70 s	–0.01
19	$-CH_3$	24.05	0.80 s	0.79 s	–0.01
20	>C<(OH)	76.19			
21	$-CH_3$	22.11	1.03 s	1.02 s	–0.01
22	>CH-	76.68			
23	$-CH_2-$	26.60			
24	$-CH_2-$	41.92			
25	>C<	69.21	–	–	–
26	$-CH_3$	30.55	1.00 s	0.99 s	-0.01
27	$-CH_3$	30.55	1.00 s	0.99 s	-0.01
γ-CD					
1	>CH-		4.83	4.83	0
2	>CH-		3.30	3.27	-0.03
3	>CH-		3.37	3.33	-0.04
4	>CH-		3.32	3.29	-0.03
5	>CH-		3.41	3.33	-0.04
6	$-CH_2-$		3.58	3.56	-0.02

previous work were used in determining NMR chemical shifts of ^{1}H and^{13}C atoms of **1** (table) in DMSO-d_6. Since a change in the solvent during NMR studies leads to a change in the chemical shift of the ^{1}H and ^{13}C atoms, two-dimensional NMR spectroscopy of HMQC (^{1}H-^{13}C) correlation through one bond and COSY (^{1}H-^{1}H) NMR correlations through three bonds was used to identify the signals.

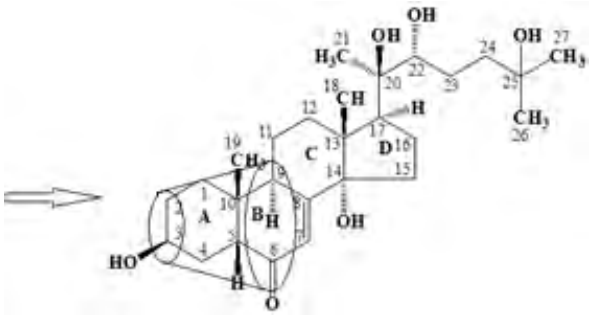
The superposition of proton NMR spectra of **1** does not allow identifying all the hydrogen atoms in the solvent chosen by us. Singlet signals of five CH_3-groups are manifested in the strong-field region at 0.72-1.03 ppmof the proton NMR spectrum. The resonance of the signals of the CH_2 groups of the molecule is foundin the area of 1.20-2.00 ppm. The multiplet signal at 2.22 ppm can be attributed to the proton of the methine group H-17, another methionine proton H-9 resonates at 3.06 ppm. Proton of the H-7 fragment -CH = C-resonates at 5.58 ppm.

In the HMQC (^{1}H-^{13}C) NMR spectraof **1**certain protons correlate with the corresponding nuclei of carbon atoms. Cross peaks corresponding to spin-spin proton interactions through three bonds are observed in the two-dimensional COSY (^{1}H-^{1}H) NMR spectra.

Thus, the obtained one- and two-dimensional NMR spectra allowed identifying all carbon atoms and detectable protons of the molecule **1**, potential substrate or guest when obtaining inclusion complexes with γ-CD.



1 **γ-CD**



1- γ-CD

The proposed scheme for the formation of a supramolecular inclusion complex **1**with γ-CD

Investigation of the structure of supramolecular complexes by the method of ^{1}H and ^{13}C NMR spectroscopy is based on the determination of the difference in the values of chemical shifts of certain signals in the spectra of substrate**1** and the γ-CD receptor in the free state and in the complex that arises as a result of intermolecular interaction. Thus, in terms of the values of the chemical shifts of the internal or external protons of the CDs, it is possible to reveal the formation of, respectively, internal or external complexes. The change in the chemical shifts of ^{1}H and ^{13}C in the substrate spectra makes it possible to determine the direction of occurrence of the latter in the cavity of the CD [19, 20].

Signals of protons belonging to substrate molecules are observed (table) in ^{1}H NMR spectra of inclusion complexes with γ-CD. There were no significant changes in chemical shifts of the identified protons**1**after complexation with γ-CD. In the inclusion complexes **1** with γ-CD, the greatest change was observed in the chemical shifts of protons H-3 and H-5 of the inner cyclodextrin cavity (table, figure).

This indicates the entry of the steroid molecule into the internal cavity of host molecules with the formation of a supramolecular inclusion complex.

Conclusion. A comparison of the values of the integrated intensities of the signals of protons **1** and γ-CD in the composition of the inclusion complex showed the formation of supramolecules of the composition of one guest molecule per molecule of the host.

The imposition of proton NMR spectra in free states and in the inclusion complex did not completely allow identifying the structure of the supramolecules with γ-CD. A slight change in the chemical shifts of the protons of the methyl groups H-26, 27, 21 and 18 allows one to make the assumption that the inclusion of the molecule **1** in the cyclodextrin cavity occurs as the entry of the guest molecule fragment A into the interior cavity of the host molecule.

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Резюме

Б. С. Темірғазиев, Т. М. Сейілханов, С. Тянах, А. М. Қожанова, О. Т. Сейілханов, Е. В. Минаева, Л. К. Сәлкеева, Б. И. Төлеуов, С. М. Әдекенов

2-ДЕЗОКСИ-20-ГИДРОКСИЭКДИЗОННЫҢ γ-ЦИКЛОДЕКСТРИНМЕН СУПРАМОЛЕКУЛАЛЫҚ ҚОСУ КОМПЛЕКСІН АЛУ ЖӘНЕ ЯМР-СПЕКТРОСКОПИЯЛЫҚ ӘДІСПЕН ЗЕРТТЕУ

Бұташық сылдыршөптің (*Silenefruticulosa* (Pall.) Schischk, *Caryophyllaceae*Juss.) жер үсті бөлігінен алғаш рет 2-дезокси-20-гидроксиэкдизон бөлініп алынды. ЯМР-спектроскопия әдісі арқылы фитоэкдистероидтың γ-циклодекстринмен комплекс түзілуі зерттелінді. Субстрат пен рецептордың протондарының химиялық жылжуларының өзгерістері бойынша, 2-дезокси-20-гидроксиэкдизон γ-циклодекстринмен 1:1 стехиометриялық құрамдағы супрамолекулалық комплекс түзіп, рецептор молекуласының қуысына субстрат молекуласы А фрагментімен енетіні анықталды.

Түйін сөздер: бұташық сылдыршөп (*Silene fruticulosa* (Pall.) Schischk, *Caryophyllaceae* Juss.), 2-дезокси-20-гидроксиэкдизон, циклодекстрин, қосу комплекстері, ЯМР-спектроскопия.

Резюме

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ПОЛУЧЕНИЕ И ИССЛЕДОВАНИЕ СУПРАМОЛЕКУЛЯРНОГО КОМПЛЕКСА ВКЛЮЧЕНИЯ 2-ДЕЗОКСИ-20-ГИДРОКСИЭКДИЗОНА С γ-ЦИКЛОДЕКСТРИНОМ МЕТОДОМ СПЕКТРОСКОПИИ ЯМР

Из надземной части смолевки кустарничковой (Silenefruticulosa (Pall.) Schischk, семейства CaryophyllaceaeJuss.) впервые выделен 2-дезокси-20-гидроксиэкдизон (2-дезоксиэкдистерон). Методом ЯМР-спектроскопии изучено комплексообразование фитоэкдистероида с γ-циклодекстрином. По изменению химических сдвигов протонов субстрата и рецептора установлено, что 2-дезокси-20-гидроксиэкдизон взаимодействует с γ-циклодекстрином с образованием супрамолекулярного комплекса включения стехиометрического состава 1:1 с вхождением фрагмента А молекулы субстрата во внутреннюю полость рецептора.

Ключевые слова: смолёвка кустарничковая (*Silenefruticulosa* (Pall.)Schischk), 2-дезокси-20-гидроксиэкдизон, циклодестрин, комплексы включения, спектроскопия ЯМР.