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PROPERTIES AND ANTIPHAGE ACTIVITY OF CONDENSED HYDRO(THIO)CHROMANS AND THEIR COPPER COMPLEXES

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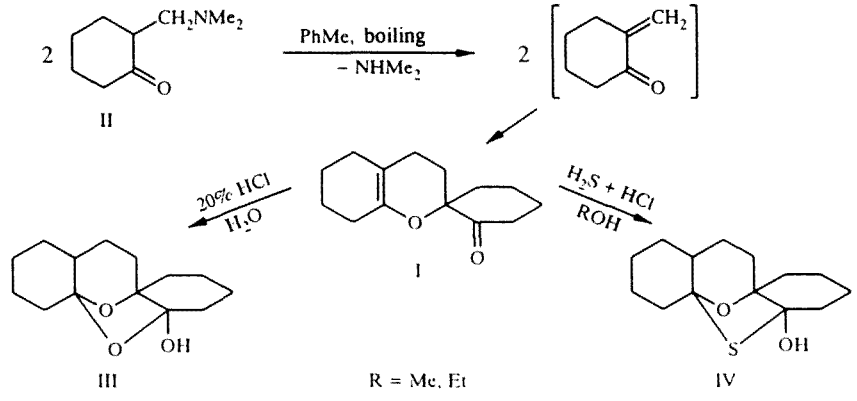
Research into the reactivity of carbonyl-substituted spirohydrochromans with hydrogen sulfide under the influence of protic and aprotic acids was continued for the case of 3,4,5,6,7,8-hexahydrospiro[chromene-2,1'-cyclohexan]-2-one. The general nature of the reactions was established. Complexes of copper(II) with substituted hydro(thio)chromans were obtained. The results from investigation of the antiphage activity of the synthesized compounds are presented.

In a continuation of our previous investigations [1], new data were obtained on the synthesis, reactivity, and biological activity (with respect to the phage *E. coli* T4) of carbonyl-substituted spirohydrochromans and the products from their transformations.

As subject for the investigation we used 3,4,5,6,7,8-hexahydrospiro[chromene-2,1'-cyclohexan]-2-one (I), which was synthesized by thermal deamination of N,N-dimethylaminomethylcyclohexanone (II) using the procedure developed for its benzannellated analog [1]. In the presence of catalytic amounts of hydroquinone, the 2-methylenecyclohexanone formed when the base (II) is boiled in toluene dimerizes by a reaction of the Diels—Alder type to compound (I), which is obtained with a yield of 57%.

The accessibility of the spiroketone made it possible to study the nature of its transformations under the influence of nucleophilic reagents (hydrogen sulfide and acids). Such an investigation was of interest in connection with the previously discovered [1] ability of compounds of the (I) type to undergo recyclization under the action of the above-mentioned reagents. In addition, the possible practical applications of the expected sulfur-containing heterocyclic compounds attracted attention.



The obtained results make it possible to trace a correlation between the strength of the protonating agent and the structure of the obtained products. We established that the spirohydrochroman (I) is converted quantitatively by the action of 20% aqueous hydrochloric acid into 2,16-dioxatetracyclo[7.6.1.$0^{3,8}$.$0^{1,11}$]hexadecan-3-ol (III). During the simultaneous action

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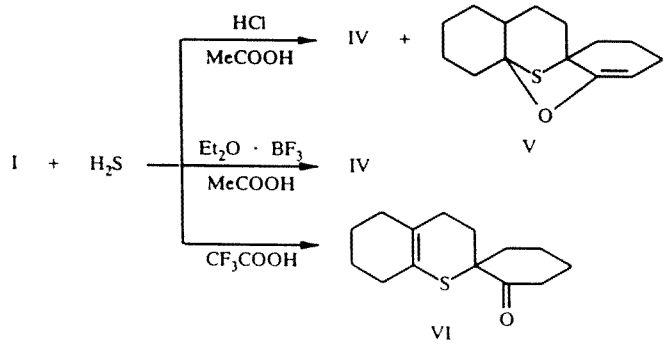
TABLE 1. Characteristics of Compounds (I, III, IV, VI-X)

Compound	Molecular formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	S		
I	$C_{14}H_{20}O_2$	76,5 76,4	9,2 9,1	—	135...137*	57
III	$C_{14}H_{22}O_3$	70,7 70,6	9,3 9,2	—	152...153	65
IV	$C_{14}H_{22}O_2S$	66,3 66,1	8,6 8,7	12,5 12,6	162...164	65
VI	$C_{14}H_{20}OS$	71,2 71,1	8,6 8,4	13,4 13,6	152...156	66
VII	$C_{20}H_{32}O_{10}Cu_2$	42,6 42,9	5,4 5,7	—	215...217	67
VIII	$C_{20}H_{38}O_{13}Cu_2$	39,3 39,1	6,3 6,2	—	195...196	54
IX	$C_{20}H_{38}O_{12}SCu_2$	38,1 38,1	6,0 6,0	5,2 5,1	154...156	57
X	$C_{20}H_{36}O_{10}SCu_2$	40,7 40,3	6,4 6,1	5,5 5,3	167...168	62

*bp/8 hPa.

of hydrochloric acid and hydrogen sulfide for 16-18 h in alcohol (methanol, ethanol), its sulfur analog 16-oxa-2-thiatetracyclo[7.6.1.$0^{3,8}$.$0^{1,11}$]hexadecan-3-ol (IV) is formed with a 65% yield.

It is known that the strength of acids varies, depending on the nature of the solvent [2]. With other conditions equal, replacement of the alcohol by acetic acid led to the formation of a mixture of products in two concurrent reactions. According to TLC and ^{13}C NMR data, the mixture contained compound (IV) and 2-oxa-16-thiatetracyclo[7.6.1.$0^{3,8}$.$0^{1,11}$]hexadec-3-ene (V). With acetic acid and boron trifluoride etherate in a ratio of 1:3 the transformation takes place in the same direction as in alcohol. The action of hydrogen sulfide on the substrate (I) in trifluoroacetic acid gave a 66% yield of 3,4,5,6,7,8-hexahydrospiro[thiochromene-2,1'-cyclohexan]-2-one (VI).



The results from study of the behavior of the substrate (I) with hydrogen sulfide and acids indicate that the transformations of the carbonyl-containing spirohydrochromans and the mechanism of their recyclization under the conditions discussed above are general in nature [1].

It is known that the complexes of copper with organic ligands belong to the group of prospective media for the preservation of diagnostic vaccines and have an inhibiting action on the bacteriophage *E. coli* T4 [3]. In view of this we obtained the respective complexes (VII-X) of copper(II) with compounds (I, III, IV, VI) with the composition $Cu_2LA_3 \cdot nH_2O$ respectively, where A = CH_3COO and n = 2-4. Complexation was realized by the reaction of the substrates with copper(II) acetate in a 1:1 mixture of DMFA (DMSO) and water at 45-50°C and with a ligand—metal ratio of 1:1.

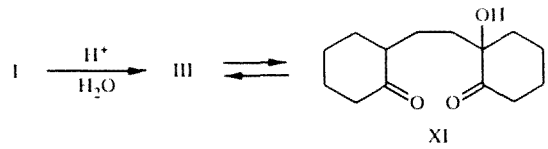
The structure of the synthesized compounds (I, III-VI) and the complexes (VII-X) agrees well with the results obtained for them by elemental and thermal analysis (Tables 1 and 2) and also with the IR (Table 3) and ^{13}C NMR (Table 4) spectra. The signals in the latter were assigned on the basis of a comparison of the spectra of compounds (III-V) with due regard to the similarities and differences in their structures. The signals of the atoms entering into the key structure-determining fragment are examined below. Thus, the signals in the ^{13}C NMR spectrum of the product (IV) in the regions of 82.89, 98.95, and 84.98 ppm can be assigned to the $C_{(8)}$, $C_{(1)}$, and $C_{(3)}$ atoms respectively. The upfield shift of the last two signals compared with the

TABLE 2. Data from Thermographic Analysis of the Copper Complexes (VII, IX, X)

Compound	Nature of thermal effect	Temperature of thermal effect, °C		Weight loss, %		Thermolysis product
		Endothermic	Exothermic	Found	Calculated	
VII	Hydrolysis	140		6,0	6,0	$C_{20}H_{28}O_8Cu_2$
	Beginning of decomposition	230				
	Decomposition to CuO		400...700	77,0	78,0	—
				—	—	Cu
IX	Dehydration	140		10,0	8,9	$C_{20}H_{30}O_8SCu_2$
	Decomposition to Cu		220...400	73,0	75,0	
						Cu
	Formation of CuO	490		—	—	Mixture of products
X	Hydrolysis	140		7,0	5,9	$C_{20}H_{30}O_7SCu_2$
	Decomposition to Cu		200...370	75,5	73,5	
						Cu
	Formation of CuO	490		—	—	Mixture of products

signals for compound (III) is explained by the fact that in the product (IV) the less electronegative sulfur atom takes part in the formation of a bridge between the $C_{(1)}$ and $C_{(3)}$ atoms. Further evidence for the proposed position of the heteroatoms is provided by the shift of the signals for the $C_{(14)}$ (18.27 ppm) and $C_{(10)}$ (24.62 ppm) atoms, since in compound (IV) at the γ position to the given atoms there is an axially oriented sulfur atom, which is much larger than the oxygen atom that occupies the analogous position in compound (III). The signal at 97.64 ppm observed in the ^{13}C NMR spectrum of the substrate (V), close in value to the signal of the $C_{(1)}$ atom of compound (IV), was assigned to the analogous atom of compound (V), also attached to the oxygen and sulfur atoms. In the last case, however, the sulfur atom is in the heterocyclic fragment of the molecule. This is demonstrated by the position of the signal of the quaternary atom $C_{(8)}$ at 47.97 ppm. The upfield shift of the signal compared with the signal of the related compounds (III) and (IV) is explained by the fact that the $C_{(8)}$ atom in the product (V) is attached to the sulfur atom, the electronegativity of which is lower than that of the oxygen. The atoms forming the double bond absorb at 134.45 (C_3) and 112.72 (C_4) ppm. The position of these signals indicates that the double bond is conjugated with the oxygen atom. The signals of the $C_{(14)}$ and $C_{(10)}$ atoms (20.81 and 25.15 ppm) are close in value to the signals of the same atoms in the semiacetal (III). This makes it possible to conclude that the bridge between the $C_{(1)}$ and $C_{(3)}$ atoms in compound (V) is closed with the participation of the oxygen atom.

Comparison of the IR absorption spectra of the initial compounds (I, III, IV, VI) and their complexes (VII-X) (Table 3) makes it possible to suppose that during complexation in an acidic aqueous medium the spirochroman (I) changes into the semiacetal (III), as shown by the absence of absorption bands for C=O and C=C in the corresponding regions and by the appearance of the stretching vibrations of the OH group at 3300 and 3270 cm^{-1} in the spectrum of the complex (VII). Analogous transformations take place with its sulfur heteroanalog (VI). Under the influence of an aqueous solution of copper(II) acetate, the semiacetal (III) probably changes into the tautomeric form (XI), which forms the complex (VIII). In the IR spectrum of the latter, the absorption bands corresponding to the stretching vibrations of the C=O bonds appear at 1700 and 1720 cm^{-1}. This agrees well with the well-known ability of condensed carbonyl-substituted spirohydrochromans to undergo such transformations under the conditions of acid hydrolysis [4-6]:



XI

The compounds (I, III, IV, VI) that we synthesized and the corresponding copper complexes (VII-X) were submitted to biological tests by the two-layer method described in [7] in the *E. coli* B—T4 phage system in dimethylformamide in order to establish the survival rate of the T4 bacteriophage in their presence. The culture medium was broth and Hottinger's agar

TABLE 3. IR Spectra of Compounds (I, III, IV, VI) and Their Copper Complexes

Compound	νOH	νCH_2	νC=O	νCOO	νC–O–C
I	—	2915, 2800	1720, 1700	—	1050...960
III	3388	2980, 2944, 2856	—	—	1060...950
IV	3380	2950, 2870	—	—	700...650*
VI	—	2920, 2860	1725	—	628...536*
VII	3300, 3270	2943, 2836	—	1604	1045...930
VIII	3480, 3320, 2676	2980	1720, 1700	1600	1150...950
IX	3376, 3272	2832	—	1600	1272, 692...628*
X	3416, 3268	2932, 2856	—	1600	692...628*

*νC–S–C.

TABLE 4. ^{13}C NMR Spectra of Compounds (III-V)

Compound	Chemical shifts, δ, ppm						
	$C_{(1)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$
III	107,21	103,04	39,73	21,06	23,69	32,12	79,31
IV	98,95	84,98	34,54	23,26	25,27	33,12	82,89
V	97,64	134,45	112,72	25,00	25,34	25,84	47,97

Compound	Chemical shifts, δ, ppm						
	$C_{(9)}$	$C_{(10)}$	$C_{(11)}$	$C_{(12)}$	$C_{(13)}$	$C_{(14)}$	$C_{(15)}$
III	32,87	25,19	40,64	30,67	25,40	22,82	35,74
IV	34,25	24,62	43,51	30,66	25,34	18,27	38,46
V	34,04	25,15	42,35	30,05	25,27	20,81	37,62

(pH 7.2), and the concentration of the substrates was 125 μg/ml. The survival rate of the T4 bacteriophage was taken as zero for values of less than 0.01%.

It was established that compounds (III, VI) and the complexes (VIII-X) can be classified as inactive substances with respect to their effect on the bacteriophage *E. coli* T4 (Table 5). Compounds of the first group are promising as possible antiviral products.

EXPERIMENTAL

The IR spectra were obtained on a UR-20 spectrometer in tablets with potassium bromide and in Vaseline oil. The ^{13}C NMR spectra were recorded on a Varian FT-80A Fourier spectrometer at 30°C in deuterochloroform. The reactions and the purity of the obtained products were monitored by TLC on Silufol UV-254 plates (hexane—ether—acetone, 4:1:1). The thermoanalytical investigations were conducted on an OD-103 derivatograph. The temperature was recorded by a Pt—Pt/Rh thermocouple. The temperature range was room temperature to 1000°C. The standard was calcined aluminum oxide.

The data from elemental analysis of compounds (I, III-X) corresponded to the calculated data. The physicochemical characteristics are given in Tables 1-4.

3,4,5,6,7,8-Hexahydrospiro[chromene-2,1′-cyclohexan)-2-one (I). To a solution of 15 g (0.1 mole) of N,N-dimethylaminomethylcyclohexanone (II) in 60 ml of toluene we added 0.15 g of hydroquinone (0.001 mole), and we boiled the mixture for 8 h. From the reaction mass by vacuum distillation we isolated 11.8 g (57%) of compound (I); bp 135-137°C at 8 hPa; R_f 0.76, n_D^{20} 1.5138.

TABLE 5. Antiphage Activity of Compounds (I, III, IV, VI) and Their Copper Complexes (VII-X)

Compound	Survival rate of T4 phage, %	Compound	Survival rate of T4 phage, %	Compound	Survival rate of T4 phage, %	Compound	Survival rate of T4 phage, %
I	35	IV	56	VII	25	IX	2
III	12	VI	5	VIII	7	X	14

2,16-Dioxatetracyclo[7.6.1.$0^{3,8}$.$0^{1,11}$]hexadecan-3-ol (III). A 5-g sample (0.02 mole) of 3,4,5,6,7,8-hexahydrospiro[chromene-2,1′-cyclohexan]-2-one (I) was stirred in 50 ml of 20% hydrochloric acid for 1 h. The crystals that separated were removed and dried, and 3.62 g (65%) of compound (III) was obtained; bp 152-153°C (ethanol, hexane), R_f 0.56.

16-Oxa-2-thiatetracyclo[7.6.1.$0^{3,8}$.$0^{1,11}$]hexadecan-3-ol (IV). We saturated 30 ml of methanol (or ethanol) with hydrogen sulfide for 1.5 h and added 2.2 g (0.01 mole) of compound (I). Gaseous hydrogen chloride and hydrogen sulfide were passed into the obtained mixture until the reaction was complete (~7 h according to TLC). The reaction mass was treated with 50 ml of water, and the product was extracted with ether (2 × 30 ml). The extract was washed with water and sodium bicarbonate solution and dried. The solvent was evaporated, and 1.65 g (65%) of compound (IV) was obtained; mp 162-164°C (ethanol), R_f 0.82.

2-Oxa-16-thiatetracyclo[7.6.1.$0^{3,8}$.$0^{1,11}$]hexadec-3-ene (V). From 2.2 g (0.01 mole) of compound (I) in 50 ml acetic acid by the method described above we obtained 1.86 g of a mixture of (IV) and (V) (R_f 0.82, 0.80 respectively).

3,4,5,6,7,8-Hexahydrospiro[thiochromene-2,1′-cyclohexan]-2-one (VI). We saturated 50 ml of absolute trifluoroacetic acid with hydrogen sulfide for 1 h, added 2.2 g (0.01 mole) of compound (I), and continued to add hydrogen sulfide until the reaction was complete (according to TLC, ~6 h). The reaction mixture was treated with 50 ml of water and extracted with chloroform (2 × 30 ml). The extract was washed with a saturated solution of sodium carbonate and with water, and dried. The solvent was evaporated, and 1.36 g (66%) of compound (VI) was obtained; mp 154-156°C (from ethanol), R_f 0.67.

General Procedure for the Preparation of the Copper(II) Complexes (VII-X). To a solution of 0.01 mole of copper(II) acetate in 10 ml of water with constant stirring at 45-50°C we added dropwise 0.01 mole of the compound (I, III, IV, VI) in 10 ml of DMFA (DMSO). The reaction mixture was cooled to room temperature. The crystals that separated were removed, washed with ether, and dried, and the respective complexes (VII-X) were obtained.

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