SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF S-R-SULFONIUM SALTS OF BICYCLIC HEMIDITHIOACETALS

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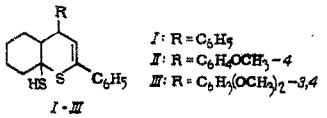
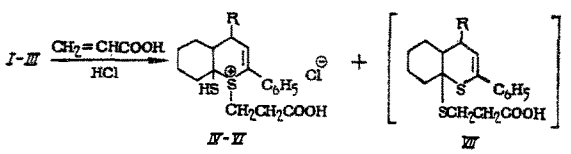
UDC 615.281:547.279.2].012.1

Bicyclic polydithioacetals such as (I-III) are readily accessible, by the reaction of 1,3-diaryl-3-(2-oxocyclohexyl)propan-1-ones with hydrogen sulfide in acidic media, and can be used for the preparation of biologically active compounds [1, 2]. The attention of workers has hitherto been largely directed towards the alkylation of the mercapto group in alkaline solution [3]. We here report attempts to alkylate the sulfide sulfur with the object of obtaining S-R-sulfonium salts. S-Methylsulfonium salts are known to play an important part in reactions occurring in the living organism involving "active methionine." However, synthetic S-R-sulfonium salts are still largely unknown in a biological respect. There have been literature reports of the pharmacological effects of S-methyl-4-hydroxy-4-phenylthiacyclohexane iodide [4], and of tests for anticholinergic properties in S-R-sulfonium salts of dihydroisonaphthene and dihydrobenzo[c,e]thiepin [5].



I-III

1-Mercapto-3,5-diaryl-2-thiabicyclo[4.4.0]dec-3-enes (I-III) were alkylated with acrylic acid in the presence of hydrogen chloride in methylene chloride. Completion of the reaction was assessed by the disappearance of the mercaptosulfides (I-III). The chlorides (IV) and (V) crystallized following dilution of the reaction mixture with hexane, but the chloride (VI) could not be isolated in the crystalline state. The yields of the salts (IV)-(VI) were 26-55%. The low yields of the required products may be due to the fact that in addition to alkylation of the sulfide sulfur, addition of the hemidithioacetal to acrylic acid evidently occurs with the involvement of the mercapto group. Addition of hydrogen sulfide or mercaptans to olefins proceeds readily in acid media, since divalent sulfur compounds are strong nucleophiles.



The products of electrophilic addition of the mercaptosulfides (I-III) to acrylic acid, such as (VII), could not be isolated in the pure state. The isolation and purification of dithioacetals such as (VII) is hindered by the presence of condensation products of acrylic acid itself.

Chlorides (IV) and (V) were obtained by alkylation of the hemidithioacetals (I) and (II) with β-chloropropionic acid in the presence of silver nitrate. The yields of salts (IV) and (V) were 52-70%. The reaction did not proceed to completion, and in the filtrates after isolation of (IV) and (V) chromatography showed the presence of the original hemithioacetals (I) and (II).

Chlorides (IV-VI) were converted into their hexachloroplatinates (VIII-X) by the action of chloroplatinic acid in a mixture of acetic acid and acetic anhydride.

The properties of the S-R-sulfonium salts are given in Table 1.

N. G. Chernyshevskii Saratov University. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 2, pp. 167-170, February, 1983. Original article submitted June 24, 1982.

0091-150X/83/1702-0113$07.50

TABLE 1. Properties of S-(2-Carboxyethyl)-1-mercapto-3,5-diaryl-2-thioniabicyclo[4.4.0]dec-3-ene Chlorides (IV, V) and Hexachloroplatinates (VIII-X)

Compound	R	Yield, %	mp, °C	Found		Molecular formula	Calculated		IR spectrum, cm^{-1}		
				C	H		C	H	ν_{C-O}	$\nu_{C=C}$	$\nu_{C=O}$
IV	C_6H_5	26	165—167	64,99	5,04	$C_{24}H_{27}O_2S_2Cl$	64,52	6,05		1605	1735
V	$C_6H_4OCH_3$-4	36	149—151	62,71	5,35	$C_{25}H_{29}O_3ClS_2$	63,02	6,09	1035, 1380	1610	1735
VIII	C_6H_5	55	193—195	46,80	4,43	$C_{48}H_{54}O_4Cl_6PtS_4$	46,83	4,39		1620	1720
IX	$C_6H_4OCH_3$-4	51	161—163	47,00	4,63	$C_{50}H_{58}O_6Cl_6PtS_4$	46,51	4,49	1040, 1285	1610	1720
X	$C_6H_3(OCH_3)_2$-3,4	26	170—171	46,94	4,33	$C_{52}H_{62}O_8Cl_6PtS_4$	46,15	4,44	1035, 1280	1605	1735

TABLE 2. Antiphage Activity of S-(2-Carboxyethyl)-1-mercapto-3,5-diaryl-2-thioniabicyclo[4.4.0]dec-3-ene Chlorides (IV) and (V), and Hexachloroplatinates (VIII-X)

Compound	Concentration, μg/ml			
	1000	100	10	1
	% inactivation of phage			
IV	34/68	31/60	24/38	8/0
V	36/22	31/11	27/8	25/0
VIII	44/36	36/25	36/22	28/11
IX	28/43	25/37	22/32	5/0
X	27/20	15/10	8/0	—

Note. The numerator shows the % inactivation of phage T_6, and the denominator, % phage M_S = 2.

We have tested chlorides (IV) and (V) and hexachloroplatinates (VIII-X) for antimicrobial and antiphage activity.

EXPERIMENTAL CHEMICAL SECTION

IR spectra were obtained on a UR-20 spectrometer (East Germany) in Vaseline oil and hexachlorobutadiene.

The 1-mercapto-3,5-diarylthiabicyclo[4.4.0]dec-3-ene starting materials were obtained as described in [1].

Alkylation of 1-Mercapto-3,5-diphenyl-2-thiabicyclo[4.4.0]dec-3-ene (I) with Acrylic Acid in the Presence of Hydrogen Chloride. 1-Mercapto-S-(2-carboxyethyl)-3,5-diphenyl-2-thioniabicyclo[4.4.0]dec-3-ene Chloride (IV). A mixture of 1 g (0.0029 mole) of (I), 0.7 ml (0.0092 mole) of acrylic acid, and 10 ml of methylene chloride was stirred with continuous passage of dry hydrogen chloride. The reaction was continued until the mercaptosulfide had reacted completely (followed by TLC). The oily product was isolated, dissolved in chloroform, and precipitated with hexane to give 0.34 g (26%), mp 165-167°C.

The alkylation of the hemidithioacetals (II) and (III) with acrylic acid was carried out similarly, but the chloride (VI) could not be isolated in the crystalline state and it was therefore converted into its hexachloroplatinate (X), as shown below.

Alkylation with β-Chloropropionic Acid in the Presence of Silver Nitrate. Chloride (V). To a mixture of 1 g (0.0029 mole) of the hemidithioacetal (I) in 20 ml of ether was added dropwise 0.01 mole of β-chloropropionic acid, followed with vigorous stirring by 0.67 g of silver nitrate. The mixture was stirred at ambient temperature for 48 h, then diluted with 50 ml of ether. The precipitate was filtered off and washed on the filter with hot methylene chloride (3 × 15 ml). Dilution of the filtrate with ether gave the chloride (IV). Yield 0.69 g (52%), mp 165-167°C.

Chloride (V) was obtained similarly from the hemidithioacetal (II). YIeld 70%, mp 149-151°C.

1-Mercapto-S-(2-carboxyethyl)-3,5-diphenyl-2-thioniabicyclo[4.4.0]-dec-3-ene Hexachloroplatinate (VIII). The chloride (IV) (0.18 g, 0.0004 mole) was added to a mixture of 7 ml of acetic acid and 2 ml of acetic anhydride containing 0.34 g (0.0006 mole) of chloroplatinic acid. After 2 days, the reaction mixture was diluted with hexane. The precipitate was isolated, and extracted with hot chloroform. The chloroform extract was evaporated and diluted with hexane to give the crystalline hexachloroplatinate (VIII). Yield 0.32 g (55%), mp 193-195°C.

Hexachloroplatinates (IX) and (X) were obtained similarly.

EXPERIMENTAL BIOLOGICAL SECTION

The antiphage activity of the compounds was determined in phage–bacterium systems comprising DNA-containing phage T_6 and *E. coli* B, and RNA-containing phage M_S-2 and *E. coli* Hfr C. The antiphage effect was measured by comparing the number of "negative" spots with the (untreated) controls using Gracci's agar layer method. The antiphage activity was expressed as a percentage inactivation as given by the formula [6]: $A = (1 - N_0/N_c) \cdot 100\%$, where N_0 is the number of surviving corpuscles in the experiment, and N_c the number of surviving corpuscles in the control.

Antimicrobial activity was determined by twofold serial dilution in Hottinger's bouillon of pH 7.2, with respect to the following test organisms: *Staph. aureus* 209 P., *E. coli* M-17, *Proteus vulgaris* 39, *Ps. aeruginosa* 165, *Candida albicans* 42.

The compounds were dissolved in DMF followed by dilution with sterile distilled water to the required concentration. Salts (IV), (V), and (VIII-X) displayed moderate antimicrobial activity, suppressing the growth of the test organisms in concentrations of 50-100 μg/ml.

Table 2 gives the results of tests for antiphage activity for compounds (IV), (V), and (VIII-X). All these compounds showed high antiphage activity, the most active against the RNA-containing phage being the chloride (IV) ($R = C_6H_5$).

In the hexachloroplatinates, slightly greater activity was shown by the 3,5-diphenyl

compound (VIII); introduction of methoxyl groups into the aromatic substituent at C-5 slightly reduced antiphage activity.

These studies have thus shown that a search for new active antiviral drugs in the S-R-sulfonium salts of bicyclic hemidithioacetals holds promise.

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COMPLEXES OF N,N'-DI-(o-HYDROXYBENZYL)ETHYLENEDIAMINE WITH COPPER COMPOUNDS

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UDC 615.281:[547.415.1:546.56].012.1

We have previously prepared [1] complexes with the compositions $CuCl_2 \cdot 2L$ (I) and $CuCl_2 \cdot CuO \cdot L$ (II) by reacting cupric chloride with the tetradentate ligand NN'-di-(o-hydroxybenzyl)-ethylenediamine (ligand L) in ethanol. These compounds possess high bacteriostatic activity, but they are highly toxic.

It is known [2] that the compositions of complexes with polydentate ligands are dependent upon the anion of the copper salt, the reaction conditions, and the proportions of the components. Continuing these studies, we have examined the reaction of NN'-di-(o-hydroxybenzyl)ethylenediamine with a variety of copper salts. The salts used were the sulfate, nitrate, citrate, undecylenate, lipoate, and hydroxide.

The syntheses were carried out using metal:ligand ratios of 1:1 and 1:2, in alcoholic and aqueous solutions, at room temperature and at the boiling point of the solvent. Complex (V), with the composition $Cu(C_8H_{13}O_2S_2)_2 \cdot 2L$ was obtained by two methods: reaction of copper lipoate with ligand L, and reaction of cupric hydroxide with lipoic acid and the ligand in a ratio of 1:2:2. The identity of the two complexes thus obtained was established by the absence of depression of melting point of a mixed sample, elemental analyses for all elements, and the IR spectra.

The compositions, elemental analyses, and melting points of the complexes are given in Table 1.

In order to establish the mode of coordination of the metal and ligand, the IR spectra of the complexes obtained in the 4000-200 cm^{-1} region were examined. Depending on the salt anion present, three modes of coordination are apparent in the complexes.

1. Coordination occurs through bridging oxygen; both NH groups and both OH groups are involved in coordination. This type of coordination is observed in (III), as in the previously described [1] compound (I). The frequency of the ν_{NH} stretching vibrations in the spectrum of (III) is reduced and split into two (ν_{NH} 3200 and 3240 cm^{-1}) as compared with the spectrum of the ligand (ν_{NH} 3295 cm^{-1}). Weak absorption at 3400 cm^{-1} may be attributed to OH groups. The strong background at 3000-3600 cm^{-1} is due to the presence of water of crystallization.

2. Copper is coordinately bonded to the nitrogen atoms, the OH group in the ring being freed from strong hydrogen bonding such as is present in the free ligand. This mode of coordination is observed in (VII). The IR spectrum of (VII) shows only one strong, narrow

Leningrad Pharmaceutical Chemistry Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 2, pp. 170-173, February, 1983. Original article submitted June 14, 1982.

0091-150X/83/1702-0116$07.50