SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SALTS OF 5-R-3,5-DIARYL-2-THIONIABICYCLO[4.4.0]DECANES

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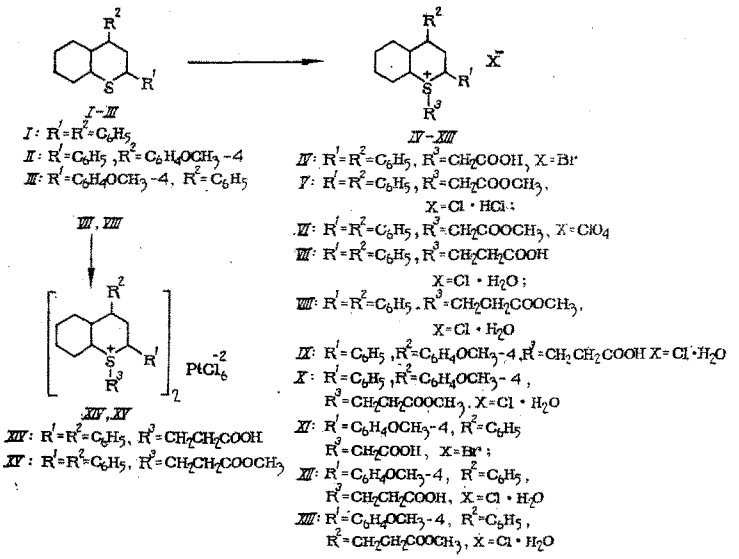
Sulfonium salts play an important part in the biosynthetic processes occurring in the living organism. S-Adenosylmethionine, an S-methyl-sulfonium salt, functions as a methyl group donor in the biosynthesis of choline, sarcosine, anserine, etc. For this reason, it is of interest to examine the biological activity of new types of synthetic sulfones.

The aim of the present study was to synthesize S-R-sulfonium salts of 2-thiabicycloalkanes bearing the residues of lower carboxylic acids on the sulfonium center, and to examine their biological activity.



The starting 3,5-diaryl-2-thioniabicyclo[4.4.0]decanes (I-III) are readily available in quantity by the reaction between 1,3-diaryl-3-(2-oxocyclohexyl)-1-propanones with hydrogen sulfide in trifluoroacetic acid [1] and liquid-phase hydrogenation of the corresponding condensed thiopyrans and dihydrothiopyrans [2].

The synthesis of salts of S-carboxymethyl-, S-methoxycarbonylmethyl-, S-(2-carboxyethyl)-, and S-(20methoxycarbonyl-ethyl)-2-thioniabicyclo[4.4.0]decanes (IV-XV) was effected by alkylating the saturated sulfides (I-III) with such alkylating agents as bromoacetic acid, methyl sulfides (I-III) with such alkylating agents as bromoacetic acid, methyl chloroacetate, acrylic acid, and methyl acrylate, in the presence of hydrogen chloride. Alkylation of (III) with bromoacetic acid to give S-carboxymethyl-3-(4-methoxyphenyl)-5-phenyl-2-thioniabicyclo[4.4.0]-decane bromide (XI) occurred when the reactants were boiled in acetone for 5 h, but S-carboxymethyl-3,5-diphenyl-2-thioniabicyclo[4.4.0]decane bromide (IV) required more vigorous conditions (heating the reagents at 90-100°C in the absence of a solvent).

Reaction of the sulfide (I) with methyl chloroacetate did not occur even at 90-100°C, and only in the presence of silver nitrate was S-methoxycarbonyl-3,5-diphenyl-2-thioniabicyclo[4.4.0]decane chloride hydrochloride (V) obtained. The sulfonium salt was readily converted by perchloric acid in acetic acid to S-methoxycarbonylmethyl-3,5-diphenyl-2-thioniabicyclo[4.4.0]decane perchlorate (VI).

The chlorides of S-(2-carboxyethyl)- and S-(2-methoxycarbonylethyl)-2-thioniabicyclo-[4.4.0]decanes (VII-X, XII, XIII) were obtained by reacting the corresponding saturated sul-

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TABLE 1. Properties of S-R-3,5-Diaryl-2-thioniabicyclo[4.4.0]-decane Salts (IV-XV)

Compound	Yield, %	mp, deg C	Found, %			Molecular formula	Calculated, %		
			C	H	S		C	H	S
IV	72	99—100	61,53	5,66	7,34	$C_{23}H_{27}BrO_2S$	61,93	5,88	7,19
V	61	148—150 (decomp)	63,12	6,62	7,16	$C_{24}H_{30}CL_2OS$	63,49	6,66	7,07
VI	73	167—170 (decomp)	59,56	6,18	6,54	$C_{24}H_{29}CLO_6S$	59,93	6,08	6,67
VII	71	87—89	65,92	7,23	7,56	$C_{24}H_{31}CLO_2S$	66,26	7,18	7,06
VIII	65	106—108 (decomp)	66,57	7,20	7,41	$C_{25}H_{33}CLO_2S$	66,87	6,96	7,14
IX	87	83—87 (decomp)	64,83	7,35	7,12	$C_{25}H_{36}CLO_4S$	64,58	7,24	6,86
X	89	87—89	65,27	7,77	6,68	$C_{26}H_{38}CLO_4S$	65,33	7,38	6,97
XI	80	139—140	60,83	6,12	6,38	$C_{24}H_{29}BrO_3S$	60,55	5,93	6,74
XII	75	85—87	64,43	7,35	7,04	$C_{25}H_{36}CLO_4S$	64,58	7,24	6,86
XIII	67	103—105	64,99	7,54	7,18	$C_{26}H_{36}CLO_4S$	65,33	7,24	6,97
XIV	26	215 (decomp)	48,79	4,94	5,30	$C_{48}H_{58}CL_6O_4PtS_2$	49,24	4,99	5,47
XV	32	159—161 (decomp)	49,54	5,04	4,99	$C_{50}H_{62}CL_6O_4PtS_2$	50,09	5,21	5,35

fides (I-III) with acrylic acid or methyl acrylate at 18-20°C in the presence of hydrogen chloride. Treatment of the chlorides (VII) and (VIII) with chloroplatinic acid in acetic acid gave the hexachloroplatinates (XIV) and (XV).

All the S-R-3,5-diaryl-2-thioniabicyclo[4.4.0]decane salts separated initially from the reaction mixture in the form of oils, which crystallized on adding dry ether or hexane. The sulfonium salts (IV-XV) were identified from their elemental analyses and IR spectra (Table 1).

In comparison with the original sulfides, the IR spectra of the sulfonium salts (IV-XV) show absorption bands due to the carbonyl or ester groups. In the spectra of salts (IV-X) and (XII-XV), there are multiple absorption bands at 1720-1760 cm^{-1}. The position of the C=O band corresponds to the monomeric form of the acid. The bromide (XI) exists as the dimer, the valence vibrations of the carbonyl group appearing as a multiple band at 1705-1690 cm^{-1}, and the hydroxyl group at 2690-2580 cm^{-1}. Identification of ν_{O-H} and ν_{C-O} was complicated in many of the salts by the presence of water in the crystal hydrates, and methoxyl groups in the aryl substituents.

A study of the data presented in Tables 2 and 3 shows that all the test compounds possess moderate antimicrobial and antiphage activity.

Bromides (IV) and (XI), which have an acetic acid grouping at the sulfonium center, are particularly active against *Staph. aureus* and *Candida albicans*. The remaining compounds do not differ significantly in their antimicrobial activity with respect to the structure of the S-R_3 group and the anion (Table 2). The antiphage activity of the chlorides (VII-XIII) and the hexachloroplatinates (XIV) and (XV) against T_6 phage is greater than that of bleomycin and rubomycin, the hexachloroplatinate (XIV) suppressing the T_6 phage activity by 25% at concentrations as low as 10 μg/ml whereas rubomycin was completely inactive at this concentration.

These findings indicate the desirability of seeking new antiviral drugs in the 2-thiabicycloalkane sulfonium salt group.

EXPERIMENTAL CHEMICAL SECTION

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

S-Carboxymethyl-3,5-diphenyl-2-thioniabicyclo[4.4.0]decane Bromide (IV). 3,5-Diphenyl-2-thiabicyclo[4.4.0]decane (I) (0.75 g, 0.0024 mole) and 0.45 g (0.0032 mole) of bromoacetic acid were mixed and heated at 90-100°C for 5 h in the absence of a solvent. The resulting oil was dissolved in 20 ml of methylene chloride, washed with water until neutral, and dried over magnesium sulfate. Partial removal of the methylene chloride under reduced pressure resulted in separation of the bromide (IV). Yield, 0.78 g (72%), mp 99-100°C.

S-Carboxymethyl-3,5-diphenyl-2-thioniabicyclo[4.4.0]decane Chloride Hydrochloride (V). To a solution of 1 g (0.0032 mole) of (I) in 10 ml of methyl chloroacetate was added 0.67 g (0.0032 mole) of finely ground silver nitrate, and the mixture was heated for 2 h at 90-100°C. The mixture was diluted with ether, and the solid was filtered off and washed on the filter

TABLE 2. Antimicrobial Activity of Salts of S-R-3,5-diaryl-2-thioniabicyclo[4.4.0]decane (IV-XV)

Compound	Staph. aureus	E. coli	Proteus vulgaris	Ps. aeruginosa	Candida albicans
	Minimum bacteriostatic concentration, μg/ml				
IV	12	50	100	50	12
V	100	100	100	100	100
VI	50	50	100	100	50
VII	100	50	50	50	50
VIII	100	50	50	50	100
IX	50	50	50	50	50
X	50	50	50	50	50
XI	6	50	100	50	6
XII	100	50	50	50	100
XIII	100	50	50	50	100
XIV	100	100	100	100	100
XV	50	50	100	50	50

TABLE 3. Antiphage Activity of Salts of S-R-3,5-Diaryl-2-thioniabicyclo-[4.4.0]decanes (VII-X, XII-XV)

Compound	% inactivation of T_B phage		% inactivation of M_{S2} phage	
	1000	100	1000	100
	concentration of compound, μg/ml			
VII	61	40	58	10
VIII	58	26	16	7
IX	28	20	13	10
X	10	8	5	0
XII	70	48	23	11
XIII	8	6	22	0
XIV	61	40	58	10
XIV	58	26	16	7
Bleomycin	43	29	91	32
Rubomycin	44	14	30	19

Note: For purposes of comparison, the table gives results for bleomycin and rubomycin.

with methylene chloride followed by hexane to give brown crystals of the chloride hydrochloride (V). Yield, 0.86 g (61%), mp 148-150°C.

S-Methoxycarbonylmethyl-3,5-diphenyl-2-thioniabicyclo[4.4.0]decane Perchlorate (VI). To 0.3 g (0.0007 mole) of the chloride hydrochloride (V) in 3 ml of glacial acetic acid was added 0.04 ml (0.007 mole) of 70% perchloric acid, and the mixture kept for 3 days at room temperature. It was then diluted with ether, when brown crystals of the perchlorate (VI) separated. Yield, 0.25 g (73%), mp 167-170°C.

S-(2-Carboxyethyl)-3,5-diphenyl-2-thioniabicyclo[4.4.0]decane Chloride Hydrate (VII). A solution of 0.5 g (0.0016 mole) of (I) in a mixture of 10 ml of benzene and 4 ml of methylene chloride was saturated for 10-15 min with hydrogen chloride, then 0.14 ml (0.002 mole) of acrylic acid was added and saturation with hydrogen chloride continued for 12 h. The oil which separated was dissolved in methylene chloride, and hexane added to precipitate crystals of the chloride (VII). Yield 0.47 g (71%), mp 87-89°C.

S-(2-Methoxycarbonylethyl)3,5-diphenyl-2-thioniabicyclo[4.4.0]decane Chloride Hydrate (VIII). A solution of 0.5 g (0.0016 mole) of (I) in a mixture of 10 ml of hexane and 4 ml of methylene chloride was saturated for 10-15 min with hydrogen chloride, then 0.17 ml (0.002 mole) of methyl acrylate was added, and saturation with hydrogen chloride continued for 12 h. The oil which separated was dissolved in methylene chloride, and ether added to precipitate crystals of the chloride (VIII). Yield 0.44 g (65%), mp 106-108°C.

S-(2-Carboxyethyl)-3-phenyl-5-(4-methoxyphenyl)-2-thioniabicyclo[4.4.0]decane Chloride Hydrate (IX). From 0.5 g (0.0015 mole) of 3-phenyl-5-(4-methoxyphenyl)-2-thiabicyclo[4.4.0]-decane (II) there was obtained by the method described above 0.52 g (87%) of chloride (IX), mp 83-87°C (decomp.).

S-(2-Methoxycarbonylethyl)-3-phenyl-5-(4-methoxyphenyl-2-thioniabicyclo[4.4.0]decane Chloride Hydrate (X). From 0.5 g (0.0015 mole) of (II) there was obtained by the method described above 0.61 g (89%) of the chloride (X), mp 87-89°C.

S-Carboxymethyl-3-(4-methoxyphenyl)-5-phenyl-2-thioniabicyclo[4.4.0]decane Bromide (XI). A mixture of 0.75 g (0.0022 mole) of 3-(4-methoxyphenyl)-5-phenyl-2-thiabicyclo[4.4.0]decane (III) and 0.36 g (0.0026 mole) of bromoacetic acid in 10 ml of acetone was boiled on the water bath for 5 h. The resulting oily product was dissolved in 20 ml of methylene chloride, washed with water, and dried over magnesium sulfate. After partial removal of the methylene chloride under reduced pressure, addition of hexane precipitated crystals of the bromide (IX). Yield 0.82 g (80%), mp 139-140°C.

S-(2-Carboxyethyl)-3-(4-methoxyphenyl)-5-phenyl-2-thioniabicyclo[4.4.0]decane Chloride Hydrate (XII). From 0.5 g (0.0015 mole) of (III) there was obtained by the method described above 0.45 g (75%) of the chloride (XII), mp 85-87°C.

S-(2-Methoxycarbonylethyl)-3-(4-methoxyphenyl)-5-phenyl-2-thioniabicyclo[4.4.0]decane Chloride Hydrate (XIII). From 0.5 g (0.0015 mole) of (III) there was obtained by the method described above 0.46 g (67%) of the chloride (XIII), mp 103-105°C.

S-(2-Carboxyethyl)-3,5-diphenyl-2-thioniabicyclo[4.4.0]decane Hexachloroplatinate (XIV). The chloride (XII) (0.2 g, 0.047 mmole) was added to a mixture of 2 ml of glacial acetic acid and 0.2 ml of acetic anhydride containing 0.41 g (0.1 mmole) of chloroplatinic acid. After 3 days, the reaction mixture was diluted with ether, and the oil which separated was dissolved in methylene chloride. Addition of hexane precipitated crystals of the salt (XIV). Yield 0.14 g (26%), mp 215°C (decomp.).

S-(2-Methoxycarbonylethyl)-3,5-diphenyl-2-thioniabicyclo[4.4.0]decane Hexachloroplatinate (XV). From 0.2 g of the chloride (XIII) there was obtained as described above 0.17 g (32%) of the hexachloroplatinate (XV), mp 159-161°C (decomp.).

EXPERIMENTAL BIOLOGICAL SECTION

The antiphage activity of the compounds was determined in a phage-bacterium system (DNA-containing phage T_6 and *E. coli*, and RNA-containing phage Ms-2 and *E. coli* HFrl). The number of surviving phage particles was determined by Grazia's agar slope method. Antiphage activity was expressed as percentage inactivation, calculated by the formula [3]: $[1 - (N_o/N_k)] \cdot 100\%$, where N_o is the number of surviving phage particles in the test, and N_k the number of surviving phage particles in the control.

Antimicrobial activity was measured by twofold serial dilution in Hottinger's bouillon of pH 7.2 with respect to the standard test microbes: *Staph. aureus* 209, *E. coli* 675, *Proteus vulgaris* 38, *Ps. aeruginosa* 165, *Candida albicans* 45. All the test compounds were dissolved in DMF followed by dilution with sterile distilled water.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 4-ARYL-1,4-DIHYDROPYRIDINES

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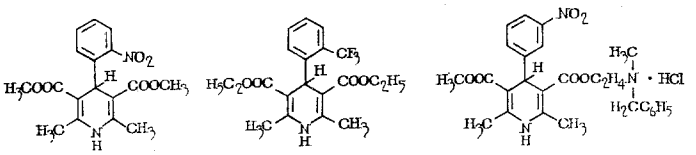
Derivatives of 1,3-dihydropyridine are known [1, 2] to exert a marked action on the cardiovascular system. The most active are the 4-aryl-1,4-dihydropyridines; these include the vasodilator nifedipine (adalat, corinfar)* — 2,6-dimethyl-3,5-dimethoxycarbonyl-4(o-nitrophenyl)-1,4-dihydropyridine [3], and the hypotensive agent SKF 24260 — 2,6-dimethyl-3,5-diethoxycarbonyl-4-(o-trifluoromethylphenyl)-1,4-dihydropyridine [4]. To these nicardipin (perdipin), 4-(3-nitrophenyl)-3-[2-(N-benzyl-N-methylamino)]ethoxycarbonyl-5-methoxycarbonyl-1,4-dihydropyridine, has recently been added [5]. The above compounds have a number of drawbacks: instability (nifedipine), high toxicity, and undesirable side effects.



Nifedipine (Fenigidin) SKF 24260 Nicardipin

*This compound was developed under the name "fenigidin" at the Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, and approved for use.

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