SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF COMPOUNDS WITH TWO THIAZOLIDINE RINGS

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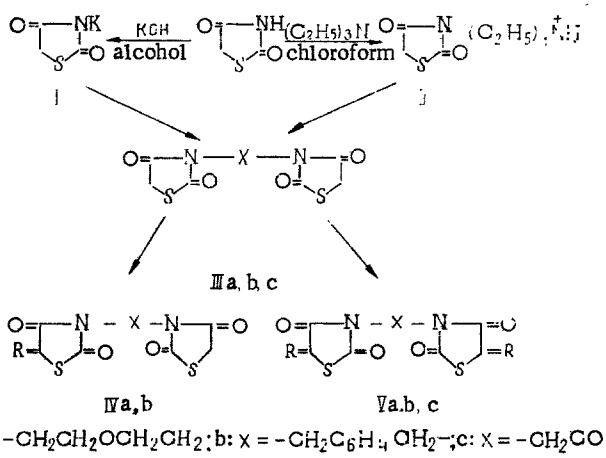
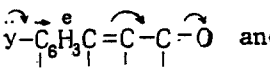
Among thiazolidine derivatives natural and semisynthetic penicillins have marked antibacterial activity [1-3]; several derivatives of 2-thio-4-thiazolidinone and 2,4-thiazolidinedione-2-hydrazone inhibit the growth of *Mycobacterium tuberculosis* [4, 5]. Other thiazolidine derivatives have so far not been systematically screened for antimicrobial activity. Our purpose in the work reported here was to synthesize compounds with two thiazolidine rings joined at positions 3 and 3' by various bridges and to examine their antimicrobial action.

We used the reactions of bis(β-chloroethyl) ether and of p-xylylene chloride with potassium 2,4-thiazolidinedione (I) to synthesize (IIIa) and (IIIb) (method A). We prepared compound (IIIc) by the reaction of sym-dichloroacetone with the triethylammonium salt of 2,4-thiazolidinedione (II) (method B):



a: X = $-CH_2CH_2OCH_2CH_2-$; b: X = $-CH_2C_6H_4CH_2-$; c: X = $-CH_2COCH_2-$

Compounds (III) are susceptible to condensation with aromatic and heterocyclic oxo compounds at position 5. Condensation of (IIIc) in glacial acetic acid in the presence of sodium acetate as catalyst (method C) or in acetic anhydride–acetic acid (method D) gave the 5,5'-diarylidene or 5,5'-diheterylidene derivatives (V). Under the same conditions (IIIa) and (IIIb) formed mainly the 5-monosubstituted derivatives (IV). Equally the condensation of (III) in dioxane in the presence of piperidine (method E) as catalyst yielded mainly the 5,5'-disubstituted derivatives. The properties of the synthetic compounds are summarized in Table 1.

The intense long-wavelength absorption maxima of the 5-unsubstituted thiazolidine derivatives (III) lie at 219-226 nm, whereas those of the products of condensation with oxo compounds, (IV) and (V), appear in the 321-417 nm region. Attachment of electron-donating substituents to the benzylidene residues forms the chromophores  and causes a bathochromic shift of the long-wavelength absorption maxima, whose position depend on the electron-donating ability of the substituents and increase in (V) in the order:

o-F<p-Cl<o-CH_3O<3-CH_3O-2-OH<o-N—C=O<p-$(CH_3)_2N$<p-$(C_2H_5)_2N$.

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TABLE 1. Compounds with Two Thiazolidine Rings

Compound	R	Method of synthesis	Yield, %	Melting point, °C	Long-wavelength λ_{max}, nm	Found, % N	Found, % S	Formula	Calculated, % N	Calculated, % S	Inhibition of microbial growth (dilution)
IIIa		A	30	123—4	219—223	9,0	21,4	$C_{10}H_{12}N_2O_5S_2$	9,2	21,1	—
IVa	C_6H_5CH	C	74	241—2	322—324	7,4	16,0	$C_{17}H_{16}N_2O_5S_2$	7,1	16,0	Staphylococcus aureus 1:2000; E. coli 1:2000; Candida albicans 1:2000
IVa	o-FC_6H_4CH	C	49	228—30	323—326	6,6	15,5	$C_{17}H_{15}FN_2O_5S_2$	6,8	15,6	Staphylococcus aureus 1:8000; E. coli 1:2000; Bac. anthracoides 1:2000
IVa	p-FC_6H_4CH	C	39	254—6	—	7,1	15,5	$C_{17}H_{15}FN_2O_5S_2$	6,8	15,6	Candida albicans 1:2000
IVa	p-ClC_6H_4CH	C	47	114—5	327—328	6,6	14,9	$C_{17}H_{15}ClN_2O_5S_2$	6,6	15,0	E. coli 1:2000
IVa	o-HOC_6H_4CH	C	88	250—1	—	7,0	15,5	$C_{17}H_{16}N_2O_6S_2$	6,9	15,7	Staphylococcus aureus 1:4000; E. coli 1:4000; Bac. anthracoides 1:4000; Candida albicans 1:2000
IVa	o-$CH_3OC_6H_4CH$	C	66	236—7	347—353	6,4	14,9	$C_{18}H_{18}N_2O_6S_2$	6,4	14,9	—
IVa	p-$CH_3OC_6H_4CH$	C	19	205—6	—	6,6	14,9	$C_{18}H_{18}N_2O_6S_2$	6,6	15,2	—
Va	3-CH_3O-4-HOC_6H_3CH	E	49	224—5	358—360	5,2	10,9	$C_{26}H_{24}N_2O_9S_2$	4,9	11,2	Staphylococcus aureus 1:4000; E. coli 1:4000; Candida albicans 1:4000
Va	m-$O_2NC_6H_4CH$	C	71	205	317—320	10,1	11,3	$C_{24}H_{18}N_4O_9S_2$	9,8	11,2	Staphylococcus aureus 1:16 000; E. coli 1:4000; Bac. anthracoides 1:2000; Candida albicans 1:2000
Va	$C_6H_5CH=CH—CH$	C	38	226—7	351—356	5,3	12,2	$C_{28}H_{24}N_2O_5S_2$	5,3	12,0	—
IVa	1-acetyl-3-isatinylidene	C	34	260 (decomp.)	364—365	9,0	13,3	$C_{20}H_{17}N_3O_7S_2$	8,8	13,5	Staphylococcus aureus 1:500 000; E. coli 1:4000; Bac. anthracoides 1:4000; Candida albicans 1:2000
Va	2-furfurylidene	E	70	222—3	344—345	6,4	14,1	$C_{20}H_{16}N_2O_7S_2$	6,1	13,9	Staphylococcus aureus 1:4000; B. coli 1:4000; Candida albicans 1:4000

TABLE 1 (Continued)

Compound	R	Method of synthesis	Yield, %	Melting point, °C	Long-wavelength λ_{max}, nm	Found, %		Formula	Calculated, %		Inhibition of microbial growth (dilution)
						N	S		N	S	
IIIc		B	53	234	222—225	9,8	22,4	$C_9H_8N_2O_5S_2$	9,7	22,2	—
Vc	o-$OCHC_6H_4CH$	C	26	180	327—[illegible]	5,1	12,6	$C_{25}H_{16}N_2O_7S_2$	5,4	12,6	—
Vc	C_6H_5CH	E	17	240	322—[illegible]	6,3	14,2	$C_{23}H_{16}N_2O_5S_2$	6,0	13,8	—
Vc	2-furfurylidene	C	65	254	348—[illegible]	6,4	14,6	$C_{19}H_{12}N_2O_7S_2$	6,3	14,6	—
IIIb		A	100	226—8	322—329	8,4	19,0	$C_{24}H_{12}N_2O_4S_2$	8,3	19,0	—
Vb	C_6H_5CH	E	31	263—4	318—[illegible]	5,5	12,6	$C_{28}H_{20}N_2O_4S_2$	5,5	12,5	Staphylococcus aureus 1:2000; Candida albicans 1:2000
Vb	o-FC_6H_4CH	E	[illegible]	210—1	319—321	5,0	11,6	$C_{28}H_{18}F_2N_2O_4S_2$	5,1	11,7	—
Vb	p-FC_6H_4CH	E	[illegible]	[illegible]—40	319—321	5,0	11,9	$C_{28}H_{18}F_2N_2O_4S_2$	5,1	11,7	—
Vb	p-ClC_6H_4CH	E	[illegible]	[illegible]—6	323—324	5,0	10,9	$C_{28}H_{18}Cl_2N_2O_4S_2$	4,8	11,0	—
IVb	o-HOC_6H_4CH	I	[illegible]	[illegible]—91	341—345	6,4	14,9	$C_{21}H_{16}N_2O_5S_2$	6,3	14,6	—
Vb	o-HOC_6H_4CH	E	[illegible]	[illegible]—2	343—345	4,9	11,9	$C_{28}H_{20}N_2O_6S_2$	5,1	11,8	—
Vb	o-$CH_3OC_6H_4CH$	E	[illegible]	[illegible]—61	343	4,7	11,0	$C_{30}H_{24}N_2O_6S_2$	4,9	11,2	—
Vb	p-$CH_3OC_6H_4CH$	E	[illegible]	[illegible]—8	337—338	4,6	11,0	$C_{30}H_{24}N_2O_6S_2$	4,9	11,2	Staphylococcus aureus 1:4000
Vb	3-CH_3O-4-HOC_6H_3CH	E	60	176—8	347—350	4,8	10,5	$C_{30}H_{24}N_2O_8S_2$	4,6	10,6	—
Vb	2,5-Br_2-6-HOC_6H_2CH	E	40	334—5	342—349	3,6	7,7	$C_{28}H_{16}Br_4N_2O_6S_2$	3,3	7,5	Staphylococcus aureus 1:4000; Candida albicans 1:4000
Vb	p-$(CH_3)_2CHC_6H_4CH$	E	27	219—20	323—326	4,9	10,7	$C_{34}H_{32}N_2O_4S_2$	4,7	10,8	E. coli 1:4000; Candida albicans 1:4000
IVb	p-$(CH_3)_2NC_6H_4CH$	C	51	228—30	390—392	8,8	13,0	$C_{23}H_{21}N_3O_4S_2$	9,0	13,0	—
Vb	p-$(CH_3)_2NC_6H_4CH$	E	27	310—11	392	9,1	10,7	$C_{32}H_{30}N_4O_4S_2$	9,4	10,7	—
Vb	p-$(C_2H_5)_2NC_6H_4CH$	E	25	269—70	397—400	8,3	9,8	$C_{36}H_{38}N_4O_4S_2$	8,6	9,8	Candida albicans 1:2000
Vb	m-$O_2C_6H_4CH$	E	39	291—2	313—315	9,5	10,8	$C_{28}H_{18}N_4O_8S_2$	9,3	10,6	—
Vb	$C_6H_5CH=CHCH$	E	35	298—9	346—348	4,7	11,4	$C_{32}H_{24}N_2O_4S_2$	5,0	11,4	—
IVb	3-isatinylidene	C	78	299—01	361—367	8,8	13,5	$C_{22}H_{15}N_3O_5S_2$	9,0	13,8	—
IVb	1-methyl-3-isatinylidene	C	17	190—92	355—357	8,6	13,3	$C_{23}H_{17}N_3O_5S_2$	8,8	13,4	—
IVb	1-Acetyl-3-isatinylidene	D	30	326—8	364—365	8,4	9,5	$C_{34}H_{22}N_4O_6S_2$	8,3	9,5	Staphylococcus aureus 1:4000; E. coli 1:4000; Candida albicans 1:4000
Vb	2-furfurylidene	E	24	230—32	339	5,9	13,0	$C_{24}H_{16}N_2O_6S_2$	5,7	13,0	—
IVb	5-nitro-2-furfurylidene	E	16	205—6	367—370	9,3	14,1	$C_{19}H_{13}N_3O_7S_2$	9,2	14,0	Staphylococcus aureus 1:32 000; E. coli 1:2000; Bac. anthracoides 1:2000; Candida albicans 1:[illegible] 000

In energy units the bathochromic shifts range from 2 (for the o-F substituent) to 81 kJ/mole [for the $p(CH_3)_2N$ substituent in (I)].

We assayed all the synthetic compounds for antimicrobial activity toward *Staphylococcus aureus* 209-P, *Streptococcus pyogenes* 295, *Escherichia coli*, *Salmonella typhi* 4446, *Shigella flexneri* 167e, *Bacillus diphtheriae* pv. 8, *Pseudomonas aeruginosa* 165, *Proteus vulgaris*, *Bacillus anthracoides*, *Mycobacterium tuberculosis*, *typus humanus* H_{37} Rv, *M. tuberculosis typus aviumi* *M.* B_5(saprophyte), *Microsporon lanosum*, *Trichophyton gypseum*, *Actinomyces albus*, and *Candida albicans*. Of the 39 thiazolidine derivatives, 15 inhibited the growth of *C. albicans*, 12 that of *S. aureus*, 11 that of *E. coli*, and 5 that of *B. anthracoides* in dilution of $\geqslant$ 1:2000. The preparations did not affect the other species. The majority of active compounds (69%) were derivatives of β,β'-bis(2,4-dioxo-3-thiazolidinyl)diethyl ether (X = $CH_2CH_2OCH_2CH_2$).

The antimicrobial activity of these compounds is undoubtedly due to the presence of the relevant active groupings. Compounds (III), which are unsubstituted at position 5, do not inhibit the growth of bacteria at concentrations $\geqslant$ 1:2000, but attachment of a benzylidene or furfurylidene residue at position 5 enhances the antimicrobial activity. Substituents that enhance the antimicrobial activity even more include o-acetylamino (in the 1-acetylisatin residue), p-isopropyl and 2,5-dibromo-6-hydroxyl in the benzylidene residue, and nitro in the benzylidene and furfurylidene residues.

The 2,4-thiazolidinedione residue may well possess antimetabolic action as regards thiamine (biochemical imitiation of the thiazole ring) and riboflavin (biochemical imitation of the O=CNC=O group, which is present in the test compounds and in riboflavin). The substituents in position 5 modify the lipophilicity of compounds (III) and increase their ability to penetrate the microbial membranes.

We can recommend for further pharmacological study 5-mono-(1-acetylisatinylidene)-β,β'-bis(2,4-dioxo-3-thiazolidinyl)diethyl ether, which inhibits the growth of *S. aureus* in a dilution of 1:500,000, and 5-mono-(5-nitrofurfurylidene)-ω,ω'-bis(2,4-dioxo-3-thiazolidinyl)-p-xylene, which inhibits the growth of *C. albicans* in a dilution of 1:256,000.

EXPERIMENTAL CHEMICAL PART

β,β'-Bis(2,4-dioxo-3-thiazolidinyl)diethyl ether (IIIa). Method A. To a solution of (I) (0.14-0.20 mole) in DMF (200 ml) was added bis(β-chloroethyl) ether or xylylene chloride (0.07-0.1 mole). The mixture was heated at 140°C for 10-30 min. Potassium chloride was filtered off. The precipitated (IIIa) was separated from the cooled filtrate and recrystallized from xylene. The filtrate was evaporated to dryness and the residue was recrystallized from benzene. Compound (IIIb) was prepared under equivalent conditions, precipitating on cooling of the filtrate alone.

sym-Bis(2,4-dioxo-3-thiazolidinyl)acetone (IIIc). Method B. To a suspension of 2,4-thiazolidinedione (0.1 mole) in chloroform (200 ml) was added first triethylamine (0.1 mole) and then sym-dichloroacetone (0.05 mole). The mixture was warmed at 35°C for 2.5 h and then cooled; (IIIc) was filtered off and recrystallized from dilute acetic acid (2:1).

Products of Condensation of (III) with Oxo Compounds. Method C. Compound (III) (5 mmole), the oxo compound (15 mmole), and sodium acetate (15 mmole) were refluxed for 3-9 h in glacial acetic acid (20 ml). The precipitate was filtered off and recrystallized from dioxane, xylene, acetic acid, or DMF. If the condensation product did not precipitate, the reaction mixture was evaporated to dryness; the residue was washed with water and recrystallized.

Method E. Compound (III) (5 mmole) and the oxo compound (15 mmole) were refluxed for 0.5-7.5 h in dioxane (10 ml) with added piperidine (4 drops). Treatment then followed method C.

Method D. Compound (IIIb) (2.5 mmole), isatin or its 1-substituted derivative (7.5 mmole), acetic anhydride (5 ml), acetic acid (10 ml), and sodium acetate (0.5 g) were refluxed for 1 h; the precipitated (Vb) was filtered off and recrystallized from DMF.

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