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SYNTHESIS AND BIOLOGICAL PROPERTIES OF YLIDENE DERIVATIVES OF THIAZOL[3,2-a]IMIDAZOL-6-ONE

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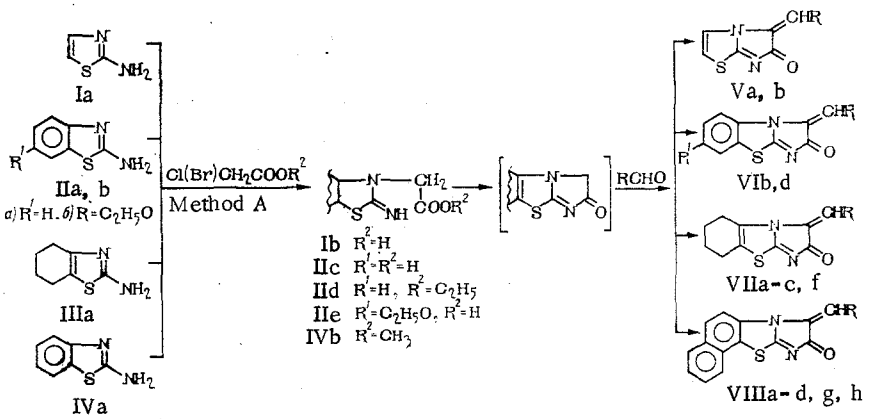
It is known that 2-aminothiazole (Ia), 2-aminobenzothiazole, and its 6-substituted derivatives (IIa-b) react with haloacetic acids and their esters via the ring nitrogen atom to form the corresponding 3-carboxymethyl-2-iminothiazolines or -benzothiazolines (Ib, IIc-e) [1-3]. Cyclization of 3-carboxymethyl-2-iminothiazoline with acetic anhydride in benzene gives a compound which has been assigned the structure of 5,6-dihydro-5,5-diacetylimidazo-[2,1-b]thiazol-6-one [4], whereas 3-carboxymethyl-2-iminobenzothiazoline under similar conditions gives benzothiazolo[3,2-a]imidazol-2-one [5].

Bearing in mind the ambiguity in the path taken by the dehydration of 3-carboxymethyl-2-iminothiazolines (Ib, IIc-e), we have studied the reaction of 3-carboxymethyl-2-iminothiazoline (Ib) with aromatic aldehydes with the object of synthesizing ylidene derivatives of thiazolo[3,2-a]imidazol-6-one and investigating their biological properties. It was established that this reaction proceeds readily in glacial acetic acid in the presence of anhydrous sodium acetate and results in the formation of ylidene derivatives of thiazolo-[3,2-a]imidazol-6-one (Va-b). It was found that this reaction is quite general, and that reaction of 3-carboxymethyl- (IIc), 3-ethoxycarbonylmethyl- (IId), and 3-carboxymethyl-6-ethoxy-2-iminobenzothiazoline (IIe), 3-ethoxycarboylmethyl-4,5,6,7-tetrahydro-2-imino-benzothiazoline (IIIb), and 3-methoxycarbonylmethyl-2-iminonaphtho[1,2-d]thiazoline (IVb) with aromatic and heterocyclic aldehydes results in the formation of ylidene derivatives of benzothiazolo[3,2-a]imidazol-2-one (VIb-d), 5,6,7,8-tetrahydrobenzothiazolo[3,2-a]imidazol-2-one (VIIa-c, f), and naphtho[1,2-d]thiazolo[3,2-a]imidazol-2-one (VIIIa-d, g,h), respectively.



Moreover, the process can be simplified by reacting together the 2-aminothiazole, the haloacetic acid or ester, and the aldehyde. In this way we synthesized VIa, d-f, VIId-e and VIIIe-f, i from IIa, b, IIIa, and IVa. Obviously, the first step in this process is the

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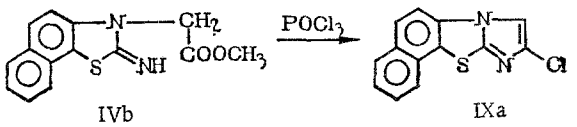
formation of compounds Ib, IIc-e, IIIb, and IVb, which are then cyclized to form thiazole-[3,2-a]imidazol-6-one derivatives, and the latter react with the aldehydes via their active methylene group.

By analogy with the synthesis of 2-chloroimidazo[2,1-b]thiazole [4], 2-chloronaphtho-[1,2-d]thiazolo[3,2-a]imidazole (IXa) was prepared by saponifying IVb in concentrated hydrochloric acid and treating the intermediate 3-carboxymethyl-2-iminonaphtho[1,2-d]thiazoline with phosphorus oxychloride.



IVb IXa

The structure of the synthesized compounds was confirmed by their elementary analysis data and IR spectra, in which CO stretching bands are observed in the 1670- to 1732-cm^{-1} region.

We studied the antibacterial, antifungal, antiviral, and neurotropic action of compounds Va, b, VIa-f, VIIa-f, VIIIa-i, and IXa* on the respiratory system, brain tissue, and liver. We discovered that compound Va has high antiviral activity against adenovirus type 23, whereas VIa, e, VIId, and VIIIe, which also contain a p-nitrobenzaldehyde residue, do not display antiviral activity. Compounds VIa and VIIIa showed moderate activity, and Vb, VIId, VIIIg, and IXa showed weak activity, against Gram-positive bacteria and pathogenic fungi. The other compounds proved to be inactive.

EXPERIMENTAL

The IR spectra were recorded with a UR-10 spectrophotometer (suspensions in mineral oil).

Compounds Ib [1], IIc [3], and IId, e [2] were prepared by known methods.

Hydrochloride of 3-Ethoxycarbonylmethyl-4,5,6,7-tetrahydro-2-iminobenzothiazoline (IIIb). A mixture of 15.4 g (0.1 mole) of 2-amino-4,5,6,7-tetrahydrobenzothiazole and 12.2 g (0.1 mole) ethyl chloroacetate in 30 ml ethanol was boiled for 16 h. The solvent was distilled off, the residue treated with a mixture of 20 ml acetone and 50 ml ether, and the precipitate filtered off and washed with ether to give 18.1 g (69%) of (IIIb)·HCl, mp 208-209°C (from acetone–water, 50:1). Found, %: C 47.4; H 5.9; Cl 12.9; N 9.9; S 11.8. $C_{11}H_{16}N_2O_2S\cdot HCl$. Calculated, %: C 47.7; H 6.2; Cl 12.8; N 10.1; S 11.6.

3-Methoxycarbonylmethyl-2-iminonaphtho[1,2-d]thiazoline (IVb). A mixture of 4 g (0.02 mole) of IVa and 3.1 g (0.02 mole) of methyl bromoacetate in 20 ml methanol was boiled for 15 h, cooled, poured into water, neutralized with a solution of sodium bicarbonate, and the precipitate filtered off to give 5.1 g (94%) of IVb, mp 162-163°C (from ethanol). Found, %: C 61.4; H 4.3; N 10.2; S 12.0. $C_{14}H_{12}N_2O_2$. Calculated, %: C 61.7; H 4.4; N 10.3; S 11.8.

Ylidene Derivatives of Thiazolo[3,2-a]imidazol-6-one (Va, b). A solution of 1.58 g (0.01 mole) of Ib in 10 ml of a mixture of acetic acid and acetic anhydride (1:1) was treated with 0.82 g (0.01 mole) of anhydrous sodium acetate and 0.01 mole of the corresponding aldehyde. The mixture was boiled for 30 min, cooled, poured into water, and the precipitate filtered off. The constants and elementary analyses of the products are given in Table 1.

Ylidene Derivatives of Benzothiazolo[3,2-a]imidazol-2-one (VIa-f), 5,6,7,8-Tetrahydrobenzothiazolo[3,2-a]imidazol-2-one (VIIa-f), and Naphtho[1,2-d]thiazolo[3,2-a]imidazol-2-one (VIIIa-i). Method A. A mixture of 0.01 mole of IIc-e, IIIb or IVb, 1.64 g (0.02 mole) of anhydrous sodium acetate and 0.01 mole of the corresponding aldehyde in 30-40 ml of glacial acetic acid was boiled for 1-2 h, cooled, poured into water, and the precipitate filtered off to give compounds VIb-d, VIIa-c, f and VIIIa-d, g-h.

Method B. A solution of 1.5 g (0.01 mole) of IIa in 15 ml of glacial acetic acid was

*These investigations were carried out at the Scientific-Research Institute for the Biological Testing of Chemical Compounds (Moscow District).

TABLE 1. Ylidene Derivatives of Thiazolo[3,2-a]imidazol-6-one (Va, b), Benzothiazolo[3,2-a]imidazol-2-one (VIa-f), 5,6,7,8-Tetrahydrobenzothiazolo[3,2-a]imidazol-2-one (VIIa-f), and Naphtho[1,2-d]-thiazolo[3,2-a]imidazol-2-one (VIIIa-i)

Compound	R	R'	Yield, %	Melting point, deg*	Found, %				Empirical formula	Calculated, %				IR spectrum, ν_{CO}, cm^{-1}
					C	H	N	S		C	H	N	S	
Va	4-$O_2NC_6H_4$	—	80	276—7	53,0	2,8	15,6	11,9	$C_{12}H_7N_3O_3S$	52,7	2,6	15,4	11,7	1680
Vb	3-$O_2NC_6H_4$	—	77	254—6	52,7	2,6	15,2	11,9	$C_{12}H_7N_3O_3S$	52,7	2,6	15,4	11,7	1695
VIa	4-$O_2NC_6H_4$	H	43	279—80	59,2	3,0	13,4	9,6	$C_{16}H_9N_3O_3S$	59,4	2,8	13,0	9,9	1720
VIb	4-$O_2NC_6H_4$	H	58	290—1	59,1	2,6	13,2	10,2	$C_{16}H_9N_3O_3S$	59,4	2,8	13,0	9,9	1720
VIc	5-Nitro-2-furfurylidene	H	80	>360	53,6	2,4	13,1	10,2	$C_{14}H_7N_3O_4S$	53,7	2,2	13,4	10,2	1720
VId	4-HOC_6H_4	C_2H_5O	89	250—2	63,7	4,2	8,7	9,8	$C_{18}H_{14}N_2O_2S$	63,9	4,2	8,3	9,5	1670
VIe	4-$O_2NC_6H_4$	C_2H_5O	43	280—1	58,9	3,9	11,8	8,8	$C_{18}H_{13}N_3O_4S$	58,8	3,6	11,4	8,7	1710
VIf	3-$O_2NC_6H_4$	C_2H_5O	71	234—5	58,7	3,3	11,1	8,9	$C_{18}H_{13}N_3O_4S$	58,8	3,6	11,4	8,7	1703
VIIa	C_6H_5	—	70	215—6	67,6	4,8	9,9	11,1	$C_{16}H_{14}N_2OS$	68,0	5,0	9,9	11,3	1690
VIIb	4-HOC_6H_4	—	34	269—70	64,4	4,9	9,4	10,9	$C_{16}H_{14}N_2O_2S$	64,4	4,7	9,4	10,7	1680
VIIc	2-$CH_3OC_6H_4$	—	64	175—7	65,2	5,0	9,0	10,2	$C_{17}H_{16}N_2O_2S$	65,4	5,2	9,0	10,3	1690
VIId	4-$O_2NC_6H_4$	—	42	256—7	59,2	4,0	12,8	9,9	$C_{16}H_{13}N_3O_3S$	58,7	4,0	12,8	9,8	1690
VIIe	3-$O_2NC_6H_4$	—	55	235—6	59,0	4,1	12,7	10,0	$C_{16}H_{13}N_3O_3S$	58,7	4,0	12,8	9,8	1692
VIIf	2-HO-5-BrC_6H_3	—	75	278—9	50,6	3,6	7,4	8,7	$C_{16}H_{13}BrN_2O_2S$	50,9	3,5	7,4	8,5	1690
VIIIa	C_6H_5	—	91	247—8	72,8	3,6	8,7	9,8	$C_{20}H_{12}N_2OS$	73,1	3,7	8,5	9,8	1702
VIIIb	4-HOC_6H_4	—	72	297—8	69,2	3,8	7,8	8,8	$C_{20}H_{12}N_2O_2S$	69,7	3,5	8,1	9,3	1679
VIIIc	2-$CH_3OC_6H_4$	—	95	260—2	70,4	4,4	7,8	9,0	$C_{21}H_{14}N_2O_2S$	70,4	3,9	7,8	8,9	1714
VIIId	4-i-PrC_6H_4	—	92	227—8	74,5	4,9	7,5	8,7	$C_{23}H_{18}N_2OS$	74,6	4,9	7,6	8,6	1698
VIIIe	4-$O_2NC_6H_4$	—	49	284—5	64,1	3,0	11,3	8,6	$C_{20}H_{11}N_3O_3S$	64,3	3,0	11,2	8,6	1710
VIIIf	3-$O_2NC_6H_4$	—	47	324—6	64,4	3,0	11,1	8,7	$C_{20}H_{11}N_3O_3S$	64,3	3,0	11,2	8,6	1714
VIIIg	2-Furfurylidene	—	91	260—2	67,8	3,3	9,1	9,7	$C_{18}H_{10}N_2O_2S$	67,9	3,2	8,8	10,1	1708
VIIIh	5-Nitro-2-furfurylidene	—	87	303—5	59,8	3,0	11,3	8,9	$C_{18}H_9N_3O_4S$	59,5	2,5	11,6	8,8	1725
VIIIi	1-(4-Nitrophenyl)-2-pyrrolyl	—	78	310—2	65,3	3,3	12,6	7,7	$C_{24}H_{14}N_4O_3S$	65,7	3,2	12,8	7,3	1732

*Compounds Va-b, VIa-e, VIIb, f, and VIIIa-c, e, f, i were crystallized from dimethylformamide, VIIa, d, e, and VIIId from ethanol–dimethylformamide (1:1), VIIIg-h from dioxane–dimethylformamide (2:1), VIIc from water–dioxane (1:2), and VIf from acetic acid.

treated with 1.67 g (0.01 mole) of ethyl bromoacetate, 1.64 g (0.02 mole) of anhydrous sodium acetate and 1.51 g (0.01 mole) of p-nitrobenzaldehyde. The mixture was boiled for 2 h, cooled, poured into water, and the precipitated VIa filtered off. Under analogous conditions, VIe-f and VIId-e were prepared from IIb and IIIa, and VIIIe-f were prepared from IVa, the only difference being that the reaction mixture was heated at 80° (in bath) for 6 h and then boiled for 30 min.

2-Chloronaphtho[1,2-d]thiazolo[3,2-a]imidazole (IXa). Concentrated hydrochloric acid (10 ml) was added to 2.72 g (0.01 mole of IVb. The mixture was boiled for 2 h, cooled, poured into water, neutralized with ammonia solution to pH 7.0, and the precipitate filtered off, washed with water, and dried. The product was treated with 15 ml of phosphorus oxychloride, boiled for 1 h the phosphorus oxychloride distilled off *in vacuo*, and the residue decomposed with ice-water, neutralized with ammonia solution, and the precipitate filtered off to give 2.4 g (93%) of IXa, mp 223-225°C (from ethanol–dimethylformamide, 1:1). Found, %: C 60.2; H 2.6; Cl 13.5; N 10.7; S 12.5. $C_{13}H_7ClN_2S$. Calculated, %: C 60.3; H 2.7; Cl 13.7; N 10.8; S 12.4.

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ESTERS OF 2,3-BIS(HYDROXYMETHYL)QUINOXALINE 1,4-DI-N-OXIDE AND THEIR BIOLOGICAL ACTION

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E. N. Padeiskaya, and G. Ya. Shvarts

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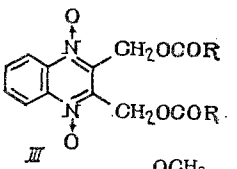
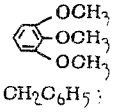
Dioxidine, i.e., 2,3-bis(hydroxymethyl)quinoxaline 1,4-di-N-oxide (I), possesses high antibacterial activity and is used for the treatment of acute bacterial infections [1].

It has been shown that the bisacetyl derivative of I, i.e., 2,3-bis(acetoxymethyl)-quinoxaline 1,4-di-N-oxide (quinoxidine, II), also has high antibacterial activity [2]. Quinoxidine (II) is indicated for the oral treatment of acute bacterial infections, in contrast to dioxidine, which is used in the form of solutions for intravenous, intraperitoneal, and topical administration. It has been postulated that II, whose acetyl groups are easily hydrolyzed, is converted into I in the organism and that I is the primary active principal. This hypothesis is supported by investigations which show that only I is found in the urine of animals treated with quinoxidine [3].

We were interested in finding out how the introduction of different acyl residues into the dioxidine molecule would affect its antibacterial activity and the characteristics of its biological action. With this object in mind, we have synthesized dioxidine esters of general formula IIIa-i.



III

a) R = *i*-C_4H_9; b) R = C_6H_{13}; c) R = C_8H_{17}; d) R =  ; e) R = $CH_2C_6H_5$; f) R = CH_2Cl; g) R = $CHCl_2$; h) R = $NHCH_3$; i) R = NHC_6H_5

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