BARBITURIC ANALOGS OF SALAZOSULFANYLAMIDES

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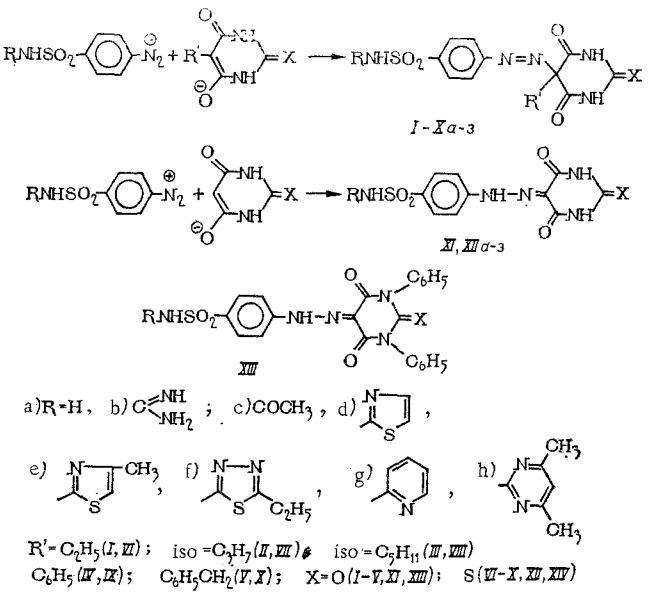
In evaluating the dependence of properties of barbiturates and thiobarbiturates on their structure the introduction into position 5 of the heterocycle of biologically active p-sulfamidophenylazo groups and the preparation in this way of the earlier unknown 5-alkyl(aryl)-5-p-sulfamidophenylazobarbituric acids and their 2-thio analogs (I-X) was of interest. These compounds can also be regarded as unique barbituric analogs of salazosulfanylamides [1-7], used successfully recently in the medical treatment of nonspecific ulcerous colitis. As such analogs it was also expedient to obtain products of azo coupling of the diazotized sulfanylamides with barbituric and 2-thiobarbituric acids (XI, XII).

The synthesis of compounds (I-XII) was achieved by azo coupling of diazotized sulfanylamides with unsubstituted or 5-alkyl(aryl)-substituted barbituric and 2-thiobarbituric acids.



The reaction was carried out in basic medium with equimolecular amounts of reacting materials and led in all cases, independently of the character of R,R', and X, to almost quantitative yield of azo coupling products (Tables 1, 2).

The synthesized preparations, among them derivatives obtained earlier [8] of 1,3-diphenylbarbituric and 1,3-diphenyl-2-thiobarbituric acids (XII, XIV), were examined for antibacterial activity. It was found that the majority of preparations (36 compounds, Table 3) possess antibacterial activity against 1-3 strains of microorganisms in a dilution of $1:(1\cdot10^{-4}-2\cdot10^{-4})$. It is interesting to note that azo derivatives are mainly active against St. aureus and E. coli, while there are materials among the hydrazones also acting on other forms, in particular, on Salmonella typhi abdominalis 69 and Shigella dysenterige Flexneri "C".

Sharp differences in effect were not established for derivatives of 2-thio analogs and barbiturates, 1,3-unsubstituted, and 1,3-diphenyl-substituted derivatives, or also for compounds distinguished by sub-

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TABLE 1. Derivatives of 5-Alkyl(aryl)-Substituted Barbituric and 2-Thiobarbituric Acids

Compound	Yield, %	Mp (deg C)	Found, %		Empirical formula	Calc., %	
			N	S		N	S
Ia	88	128—30[C]	26,23	10,05	$C_{12}H_{13}N_5O_5S$	26,37	9,44
IIa	91	225—6[E]	19,78	9,10	$C_{13}H_{15}N_5O_5S$	19,81	9,08
IIIa	87	160—1[C]	17,96	8,41	$C_{15}H_{13}N_5O_5S$	18,10	8,40
IVa	87	186—7[C]	18,10	8,58	$C_{16}H_{13}N_5O_5S$	18,07	8,27
Va	87	158—9[A]	17,73	7,96	$C_{17}H_{15}N_5O_5S$	17,69	7,98
VIa	86	120—2[C]	19,95	18,46	$C_{12}H_{13}N_5O_4S_2$	19,98	18,04
VIIa	86	123[A]	18,73	17,46	$C_{13}H_{15}N_5O_4S_2$	18,95	17,35
VIIIa	90	142—3[C]	17,56	16,01	$C_{15}H_{19}N_5O_4S_2$	17,61	16,13
IXa	87	178—9[C]	17,26	15,73	$C_{16}H_{13}N_5O_4S_2$	17,35	15,89
Xa	88	120—2[C]	16,62	15,32	$C_{17}H_{15}W_5O_4S_2$	16,77	15,36
Ib	79	168—9[D]	25,59	8,30	$C_{13}H_{15}N_7O_5S$	25,71	8,40
IIb	87	166—7[B]	24,91	8,13	$C_{14}H_{17}N_7O_5S$	24,79	8,10
VIb	90	200—2[C]	24,53	16,25	$C_{13}H_{15}N_7O_4S_2$	24,66	16,13
VIIb	86	144[A]	23,75	15,64	$C_{14}H_{17}N_7O_4S_2$	23,62	15,58
Ic	91	179—80[C]	18,47	8,07	$C_{14}H_5N_5O_6S$	18,41	8,42
IIc	90	185—6[D]	18,15	8,25	$C_{15}H_{17}N_5O_6S$	17,75	8,12
VIc	93	235—6[C]	17,53	16,38	$C_{14}H_{15}N_5O_5S_2$	17,66	16,17
VIIc	88	116[A]	16,97	15,65	$C_{15}H_{17}N_5O_5S_2$	17,06	15,62
Id	90	218—20[A]	19,63	15,35	$C_{15}H_{14}N_6O_5S_2$	19,89	15,18
IId	86	190—2[A]	19,13	14,75	$C_{16}H_{16}N_6O_5S_2$	19,25	14,69
Vd	88	175—6[E]	17,40	13,16	$C_{20}H_{16}N_6O_5S_2$	17,34	13,23
VId	91	213—4[C]	18,96	22,02	$C_{15}H_{14}N_6O_4S_3$	19,16	21,93
VIId	93	194—5[A]	17,47	21,86	$C_{16}H_{16}N_6O_4S_3$	18,57	21,25
Ie	88	212—3[A]	19,32	14,58	$C_{16}H_{16}N_6O_5S_2$	19,25	14,69
IIe	89	240—1[A]	18,69	14,30	$C_{17}H_{18}N_6O_5S_2$	18,65	14,23
Ve	86	250—1[E]	16,49	12,81	$C_{21}H_{18}N_6O_5S_2$	16,85	12,86
VIe	89	210[C]	18,36	21,10	$C_{16}H_{16}N_6O_4S_3$	18,57	21,25
VIIe	93	194—5[A]	17,86	21,08	$C_{17}H_{18}N_6O_4S_3$	18,01	20,62
If	89	105—6[A]	21,63	14,26	$C_{16}H_{17}N_7O_5S_2$	21,71	14,20
IIf	91	148—150[E]	21,20	14,00	$C_{17}H_{19}N_7O_5S_2$	21,27	13,77
Vf	88	156—7[E]	19,06	12,42	$C_{21}H_{19}N_7O_5S_2$	19,09	12,48
VIf	85	206—7[C]	18,10	20,45	$C_{16}H_{17}N_7O_4S_3$	18 04	20,57
VIIf	89	88[A]	20,38	20,03	$C_{17}H_{19}N_7O_4S_3$	20.35	19,97
Ig	86	214—5[C]	19,86	7,63	$C_{17}H_{16}N_6O_5S$	20,13	7,68
IIg	88	193—4[A]	19,43	7,49	$C_{18}H_{18}N_6O_5S$	19,47	7,43
Vg	93	152—3[E]	17,53	6,78	$C_{22}H_{18}N_6O_5S$	17,52	6,68
VIg	93	155—6[B]	18,23	15,01	$C_{17}H_{16}N_6O_4S_2$	18,38	14,79
VIIg	91	169—70[A]	18,57	14,35	$C_{18}H_{18}N_6O_4S_2$	18,77	14,33
Ih	88	195—6[B]	21,87	7,62	$C_{18}H_{19}N_7O_5S$	22,01	7,19
IIh	89	178—80[A]	21,22	6,77	$C_{19}H_{21}N_7O_5S$	21,33	6,97
Vh	90	202—3[E]	19,45	6,53	$C_{23}H_{21}N_7O_5S$	19,31	6,31
VIh	89	174—5[C]	21,15	13,76	$C_{18}H_{19}N_7O_4S_2$	21,24	13,89
VIIh	85	176—7[A]	20,43	13,80	$C_{19}H_{21}N_7O_4S_2$	20,62	13,48

Note. Crystallization solvents: A) water; B) ethanol; C) aqueous acetic acid; D) glacial acetic acid; E) aqueous ethanol. Electronic spectra λ_{max}, nm (ε units), in 0.1 N sodium hydroxide solution: (Ia) 251 (4.08); (IIa) 251 (4.12); (IIIa) 264 (4.33); (IVa) 253 (4.37); (Va) 255 (4.11); (VIa) 258 (4.31); (VIIa) 262 (4.53); (VIIIa) 265 (4.34); (IXa) 258 (4.38); (Xa) 256 (4.30); in ethanol: (Ia) 271 (4.26); (IIa) 254 (4.21); (IVa) 264 (4.29); (Va) 268 (4.10); (VIIa) 288 (4.03); (IXa) 259 (4.36); (Xa) 258 (4.37).

stituents in the sulfamide residue. Ethazole derivatives have the largest latitude in spectrum of effect in the hydrazone series. In the series of azo derivatives a large latitude in spectrum of effect is seen clearly for derivatives of 5-isopropylbarbituric acid and its 2-thio analog, in comparison with derivatives of 5-ethylbarbituric acid and its 2-thio analog. Of all the compounds only the coupling product of 5-benzylbarbituric acid with diazotized ethazole (Vf) was found to be active against Pseudomonas pyocyaneum 104.

TABLE 2. Derivatives of Barbituric and 2-Thiobarbituric Acids

Compound	Yield, %	Mp (deg)	Found, %		Empirical formula	Calc., %		λ_{max}, nm		lg ε	
			N	S		N	S	in 0.1 N	NaOH		
XIa	88	252	23,25	10,10	$C_{10}H_9N_5O_5S$	23,42	10,30	243	374	4,16	4,33
XIIa	97	310—11	21,36	19,60	$C_{10}H_9N_5O_4S_2$	21,50	19,59		384		4,50
XIb	88	294—5	27,35	9,08	$C_{11}H_{11}N_7O_5S$	27,74	9,07	243	376	4,15	4,34
XIIb	92	278—9	26,38	17,23	$C_{11}H_{11}N_7O_4S_2$	26,54	17,36		387		4,51
XIc	86	300—1	19,89	9,16	$C_{12}H_{11}N_5O_6S$	19,87	9,10	242	375	4,21	4,25
XIIc	97	275—6	18,86	17,7	$C_{12}H_{11}N_5O_5S_2$	19,01	17,40		387		4,43
XId	95	283	21,18	16,63	$C_{13}H_{10}N_6O_5S_2$	21,40	16,23	256	386	4,23	4,14
XIId	77	285—7	20,62	23,46	$C_{13}H_{10}N_6O_4S_3$	20,48	23,44		391		4,41
XIe	92	298	20,47	15,74	$C_{14}H_{12}N_6O_5S_2$	20,65	15,70		392		3,94
XIIe	83	248—50	19,68	22,48	$C_{14}H_{12}N_6O_4S_3$	19,80	22,66	249	404	4,19	4,36
XIf	74	315—7	23,26	14,94	$C_{14}H_{13}N_7O_5S_2$	23,25	15,14	250	380	4,23	4,40
XIIf	87	291—2	22,35	21,53	$C_{14}H_{13}N_7O_4S_3$	22,40	21,88		389		4,58
XIg	87	315	21,43	8,50	$C_{15}H_{12}N_6O_5S$	21,67	8,23	241	377	4,39	4,41
XIIg	96	276—8	20,56	15,95	$C_{15}H_{12}N_6O_4S_2$	20,73	15,82	231	389	4,42	4,43
XIh	91	308	23,49	8,0	$C_{16}H_{15}N_7O_5S$	23,60	7,70	241	377	4,46	4,22
XIIh	94	282—3	22,29	14,46	$C_{16}H_{15}N_7O_4S_2$	22,62	14,79	231	387	4,44	4,46

Note. Compounds (XIIb) and (XIIc) were crystallized from water; the remaining compounds were crystallized from ethanol. For (XIa) in ethanol λ_{max} 382 (lg ε 4.67); for (XIIa) in ethanol λ_{max} 408 (lg ε 4.61).

TABLE 3. Antibacterial Activity of Derivatives of Barbituric and 2-Thiobarbituric Acids

Compound	I		II		III		IV	
	1	2	1	2	1	2	1	2
Ic	+	+		−				
Id	+							
Ih	+							
IIa	+		+					
IIb	++	+	+					
IIc	++	+	+					
IId	+	+	+					
IIf	+							
IIg	+	+	+					
IIa	+	+	+					
III a	+	+	+					
IV a	+	+	+	+				
V d	+		+					
V f					+	+		
VI b	+							
VI c	+							
VI f	++	+						
VI g	+							
VI h	+							
VII d	+	+	+					
VII e	+		+					
VII f	+	+	+					
VII g	+		+	+				
VII h	+	+	+	+				
VIII a	+		+					
XI f					+	+	+	+
XII c	+							
XII f			+	+	+	+	+	+
XII h	+							
XIII c	+				+	+	+	+
XIII f	+							
XIII h					+	+		
XIV c	+							
XIV f	+	+						
XIV h	+	+						

Designation: I) St. aureus 209; II) E. coli 138; III) Sal. typhi abdominalis 69; IV) Shigella dys. Flexneri C. 1) Bacteriostatic effect; 2) bactericidal effect. Dilution + 1/10,000 ++ 1/20,000.

Note. All preparations are inactive in relation to Bacterium Friedlanderi, Proteus vulgaris, Bacterium subtilis, Candida albicans, and Asp. fumigatus.

EXPERIMENTAL

We dissolved 0.001 mole of the corresponding sulfanylamide in 1 ml of conc. hydrochloric acid, cooled to 0-5°, and added with stirring 0.0011 mole of sodium nitrite in 1 ml of water. Then the diazo salt was added to a solution of 0.001 mole of the unsubstituted or 5-alkyl-substituted barbituric or 2-thiobarbituric acid in 6 ml of a 10% sodium hydroxide solution. After stirring for 10 min and maintaining for 2 h at 0-5° the mixture was acidified with acetic acid; after 2 h the precipitate was filtered and dried in a vacuum desiccator over conc. sulfuric acid. After recrystallization the precipitate was dried in vacuum over phosphorus pentoxide. Azo coupling products are orange-colored materials, slightly soluble in water and organic solvents, and soluble in dimethylformamide and sodium hydroxide, potassium hydroxide, and sodium carbonate solutions. Azo derivatives (I-X) are soluble in methanol, ethanol, acetic acid. Results of elemental analysis, melting points, and spectral characteristics of the obtained compounds are presented in Tables 1 and 2.

Electronic spectra were taken in ethanol or 0.1 N sodium hydroxide solutions on an SF-4A spectrophotometer at a layer thickness of 10 mm and a concentration of $(1.2\text{-}2) \cdot 10^{-5}$ mole/liter.

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