CONDENSED HETEROCYCLIC SYSTEMS WITH A THIAZOLE RING.

11.* THIAZOLO[3,4-b]-1,2,4-TRIAZINONES

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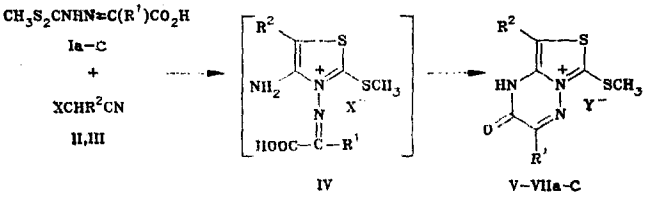
Syntheses are reported for substituted 2-oxo-1,2-dihydrothiazolo[3,4-b]-1,2,4-triazinium salts. The action of bases on these salts leads to the corresponding mesoionic compounds.

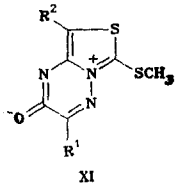
Among the reported thiazolotriazines, greatest physiological activity is found for the corresponding oxo-derivatives [2-4]. Hence, interest was found in the preparation of the new heterocyclic system reported in our previous work [1], namely thiazolo[3,4-b]-1,2,4-triazine.



I, V—VII a $R^1=CH_3$; b $R^1=(CH_2)_2COOH$; c $R^1=C_6H_5$; II, V X,Y=Br, $R^2=H$; III, VI X,Y=$C_6H_5SO_3$, $R^2=C_6H_5$; VII Y=ClO_4, $R^2=C_6H_5$

We might have expected that, similarly to the reaction of acetonitriles III with methyldithiohydrazonates of 1,2-diketones [1], substituted 4-aminothiazole IV would be formed in the first step and then cyclized to give the desired product.

However, upon heating a mixture of the starting components, dihydrothiazolotriazine salts V-VII are immediately formed. The structure of these compounds was confirmed by IR and PMR spectroscopy (Tables 1a and 2). Thus, for example, the IR spectra of V-VII have amide C=O stretching bands at 1700-1715 cm^{-1}. The action of bases on salts V-VII leads to the loss of an acid and the formation of mesoionic thiazolotriazinium oxides VIII and IX.



VIII $R^2=H$; IX $R^2=C_6H_5$

The IR spectra of these compounds lack the carbonyl stretching band of the starting thiazolotriazines but show a new band at 1515-1545 cm^{-1} which may be assigned to vibrations of the N=C—O⁻ group. As expected, the PMR spectra of solutions of VIIIa and VIIIc, the signal for the proton at position 8 is shifted upfield relative to the analogous values of the corresponding salts Va and Vc due to the electron-donor effect of the oxide group. In addition, we should note that, similar to other types of mesic compounds [5,6], oxides VIII and IX are more deeply colored than their salt-like analogs. The action of acids on oxides

*For communication 10, see [1].

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TABLE 1. UV and IR Spectra of the Compounds Synthesized

Compound	λ_{max}[a], nm (lg ε)	ν, cm^{-1}
Ia	317 (4,33)	1520, 1615, 1755, 2930, 3000, 3260, 3330
Ib	320 (4,27)	1520, 1615, 1680, 1710, 2580, 2670, 2800—3200
Ic	342 (4,24)	1520, 1605, 1710, 2500, 2580, 2670, 2850, 3000, 3200
Va	272 (3,99), 365 (3,47)	1610, 1640, 1710, 2730, 2860, 2990, 3020, 3130
Vb	271 (3,99), 361 (3,48)	1605, 1625, 1710, 1740, 2750, 2930
Vc	307 (4,24), 385 (2,58)	1550, 1630, 1710, 2750, 2920
VIa	276 (4,11), 430 (3,64)	
VIb	273 (4,26), 410 (3,72)	
VIc	303 (4,39), 450 (3,52)	
VIIa	277 (4,10), 430 (3,64)	1495, 1615, 1640, 1715, 2840, 3000
VIIb	273 (4,25), 411 (3,71)	1500, 1550, 1615, 1700, 1725, 2740, 3080
VIIc	303 (4,40), 450 (3,52)	1500, 1560, 1580, 1630, 1700, 3100, 3200
VIIIa	320 (3,54), 407 (3,61)	1545, 1600, 1630, 2920, 2980, 3170
VIIIc	311 (4,26), 435 (3,56)	1515, 1560, 1610, 3055
IXa	453 (3,82)	1540, 1580, 1630, 2920, 2980
IXc	302 (4,44), 485 (3,70)	1525, 1600, 1630, 2920, 3050
X	298 (4,48), 434 (3,54)	1530, 1580, 1600, 2950
XI	312 (4,33), 395 (3,51)	1495, 1565, 1590, 1625, 1705, 2950, 3020, 3060

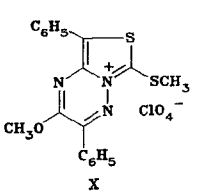
[a]The spectra of salts (Va-c)-(VIIa-c) were obtained in acetic acid, while the remaining spectra were taken in acetonitrile.

TABLE 2. PMR Spectra

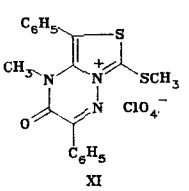
Comp.	R^1	R^2	V	Solvent	Chemical shift, δ, ppm			
					SCH_3	R^1	8-H	Ar-H
Va	CH_3	H	Br	CF_3COOH	2,47	2,17	6,88	
				D_2O[a]	2,41	2,85	7,08	
Vb	$(CH_2)_2CO_2H$	H	Br	CF_3COOH	2,50	2,60 t (2H); 2,90 t (2H)	6,93	
Vc	C_6H_5	H	Br	CF_3COOH	2,52		6,93	7,0—7,3 (3H), 7,6—7,8 (2H)
				D_2O[a]	2,96		7,20	7,4—7,6 (3H), 8,0—8,2 (2H)
				DMSO-d_6	2,97		7,14	7,4—7,6 (3H), 7,8—8,0 (2H)
VIb	$(CH_2)_2CO_2H$	C_6H_5	$C_6H_5SO_3$	CF_3COOH	2,50	2,60 t (2H); 2,90 t (2H)		6,9—7,2 (8H), 7,3—7,5 (2H)
VIIa	CH_3	C_6H_5	ClO_4	CF_3COOH	2,52	2,20		7,12 (5H)
VIIc	C_6H_5	C_6H_5	ClO_4	CF_3COOH	2,50			6,9—7,2 (8H), 7,6—7,8 (4H)
VIIIa	CH_3	H		D_2O[a]	2,40	2,83	6,84	
VIIIc	C_6H_5	H		DMSO-d_6	2,81		6,71	7,5—8,1 (5H)
X	C_6H_5	C_6H_5	ClO_4	CF_3CO_2H	2,50; 3,82[b]			7,0—7,3 (6H), 7,5—7,8 (4H)
XI	C_6H_5	C_6H_5	ClO_4	CF_3COOH	2,45 2,80[c]			7,0—7,2 (8H), 7,6—7,8 (2H)

[a]200 MHz, [b]O—CH_3, [c]N—CH_3.

VIII and IX gives the corresponding salts, while the action of dimethyl sulfate gives the products of the O- and N-alkylation, X and XI. While both the O-isomer and a significant amount of the N-isomer is obtained upon heating in DMF, salt X is the major product in the absence of solvent.



X



XI

TABLE 3. Characteristics of Compounds Synthesized I, V-XI

Compound	mp, °C	Found, %		Chemical formula	Calc., %		Yield, %
		N(Hal)	S		N(Hal)	S	
Ia	144—145	14,8	33,0	$C_5H_8N_2O_2S_2$	14,6	33,3	70
Ib	155—156 (157—158 [7])	11,2	25,0	$C_7H_{10}N_2O_4S_2$	11,2	25,6	80
Ic	135—136	11,3	24,7	$C_{10}H_{10}N_2O_2S_2$	11,0	25,2	79
Va	228—230	(27,2)	22,0	$C_7H_8BrN_3OS_2$	(27,2)	21,8	61
Vb	203—204	(22,5)	18,0	$C_9H_{10}BrN_3O_3S_2$	(22,7)	18,2	40
Vc	212—213	(22,3)	17,7	$C_{12}H_{10}BrN_3OS_2$	(23,4)	18,0	52
VIa	243—244	9,4	21,3	$C_{19}H_{17}N_3O_4S_3$	9,4	21,5	82
VIb	241—242	8,3	18,5	$C_{21}H_{19}N_3O_6S_3$	8,3	19,0	87
VIc	256—257	8,5	18,6	$C_{24}H_{19}N_3O_4S_3$	8,2	18,9	63
VIIa	251—252	(9,2)	16,2	$C_{13}H_{12}ClN_3O_5S_2$	(9,1)	16,4	90
VIIb	252—253	(8,2)	14,3	$C_{15}H_{14}ClN_3O_7S_2$	(7,9)	14,3	92
VIIc	265—266	(8,0)	14,0	$C_{18}H_{14}ClN_3O_5S_2$	(7,8)	14,2	76
VIIIa	>170 (dec.)	19,9	30,2	$C_7H_7N_3OS_2$	19,7	30,1	72
VIIIc	>170 (dec.)	15,2	23,0	$C_{12}H_9N_3OS_2$	15,3	23,3	78
IXa	247—248	14,7	22,3	$C_{13}H_{11}N_3OS_2$	14,5	22,2	89
IXc	223—224	11,8	18,1	$C_{18}H_{13}N_3OS_2$	11,9	18,2	84
X	242—243	(7,8)	13,5	$C_{19}H_{16}ClN_3O_5S_2$	(7,6)	13,8	30
XI	273—274	(7,4)	13,6	$C_{19}H_{16}ClN_3O_5S_2$	(7,6)	13,8	90

The IR spectrum of perchlorate XI shows a C=O stretching band at 1705 cm^{-1} lacking in the spectrum of salt X which displays only a C=N band at 1580-1600 cm^{-1}. Due to the shielding effect of the ring current of the phenyl ring at $C_{(8)}$ in thiazolotriazinone XI, the signal of the nearby N—CH_3 group is at higher field than usually observed.

EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrometer in KBr pellets, while the electronic absorption spectra were taken on an SF-8 spectrophotometer. The PMR spectra were taken on a BS-467 spectrometer at 60 MHz and Bruker WP-200 spectrometer with HMDS as the internal standard.

The characteristics of synthesized compounds are shown in Table 3.

Methyldithiohydrazonates (Ia-c). A mixture of 1 mmole of the corresponding α-ketoacid, 0.12 g (1 mmole) methyldithiohydrazinate and 2 ml acetic acid was heated to reflux. Upon cooling to room temperature, 2 ml water was added and the precipitate was filtered off.

1,2-Dihydro-3-R^1-6-methylthio-2-oxothiazolo[3,4-b]-1,2,4-triazinium Bromides (Va-c). A mixture of 1 mmole methyldithiohydrazonate Ia-c and 0.13 g (1.1 mmole) bromoacetonitrile II was heated at 100°C for 20 min. The melt was triturated with acetone. The product was filtered off and Va was crystallized from methanol, Vb was crystallized from 5:1 CH_3CO_2H—HCO_2H and Vc was crystallized from water [8].

1,2-Dihydro-3-R^1-6-methylthio-2-oxo-8-phenylthiazolo[3,4-b]-1,2,4-triazinium Benzenesulfonates (VIa-c). A mixture of 1 mmole methyldithiohydrazonate Ia-c and 0.30 g (1.1 mmole) α-cyanobenzyl benzenesulfonate III was heated at 80°C for 10 min. The melt was triturated with acetone. The precipitate was filtered off and crystallized from 3:1 acetic acid—ethyl acetate.

Perchlorates VIIa-c were obtained by the addition of sodium perchlorate to an acetic acid solution of the corresponding benzenesulfonate VI with subsequent crystallization from CH_3CO_2H—HCO_2H.

3-R^1-8-R^2-6-Methylthiothiazolo[3,4-b]-1,2,4-trazinium-2 oxides (VIIIa,c and IXa,c). A mixture of 1 mmole of the corresponding salt and 10 ml ethanol was brought to reflux and 0.1 g (1 mmole) triethylamine was added. The precipitate was filtered off and IXa was crystallized from 1:1 ethanol—nitromethane and IXc was crystallized from nitromethane.

Methylation of Oxide IXc. A. A solution of 0.35 g (1 mmole) oxide IXc in 3 ml DMF and 0.25 g (2 mmoles) dimethyl sulfate was maintained at 125°C for 1 h and a solution of 0.14 g (1.1 mmole) sodium perchlorate in 20 ml water was added. The precipitate (0.41 g) was filtered off and crystallized from 4:1 CH_3CO_2H—HCO_2H. The precipitate formed (0.22 g) is salt

X with a trace of salt XI. The mother liquor was diluted by an equal volume of water to yield 0.14 g analytically pure salt XI.

B. A mixture of 0.35 g (1 mmole) oxide IXc and 0.25 g (2 mmoles) dimethyl sulfate was heated for 30 min at 100°C. The melt was dissolved in 10 ml acetic acid and 0.12 g (1 mmole) sodium perchlorate was added. The precipitate was filtered off and crystallization from acetonitrile and gave 0.42 g salt X.

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