CONDENSED HETEROCYCLES WITH A THIAZOLE NUCLEUS.

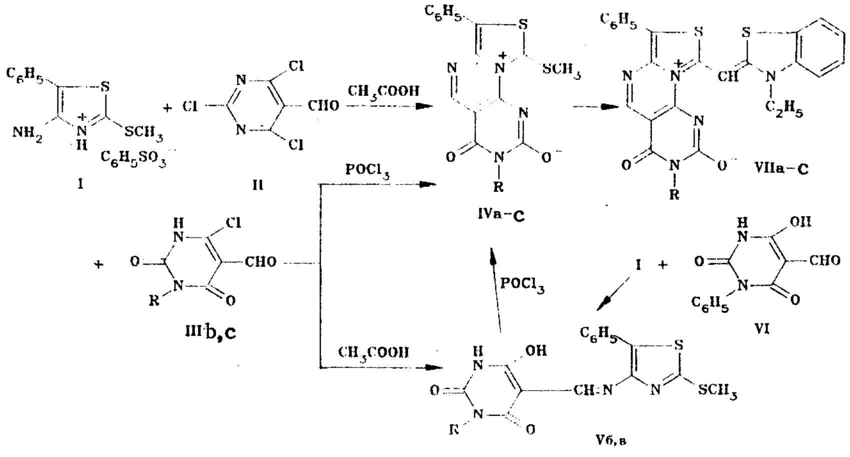
8.* THIAZOLO[4,3-a]PYRIMIDO[5,4-e]PYRIMIDINES

E. K. Mikitenko and N. N. Romanov

UDC 547.792.9'859:542.953.5:
668.619.45:543.422.25'4

Condensation of 4-amino-2-methylthiothiazolium salts with 2,4,6-trichloro-5-formylpyrimidine or 3-R-2,4-dioxo-6-chloro-5-formyl-1,2,3,4-tetrahydropyrimidines yielded mesoionic derivatives of a new heterocyclic system — thiazolo[3,4-a]pyrimido[5,4-e]-pyrimidine — which can be used for the synthesis of polymethine dyes. The absorption maxima of these dyes are bathochromically shifted by 10-20 nm relative to the maxima of the thiazolopyrimidine analogs. The structure of the compounds synthesized was demonstrated by the PMR and IR spectra.

Earlier [2] it was shown that two bands of close intensity are observed in the visible portion of the absorption spectra of solutions of polymethine dyes with a thiazolo[3,4-a]-pyrimidine nucleus; their position and shape are determined by the substituents in the pyrimidine fragment of the molecules. For a further investigation of the spectral characteristics of cyanides of the indicated type, we were interested in synthesizing new derivatives of heterocycles containing a thiazolopyrimidine ring, which might be used in the synthesis of polymethine dyes. For this purpose we studied the interaction of salts of 4-amino-2-methylthio-5-phenylthiazole (I) with 6-chloro-5-formylpyrimidines II, IIIb, c.



a R=H; b R=CH$_3$; c R=C$_6$H$_5$

Since it is known [3, 4] that substituted pyrimidines with the structures II, IIIb, c are used for the synthesis of condensed heterocycles, including those with a nodal nitrogen atom, we might also expect the formation of a condensed heterocyclic system in our case. Actually, when the salt I interacts with 2,4,6-trichloro-5-formylpyrimidine (II) in acetic acid (i.e., under conditions of this type of condensation [5]), there is a closing of the thiazolopyrimidopyrimidine ring; moreover, evidently simultaneously with the cyclization, the chlorosubstituted product formed is hydrolyzed to a mesoionic oxide IVa.

Analogously to the condensation of the salt I with pyrimidines IIIb, c, we hoped to obtain thiazolopyrimidopyrimidines IVb, c, substituted in the 3-position, as well. However, it was found that when the reaction is conducted in acetic acid there is only a condensation

---

*For communication 7, see [1].

Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev 252660. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1126-1128, August, 1984. Original article submitted April 4, 1983; revision submitted December 27, 1983.

0009-3122/84/2008-0921$08.50

TABLE 1. PMR Spectra of Compounds IVa-c, Vb, c

Compound	δ, ppm (number of protons)			
	S—CH₃	N—CH₃	Ar—H	5-H or CH=N
IVa	2,53	—	7,20 (5H)	8,60
IVb	2,50	3,10	7,20 (5H)	8,67
IVc	2,50	—	6,7—7,3 (10H)	8,52
Vb	2,50	2,90	7,10 (5H)	8,96
Vc	2,43	—	6,8—7,1 (10H)	9,02

at the aldehyde group and a replacement of the chlorine atom by a hydroxyl group with the formation of the corresponding anils (Vb, c), the structure of which was confirmed by the data of the PMR (Table 1) and IR spectra. The bands of the stretching vibrations of the C=N, C=O, N—H and O—H bonds are observed in the latter at 1615-1650, 1695-1735, 3040-3080, and 3120-3200 cm^{-1}, respectively. A final conclusion on the correctness of the structure adopted was given by counter-synthesis of compound Vc by condensation of the salt I with formylbarbituric acid (VI).

Further investigations showed that cyclization to mesoionic oxides IVb, c occurs when substituted thiazoles Vb, c are heated in phosphorus oxychloride. The structure of the mesoionic compounds isolated was demonstrated by the data of the PMR (Table 1) and IR spectra. In the latter the bands of the stretching vibrations of the $C-O^- \leftrightarrow C=O$ and $C-N^- \leftrightarrow C=N$ bonds are observed at 1560-1570, 1680-1695, and 1520-1525, 1610-1620 cm^{-1}, respectively.

As a result of the mesoionic structure of the molecules of the oxides IV, the methylthio group in them, just as in the usual quaternary 2-methylthiothiazolium salts, is readily replaced by a residue of nucleophilic reagents, used for the synthesis of polymethine dyes. Thus, in the interaction with 2-methyl-3-ethylbenzothiazolium toluenesulfonate, the monomethines VIIa-c were obtained. In the visible part of the absorption spectra of solutions of the dyes VIIa-c, just as in the spectra of their thiazolopyrimidine analogs [2], two bands are observed: short-wave (430, 454-456 nm) and long-wave (554-556 nm). Annelation of still another pyrimidine ring to thiazolo[3,4-a]pyrimidine leads to bathochromic shift of the absorption maxima of both bands of the corresponding dyes by 10-20 nm.

EXPERIMENTAL

The electronic spectra were obtained on an SF-8 spectrophotometer (in DMFA), the IR spectra on a UR-10 (in KBr tablets), the PMR spectra on a Tesla BS 467 spectrometer (60 MHz, internal standard HMDS) in CF_3COOH.

4-Oxo-9-methylthio-7-phenyl-3,4-dihydrothiazolo[3,4]pyrimido[5,4-e]pyrimidinium-2-oxide (IVa). A mixture of 0.38 g (1 mmole) of the benzenesulfonate I, 0.21 g (1 mmole) of the pyrimidine II [7], and 3 ml of acetic acid was heated for 1 h 30 min at 100°C. The precipitate that formed after cooling was filtered off and crystallized from acetic acid. Yield 0.28 g (Table 2).

6-Hydroxy-2-methyl-5-[(2-methylthio-5-phenyl-4-thiazolyl)imino]methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (Vb). A mixture of 0.38 g (1 mmole) of the benzenesulfonate I and 0.19 g (1 mmole) of the chloroaldehyde IIIb [7, 8] in 5 ml of acetic acid was heated for 30 min at 100°C. The precipitate formed was filtered off and crystallized from a 1:3 mixture of alcohol and DMFA.

6-Hydroxy-5-[(2-methylthio-5-phenyl-4-thiazolyl)imino]methyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydropyrimidine (Vc). A. Produced analogously to Vb from the salt I and the chloroaldehyde IIIc [7, 8].

B. A mixture of 0.76 g (2 mmoles) of the benzenesulfonate I, 0.46 g (2 mmoles) of 1-phenyl-5-formylbarbituric acid [9] in 10 ml of alcohol, and 5 ml of DMFA was boiled for 10 min. The precipitate formed was filtered off and crystallized. Yield 0.76 g (87%).

4-Oxo-9-methylthio-3-R-7-phenyl-3,4-dihydrothiazolo[3,4-a]pyrimido[5,4-e]pyrimidinium-2-oxide (IVb, c). A. 1 mole of the corresponding azomethine (Vb, c) in 3 ml of $POCl_3$ was heated for 10 h at 100-110°C. The excess $POCl_3$ was distilled off under vacuum, the residue washed with petroleum ether and decomposed with water. The product was filtered off and crystallized from acetonitrile.

TABLE 2. Characteristics of the Compounds Synthesized

Compound	mp, °C	UV spectrum, λ_{max}, nm (log ε), in DMFA	Found, %		Empirical formula	Calculated		Yield, %
			N	S		N	S	
IVa	267—268	385 (4,10), 396 (4,10), 446 (4,09)	16,4	18,4	$C_{15}H_{10}N_4O_2S_2$	16,3	18,7	83
IVb	294—295	387 (4,04), 396 (4,04), 440 (4,01)	15,7	17,2	$C_{16}H_{12}N_4O_2S_2$	15,7	17,8	57
IVc	283—284	387 (4,16), 398 (4,15), 445 (4,11)	13,2	14,7	$C_{21}H_{14}N_4O_2S_2$	13,4	15,3	92
Vb	315—316	280 (4,07), 364 (4,40)	15,1	17,1	$C_{16}H_{14}N_4O_3S_2$	14,9	17,1	86
Vc	300—301	282 (4,10), 366 (4,41)	12,7	14,2	$C_{21}H_{16}N_4O_3S_2$	12,8	14,6	89
VIIa	297—298	430 (4,16), 454 (4,10), 555 (4,51)	14,7	13,8	$C_{24}H_{17}N_5O_2S_2$	14,9	13,6	56
VIIb	320—321	430 (4,05), 454 (3,97), 554 (4,40)	15,0	13,3	$C_{25}H_{19}N_5O_2S_2$	14,4	13,2	61
VIIc	318—319	430 (4,10), 456 (4,05), 556 (4,50)	12,8	11,4	$C_{30}H_{21}N_5O_2S_2$	12,8	11,7	55

B. A mixture of 0.38 g (1 mmole) of the benzenesulfonate I and 1 mmole of the corresponding chloroaldehyde (IVb, c) in 3 ml of $POCl_3$ was heated for 2 h at 100-110°C. It was isolated analogously to the preceding product.

4-Oxo-3-R-7-phenyl-9-(3-ethyl-2(3H)-benzothiazolylidine)methyl)3,4-dihydrothiazolo[3,4-a]pyrimido[5,4-e]pyrimidinium-2-oxide (VIIa-c). A mixture of 0.35 g (1 mmole) of 2-methyl-3-ethylbenzothiazolinium toluenesulfonate and 1 mmole of the corresponding mesoionic compound IVa-c was dissolved with heating in 6 ml of absolute alcohol, and 0.1 g (1 mmole) of triethylamine was added. The dye that precipitated was filtered off and crystallized from a 1:3 mixture of alcohol and DMFA.

LITERATURE CITED

1. E. K. Mikitenko and N. N. Romanov, Khim. Geterotsikl. Soedin., No. 7, 939 (1983).
2. A. D. Kachkovskii, E. K. Mikitenko, and N. N. Romanov, Khim. Geterotsikl. Soedin., No. 5, 639 (1982).
3. F. Joneda, K. Mori, M. Oro, J. Kodakawa, E. Nagao, and H. Jamaquchi, Chem. Pharm. Bull., 28, 3514 (1980).
4. A. Dieter, Federal Republic of Germany Patent No. 2929414; Ref. Zh. Khim., 22N232P (1981).
5. E. K. Mikitenko and N. N. Romanov, Khim. Geterotsikl. Soedin., No. 4, 204 (1983).
6. Z. Schlager, Ger. OF. 2310334; Chem. Abstr., 79, 146549 (1973).
7. S. Shigeo, H. Kosaku, and J. Mitsuomi, J. Pharm. Soc. Jpn., 91, 1372 (1971).
8. R. O. Kochkanyan, S. S. Radkova, N. P. Klyuev, L. Yu. Petrovskaya, and S. N. Baranov, Khim. Geterotsikl., Soedin., No. 2, 1687 (1978).
9. M. Ridi, Gazz. Chim. Ital., 82, 746 (1952).