MESOIONIC COMPOUNDS WITH A BRIDGE NITROGEN ATOM.

12.* INVESTIGATION OF THE CYCLIZATION OF (2-PYRIMIDINYLTHIO)ACETIC ACID

K. V. Fedotov, N. N. Romanov, and A. I. Tolmachev

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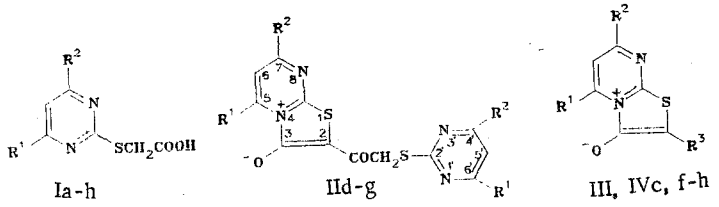
In the cyclization of (2-pyrimidinylthio)acetic acids, extremely reactive thiazolo[3,2-*a*]pyrimidinium-3-oxides are formed, which, depending on the conditions of the reaction, can either undergo self-condensation or interact with electrophilic reagents. The structure of the compounds obtained was demonstrated by the data of the PMR, UV, and IR spectra.

Earlier [2] it was shown that in the cyclization of (2-quinolinylthio)acetic acids, depending on the conditions of the reaction, reactive derivatives of thiazolo[3,2-*a*]quinolinium-1-oxide are obtained. It was of interest to investigate the analogous conversions in the series of other (heterylthio)acetic acids in order to determine the patterns in the formation of mesoionic compounds.

We found that under the action of a mixture of acetic anhydride and acetic acid on (2-pyrimidylthio)acetic acids Ia-h, they are also converted to new compounds. However, we were able to isolate and identify only the conversion products of 4,6-disubstituted acids, to which, on the basis of the data of elementary analysis and the PMR spectra of their solutions in trifluoroacetic acid (Table 1), we can ascribe the structure IId-g.



Ia-h IId-g III, IVc, f-h

I—IV a $R^1=R^2=H$; b $R^1=H$, $R^2=CH_3$; c $R^1=H$, $R^2=C_6H_5$; d $R^1=R^2=CH_3$; e $R^1=CH_3$, $R^2=N(C_2H_4)_2O$; f $R^1=CH_3$, $R^2=C_6H_5$; g $R^1=CH_3$, $R^2=p$-$CH_3OC_6H_4$; h $R^1=R^2=C_6H_5$; III $R^3=H$; IV $R^3=COCF_3$

Actually, the spectra of the compounds obtained are extremely similar to the spectra of the corresponding products obtained under analogous conditions from (2-pyridylthio)- and (2-quinolinylthio)acetic acids [2-6]. In them, just as in the case, for example, of 2-[(2-pyridylthio)acetyl]thiazolo-[3,2-*a*]pyridinium-3-oxide [2], two sets of signals of the protons of the heterocyclic residue and the signal of the protons of the methylene group are observed. Thus, the PMR spectrum of the compound formed in the cyclization of the acid Id under these conditions contains the singlets of the protons of four methyl groups and one methylene group, as well as two singlets of the protons of the pyrimidine ring (Table 1). The substantial shift of the signal of the protons of one of the methyl groups in the weak-field direction, just as in the case of 5,7-dimethyl-2-phenylthiazolo[3,2-*a*]pyrimidinium-3-oxide, obtained in the cyclization of the corresponding (2-pyrimidinylthio)phenylacetic acid [7], is due to the influence of the unshared electron pairs of the oxygen atom [8] of the thiazolopyrimidinium oxide molecule on the protons of the close-lying methyl group in the 5-position. The coincidence of the chemical shifts of the protons of the methyl group in the 7-position of the meso-

*For Communication 11, see [1].

Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev 252660.
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TABLE 1. PMR Spectra of Compounds IId-g

Compound	δ, ppm					
	5-CH_3	4′-CH_3	7-R^2, 6′-R^2	S—CH_2	6-H	5′-H
IId	2,77		2,40 (9H, s)	4,67	7,10	7,00
IIe	2,47	2,07	3,67 (18H,m)		6,33	6,20
IIf	2,80	2,40	7,0—8,1 (10H,m)	4,73	7,57 (2H)	
IIg	2,75	2,38	3,35 (3H, s); 3,33 (3H, s); 6,78 (4H, d, J=9 Hz); 7,85 (2H, d); 8,03 (2H, d)	4,63	7,45	7,38

TABLE 2. PMR Spectra of Compounds IVc, f-h

Compound	δ, ppm		
	R^1	R^2	6-H
IVc	8,77 (1H,d, J=7Hz)	6,9—7,4 (3H,m); 7,6—8,1 (3H,m)	
IVf	2,80 (s)	6,8—7,4 (3H, m); 7,7—8,4 (2H,m)	7,48 (s)
IVg	2,70 (s)	3,55 (3H, s); 6,70 (2H, d, J=9 Hz); 8,00 (2H, m)	7,38 (s)
IVh	7,0—7,5 (6H, m), 7,7—8,1 (4H, m)		7,47 (s)

ionic fragment and the methyl groups of the pyrimidine residue is probably caused by protonation of the latter under the conditions of recording of the spectra.

The structure proposed for compounds IId-g is also confirmed by the similarity of their UV spectra to the spectrum of the closest structural analog — 2-{[(4-methylpyridyl-2)thio]-acetyl}-7-methylthiazolo[3,2-a]pyridinium-3-oxide, which in methanol has λ_{max} 248, 290, and 429 nm [9]. Thus, for a methanol solution of the oxide IId λ_{max} 250, 286 and 430 nm.

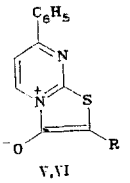
Let us note that in the case of cyclization of the acids Ie-g, in which $R^1 \neq R^2$, we might expect the formation of two isomeric products. However, judging by the PMR spectra of the unpurified oxides IIe-g, in all cases only one of the possible thiazolopyrimidinium oxides is obtained; moreover, closing of the thiazole ring, as follows from a comparison of the chemical shifts of the protons of the methyl group of the oxides IIe-g and the corresponding 5,7-disubstituted 2-phenylthiazolo[3,2-a]pyrimidinium-3-oxides [7], occurs at the nitrogen atom adjacent to the smaller-sized substituents.

The data obtained are evidence that under the action of acetic anhydride on acids of type I, extremely reactive mesoionic thiazolo[3,2-a]pyrimidinium-3-oxides (III) are formed as an intermediate product; as a result of the presence of electrophilic ($C_{(3)}$) and nucleophilic ($C_{(2)}$) sites in their molecules [1], under the conditions of the reaction (the presence of acetic acid) they interact with one another forming derivatives of type II. In the presence of other electrophilic reagents in solution, the oxides III can interact with them, which leads to the corresponding 2-substituted derivatives.

Actually, in the action of a mixture of acetic and trifluoroacetic anhydrides on the acids Ia-h, in a number of cases it was possible to isolate 2-trifluoroacetyl derivatives of thiazolo[3,2-a]pyrimidinium-3-oxides (IVc, f-h), the structure of which is confirmed by their PMR spectra and by the data of elementary analysis (Table 2).

On the example of the acid Ic we were able to confirm the formation of the corresponding oxides IIc. Thus, in the PMR spectrum in a pyridine-D_5 solution of the reaction product formed under the action of a mixture of acetic anhydride and triethylamine on the acid Ic, in addition to the signals of the aromatic protons, the singlet of the proton in the 2-position and the doublet of the proton in the 5-position with chemical shifts 5.58 (1H) and 9.13 ppm (1H, J = 8 Hz), respectively, are observed. The structure of the thiazolopyrimidine IIIc is also confirmed by its chemical conversions. For example, it reacts readily with p-nitrophenyldiazonium tetrafluoroborate and phenyl isothiocyanate, forming compounds V and VI (see experimental section). (Formula, top, following page.)

The oxide IIIc is extremely unstable, and in solutions it undergoes further conversion. Thus, in the PMR spectrum of its solution in pyridine-D_5, the indicated signals gradually dis-



V, VI

V R=—N=N=$C_6H_4NO_2$-*p*; VI R=—C(S)NHC_6H_5

appear, and new ones appear: a weak-field doublet (9.09 ppm, J = 8 Hz) and two doublets at 6.08 and 6.41 ppm (J = 6 Hz), which evidently is due to intermolecular autocondensation of the oxide IIIc with the participation of the carbon atoms of the thiazole and pyrimidine fragments of the molecule, like the conversions that we observed earlier [7]. This may also be precisely the reason that we were unable to purify and identify the products formed in the cyalization of the acids Ia-c.

Like the previously described thiazoloazinium oxides [1, 2, 9, 10], the compounds synthesized exhibit negative solvatochromism. From the data cited in Table 3 it is evident that replacement of the methyl group in the 7-position of the oxide IId by an electron donor morpholine residue leads to a 45 nm increase in the color (oxide IIe), and by a phenyl group to a 52 nm deepening of it (oxide IIf). The introduction of an electron acceptor trifluoroacetyl or phenylthiocarbamoyl group into the 2-position of the oxide IIIc (thiazolopyrimidines IVc and VI) leads to a hypsochromic shift of 50 and 4 nm, respectively; the appearance of phenyl [10] and p-nitrophenylazo groups (V) leads to bathochromic shifts of 51 and 70 nm.

Analogously, for 5,7-dimethyl-2-phenylthiazolo[3,2-*a*]pyrimidinium-3-oxide, when the methyl group in the 7-position was replaced by a morpholine residue, a 56 nm hypsochromic shift was observed, while when a phenyl group was introduced into the same position, a 72 nm bathochromic shift was observed [10]; in the case of 5-methylthiazolo[3,2-*a*]quinolinium-1-oxide [2], an acetyl group in the 2-position increased the color by 18 nm, while a phenyl group deepened it by 33 nm.

TABLE 3. Characteristics of the Compounds Obtained

Compound	mp, °C	λ_{max}, nm (lg ε)		Found, %		Gross formula	Calculated, %		Yield, %
		CH_3CN	CCl_4	N (F)	S		N (F)	S	
IId	210—211	285 (4,12), 430 (3,93)	470	15,7	17,1	$C_{16}H_{16}N_4O_2S_2$	15,5	17,8	50
IIe	264—265	240 (4,42), 292 (4,44), 385 (4,16)	410	16,9	12,6	$C_{22}H_{26}N_6O_4S_2$	16,7	12,8	81
IIf	236—237	257 (4,50), 316 (4,56), 482 (4,04)	532	11,4	13,1	$C_{26}H_{20}N_4O_2S_2$	11,6	13,2	68
IIg	256—257	262 (4,31), 285 (4,38), 346 (4,53), 480 (4,07)	526	10,7	11,8	$C_{28}H_{24}N_4O_4S_2$	10,3	11,8	80
IIIc	221—222	295 —, 410 —, 510 —	548	12,3	13,7	$C_{12}H_8N_2OS$	12,3	14,0	55
IVc	250—251	318 (4,47), 460 (4,00)	500	(17,6)	10,0	$C_{14}H_7F_3N_2O_2S$	(17,6)	9,9	22
IVf	236—237	318 (4,50), 467 (4,00)	499	(16,6)	9,5	$C_{15}H_9F_3N_2O_2S$	(16,9)	9,5	27
IVg	249—250	358 (4,53), 455 (4,14)	484	(15,5)	8,9	$C_{16}H_{11}F_3N_2O_3S$	(15,5)	8,7	54
IVh	265—266	327 (4,46), 480 (4,05)	516	(13,9)	8,3	$C_{20}H_{11}F_3N_2O_2S$	(14,2)	8,0	30
V	240—241	322 (4,30), 412 (4,29), 580 (4,55)	606	18,8	8,8	$C_{18}H_{11}N_5O_3S$	18,6	8,5	69
VI	263—264	296 (4,41), 328 (4,45), 506 (4,27)	545	11,9	17,7	$C_{19}H_{13}N_3OS_2$	11,6	17,7	76

EXPERIMENTAL

The PMR spectra were measured on a Tesla BS-467 spectrometer (60 MHz) in trifluoroacetic acid. The spectrum of the oxide IIIc was measured on a Bruker WP-200 instrument (200 MHz) in pyridine-D_5. Internal standard HMDS. The IR spectrum was recorded on a UR-10 spectrometer, the UV spectra on a SF-8 spectrophotometer. The acids Ia-h were produced according to the methods of [11-13]. Data on the properties of the new compounds are cited in Table 3.

Substituted 2-[(2-Pyrimidylthio)acetyl]thiazolo[3,2-*a*]pyrimidinium-3-oxides (IId-g). To a solution of 20 mmoles of the corresponding acid Id-g in 7.5 ml of acetic acid we added 7.5 ml of acetic anhydride and heated to boiling. After cooling the product was filtered off and recrystallized from acetic anhydride.

7-Phenylthiazolo[3,2-*a*]pyrimidinium-3-oxide (IIIc). A mixture of 0.49 g (2 mmoles) of the acid Ic, 3 ml of acetic anhydride, and 3 ml triethylamine was mixed for 5 min. After 1 h the product was filtered off and washed with ether. Yield 0.25 g. It was subsequently used without purification.

Substituted 2-Trifluoroacetylthiazolo[3,2-*a*]pyrimidinium-3-oxides (IVc, f-h). To a solution of 1 mmole of the corresponding acid Ic, f-h in 2 ml acetic anhydride we added 2 ml trifluoroacetic anhydride dropwise and left at room temperature for 5 h. The precipitated reaction product was filtered off and recrystallized from acetic anhydride.

2-(p-Nitrophenylazo)-7-phenylthiazolo[3,2-*a*]pyrimidinium-3-oxide (V). To a solution of 0.11 g (0.5 mmole) of the oxide IIIc in 10 ml acetonitrile we added 0.1 g (1.0 mmole) triethylamine and 0.12 g (0.5 mmole) p-nitrophenyldiazonium tetrafluoroborate. The precipitated dye was filtered off and recrystallized from acetic anhydride. Yield 0.13 g. PMR spectrum: 8.80 (1H, d, J = 8 Hz); 7.8-8.3 (6H, m); 7.0-7.5 ppm (4H, m).

7-Phenyl-2-phenylthiocarbamoylthiazolo[3,2-*a*]pyrimidinium-3-oxide (VI). To a solution of 0.11 g (0.5 mmole) of the oxide IIIc in 1 ml (8.4 mmoles) phenyl isothiocyanate we added 0.1 g (1.0 mmole) triethylamine and heated to boiling. The reaction mass was triturated with ethanol, the product filtered off and recrystallized from acetic anhydride. Yield 0.13 g. IR spectrum (KBr): 1410, 1500 (C=S), 1600 (C=N), 1640 (C=O) and 3070 cm^{-1} (N-H). PMR spectrum: 8.80 (1H, d, J = 8 Hz); 7.7-8.2 (3H, m); 6.9-7.4 ppm (8H, m).

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