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N-3-OXOALKYLAMIDES AND -THIOAMIDES IN SYNTHESIS OF HETEROCYCLIC COMPOUNDS.

2.* SYNTHESIS OF 6-ACETOXY-5,6-DIHYDRO-4H-1,3-OXAZINIUM PERCHLORATES. NEW METHOD OF PREPARATION OF N-3-OXOALKYLTHIOAMIDES

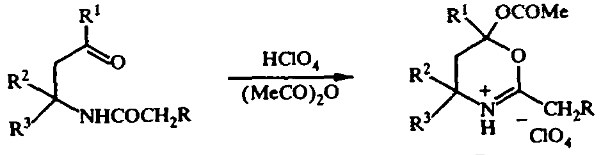
A. S. Fisyuk, M. A. Vorontsova, and D. V. Temnikov

Previously unknown 6-acetoxy-5,6-dihydro-4H-1,3-oxazinium perchlorates were obtained by reacting N-3-oxoalkylamides with perchloric acid in acetic anhydride. It was found that the reaction of 6-acetoxy-5,6-dihydro-4H-1,3-oxazinium perchlorates with sodium hydrosulfide yields N-3-oxoalkylthioamides.

We previously reported on cyclization of N-3-oxoalkylamides into 5,6-dihydropyridin-2(1H)-ones in the presence of bases [2, 3], of interest as biologically active compounds and intermediate products in synthesis of alkaloids [4, 5]. Our method was used to study the characteristics of cyclization of sulfur analogs of N-3-oxoalkylamides, since there was no information on synthesis of N-3-oxoalkylthioamides until recently.

The standard procedure for conversion of amide into thioamide by P_2S_5 and Lawesson's reagent is not applicable in this case. The published data indicate that when carbonyl and carbamoyl groups are present in the molecule, sulfuring of the carbonyl group takes place under the effect of Lawesson's reagent [6], while N-3-oxoalkylamides are converted into 4H-1,3-thiazines under the effect of P_2H_5 [7].

We developed an original method of converting N-3-oxoalkylamides into thioamides IIIa-e. Previously unknown 6-acetoxy-5,6-dihydro-4H-1,3-oxazinium perchlorates IIa-e were obtained with a yield of 70-90% by reacting compounds Ia-e with $HClO_4$ in acetic anhydride.



Ia-e IIa-e

a $R^1 = R^2 = R^3 = Me$, $R = H$; b $R^1 = R^2 = R^3 = R = Me$;
c $R^1 = R^2 = R^3 = Me$, $R = Ph$; d $R^1 = R^2 = Me$, $R^3 = R = H$;
e $R^1 = Me$, $R^2 = H$, $R^3 = R = Ph$

In reacting with hydrogen sulfide, imidates form thioamides as by-products [8], while oxazines IIa-e are essentially cyclic imidates. As a result of studying the reaction of compounds IIa-e with sodium hydrosulfide in methanol, we found that the reaction results in the formation of N-3-oxoalkylthioamides IIIa-e after 48 h with yields of 62-80%. In DMF, the time is reduced to 6 h with almost quantitative yields of the N-3-oxoalkylthioamides.

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*See [1] for Communication 1.

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TABLE 1. Properties and Yields of Synthesized Compounds IIa-e and IIIa-e

Compound	Empirical formula	Found, % / Calculated, %		mp, °C*	IR spectrum, ν, cm^{-1}	Yield, %
		C	H			
IIa	$C_{10}H_{18}NO_7Cl$	40,02 40,08	6,10 6,05	95...97	1770, 1675, 1120	70
IIb	$C_{11}H_{20}NO_7Cl$	42,21 42,16	6,39 6,44	84...85	1770, 1675, 1130*2	80
IIc	$C_{16}H_{22}NO_7Cl$	51,33 51,14	5,79 5,90	125...126	1775, 1600, 1675, 1130	89
IId	$C_9H_{16}NO_7Cl$	37,85 37,84	5,71 5,65	100...101	1170, 1670, 1125	81
IIe	$C_{20}H_{22}NO_7Cl$	57,03 56,68	5,24 5,23	112...113	1775, 1600, 1665, 1120	67
IIIa	$C_8H_{15}NOS$	56,15 55,45	8,72 8,73	85...86	3380, 1740, 1520	75*3
IIIb	$C_9H_{17}NOS$	57,28 57,71	9,18 9,15	51...52	3380, 1715, 1515	75*3 (99)*4
IIIc	$C_{14}H_{19}NOS$	67,59 67,43	7,89 7,68	69...70	3335, 1720, 1600, 1505	80*3
IIId	$C_7H_{13}NOS$	52,82 52,80	8,21 8,23	—	3370, 1715, 1510	62*3
IIIe	$C_{18}H_{19}NOS$	72,60 72,69	6,51 6,44	102...103	3350, 1720, 1600, 1530	82*3

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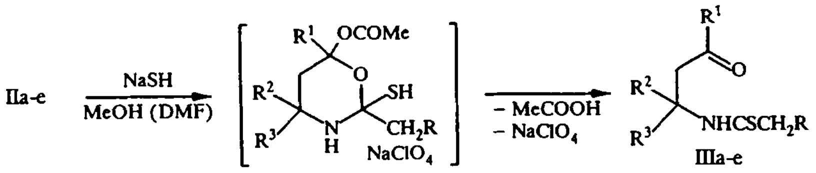
*Solvent of IIa-e: acetonitrile–ether; IIIa-c, e: hexane; IIId was purified by column chromatography (silica gel, chloroform–ethyl acetate, 95:5).

*2Liquid petrolatum.

*3NaSH in CH_3OH.

*4NaSH in DMF.



II, III a R^1 = R^2 = R^3 = Me, R = H; b R^1 = R^2 = R^3 = R = Me;
c R^1 = R^2 = R^3 = Me, R = Ph; d R^1 = R^2 = Me, R^3 = R = H;
e R^1 = Me, R^2 = H, R^3 = R = Ph

Absorption bands of the acetoxy group C=O bond (1770-1780) and a band characteristic of vibrations of a C=N bond (1665-1685 cm^{-1}) are observed in the IR spectra of compounds IIa-e. There are the following absorption bands in the IR spectra of N-3-oxoalkylthioamides IIa-e: carbonyl group (1710-1720), "thioamide II" (1430-1420), stretching vibrations of an N–H bond (3390-3350 cm^{-1}).

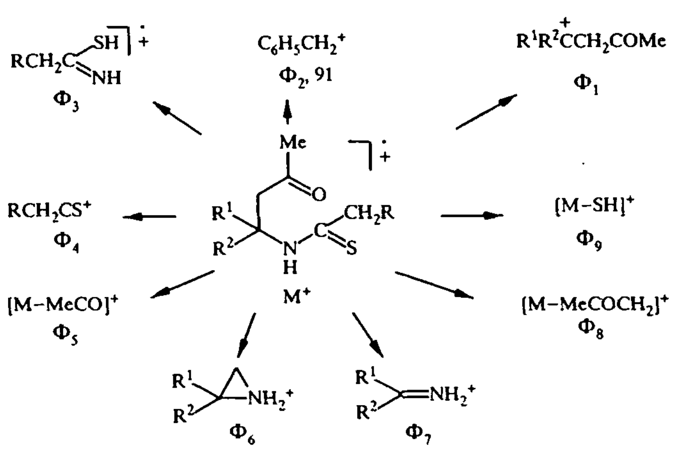


TABLE 2. PMR Spectra of Compounds II and III

Compound	CH_3COO	R^1	$-CH_2-$		R^2 (J^3)	R^3	R (J^3)	CH_2CNO (CH_2CNS)	(NH)
			H (J^2) (J^3)	H (J^2) (J^3)					
IIa	2,02	1,84	2,63 (15,2)	2,15 (15,2)	1,37	1,32	2,27		6,19
IIb	1,94	1,77	2,57 (15,5)	2,08 (15,5)	1,31	1,26	1,01 (7,7)	2,49	7,25
IIc	1,86	1,79	2,65 (15,2)	2,16 (15,2)	1,38	1,38	7,30	3,89	–
IIe	2,01	1,95	*2,78 (15,5) (5,0)	*2,47 (15,5) (12,0)	5,00	7,37	7,43	4,03	–
IIIa	–	1,98	3,37		1,40	1,40	2,30		9,42
IIIb	–	2,08	2,90		1,35	1,35	1,05 (7,6)	2,09	5,90
IIIc	–	1,92	3,34		1,43	1,43	7,28	3,81	9,67
IIId	–	2,14	2,86 (17,3) (4,5)	2,73 (17,3) (6,1)	4,83 (6,2)	1,26 (6,2)	2,46		9,50
IIIe	–	2,10	3,21 (14,0) (5,7)	2,97 (14,0) (5,7)	6,12	7,43...7,16		4,22	8,51

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*Solvent: DMSO-D6 IIa-c, IIIa, c; CH_3CN IIe; $CDCl_3$ IIIb, d, e.

TABLE 3. Relative Intensity of Peaks of Characteristic Fragmentary Ions in the Mass Spectra of Compounds IIIa, c, e

Compound	m/z (relative intensity, %)									
	M^+	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	Φ_8	Φ_9
IIIa	173 (100)	99 (37,4)	–	75 (67,6)	59 (35,2)	130 (11,1)	72 (18,3)	58 (39,9)	116 (11,7)	140 (13,3)
IIIc	249 (73,5)	99 (100)	91 (58,2)	151 (40,5)	135 (13,1)	206 (6,6)	72 (8,6)	58 (16,9)	–	216 (3,6)
IIIe	297 (31,6)	147 (9,6)	91 (52,3)	151 (23,6)	135 (23,5)	254 (16,2)	120 (100)	106 (5,1)	–	264 (7,5)

TABLE 4. Mass Spectra of Compounds IIIa, c, e

Compound	m/z (relative intensity %)*
IIIa	173 (100); 99 (37,4); 85 (21,6); 83 (57,4); 76 (88,2); 75 (67,6); 72 (18,3); 69 (22,4); 59 (35,2); 58 (39,9); 55 (27,3)
IIIc	249 (73,5); 158 (14,1); 152 (17,6); 151 (40,5); 135 (13,1); 134 (24,6); 100 (16,6); 99 (100); 92 (41,4); 91 (58,2); 58 (16,9)
IIIe	297 (31,6); 254 (16,2); 151 (23,6); 137 (23,9); 135 (23,6); 134 (11,7); 120 (100); 103 (23,7); 92 (14,6); 91 (52,3); 77 (21,3) *

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*The peaks of M^+ and the ten most intense ions are reported.

The behavior of N-3-oxoalkylamides under electron impact has not been investigated, but it is known that if the molecule contains several isolated functional groups, the direction of fragmentation is determined by the one with the lowest ionization potential. In the case of N-3-oxoalkylthioamides, the basic directions of fragmentation are determined by the thioamide group, as indicated by the presence of intense signals of ions Φ_1 and Φ_3, formed by breaking of a C–N bond, and ions Φ_6 and Φ_7, characteristic of amides and thioamides, in the mass spectra of compounds IIIa, c, e [9, 10] (see scheme on page 1462). Decomposition of M^+ with rupture of a C–N bond is the most pronounced direction of fragmentation of the molecules of compounds IIIa and IIIc, which have the same substituents in the N-3-oxoalkyl chain. The peaks of ions Φ_1 and Φ_3 in the mass spectra of these compounds have the maximum intensity. Splitting of the C–C bond in the α position with respect to the carbonyl group with formation of ion Φ_6 becomes the basic direction of fragmentation of M^+ for compound IIIe.

The PMR spectra of compounds IIa-e and IIIa-e (Table 2) totally correspond to their structure.

We thus investigated cyclization of N-3-oxoalkylamides in the perchloric acid–acetic anhydride system, obtained previously unknown 6-acetoxy-5,6-dihydro-1,3-oxazinium perchlorates, and developed a method for obtaining N-3-oxoalkylthioamides.

EXPERIMENTAL

The PMR spectra were recorded on Bruker-AC 200 P and Tesla BS-587 (80 MHz) instruments in $CDCl_3$. TMS was the internal standard. The IR spectra were recorded on a Specord IR-75 spectrometer in solutions of $CHCl_3$. The mass spectra were made on an MAT-112 (Finnigan) spectrometer using direct introduction of the substance in the ion source, ionization energy of 70 eV. The evolution of the reaction and purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates, with development with iodine vapors and UV light. N-3-Oxoalkylamides Ia-e were obtained with the methods in [2, 3].

6-Acetoxy-5,6-dihydro-4H-1,3-oxazinium Perchlorates IIa-e. Here 1.13 ml (7.84 mmole) of 70% $HClO_4$ in 3.10 ml of acetic anhydride was added by drops to a solution of 7.12 mmole of N-3-oxoalkylamide in 4.00 ml of acetic anhydride at 0°C. The reaction mass was left for 1 h at room temperature, then treated with absolute ether. The precipitated sediment was filtered off and washed on the filter with ether.

N-3-Oxoalkylthioamides IIIa-e. Here 6.7 mmole of 6-acetoxy-5,6-dihydro-4H-1,3-oxazinium perchlorate was added to 40 ml of a 1.5 M solution of NaSH in absolute methanol. The reaction mixture was stirred for 48 h, neutralized with a 10% solution of HCl, the solvent was distilled off, and the residue was extracted with chloroform (2 × 20 ml). After distillation of the solvent, the residue was purified by column chromatography on silica gel in chloroform–ethyl acetate solution, 95:5.

N-(2-Methyl-4-oxopeptyl-2)propiothioamide (IIIb). At room temperature and while stirring in a magnetic mixer, 3.0 g of 6-acetoxy-4,6,6-trimethyl-2-ethyl-5,6-dihydro-4H-1,3-oxazinium perchlorate (IIb) was added by portions to a suspension of 4.75 g of NaSH in 30 ml of DMF. Stirring was continued for 6 h, then the reaction mass was diluted with water and extracted with chloroform (5 × 20 ml). The extract was washed with a 10% solution of NaCl (2 × 20 ml) and dried with $MgSO_4$. The solvent was vacuum distilled and the sediment was recrystallized from hexane, yielding 1.77 g (99%) of compound IIIb.

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