5-ARYLIDENE-2-THIO-4-OXAZOLIDINONES IN HYDROXY- AND AMINOMETHYLATION REACTIONS

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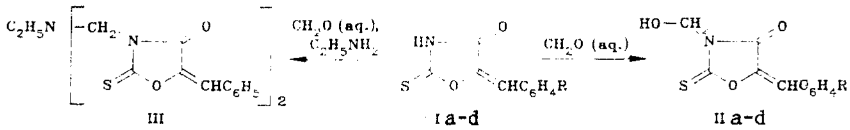
UDC 547.787.1.04:543.422.25

Hydroxymethylation and aminomethylation reactions of 5-arylidene-2-thio-4-oxazolidinones lead to the formation of substitution products at the ring nitrogen atom; this has been attributed to thermodynamic reaction control.

2-Thio-4-thiazolidinones undergo hydroxy- and aminomethylation exclusively at the ring nitrogen atom [1, 2]. By analogy, only 3-hydroxymethyl derivatives are formed in the reactions of 5-arylidene-2,4-thiazolidinones with formaldehyde [3]. In contrast, hydroxy- and aminomethylation of 2-imino-4-thiazolidinones lead to substitution products at the exocyclic nitrogen atom [4-6]. We propose that these results can be interpreted in terms of thermodynamic control of the reaction products due to the reversibility of the reactions [7, 8], especially in the case of hydroxyl-containing media, where of two possible isomers only one, the thermodynamically more stable one, is formed; logically, this isomer also exists in the structure of the more stable tautomeric form of the heterocyclic precursor or its corresponding monosubstituted derivative. Thus, in 2-thio- and 2-oxo-4-thiazolidinones the diketo form predominates [1, 3], while 2-methylamino substituted 4-thiazolinones exist in the amino form [9, 10].

This simple rule explains the positional selectivity observed in the hydroxy- and aminomethylation of 5-arylidene-2-thio-4-oxazolidinones (Ia-d), in which the thione form predominates [11]: reaction of compounds Ia-d with aqueous formaldehyde in acetone leads to the 3-hydroxymethyl derivatives IIa-d (Table 1), while reaction of compound Ia with aqueous formaldehyde and ethylamine in acetone gives the Mannich base III.



I, II a R=H, b R=*p*-Br, c R=*p*-NO₂, d R=*m*-NO₂

The fact that hydroxymethylation of compounds Ia-d occurs at the ring nitrogen atom $N_{(3)}$ is indicated by the high-frequency carbonyl group absorption in the product, at 1740-1755 cm^{-1}, and by the presence of a characteristic C=S vibrational band (at 1030-1065 cm^{-1}), in the IR spectra of the hydroxymethyl derivatives IIa-d. For compound IIb the position of the hydroxymethyl group is also confirmed by comparison of its PMR spectral data with the spectrum of 5-p-bromobenzylidene-3-ethyl-2-thio-4-oxazolidinone: the aromatic and methine proton signals in the two compounds are practically superimposable on one another.

The PMR spectra of compounds IIa-d contain, in addition to the signals given in Table 1, weak methine proton signals corresponding to compounds Ia-d (6.64, 6.68, 6.75, and 6.89 ppm, respectively), and methylene proton signals due to hydrated formaldehyde (4.55 ppm); this is attributed to partial hydrolysis of the hydroxymethyl derivatives IIa-d by residual water present in DMSO-D_6: IIa-d + $H_2O \rightleftharpoons$ Ia-d + $CH_2(OH)_2$.

The structure of compound III was reliably established based on the characteristic stretching vibrational bands of its unconjugated carbonyl and thiocarbonyl groups. The IR spectrum of the Mannich base obtained from compound Ia exhibits bands due to C=O (1740) and C=S (1080 cm^{-1}), but does not contain any NH bands, which provides evidence in favor of sub-

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Lensovet Leningrad Technological Institute, Leningrad. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 106-108, January, 1989. Original article submitted July 9, 1987.

TABLE 1. Physical Properties of Compounds IIa-d

Compound	R	Molecular formula	mp, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}			PMR spectrum, ppm				Yield, %
					O—H	C=O	C=S	Ar, m	CH, s	OH	CH_2, s	
II a	H	$C_{11}H_9NO_3S$	133	270 (4,82), 340 (4,48)	3470	1755	1030	7,42 . . . 7,78	6,88	6,72	5,08	82
II b	*p*-Br	$C_{11}H_8BrNO_3S$	188	260 (4,51) 351 (4,43)	3410	1740	1062	6,62 . . . 7,72	6,90	6,58	5,09	68
II c	*p*-NO_2	$C_{11}H_8N_2O_5S$	157	345 (3,95), 370 (4,35)	3410	1750	1065	8,16 . . . 8,32	7,09	6,89	5,16	71
II d	*m*-NO_2	$C_{11}H_8N_2O_5S$	150	225 (4,34), 342 (4,41)	3410	1755	1060	7,69 . . . 8,67	7,12	6,79	5,14	65

stitution at the $N_{(3)}$ atom and the formation, in analogy with the aminomethylation of the thia analog of compound Ia [2], of bis(heterylmethyl)ethylamine (III). In the PMR spectrum of this product the resonance signals due to the methine ($C_{(5)}=CH$) and methylene ($N_{(3)}CH_2$) protons are doubled, 6.90, 6.51, and 5.10, 5.00 ppm, respectively, and the downfield components of these "doublets" are approximately two times as intense as the upfield components. We ascribe this signal doubling to the instability of compound III, which undergoes hydrolysis by residual water in DMSO-D_6 to give the hydroxymethyl derivative IIa: III + $2H_2O \rightleftharpoons$ IIa + $C_2H_5NH_2$. The signals at 6.51 ($C_{(5)}=CH$) and 5.00 ppm ($N_{(3)}CH_2$) are assigned to compound III, the signals at 6.90 and 5.10 ppm to the corresponding protons in compound IIa. At higher power the PMR spectrum of compound III also reveals the presence of two weak signals at 6.69 and 4.53 ppm, which are assigned to resonance of the oxazolidinone Ia and hydrated formaldehyde, respectively, which are formed by hydrolysis of the hydroxymethyl derivative IIa.

Mannich bases of compound Ia could not be isolated when using propylamine or hexylamine as the amine component, but in both cases the hydroxymethyl derivative IIa was isolated.

EXPERIMENTAL

PMR spectra were recorded on a Tesla BS-497C (100 MHz) spectrometer using solutions in DMSO-D_6 versus HMDS as internal standard; IR spectra were obtained on an IKS-29 spectrophotometer (using KBr pellets), while UV spectra were measured on an SF-16 spectrophotometer using solutions in ethanol. The results of N, S (Br) elemental analysis for compounds IIa-d, and C, H, N, and S elemental analysis of compound III, agreed with calculations.

5-Arylidene-3-hydroxymethyl-2-thio-4-oxazolidinones (IIa-d). To a solution of 2.5 mmoles compound Ia in 100 ml acetone was added 2.0 ml (25 mmoles) formalin, and the reaction mixture was stirred for 2 h at 60°C; the resulting precipitate was filtered and dried under vacuum.

Bis[(5-benzylidene-2-thio-4-oxooxazolidinyl-3)methyl]ethylamine (III, $C_{24}H_{21}N_3O_4S_2$). To a solution of 2.0 g (10 mmoles) compound Ia in 150 ml acetone at 0°C was added with vigorous stirring 2.25 g (50 mmoles) ethylamine and 0.8 ml (10 mmoles) formalin; the reaction mixture was refluxed for 3.5 h, evaporated under vacuum to 1/3 of its initial volume, and the resulting precipitate was filtered, washed with water, and crystallized from a mixture of benzene–hexane (1:1). Yield 1.9 g (79%), mp 203°C. IR spectrum: 1740 (C=O), 1080 cm^{-1} (C=S). UV spectrum, λ_{max} (log ε): 240 (4.68), 260 (4.98), 348 nm (4.97). PMR spectrum: 7.42-7.76 (10H, m, C_6H_5); 6.90, 6.51 (2H, s, $C_{(5)}=CH$); 5.10, 5.00 (4H, s, $N_{(3)}CH_2N$); 2.76 (2H, m, $\mathbf{CH_2}CH_3$); 1.00 ppm (3H, m, $CH_2\mathbf{CH_3}$).

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