A NEW ELECTROPHILIC REARRANGEMENT

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A new electrophilic rearrangement of 2-substituted 4-alkoxy-5-mercapto-2*H*-pyridazin-3-ones to 2-substituted 5-alkylthio-4-hydroxy-2*H*-pyridazin-3-ones is described.

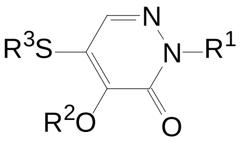
Key words: 2-Substituted 4-alkoxy-5-mercapto-2*H*-pyridazin-3-ones; 2-Substituted 5-alkylthio-4-hydroxy-2*H*-pyridazin-3-ones.

It is known[1] that 2-substituted 4-halogeno-5-mercapto-2*H*-pyridazin-3-ones with various electrophiles form the corresponding 2-substituted 4-halogeno-5-alkyl(aryl)thio-2*H*-pyridazin-3-ones. In our laboratory, the reaction of 2-substituted 4-alkoxy-5-mercapto-2*H*-pyridazin-3-ones (**1**) with electrophilic agents was studied. The reaction of compounds **1** with acyl halogenides or acid anhydrides in organic solvents like xylene afforded only products of the structure **2**. However, no reaction of **1** with *O*,*O*-dialkyl chlorothiophosphates was observed under the same conditions. On the other hand the same compounds or their sodium salts with or without the presence of *O*,*O*-dialkyl chlorothiophosphates by reflux in basic solvents like *N*,*N*-dimethylformamide (DMF), pyridine, and triethylamine (TEA) gave new compounds with the structure **3**.

By detailed study of this reaction we have found that 2-substituted 4-hydroxy-5-alkylthio-2*H*-pyridazin-3-ones (**3**) are formed by the rearrangement of **1**. This electrophilic rearrangement can be explained in terms of higher nucleophilicity of the sulfur atom in comparison with the oxygen atom. The dependence of the rearrangement course on the nature of the solvent is summarized in Table I. The nucleophilicity of the sulfur atom is increased due to the formation of intermolecular hydrogen bonds between the proton accepting solvents and the SH group, followed by proton transfer, facilitating probably the rearrangement of the alkyl group. Although rearrangement of compounds **1** to form compounds **3** does not proceed in solvents like ethanol and 2-propanol (Table I), the alkaline salts of **1** rearrange even in the mentioned solvents and xylene.

TABLE I
The influence of the solvent on the electrophilic rearrangement of compounds **1a**, **1d** and their sodium salts (+ rearranged, – not rearranged, ± the reaction was not completed)

Solvent	**1a**	**1a** salt	**1d**	**1d** salt
DMF	+	+	+	+
DMSO	+	+	+	+
TEA	+	+	+	+
Pyridine	+	+	+	+
Ethanol	–	+	–	+
2-Propanol	–	+	–	+
Xylene	–	–	–	±



1-3

	R^1	R^2	R^3
1a	CH_3	CH_3	H
1b	CH_3	C_2H_5	H
1c	CH_3	C_3H_7	H
1d	C_6H_5	CH_3	H
1e	C_6H_5	C_2H_5	H
1f	C_6H_5	i-C_3H_7	H
1g	3-$CH_3C_6H_4$	CH_3	H
1h	3-Cl-C_6H_4	CH_3	H
1i	3-CF_3-4-Cl-C_6H_3	CH_3	H
2a	C_6H_5	CH_3	CH_3CO
2b	C_6H_5	CH_3	C_2H_5OCO
3a	CH_3	H	CH_3
3b	CH_3	H	C_2H_5
3c	CH_3	H	C_3H_7
3d	C_6H_5	H	CH_3
3e	C_6H_5	H	C_2H_5
3f	C_6H_5	H	i-C_3H_7
3g	3-$CH_3C_6H_4$	H	CH_3
3h	3-Cl-C_6H_4	H	CH_3
3i	3-CF_3-4-Cl-C_6H_3	H	CH_3

The structure of compounds **1** and **3** was proven by comparison of the model compounds spectral data[2–6]. In their IR spectra (Tables II and III) the ν(SH) bands at 2 585 cm^{-1} of compounds **1a–1i** and the ν(OH) at 3 370 cm^{-1} of compounds 3**a–3i** were present. UV spectra of compounds **3** contained bands at longer wavelengths (λ_{max} 291–308 nm) than those in compounds **1** (λ_{max} 285–296 nm, Tables II and III).

EXPERIMENTAL

UV spectra (λ_{max}, nm (log ε)) were measured on a Specord M 40 Zeiss spectrophotometer. IR spectra ($\tilde{\nu}$, cm^{-1}) were recorded on a Specord M 80 Zeiss spectrophotometer and ^1H NMR spectra (δ, ppm)

TABLE II
Characteristic data of compounds **1a–1i**

Compound	M.p., °C	$\tilde{\nu}$(C=O)	$\tilde{\nu}$(S–H)	λ_{max} (log ε)		
1a	88–90	1 650	2 585	230 (3.12)	255 (2.79)	285 (2.72
1b	67–69	1 650	2 585	232 (3.16)	259 (3.01)	290 (2.90)
1c	52–53	1 651	2 587	234 (3.18)	262 (3.19)	293 (2.96)
1d	140–142	1 663	2 585	230 (3.20)	263 (3.02)	290 (2.91)
1e	104–106	1 663	2 585	235 (3.24)	263 (3.09)	297 (2.98)
1f	78–80	1 663	2 586	232 (3.19)	264 (3.11)	292 (2.94)
1g	116–118	1 663	2 585	233 (3.18)	265 (3.24)	292 (2.94)
1h	147–149	1 665	2 585	235 (3.20)	263 (3.20)	294 (3.02)
1i	98–100	1 665	2 582	240 (3.22)	268 (3.19	296 (3.05)

TABLE III
Spectral data of compounds **3a–3i**

Compound	$\tilde{\nu}$(C=O)	$\tilde{\nu}$(O–H)	λ_{max} (log ε)	
3a	1 635	3 375	215 (4.17)	306 (3.75)
3b	1 632	3 370	215 (4.11)	303 (3.82)
3c	1 635	3 372	215 (4.19)	308 (3.75)
3d	1 635	3 375	214 (4.28)	291 (3.81)
3e	1 635	3 370	215 (4.32)	295 (3.71)
3f	1 633	3 372	213 (4.30)	293 (3.78)
3g	1 634	3 370	214 (4.22)	295 (3.76)
3h	1 632	3 370	214 (4.20)	294 (3.80)
3i	1 634	3 372	215 (4.22)	296 (3.76)

on a Varian VXR-300 (300 MHz) spectrometer. 2-Substituted 4-alkoxy-5-mercapto-2*H*-pyridazin-3-ones (**1a–1i**) were prepared according to the procedure given in ref.[3].

2-Phenyl-4-methoxy-5-acetylthio-2*H*-pyridazin-3-one (**2a**)

Acetic anhydride (25 ml) was added to 2-phenyl-4-methoxy-5-mercapto-2*H*-pyridazin-3-one (2.3 g, 0.01 mol), the reaction mixture was refluxed for 5 h. After cooling the unreacted acetic anhydride was distilled off under reduced pressure and the residue was crystallized from ethanol giving white crystalline compound **2a**; yield 1.9 g (69%), m.p. 101.5 °C. For $C_{13}H_{12}N_2O_3S$ (276.3) calculated: 56.51% C, 4.38% H, 10.14% N, 11.60% S; found: 56.03% C, 4.30% H, 10.11% N, 11.64% S. IR

TABLE IV
Characteristic data of compounds **3a–3i**

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found			
			% C	% H	% N	% S
3a	$C_6H_8N_2O_2S$	155–157	41.84	4.68	16.26	18.61
	(172.2)	76	41.95	4.80	16.19	18.80
3b	$C_7H_{10}N_2O_2S$	143–145	45.15	5.41	15.04	17.21
	(186.2)	72	45.22	5.55	15.13	17.30
3c	$C_8H_{12}N_2O_2S$	118–120	48.00	6.04	14.00	16.01
	(200.2)	78	48.11	6.15	14.10	16.18
3d	$C_{11}H_{10}N_2O_2S$	111–117	56.39	4.30	11.95	13.68
	(234.3)	84	56.45	4.41	12.02	13.80
3e	$C_{12}H_{12}N_2O_2S$	132–134	58.04	4.87	11.28	12.91
	(248.3)	77	58.16	4.91	11.39	12.82
3f	$C_{13}H_{14}N_2O_2S$	101–103	59.52	5.38	10.68	12.22
	(262.3)	64	59.71	5.41	10.80	12.35
3g	$C_{12}H_{12}N_2O_2S$	169–171	58.04	4.87	11.28	12.91
	(248.3)	72	58.18	4.95	11.38	12.98
3h[a]	$C_{11}H_9ClN_2O_2S$	227–229	49.16	3.38	10.42	11.93
	(268.7)	75	49.22	3.41	10.51	12.11
3i	$C_{12}H_8ClF_3N_2O_2S$	162–164	42.80	2.38	8.32	9.52
	(336.7)	80	42.99	2.41	8.46	9.68

[a] % Cl: calculated 13.19, found 13.26.

spectrum ($CHCl_3$): 1 660 (C=O), 1 720 (CO–S). UV spectrum (CH_3OH): 217 (3.22), 260 (3.18), 335 (2.97). ^{1}H NMR spectrum ($CDCl_3$): 2.61 s, 3 H (CH_3CO); 3.90 s, 3 H (CH_3O); 7.12–7.75 m, 5 H (C_6H_5); 8.17 s, 1 H (H-6).

2-Phenyl-4-methoxy-5-ethoxycarbonylthio-2*H*-pyridazin-3-one (**2b**)

To 2-phenyl-4-methoxy-5-mercapto-2*H*-pyridazin-3-one (6.9 g, 0.03 mol) in xylene (50 ml), ethyl chloroformate (4 g, 0.037 mol) was added with stirring. The stirring was continued for 7 h at reflux temperature until the evolution of HCl ceased, then xylene was distilled off under reduced pressure and the residue was crystallized from cyclohexane giving white crystals of the compound **2b**; yield 5.9 g, (58%), m.p. 60.6 °C. For $C_{14}H_{14}N_2O_4S$ (276.3) calculated: 54.89% C, 4.61% H, 9.14% N, 10.47% S; found: 54.80% C, 4.52% H, 9.22% N, 10.87% S.

2-Substituted 4-Hydroxy-5-alkylthio-2*H*-pyridazin-3-ones (**3a–3i**)

Method A. A mixture of compounds **1a–1i** (3 g) and solvent (40 ml) was refluxed for 4 h. After cooling the solvent was removed under reduced pressure and the residue was crystallized from toluene and ethanol.

Method B. The sodium salts of compounds **1a–1i** were prepared by addition of sodium methylate to appropriate pyridazine derivative **1a–1i** and methanol was removed under reduced pressure (26 Pa) at 40 °C with stirring. A mixture of sodium salts **1a–1i** (1.5 g) and solvent was refluxed for 4 h. After cooling the solvent was removed under reduced pressure, the residue was dissolved in water (60 ml) and on acidification with 1 M HCl the precipitated compound was filtered off and crystallized from toluene or ethanol. Characteristic data of compounds **3a–3i** are given in Table IV.

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