ml (5 mmole) of concentrated HCl, and 30 ml of butanol (or ethanol for XX) was refluxed for 2 h, after which the resulting precipitate (after evaporation of the solvent in the case of XX) was triturated in 30 ml of 25% ammonium hydroxide, washed successively with water and ethanol, and crystallized from ethanol–benzene (4:1).

Compound XVIII. This compound, with mp 234-235°C, was obtained in 28% yield. Found: C 71.3; H 4.0; Cl 17.4; N 6.6%. $C_{24}H_{24}Cl_{12}N_2$. Calculated: C 71.8; H 3.5; Cl 17.7; N 7.0%.

Compound XIX. This compound, with mp 237-238°C, was obtained in 21% yield. Found: C 64.6; H 3.0; Br + Cl 25.8; N 6.6%. $C_{24}H_{14}BrClN_2$. Calculated: C 64.6; H 3.1; Br + Cl 25.9; N 6.3%.

Compound XX. This compound, with mp 183-184°C, was obtained in 12% yield. Found: C 65.2; H 3.7; Br 22.6; N 7.9%. $C_{19}H_{13}BrN_2$. Calculated: C 65.3; H 3.8; Br 22.9; N 8.0%.

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SELECTIVE O- AND N_3-ALKYLATION OF 2-ALKYLTHIO-4-HYDROXYPYRIMIDINES BY HALOACETATES

P. I. Vainilavichyus and V. Yu. Syadyaryavichyute

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The effect of a number of factors on the regioselectivity of alkylation of 2-alkylthio-4-hydroxypyrimidines by methyl bromoacetate has been studied. In non-polar and low-polarity solvents N_3-alkylation predominated whereas O-alkylation occurred in aprotic dipolar solvents. Preparative methods for the synthesis of O- and N_3-carbomethoxymethyl 2-alkylthio-4-hydroxypyrimidines have been developed.

We have previously shown [1] that the sodium salts of 2-methylthio-4-hydroxypyrimidines (Ia, b) form a mixture of O- and N_3-alkylation products (IIa, b; IIIa, b) in methanol.

With a view to developing a preparative method for O- and N_3-carbalkoxymethyl 2-alkylthio-4-hydroxypyrimidines (II, III) we have studied the effects of a number of factors on the regioselectivity of alkylation of 4-hydroxypyrimidines I using methyl chloro- and bromoacetates

V. Kapsukas State University, Vilnyus, 232734.

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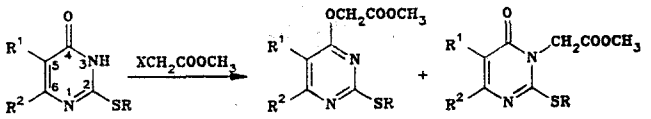

Ia-g IIa-g IIIa-g

I—III a $R=CH_3$, $R^1=R^2=H$; b $R=R^2=CH_3$, $R^1=H$; c $R=C_2H_5$, $R^1=H$, $R^2=CH_3$; d $R=CH(CH_3)_2$, $R^1=H$, $R^2=CH_3$; e $R=CH_2C_6H_5$, $R^1=H$, $R^2=CH_3$; f $R=R^2=CH_3$, $R^1=C_2H_5$; g $R=C_2H_5$, $R^1=CH(CH_3)_2$, $R^2=CH_3$; X=Cl, Br

On the basis of [2] it would be expected that an increase in the steric hindrance of substituents in positions 2 or 5 of the pyrimidine ring of anions of I would give rise to a change in the ratio of O- and N_3-alkylation products. For verification we have investigated the alkylation of the 4-hydroxypyrimidines Ic-g by methyl bromoacetate in methanol—sodium methylate. Data in Table 2 shows that the isomer ratio under these conditions varied little with the structure of the anions I.

Among factors influencing the direction of alkylation of ambident anions the most important is apparently the nature of the solvent [2]. We have alkylated the sodium salt of Ib in different solvents. As apparent from Table 1 non-polar and low-polarity solvents led only to the N_3-isomer IIIb (with the exception of diethyl ether which gave IIb and IIIb in the ratio 1:4). A significant increase in the O-alkyl contribution was observed in aprotic dipolar solvents but the effect on the regioselectivity was nonuniform. Thus, acetone and acetonitrile led to a mixture of IIb and IIIb in the ratio 1:3 and 1:4:1, respectively, but in dimethyl formamide and hexamethylphosphoric triamide to IIb only. Thus solvent variation can direct the regioselectivity of alkylation of Na salts of 2-alkylthio-4-hydroxypyrimidines by methyl bromoacetate.

A study of the alkylation of ambident anions has shown that their tendency to react at the center of highest electron density increases with growth of the cation radius [2]. When triethylamine was used as base and solvent and tetrabutylammonium bromide as phase transfer catalyst the alkylation of 4-hydroxypyrimidines I by methyl bromoacetate occurred regioselectively at the oxygen atom and depended on temperature. Thus, If, g up to 10°C and Ia-e up to 60°C gave only the O-isomers II. Increase in temperature led to the appearance of the O-isomers II and N_3-isomers III which contradicted the behavior of the majority of ambident anions [2]. A similar decrease in the O-alkylation component of acetoacetate enolate with increase in temperature was recorded in [3] for N-methylpyrrolidone. We did not observe isomerization of II to III. Exchange of methyl chloroacetate for methyl bromoacetate had virtually no effect on the formation of II. This type of O-alkylation of the 4-hydroxypyrimidines I differed conveniently from the alkylation of I anions in aprotic dipolar solvents because it avoided the need to pre-synthesize the Na salts of I.

In order to prove the structure of isomers IIc-g and IIIc-g we have compared their UV, IR, and PMR spectra (Table 3) with those of the previously reported [1] O- and N_3-isomers (IIa, b; IIIa, b). The UV spectra of IIc-g showed absorptions at 253-256 nm and IIIc-g at 291-293 nm. In their IR spectra the O-isomers IIc-g had ester absorption at 1744-1747 cm^{-1}

TABLE 1. Effect of Solvent on the Alkylation of the Na-Salts of 6-Methyl-2-methylthio-4-hydroxypyrimidine (Ib) by Methyl Bromoacetate

Solvent	Overall yield, %	Relative yield, %	
		O-isomer	N_3-isomer
Carbon tetrachloride	77	0	100
Dioxane	75	0	100
Tetrahydrofuran	70	0	100
Toluene	56	Traces	~100
Diethyl ether	64	20	80
Acetone	66	25	75
Methanol*	73	50	50
Acetonitrile	70	59	41
Dimethylformamide	68	100	0
Hexamethylphosphoric triamide	70	100	0

*From [1].

TABLE 2. Parameters of the Compounds Synthesized

Compound*	R_f	mp, °C or bp, °C (hPa)	Found, %			Empirical formula	Calculated, %			Yield, %**		
			C	H	N		C	H	N	A	B	C
IIa	0,38	54—55								26	52	
IIb	0,57	80,5—81,5								33	72	
IIc	0,62	55—56	49,9	6,0	11,7	$C_{10}H_{14}N_2O_3S$	49,6	5,8	11,6	40	79	
IId	0,59	67—68	52,4	6,1	10,8	$C_{11}H_{16}N_2O_3S$	51,5	6,3	10,9	45	76	
IIe	0,69	53—54	59,7	5,5	9,2	$C_{15}H_{16}N_2O_3S$	59,2	5,3	9,2	47	68	
IIf	0,64	54—55	51,9	6,4	11,0	$C_{11}H_{16}N_2O_3S$	51,5	6,3	10,9	44	71	
IIg	0,64	160 (8)	55,3	7,0	10,1	$C_{13}H_{20}N_2O_3S$	54,9	7,1	9,9	43	60	
IIIa	0,23	95—96								22		45
IIIb	0,45	76—77								33		77
IIIc	0,50	50—51	49,8	5,9	11,9	$C_{10}H_{14}N_2O_3S$	49,6	5,8	11,6	35		60
IIId	0,47	54—55	52,0	6,5	11,2	$C_{11}H_{16}N_2O_3S$	51,5	6,3	10,9	30		62
IIIe	0,50	71	59,0	5,3	9,3	$C_{15}H_{16}N_2O_3S$	59,2	5,3	9,2	38		77
IIIf	0,56	94—95	51,7	6,0	11,0	$C_{11}H_{16}N_2O_3S$	51,5	6,3	10,9	44		75
IIIg	0,52	135 (1,3)	55,2	7,6	10,1	$C_{13}H_{20}N_2O_3S$	54,9	7,1	9,9	43		58

*For IIa, b and IIIa, b see [1].

**A) Data for alkylation of Ia-g Na-salts by methyl bromoacetate in methanol. B) Alkylation of Ia-g by methyl bromoacetate in triethylamine in the presence of tetrabutylammonium bromide. C) Alkylation of Ia-g Na-salts by methyl bromoacetate in carbon tetrachloride.

whereas N_3-isomers IIIc-g showed the ester at 1740-1746 cm^{-1} together with a clear lactam C=O band at 1660-1680 cm^{-1}. The PMR spectra were characterized by signals (among others) for the OCH_2 protons at 4.73-4.85 ppm in IIc-g and by the NCH_2 protons at 4.65-4.72 ppm in IIIc-g.

Alkylation of 2-alkylthio-4-hydroxypyrimidines I by methyl haloacetates did not lead to N_1-alkylation products (in contrast to the alkylation of 4-hydroxypyrimidines by alkyl halides [4]).

The obtained data can be explained by the general rules characterizing classical ambident anions and serves as a basic method for selective O- and N_3-alkylation of 2-alkylthio-4-hydroxypyrimidines by haloacetates.

EXPERIMENTAL

Monitoring of reactions and product purities was carried on TLC using Silufol plates and iodine vapor visualization. Column chromatography was performed on Chemapol L 100/160 silica gel using chloroform: ethyl acetate (5:1) as eluent. UV spectra were measured on a Specord UV-vis spectrometer with ethanol solvent and IR spectra on a Specord IR-75 spectrometer with Vaseline mulls. PMR Spectra were recorded on a Tesla BS-487C (80 MHz) instrument using trifluoroacetic acid solvent and HMDS internal standard.

2-Alkylthio-4-hydroxypyrimidines (I) were obtained by method [5] (Ia, b, f), [6] (Ic), or [7] (Ie). Compound Id was prepared by alkylation of the Na-salt of 4-methyl-2-thiouracil by isopropyl iodide in DMF in 76% yield with mp 152-153°C (from ethanol). Found: C 51.9; H 6.6; N 15.1%. $C_8H_{12}N_2OS$. Calculated: C 52.2; H 6.6; N 15.2%; M 184. 4-Hydroxypyrimidine Ig was obtained similarly by [8] in 75% yield with mp 128-130°C (ethanol). Found: C 56.3; H 7.4; N 13.3%. $C_{10}H_{16}N_2OS$. Calculated: C 56.6; H 7.6; N 13.2%; M 212. The sodium salts of the 4-hydroxypyrimidines I were synthesized similarly [4]. Parameters and spectral data for new compounds are given in Tables 2 and 3.

Alkylation of 2-alkylthio-4-hydroxypyrimidine Na-salts (Ia-g). A mixture of Ia-g Na-salt (10 mmole), methyl bromoacetate (1.84 g, 12 mmole), and the appropriate solvent (5 ml) were stirred for 1 h at 90°C. The precipitate was removed, the solvent evaporated in vacuo and the residue was washed with water, dried, and column chromatographed. The separated isomers were crystallized from hexane or distilled in vacuo.

2-Alkylthio-4-carbomethoxymethoxypyrimidines (IIa-g). The methyl haloacetate (0.12 mole) was added dropwise with stirring to Ia-g (0.1 mole) and tetrabutylammonium bromide (3.2 g, 0.01 mole) in triethylamine (40 ml) at 0-10°C (If, g) or at 50-60°C (Ia-e). The mixture was held at the stated temperature for 3 h (If, g) or 5 min (Ia-e), cooled, and diluted with water (1.5 liter). With the exception of IIg, the crystalline product was filtered off,

TABLE 3. Spectral Data for IIc-g, IIIc-g

Compound	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, ν, cm⁻¹ C=O (ester)	IR spectrum, ν, cm⁻¹ C=O (lactam)	PMR spectrum, δ, ppm (J, Hz) R	R'	$R^2=CH_3$ (3H, s)	OCH_2 or NCH_2 (2H, s)	OCH_3 (3H, s)
IIc	204 (4,12), 256 (4,17)	1747		0,98 (3H, t, $J=7$); 2,85 (2H, q, $J=7$)	6,34 (1H, s)	2,13	4,78	3,45
IId*	207 (3,90), 254 (4,17)	1747		1,31 (6H, d, $J=7$); 3,54—3,93 (1H, m)	6,25 (1H, s)	2,28	4,79	3,64
IIe	204 (4,39), 254 (4,16)	1744		4,10 (2H, s); 6,88 (5H, s)	6,38 (1H, s)	2,18	4,73	3,43
IIf	203 (3,95), 253 (4,14)	1746		2,23 (3H, s)	0,78 (3H, t, $J=7$); 2,20 (2H, q, $J=7$)	2,18	4,85	3,46
IIg	204 (3,96), 254 (4,24)	1745		0,96 (3H, t, $J=8$); 2,80 (2H, q, $J=8$)	0,90 (6H, d, $J=7$); 2,67—2,98 (1H, m)	2,18	4,82	3,46
IIIc	226 (3,74), 292 (3,95)	1746	1670	1,07 (3H, t $J=8$); 3,31 (2H, q $J=8$)	6,09 (1H, s)	2,06	4,69	3,47
IIId*	228 (3,72), 293 (3,94)	1740	1680	1,33 (6H, d, $J=7$); 3,75—4,13 (1H, m)	5,94 (1H, s)	2,13	4,65	3,65
IIIe	222 (shoulder) 292 (3,94)	1746	1671	4,38 (2H, s); 7,00 (5H, s)	6,06 (1H, s)	1,96	4,66	3,44
IIIf	226 (3,74), 293 (4,02)	1743	1660	2,60 (3H, s)	0,72 (3H, t, $J=7$); 2,12 (2H, q, $J=7$)	2,12	4,72	3,51
IIIg	249 (3,85), 291 (3,91)	1744	1668	1,04 (3H, t, $J=8$); 3,10 (2H, q, $J=8$)	0,85 (6H, d, $J=7$); 2,95—3,28 (1H, m)	2,08	4,66	3,48

*PMR Spectrum recorded in $CDCl_3$

washed with water, and recrystallized from hexane. For the liquid product IIg, it was separated, dissolved in ether, dried over $CaCl_2$, the ether removed, and distilled in vacuo.

2-Alkylthio-3-carbomethoxymethyl-4-pyrimidones (IIIa-g). A mixture of Ia-g Na-salts (0.1 mole), the methyl haloacetate (0.12 mole), and carbon tetrachloride or dioxan (50 ml) was stirred at reflux for 1 h. The precipitate was removed by filtration, the solvent removed in vacuo, and the residue was crystallized from hexane (IIIg was distilled in vacuo).

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