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AMIDOALKYLATION OF MONO- AND DIMERCAPTO-PYRIMIDINES

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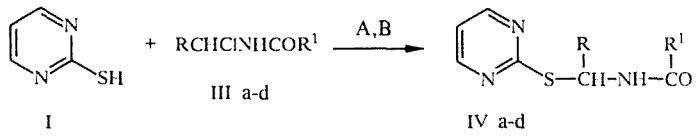
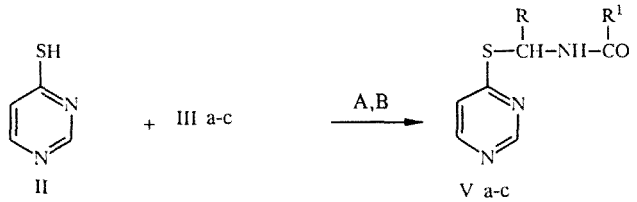
Reaction of 2- and 4-mercapto- and 2,4-dimercaptopyrimidines with N-(1-chloroalkyl)amides of carboxylic acids and N-acylimines forms only the S-substituted products.

Amidoalkylation of mercaptopyrimidines has not been studied, in contrast with their rather well studied alkylation. The presence of several nucleophilic centers in mono- and dimercaptopyrimidines makes amidoalkylation possible at both the S and N atoms of the ring.

We have shown that the reaction of 2- and 4-mercaptopyrimidines (I, II) with chloroalkylamides of carboxylic acids (IIIa-d) in the presence of equimolar amounts of NaOH at 0 °C (method A) or triethylamine at 20 °C (method B) gives only the S-substituted compounds IVa-d and Va-c, respectively (Table 1).



I III a-d IV a-d

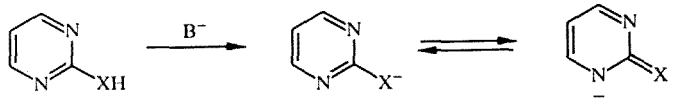


II III a-c V a-c

III—V a R = CCl_3, R^1 = Ph; b R = CCl_3, R^1 = *t*-Bu; c R = COPh, R^1 = Ph; III,IV d R = H, R^1 = Ph

The structures of IV and V were proved by ^{13}C NMR spectra (Table 2). The significant features are the chemical shifts of $C_{(2)}$ and $C_{(4)}$ (they are known to lie in the range 175-178 for =C=S and 157-168 ppm for ≡C—SR). Furthermore, the chemical shift of the α-carbon of the amidoalkyl fragment =N—CH—S— in IV and V is 65.1-67.7; of the =N—CH—N= group, 70.7-71.4 ppm [1].

Amidoalkylation of mercaptopyrimidines is substantially different from that of hydroxypyrimidines [2], which form the N-substituted products. Several factors explain such a difference. In both instances the reaction with chloroalkylamides occurs in the presence of bases, i.e., thiolate and alkoxide anions are formed during the reaction.



X = S, O

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TABLE 1. Properties of Synthesized Compounds IV, V, and VIII-IX

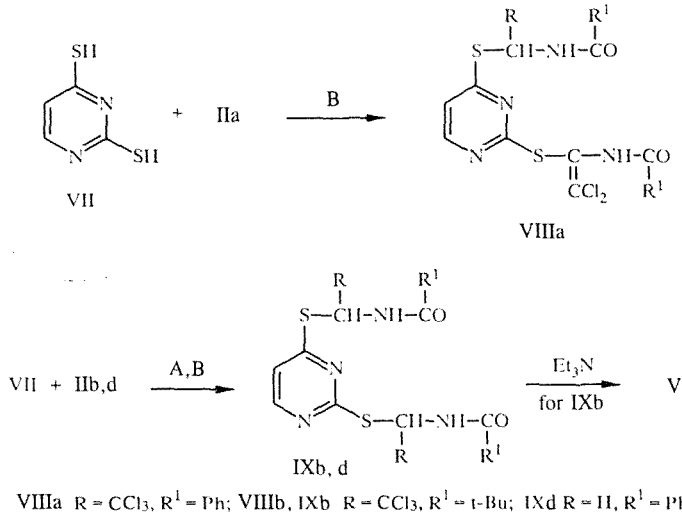
Compound	Empirical formula	mp, °C	Solvent for crystallization	Yield, % (method)
IVa	$C_{13}H_{10}Cl_3N_3OS$	144...145	Benzene	93,0 (A), 78,5 (B), 88,0 (C)
IVb	$C_{11}H_{14}Cl_3N_3OS$	167...170	CCl_4	75,0 (B)
IVc	$C_{19}H_{15}N_3O_2S$	165...167	MeCN	84,5 (A)
IVd	$C_{12}H_{11}N_3OS$	122...124	Benzene	96,0 (B)
Va	$C_{13}H_{10}Cl_3N_3OS$	136...137	Benzene	95,0 (B), 87,7 (C)
Vb	$C_{11}H_{14}Cl_3N_3OS$	119...120	Benzene	93,3 (A), 77,0 (B)
Vc	$C_{19}H_{15}N_3O_2S$	145...147	Ethylacetate	96,6 (B)
VIIIa	$C_{22}H_{15}Cl_5N_4O_2S_2$	204...205	Benzene	44,5 (B)
VIIIb	$C_{18}H_{23}Cl_5N_4O_2S_2$	180...181	Benzene	65,0 (D)
IXb	$C_{18}H_{24}Cl_6N_4O_2S_2$	174...175	Ethylacetate	57,9 (A), 47,0 (B)
IXd	$C_{20}H_{18}N_4O_2S_2$	206...208	Dioxane	66,0 (B)

The thiolate anion, in contrast with alkoxide, is a soft base in terms of the hard-and-soft acid-base principle of Pearson. The amidoalkylating agent is a "soft" electrophile and attacks the soft center, S. The high nucleophilicity of thiolate compared with alkoxide and the $=N^-$ anion is due to the large polarizability of the S atom. The transition state of the mercapto compounds, for which the negative charge on the atom neighboring S is increased, is stabilized by α-orbital resonance. Attack at the S forms more stable products that persist in alkaline medium at room temperature for long periods.

For amidoalkylation of 2- and 4-mercaptopyrimidines, N-(benzoyl)trichloroacetaldimine (VI) [3] (method B) was also used. The negative inductive effect of the trichloromethyl group and the conjugation of the azomethine group with the carbonyl [4] make VI highly reactive toward nucleophiles. The high reactivity of VI and the absence of base might have changed the direction of the amidoalkylation. However, only the S-substituted products IVa and Va, respectively, were obtained.

2,4-Dimercaptopyrimidine VII reacts with chloroalkylamides IIa, -b, and -d to form doubly S-substituted products.

For chloroalkylamide IIa, the substitution is accompanied by dehydrochlorination and formation of VIIIa. Products IXb and -d are obtained through amidoalkylation with chloroalkylamides IIb and -d. Compound IXb is dehydrochlorinated by triethylamine to form the unsaturated product VIIIb, which is similar to VIIIa. The substituted vinylmercapto group in VIIIa and -b is probably located at the 2-position of the pyrimidine ring since we observed the analogous dehydrochlorination during amidoalkylation of 2-thiouracil [1]. Dehydrochlorination occurs with the $SCH(CCl_3)NHCOR^1$ substituent in the 4-position of the pyrimidine ring. Product IVa, which has no such substituent, is not dehydrochlorinated under these same conditions.



VIIIa R = CCl_3, R^1 = Ph; VIIIb, IXb R = CCl_3, R^1 = t-Bu; IXd R = H, R^1 = Ph

TABLE 2. ^{13}C NMR Spectra of III, V, VIII, and IX

Compound	Chemical shifts,* δ, ppm											
	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(1)'}$	$C_{(2)'}$	$C_{(3)'}$	$C_{(4)'}$	$C_{(5)'}$	$C_{(6)'}$	$C_{(7)'}$	other signals
IVa	166,25	158,22	118,39	158,22	67,72	101,91	167,90	132,92	127,85	128,33	132,04	–
Vb	168,09	158,12	118,28	158,12	67,30	102,13	176,84	–	–	–	–	38,31 [– C(CH$_3$)$_3$] 26,71 (CH$_3$)
Va	165,45	158,03	119,42	155,97	65,48	101,72	166,37	132,90	127,95	128,39	132,15	–
Vb	165,70	157,96	119,33	155,89	65,19	101,87	177,01	–	–	–	–	38,41 [– C(CH$_3$)$_3$] 26,72 (CH$_3$)
VIIIa	166,21	166,50	115,53	156,37	66,13 67,86	101,18 101,74	167,02 167,84	132,95	127,88	128,23	132,05	–
VIIIb	167,03	168,14	115,75	156,18	66,58 67,65	101,05 101,79	176,84 177,07	–	–	–	–	38,32 & 38,38 [2C(CH$_3$)$_3$] 26,59 & 26,68 (2CH$_3$)

*δ of $C_{(2)}$ and $C_{(4)-(6)}$ are chemical shifts of the C atoms of the pyrimidine ring; δ of $C_{(1)'-(7)'}$ are chemical shifts of C atoms of the amidoalkyl group

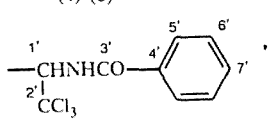


TABLE 3. PMR Spectra of I, III-V, and VII-IX

Compound	Chemical shifts, δ, ppm (J, Hz)					
	2-H, s	5-H, t	6-H, d	—CH—NH, d	NH—CH, d	other signals*
I	—	6,82	8,25	—	—	12,8 (1H, s, SH)
II	8,31	7,20 d	7,89	—	—	14,06 (1H, s, SH)
IVa	—	*[2]	8,77 (4,8)	7,87 (9,3)	9,86 (9,3)	—
IVb	—	7,29 (4,9)	8,70 (4,9)	7,33 (9,5)	8,77 (9,5)	1,10 [9H, s, $C(CH_3)_3$]
IVd	—	7,24	8,67 (5,0)	—	9,30 t	5,10 (2H, d, CH_2)
Va	9,11	*[2]	8,57 (5,4)	*[2]	9,9 (9,4)	—
Vb	9,05	7,57 (5,4)	8,56 (5,6)	7,45 (9,4)	8,8 (9,4)	1,11 [(9H, s, $C(CH_3)_3$]
VII	—	6,44 d	7,19 d	—	—	12,80 (1H, s, 2-SH); 13,53 (1H, s, 4-SH)
VIIIa	—	*[2]	8,38 (5,2)	*[2]	10,22	10,24 (1H, s, NH)
IXb	—	7,35 (5,4)	8,49 (5,4)	7,14 (9,4) 7,28 (9,6)	8,76 (9,6)	1,08 [(9H, s, $C(CH_3)_3$] 1,13 [(9H, s, $C(CH_3)_3$]
IXd	—	7,22 (5,4)	8,33 (5,4)	—	9,33 m	5,22 (4H, t, $2CH_2$—NH)

*Multiplet of aromatic protons at 7.30-7.88 ppm.

**Signal overlapped by the multiplet of phenyl protons.

The structures of the synthesized compounds are confirmed using PMR spectra (Table 3).

EXPERIMENTAL

A Varian VXP-300 spectrometer was used to record ^1H and ^{13}C NMR spectra in DMSO-D_6 (TMS internal standard).

Elemental analyses of the synthesized compounds for C, H, Cl, N, and S agreed with the calculated values.

2- and 4-mercaptopyrimidines were obtained by known methods [5, 6]; 2,4-dimercaptopyrimidine, by the literature method [7]; chloroalkylamides of carboxylic acids, by previous methods [8-12].

The properties of the synthesized compounds are listed in Tables 1-3.

2-(1-Acylamino-2,2,2-trichloroethylthio)pyrimidine (IVa-d), 4-(1-Acylamino-2,2,2-trichloroethylthio)pyrimidine (Va-c), 2-(1-Benzoylamino-2,2-dichloroethenylthio)-4-(1-benzoylamino-2,2,2-trichloroethylthio)pyrimidine (VIIIa), and 2,4-Di-(1-acylamino-2,2,2-trichloroethylthio)pyrimidine (IVb,d). General Synthesis Methods. A. A solution of chloroalkylamide III (10 mmole, 20 mmole for the dimercaptopyrimidine) in acetone (60 ml) was added dropwise at 0 °C with stirring to the mono- or dimercaptopyrimidine I, II, or VII (10 mmole) and NaOH (10 mmole) in H_2O (20 ml). The resulting precipitate was filtered off, washed with H_2O, and dried in air.

B. A solution of chloroalkylamide III (10 mmole, 20 mmole for the dimercaptopyrimidine VII) in absolute CH_3CN (50 ml) was added dropwise to a suspension of the mono- or dimercaptopyrimidine (10 mmole) and triethylamine (10 mmole) in absolute CH_3CN (30 ml). The suspension was stirred at 20 °C for 20 h. The precipitate was filtered off. The filtrate was evaporated to half its volume. The resulting precipitate was combined with the first, washed with H_2O, and dried in air.

C. A mixture of mercaptopyrimidine II or III (10 mmole) and N-(benzoyl)trichloroacetaldimine (10 mmole) in absolute CH_3CN (70 ml) was stirred at 20 °C for 20 h. The solution was evaporated to dryness. The residue was crystallized from benzene.

For each amidoalkylation product, the preparation method, yield, and melting point are given in Table 1.

2-(1-Pivaloylamino-2,2-dichloroethenylthio)-4-(1-pivaloylamino-2,2,2-trichloroethylthio)pyrimidine (VIIIb). D. Triethylamine (1.2 g, 12 mmole) in absolute CH_3CN (15 ml) was added dropwise at 20 °C to a suspension of IXb (2.0 g, 3 mmole) in absolute CH_3CN (60 ml). The mixture was stirred at 20 °C for 4 h and left overnight in a refrigerator. The precipitate was filtered off, washed with H_2O, and dried in air (see Table 1).

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