CHEMICAL PROPERTIES OF ACYLATED DERIVATIVES OF 4,6-DIAMINO-2-MERCAPTOPYRIMIDINE

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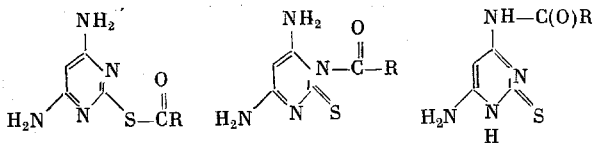
Previously we had shown [1] that, depending on the conditions, the acylation of 4,6-diamino-2-mercaptopyrimidine with carboxylic acid chlorides (CAC) leads to the formation of 2-acylthio-4,6-diaminopyrimidines (I), 1-acyl-4,6-diamino-1,2-dihydro-2-pyrimidinethiones (II), and 6-amino-4-acylamido-1H(3H)-dihydro-2-pyrimidinethiones (III).



(I) (II) (III)

Some of the chemical properties of (I)-(III) are described in the present communication.

Compounds (I) and (II) react under mild conditions with water, alcohols, and amines to give 4,6-diamino-2-mercaptopyrimidine (IV) and the corresponding carboxylic acid derivatives in high yields. The 2-acylthio-4,6-dimethylpyrimidines react with the indicated nucleophilic reagents in a similar manner. The high yields, unambiguous progress of the reactions, and ease of isolating the formed products make it possible to use (I) and (II) as mild acylating agents. The (I) and (II) compounds are not acylated by CAC in the presence of Et_3N in DMF at 120-130°C. The (III) compounds remain unchanged when refluxed in alcohols. Treatment of the (III) compounds with sodium alcoholate solution gives the Na salts, which are alkylated by alkyl halides in DMF at 50-60° to the corresponding 2-alkylthio derivatives (Table 1). Compound (III) (R = Ph) is acylated at the S atom when treated with benzoyl chloride in the presence of Et_3N at 20-80°. The IR spectrum of the obtained 6-amino-4-benzamido-2-benzoylthiopyrimidine has absorption bands at 1680 and 1705 ($\nu C=O$), 1630 (δNH_2) [2], 3100-3300 (νNH_2) [3], and 3420 cm^{-1} (νNH) [4]. Absorption at 1100 ($\nu C=S$) and 3000-3100 cm^{-1} (νNH of thiolactams) [5] is absent in the IR spectrum. The acylation of (III) (R = Ph) with p-methoxybenzoyl chloride at 110-120° in DMF, in the presence of Et_3N, gives 4-benzamido-6-p-methoxybenzamido-1H(3H)-dihydro-2-pyrimidinethione. Its IR spectrum has bands at 1710 ($\nu C=O$), 3040 (νNH of thiolactam) [5], and 3420 cm^{-1} (νNH) [4], and absorption is absent at 1100 ($\nu C=S$) [5] and 1630 cm^{-1} (δNH_2) [2].

The (I) compounds remain unchanged after refluxing in CH_3CN for 6 h, but when refluxed in DMF they form mixtures of (II) and (III). The isomerization time depends on the nature of the substituent in the benzene ring of the acyl radical (Table 2). The (I) compounds, having in the benzene ring of the acyl radical substituents with $\sigma_I \leq 0$, are isomerized in 8-9 h, and in 3-5 min when $\sigma_I > 0$. The obtained (II) and (III) compounds (R = Ph or p-$CH_3C_6H_4$) are identical with those previously described in [1]. It should be mentioned that the remaining (II) compounds cannot be obtained by acylating (IV) with CAC in the presence of Et_3N [1]. The IR spectra of the (II) compounds have intense bands at 1670 ($\nu C=O$), 1100 ($\nu C=S$) [5], 1630-1640 (δNH_2) [2], and 3100-3400 cm^{-1} (νNH_2) [3]. Absorption is absent in the 3000-3100 cm^{-1} region (νNH of thiolactams) [5]. The constants of the previously unknown (II) compounds are given in Table 3.

In contrast to the (I) compounds, all of the (II) compounds remain unchanged when refluxed in DMF, but when refluxed in CH_3CN they isomerize to either the (I) or (III) compounds. The direction of the isomerization correlates with the Hammett σ^+ constants. In the (I) compounds the benzoic, p-toluic, and p-methoxybenzoic

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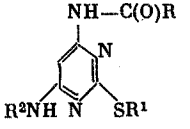
TABLE 1. Derivatives of 4-Acylamido-2-mercaptopyrimidines



R	R¹	R²	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
					C	H	N		C	H	N
$C_6H_5CH_2$	C_3H_7	H	56	179–180	59,41	5,89	18,88	$C_{15}H_{18}N_4OS$	59,57	6,00	18,52
C_6H_5	CH_3	H	64	201–202	55,12	4,88	21,36	$C_{12}H_{12}N_4OS$	54,98	4,64	21,52
C_6H_5	$C_6H_5C(O)$	H	85	185–186	61,84	4,13	15,72	$C_{18}H_{14}N_4O_2S$	61,69	4,02	15,99
C_6H_5	H	*p*-CH_3O $C_6H_4C(O)$	78	212–213 (decompn)	60,24	4,00	14,70	$C_{19}H_{16}N_4O_3S$	59,98	4,24	14,73

TABLE 2. Isomerization Products of 2-Acylthio-4,6-diaminopyrimidines (I)

R	Isomerization time, min	σ_I	Composition of mixture of products, %	
			(II)	(III)
p-$CH_3C_6H_4$	8 h	−0,08	54	40
C_6H_5	8 h	0	50	40
p-$CH_3OC_6H_4$	3–5	0,29	100	–
m-$CH_3OC_6H_4$	3–5	0,29	30	63
p-BrC_6H_4	3–5	0,44	66	25
β-C_5H_4N	3–5	0,52	60	25
p-$NO_2C_6H_4$	3–5	0,60	63	33
m-$NO_2C_6H_4$	3–5	0,60	66	26

TABLE 3. 1-Acyl-4,6-diamino-1,2-dihydro-2-pyrimidinethiones (II)

R	Yield, %	mp, °C (decomp)	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
p-$NO_2C_6H_4$	68	220	45,21	3,74	26,50	$C_{11}H_9N_5O_3S$	45,61	3,44	26,60
m-$NO_2C_6H_4$	66	250	45,83	3,56	26,54	$C_{11}H_9N_5O_3S$	45,61	3,44	26,60
p-$CH_3OC_6H_4$	100	262	52,40	4,60	21,24	$C_{12}H_{12}N_4O_2S$	52,16	4,37	21,36
m-$CH_3OC_6H_4$	30	300	52,32	4,45	21,00	$C_{12}H_{12}N_4O_2S$	52,16	4,37	21,36
β-C_5H_4N	60	320	48,43	4,27	28,36	$C_{10}H_9N_5OS$	48,56	3,66	28,38
p-BrC_6H_4	66	300	40,38	3,00	17,38	$C_{11}H_9BrN_4OS$	40,62	2,78	17,23

acid derivatives, with $\sigma^+ = 0$ to -0.76, are isomerized; the isomerization time is 3-5 min. In the (III) compounds the nicotinic acid and m- and p-nitrobenzoic acid derivatives ($\sigma^+ = 0.62$-0.79) are isomerized; the isomerization time is 5-6 h. The isomerization of the (I) and (II) compounds is not due to tautomeric equilibrium, as in the case of the acylated hydroxypiridines [6]. This is confirmed by the fact that the (I) and (II) compounds, when R = Ph, can be quantitatively recrystallized from DMF, in which connection, based on the TLC data, the other isomer is absent in both the precipitate and in solution.

The obtained data show that the formation of various derivatives by the acylation of (IV) with CAC in the presence of Et_3N [1] is not related to the isomeric transformations of the initially formed acylation of (IV) in either DMF or MeCN at ~ 20°, i.e., under conditions where isomerization is absent. The (II) compounds are formed by the acylation of (IV) at 80°, with a reverse order of adding the reactants to the MeCN or DMF only in the case of the benzoic and p-toluic acid derivatives. These same (II) compounds can be obtained by the isomerization of the (I) compounds when refluxed in DMF, but here the (III) compounds are always also formed, which were not detected in a single case during acylation. The (III) compounds are formed only by the acylation of (IV) at 110-120° in DMF. When the (I) compounds are refluxed in DMF they are isomerized to the (III) compounds, but here a substantial amount of the (II) compounds is always formed, which is not observed during the acylation of (IV). In addition, some of the (III) compounds can be obtained by the isomerization of the (II) compounds in MeCN, i.e., under conditions where the (III) compounds are not formed during the acylation of (IV).

EXPERIMENTAL

The IR spectra were measured on a UR-10 spectrophotometer as Nujol mulls.

Reaction of 2-Acylthiopyrimidines and 1-Acyl-4,6-diamino-1,2-dihydro-2-pyrimidinethiones (II) with Nucleophilic Reagents. a) With Water. A mixture of 1 g (4 mmoles) of (I) (R = Ph) and 50 ml of water was refluxed for 3 min, cooled, and the precipitate (IV) was filtered. The yield of product was 0.55 g (96%), mp 320° (decompn.).

b) With Alcohols. A mixture of 2 g (8 mmoles) of (II) (R = Ph) and 50 ml of MeOH was refluxed for 15 min, cooled, the precipitate (IV) (1.15 g, 100%) was filtered, and the methanol was removed in vacuo. We obtained 0.85 g (80%) of methyl benzoate.

c) With Amines. To a solution of 12.2 g (0.05 mole) of 2-benzoylthio-4,6-dimethylpyrimidine in 50 ml of benzene was added in drops 7.3 g (0.1 mole) of Et_2NH. The mixture was stirred for 15 min, the precipitate of 7 g (100%) of 4,6-dimethyl-2-mercaptopyrimidine was filtered, and the benzene was removed from the filtrate in vacuo. We obtained 8.5 g (97%) of benzoic acid diethylamide, bp 141° (10 mm).

6-Amino-2-propylthio-4-phenylacetamidopyrimidine. To a solution of the Na salt, obtained from 2.2 g (8 mmoles) of (III) (R = $PhCH_2$) and an equimolar amount of EtONa, in 20 ml of DMF at 40° was added in drops 1.4 g (8 mmoles) of propyl iodide. The mixture was stirred for 0.5 h at 60°, cooled, poured into water, extracted with 3 × 50 ml of $CHCl_3$, dried over $CaCl_2$, the $CHCl_3$ was removed in vacuo, and the residue was recrystallized from i-BuOH. The yield and properties are given in Table 1.

6-Amino-4-benzamido-2-methylthiopyrimidine was obtained in a similar manner from (III) (R = Ph).

6-Amino-4-benzamido-2-benzoylthiopyrimidine. To a mixture of 3 g (12 mmoles) of (III) (R = Ph) and 1.3 g (15 mmoles) of Et_3N in 30 ml of MeCN at 20° was added in drops 1.7 g (12 mmoles) of benzoyl chloride. The mixture was stirred for 1 h at 20°, and the precipitate was filtered, washed with $CHCl_3$, and recrystallized from MeCN. See Table 1 for the yield and properties.

4-Benzamido-6-p-methoxybenzamido-1H(3H)-dihydro-2-pyrimidinethione. To a solution of 3 g (12 mmoles) of (III) (R = Ph) and 2.1 g (12 mmoles) of p-methoxybenzoyl chloride in 20 ml of DMF at 110° was added in drops 1.4 g (12 mmoles) of Et_3N, after which the mixture was stirred for 0.5 h at 110-120°, cooled, the precipitate was filtered, and the DMF was removed in vacuo. The residue was recrystallized from PrOH. See Table 1 for the yield and properties.

Isomerization of 2-Acylthio-4,6-diaminopyrimidines (I). A solution of 5.6 g (0.02 mole) of (I) (R = m-$MeOC_6H_4$) in 20 ml of DMF was refluxed for 5 min, cooled, and the obtained crystals of the corresponding (II) were filtered. The DMF was removed from the filtrate in vacuo, and the residue was recrystallized from ethanol. The yield of (III) (R = m-$CH_3OC_6H_4$) was 3.5 g (63%), mp 300° (decompn.) (cf. [1]).

The isomerization of the remaining (I) compounds was run in a similar manner. The yields and constants of the previously unknown (II) compounds are given in Table 3.

2-Benzoylthio-4,6-diaminopyrimidine. A solution of 1 g (4 mmoles) of (II) (R = Ph) in 30 ml of MeCN was refluxed for 3 min, cooled, and the precipitate was filtered. The yield of (I) (R = Ph) was 1 g (100%), mp 260° (cf. [1]).

The isomerization of (I) (R = p-$CH_3C_6H_4$ and p-$CH_3OC_6H_4$) was run in a similar manner.

6-Amino-4-p-nitro-1H(3H)-dihydro-2-pyrimidinethione. A solution of 1 g (3 mmoles) of (II) (R = p-$NO_2C_6H_4$) in 30 ml of MeCN was refluxed for 5 h, cooled, and the precipitate was filtered. The yield of (III) (R = p-$NO_2C_6H_4$) was 1 g (100%), mp 300° (decompn.) (cf. [1]).

The isomerization of (II) (R = m-$NO_2C_6H_4$ and β-C_5H_4N) was run in a similar manner.

CONCLUSIONS

1. 2-Acylthiopyrimidines and 1-acyl-4,6-diamino-1,2-dihydro-2-pyrimidinethiones react with nucleophilic reagents to give 2-mercaptopyrimidines and the corresponding carboxylic acid derivatives.

2. The 6-amino-4-acylamido-1H(3H)-dihydro-2-pyrimidinethiones are acylated by acyl halides either at the S atom or at the NH_2 group, while their salts are alkylated by alkyl halides at the S atom.

3. 2-Acylthio-4,6-diaminopyrimidines and 1-acyl-4,6-diamino-1,2-dihydro-2-pyrimidinethiones are capable of rearranging to the isomeric acyl derivatives.

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