CONVERSIONS OF METHYL ESTERS OF (6-METHYL-2-METHYLTHIO-4-PYRIMIDINYLOXY)- AND (3,4-DIHYDRO-6-METHYL-2-METHYLTHIO-4-OXO-3-PYRIMIDINYL)ACETIC ACIDS

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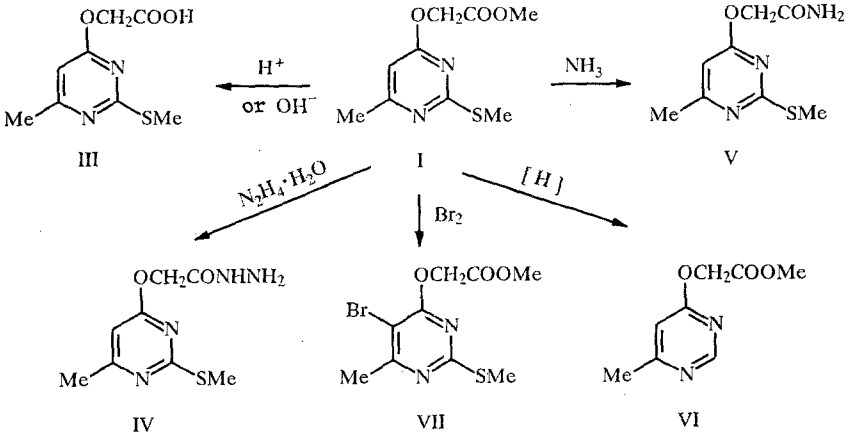
A study has been made of nucleophilic reactions (hydrolysis, hydrazinolysis, ammonolysis, reduction) and electrophilic reactions (bromination, nitration) of isomeric methyl esters of (6-methyl-2-methylthio-4-pyrimidinyloxy)acetic acid and (3,4-dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)acetic acid. Carboxyl-group derivatives and also derivatives with substituents in position 5 of the pyrimidine ring have been synthesized.

As reported previously [1], we had investigated the alkylation of 2-alkylthio-4-hydroxypyrimidines by esters of haloacetic acids, and we had developed preparative methods for the synthesis of *O*- and $N_{(3)}$-alkoxycarbonylmethyl derivatives of 2-alkylthio-4-hydroxypyrimidines, thus making these compounds available for study of their properties.

The molecules of these compounds contain three electrophilic centers — the ester group and the $C_{(2)}$ and $C_{(4)}$ atoms of the pyrimidine ring — and one nucleophilic center — the $C_{(5)}$ atom of the pyrimidine ring. Therefore, these compounds offer considerable promise as starting materials for the synthesis of an extensive series of previously unknown pyrimidine derivatives. Another area of independent interest is the determination of differences in monotypical reactions due to the difference in structure of the isomers I and II.



We have subjected the *O*-isomer (I) and the $N_{(3)}$-isomer (II) to acidic and alkaline hydrolysis. In either an acidic or alkaline medium, the hydrolysis of the *O*-isomer I proceeds with the formation of compound III. Hydrolysis of the $N_{(3)}$-isomer II may proceed with the formation of any one of three products, VIII, IX, or X, depending on the reaction conditions. Under severe conditions of acidic or alkaline hydrolysis, compound VIII is formed. Under milder conditions, acidic hydrolysis yields compound IX, alkaline hydrolysis compound X. Thus, in an alkaline medium, the carboxyl atom is more electrophilic; and

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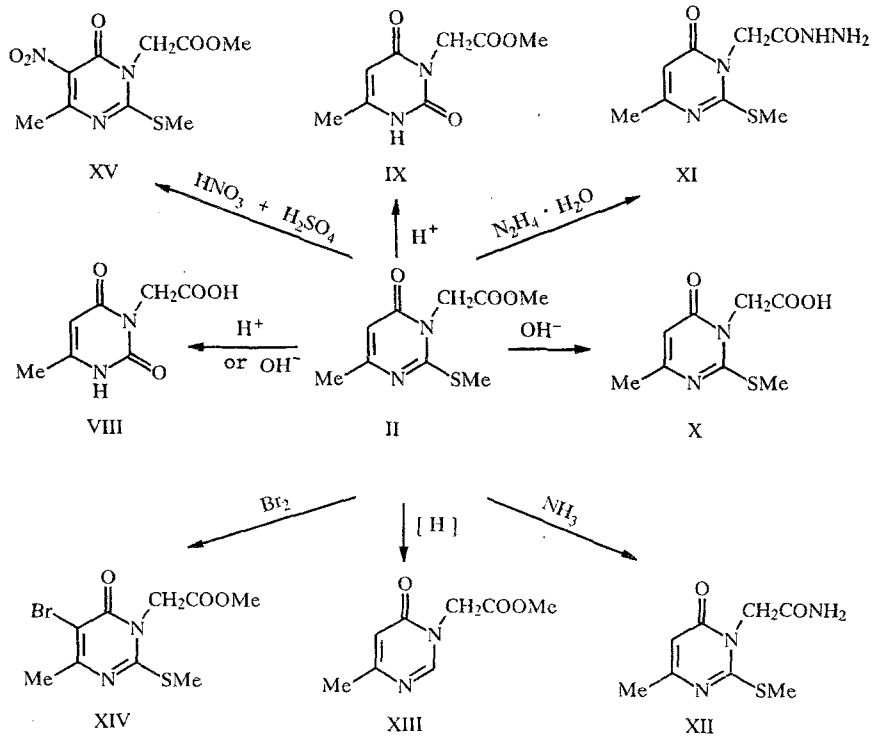
this is also the site of nucleophilic attack by the OH anion. In an acidic medium, apparently, owing to the protonation of the pyrimidine ring nitrogen atom, the $C_{(2)}$ atom becomes more electrophilic, and this is where nucleophilic substitution takes place.



In order to study the reactivity of the carboxyl carbon atom and to obtain hydrazides and amides, we investigated the interaction of compounds I and II with hydrazine hydrate and ammonia. The esters of the pyrimidinecarboxylic acids, when they interact with hydrazine hydrate, form hydrazides [2—4]. However, since the heterocyclic nitrogen atoms in the pyrimidine ring are activated by groups in the α- and γ-positions relative to this nitrogen atom, alkylthio groups in position 2 are often replaced by the hydrazino group in reactions with hydrazine hydrate [5, 6]. With the aim of avoiding the formation of the corresponding 2-hydrazinopyrimidines, the hydrazide IV was synthesized in ethanol with a threefold excess of 99% hydrazine hydrate, at room temperature; the hydrazide XI was synthesized at 10°C. The amides V and XII were synthesized by holding compounds I and II in a methanol solution of ammonia at room temperature for 1 or 2 days, respectively.

The reactions of reduction of the isomers I and II proceed smoothly in methanol over Raney nickel with refluxing (I) or at room temperature (II), with the formation of compound VI or XIII, respectively. The required reaction time is the same in both cases. However, the fact that the reduction of the $N_{(3)}$-isomer II to form compound XIII will proceed even at room temperature is evidence of a higher mobility of the methylthio group in position 2 of the pyrimidine ring of compound II.

We have investigated two electrophilic substitution reactions — bromination and nitration. The isomers I and II behave identically in bromination reactions. Compounds VII and XIV are formed at room temperature by the action of bromine in glacial acetic acid on I or II. Both isomers I and II are nitrated by a mixture of nitric and sulfuric acids at room temperature. The reaction of the $N_{(3)}$ isomer II proceeds smoothly, with the formation of compound XV.

The structures of the compounds III—VII and IX—XV were confirmed by elemental analyses and by UV, IR, and PMR spectra (Tables 1 and 2). In the UV spectra of compounds III—VII, there are absorption maxima at 247—258 nm, characteristic for *O*-isomers, and in the spectra of compounds IX—XV at 263—305 nm, characteristic for $N_{(3)}$-isomers [7]. In the IR spectra of compounds IX—XV, along with the absorption bands of other groups, there is a peak of the lactam C=O in the 1640—1683 cm^{-1} region. In the PMR spectra of all of the compounds, along with signals from protons of groups which are individual for each compound and which confirm their structure, for compounds III—VII there are signals from protons of OCH_2 groups at 4.61—4.88 ppm; and for compounds IX—XV there are signals from protons of NCH_2 groups at 4.45—4.74 ppm.

TABLE 1. Characteristics of Synthesized Compounds III—VII and IX—XV

Compound	Empirical formula	mp, °C	UV spectrum, λ_{max}, nm (and log ε)	IR spectrum, ν, cm^{-1}			Yield, %
				C=O (lactam)	C=O	NH	
III	$C_8H_{10}N_2O_3S$	185...187	208 (3,89), 254 (4,05)		1747		56*, 67**
IV	$C_8H_{12}N_4O_2S$	161...162	208 (4,05), 252 (4,14)		1667	3313, 3233	67
V	$C_8H_{11}N_3O_2S$	150...151	207 (3,96), 252 (4,17)		1680	3300, 3153	94
VI	$C_8H_{10}N_2O_3$	31...33	216 (3,64), 247 (3,50)		1747		66
VII	$C_9H_{11}BrN_2O_3S$	88...90	207 (3,47), 258 (4,26)		1753		59
IX	$C_8H_{10}N_2O_4$	151...153	211 (3,82), 263 (3,88)	1640, 1613	1733		51
X	$C_8H_{10}N_2O_3S$	190...191	225 (3,71), 240 i, 290 (3,82)	1653	1727		63
XI	$C_8H_{12}N_4O_2S$	198...199	228 i, 238 i, 292 (3,94)	1660	1687	3270	57
XII	$C_8H_{11}N_3O_2S$	245...246	228 (3,80), 238 i, 292 (3,94)	1667	1680	3407, 3287	75
XIII	$C_8H_{10}N_2O_3$	44...46	225 (3,67), 275 (3,51)	1680	1753		88
XIV	$C_9H_{11}BrN_2O_3S$	112...113	246 (3,71), 304 (3,96)	1680	1747		64
XV	$C_9H_{11}N_3O_5S$	137...139	214 (3,94), 246 i, 305 (3,97)	1683	1747		52

*Acidic hydrolysis.

**Alkaline hydrolysis.

EXPERIMENTAL

The course of the reaction and the purity of the compounds were monitored on Silufol plates. The UV spectra were measured in ethanol in a Specord UV-Vis spectrometer. The IR spectra were recorded in a Specord IR-75 spectrometer, on suspensions in white mineral oil. The PMR spectra were taken in a Tesla BS-487C instrument (80 MHz), internal standard HMDS.

Elemental analyses for C, H, and N matched the calculated values.

Compounds I, II, and VIII were synthesized in accordance with [1].

(6-Methyl-2-methylthio-4-pyrimidinyloxy)acetic Acid (III, $C_8H_{10}N_2O_3S$). A. Acidic hydrolysis of I. A 1.14-g quantity (5 mmoles) of compound I and 3.4 ml of 2 N HCl was held at room temperature for two days. The precipitate was filtered off, washed with water, and crystallized from water. Yield 0.6 g.

B. Alkaline hydrolysis of I. A 1.14-g quantity (5 mmoles) of compound I and 5.7 ml of a 2 N NaOH solution was held at room temperature for 2 h and then acidified with 2 N HCl to pH 4. The precipitate was filtered off, washed with water, and crystallized from water. Yield 0.72 g.

Methyl Ester of (1,2,3,4-Tetrahydro-6-methyl-2,4-dioxo-3-pyrimidinyl)acetic Acid (IX, $C_8H_{10}N_2O_4$). This compound was synthesized under conditions of acid hydrolysis of compound II, analogous to the conditions for acid hydrolysis of compound I. Yield 0.5 g.

(3,4-Dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)acetic Acid (X, $C_8H_{10}N_2O_3S$). A mixture of 1.14 g (5 mmoles) of compound II, 2.07 g (15 mmoles) of K_2CO_3, and 8 ml of water was stirred for 6 h at 40°C. The solution was cooled and then acidified with 2 N HCl solution to pH 4. The precipitate was filtered off, washed with water, and crystallized from water. Yield 0.67 g.

TABLE 2. PMR Spectra of Compounds III—VII and IX—XV in CF_3COOH

Compound	δ, ppm					
	6-CH_3 (3H, s)	2-SCH_3 (3H, s)	OCH_2 (2H, s)	NCH_2 (2H, s)	5-CH (1H, s)	other protons
III	2,20	2,27	4,82		6,36	
IV*	2,23	2,38	4,67		6,41	4,20 (2H, m, NH_2); 9,21 (1H, s, NH)
V*	2,25	2,37	4,61		6,40	7,15, 7,41 (2H, 2s, NH_2)
VI	2,33		4,86		6,81	3,48 (3H, s, OCH_3); 8,55 (1H, s, 2-CH)
VII	2,27	2,32	4,88			3,53 (3H, s, OCH_3)
IX	1,88			4,45	5,64	3,46 (3H, s, OCH_3)
X	2,11	2,65		4,74	6,13	
XI*	2,10	2,43		4,50	5,95	4,15 (2H, m, NH_2); 9,15 (1H, s, NH)
XII*	2,07	2,40		4,45	5,88	7,13, 7,53 (2H, 2s, NH_2)
XIII	2,27			4,66	6,33	3,46 (3H, s, OCH_3); 9,02 (1H, s, 2-CH)
XIV	2,26	2,64		4,74		3,50 (3H, s, OCH_3)
XV	2,18	2,35		4,65		3,50 (3H, s, OCH_3)

*In DMSO-d_6.

Hydrazides of (6-Methyl-2-methylthio-4-pyrimidinyloxy)acetic Acid (IV, $C_8H_{12}N_4O_2S$) and (3,4-Dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)acetic Acid (XI, $C_8H_{12}N_4O_2S$). A mixture of 2.28 g (10 mmoles) of compound I or II, 1.5 g (30 mmoles) of 99% hydrazine hydrate, and 15 ml of ethanol was allowed to stand for 3 h at room temperature or 10°C, respectively. Then, 10 ml of ether was added to the mixture, which was held for 1 h at 3—5°C. The precipitate was filtered off, washed with 1:1 ethanol—ether, and crystallized from ethanol. Yield of IV 1.53 g, yield of XI 1.3 g.

Amides of (6-Methyl-2-methylthio-4-pyrimidinyloxy)acetic Acid (V, $C_8H_{11}N_3O_2S$) and (3,4-Dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)acetic Acid (XII, $C_8H_{11}N_3O_2S$). To 9 ml of methanol saturated with gaseous ammonia, 2.28 g (10 mmoles) of compound I or II was added. The reaction mixture was held at room temperature for 1 or 2 days, respectively. The precipitate was filtered off, washed with methanol, and crystallized from methanol. Yield of V 2 g, yield of XII 1.6 g.

Methyl Esters of (6-Methyl-4-pyrimidinyloxy)acetic Acid (VI, $C_8H_{10}N_2O_3$) and (3,4-Dihydro-6-methyl-4-oxo-3-pyrimidinyl)acetic Acid (XIII, $C_8H_{10}N_2O_3$). To a solution of 2.28 g (10 mmoles) of compound I or II in 30 ml of methanol, 7.5 g of Raney nickel was added, and the mixture was refluxed 1 h (for compound I) or stirred 1 h at room temperature (for compound II). The catalyst was filtered off, the filtrate was evaporated down, and the residue was crystallized from hexane. Yield of VI 1.2 g, yield of XIII 1.6 g.

Methyl Esters of (5-Bromo-6-methyl-2-methylthio-4-pyrimidinyloxy)acetic Acid (VII, $C_9H_{11}BrN_2O_3S$) and (5-Bromo-3,4-dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)acetic Acid (XIV, $C_9H_{11}BrN_2O_3S$). To a solution of 2.28 g (10 mmoles) of compound I or II in 10 ml of CH_3COOH, 2.5 g (16 mmoles) of bromine was added dropwise at room temperature. The mixture was stirred 1 h, and the precipitate was filtered off and then washed with water until the yellow color disappeared, after which it was crystallized from hexane. Yield of VIII 1.81 g, yield of XIV 1.96 g.

Methyl Ester of (3,4-Dihydro-6-methyl-2-methylthio-5-nitro-4-oxo-3-pyrimidinyl)acetic Acid (XV, $C_9H_{11}N_3O_5S$). To a solution of 2.28 g (10 mmoles) of compound II in 10 ml of concentrated H_2SO_4, at room temperature, 0.62 ml (14 mmoles) of HNO_3 (d = 1.45) was added dropwise. The mixture was stirred 0.5 h and then poured onto ice. The resulting precipitate was filtered off, washed with water, and crystallized from hexane. Yield 1.42 g.

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