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TRANSFORMATIONS OF METHYL 6-METHYL-2-METHYLSULFANYL-4-OXO-3,4-DIHYDRO-3-PYRIMIDINYLACETATE UNDER OXIDATIVE CONDITIONS

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The oxidation of methyl 6-methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinylacetate by reagents which oxidized the SMe group to SO_2Me gave the products of the further transformation of the corresponding 2-methylsulfonyl-substituted ester obtained: methyl 5,5-dichloro-6-methoxy-6-methyl-2,4-dioxohexahydro-3-pyrimidinylacetate (using Cl_2 in 70 or 50% MeOH), its mixture (about 1:10) with methyl 6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinylacetate (Cl_2 in 30% MeOH) or only to the latter compound (Cl_2 in H_2O, m-$ClC_6H_4CO_3H$ in $CHCl_3$, H_2O_2 in MeOH). The reaction did not take place with NaOCl in DMF.

Keywords: methyl 6-methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinylacetate, methyl 5,5-dichloro-6-methoxy-6-methyl-2,4-dioxohexahydro-3-pyrimidinylacetate, methyl 6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinylacetate.

The alkylsulfonyl group which readily undergoes exchange with nucleophiles is widely used for functionalization of pyrimidines [1-5]. We have previously synthesized the corresponding 2-amino substituted products by treating methyl 6-methyl-2-methylsulfonyl-4-pyrimidinyloxyacetate with amines to give substances having anti-inflammatory activity [6]. The starting ester indicated was readily prepared by oxidation of the corresponding 2-methylsulfanyl-substituted ester using gaseous chlorine in 70% MeOH at -5°C. In this work we have studied the oxidation of methyl 6-methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinylacetate (**1**) by oxidants widely used for conversion of an SMe to SO_2Me group, i.e. gaseous chlorine in aqueous methanol and water [2], hydrogen peroxide [2, 7], sodium hypochlorite [2, 8], and *m*-chloroperoxybenzoic acid [3, 5]. The results obtained are given in Table 1.

The oxidation of compound **1** with gaseous chlorine in 70 or 50% methanol at -7 to -5°C (methods A and B) gave, in place of the expected methylsulfonyl-substituted ester **2**, only the corresponding hexahydropyrimidinedione methyl 5,5-dichloro-6-methoxy-6-methyl-2,4-dioxohexahydro-3-pyrimidinylacetate (**3**) in 58 and 57% yield respectively (Scheme 1). The structure was confirmed by the results of elemental analytical and spectroscopic data.

The IR spectrum shows three C=O absorption bands at 1712, 1737, and 1756 cm^{-1} and NH group stretching vibrations at 3357 cm^{-1} and the absorption characteristic of an SO_2Me group at 1300-1330 cm^{-1} [4, 7] is absent. The UV spectrum shows only one absorption maximum at 217 nm. It should be noted that the UV spectra of the $N_{(3)}$-alkyl-substituted 4-pyrimidinones and 2,4-pyrimidinediones (including compounds **1, 4**) [9,

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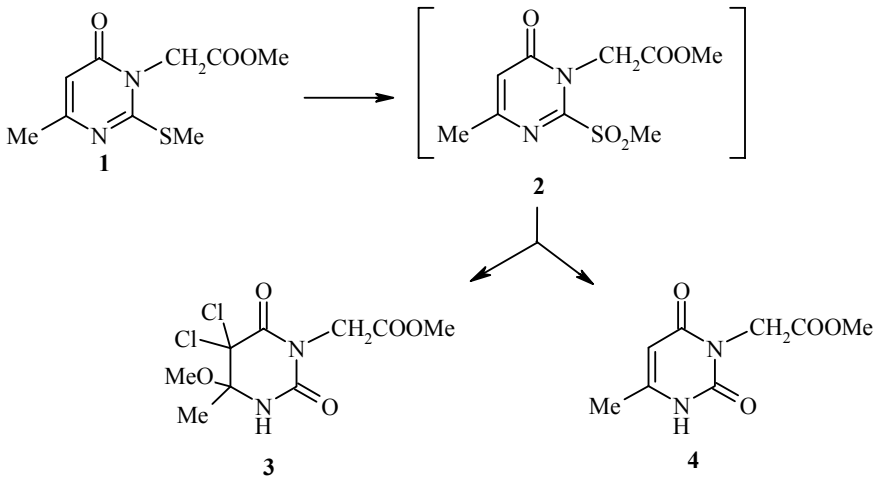
Scheme 1



10] previously synthesized by us have two absorption maxima. Thus the UV spectrum of ester **1** has bands at 226 and 290 nm [10] and the ester **4** at 211 and 263 nm [9]. The ^{1}H NMR spectrum shows the presence of singlets for two OCH_3 groups at 3.37 and 3.78 ppm and the absence of a signal for the H-5 proton. A singlet at 7.71 ppm is clearly assigned to the NH group since the intensity of this signal is markedly decreased upon addition of deuterated water to the solution studied. A comparison of the ^{13}C NMR spectra of compounds **1, 3** and **4** supports structure **3** (Table 2). The signals for the $C_{(5)}$ and $C_{(6)}$ atoms of ester **3** are significantly shifted to higher field relative to the analogous signals for esters **1** and **4** thus pointing to a change in the nature of the bond between these atoms.

It should be noticed that a similar structure was previously assigned to the oxidation products of 2-alkylsulfanyl-4-pyrimidinones using gaseous chlorine in aqueous alcohol and confirmed by reduction of these products to known uracil derivatives [11].

The oxidation of ester **1** by gaseous chlorine in 30% methanol gave a mixture (about 1:10) of the hexahydropyrimidinedione **3** and tetrahydropyrimidinedione **4**. The use of water as solvent (D) gave only a low yield of product **4** which separated as a mixture (1:1) with the starting ester **1** (the ratio of compounds **1** and **4**

TABLE 1. Conditions and Results for Oxidation of Ester **1**

Method	Oxidation conditions		Product yield, %	
	Oxidant	Solvent	**3**	**4**
A	Cl_2	70% MeOH	58	—
B	Cl_2	50% MeOH	57	—
C	Cl_2	30% MeOH	7	73
D	Cl_2	H_2O	—	49*
E	*m*-$ClC_6H_4CO_3H$	$CHCl_3$	—	53*[2]
F	H_2O_2	MeOH	—	76
G	NaOCl	DMF	—	—

* Yield calculated from ^{1}H NMR data for the separated mixture (1:1) of compounds **1** and **4**.

*[2] Yield calculated as in method D for the separated mixture (1:4) of compounds **1** and **4**.

TABLE 2. ^{13}C NMR Spectra of Compounds **1, 3, 4**

Carbon atom	Chemical shifts, δ, ppm		
	1	**3**	**4**
SCH_3	15.22	—	—
CH_3	23.80	16.55	18.55
NCH_2	44.54	42.77	41.23
OCH_3	—	51.11	—
$COO\underline{CH_3}$	52.91	52.70	52.60
$C_{(5)}$	107.38	88.04	99.87
$C_{(6)}$	161.71	83.61	151.30
$C_{(2)}$	162.13	151.46	152.93
$C_{(4)}$	163.25	163.15	162.76
C=O	167.54	168.08	168.68

was determined from the intensities of the H-5 signals in the ^1H NMR spectrum which were seen at 6.07-6.12 and 5.63-5.70 ppm respectively). A similar product was also obtained in the case of *m*-chloroperoxybenzoic acid (E). Compound **4** was separated as a 1:2 mixture with the starting ester **1**. The use of the strong oxidant hydrogen peroxide (F) gave a high yield of compound **4** but sodium hypochlorite in DMF (G) did not oxidize compound **1**.

The mechanism of the oxidation of ester **1** in the system gaseous chlorine – aqueous methanol (methods A-B) is apparently similar to the mechanism established in the studies [12, 13] which cover the reaction of uracil and orotic acid with bromine water.

It seems likely that in the first stage under the conditions in methods A-E the SMe group in the starting compound **1** is oxidized to the SO_2Me group which is rapidly hydrolyzed. Moreover, chlorination occurs with these reactions since the target sulfone **2** could not be separated.

EXPERIMENTAL

Monitoring of the course of the reaction and the compound purity was carried out on Alugram SIL G/UV-254 plates in the system chloroform–ethyl acetate (1:1). ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Inova (300 and 75 MHz respectively) instrument using CD_2Cl_2 and were relative to TMS. IR and UV spectra were taken on a Perkin Elmer Bx FT-IR spectrometer for KBr tablets or in ethanol solution respectively.

The *m*-chloroperoxybenzoic acid was used from the firm Aldrich.

The synthesis of compound **1** has been reported in [14].

Oxidation of Methyl 6-Methyl-2-methylsulfanyl-4-oxo-3,4-dihydro-3-pyrimidinylacetate (1). A. Gaseous chlorine was passed through a stirred suspension of compound **1** (2.28 g, 0.01 mol) in 70% methanol (30 ml) at a temperature of -7 to -5°C to full solution of the starting material and to a greenish coloration of the solution. The reaction mixture was held for 12 h at -8°C. The precipitate formed was filtered off, washed with 1% $Na_2S_2O_3$ solution and water, and recrystallized from water to give methyl 5,5-dichloro-6-methoxy-6-methyl-2,4-dioxohexahydro-3-pyrimidinylacetate (**3**) (1.73 g, 58%); mp 143-144°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 1712, 1737, 1756 (C=O), 3357 (NH). UV spectrum, λ_{max}, nm (log ε): 217 (3.66). ^1H NMR spectrum, δ, ppm: 1.78 (3H, s, CH_3); 3.37 (3H, s, 6-OCH_3); 3.78 (3H, s, OCH_3); 4.52-4.65 (2H, m, NCH_2); 7.71 (1H, s, NH). Found, %: C 36.37; H 4.27; Cl 23.28; N 9.62. $C_9H_{12}Cl_2N_2O_5$. Calculated, %: C 36.14; H 4.04; Cl 23.71: N 9.37.

B. Oxidation of ester **1** (2.28 g, 0.01 mol) using method A but in 30 ml of 50% methanol gave the product **3** (1.7 g) which was identical by TLC with the product obtained using method A.

C. Oxidation of compound **1** (2.28 g, 0.01 mol) using method A but in 30 ml of 30% methanol and without holding the reaction mixture for 12 h at -8°C gave methyl 6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinylacetate (**4**) (1.45 g); mp 151-152°C (mp 151-153°C [9]), R_f 0.28. The filtrate after separation of product was held at -8°C for 12 h. The precipitated product was filtered off, washed with 1% $Na_2S_2O_3$ solution and water, and dried to give compound **3** (0.2 g) which was identical to the product prepared by method A (TLC data).

D. Oxidation of compound **1** (2.28 g, 0.01 mol) using method C but in water (30 ml) and at 0°C gave a 1:1 mixture (2.08 g) of compound **1** (R_f 0.69) and **4** (R_f 0.28).

E. *m*-Chloroperoxybenzoic acid (3.63 g, 57-86%, 0.012-0.018 mol of 100% material) was added portionwise with stirring to a solution of compound **1** (2.28 g, 0.01 mol) in chloroform (20 ml) at a temperature from -10 to 0°C. The reaction mixture was stirred at the same temperature for 1 h, held for 5 days at room temperature, cooled, and the precipitate was filtered off and washed with chloroform. The filtrate was dried over Na_2SO_4 and evaporated to give 1.65 g of a 1:2 mixture of compounds **1** and **4**.

F. 20% H_2O_2 (4.7 ml) was added dropwise with stirring to a suspension of compound **1** (2.28 g, 0.01 mol) in methanol (3 ml) at a temperature from -7 to 0°C. The reaction mixture was stirred at room temperature for 1 h and held at the same temperature for 3 days. The precipitate was filtered off, washed with water, and dried to give compound **4** (0.91 g). The filtrate was extracted with chloroform and the extract was dried over Na_2SO_4 and chloroform was distilled off to give compound **4** (0.6 g).

G. A solution of NaOCl (2 M, 10 ml) was added dropwise with stirring and cooling in iced water to a solution of compound **1** (2.28 g, 0.01 mol) in DMF (10 ml). The reaction mixture was stirred at room temperature for 1 h and held for 2 days at the same temperature. After cooling, the precipitate formed was filtered off, washed with water, and dried to give the starting compound **1** (1.5 g). The filtrate was extracted with ether, dried over Na_2SO_4, and ether was distilled off to give an additional amount of compound **1** (0.5 g).

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