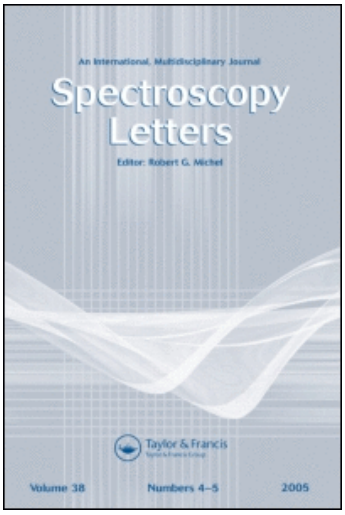

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Structural Assignment of Isomeric *S*- and *S*,*N*-1-Alkoxycarbonylalkylated 6-Amino-2-thiouracil Derivatives by Means of ^{1}H and ^{13}C NMR Spectroscopy

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ABSTRACT

The structures of new isomeric 2-alkoxycarbonylalkylthio- and 2-alkoxycarbonylalkylthio-1-alkoxycarbonylalkyl-6-aminouracils (**1**–**21**) have been established on the basis of the ^{1}H NMR and ^{13}C NMR spectroscopic data. The ^{1}H NMR and ^{13}C NMR spectra of **1**–**21** have been fully assigned by a combination of two-dimensional experiments [heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple

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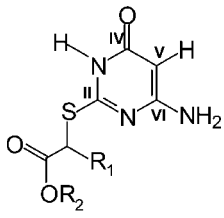
bond correlation (HMBC)]. The ^{13}C NMR spectra have been shown to be able to differentiate between isomers.

Key Words: NMR; ^{1}H NMR; ^{13}C NMR; ^{1}H ^{13}C correlation; Chemical shifts; 2-Thio-6-aminouracil.

INTRODUCTION

Chemical modifications of thio analogs of pyrimidine bases have led to a large number of mono- and di-*S* and *N* (*N*-1, *N*-3) substituted analogs that show therapeutic properties, especially antiviral, antithyroid, and antitumor



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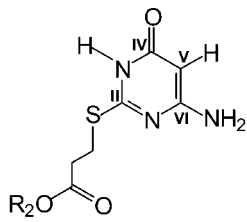

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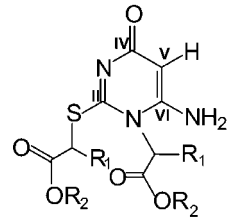


13 - 21

1 $R_1 = H$, $R_2 = CH_3$

2 $R_1 = H$, $R_2 = C_2H_5$

3 $R_1 = H$, $R_2 = n\text{-}C_3H_7$

4 $R_1 = H$, $R_2 = n\text{-}C_4H_9$

5 $R_1 = H$, $CH_2\text{-}C_6H_5$

6 $R_1 = CH_3$, $R_2 = CH_3$

7 $R_1 = CH_3$, $R_2 = C_2H_5$

8 $R_1 = CH_3$, $R_2 = n\text{-}C_3H_7$

9 $R_1 = C_2H_5$ $R_2 = C_2H_5$

10 $R_2 = C_2H_5$

11 $R_2 = n\text{-}C_3H_7$

12 $R_2 = i\text{-}C_3H_7$

13 $R_1 = H$, $R_2 = CH_3$

14 $R_1 = H$, $R_2 = C_2H_5$

15 $R_1 = H$, $R_2 = n\text{-}C_3H_7$

16 $R_1 = H$, $R_2 = n\text{-}C_4H_9$

17 $R_1 = H$, $R_2 = CH_2\text{-}C_6H_5$

18 $R_1 = CH_3$, $R_2 = CH_3$

19 $R_1 = CH_3$, $R_2 = C_2H_5$

20 $R_1 = CH_3$, $R_2 = n\text{-}C_3H_7$

21 $R_1 = C_2H_5$ $R_2 = C_2H_5$

Scheme 1. The structures and numbering of carbon of uracil ring of **1–21**.

activities.[1–6] The 6-amino-substituted pyrimidine thioethers have been reported to constitute a novel class of non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) with activity against *bis*(heteroaryl)piperazine (BHAP)-resistant HIV.[7]

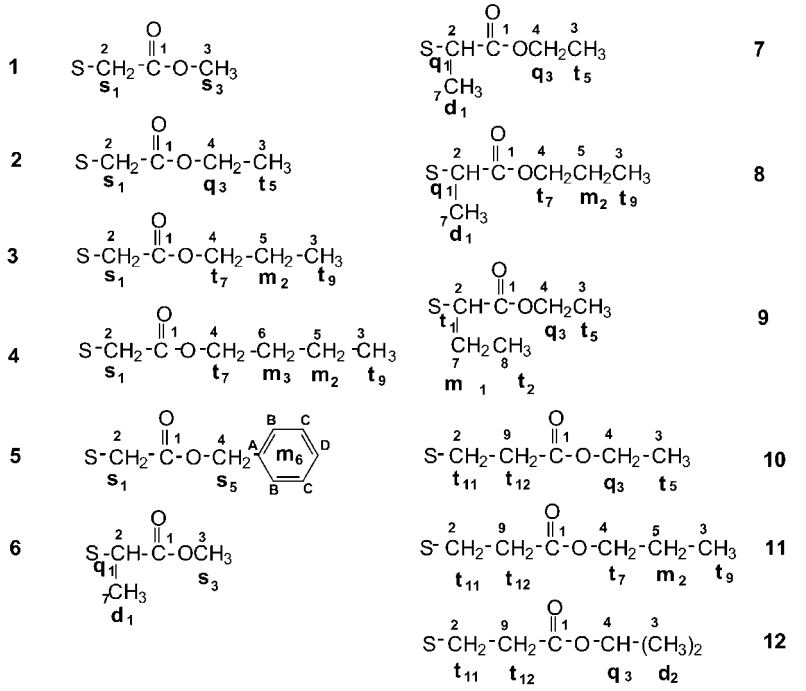
The ^{1}H NMR[8,9] and ^{13}C NMR data[10,11] of S-alkylated aminothiouracil substructure have been assigned in various references. The ^{13}C NMR spectra of 2-alkoxycarbonylalkylthiouracils and 2-alkoxycarbonylalkylthio-6-methyluracils have also been reported.[12] However, to the best of our knowledge, no work has been published on the ^{1}H and ^{13}C NMR assignments of *S*-mono and *S*,*N*-1-dialkoxycarbonylalkyl substituted derivatives of 6-amino-2-thiouracil.

In this work, we report the ^{1}H and ^{13}C NMR assignments of a series of new isomeric *S*-mono (**1**–**12**) and *S*,*N*-1-di(**13**–**21**)alkoxycarbonylalkyl substituted derivatives of 6-amino-2-thiouracil (**1**–**21**, see Sch. 1). On the basis of the spectral data, the structures of **1**–**21** have been established. ^{13} C NMR spectra of **1**–**21** have been found to differentiate between isomers. These spectra can be used for distinction of *S*,*N*-1; *S*,*N*-3, and *S*,*O*-dialkoxy carbonylalkyl substituted derivatives of 6-amino-2-thiouracil.

RESULTS AND DISCUSSION

The 2-alkoxycarbonylalkylthio-6-amino uracils (**1**–**12**) were prepared from 6-amino-2-thiouracil at room temperature by reaction with the corresponding methyl (ethyl, *n*-propyl, propyl, *n*-butyl and benzyl) esters of bromoacetic (α-propionic, β-propionic, and α-butyric acid) in aqueous 0.1 M NaOH. The 2-alkoxycarbonylalkylthio-1-alkoxycarbonylalkyl-6-amino-uracils (**13**–**21**) were prepared from 6-amino-2-thiouracil at room temperature by reaction with the corresponding methyl esters of haloalkanocarboxylic acids in DMF solution in the presence of K_2CO_3 as has been reported previously.[9,10] **1**–**21** were thus obtained as stable crystalline solids in good yields. It ought to be pointed out that according to the recent literature 6-amino-2-thiouracil is predicted to have its lowest energy tautomeric structure as the enol–thiol form.[13] The results obtained in the S-alkoxycarbonylalkylation and *S*,*N*-1-dialkoxycarbonylalkylation of 6-amino-2-thouracil in the presence of base were a consequence of the basic medium. These results are consistent with a consideration of total atomic charges calculated for the most relevant atoms of 6-amino-2-thiouracil and 6-amino-2-thiouracil anion.[14]

The structures and numbering of the uracil ring carbons of compounds **1**–**21** are presented in Sch. 1. Schemes 2 and 3 present the numbering of the carbons of alkoxycarbonylalkyl substituents of compounds **1**–**12** and



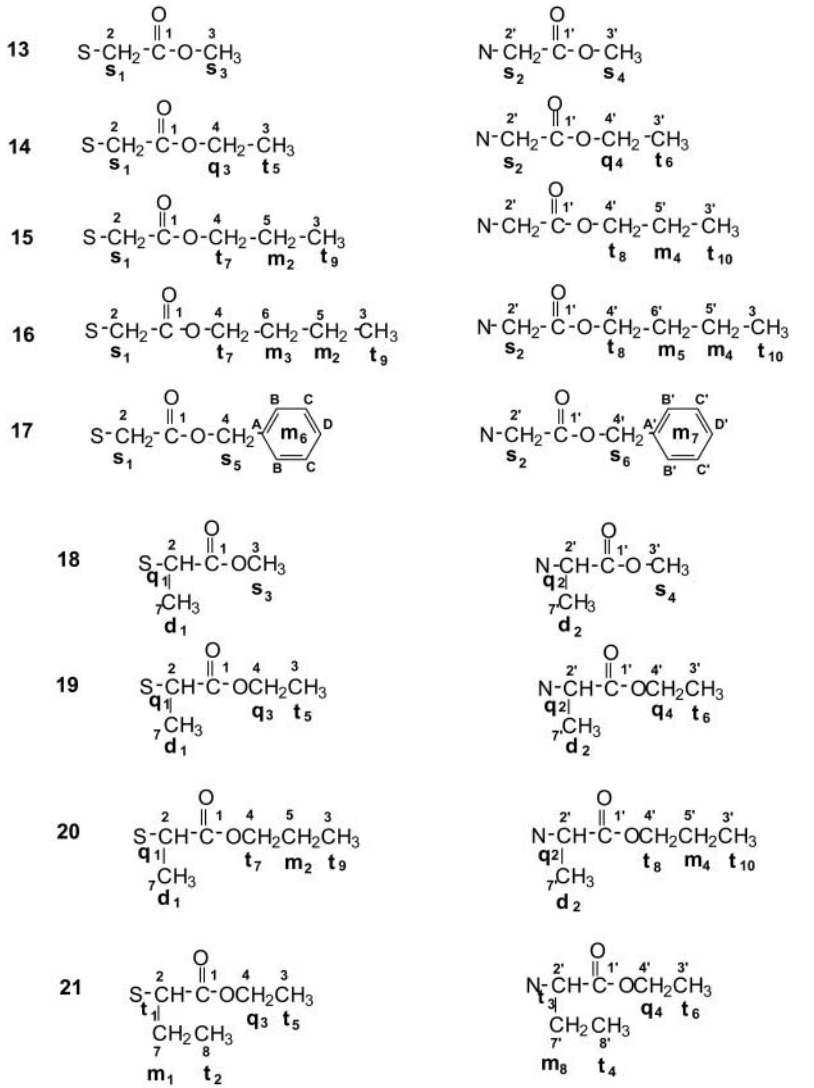
Scheme 2. The numbering of carbons of alkoxycarbonylalkylthio groups of compounds **1–12**.

13–21. Their ^{1}H NMR chemical shifts are collected in Tables 1–4, while the ^{13}C NMR chemical shifts in Tables 5 and 6.

In order to assign all NMR signals unequivocally we used two-dimensional techniques such as heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond correlation (HMBC). The results of the HMQC experiments are summarized in Table 7, while those of the HMBC experiments in Table 8.

^{1}H NMR spectra at 300 MHz of 2-alkoxycarbonylalkylthio-6-aminouracils **1–12** exhibit signals of heteroaromatic N–H, CV–H, and CVI–NH_2 protons of pyrimidine ring as well as the aliphatic protons of alkoxycarbonylalkylthio substituent (Tables 1 and 2).

The ^{1}H NMR spectra of 2-alkoxycarbonylalkylthio-6-aminouracils **1–12** show three singlets in the range 11.34–11.96, 6.43–6.50 and 4.93–5.03 ppm corresponding to the NH, CVI–NH_2, and CV–H protons of uracil, respectively (see Table 1). It ought to be pointed out that according to literature[10,15] a convenient way to distinguish between *N*-1 and *N*-3 substituted



Scheme 3. The numbering of carbons of alkoxycarbonylalkylthio groups of compounds **13–21**.

6-amino-2,4(1H, 3H)pyrimidinedione derivatives is a comparison of the values of the chemical shifts for the signals of the protons of CVI–NH_2 amino group in the ^{1}H NMR spectra. *N*-1 substitution causes a downfield shift when compared with the unsubstituted 6-amino-2,4(1H, 3H)pyrimidinedione, while

Table 1. ^{1}H NMR data for compounds **1**–**12** (δ, ppm; J, Hz).

Compound	NH (s)	CV–H (s)	CVI–NH2 (s)	s_1	t_{11}/t_{12}	q_1/t_1	d_1	t_2	m_1
1	11.36	5.01	6.47	3.98	—	—	—	—	—
2	11.34	5.00	6.45	3.96	—	—	—	—	—
3	11.36	5.00	6.44	3.98	—	—	—	—	—
4	11.36	4.99	6.43	3.97	—	—	—	—	—
5	11.34	5.02	6.44	4.06	—	—	—	—	—
6	11.36	4.93	6.50	—	—	q_1 4.54 $J = 7.0$	d_1 1.48 $J = 7.1$	—	—
7	11.34	5.03	6.49	—	—	q_1 4.54 $J = 7.0$	d_1 1.48 $J = 7.1$	—	—
8	11.38	5.03	6.49	—	—	q1 4.53 $J = 7.0$	d_1 1.49 $J = 7.1$	—	—
9	11.46	5.02	6.49	—	—	t_1 4.46 $J = 7.0$	—	t_2 0.95 $J = 7.1$	m_1 1.84
10	11.38	4.93	6.48	—	t_{11} 2.74 $J = 6.6$ t_{12} 3.29 $J = 6.6$	—	—	—	—
11	11.38	4.93	6.50	—	t_{11} 2.74 $J = 6.6$ t_{12} 3.23 $J = 6.7$	—	—	—	—
12	11.40	4.93	6.49		t_{11} 2.72 $J = 6.5$ t_{12} 3.24 $J = 6.7$	—	—	—	—

Table 2. ^{1}H NMR data for compounds **1**–**12** (δ ppm; J, Hz).

Compound	s_3	q_3/t_5	$t_7/m_3/m_2/t_9$	q_3/d_2	s_5/m_6
1	s 3.65	—	—	—	—
2	—	q_3 4.12 $J = 7.0$ t_5 1.19 $J = 7.0$	—	—	—
3	—	—	t_7 4.06 $J = 7.1$ m_2 1.58 t_9 0.87 $J = 7.2$	—	—
4	—	—	t_7 4.06 $J = 7.0$ m_3 2.49 m_2 1.50 t_9 0.86 $J = 7.0$	—	—
5	—	—	—	—	s_5 5.16 m_6 7.36
6	s 3.66	—	—	—	—
7	—	q_3 4.13 $J = 7.0$ t_5 1.18 $J = 7.0$	—	—	—
8	—	—	t_7 4.04 $J = 7.0$ m_2 1.56 t_9 0.86 $J = 7.0$	—	—

(*continued*)

Table 2. Continued.

Compound	s_3	q_3/t_5	$t_7/m_3/m_2/t_9$	q_3/d_2	s_5/m_6
9	—	q_3 4.13 $J = 7.0$ t_5 1.19 $J = 7.0$	—	—	—
10	—	q_3 4.08 $J = 7.0$ t_5 1.19 $J = 7.0$	—	—	—
11	—	—	t_7 4.00 $J = 7.0$ m_2 1.58 t_9 0.87 $J = 7.0$	—	—
12	—	—	—	q_3 4.90 $J = 6.0$ d_2 1.18 $J = 6.0$	—

Table 3. ^{1}H NMR data for compounds **13–21** (δ, ppm; J, Hz).

Compound	CV–H (s)	CVI–NH_2 (s)	s_1/s_2	$d_1/d_2/q_1/q_2$	$t_1/t_2/t_3/t_4/m_1/m_8$
13	5.51	6.83	s_1 3.85	—	—
			s_2 4.82	—	—
14	5.51	6.82	s_1 3.84	—	—
			s_2 4.79		
15	5.51	6.82	s_1 3.85	—	—
			s_2 4.81		
16	5.51	6.82	s_1 3.84	—	—
			s_2 4.80		
17	5.52	6.83	s_1 3.86	—	—
			s_2 4.80		
18	5.49	6.85	—	d_1 1.43 $J = 7.1$	—
				d_2 1.46 $J = 7.1$	
				q_1 4.35 $J = 7.1$	
				q_2 5.23 $J = 7.1$	
19	5.50	6.83	—	d_1 1.43 $J = 7.0$	—
				d_2 1.45 $J = 7.0$	
				q_1 4.33 $J = 7.1$	
				q_2 5.18 $J = 7.1$	
20	5.48	6.82	—	d_1 1.45 $J = 7.0$	—
				d_2 1.49 $J = 7.0$	
				q_1 4.29 $J = 7.1$	
				q_2 5.18 $J = 7.1$	
21	5.50	6.83	—	—	t_1 4.29 $J - = 7.0$
					t_3 5.00 $J = 7.0$
					t_2 0.95 $J = 7.0$
					t_4 0.94 $J = 7.0$
					m_1 1.82 $J = 7.0$
					m_8 1.84 $J = 7.0$

substituents in the N-3 position have no, or only a slight effect on the chemical shift of the signal of the NH_2 protons. In the ^{1}H NMR spectrum of 6-amino-2,4(1H, 3H)pyrimidinedione, the signals of protons of CVI–NH_2 occur at δ 6.15.[15] In the ^{1}H NMR spectra of *N*-3-alkyl (methyl, ethyl, *n*-propyl) substituted derivatives of this compound, these signals are at 6.14 ppm, while for their *N*-1-alkyl substituted isomers they are in the range 6.73–6.78 ppm. In the ^{1}H NMR spectra, of 6-amino-4(3H)pyrimidione-2(1H)thione and 6-amino-2-methylthio-4(3H)pyrimidione,[10] the singlets of protons of CVI–NH_2 groups are seen at 6.4 ppm. The presence in the ^{1}H NMR spectra of **1–12** of the singlets of protons of CVI–NH_2 groups in the range

Table 4. ^{1}H NMR data for compounds **13–21** (δ, ppm; J, Hz).

Compound	s_3/s_4	$q_3/q_4/t_5/t_6/s_5/s_6/m_6/m_7$	$t_7/t_8/t_9/t_{10}/m_2/m_4$	$t_7/t_8/t_9/t_{10}/m_2/m_4/m_3/m_5$
13	s_3 3.63 s_4 3.67	—	—	—
14	—	q_3 4.11 $J = 7.1$ q_4 4.13 $J = 7.1$ t_5 1.19 $J = 7.1$ t_6 1.20 $J = 7.1$	—	—
15	—	—	t_7 4.00 $J = 7.1$ t_8 4.04 $J = 7.1$ t_9 0.86 $J = 7.0$ t_{10} 0.85 $J = 7.0$ m_2 1.57 $J = 7.3$ m_4 1.59 $J = 7.3$	—
16	—	—	—	t_7 4.04 $J = 6.3$ t_8 4.04 $J = 6.3$ t_9 0.86 $J = 6.0$ t_{10} 0.85 $J = 6.0$ m_2 1.57 $J = 7.2$ m_4 1.59 $J = 7.2$ m_3 2.49 $J = 7.0$ m_5 2.50 $J = 7.0$
17	—	s_5 5.11 s_6 5.14 m_6 7.31 m_7 7.34	—	—
18	s_3 3.64 s_4 3.66	—	—	—
19	—	q_3 4.11 $J = 7.1$ q_4 4.12 $J = 7.1$ t_5 1.17 $J = 7.0$ t_6 1.18 $J = 7.0$	—	—
20	—	—	t_7 4.01 $J = 7.1$ t_8 3.97 $J = 7.1$ t_9 0.81 $J = 7.0$ t_{10} 0.83 $J = 7.0$ m_2 1.55 $J = 7.0$ m_4 1.57 $J = 7.0$	—
21	—	q_3 4.12 $J = 7.0$ q_4 4.15 $J = 7.0$ t_5 1.17 $J = 7.0$ t_6 1.19 $J = 7.0$	—	—

Table 5. ^{13}C NMR data for compounds **1–12** (δ, ppm).

Compound	CII	CIV	CV	CVI	C1	C2	C3	C4	C5	C6	C7	C8	C9
1	162.89	165.38	81.39	163.87	169.36	31.17	52.31	—	—	—	—	—	—
2	162.35	164.96	81.28	163.56	168.51	31.39	14.08	61.02	—	—	—	—	—
3	162.30	165.27	81.36	163.82	168.80	31.87	10.11	66.40	21.42	—	—	—	—
4	162.30	165.08	81.28	163.57	168.55	31.92	13.59	64.30	18.56	30.12	—	—	—
5	162.35	165.42	81.40	163.88	168.73	31.88	—	66.33	C_A135.91 C_B128.41 C_C128.01 C_D127.78	—	—	—	—
6	162.67	165.58	81.43	163.96	172.15	40.90	52.31	—	—	—	17.83	—	—
7	162.54	165.50	81.47	163.97	171.64	41.23	13.90	61.04	—	—	17.92	—	—
8	162.56	165.50	81.41	163.97	171.69	41.21	10.08	66.41	21.39	—	17.94	—	—
9	162.24	165.20	81.39	163.66	170.87	47.46	14.07	60.98	—	—	25.42	11.41	—
10	162.58	164.73	81.32	163.72	171.44	33.77	14.02	60.11	—	—	—	—	24.65
11	162.12	164.41	81.26	163.48	171.30	33.80	10.35	65.61	21.50	—	—	—	24.76
12	162.18	164.46	81.26	163.18	170.74	34.07	24.41	67.65	—	—	—	—	24.71

Table 6. ^{13}C NMR data for compounds **13–21** (δ, ppm).

Compound	CII	CIV	CV	CVI	C1 C1′	C2 C2′	C3 C3′	C4 C4′	C5 C5′	C6 C6′	C7 C7′	C8 C8′
13	167.57	165.06	82.12	167.32	168.77	32.24	51.70	—	—	—	—	—
					169.41	61.67	54.14	—	—	—	—	—
14	167.55	165.04	82.07	167.30	168.24	32.45	13.99	60.45	—	—	—	—
					168.86	61.79	14.02	60.85	—	—	—	—
15	167.80	165.30	82.15	167.60	168.58	32.35	10.00	65.86	21.37	—	—	—
					169.15	61.81	10.22	66.28	21.40	—	—	—
16	167.84	165.34	82.15	167.60	168.63	32.39	13.40	64.53	18.44	30.07	—	—
					169.20	61.83	13.45	64.90	18.46	30.09	—	—
17	167.50	165.05	82.14	167.30	168.23	32.41	—	66.30	—	—	—	C_A 135.91
					168.80	61.80	—	66.40				C_B 128.41
												C_C 128.01
												C_D 127.78
18	167.39	165.34	82.28	167.32	172.33	40.99	51.86	—	—	—	17.78	—
					172.49	69.31	52.27	—	—	—	18.05	—
19	167.52	165.37	82.32	167.44	171.83	41.31	13.89	60.60	—	—	17.61	—
					172.14	69.37	13.95	60.89	—	—	18.37	—
20	167.22	165.05	82.14	167.19	171.06	41.33	10.00	65.90	21.35	—	17.37	—
					171.51	69.45	10.10	66.26	21.39	—	18.39	—
21	167.67	165.31	82.30	167.50	171.21	47.61	13.91	60.79	—	—	11.26	9.35
					171.55	73.96	13.95	60.84	—	—	11.33	9.39

Table 7. ^{1}H (300.068 MHz) and ^{13}C (75.45 MHz) NMR for **2,7,9,11** including results obtained by heteronuclear 2 D shift correlated HMQC [^{1}J(C,H)].

Compound	Atom	δ_C	δ_H
2	2	31.39	s_1 3.98
	3	14.08	t_5 1.19
	4	61.02	q_3 4.12
	V	81.28	s 5.00
7	2	41.23	q_1 4.54
	3	13.90	t_5 1.18
	4	61.04	q_3 4.13
	7	17.92	d_1 1.48
	V	81.47	s 5.08
9	2	47.46	t_1 4.46
	3	14.07	t_5 1.19
	4	60.98	q_3 4.13
	7	25.42	m_1 1.84
	8	11.41	t_2 0.95
	V	81.39	s 5.02
11	2	33.80	t_{11} 2.74
	9	24.76	t_{12} 3.23
	3	10.35	t_9 4.13
	4	65.61	t_7 1.84
	5	21.50	m_2 0.95
	V	81.26	s 5.02

of 6.43–6.50 ppm allows the identification of **1**–**12** as 6-amino-2-alkoxycarbonylalkylthio-4(3H)pyrimidinones.

The ^{1}H NMR spectra of 1,2-dialkoxycarbonylalkyl substituted derivatives of 2-thio-6-aminouracil **13**–**21** show signals assigned to the heteroaromatic CV–H and CVI–NH_2 protons as well as the aliphatic protons of the alkoxycarbonylalkylthio substituent and alkoxycarbonylalkyl group situated at *N*-1 of the uracil ring. The chemical shifts of the signals of the protons of alkoxycarbonylalkylthio substituents of **13**–**21** appear in the range previously observed in the ^{1}H NMR spectra of **1**–**12**. The signals corresponding to the higher frequency are assigned to the protons of the alkoxycarbonylalkyl group at N-1 (Tables 3 and 4). These assignments are supported by the HMBC data (Table 8). After the assignment of the ^{1}H NMR resonances of **1**–**21**, the ^{13}C NMR resonances were assigned in a straightforward manner by the analysis of the HMQC and HMBC spectra (Tables 7 and 8) on the

Table 8. ^{1}H and ^{13}C chemical shifts and characteristic HMBC [^{n}J (C, H); $n = 1–3$] data for **13–21** in DMSO.

Compound	Atom	δ_C	δ_H	HMBC (^{1}H partners) [^{13}C partners]
1–5	II	162.30–162.89		(s_1CH_2)
	IV	163.56–163.88		(s CV–H)
	V	81.28–81.40	s 4.99–5.05	(s CVI–NH_2) [CIV,CVI]
	VI	164.97–165.42		(s CVI–NH_2, s CV–H)
	2	31.17–31.92	s 3.96–4.06	[2, 1, II]
6–8	II	162.54–162.67		(q_1CH)
	IV	163.96–163.97		(s CV–H)
	V	81.41–81.47	s 4.93–5.03	[CIV,CVI], (s CVI–NH_2)
	VI	165.50–165.58		(s CVI–NH_2, s CV–H)
	2	40.90–41.23	q_1 4.53–4.54	[2, 1, II]
9	II	162.24		(t_1CH)
	IV	163.60		(s CV–NH_2)
	V	81.39	s 5.02	[CIV,CVI], (s CVI–NH_2)
	VI	165.20		(s CVI–NH_2), s CV–H
	2	47.46	t_1 4.46	[2, 1, II]
10–12	II	162.12–162.58		($t_{11}CH_2$)
	IV	163.18–163.72		(s CV–H)
	V	81.26–81.32	s 4.93	[CIV,CVI], (s CVI–NH_2)

	VI	164.41–164.73		(s CVI–NH_2), s CV–H
	2	33.77–34.07	t_{11} 2.72–2.74	[2, 1, II]
13–17	II	167.50–167.84		(s_1 CH_2, s_2 CH_2)
	IV	165.05–165.30		(s CV–H)
	V	82.07–82.15	s 5.51–5.52	[CIV,CVI], (s CVI–NH_2)
	VI	167.32–167.60		(s_2CH_2, s CVI–NH_2, s CV–H)
	2	32.24–45.00	s_1 3.84–3.86	[2, 1, II]
	2′	61.67–61.83	s_2 4.79–4.82	[2′, 1′, VI, II]
18–20	II	167.22–167.52		(q_1 CH ; q_3CH)
	IV	165.05–165.37		(s CV–H)
	V	82.14–82.32	s 5.48–5.50	[CIV,CVI], (s CVI–NH_2)
	VI	167.19–167.44		(q_3CH, s CV–H, s CVI–NH_2)
	2	40.99–41.33	q_1 4.29–4.35	[2, 1, II]
	2′	69.31–69.45	q_2 5.18–5.23	[2′, 1′, VI, II]
21	II	167.67		(t_1CH, t_3CH)
	IV	165.31	s 5.50	(s CV–H)
	V	82.30		[CIV,CVI], (s CVI–NH_2)
	VI	167.50		(sCV–H, s CVI–NH_2, t_3CH)
	2	47.61	t_1 4.99	[2, 1, II]
	2′	73.96	t_3 5.07	[2′, 1′, VI, II]

basis of the chemical shift theory and substituent effects. The ^{13}C NMR of **1**–**21** exhibit signals in the carbonyl, heteroaromatic, and aliphatic regions (see Tables 5 and 6).The HMBC measurements have proved to be the method of choice allowing a consecutive assignment of the signals of carbons and protons within the uracil ring and alkoxycarbonylalkyl as well as alkoxycarbonylalkylthio substituents, and thus the one-, two- and three-bond correlations of the protons have proven the 1,2-disubstitution of the uracil ring (Table 8).

In order to exemplify the attributions made for each compound, on the basis of the analysis of the HMBC spectra, the case of 1-benzyloxycarbonylmethylene-2-benzyloxy-carbonylmethylenethio-6-aminouracil (**17**) is discussed. For this compound the ^{1}H NMR spectrum exhibits six singlets, at 3.80; 4.80; 5.11; 5.14; 5.52; and 6.83 ppm, assigned to the protons SCH_2 (s_1); N-1CH_2 (s_2); PhCH_2 (s_5); PhCH_2 (s_6); CV–H; and CVI–NH_2. In the HMBC spectrum, the double cross peaks of one-bond correlations connect the protons of S–CH_2 (s_1) with the carbon atom C2 (32. 41 ppm) of this group, the protons of N1–CH_2 (s_2) with the carbon atom C2′ (61.80 ppm) of this group, the protons of the methylene group (s_5) situated in the benzyloxycarbonyl methylene thio substituent with the carbon C4 (66.30 ppm) of this group, the protons of the methylene group (s_6) situated in benzyloxycarbonyl part of benzyloxycarbonyl methylene substituent with the carbon atom C 4′ (66.40 ppm) of this group, and the proton situated at CV of uracil ring with this carbon CV (82.14 ppm). The HMBC spectrum of **17** also shows the peaks corresponding to two bond correlations for S–CH_2 (s_1)/C1 (168.23 ppm); N–CH_2 (S_2)/C-1′ (168.80 ppm); CV–H/C–IV (165.05 ppm), CV–H/CVI (167.30 ppm) and CVI–NH_2/CVI (167.30). The same spectrum also reveals the peaks corresponding to the three-bond correlations for S–CH_2(s_1)/CII (167.50 ppm); N1–CH_2 (s_2)/CII (167.50 ppm); N1–CH_2 (s_2)/CVI (167.30 ppm); CVI–NH2/CV (82.14); PhCH_2 (s_5)/C1 (168.23 ppm); and PhCH_2 (s_6)/C1′ (168.80 ppm).

It is interesting to point out that all compounds showed a similar trend in the chemical shifts of the common moiety of the molecular backbone (see Tables 1–6). The information derived from the ^{13}C NMR spectra of **1**–**21** (Tables 5 and 6) can be used to differentiate isomers. A comparison of the number and positions of the carbon signals in the region 10–20 ppm (C3, C5, C7, C8) allows differentiation between isomeric 2-alkoxycarbonylalkylthio-6-aminouracils (**2**, **6**; **3**, **7**,**10**; **4**, **8, 9**, **11**, **12**). A comparison of the number and positions of the carbon signals in the region 20–30 ppm (C5, C5′; **15**, **19**); 50–65 ppm (C4, C4′, C3, C3′; **14**, **18**) and 65–75 ppm (C4, C4′, C2, C2′; **16**, **20**, **21**) allows differentiation between isomeric 2-alkoxycarbonylalkylthio-1-alkoxycarbonylalkyl-6-aminouracils (**15**, **19**; **14**, **18**; **16**, **20**, **21**). The ^{1}H and ^{13}C NMR data obtained provide a

reliable method for identification of the site of alkoxycarbonylalkylation (S; N-1; N-3; O) and dialkoxycarbonylalkylation (N-1–S; N-3–S; O–S) in the series of the derivatives of 2-thio-6-aminouracil. The presence in the ^{1}H NMR spectra of **1**–**12** of the singlets of the protons of methylene groups in the range 3.39–4.06 ppm (**1**–**5**), quartets (or triplet) of methine group in the range 4.46–4.54 ppm (**6**–**9**), as well as triplets of methylene group in the range 2.72–3.29 ppm (**10**–**12**) indicates the substitution of alkoxycarbonylalkyl group at the sulfur atom of the uracil ring (Table 1). The presence in the ^{13}C NMR spectra of **1**–**12** of the signals assigned to the carbons of methylene (or methine) groups in the range 31.17–47.46 ppm indicates the substitution of alkoxycarbonylalkyl group at the sulfur atom of the uracil ring (Table 5). The presence in the ^{1}H NMR spectra of **13**–**21** of the signals assigned to the protons of methylene (**13**–**17**) or methine (**18**–**21**) groups in the ranges 3.84–4.35 and 4.79–5.23 ppm, respectively, indicates the substitution of alkoxycarbonylalkyl group at the sulfur atom and the annular N-1 atom of the uracil ring (Table 3). The presence in the ^{13}C NMR spectra of **13**–**21** of the signals of the carbons of methylene (or methine) groups in the range 32.24–47.61 and 61.67–73.96 ppm, respectively, indicates the substitution of alkoxycarbonyl group at the sulfur atom and the annular N-1 atom of the uracil ring (Table 6).

EXPERIMENTAL

The NMR measurements were performed on a Varian Mercury spectrometer operating at 300.07 MHz (proton) or 75.46 MHz (carbon). Data were obtained from DMSO-d_6 solutions at concentrations between 0.25 and 0.40 M at ambient temperature. The chemical shifts were referenced to tetramethylsilane. ^{1}H NMR spectra were recorded at a proton frequency of 300.07 MHz with a spectral width of 9000 Hz. The acquisition time was 2 sec and a relaxation delay 1 sec; 64 scans with 44,922 data points each were used.

The ^{13}C NMR spectra were obtained using a spectral width of 23, 000 Hz and 1.5 sec acquisition time; 2476 scans with 68992 data points each were used. The HMQC experiments were performed by accumulating 32 transients for each of 256 increments of the evolution time using a relaxation delay of 1 sec and a spectral width 3963.7 Hz for ^{1}H and 22630.8 Hz for 2D. The carbon decoupling during acquisition was made using WALTZ-16.[18] The spectra were optimized for coupling constants of 140 Hz. Data sets were zero filled to a 1 K × 4 K matrix and Gaussian apodization was used in both dimensions.

A Bruker Avance DRX 600 Spectrometer operating at 600.05 MHz (^{1}H) or 150.89 MHz (^{13}C) was used for acquisition of HMBC spectra.

Measurements were carried out at a probe temperature of 25°C in DMSO-d_6 as solvent. Tetramethylsilane was used as an internal reference. All spectra were acquired with a Bruker 5 mm TBI probehead. The HMBC spectra were obtained using the inv4gplplrndgf program in the Bruker software and the parameters were as follows: relaxation delay $d_1 = 1$ sec; delay of the low-pass y-filter $d_2 = 3.44$ msec; delay for evolution of long range coupling $d_6 = 65$ msec with gradient ratio 2048 data points in t_2, spectral width 1.650 Hz in F_2 and 133. 200 Hz in F_1; 256 increments in t_1; linear prediction to 512; zero filling up to 2K. Gaussian apodization was used in both dimensions.

The Synthesis of 2-Alkoxycarbonylalkylthio-6-aminouracils (1–12)[17]

A water solution of 1 mmol of 6-amino-2-thiouracil in 10 mL of 0.1 M NaOH was stirred at room temperature while 1.3 mmol of the corresponding ester of haloalkanocarboxylic acid were added dropwise. After stirring for 24 hr at room temperature the precipitated solid of **1**–**12** were filtered, dried, and recrystallized from distilled water. **1**: mp 205–207°C, yield 80%; **2**: mp 179–181°C, yield 83%; **3**: mp 155–157°C, yield 85%; **4**: mp 158–160°C, yield 88%; **5**: mp 199–201°C, yield 81%; **6**: mp 177–180°C, yield 85%; **7**: mp 164–166°C, yield 85%; **8**: mp 121–123°C, yield 88%; **9**: mp 142–144°C, yield 80%; **10**: mp 184–186°C, yield 81%; **11**: mp 169–171°C, yield 86%; **12**: mp 186–188°C, yield 81%;

The Synthesis of 1-Alkoxycarbonylalkyl-2-alkoxycarbonylthio-6-aminouracils (13–21)[16]

A mixture of 1 mmol of 6-amino-2-thiouracil and 1 mmol of Na_2CO_3 in 16 mL of DMF was stirred at room temperature while 2.1 mmol of corresponding ester of haloalkanocarboxylic acid was added dropwise. After stirring for 6 hr, 10 mL of distilled water was added. The reaction mixture was kept at room temperature for 24 hr. The precipitated solid was isolated by filtration, dried and recrystallized from the mixture of H_2O : DMF (2 : 3). **13**: mp 153–155°C, yield 90%; **14**: mp 142–144°C, yield 92%; **15**: mp 100–102°C, yield 93%; **16**: mp 81–83°C, yield 90%; **17**: mp 82–84°C, yield 89%; **18**: mp 141–143°C, yield 82%; **19**: mp 120–122°C, yield 81%; **20**: mp 102–103°C, yield 80%; **21**: mp 110–112°C, yield 83%;.

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