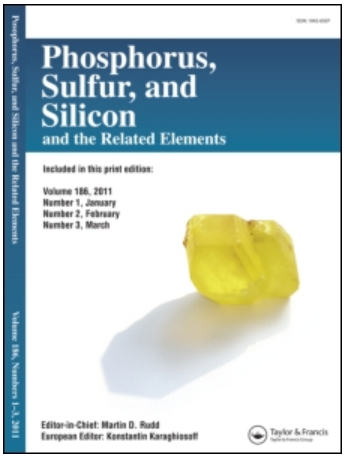

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Syntheses, EIMS and 13 C NMR Study of 1,2-DI-Substituted Derivatives of 2-thio-6-aminouracil

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SYNTHESES, EIMS AND ^{13}C NMR STUDY OF 1,2-DI-SUBSTITUTED DERIVATIVES OF 2-THIO-6-AMINOURACIL

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Ten new ortho, meta, and para substituted derivatives of 2-benzylthio-1-benzyl-6-aminouracils have been prepared. Electron impact (EI) induced mass spectral fragmentation of these compounds was investigated. Fragmentation pathways are proposed on the basis of accurate mass and metastable transitions measurements. The correlation between the intensities of the $M^{+\cdot}$ and the selected fragment ions of these compounds is discussed. The data obtained create the basis for distinguishing isomers. The ^{1}H and ^{13}C NMR spectra of these compounds were assigned unambiguously using a two-dimensional $^{13}C,^{1}H$-Long Range correlation (HMBC) spectra. The data derived from these spectra can be used to differentiate the isomers.

Keywords: 1,2-disubstituted uracils; 2-Thio-6-aminouracil; ^{13}C NMR; EIMS

Literature survey has shown that the reaction of thio analogs of pirymidine bases with various halo substituted organic compounds gives S-mono substituted and S-N1/N3 disubstituted derivatives, which are of interest due to their biological activity.[1–8] The regioselectivity of these methods of preparation of the modified derivatives of thio analogs of pyrimidine bases depends upon the structures of substrates and the conditions of the reactions (i.e., the stoichiometry, solvents, temperature, catalyst, time, and basicity).[9–24]

Recently, we have reported on the synthesis and physicochemical properties, as well as mass spectrometric study of new isomeric

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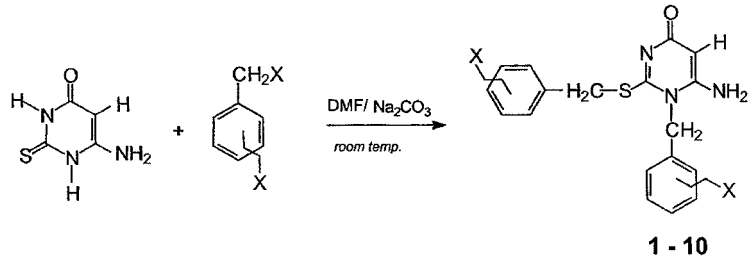
2-*ortho*-(*meta*- and *para*-) chloro-(bromo- and nitro-) benzylthio-6-aminouracils.[25] However, to the best of our knowledge, no work has been published on the synthesis and physicochemical properties of 1,2-dibenzyl substituted derivatives 2-thio-6-aminouracils. This fact has stimulated us to prepare a series of 1, 2-di [*ortho*- (*meta*- and *para-)* chloro- (bromo- and nitro-) benzyl]-2-thio-6-aminouracils (**1–9**) as well as 1, 2-di [2′-chloro-4′-nitrobenzyl]-2-thio-6-aminouracil (**10**) (Figure 1).

This article deals with the synthesis and physicochemical properties of **1–10**. The analyses of ^{13}C NMR and EI mass spectra of these compounds have been performed to check the possibility of the differentiation of positional isomers. The differences in the mass fragmentation of isomeric **1–10** have been quantified by comparing the calculated values of the coefficient μ, i.e., the abundances of selected odd-electron ($OE^{+\cdot}$) or even-electron (EE^{+}) fragment ions relative to the abundance of the molecular ion. The physical meaning of the coefficient μ, as a measure of the intensity ratio of fragment ion and molecular ion characterizing



1 X = *o* - Cl

2 X = *m* - Cl

3 X = *p* - Cl

4 X = *o* - Br

5 X = *m* - Br

6 X = *p* - Br

7 X = *o* – NO_2

8 X = *m* – NO_2

9 X = *p* – NO_2

10 X = 2 – Cl, 4 – NO_2

FIGURE 1 The synthesis and list of the structures of compounds **1–10**.

fragmentation processes of the molecular ions of **1–10**, is dependent on the rate constant for $M^{+\cdot} \rightarrow OE^{+\cdot}$ (or EE^{+}) fragment ion, the sum of the rate constants of other competing molecular ion dissociations, and the sum of the rate constants for consecutive dissociations of the $OE^{+\cdot}$ or (EE^{+}) fragment ion. The abundance of the ions depends on their stability, the amount of the energy needed to ionize the molecule, and the stability of the product ions, as well as the stability of the neutral products. We wished to establish whether it would be possible to determine the position of halo- (or nitro-) groups in the phenyl ring on the basis of differences in the values of $\mu_1 - \mu_4$ and to compare the data with those previously obtained in our laboratory.[25]

RESULTS AND DISCUSSION

A series of ten new *ortho-* (*meta-* and *para-*) chloro-(bromo- and nitro-) substituted 1, 2-dibenzyl-2-thio-6-aminouracils **1–10** has been synthesized in the reaction of 2-thio-6-aminouracil with corresponding benzyl halides. Treatment of 2-thio-6-aminouracil with *o-*(*m-* and *p-*) chloro-(bromo- and nitro-) benzyl bromides (or chlorides) as well as 2-chloro-4-nitro- benzyl chloride in DMF solution in the presence of Na_2CO_3 at room temperature led to **1–10** in 21–100% crude yield (Figure 1). It should be emphasized that there is a correlation between the yields of the products **1–10** and the structure of *ortho-* (*meta-* and *para-*) chloro-(bromo- and nitro-) benzyl halides. When the substituent is at the *ortho* position at the phenyl ring of benzyl halide, the reaction yield is the highest almost quantitative. The structures of all compounds obtained were determined by examining their UV/VIS, IR, ^1H, and ^{13}C NMR spectra as well as on the basis of elemental analyses (Tables I–IV). Noteworthy is the fact that the presence of the second *ortho-* (*meta-* and *para-*) chloro-(bromo- and nitro-) benzyl substituent at the annular nitrogen atom N-1 of the pyrimidine ring of the molecules of **1–10** changes the physicochemical properties of these compounds in comparison with the series of their S-mono substituted counterparts.[25] In particular the values of the melting points of **1–10** are lower in the range of 100–180°C and the R_f values are higher by 0.3–0.5 unit. The ^1H and ^{13}C NMR data of **1–10** are given in Tables III and IV. Assignments of the ^1H NMR and ^{13}C NMR resonances of these compounds were deduced on the basis of signal multiplicities, and by the concerted application of two-dimensional ^1H, ^{13}C Long Range Heteronuclear Multiple-Bond correlation (HMBC) spectra. The HMBC spectrum clearly shows the connectivities of all hydrogen and carbon atoms involved, including quaternary carbons. The HMBC results allow an unequivocal assignment

TABLE I Chemical and Physical Data of Compounds **1–10**

Comp.	X	Formula (mol. wt.)	m.p. [°C]	Yield (%)	R_f TLC
1	o-Cl	$C_{18}H_{15}N_3OSCl_2x\ ^1/_2\ H_2O$ 401.33	139–141	87	0.87
2	m-Cl	$C_{18}H_{15}N_3OSCl_2x\ ^1/_2\ H_2O$ 401.33	64–67	24	0.92
3	p-Cl	$C_{18}H_{15}N_3OSCl_2$ 392.33	122–124	30	0.88
4	o-Br	$C_{18}H_{15}N_3OSBr_2$ 481.43	138–141	100	0.83
5	m-Br	$C_{18}H_{15}N_3OSBr_2$ 481.43	80–83	21	0.82
6	p-Br	$C_{18}H_{15}N_3OSBr_2$ 481.43	137–141	27	0.88
7	o-NO_2	$C_{18}H_{15}N_5O_5S$ 413.45	152–154	100	0.82
8	m-NO_2	$C_{18}H_{15}N_5O_5S$ 413.45	159–160	29	0.82
9	p-NO_2	$C_{18}H_{15}N_5O_5S$ 413.45	154–159	81	0.83
10	o-Cl p–NO_2	$C_{18}H_{13}N_5O_5Cl_2S$ 482.33	196–197	68	0.92

of S, N-1 disubstitution of benzyl groups at uracil ring of **1–10**. The HMBC experiment is conducted without ^{13}C decoupling so that correlations via one or more bond can be discerned and one-bond correlation affords double cross peaks in the ^1H dimension.

The ^1H NMR spectra of **1–10** show singlets of C-5H, N—CH_2, S—CH_2, and NH_2 protons situated at 5.49–5. 61; 5. 26–5.54; 4.26–4.53, and 6.18–6.91 respectively. The signals of protons of *ortho*- (*meta* and *para*-) substituted groups of **1–10** appear in the range of 7.21–8.26 ppm (Table III). Table IV gives the ^{13}C NMR data for **1–10**. In order to exemplify the attributions made for each compound on the basis of the analysis of HMBC spectra the case of **4** is discussed.

For this compound the ^1H NMR spectrum exhibits four singlets at 4.29; 5.27; 5.51 and 6.84 ppm ascribed to protons of S—CH_2, N—CH_2, C—5H, and NH_2 respectively. In the HMBC spectrum the double-cross peaks of one-bond correlations connect protons of S-substituted methylene group with carbon atom of this group (34.29 ppm), protons of N-substituted methylene group with carbon of this group (66.49 ppm) and the proton situated at C-5 with the appropriate carbon (82.01 ppm). The HMBC spectrum of **4** also shows peaks corresponding to two-bond correlations for SCH_2/C-1′ (137.36 ppm), and three-bond correlations for SCH_2/C-2 (168.10 ppm); S—CH_2/C-2′ (123.90 ppm) and S-CH_2/C-6′

TABLE II Elemental Analyses and UV/VIS, and IR Data of Compounds **1–10**

Comp.	UV/VIS λ_{max} [nm] (log ε) DMF	IR ν [cm^{-1}] ν S—CH_2	ν NH_2 δNH_2	ν CO	Elemental analysis (%) Calc. C	H	N	Found C	H	N
1	267.0 (3.90)	2942 2724	3481 1587	1648	53.86	3.76	10.47	53.92	3.54	10.58
2	267.5 (3.85)	2950 2736	3486 1581	1670	53.86	3.76	10.47	54.02	3.71	10.71
3	267.0 (3.94)	2927 2718	3487 1585	1644	55.10	3.86	10.71	54.90	3.93	10.63
4	267.0 (3.90)	2942 2720	3486 1582	1646	44.90	3.15	8.73	44.77	3.18	8.42
5	267.0 (3.88)	2950 2736	3367 1579	1669	44.90	3.15	8.73	45.36	3.30	8.51
6	267.0 (3.95)	2931 2717	3486 1586	1644	44.90	3.15	8.73	44.91	3.14	8.59
7	268.0 (4.20)	2956 2681	3484 1583	1638	52.29	3.66	16.94	51.99	3.76	16.82
8	269.0 (4.30)	2942	3454 1588	1636	52.29	3.66	16.94	51.89	3.57	16.95
9	273.0 (4.35)	2960 2707	3482 1580	1673	52.29	3.66	16.94	51.94	3.21	16.84
10	270.0 (4.37)	2916	3425 1584	1644	44.82	2.72	14.52	44.71	2.71	14.46

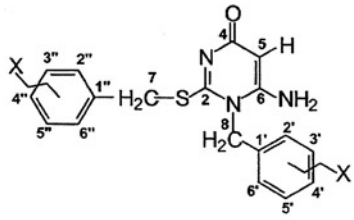
(131.10 ppm). The signal for three-bonds correlations for N—CH_2/C-6 (167.99 ppm) and N—CH_2/C-2 (168.10 ppm) is of special interest since it proves that the benzyl group is attached to N-1. The spectrum also reveals signals corresponding to two-bond correlations for N—CH_2/C-1″

TABLE III ^{1}H-NMR Shifts of **1–10**[a]

Compound	S—CH_2 (s)	N—CH_2 (s)	C-5H (s)	NH_2 (s)	Ar (m)
1	4.38	5.38	5.54	6.87	7.21–7.54
2	4.29	5.28	5.51	6.86	7.27–7.96
3	4.27	5.27	5.49	6.18	7.29–7.65
4	4.29	5.27	5.51	6.84	7.23–7.95
5	4.29	5.27	5.51	6.84	7.23–7.95
6	4.26	5.26	5.50	6.83	7.29–7.58
7	4.53	5.54	5.53	6.91	7.48–8.12
8	4.43	5.43	5.56	6.89	7.54–8.25
9	4.37	5.44	5.56	6.91	7.37–8.19
10	4.40	5.42	5.61	6.99	7.58–8.26

[a]Spectra determined in dimethyl-d_6 sulfoxide at 25°C and shifts are reported in ppm (δ) downfield from tetramethylsilane.

TABLE IV ^{13}C NMR Shifts of **1–10**[a]



	Compound									
Carbon	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
C-2	168.12	168.24	168.24	168.10	168.18	168.54	168.01	168.24	168.18	167.61
C-4	165.06	165.28	164.98	165.09	165.01	165.27	165.07	165.34	165.37	165.52
C-5	81.96	82.16	82.01	82.01	82.04	82.11	82.06	82.26	82.28	82.31
C-6	168.00	168.34	168.07	167.99	168.06	168.34	167.89	168.29	168.18	167.52
C-7	31.74	30.74	32.91	34.29	33.02	32.94	35.82	32.66	32.94	31.56
C-8	64.24	66.03	65.95	66.49	65.96	66.01	63.85	65.95	65.63	63.52
C-1′	135.66	141.58	137.78	137.36	141.65	138.43	132.46	141.68	146.80	147.05
C-2′	133.02	128.57	130.43	123.90	131.28	131.32	147.89	123.23	129.84	133.58
C-3′	129.53	133.06	128.22	132.47	121.48	130.97	124.77	147.74	123.51	123.82
C-4′	129.51	126.81	132.16	127.78	129.57	119.87	128.88	121.88	145.26	147.05
C-5′	127.81	130.35	128.22	129.59	130.28	130.97	133.50	129.99	123.51	121.74
C-6′	132.09	127.50	130.43	131.10	127.71	131.32	133.98	135.48	129.84	131.33
C-1″	135.60	139.61	135.94	135.81	139.63	136.58	132.11	139.50	146.23	146.60
C-2″	134.94	127.73	129.25	122.27	130.46	131.15	147.05	122.59	127.83	131.85
C-3″	129.50	132.81	128.04	132.43	121.28	129.70	124.68	147.63	123.31	122.12
C-4″	128.78	126.17	131.20	127.65	129.50	119.87	128.57	121.76	143.37	146.60
C-5″	127.02	130.16	128.04	129.08	130.09	129.70	133.46	129.71	123.31	121.74
C-6″	130.96	127.34	129.25	129.83	126.43	131.15	133.84	133.99	127.83	129.01

[a]Spectra determined in dimethyl-d_6 sulfoxide at 25°C and shifts are reported in ppm (δ) downfield from tetramethylsilane.

(135.81) ppm; N—CH_2/C-2″ (122.27 ppm)and N—CH_2/C-6″ (129.83 ppm) as well as C-5H/C-6 (167.99 ppm). The protons of amino group correlate via two-bonds with C-6 (167.99 ppm) and via three-bonds with C-5 (82.01 ppm). The same spectrum also indicates that the C-5 proton correlates via two-bonds with C-6 (167.99 ppm). It ought to be pointed out that the ^{1}H NMR spectrum of **4** exhibits four doublets at 7.64; 7.62; 7.58 and 7.48 ppm ascribed to C-3′H or (C-3″H) and C-6′-H (or C-6″) of the benzyl groups respectively. It also includes four triplets at 7.38; 7.45; 7.28; and 7.18 ppm ascribed to C-4′H (or C-4″H) as well as C-5′H (or C-5″H) of the benzyl groups. The HMBC spectrum of **4** shows peaks corresponding to three-bonds correlations for C-3″Hd/C-1″ (137.36 ppm); C-5″Ht/C-1″ (137.36 ppm); C-4″Ht/C-2″ (123.90 ppm);

C-6″Hd/C-2″(123.90 ppm); C-4″Ht/C-6′ (131.10); C-6″Hd/C-4″ (127.78 ppm); C-3′Hd/C-1′ (135.81 ppm); C-5′Ht/C-1′ (135.81 ppm); C-4′Ht/C-2′ (122.27 ppm); C-6′Hd/C-2′ (122.27 ppm) and C-5′Ht/C-3′ (132.43 ppm). There are also peaks two-bonds correlations for C-3″Hd/C-2″ (129.90 ppm); C-3″Hd/C-4′ (127.78); C-3′Hd/C-2′ (122.27); C-4′Ht/C-5′ (129.08); C-6′Hd/C-5′ (129.08 ppm), and C-4′Ht/C-3′ (132.43 ppm). The double-cross peaks of the one-bond correlations indicate that the protons of C-6″Hd correspond to C-6″ (131.10 ppm); C-4″Ht with C-4″ (127.78 ppm); as well as C-3′Hd with C-3′ (132.43 ppm).

A comparison of the number and positions of the signals of the carbon atoms in the range of 115–125, 135–145 as well as 140–150 ppm in ^{13}C NMR spectra of **1–9** allows a differentiation between *ortho*-, *meta*-, and *para*- substituted in benzyl groups isomers.

The data are given in tabulated form below:

1–3 (Cl substituted isomers) 135–145 ppm

ortho	*meta*	*para*
C-1″ 135.66 ppm	C-1″ 141.58 ppm	C-1″ 137.36 ppm
C-1′ 135.00 ppm	C-1′ 139.61 ppm	C-1′ 135.81 ppm

4-6 (Br substituted isomers) 115—125 and 135—145 ppm

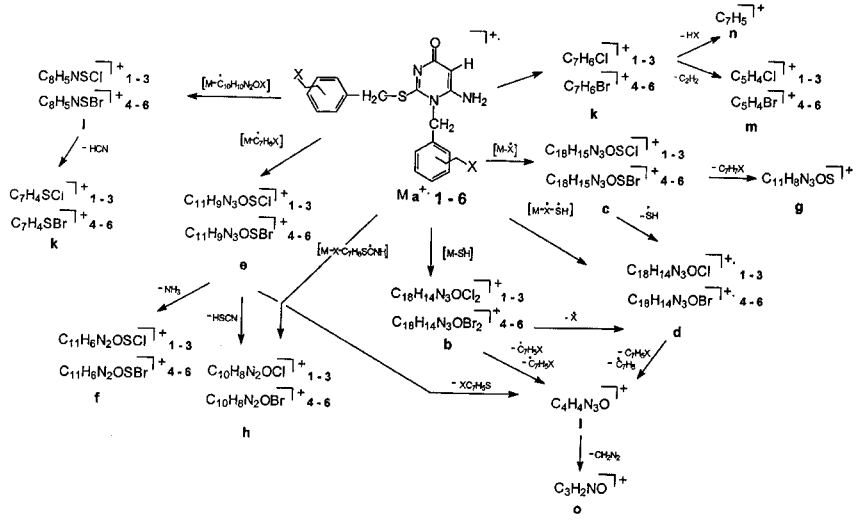
ortho	*meta*	*para*
C-2″ 129.90 ppm	C-3″ 121.48 ppm	C-4″ 119.87 ppm
C-2′ 122.27 ppm	C-3′ 121.28 ppm	C-1″ 138.43 ppm
C-1″ 137.36 ppm	C-1″ 141.65 ppm	C-1′ 136.58 ppm
C-1′ 135.81 ppm	C-1′ 139.63 ppm	

7–9 (NO_2 substituted isomers) 140–150 ppm

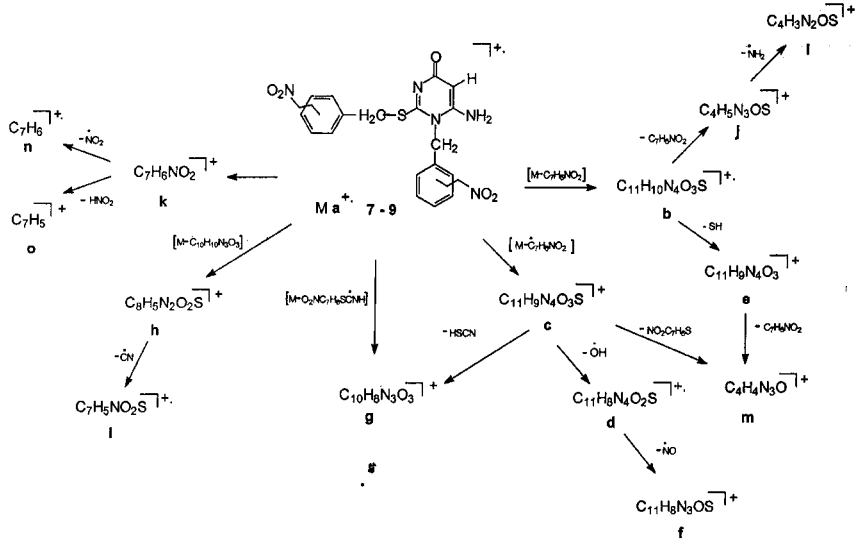
ortho	*meta*	*para*
C-2″ 147.89 ppm	C-3″ 147.74 ppm	C-1″ 146.80 ppm
C-2′ 147.05 ppm	C-3′ 147.63 ppm	C-1′ 146.23 ppm
	C-1″ 141.68 ppm	C-4′ 145.26 ppm
		C-4″ 143.37 ppm

On the basis of low and high resolution electron–impact as well as B/E linked scan mass spectra (Tables V–VII), the principal mass spectral fragmentation routes of compounds **1–6** are interpreted as shown in Scheme 1, and those of **7–9** and **10** in Scheme 2 and 3 respectively.

As can be seen from Schemes 1–3 and Tables V–VII, the principal mass fragmentation pathways of 1, 2-dibenzyl-2-thio-6-aminouracils **1–10** are similar in some respect to those of 2-benzyl-thio-6-aminouracils investigated by us earlier.[25] The common features of the mass spectral fragmentation of the molecular ions of **1–10** are simple cleavages of Csp2-X, Csp3-S, and Csp3-N bonds in the benzylthio and benzyl substituents, i.e., eliminations of $^{\cdot}C_7H_6X$ and $^{\cdot}X$ radicals. During the

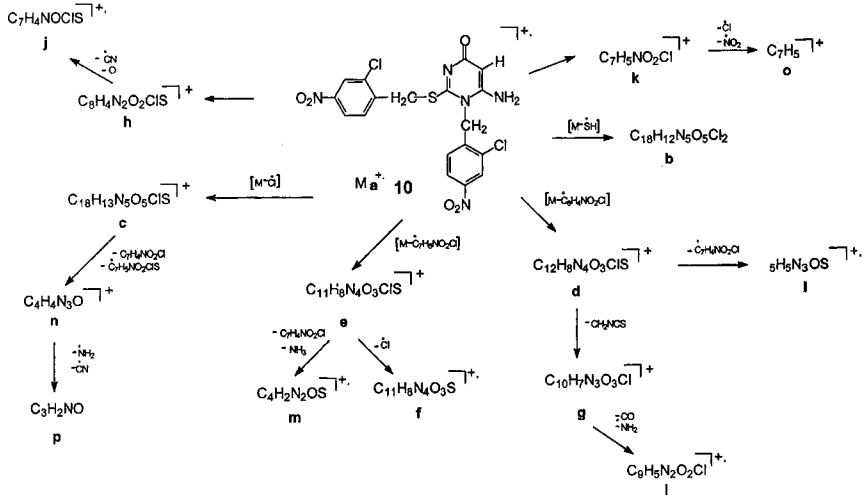


SCHEME 1



SCHEME 2

processes of cleavage of Csp3-S and Csp3-N bonds of the benzylthio and benzyl substituent of the molecular ions of **1–7**, the positive charge is stabilized more effectively on the benzyl fragment. The even–electron fragment ions $C_7H_6X]^+$ are the base peaks in the mass spectra of **1**, **3**,



SCHEME 3

4, and **7**. The base peaks in the mass spectra of **2**, **8**, and **9** are the even-electron fragment ions [M- $C_7H_6X]^+$. In the mass spectra of **5**, **6**, and **10** the base peaks are those corresponding to the even-electron fragment ions $C_4H_4N_3O]^+$ (m/z 110). It was found that these ions are formed from the molecular ions by consecutive ejections of XC_7H_6 radicals and XC_7H_5S neutral molecules. The molecular ions of **1–6** and **10** readily lose ·SH radicals giving even-electron fragment ions **b** (Schemes 1 and 3; Tables V and VII). The same process of mass fragmentation is seen only in the second step of mass decomposition of the molecular ions of **7–9** (**b**→ **e**, Scheme 2, Table VI). For this loss to occur a skeletal rearrangement is required with a formation of new carbon-carbon and carbon-nitrogen bonds. The even-electron fragment ions **b** (**1–6**, **10**) and **e** (**7–9**) which are formed after this rearrangement may have a monocyclic or bicyclic structure. In the first case the charge is localized on the carbon atom of benzyl substituent and in the second on the nitrogen annular atom of pyrimidine ring. It should be mentioned that loss of a sulphydryl radical is common for aromatic thioethers. As can be seen from Schemes 1–3 and the data in Tables V–VII, the processes of the mass fragmentation of the molecular ions of **1–10** involves the characteristic cleavages of two bonds of uracil ring (C-4/N-3 as well as N-1/C-2) with elimination of XC_7H_6S·CNH radicals [the even-electron fragment ions **h** (**1–6**) and **g**(**7–10**); Schemes 1–3, Tables V–VII] or $C_{10}H_{10}N_2OX$· radicals [the even-electron fragment ions **i** (**1–6**) and **h** (**7–10**); Schemes 1–3, Tables V–VII]. In the first case the charge is localized on benzylthio

TABLE V Elemental Composition and Relative Intensities of the Ion Peaks in the Spectra of **1–6** According to High Resolution Data

Ion	M/z	Elemental composition	Relative intensities (%)					
			1	**2**	**3**	**4**	**5**	**6**
$M^{+\cdot}$ **a**	391	$C_{18}H_{15}N_3OSCl_2$	43	48	45	—	—	—
	481	$C_{18}H_{15}N_3OSBr_2$	—	—	—	53	77	40
b	358	$C_{18}H_{14}N_3OCl_2$	7	1	2	—	—	—
	447/449	$C_{18}H_{14}N_3OBr_2$	—	—	—	1	6	1
c	356	$C_{18}H_{15}N_3OSCl$	13	—	—	—	—	—
	400/402	$C_{18}H_{15}N_3OSBr$	—	—	—	14/13	2/2	1/1
d	323	$C_{18}H_{14}N_3OCl$	2	—	—	—	—	—
	367/368	$C_{18}H_{14}N_3OBr$	—	—	—	1/1	3/2	1/1
e	266	$C_{11}H_9N_3OSCl$	71	100	69	—	—	—
	310/312	$C_{11}H_9N_3OSBr$	—	—	—	81/80	98/97	55/54
f	249	$C_{11}H_6N_2OSCl$	8	10	12	—	—	—
	293/295	$C_{11}H_6N_2OSBr$	—	—	—	5/4	11/10	8/7
g	230	$C_{11}H_8N_3OS$	19	5	2	25	8	4
h	207	$C_{10}H_8N_2OCl$	14	17	15	—	—	—
	251/252	$C_{10}H_8N_2OBr$	—	—	—	13/12	15/14	10/9
i	182	C_8H_5NSCl	12	16	17	—	—	—
	226/228	C_8H_5NSBr	—	—	—	11/10	14/13	13/12
j	155	C_7H_4SCl	8	9	6	—	—	—
	199/201	C_7H_4SBr	—	—	—	6/5	10/9	7/6
k	125	C_7H_6Cl	100	99	100	—	—	—
	169/171	C_7H_6Br	—	—	—	100/99	79/78	73/72
l	110	$C_4H_4N_3O$	69	84	82	85	100	100
m	99	C_5H_4Cl	12	15	11	—	—	—
	143/145	C_5H_4Br	—	—	—	4/3	7/6	6/5
n	89	C_7H_5	34	37	31	52	52	37
o	68	C_3H_2NO	15	16	13	23	27	17

carbimine species and in the second on benzyl substituted azacyclobutanone species.

The differences in the fragmentation of isomeric o*rtho*- (*meta*- and *para*-) chloro-(bromo and nitro-)1, 2-dibenzyl-2-thio-6-aminouracils (**1–9**) have been quantified by comparing the calculated values of the coefficients μ, i.e., the abundances of the selected even- and odd- electron fragment ions relative to the abundances of the molecular ions. It has been established by us previously[25–27] that differences in the values of the coefficients μ are useful for differentation of the positional isomers in the family of the derivatives of thiouracils. For compounds **1–9**, Table VIII presents the ratios of the intensities of the $[M\text{-}\cdot C_7H_6X]^+$, $[M\text{-}\cdot C_7H_6X\text{-}HX]^{+\cdot}$ and $[M\text{-}\cdot C_7H_6X\text{-}\cdot C_7H_5XS]^{+\cdot}$ as well as $[C_7H_6X]^+$ ion peaks to those of the parent ions peaks, i.e.,

TABLE VI Elemental Composition and Relative Intensities of the Ion Peaks in the Spectra of **7–9** According to High Resolution Data

Ion	M/z	Elemental composition	Relative intensities (%) 7	8	9
$M^{+\cdot}$ **a**	413	$C_{18}H_{15}N_5O_5S$	53	76	76
b	278	$C_{11}H_{10}N_4O_3S$	28	18	22
c	277	$C_{11}H_9N_4O_3S$	1	100	100
d	260	$C_{11}H_8N_4O_2S$	1	5	8
e	245	$C_{11}H_9N_4O_3$	1	10	11
f	230	$C_{11}H_8N_3OS$	4	5	2
g	218	$C_{10}H_8N_3O_3$	1	12	14
h	193	$C_8H_5N_2O_2S$	1	9	8
i	167	$C_7H_5NO_2S$	1	2	2
j	143	$C_4H_5N_3OS$	30	3	2
k	136	$C_7H_6NO_2$	100	53	39
l	127	$C_4H_3N_2OS$	4	17	18
m	110	$C_4H_4N_3O$	10	99	80
n	90	C_7H_6	4	75	32
o	89	C_7H_5	40	37	37

TABLE VII Elemental Composition and Relative Intensities of the Ion Peaks in the Spectra of **10** According to High Resolution Data

Ion	M/z	Elemental composition	Relative intensities (%) 10
$M^{+\cdot}$ **a**	481	$C_{18}H_{13}N_5O_5Cl_2S$	34
b	448	$C_{18}H_{12}N_5O_5Cl_2$	4
c	446	$C_{18}H_{13}N_5O_5ClS$	6
d	325	$C_{12}H_8N_4O_3ClS$	4
e	311	$C_{11}H_8N_4O_3ClS$	69
f	276	$C_{11}H_8N_4O_3S$	9
g	252	$C_{10}H_7N_3O_3Cl$	10
h	227	$C_8H_4N_2O_2ClS$	6
i	208	$C_9H_5N_2O_2Cl$	6
j	185	C_7H_4NOClS	5
k	170	$C_7H_5NO_2Cl$	15
l	155	$C_5H_5N_3OS$	7
m	128	$C_4H_2N_2OS$	72
n	110	$C_4H_4N_3O$	100
o	89	C_7H_5	51
p	68	C_3H_2NO	15

TABLE VIII The Values of μ_1-μ_4 Calculated from the EI Mass Spectra of **1–9**

Comp.	μ_1	μ_2	μ_3	μ_4
1	1.65	1.60	0.44	2.32
2	2.08	1.75	0.10	2.06
3	1.53	1.82	0.04	2.22
4	1.52	1.60	0.47	1.88
5	1.27	1.29	0.10	1.02
6	1.37	2.50	0.10	1.82
7	0.01	0.18	0.07	1.88
8	1.31	1.30	0.06	0.69
9	1.31	1.05	0.07	0.51

$$\mu_1 = \frac{\%\text{rel.int.}[\text{M}-\cdot\text{C}_7\text{H}_6\text{X}]^+}{\%\text{rel.int.M}^{+\cdot}};$$
$$\mu_2 = \frac{\%\text{rel.int.}[\text{M}-\cdot\text{C}_7\text{H}_6\text{X}-\cdot\text{C}_7\text{H}_5\text{XS}]^{+\cdot}}{\%\text{rel.int.M}^{+\cdot}};$$
$$\mu_3 = \frac{\%\text{rel.int.}[\text{M}-\cdot\text{C}_7\text{H}_6\text{X}-\cdot\text{HX}]^+}{\%\text{rel.int.M}^{+\cdot}};$$
$$\mu_4 = \frac{\%\text{rel.int.C}_7\text{H}_6\text{X}^+}{\%\text{rel.int.M}^{+\cdot}}.$$

μ_1 = % rel. int. [M-·C_7H_6X]$^+$/ % rel. int. $M^{+\cdot}$
μ_2 = % rel. int. [M-· C_7H_6X-·C_7H_5XS]$^{+\cdot}$/ % rel. int. $M^{+\cdot}$
μ_3 = % rel. int. [M-·C_7H_6X-HX]$^{+\cdot}$/ % rel. int. $M^{+\cdot}$
μ_4 = % rel. int. [C_7H_6X]$^+$/ % rel. int. $M^{+\cdot}$

As can be seen from the data in Table VIII, the differences between the relative intensities of the peaks of selected fragment ions and $M^{+\cdot}$ions, i.e., the values of μ_1, μ_2, μ_3, and μ_4 for o*rtho-* (*meta-* and *para-*) chloro-(bromo and nitro-) substituted 1, 2-dibenzyl-2-thio-6-aminouracils **1–9** may be sufficient to differentiate between particular isomers.

Ortho- (*meta-* and *para-*) chloro-(bromo- and nitro-) substituted isomers of 1, 2-dibenzyl-2-thio-6-aminouracils (**1–9**) may be differentiated on the basis of the following sequences of the values of $\mu_1 - \mu_4$.

μ_1 *meta* > μ_1 *ortho* > μ_1 *para* **1–3**
μ_1 *ortho* > μ_1 *para* > μ_1 *meta* **4–6**
μ_2 *para* > μ_2 *meta* > μ_2 *ortho* **1–3**
μ_2 *para* > μ_2 *ortho* > μ_2 *meta* **4–6**
μ_2 *meta* > μ_2 *ortho* > μ_2 *para* **7–9**
μ_3 *ortho* > μ_3 *meta* > μ_3 *para* **1–3**
μ_4 *ortho* > μ_4 *para* > μ_4 *meta* **1–3**
μ_4 *ortho* > μ_4 *meta* > μ_4 *para* **7–9**

Moreover, o*rtho*- (*meta*- and *para*-) chloro-(bromo and nitro-) substituted 1, 2-dibenzyl-2-thio-6-aminouracils (**1**, **4**, **9**) may be distinguished from isomeric *meta*- (**2**, **5**, **8**) and *para*- (**3**, **6**, **9**) substituted 1, 2-dibenzyl-2-thio-6-aminouracils on the basis of the highest values of μ_1. *Para*- halo-(chloro- and bromo-) substituted 1, 2–dibenzyl-2-thio-6-aminouracils (**3**, **6**) may be distinguished from their *ortho*- (**1**, **4**) and *meta*- (**2**, **5**) substituted counterparts on the basis of the highest values of μ_2.

CONCLUSIONS

The reactions of 2-thio-6-aminouracil with 2-fold molar excess of *ortho*- (*meta*- and *para*-) chloro- (bromo- and nitro-) benzyl halides in DMF in the presence of 1 equivalent of Na_2CO_3 at room temperature lead to 1, 2- dibenzyl substituted 2-thio-6-aminouracils **1–10**. For compounds **4** and **7** these reactions are regioselective, for **1**, **9**, and **10** they show a high level of regioselectivity. **2**, **3**, **5**, and **6** were obtained in 21–30% yield.

The basic mass fragmentation of **1–10** is due to cleavages of the Csp3-S, Csp2-S, Csp3-N of N-1 and C-2-S substituted benzyl groups, as well as Csp2-X bonds of X substituted phenyl groups. The values of μ_1, μ_2, μ_3, and μ_4 (i.e., the ratio of the intensities of the selected fragment ion peaks to those of the molecular ion peaks $M^{+\cdot}$) depend on the structures of o*rtho*- (*meta*- and *para*-) chloro-(bromo and nitro-) substituted 1, 2-dibenzyl-2-thio-6-amino- uracils **1–9**. The differences in. the values of $\mu_1 - \mu_4$ in the series of **1–9** are useful for differentiation between o*rtho*- (*meta*- and *para*-) substituted isomers of 1, 2-dibenzyl-2-thio-6-aminouracils **1–9**.

The differences in the ^{13}C NMR spectra of **1–9** in the number and positions of the signals of the carbon atoms in the range of 135–145 ppm (**1–3**); 115–125 ppm and 135–145 ppm (**4–6**) as well as 140–150 ppm (**7–9**) allow a differentiation between o*rtho*- (*meta*- and *para*-) substituted in benzyl groups isomers.

EXPERIMENTAL

Purity of all studied compounds was checked by m.p.s, TLC, and elemental analysis. Melting points (uncorrected) were determined on a Böetius microscope hot stage. R_f values refer to TLC silica gel F_{254}TLC plates (Merck) developed with $CHCl_3$-MeOH 5:1 and observed under UV light ($\lambda = 254$ and 366 nm). UV/VIS spectra were recorded with a

Specord UV/VIS spectrophotometer in DMF. IR spectra were recorded with a FT-IR Bruker IFS–113 v Spectrophotometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were determined with a Varian Gemini 300 (300 MHz) spectrophotometer in DMSO-d_6 solution with TMS as internal standard. The ^{1}H NMR (300 MHz) and ^{13} C NMR (75 MHz) spectra were recorded on a Varian Gemini 300 spectrophotometer in DMSO-d_6 at a concentration between 0.25 and 0.40 M in 5 mm sample tubes at ambient temperature. Chemical shifts are given in the δ scale (ppm) and coupling constants in Hz. ^{1}H NMR (300.070) spectra were recorded with spectral width 9 kHz, acquisition time 2.0 s, pulse width 6 μs and double precision acquisition. ^{13}C NMR (75.460) spectra were recorded with spectral width 18.76 kHz, acquisition time 1.0 s, recycle delay 1.0 s, and pulse width 15 μs. Homonuclear ^{1}H-^{1}H shift correlated two-dimensional diagrams were obtained on Varian Gemini 300 spectrophotometer using the COSY pulse sequence. The spectral width was 4.97 kHz, acquisition time 0.206 s, number of increments in $t_1$512 and number of scans 16. Heteronuclear two-dimensional ^{13}C, ^{1}H Long Range chemical shift correlation experiments were carried out using HMBC spectra. Elemental analyses were performed with a Vector Euro EA 3000 analyzer. Low- and high-resolution mass spectra were recorded on an AMD-Intectra GmbH-Harpstedt D-27243 Model 402 two-sector mass spectrometer (ionizing voltage 70 eV, accelerating voltage 8 kV, resolution 10,000). Samples were introduced by a direct insertion probe at the source temperature of $\sim$150°C. The elemental compositions of the ions were determined by a peak matching method relative to perfluorokerosene and using the same instrument. All masses measured agreed with those of the composition listed in column three of the Tables V–VII to within $\pm$ 2 ppm. The B/E linked scan spectra in the first field-free region were investigated using helium as the collision gas at a pressure of $1{,}73 \times 10^{-5}$ with the ion source temperature of 180°C, ionization energy of 70 eV and an accelerating voltage of 8 kV. The values of $\mu_1 - \mu_4$, were calculated as averages of three measurements.

2-Thio-6-aminouracil was obtained according to literature.[28,29]

The Synthesis of 2-*Ortho*- (*Meta*- and *Para*-) Chloro-(Bromo- and Nitro-) benzylthio-1-*Ortho*- (*Meta*- and *Para*-) Chloro-(Bromo- and Nitro-)benzyl-6-aminouracils (1-9) and 2-[2′-Chloro-4′-nitrobenzylthio]-1-[2′-chloro-4′-nitrobenzyl]-6-aminouracil (10)

A mixture of 1 mmol of 2-thio-6-aminouracil and 1 mmol of Na_2CO_3 in 10 ml of DMF was stirred at room temperature while 2 mmol of

corresponding *ortho*- (*meta*- and *para*-) chloro-(bromo- and nitro-) benzyl halide, (or 2-chloro-4-nitrobenzyl bromide) were added dropwise. After stirring for 24 h 10 ml of distilled water was added. The reaction mixture was kept at room temperature 24 h. The precipitated solid was isolated by filtration, dried at room temperature, and recrystallized from the mixture of H_2O:DMF (2:3).

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