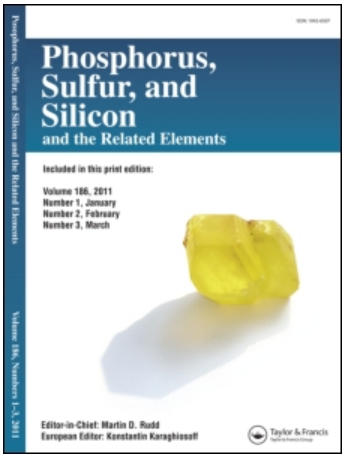

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Syntheses, EIMS, ^{1}H NMR, and ^{13}C NMR Study of 2-Mono, 1,2-Di, and 2,4-Di Substituted Derivatives of 2-Thiocytosine

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To cite this Article Wyrzykiewicz, Elżbieta , Pospieszny, Tomasz and Mielcarek, Sebastian(2005) 'Syntheses, EIMS, ^{1}H NMR, and ^{13}C NMR Study of 2-Mono, 1,2-Di, and 2,4-Di Substituted Derivatives of 2-Thiocytosine', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 9, 2051 — 2070
To link to this Article: DOI: 10.1080/104265090902840
URL: http://dx.doi.org/10.1080/104265090902840

Phosphorus, Sulfur, and Silicon, 180:2051–2070, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090902840

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Syntheses, EIMS, ^{1}H NMR, and ^{13}C NMR Study of 2-Mono, 1,2-Di, and 2,4-Di Substituted Derivatives of 2-Thiocytosine

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*Seventeen new S-ortho-(meta- and para-) bromo-(chloro- and nitro-) benzylsubstituted 2-thiocytosines as well as S and N-1 (S- and N-4) ortho-(meta- and para-) bromo-(chloro- and nitro-) benzyl disubstituted hydrohalides of 2-thiocytosines have been prepared. The ^{1}H and ^{13}C NMR spectra of these compounds have been assigned unambiguously using a two-dimensional ^{13}C, ^{1}H-one-bond correlation (HETCOR) (**1–9**) and a two-dimensional ^{13}C, ^{1}H -Long Range correlation (HMBC) (**10–18**) spectra. Electron-impact (EI)-induced mass spectral fragmentation of S-benzyl substituted derivatives of 2-thiocytosine has been investigated. The data obtained make the basis for distinguishing isomers.*

Keywords 1,2- and 2,4-di benzyl substituted hydrohalides of 2-thiocytosines; 2-benzylthiocytosines; ^{13}C NMR; ^{1}H NMR; EIMS; structural isomers

INTRODUCTION

The compound of 2-thiocytosine is a minor component of t-RNA, and its modified derivatives of 2-thiocytosines are of interest because of their biological and pharmacological activities.[1–4] The prototropic tautomerism of 2-thiocytosine has attracted much attention in the last decade.[5–9] 2-thiocytosine can occur in 6 tautomeric forms as a result of the thiol-thione and amino-imino equilibria. The tautomeric equilibrium of 2-thiocytosine exhibits a strong dependeance on the interaction with its environment and is significantly different in low-temperature matrices in solutions and in solids.[10–14] According to literature, in the gas-phase the predominant tautomer of 2-thiocytosine is the thiol-amino form, but in solution the predominant tautomer is the

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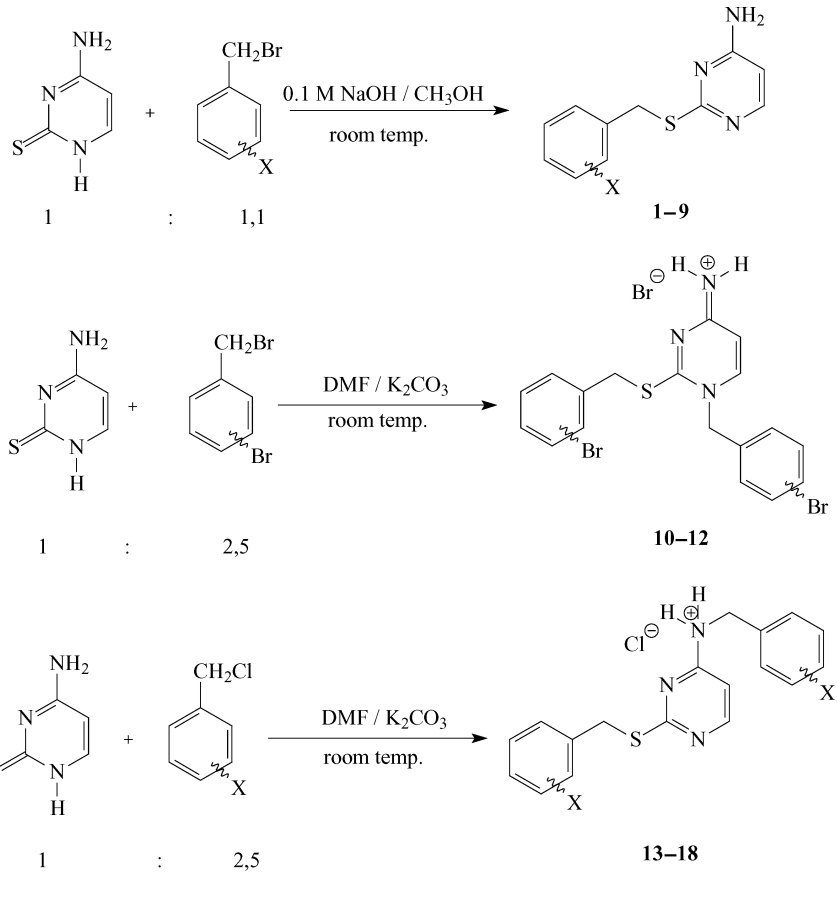
1H-thione-amino form.[6] The tautomeric forms of 2-thiocytosine having an imino group are less stable in both phases.

Literature survey has shown that the reaction of 2-thiocytosine with various halo substituted organic compounds gives S-mono as well as S and N disubstituted derivatives.[15–22] The regioselectivity of these methods of preparation of the modified derivatives of 2-thiocytosine depends upon the structures of substrates and the conditions of reactions (i.e. the stoichiometry, solvents, temperature, catalyst, time and basicity).

Recently, we have reported on the synthesis and physicochemical properties of new flourescent 2-*ortho*-(*meta*- and *para*-) chloro-(and bromo-) benzylthio-N-phenylcytosines and 6-methylcytosines,[23] as well as 1,2-di-*ortho*-(*meta*- and *para*-)chloro-(bromo- and nitro-) benzyl-substituted derivatives of 2-thio-6-aminouracil.[24] However, to the best of our knowledge, no work has been published on the chemoselective synthesis of S-monobenzyl-substituted derivatives of 2-thiocytosines and the regioselective synthesis of S and N-1 as well as S and N-4 dibenzyl substituted derivatives of 2-thiocytosines. This fact has stimulated us to investigate the reaction of 2-thiocytosine with the series of *ortho*-(*meta*- and *para*-) bromo-(chloro- and nitro-) benzyl halides (Figure 1).

This article deals with the synthesis and physicochemical properties of 2-*o*-(*m*- and *p*-) bromo-(chloro- and nitro-) benzylthiocytosines (**1–9**), hydrobromides of 2-*o*-(*m*- and *p*-) bromobenzylthio-1-*o*-(*m*- and *p*-) bromobenzylthiocytosines (**10–12**) and hydrochlorides of 2-*o*-(*m*- and *p*-) chloro-(nitro-) benzylthio-1-*o*-(*m*- and *p*-) chloro-(nitro-) benzylcytosines **13–18** (Figure 1). The EIMS, ^{1}H NMR, and ^{13}C NMR spectra of these compounds have been analyzed to check the possibility of differentiation of positional isomers, i.e., *ortho* (**1**, **4**, **7**, **10**, **13**, **16**), *meta* (**2**, **5**, **8**, **11**, **14**, **17**), and *para* (**3**, **6**, **9**, **12**, **15**, **18**) bromo-(chloro- and nitro-) substituted derivatives of 2-benzylthiocytosines (**1–9**), hydrobromides of 2-benzylthio-1-benzylcytosines (**10–12**) and hydrochlorides of 2-benzylthio-1-benzylcytosines (**13–18**). The ^{1}H NMR and ^{13}C NMR spectra have been also checked for the ability to distinguish between the S and N-1 (**10–12**) disubstituted as well as S and N-4 (**13–18**) disubstituted isomers of hydrohalides of 2-thiocytosine. The differences in the EI mass fragmentation of **1–9** have been quantified by comparing the calculated values of the coefficient μ, i.e., the abundances of the selected fragment ions relative to the abundance of the molecular ion. 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 the differences in the values of μ and to compare the data with these previously obtained in our laboratory.[23–25]



1 X = *o*- Br
2 X = *m*- Br
3 X = *p*- Br
4 X = *o*- Cl
5 X = *m*- Cl
6 X = *p*- Cl
7 X = *o*- NO_2
8 X = *m*- NO_2
9 X = *p*- NO_2

10 X = *o*-Br
11 X = *m*-Br
12 X = *p*-Br
13 X = *o*-Cl
14 X = *m*-Cl
15 X = *p*-Cl
16 X = *o*-NO_2
17 X = *m*-NO_2
18 X = *p*-NO_2

FIGURE 1 The synthesis and list of the structures of compounds **1–18**.

RESULTS AND DISCUSSION

A series of eight new *ortho*-(*meta*- and *para*-) chloro-(bromo- and nitro-) substituted 2-benzylthiocytosines **1–5**, **7–9** has been synthesized in the reaction of 2-thiocytosine with the appropriate benzyl halides.

2-*p*-chlorobenzylthiocytosine has been prepared earlier by Ward and Baker in the reaction of 2-thiocytosine in boiling ethanol with p-chlorobenzyl halide and KOH (excess). The yield of **6** was 56%.[26] Treatment of 2-thiocytosine with *o*-(*m*- and *p*-) chloro-(bromo- and nitro-) benzyl bromides (or chlorides) in 0.1 M solution of NaOH in methanol at room temperature afforded chemoselectively **1–9** in 70–95% crude yield (Figure 1). A series of three new hydrobromides of ortho-(meta- and para-) bromo substituted 1,2-dibenzyl-2-thiocytosines (**10–12**) has been synthesized regioselectively in the reaction of 2-thiocytosine with the appropriate benzyl bromides. Treatment of 2-thiocytosine with *o*-(*m*- and *p*-) bromobenzyl bromides in DMF solution in the presence of K_2CO_3 at room temperature led to **10–12** in 75–80% crude yield (Figure 1). A series of the six new hydrochlorides of *ortho*-(*meta*- and *para*-) chloro-(nitro-) substituted 2,4-dibenzyl-2-thiocytosines (**13–18**) has been synthesized unexpectedly in the reaction of 2-thiocytosine with the proper benzyl chlorides. Treatment of 2-thiocytosine with *o*-(*m*- and *p*-) chloro-(nitro-) benzyl chlorides in DMF solution in the presence of K_2CO_3 at room temperature led regioselectively to **13–18** in 72–78% crude yield (Figure 1). The structures of all compounds obtained were determined by examining their UV/VIS, IR, ^{1}H- and ^{13}C NMR spectra as well as the basis of their elemental analyses (Tables I–VII). Noteworthy is the fact that the presence of the second *ortho*-(*meta*- and *para*-) chloro-(bromo- and nitro-) benzyl substitutent at the annular nitrogen atom N-1 of the pyrimidine ring of the molecules of hydrobromides of **10–12**, as well as the angular nitrogen atom N-4 of the pyrimidine ring of the molecules of hydrochlorides of **13–18**, changes the physicochemical properties of these compounds relative to those of the series of their S-mono–substituted counterparts. In particular, the values of the melting points of **10–12** are higher in the range of 20–90°C, but the values of the melting points of **13–18** are lower in the range of 46–133°C. The ^{1}H and ^{13}C NMR data of **1–9** are given in Tables III–V. Assignments of the ^{1}H 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 NMR technique HETCOR. The HETCOR results allow unequivocal assignment of the ^{13}C NMR spectra proposed on the basis of the chemical shifts theory, additivity rules, and by comparing the measured and calculated chemical shifts. The ^{1}H NMR spectra of **1–9** show dublets of CV-H, and CVI-H protons, as well as the singlets of SCH_2- and NH_2 protons situated at 6.19–6.57, 7.84–8.04, 4.29–4.77, and 8.90–8.92, respectively. The signals of the protons of *ortho*-(*meta*- and *para*-) substituted benzyl groups of **1–9** appear in the range 7.20–8.33 ppm (Table III). Table V gives the ^{13}C NMR data for **1–9**. In order to exemplify the

TABLE I Chemical and Physical Data of Compounds 1–18

Comp.	Formula (mol. weight)	M. p. [°C]	Yield (%)	R_f TLC
1	$C_{11}H_{10}N_3SBr$ (296.18)	130–3	80	0. 70
2	$C_{11}H_{10}N_3SBr$ (296.18)	100–2	82	0. 68
3	$C_{11}H_{10}N_3SBr$ (296.18)	198–200	79	0.66
4	$C_{11}H_{10}N_3SCl$ (251.73)	170–2	82	0. 77
5	$C_{11}H_{10}N_3SCl$ (251.73)	107–9	80	0. 70
6	$C_{11}H_{10}N_3SCl$ (251.73)	145–7	81	0. 74
7	$C_{11}H_{10}N_4O_2S$ x $3H_2O$ (316.26)	199–200	95	0. 71
8	$C_{11}H_{10}N_4O_2S$ x $3H_2O$ (316.26)	258–60	69	0. 75
9	$C_{11}H_{10}N_4O_2S$ x $3H_2O$ (316.26)	168–70	70	0. 73
10	$C_{18}H_{16}N_3SBr_3$ (546.12)	220–1	80	0. 72
11	$C_{18}H_{16}N_3SBr_3$ (546.12)	180–2	75	0.71
12	$C_{18}H_{16}N_3SBr_3$ (546.12)	218–9	78	0.74
13	$C_{18}H_{16}N_3SCl_3$ (414.76)	94–5	78	0.72
14	$C_{18}H_{16}N_3SCl_3$ (414.76)	61–2	74	0.72
15	$C_{18}H_{16}N_3SCl_3$ (414.76)	87–8	75	0.72
16	$C_{18}H_{16}N_5O_4SCl$ (434.87)	75–6	85	0.86
17	$C_{18}H_{16}N_5O_4SCl$ (434.87)	80–1	77	0.85
18	$C_{18}H_{16}N_5O_4SCl$ (434.87)	125–6	72	0.86

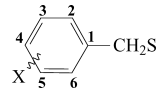
attributions made for each compound on the basis of the analysis of the HETCOR spectra, the case of **7** is discussed. For this compound the ^{1}H NMR spectrum exhibits two doublets at 7.80 and 8.00 ppm, ascribed to C3-H and C5-H, respectively. The correlation between the pair of signals at 124.98 ppm and 132.91 ppm with ^{1}H NMR signals at 7.80 and 8.00 ppm allows the assignment of these signals to C-3 and C-6, respectively. Moreover, the triplet at 7.70 ppm due to C4-H in the ^{1}H NMR

TABLE II Elemental Analyses and UV/VIS and IR Data of Compounds 1–18

Comp.	UV/VIS λ_{max} [nm] (log ε)	IR cm^{-1}	Elemental analyses % Calcd. (Found)			
			C	H	N	S
1	223 4.29	1660	44.59	3.37	14.18	10.81
			(44.60)	(3.30)	(14.24)	(10.00)
2	225 4.32	1687	44.59	3.37	14.18	10.81
			(44.58)	(3.28)	(14.26)	(11.00)
3	227 4.41	1650	44.59	3.37	14.18	10.81
			(44.56)	(3.11)	(14.49)	(10.50)
4	225 4.28	1649	52.58	3.98	16.73	12.74
			(52.22)	(3.99)	(16.54)	(12.80)
5	224 (4.28)	1654	52.58	3.98	16.73	12.74
			(52.60)	(4.01)	(16.56)	(12.52)
6	227 (4.40)	1647	52.58	3.98	16.73	12.74
			(52.50)	(4.11)	(16.59)	(12.60)
7	224 4.30	1652	41.77	5.06	17.72	10.12
			(41.70)	(4.95)	(17.96)	(10.00)
8	224 4.34	1655	41.77	5.06	17.72	10.12
			(41.58)	(5.12)	(17.73)	(9.80)
9	224 4.35	1650	41.77	5.06	17.72	10.12
			(41.50)	(5.26)	(17.78)	(9.92)
10	251 4.34	1630	39.56	2.93	7.69	5.86
	213 4.27		(39.78)	(2.98)	(7.56)	(5.81)
11	251 4.29	1630	39.56	2.93	7.69	5.86
	214 4.20		(39.07)	(2.92)	(7.43)	(5.67)
12	249 4.38	1640	39.56	2.93	7.69	5.86
	211 4.23		(39.67)	(2.92)	(7.70)	(5.95)
13	249 4.34	1633	52.17	3.86	10.14	7.72
	226 4.40		(52.39)	(3.86)	(10.57)	(7.45)
14	249 4.21	1647	52.17	3.86	10.14	7.72
	228 4.42		(52.15)	(3.95)	(10.43)	(7.76)
15	249 4.22	1645	52.17	3.86	10.14	7.72
	228 4.45		(52.00)	(3.87)	(10.31)	(7.99)
16	239 4.12	1638	49.76	3.68	16.12	7.37
	225 4.45		(49.80)	(3.70)	(15.97)	(7.42)
17	250 4.34	1633	49.76	3.68	16.12	7.37
	224 4.41		(49.49)	(3.77)	(16.06)	(7.50)
18	266 4.35	1649	49.76	3.68	16.12	7.37
	216 4.26		(49.69)	(3.57)	(16.07)	(7.30)

spectrum correlates with the signal at 129.20 ppm in the ^{13}C NMR spectrum, as well as the triplet at 7.55 ppm due to C5-H in which the ^{1}H NMR spectrum correlates with the signal at 133.93 ppm in ^{13}C NMR spectrum. These correlations allow the assignments of these signals to C4 and C5, respectively. The remaining three carbons at 31.22, 101.44,

TABLE III ^{1}H-NMR Shifts of 1–9 (δ, ppm). Spectra Determined in Dimethyl-d_6 Sulfoxide at 25°C and Shifts are Reported in ppm (δ) Downfield from Tetramethylsilane

Comp.	S—CH_2 **s**	CV—H **d**	CVI—H **d**	—NH_2 **s**	
1	4. 50	6.56	8.02	8.92	C3-H d 7.70 C5-H t 7.29
		J = 7 Hz	J = 7 Hz		C4-H t 7.31 C6-H d 7.48
2	4. 48	6.53	8.03	8.90	C2-H s 7.52 C5-H t 7.20
		J = 7 Hz	J = 7 Hz		C4-H d 7.40 C6-H t 7.34
3	4. 45	6.51	8.01	8.91	C2,6- H d 7.50
		J = 7 Hz	J = 7 Hz		C3,5- H d 7.42
4	4. 57	6.57	8.04	8.91	C3H-d 7.72 C5-H t 7.30
		J = 7 Hz	J = 7 Hz		C4H- t 7.47 C6-H d 7.69
5	4. 30	6.20	7.92	8.92	C2-H s 7.53 C5-H t 7.20
		J = 7 Hz	J = 7 Hz		C4-H d 7.40 C6-H t 7.34
6	4. 29	6.19	7.84	8.91	C2,6- H d 7.49
		J = 7 Hz	J = 7 Hz		C3,5- H d 7.42
7	4. 77	6.51	8.01	8. 92	C3-H d 7.80 C5-H t 7.55
		J = 7 Hz	J = 7 Hz		C4-H t 7.70 C6-H d 8.00
8	4. 60	6.48	8.00	8.90	C2-H s 8.73 C5-H t 7.60
		J = 7 Hz	J = 7 Hz		C4-H d 8.12 C6-H t 8.10
9	4. 41	6.38	7.92	8.90	C2,6- H d 8.20
		J = 7 Hz	J = 7 Hz		C3,5- H d 7.80

and 147.61 correspond to the singlets of S-CH_2, CV-H, and CVI-H at 4.71, 6.51 and 8.01 ppm, respectively.

A comparison of the number and positions of the signals of the carbon atoms in the range 125–130 and 130–140 ppm in ^{13}C NMR spectra of **1–9** allows a differentiation between *ortho-* *meta-* and *para-* substituted in benzylthio group isomers. These data are given in the tabular form below:

1–3 (Br substituted isomers) 125–130 ppm

ortho	C4	127.80 ppm	*meta*	C6	128.53 ppm	*para*	————
	C5	129.52 ppm					

4–6 (Cl substituted isomers) 130–140 ppm

ortho	C1	133.74 ppm	*meta*	C3	132.81 ppm	*para* C1	137.40 ppm
	C2	133.26 ppm		C5	130.16 ppm	C2,6	131.04 ppm
	C6	131.94 ppm				C4	131.02 ppm

7–9 (NO_2 substituted isomers) 130–140 ppm

ortho	C1	132.25 ppm	*meta*	C1	139.30 ppm	*para* C2,6	130.19 ppm
	C6	132.01 ppm		C6	136.16 ppm		
	C5	133.93 ppm					

TABLE IV ^{1}H-NMR shifts of 10–12 and 13–18 (δ, ppm). Spectra Determined in Dimethyl-d_6 Sulfoxide at 25°C and Shifts are Reported in ppm (δ) Downfield from Tetramethylsilane

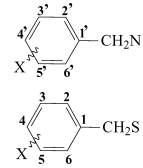
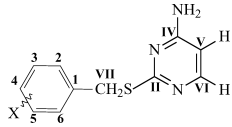
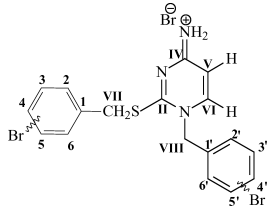
Comp.	S-CH_2 **s**	N1-CH_2 **s**	CVI-H **d**	CV-H **d**	$=NH_2^+$ **s**	
10	4. 62	5.33	6.68 J = 7 Hz	8.18 J = 7 Hz	9.28 9.22	C3-H d 7.71 C5-H t 7.25 C3′-H d 7.65 C5′-H t 7.20 C4-H d 7.31 C6-H t 7.48 C4-H d 7.29 C6′-H t 7.40
11	4. 52	5.33	6.69 J = 7 Hz	8.18 J = 7 Hz	9.28 9.22	C2-H s 7.55 C5-H t 7.20 C2′-H s 7.50 C5-H t 7.19 C4-H d 7.42 C6-H d 7.34 C4′-H d 7.38 C6′-H d 7.30
12	4. 50	5.33	6.71 J = 7 Hz	8.38 J = 7 Hz	9.23 9.13	C-2,6 H d 7.59 C-2′,6′ H d 7.52 C-3,5 H d 7.45 C-3′,5′ H d 7.45
Comp.	S-CH_2 s	N4-CH_2 s	CV-H d	CVI-H d		
13	4. 38	4.61	6.16 J = 7 Hz	7.93 J = 7 Hz	7.05	C3-H d 7.71 C5-H t 7.29 C3′-H d 7.70 C5′-H t 7.28 C4-H t 7.47 C6-H d 7.69 C4′-H t 7.46 C6′-H d 7.68
14	4. 29	4.77	6.16 J = 7 Hz	7.92 J = 7 Hz	7.02	C2 = H s 7.53 C5-H t 7.19 C2′-H s 7.48 C5′-H t 7.15 C4-H d 7.42 C6-H d 7.34 C4′-H d 7.40 C6′-H d 7.32
15	4. 28	4.77	6.16 J = 7 Hz	7.91 J = 7 Hz	6.99	C2,6- H d 7.46 C2′,6- H d 7.40 C3,5- H d 7.36 C3′,5′- H d 7.30
16	4. 56	5.03	6.15 J = 7 Hz	7.85 J = 7 Hz	7.02	C3-H d 8.08 C5-H t 7.53 C3′-H d 7.99 C5′-H t 7.50 C4-H t 7.89 C6-H d 7.86 C4′-H t 7.78 C6′-H d 7.82
17	4. 43	4.98	6.14 J = 7 Hz	7.91 J = 7 Hz	7.06	C2-H s 8.33 C5-H t 7.60 C2′-H s 7.30 C5′-H t 7.50 C4-H d 8.15 C6-H d 8.10 C4′-H d 8.12 C6′-H d 7.80
18	4. 40	4.91	6.15 J = 7 Hz	7.90 J = 7 Hz	7.02	C2,6- H d 8.24 C2′,6′- H d 8.14 C3,5- H d 7.73 C3′,5′- H d 7.69

TABLE V ^{13}C NMR Shifts of 1–9. Spectra Determined in Dimethyl-d_6 Sulfoxide at 25°C and Shifts are Reported in ppm (δ) Downfield from Tetramethylsilane



	Carbon										
Comp.	II	IV	V	VI	VII	1	2	3	4	5	6
1	164.89	161.72	102.94	148.10	32.74	137.05	124.12	132.70	127.80	129.52	131.90
2	164.07	163.20	101.52	144.88	32.84	139.98	131.89	121.59	130.41	130.62	128.53
3	163.85	162.89	101.34	144.55	32.93	136.39	131.43	131.13	120.50	131.13	131.43
4	163.51	162.94	101.43	144.34	31.97	133.74	133.26	129.63	129.38	127.24	131.94
5	163.90	163.19	101.50	144.92	32.93	141.66	128.80	132.81	126.79	130.16	128.65
6	166.02	162.59	101.94	144.08	32.80	137.40	131.04	128.21	131.02	128.21	131.04
7	163.99	162.89	101.44	147.61	31.22	132.25	145.26	124.98	129.20	133.93	132.91
8	164.25	163.17	101.50	145.62	32.68	139.30	123.82	147.84	122.38	129.89	136.19
9	164.69	165.19	101.54	145.04	32.94	146.37	130.19	123.77	147.52	123.77	130.19

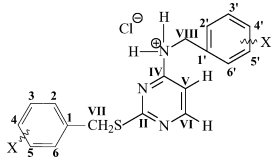
TABLE VI ^{13}C NMR Shifts of 10–12. Spectra Determined in Dimethyl-d_6 Sulfoxide at 25°C and Shifts are Reported in ppm (δ) Downfield from Tetramethylsilane



10 *o*-Br (C2 and C2')
11 *m*-Br (C3 and C3')
12 *p*-Br (C4 and C4')

	Carbon					
Comp.	II	IV	V	VI	VII	VIII
10	164.71	161.36	102.81	147.91	36.30	56.59
11	164.81	161.49	102.78	148.36	34.36	55.60
12	164.68	161.23	102.59	148.09	34.56	55.72
	C1	**C2**	**C3**	**C4**	**C5**	**C6**
10	135.81	121.96	132.16	127.79	130.08	132.08
11	136.27	131.35	121.57	128.56	130.54	126.29
12	132.86	131.48	129.39	120.76	129.39	131.48
	C1′	**C2′**	**C3′**	**C4′**	**C5′**	**C6′**
10	137.36	124.15	132.68	128.27	130.34	132.08
11	139.02	131.94	122.08	130.09	131.02	126.29
12	135.40	131.62	131.14	121.54	131.14	131.62

TABLE VII ^{13}C NMR Shifts of 13–18. Spectra Determined in Dimethyl-d_6 Sulfoxide at 25°C and Shifts are Reported in ppm (δ) Downfield from Tetramethylsilane



13 X = *o*-Cl (C2 and C2')
14 X = *m*-Cl (C3 and C3')
15 X = *p*-Cl (C4 and C4')
16 X = *o*-NO_2 (C2 and C2')
17 X = *m*-NO_2 (C3 and C3')
18 X = *p*-NO_2 (C4 and C4')

	Carbon					
Comp.	II	IV	V	VI	VII	VIII
13	168.59	162.89	101.29	154.66	31.74	45.00
14	168.63	162.87	101.32	154.98	32.98	44.98
15	168.74	162.85	101.26	154.69	32.83	45.14
16	168.32	162.91	101.36	154.59	30.57	42.59
17	168.61	163.11	101.52	154.93	32.67	44.47
18	168.30	162.88	101.38	154.74	32.91	44.44
	C1	**C2**	**C3**	**C4**	**C5**	**C6**
13	133.35	132.81	129.73	129.14	127.22	131.79
14	139.90	128.10	132.60	126.52	130.57	127.38
15	136.55	130.58	128.03	131.20	128.03	130.53
16	131.67	148.30	124.44	128.31	132.77	133.93
17	139.86	123.19	147.65	121.77	130.31	135.48
18	147.02	129.87	123.21	144.84	123.21	129.87
	C1′	**C2′**	**C3′**	**C4′**	**C5′**	**C6′**
13	135.72	133.66	129.88	129.39	127.75	132.04
14	141.42	128.46	132.89	126.62	131.51	127.47
15	137.83	130.58	128.48	132.76	128.48	130.58
16	132.00	148.32	124.99	130.05	133.32	130.99
17	141.73	123.39	147.78	121.71	130.50	135.72
18	147.27	129.98	123.65	146.11	123.65	129.98

^{1}H and ^{13}C NMR data of **10–12** are given in Tables IV and VI. Assigments of the ^{1}H 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 ^{1}H and ^{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 the quaternary carbons. The HMBC results allow an unequivocal assigment of S and N-1 disubstitution of benzyl group at the cytosine ring of **10–12**. The HMBC experiment is conducted without ^{13}C decoupling so that the correlations via one or more bond can be

discerned and one-bond correlation affords double cross peaks in the ^{1}H-dimension. The ^{1}H NMR spectra of **10–12** show doublets of CV-H and CVI-H protons, as well as singlets of S—CH_2, N-1-CH_2, and =NH_2^+ protons situated at 6.68–6.71, 8.18–8.38, 4.50–4.62, 5.33, and 9.13–9.22, 9.23–9.28 ppm, respectively. It should be pointed out that two singlets at 9.13–9.22 and 9.23–9.28 ppm belong to =NH_2^+ group. Due to a restricted rotation about the C=N bond, the two N—H protons appear separately. The signals of protons of *ortho*-(*meta*- and *para*-)–substituted benzyl groups of **10–12** appear in the range 7.00–7.70 ppm (Table IV). Table VI gives the ^{13}C NMR data for **10–12**. In order to exemplify the attributions made for each compound on the basis of the analysis of HMBC spectra, the case of **12** is discussed. For this compound, the ^{1}H NMR spectrum exhibits six doublets situated at 6.71 and 8.30 ppm ascribed to protons CV-H and CVI-H respectively, as well as 7.59, 7.45, 7.52, and 7.25 ppm ascribed to protons C2,6-H, C2′6′-H, C3,5-H, and C3′5′-H, respectively. In this spectrum there are also four singlets at 9.21, 9.13, 5.33, and 4.50 ppm ascribed to the of protons =NH_2^+, N1-CH_2 and S-CH_2, respectively. In the HMBC spectrum, the double-cross peaks of one-bond correlations connect protons of S—CH_2 substituent with carbon of methylene group (34.56 ppm), protons of N-1-CH_2 with carbon of methylene group (55.72 ppm), and the protons situated at CV and CVI with the appropriate carbons (102.59 and 148.09 ppm, respectively). The double-cross peaks of one bond correlation connect also protons at C2,6, C2′6′, C3,5, and C3′5′ with the appropriate carbons of phenyl rings (131.48, 131.62, 129.32, and 131.14 ppm, respectively). In the HMBC spectrum of **12**, there are also peaks corresponding to the two-bond correlations for S—CH_2/C-1 (132.86 ppm), CV-H/CIV(161.23 ppm), CV-H/CVI(148.09 ppm), N1-CH_2/C1′(135.4 ppm), CVI-H/CV (102.59 ppm), =NH_2^+/CVI (161.23 ppm) and the three-bond correlations for =NH_2^+/CV (102.59 ppm), CVI-H/CVIII (55.72 ppm); CVI-H/CIV(161.23) ppm, CVI-H/CII (164.68 ppm), N1-CH_2/CII (164.68 ppm), N1-CH_2/CVI (148.09 ppm), N1-CH_2/C2′ (131.62 ppm), S—CH_2/CII (164. 68 ppm), S—CH_2/C2′ (131.48 ppm). The HMBC spectrum of **12** also shows peaks corresponding to the four-bond correlations for =NH_2^+/CII (164.68 ppm) and CV-H/CII (164.68 ppm). The signal for the three-bond correlations for N1-CH_2/CVI (148.09 ppm) and N1-CH_2/CII (164.68 ppm) is of special interest since it proves that the benzyl group is attached to N1.

A comparison of the number and positions of the signals of the carbon atoms in the range of 135–140 in ^{13}C NMR spectra of **10–12** allows a differentiation between *ortho*-, *meta*-, and *para*- substituted in benzyl groups isomers.

The data are given in the tabulated form below:

10–12 (Br substituted isomers) 135–140 ppm
ortho C1′ 137.36 ppm *meta* C 1′ 139.02 ppm *para* C1 135.4 ppm
C1 135.81 ppm C 1 136.27 ppm

The ^{1}H NMR spectra of **13–18** show dublets of CV-H and CVI-H protons, as well as singlets of SCH_2, N4-CH_2, and H_2-N^+ protons situated at 6.14–6.15, 7.85–7.93, 4.28–4.56, 4.61–5.03, and 6.99–7.05 ppm, respectively. The signals of protons of *ortho*-(*meta*- and *para*-) substituted benzyl groups of **13–18** appear in the range 7.20–8.40 ppm (Table IV). Table VII gives the ^{13}C NMR data for **13–18**.

In order to exemplify the attributions made for each compound on the basis of the analysis of HMBC spectra, the case of **16** is discussed. For this compound the ^{1}H NMR spectrum exhibits six doublets situated at 6.15, 7.82, 7.85, 7.89, 7.99, and 8.05 ppm, ascribed to the protons CV-H, C6′-H, CVI-H, C6-H, C3′-H, and C3-H respectively. In this spectrum there are also three singlets at 7.02, 5.03, and 4.56 ppm ascribed to the protons H_2N^+, N4-CH_2, and S-CH_2, respectively, as well as four triplets at 7.89, 7.78, 7.53, and 7.50 ppm ascribed to protons C4-H, C4′-H, C5-H, and C5′-H, respectively. In the HMBC spectrum of **16**, the double-cross peaks of one-bond correlations connect protons of the N4-substituted methylene group with the carbon of this group (42.59 ppm), the protons of S—CH_2 group with the carbon of this group (30.57 ppm), and the protons of CV-H and CVI-H of cytosine ring with appropriate carbons (101.36 ppm and 154.59 ppm, respectively). The double-cross peaks also connect the protons situated at C3, C4, C5, and C6 of the phenyl ring of the N4-benzyl substituent with the appropriate carbons (124.44, 128.31, 132.77, and 133.93 ppm, respectively), as well as the protons situated at C3′, C4′, C5′, and C6′ of the phenyl ring of an S-benzyl substituent with the appropriate carbons (124.99, 130.05, 133.02, and 133.99, respectively). The HMBC spectrum of **16** also shows peaks corresponding to the two bond correlations for S—CH_2/C-1 (131.67 ppm); CV-H/CIV (162.91 ppm); CV-H/CVI (154.59 ppm); CVI-H/CV (101.36 ppm) N4-CH_2/C1′(132.00 ppm) as well as C3-H/C4-H (128.31 ppm), C3-H/C2 (148.22 ppm), C4-H/C3 (124.44 ppm), C4-H/C5 (132.77 ppm), C5-H/C4 (128.31 ppm) C5-H/C6 (133.99 ppm), and C6-H/C5 (132.77 ppm). The HMBC spectrum of **16** also shows the peaks corresponding to the three-bond correlations for CVI-H/CIV (162.91 ppm), CVI-H/CII (168.32 ppm), N4-CH_2/C6′ (133.99 ppm), S-CH_2/CII (168.32 ppm) and S-CH_2/C6 (133.93). Finally, it should be pointed out that a complete assignment of the N4-benzyl–substituted structure of **13–18** is proven by inspecting the HMBC spectra of these compounds. The lack of signals connecting the carbons of the cytosine ring with the protons of the $=NH_2^+$ and

TABLE VIII Elemental Composition and Relative Intensities of the Ion Peaks in the Spectra of 1–9 According to High Resolution Data

Ion	M/z	Elemental composition	% rel. intensities								
			1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
M$^{+\cdot}$	295/297	$C_{11}H_{10}N_3SBr$	10/10	89/88	100/99	—	—	—	—	—	—
a	251	$C_{11}H_{10}N_3SCl$	—	—	—	52	100	72	—	—	—
	262	$C_{11}H_{10}N_4O_2S$	—	—	—	—	—	—	3	100	90
b	245	$C_{10}H_9N_4O_2S$	—	—	—	—	—	—	2	19	1
c	262/264	$C_{11}H_9N_3Br$	3/2	54/52	46/45	—	—	—	—	—	—
	218	$C_{11}H_9N_3Cl$	—	—	—	15	65	13	—	—	—
	229	$C_{11}H_9N_4O_2$	—	—	—	—	—	—	1	13	14
d	216	$C_{11}H_{10}N_3S$	92	5	7	100	3	3	4	3	3
e	215	$C_{11}H_9N_3S$	—	—	—	—	—	—	1	6	2
f	183	$C_{11}H_9N_3$	21	43	53	32	21	24	1	8	13
g	140	$C_5H_6N_3S$	4	15	14	8	16	9	1	9	9
h	169/171	C_7H_6Br	100/99	23/22	44/43	—	—	—	—	—	—
	125	C_7H_6Cl	—	—	—	33	30	48	—	—	—
	136	$C_7H_6NO_2$	—	—	—	—	—	—	6	6	2
i	121	C_7H_5S	9	11	13	3	5	3	5	6	6
j	95	$C_4H_5N_3$	21	100	85	100	85	15	100	99	100
k	90	C_7H_6	67	31	49	4	6	9	3	16	18
l	89	C_7H_5	52	25	42	15	19	26	9	16	14
m	78	C_6H_6	6	5	11	2	3	4	4	4	11
n	77	C_7H_5	5	6	14	3	4	5	12	5	5
o	68	$C_3H_4N_2$	7	16	24	8	13	19	8	16	16
p	67	$C_3H_3N_2$	8	12	29	5	8	13	11	8	8
r	52	C_3H_2N	7	6	17	3	3	6	7	4	4

N4-CH_2 groups proves that the benzyl substituents are situated at N4 positions of the skeletons of **13–18**.

A comparison of the number and positions of the signals of the carbon atoms in the range 135–145 ppm in the ^{13}C NMR spectra of **13–15** and 140–150 ppm in the ^{13}C NMR spectra of **16–18** allows a differentiation between *ortho*-, *meta*- and *para*–substituted benzyl-group isomers.

The data are given in the tabulated form below:

13–15 (Cl substituted isomers) 135–145 ppm

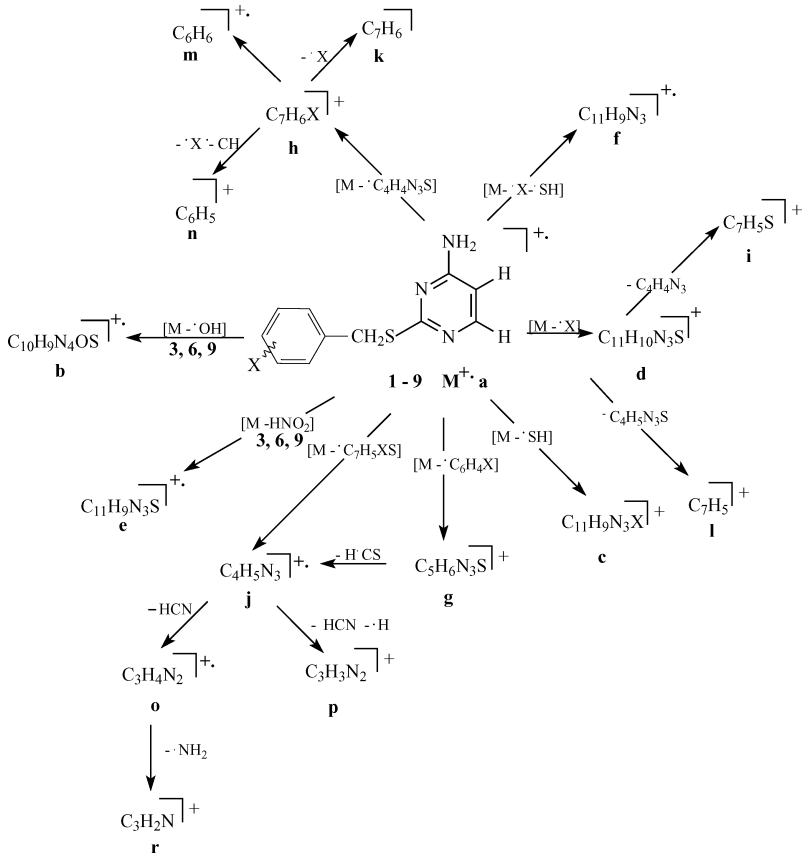
ortho	C1′	135.72 ppm	*meta*	C1	139.90 ppm	*para*	C1	136.55 ppm
				C1′	141.42 ppm		C1′	137.87 ppm

16–18 (NO_2 substituted isomers) 140–150 ppm

ortho	C2	148.30 ppm	*meta*	C1′	141.73 ppm	*para*	C1	147.02 ppm
	C2′	148.32 ppm		C3′	147.78 ppm		C1′	147.27 ppm
							C4	144.84 ppm
							C4′	146.11 ppm

A comparison of the positions of the carbon atoms signals in the range 30–50 ppm in the ^{13}C NMR spectra of **10–18** allows a differentiation between the S and N-1 as well as S and N-4 dibenzyl-disubstituted derivatives of hydrohalides of 2-thiocytosines. As can be seen from Tables VI and VII, the signals of S—CH_2 and N1-CH_2 in the ^{13}C NMR spectra of **10–12** are situated at 34.36–36.60 and 55.59–55.72 ppm, respectively, as well as the signals of S—CH_2 and N-4-CH_2 in the ^{13}C NMR spectra of **13–18**, which are situated at 30.57–32.91 and 42.59–45.00 ppm, respectively.

On the basis of the low- and high- resolution electron impact as well as B/E-linked scan mass spectra (Table IX), the principal mass spectral fragmentation routes of compounds **1–9** are interpreted as shown in Scheme 1. The common features of the mass spectral fragmentation of



SCHEME 1 The pathways of the EI–mass fragmentation of the molecular ions of **1–9**.

TABLE IX The Values of μ_1–μ_2 Calculated from the EI Spectra of 1–9

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
μ_1	2.10	0.48	0.53	0.61	0.21	0.32	0.33	0.08	0.14
μ_2	2.10	1.12	0.85	1.92	0.85	0.20	6.75	0.99	1.11

the molecular ions of **1–9** are simple cleavages of Csp2-X and Csp3-S bonds, i.e., eliminations of $C_4H_4N_3S$ and X radicals. During the processes of cleavage of Csp3-S bonds of the benzylthio substituent, the positive charge is stabilized on the benzyl fragment. It has been found that the even-electron fragment ions [M-X]**d** in the mass spectra of **1** and **4** have 92% and 100% relative intensity. In the mass spectra of **2**, **3**, **5**, and **6**, relative intensity of these ions is in the range 3–7%. Hence, it is obvious that the elimination of X (Cl, Br) from **1** and **4** is strongly connected with the ortho-effect. The loss of the substituent radical from the ortho position of the phenyl ring is favored because it involves the formation of a very stable even-electron tricyclic ion characterized by the quaternization of N(1) or N(3) (**1**, **4**) of the pyrimidynyl moiety. In the mass spectra of **7–9**, the even electron fragment ions [M-X]**d** have almost the same very low abundances (Table IX). The base peaks in the mass spectra of **2**, **4**, **7**, and **9** and the odd electron fragment **j** (m/z 95-$C_4H_5N_3$), as well as the base peaks in the mass spectra of **3**, **5**, **8**, are the molecular ions **a**. The even electron fragment ion **h** (m/z 169/171-C_7H_6Br) corresponds to the base peak in the mass spectrum of **1**. It was found that the ion **g** is formed from the molecular ion by ejection of the C_6H_4X radical. The molecular ions of **1–9** lose also SH radicals, giving even-electron fragmnet ions **c** (Table X). For this loss to occur, a skeletal rearrangemnet is required with the formation of new carbon-carbon and carbon-nitrogen bonds.

The differences in the fragmentation of isomeric *ortho*-(*meta*- and *para*-) substituted 2-benzylthiocytosines (**1–9**) have been quantified by comparing the calculated values of the coefficients μ: i.e., the abundances of the selected fragment ions relative to the abundances of the molecular ions. For compounds **1–9**, Table IX presents the ratios of the intensities of the $[M^{\cdot} - SH^{\cdot} - X]^{+\cdot}$ **f** and $[M^{\cdot} - XC_7H_5S]^{+\cdot}$ **j** ion peaks to those of the parent ions peaks, i.e.

$$\mu_1 = \%\text{rel. int. } [M^{\cdot} - SH^{\cdot} - X]^{+\cdot}\mathbf{f}/\%\text{ rel. int. } M^{+\cdot}\ \mathbf{a}$$

$$\mu_2 = \%\text{ rel. int. } [M - XC_7H_5S]^{+\cdot}\mathbf{j}/\%\text{rel. int. } M^{+\cdot}\mathbf{a}$$

As can be seen from the data in Table IX, the differences between the relative intensities of the peaks of selected fragment ions and $M^{+\cdot}$ ions,

i.e., the values of μ_1 and μ_2 for **1–9** may be sufficient to differentiate isomers.

CONCLUSIONS

The reactions of 2-thiocytosine with 1.2-fold molar excess of *ortho*- (*meta*- and *para*-) chloro- (bromo- and nitro-) benzyl bromides (chlorides) in 0.1 M solution of NaOH in methanol at room temperature lead chemoselectively to 2-*o*-(*m*- and *p*-) bromo- (chloro- and nitro-) benzylthiocytosines **1–9**.

The reactions of 2-thiocytosine with 2.5-fold molar excess of *ortho*- (*meta*- and *para-) ch*loro- (bromo- and nitro-) benzyl halides in DMF in the presence of 1 equivalent of K_2CO_3 at room temperature are largely governed by the nature of the benzylation agent and lead regioselectively to 1,2- and 2,4-dibenzyl–substituted hydrochlorides of 2-thiocytosines.

Dibenzylation of 2-thiocytosine in DMF in the presence of 1 equivalent of K_2CO_3 at room temperature is probably promoted by prior conversion of this compound into their respective 2-benzylthiocytosine. The competition in the further benzylation is between N-1, N-3, and N-4.

The reactions of 2-thiocytosine with 2.5-fold molar excess of soft electrophiles (i.e., in some respect soft acids) *ortho*- (*meta*- and *para*-) bromobenzyl bromides in DMF in the presence of 1 equivalent of K_2CO_3 at room temperature led regioselectively to 1,2-dibenzyl substituted hydrobromides of 2-thiocytosines **10–12**.

The reactions of 2-thiocytosine with 2.5-fold molar excess of relatively hard electrophiles (i.e., in some respect relatively hard acids) *ortho*- (*meta*- and *para*-) chloro-(nitro-) benzyl chlorides in DMF in the presence of 1 equivalent of K_2CO_3 at room temperature led regioselectively to 2,4-dibenzyl substituted hydrochlorides of 2-thiocytosines **13–18**.

The differences in reactivity of *o*-(*m*- and *p*-) bromobenzyl bromides and *o*-(*m*- and *p*-) chloro-(nitro-) benzyl chlorides give the regioselectively of S and N-1 as well as S and N-4 dibenzyl-substituted derivatives of 2-thiocytosine in DMF/K_2CO_3 at room temperature. These facts have allowed us to suggest that the regioselectivity of these reactions is probably connected also with the soft-base nature of the N-1 annular nitrogen atom of 2-*o*-(*m*- and *p*-) bromobenzylthiocytosine, as well as the relatively hard-base nature of the N-4 angular nitrogen atom of 2-*o*-(*m*- and *p*-) chloro-(nitro-) benzylothiocytosine.

The differences in the values of coefficients μ_1 and μ_2, i.e., the ratio of the intensities of the selected fragment ion peaks to those of the molecular ion peaks $M^{+\cdot}$ calculated from the EIMS spectra of **1–9**

(Table IX) can be used for differentiation between *ortho*-(*meta*- and *para*-) substituted isomers of **1–9**.

The differences in the ^{13}C NMR spectra of **1–18** in the number and positions of the signals of the carbon atoms in the range of 125–130 ppm (**1–3**); 130–140 ppm (**4–9**), 135–140 ppm (**10–12**), and 140–150 ppm (**13–18**) allow a differentiation between *ortho*-, *meta*-, and *para*- substituted in benzyl groups isomers.

The differences in the ^{13}C NMR spectra of **10–12** and **13–18** in the positions of the signals of N1-CH_2 carbon atoms (55.60–56.59 ppm) and N-4-CH_2 carbon atoms (42.59–45.15 ppm) allow a differentiation between S and N-1 (**10–12**) as well as S and N-4 (**13–18**) *para*-) dibenzyl disubstituted hydrohalides of 2-thiocytosines (**10–18**).

The presence of two singlets at 9.13–9.22 ppm and 9.23–9.28 ppm belonging to protons of $=NH_2^+$ group in the ^{1}H NMR spectra of hydrobromides of 2-*o*-(*m*- and *p*-) bromobenzylthio-1-*o*-(*m*- and *p*-) bromobenzylcytosines (**10–12**) allows a differentiation between **10–12** and **13–18**, i.e., hydrobromides of 2-*o*-(*m*- and *p*-) bromobenzylthio-1-*o*-(*m*- and *p*-) bromobenzylcytosines and hydrochlorides of 2-*o*-(*m*- and *p*-) chloro-(nitro-) benzylthio-4-*o*-(*m*- and *p*-) chloro-(nitro-) benzylcytosines.

EXPERIMENTAL

The purity of all described 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 methanol. IR spectra were recorded with an FT-IR Bruker IFS–113 v spectrophotometer in KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra were determined with a Varian Mercury spectrometer operating at 300.07 MHz (proton) or 75.40 MHz (carbon). The data were obtained from DMSO-d_6 solution at a concentration between 0.25 and 0.40 M at ambient temperature. The chemical shifts were referenced to tetramethylsilane.The ^{1}H NMR spectra were recorded at the proton frequency of 300.07 MHz with a spectral width 9000 Hz. The acquisition time was 2 s and the relaxation delay was 1 s; 64 scans with 44922 data points each were used. The ^{13}C NMR spectra were obtained using a spectral width of 23,000 Hz and 1.5 s. acquisition time; 2476 scans with 68992 data points each were used. The heteronuclear 2D ^{13}C NMR and ^{1}H NMR chemical shift correlation experiments were carried out using HETCOR spectra. The spectra were acquired with 2K data points, 256 increments and spectral width 19. 63 KHz for ^{13}C and 4.97 KHz for ^{1}H. A Bruker Advance DRX 600

Spectrometer operating at 600.05 MHz (^{1}H) or 150.89 (^{13}C) was used for taking the HMBC spectra. Measurements were carried out at the probe temperature of 25°C in DMSO-d_6 as a solvent. Tetramethylsilane was used as an internal reference. All spectra were acquired with 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, $d_1 = 1$s; delay of the low pass y-filter d_2, 3.44 ms; delay for evolution of long range coupling, $d_6 = 65$ ms with gradient ratio 2048 data points in t_2, spectral width 16.50 Hz in F_2 and 133.20 Hz in F_1; 256 increments in t_1; linear prediction to 512; zero filling up to 2 K Gaussian apodization was used in both dimensions.

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 ~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 were in agreement with those of the composition given in column three of the Table X, to within ± 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 173×10^{-5} with the ion source temperature of 180°C, ionization energy of 70 eV, and an accelerating voltage of 8 kV. The values of μ_1 and μ_2 were calculated as averages of three measurements. 2-thiocytosine was available from Aldrich Co. and *o*-(*m*- and *p*-) bromobenzyl bromide as well as *o*-(*m*- and *p*-) chloro-(nitro-) benzyl chlorides were available from Merck Company.

The Synthesis of 2-*Ortho-(Meta- and Para-)* Bromo-(Chloro- and Nitro-) Benzylthiocytosines 1–9

A methanol solution consisting of 1mmol of 2-tiocytosine in 20 mL of 0.1 M NaOH was stirred at room temperature while 1.2 mmoles of corresponding *ortho*-(*meta*- and *para*-) chloro-(bromo-) benzyl halides were added.

The reaction mixture was stirred at room temperature for 12 h and acidified (pH 3) with 1 M HCl. Than the precipitated solid was collected by filtration, washed with cold ethanol, and dried at room temperature under vacum. Recrystallization from ethanol afforded compounds **1–9**.

The Synthesis of Bromides of 2-*Ortho*-(*Meta*- and *Para*-) Bromobenzylthio-1-*ortho*-(*Meta*- and *Para*-) Bromobenzylcytosines (10–12) and Chlorides of 2-*Ortho*-(*Meta*- and *Para*-) Chloro-(Nitro-) Benzylthio-1-*ortho*-(*Meta*- and *Para*-) Chloro-(Nitro-) Benzylcytosines (13–18)

A mixture of 1.4 mmole of K_2CO_3 and 1.6 mmol of 2-thiocytosine in 20 mL of DMF was stirred at room temperature for 1 h. Next, 4.0 mmoles of corresponding *ortho*-(*meta*- and *para*-) bromobenzyl bromide [or *o*-(*m*- and *p*-) chloro-(nitro-) benzyl chloride] were added. After stirring at room temperature for 5 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 methanol afforded compounds **10–18**.

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