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In the reaction of ethyl isothiocyanatoacetate with diamines, followed by cyclization of the intermediate product, 3-monosubstituted thiohydantoins have been obtained. It was found that the reaction course depends on the purity of the isothiocyanate used and also, in the case of dialkylaminoamines, the self-cyclization occurs. Besides the dialkylamino derivatives of 3-monosubstituted 2-thiohydantoins also new monoalkylamino, amino and heterocyclic derivatives were synthesized. The aryldiazonium derivative of 3-monosubstituted 2-thiohydantoin yielded both respective phenol derivative after hydrolysis and the product of coupling with 2-naphthol.

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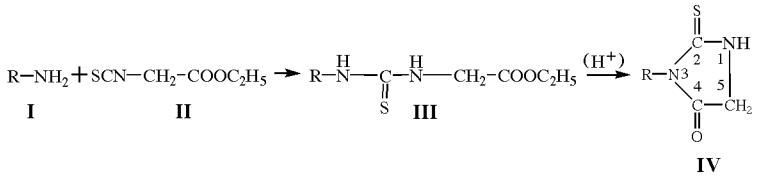
2-Thiohydantoins, in common with their 2-oxo analogs, have interesting pharmacological activity [1-3], technical applications [4,5] and properties [6,7]. Investigations on these compounds is less active in comparison to hydantoins due to their difficult synthesis and higher toxicity. A relatively small number of 3-monosubstituted 2-thiohydantoins have been synthesized to date, and only a few among them possess dialkylamino substituents [8-10]. 2-Thiohydantoins with amino or hydroxy group in the substituent in 3 position are not reported in the literature. This is due mainly to difficulty of synthesis, because it is impossible to obtain aliphatic or aromatic isothiocyanates with a free amino group, as well as aliphatic ones with hydroxy group. Such isothiocyanates are pre-requisite in the standard synthesis [11] of 3-monosubstituted 2-thiohydantoins.

Results and Discussion.

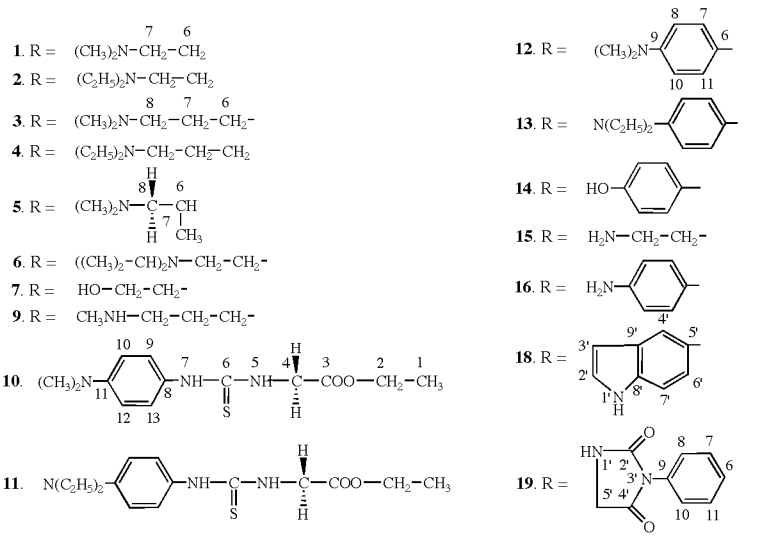
The dialkylamino, amino and hydroxy derivatives of 3-monosubstituted 2-thiohydantoin described in this paper were obtained by the literature method [12] using ethyl isothiocyanatoacetate and respective diamine, aminoalcohol or aminophenol. Mass spectrometry investigations showed that the starting isothiocyanate contains small amounts of thiophosgene and carbon disulfide. These contaminants could not be removed from the reagent obtained according to literature [13] by standard procedures like vacuum distillation (an azeotrope was formed).

It was found that these minor contaminants markedly influence the reaction, yielding tar-like products of unidentified composition. Using highly pure isothiocyanate, obtained by removal of contaminants by purging with

Scheme 1



I **II** **III** **IV**



gaseous nitrogen for several days, the reaction goes smoothly yielding high yields and pure products. Using this approach [12] N-substituted esters of thiohydantoic acid were obtained from diamines and ethyl isothiocyanatoacetate. These products were further cyclized in acid medium (HCl) to 3-monosubstitued 2-thiohydantoins.

Physicochemical data and tlc and ms results of the final products are summarized in Table 1, whereas ir, ^{1}H nmr and ^{13}C nmr data are given in Table 2.

When using dialylaminoalkyl amines and running the reaction both at room temperature and at –5 °C the intermediate products **III**, *i.e.*, N-substituted ester of thiohydantoic acid, could not be isolated since these spontaneously cyclized to 3-monosubstitued 2-thiohydantoins **IV 1-6** in high purity and yield. It was found that for some dialkylaminoalkyl amines the reaction course depends on

Table 1

Preparative, Physical and Analytical Data for Compounds **1-19**

Compound (Formula)	Yield (%)	Mp°C Solvent	Recryst.	Analyses Found/Calcd C	H	N	m/z $M^{+\cdot}$	TLC (UV, I_2)
1 [a]	99.7	149-51	Benzene				187	DMF:$CHCl_3$
$C_7H_{13}N_3OS$								Light petroleum 5:3:15 Rf = 0.50
1 a		206-7	EtOH	37.6	6.3	18.8		
$C_7H_{13}N_3OS\cdot HCl$				37.4	6.3	18.5		
2 [a]								
$C_9H_{17}N_3OS$	99.8	75-6	Cyclohexane + Benzene				215	DMF:$CHCl_3$: Light petroleum 5:3:15 Rf = 0.40
2 a		215-17	EtOH	42.9	7.2	16.7		
$C_9H_{17}N_3OS\cdot HCl$				42.9	7.3	16.7		
3 [a]	99.6	143-4	Benzene + Cyclohexane				201	DMF:$CHCl_3$: Light petroleum 5:3:15 Rf = 0.31
$C_8H_{15}N_3OS$								
3 a [10]		209-10	EtOH	40.4	6.8	17.7		
$C_8H_{15}N_3OS\cdot HCl$				40.6	6.7	17.6		
4 [a]	94.0	103-4	Cyclohexane + Benzene				229	DMF:$CHCl_3$: Light petroleum 5:3:15 Rf = 0.30
$C_{10}H_{19}N_3OS$								
4 a [10]		154-5	EtOH	45.2	7.6	15.8		
$C_{10}H_{19}N_3OS\cdot HCl$				45.0	7.7	16.0		
5 [a]	94.6	149-51	Cyclohexane + Benzene				201	DMF:$CHCl_3$: Light petroleum 1:2:15 Rf = 0.18
$C_8H_{15}N_3OS$								
5 a		214-15	Pr^iOH	40.4	6.8	17.7		
$C_8H_{15}N_3OS\cdot HCl$				40.0	7.0	17.9		
6 [a]	99.8	97-8	Benzene + Light petroleum	54.3	8.7	17.3	219	DMF:$CHCl_3$: Light petroleum 1:2:15 Rf = 0.39
$C_{11}H_{21}N_3OS$				54.2	8.6	17.0		
6 a		245-6	EtOH					
$C_{11}H_{21}N_3OS\cdot HCl$								
7	86.7	151-2	Acetone+	37.5	5.0	17.5	160	Acetone: $CHCl_3$
$C_5H_8N_2O_2S$			Benzene	37.1	4.9	17.4		1:1 Rf = 0.42
8 [16]	60.5	259-60	EtOH					Acetone: $CHCl_3$
$C_9H_8N_2OS$								1:1 Rf = 0.74
9	24.3	233-4	EtOH	37.6	6.3	18.8	187	
$C_7H_{13}N_3OS\cdot HCl$				37.3	6.6	18.8		
10	100.0	144-5	Benzene	55.5	6.8	14.9		
$C_{13}H_{19}N_3O_2S$				55.4	6.7	14.9		
11	100.0	124-5	Benzene	58.2	7.5	13.6		
$C_{15}H_{23}N_3O_2S$				57.8	7.2	13.7		
12 [8]	96.1	222-3	EtOH	48.6	5.2	15.5	235	anh. EtOH
$C_{11}H_{13}N_3OS\cdot HCl$				48.6	5.3	15.4		Rf = 0.67
13	92.1	216-17	EtOH	52.1	6.0	14.0	263	anh. EtOH
$C_{13}H_{17}N_3OS\cdot HCl$				51.9	6.0	13.8		Rf = 0.70
14	69.3	302-3	H_2O	51.9	3.9	13.4	208	Acetone: $CHCl_3$
$C_9H_8N_2O_2S$				51.9	3.8	13.5		1:1 Rf = 0.51
15	40.2	234-5	EtOH	30.7	5.1	21.5	159	
$C_5H_9N_3OS\cdot HCl$				30.3	5.2	21.0		

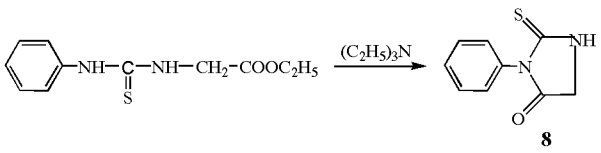
Table 1 (continued)

16	83.4	248-9	MeOH	44.3	4.1	17.2	207	
$C_9H_9N_3OS\cdot HCl$				44.4	4.1	17.1		
17	89.1	269-70	AcOH	63.0	3.9	15.5	362	Acetone: $CHCl_3$
$C_{19}H_{14}N_4O_2S$				62.6	3.71	5.6		1:1 Rf = 0.50
18	54.3	370 decomp.	EtOH	[b]			231	$MeOH:CH_2Cl_2$
$C_{11}H_9N_3OS$								1:5 Rf = 0.42
19	67.0	> 370	DMF +	49.6	3.5	19.3	290	$DMF:CHCl_3$:
$C_{12}H_{10}N_4O_3S$		decomp.	Benzene	49.5	3.4	19.2		Light petroleum
								1:2:4 Rf = 0.34

[a] Free bases change their composition after some time; [b] Forms coke-like uncombustible residue.

the solvent used. In some cases the use of a more polar solvent, for instance chloroform, gave unsatisfactory results, affording oligomeric products of undefined composition. Alternatively, solvents of low polarity (light petroleum) proved to be an excellent reaction medium. The cyclization of pure ethyl ester of N-phenylthiohydantoic acid [14] in the presence of $N(C_2H_5)_3$ [15] was run both in chloroform and anhydrous ethanol to investigate the effect of solvent on that reaction.

Scheme 2



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It was found that in chloroform the cyclization does not occur either after 24 hours at room temperature or after reflux for 3 hours. In the ethanol solution the reaction was complete after several hours at room temperature yielding 3-phenyl-2-thiohydantoin **8** [16] (Scheme 2). However, the yield and purity of the product obtained was inferior to that when the cyclization was run in acid solution [12]. The reaction course was monitored by tlc. Since in the synthesis with dialkylaminoalkylamines chloroform or light petroleum was used as a solvent, it was assumed that the cyclization of intermediate **III** does not depend on the presence of strongly alkaline dialkylaminoalkylamine in the reaction medium. This was confirmed in the reaction of ethyl isothiocyanatoacetate with ethanolamine where also the intermediate without the dialkylamino group but having instead the hydroxy substituent could not be isolated. The only product of this reaction was 3-(2-hydroxyethyl)-2-thiohydantoin **7**. This shows that the process of self-cyclization is an individual property of some esters of 2-thiohydantoic acid. Analogous esters of hydantoic acid under the same circumstances do not show self-cyclization. However, when a monoalkyldiamine such as *N*-methyl-1,3-propanediamine was used, the intermediate **III** was isolated and without purification cyclized to 2-thiohydantoin derivative **9**. The analogous reaction with ethyl isocyanatoacetate yields unidentified products, but not the monoalkyl derivative of hydantoin. The fact that

Table 2

IR, ^{1}H NMR and ^{13}C NMR Spectroscopic Data for Compounds **1-19**

Compound	ν_{max} (KBr) cm^{-1}	δ_H [500 MHz]	δ_C [125 MHz]
1	3009 (NH)	2.32 (s, 6H, $N(CH_3)_2$), 2.66 (t, 2H, J= 6.5 Hz, $C(7)H_2$),	38.96 ($C(6)H_2$), 45.49- ($N(CH_3)_2$), 48.67 ($C(7)H_2$),
	1716 (CO)	3.39 (t, 2H, J= 6.5Hz, $C(6)H_2$), 4.10 (s, 2H, $C(5)H_2$), 8,60 (br s, 1H, N(1)H)	56.24 ($C(5)H_2$), 171.92 (C(2)S), 185.15 (C(4)O)
2	3087 (NH)	1.04 (t, 6H, J=7.1 Hz, $N(CH_3\text{-}CH_2)_2$), 2.60 (q, 4H, J=7.1 Hz,	11.95 ($N(CH_3\text{-}CH_2)_2$), 38.98 ($C(6)H_2$), 47.22
	1737 (CO)	$N(CH_3\text{-}CH_2)_2$), 2.73 (t, 2H, J=7.2 Hz, $C(7)H_2$), 3.90 (t, 2H, J=7.2 Hz, $C(6)H_2$), 4.08 (s, 2H, $C(5)H_2$), 7,95 (br s, H, N(1)H)	($N(CH_3\text{-}CH_2)_2$), 48.47 ($C(7)H_2$), 49.32 ($C(5)H_2$), 171.61 (C(2)S), 185.08 (C(4)O)
3	3250 (NH)	1.90 (quint, 2H, J=6.7 Hz and J=7.4 Hz $C(7)H_2$), 2.28 (s,	25.98 ($C(7)H_2$), 39.21 ($C(6)H_2$), 44.93 ($N(CH_3)_2$),
	1726 (CO)	6H, $N(CH_3)_2$), 2.42 (2H, t, 2H, J=7.4 Hz, $C(8)H_2$), 3.82 (t, 2H, J=6.7 Hz $C(6)H_2$), 4.06 (s, 2H, $C(5)H_2$)	48.69 ($C(8)H_2$), 55.87 ($C(5)H_2$), 172.42 (C(2)S), 184.95 (C(4)O)
4	3240 (NH)	1.03 (t, 6H, J=7.1 Hz, $N(CH_3\text{-}CH_2)_2$), 1.90 (quint, 2H,	10.82 ($N(CH_3\text{-}CH_2)_2$), 25.15 ($C(7)H_2$), 39.47
	1733 (CO)	J=7.0 Hz and J=7.5 Hz, $C(7)H_2$), 2.60 (t, 2H J=7.5 Hz, $C(8)H_2$), 2.65 (q, 4H, J=7.1Hz, $N(CH_3\text{-}CH_2)_2$), 3.81 (t, 2H, J=7.0 Hz, $C(6)H_2$), 4.06 (s, 2H, $C(5)H_2$)	($C(6)H_2$), 45.89 ($N(CH_3\text{-}CH_2)_2$), 48.61 ($C(6)H_2$), 49.89 ($C(5)H_2$), 172.18 (C(2)S), 184.88 (C(4)O)
5		1.39 (d, 3H, J= 6.5 Hz, $C(7)H_3$), 2.22 (dd, 1H, J=4.3 Hz and	15.74 ($C(7)H_3$), 45.75 ($N(CH_3)_2$), 48.44 (C(6)H),
	3100 (NH)	J=12.8 Hz $C(8)H^xH^y$), 2.28 (s, 6H, $N(CH_3)_2$), 3.46 (br s,	48.86 ($C(5)H_2$), 60.80 ($C(8)H_2$), 172.23 (C(2)S),
	1720 (CO)	1H, $C(8)H^yH^x$), 4.07(dd, 2H, J=18.9 Hz, $C(5)H_2$), 4.91(br s, 1H, C(6)H), 8.49(br s, 1H, N(1)H)	185. 99 (C(4)O)

Table 2 (continued)

6	3245 (NH) 1705 (CO)	1.01 (d, 6H, J=6.4 Hz, N((CH_3)$_2$-CH)$_2$), 2.67 (t, 2H, J= 7.2 Hz, C(7) H_2), 3.03 (m, 2H, J=6.4 Hz, N((CH_3)$_2$-CH)$_2$), 3.79 (t, 2H, J=7.2 Hz, C(6)H_2), 4.06 (s, 2H, C(5)H_2), 7.48 (br s, 1H, (N(1)H)	20.73 N((CH_3)$_2$-CH)$_2$), 41.93 N((CH_3)$_2$-CH)$_2$), 42.16 (C(7)H_2), 48.38 (C(6)H_2), 48.74 (C(5)H_2), 171.47 (C(2)S), 185.33 (C(4)O)
7	3140 (NH) 2475 OH) 1725 (CO)	3.73 (q, 2H, J=6.2 Hz, C(6)H_2), 3.82 (t, 1H, J=6.2 Hz, OH), 3.88 (t, 2H, J=6.2 Hz, C(7)H_2), 4.14 (s, 2H, C(5)H_2), 8.90 (br s, 1H, N(1)H)	43.69 (C(7)H_2), 49.05 (C(6)H_2), 59.42 (C(5)H_2), 173.19 (C(2)S), 185.78 (C(4)O)
8	3145 (NH) 2995 (CH_2) 1755 (CO)	4.34 (s, 2H, C(5)H_2), 7.41 (m, 5H, J=7.3 Hz, Ph), 9.10 (br s, 1H, N(1)H)	49.71 (C(5)H_2), 129.28 (C(7,11)H), 129.43 (C(9)H), 129.68 (C(8,10)H), 134.93 (C(6)), 172.43 (C(2)S), 185.61 (C(4)O)
9	3170 (NH) 2470 (H^+) 1725 (CO)	1.91 (quint, 2H, J=6.9 Hz and J=7.9 Hz, C(7)H_2), 2.88 (t, 2H, J=7.9 Hz, C(8)H_2), 3.34 (s, 3H, NH-CH_3), 3.72 (t, 2H, J=6.9 Hz, C(6)H_2), 4.13 (s, 2H, C(5)H_2), 8.85 (br s, 1H, N(1)H)	24.16 (C(7)H_2), 32.20 (NH-CH_3), 39.00 (C(6)H_2), 45.72 (C(8)H_2), 48.50 (C(5)H_2), 172.86 (C(2)S), 183.04 (C(4)O)
10	3350 (NH 1) 3150 (NH 2) 1730 (CO)	1.27 (t, 3H, J=7.1 Hz, C(1)H_3), 2.98 (s, 6H, N(CH_3)$_2$), 4.19 (q, 2H, J=7.1 Hz, C(2)H_2), 4.41 (d, 2H, J=4.9 Hz, C(4)H_2), 6.4 (br s, 1H, N(5)H), 6.73 (d, 2H, J= 8.8 Hz, C(10,12)H), 7.12 (d, 2H, J=8.8 Hz, C(9,13)H), 7.75 (br s, 1H, N(7)H)	14.09 (C(1)H_3), 40.45 (C(4)H_2), 46.77 (N(CH_3)$_2$), 61.55 (C(2)H_2), 113.10 (C(9,13)H), 123.79 (C(8)), 127.28 (C(10,12)H), 149.86 (C(11)), 169.72 C(6)S, 181.33 C(3)O
11	3350 (NH 1) 3180 (NH 2) 1735 (CO)	1.17 (t, 6H, J=7.0 Hz, N(CH_3-CH_2)$_2$), 1.27 (t, 3H, J= 7.1 Hz, C(1)H_3), 3.36 (q, 4H, J=7.0 Hz, N(CH_3-CH_2)$_2$), 4.20 (q, 2H, J=7.1 Hz, C(2)H_2), 4.43 (d, 2H, J=4.9 Hz, C(4)H_2), 6.38 (br s, 1H, N(5)H), 6.60 (d, 2H, J=7.9 Hz, C(10,12)H), 7.08 (d, 2H, J=7.9 Hz, C(9,13)H), 7.66 (br s, 1H, N(7)H)	12.40 (N(CH_3-CH_2)$_2$), 14.07 (C(1)H_3), 44,39 (C(4)H_2), 46.75 (N(CH_3-CH_2)$_2$), 61.51 (C(2)H_2), 112.15 (C(9,13)H), 122.43 (C(8)), 127.64 (C(10,12)H), 147.41 (C(11)), 169.69 C(6)S, 181.44 C(3)O
12	3140 (NH) 2520 (H^+) 1730 (CO)	3.06 (s, 6H, N(CH_3)$_2$), 4.28 (s, 2H, C(5)H_2), 7.30 (m, 4H C(7,8,10,11)H)	br 44.05 (N(CH_3)$_2$), 49.15, (C(5)H_2), br 119.24 (C(6)), 129.46 (C(7,8,10,11)H), br 144.91 (C(9)), 172.14 (C(2)S), 183.05 (C(4)O)
13	3130 (NH) 2520 (H^+) 1725 (CO)	1.08 (m, 6H, N(CH_3-CH_2)$_2$), 3.54 (br s, 4H, N(CH_3-CH_2)$_2$), 4.30 (s, 2H, C(5)H_2), 7.52 (br s, 2H C(8, 10)H), 7.94 (br s, 2H, C(7,11)H), 10.49 (br s, 1H, N(1)H)	10.21 (N(CH_3-CH_2)$_2$), 49.30 (C(5)H_2), br 51.68 (N(CH_3-CH_2)$_2$), br 122.51 (C(6)), 130.49 (C\(7,8,10,11)H), br 138.50 (C(9)), 172.07 (C(2)S), 182.81 (C(4)O)
14	3400 (OH) 3150 (NH) 1740 (CO)	4.26 (s, 2H, C(5)H_2), 6.83 (d, 2H, J= 8.7 Hz, C(8,10)H), 7.04 (d, 2H, J=8.7 Hz, C(7,11)H), 9.73 (br s, 1H, N(1)H), 10.30 (br s, 1H, OH)	48.93 (C(5)H_2), 115.22 (C(8,10)H), 124.51 (C(7,11)H), 129.90 (C(6)), 157.44 (C(9)), 172.42 (C(2)S), 183.90 (C(4)O)
15	3180 (NH) 2610 (H^+) 1720 (CO)	3.05 (t, 2H, J=6.0 Hz, C(7)H_2), 3.90 (t, 2H, J=6.0 Hz, C(6)H_2), 4.08 (s, 2H, C(5)H_2), 8.20 (br s 2H, NH_2), 10.36 (br s, 1H, N(1)H)	36.91 (C(7)H_2), 37.68 (C(6)H_2), 48.80 (C(5)H_2), 173.23 (C(2)S), 182.65 (C(4)O)
16	3150 (NH) 2550 (H^+) 1725 (CO)	4.92 (d, 2H, J=1.0 Hz, C(5)H_2), 7.32 (d, 2H, J=7.8 Hz, C(7,11)H), 7.37 (d, 2H, J=7.8 Hz, C(8,10)H), 9.72 (br s, 2H, NH_2), 10.46 (br s, 1H, N(1)H)	49.16 (C(5)H_2), 122.15 (C(8,10)H), 130.09 (C(7,11)H), 131.26 (C(6)), 134.57 (C(9)), 172.16 (C(2)S), 183 11 (C(4)O)
17	3140 (NH) 1730 (CO)	4.33 (s, 2H, C(5)H_2), 6.91 (d, 1H, J=9.42 Hz, C(16)H), 7.46 (m, 3H, J=8.6 Hz, C(7,11)H and C(19)H), 7.62 (m, 1H, J=7.4 Hz and J=8.0 Hz, C(20)H), 7.79 (d, 1H, J= 7.7 Hz, C(18)H), 7.97 (m, 3H, J=8.0 Hz, C(8,10)H and C(17)H), 8.56 (d.1H, J=8.0 Hz, C(21)H), 10.48 (br s, 1H, N(1)H)	49.12 (C(5)H_2), 118.70 (C(7,11)H), 121.42 , 124.15, 126.03, 127.86, 128.89, 129.13, 129.49, 132.36, 132.69, 140.49, 144.49 (C(6,9,14,15,16, 17,18,-19, 20,21,22 and 23), 130.11 (C(8,11)H), 172,02 (C(2)S), 183.09 (C(4)O)
18	3340 (NH) 1725 (CO)	4.26 (s, 2H, C(5)H_2), 6.85 (dd, 1H, J=8.5 Hz and J= 1.8 Hz, C(3')H), 7.17 (br s, 1H, C(7')H), 7.26 (d, 1H, J=2.5 Hz, C(6')H), 7.34 (d, 1H, J=8.5 Hz, C(2')H), 7.47 (d, 1H, J=1.7 Hz, C(4')H), 10.24 (br s, 1H, N(1)H), 10.99 (d, 1H, J=1.8 Hz, N(1')H)	48.85 (C(5)H_2), 111.18, 117.89, 119.23, 121.33, 124.00, 124.23, 126.03, 135.95 (C(2',3',4', 5',6' ,7',8',9'), 172.5 (C(2)S), 184.44 (C(4)O)
19	3190 (NH) 1750, 1705 (CO)	4.09 (s, 2H, C(5')H_2), 4.31 (s, 2H, C(5)H_2), 7.39 (m, 2H, J=8.6 Hz, C(8,10)H), 7.47 (m, 2H, J=8.6 Hz, C(7,11)H), 8.39 (br s, 1H, N(1')H), 10.46 (br s, 1H, N(1)H),	46.04 (C(5')H_2), 49.18 (C(5)H_2), 126.82 (C(8,10)H), 129.17 (C(7,11)H), 132.22 (C(9)), 132.50 (C(6)), 156.28 (C(2')O), 171.03 (C(4')O), 172.19 (C(2)S), 183.07 (C(4)O)

Compounds **1-6** and **10**, **11** were measured in $CDCl_3$, **9**, **12-19** in DMSO-d_6, **7**, **8** in acetone-d_6.

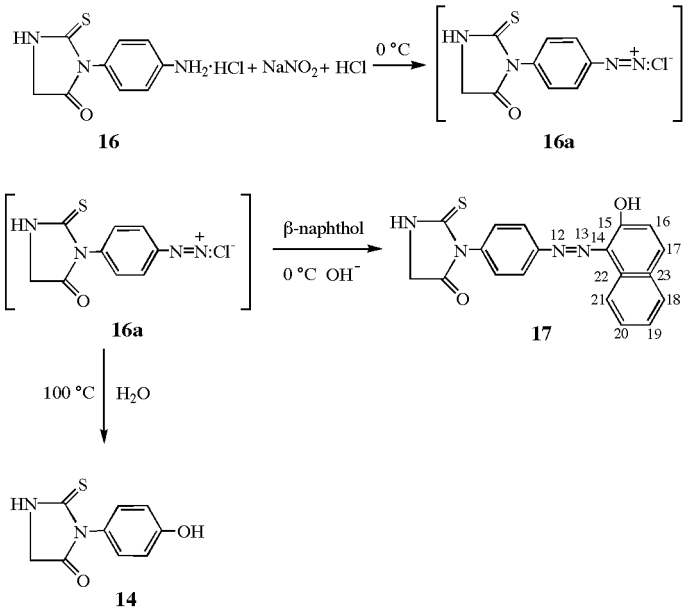
intermediate **III** obtained from monoalkylaminoalkylamine shows no self-cyclization confirms the conclusion that such self-cyclization depends mainly on the structure of the ester and not on its basicity (pK_b of dialkylamines with NH group is higher than that of trialkylamines).

Syntheses where aromatic diamines are used, (similar to those with aliphatic diamines having dialkylamine group) are efficient and lead to 3-monosubstituted 2-thiohydantoins of high purity. It was confirmed that the reaction with aromatic diamines which have dialkylamine group

proceeds *via* an N-substituted ester of thiohydantoic acid **10, 11**, that may be isolated. A similar reaction course was found in the case of reaction of 4-aminophenol with ethyl isothiocyanatoacetate. The experiments proved that the self-cyclization takes place only for substituents being an alkyl group, but not for those with aryl moiety.

Derivatives of 3-monosubstituted 2-thiohydantoin with amine groups as the substituent were obtained by reaction of an aliphatic or aromatic monoacetyldiamine with ethyl isothiocyanatoacetate. Due to solubility requirements of monoacetyldiamines, the reaction was run in anhydrous ethanol. The intermediate **III** was cyclized (HCl) to the respective 3-monosubstituted 2-thiohydantoins **15**, **16**. This last compound was diazotized to yield phenyldiazonium salt **16a**, which is quite stable in the room temperature.

Scheme 3



Compound **16a** was hydrolyzed to 3-(4-hydroxyphenyl)-2-thiohydantoin **14** (identical with that obtained by synthesis) but in very low yield (*ca.* 1%) in comparison to analogous reaction of the hydantoin derivative [17] (*ca* 45%). The coupling reaction of **16a** with 2-naphthol was run in alkaline solution and yielded azo dye **17** with indicator properties. This reaction did not cause opening of the thiohydantoin ring although 2-thiohydantoins are more susceptible to alkaline medium than their 2-oxo analogs and easily decompose in it.

Synthesis of 3-(5'indolyl)-2-thiohydantoin **18** was accomplished starting from 5-aminoindole and ethyl isothiocyanatoacetate. The intermediate **III** was cyclized without isolation in acetic acid and HCl medium. In the case of hydantoin a similar reaction failed. Compound **19,** containing hydantoin and 2-thiohydantoin rings was obtained from 3-(4-aminophenyl)-hydantoin and ethyl isothiocyanatoacetate. This reaction indicates that heterocyclic derivatives of 3-monosubstituted 2-thiohydantoins may be conveniently prepared by this means.

EXPERIMENTAL

Elemental analysis for C,H,N was run on a Perkin Elmer 2400 analyser. The ir spectra were made in KBr discs and registered on SPECORD 75 IR and JASCO FT/IR-670 spectrometers. Melting points were measured on a hot stage Boetius apparatus and are uncorrected. The ^{1}H nmr and ^{13}C nmr spectra were acquired on a Bruker 500 apparatus, using $CDCl_3$ (for **1** – **6**, **10**, and **11)** or DMSO-d_6 (for **9**, **12** – **19**) and TMS as internal standard. Coupling constants are given in Hz. Interpretation of nmr spectra was assisted by gNMR V3.6 programme. The mass spectra were recorded using Finnigan INCOS 500 and Varian MAT-112 spectrometers at 70 eV. Tlc was performed on aluminum foil covered with silicagel 60 F_{254} (Merck). The spots were visualized under uv light at 254 nm or with iodine vapors. All reagents were from Aldrich. Reactions with hazardous solvents (benzene, chloroform) were run in an efficient fume cupboard.

General procedures

Ethyl Isothiocyanatoacetate **II**.

Ethyl isothiocyanatoacetate **II** (123 g) was obtained according to literature [13] and rectified under vacuum was slowly purged with oxygen free nitrogen for 10 days. Then the product was distilled under vacuum yielding 120 g (97.5%) of **II** free from thiophosgene and carbon disulfide.

Synthesis of Compounds **1**-**7**.

To 1 g of **II** (6.9 mmol) in 20 cm^3 of chloroform (**1**, **6**) or 20 cm^3 of dichloromethane (**5**, **7**) or 20 cm^3 of light petroleum (40-60 °C) (**2**-**4**) was added an equimolar amount of dialkyloaminoalkylamine (**1**-**6**) or ethanolamine (**7**) in 20 cm^3 of the same solvent in which the isothiocyanate was dissolved, dropwise at room temperature or at –5 °C. After some time (usually several minutes) in the case of compounds **2**-**4** the oily product was separated and crystallized quickly. For **7** after 1 h a precipitate was formed, whereas for other compounds the solution stayed homogeneous. After 4 h the reaction mixture was evaporated to dryness under vacuum in rotary evaporator and the residue was crystallized from the appropriate solvent (see Table 1). Compounds **1**-**6** were converted into hydrochlorides with an ethanol solution of HCl (2 *M*), the solvent being evaporated under vacuum and the residue was crystallized from appropriate solvent (Table 1).

3-(Phenyl)-2-thioxo-4-imidazolidinone (**8**) [16] (cyclization with $(C_2H_5)_3N$).

Pure *N*-(phenylthiocarbamoyl)glycine ethyl ester (1.00 g, 4.2 mmol) obtained from ethyl isothiocyanatoacetate and aniline (ir, ^{1}H nmr , ^{13}C nmr, tlc (chloroform (Rf = 0.21); uv, I_2, mp 89 °C), was dissolved in 25 cm^3 of anhydrous ethanol. Then an equimolar amount (0.424 g) of $(C_2H_5)_3N$) was added. After *ca*. 2 h a precipitate started to separate. After 5 h the precipitate was collected by filtration yielding 0.75 g of **8**. After recrystallization from ethanol

a yield of 60.5%, mp 259-60 °C was obtained. When chloroform was used as a solvent instead of ethanol no precipitate was formed either after 24 h at the room temperature or after 3 h reflux.

N-(4-Dialkylaminophenylthiocarbamoyl)glycine Ethyl Esters (**10**, **11**).

To a solution of 1.00 g (6.9 mmol) of ethyl isothiocyanatoacetate in 20 cm^3 of chloroform an equimolar amount of appropriate 4-dialkylaminophenylamine (methyl or ethyl) in 20 cm^3 of chloroform was added dropwise during 15 min. After 24 h the solvent was evaporated under vacuum and the solid residue was crystallized from appropriate solvent (see Table 1)

Synthesis of Compounds **9**, **12**-**16** and **19**.

To 1.00 g (6.9 mmol) of **II** in 25 cm^3 of chloroform (**9**,**12**,**13**) or 50 cm^3 of anhydrous ethanol (**14**-**16**,**19**) an equimolar amount of diamine (**9**, **12**, **13**, **19**), monoacetyldiamine (**15**, **16**) or aminophenol (**14**) in the same amount of the same solvent was added dropwise with constant stirring at room temperature. The reaction mixture was stirred for 4 h and then the solvent was evaporated under vacuum. The solid residue was dried at 40 °C under vacuum. In the case of compound **19** the residue was crystallized (72% yield) and the purity was checked by tlc (acetone:chloroform 1:1, v/v (Rf = 0.40); uv, I_2). Mp 208-210 °C. For other compounds the product was dissolved in 25 cm^3 of ethanol and 25 cm^3 of HCl solution (1:1) was added. The solution was refluxed for 4 h, then the solvent was evaporated and the solid residue was crystallized from appropriate solvent.

3-(5'-Indolyl)-2-thioxo-4-imidazolidinone (**18**).

To a solution of 0.22 g of ethyl isothiocyanatoacetate in 20 cm^3 of anhydrous ethanol, an equimolar amount (0.20 g) of 5-aminoindole in 50 cm^3 of anhydrous ethanol was added. After 24 h the reaction mixture was evaporated under vacuum, dissolved in 50 cm^3 of glacial acetic acid and refluxed for 3 h. Then the solvent was evaporated and the residue was dissolved in 50 cm^3 of ethanol then 2 *M* HCl was slowly added until the solution became opaque. Finally, 20 cm^3 of ethanol was added and the solution was refluxed for 4 h. The solvent was evaporated under vacuum and the residue was crystallized from diluted ethanol to yield 0.19 g (54.3%) of **18**.

4-[3'-(2-Thioxo-4'-imidazolidinonyl-)]benzenediazonium Chloride (**16a**).

To a solution of 2.00 g (8.2 mmol) of 3-(4'-aminophenyl)-2-thiohydantoin hydrochloride **16** in 50 cm^3 of water 1.6 cm^3 of conc. HCl was added and the mixture was cooled to 0 °C. Then at that temperature with constant stirring 0.57 g of $NaNO_2$ (8.3 mmol) in 1.6 cm^3 of water was added during 45 min. After addition of $NaNO_2$ the solution was stirred for 15 min to give a solution of **16a** that was used without purification.

3-(4'-Hydroxyphenyl)-2-thioxo-4-imidazolidinone (**14**).

To diazonium salt **16a** (made as described above from 4 g of amine **16**) 40 cm^3 of water was added and the mixture was refluxed for 4 h at 100 °C. The reaction course was monitored by taking out a small sample and adding alkaline solution of 2-naphthol. A red color confirmed the presence of residual diazonium salt. After completion of reaction the mixture was evaporated under vacuum, the residue was dried and then extracted twice with 25 cm^3 of boiling acetone. The solid was filtered off and the combined acetone filtrates were evaporated to dryness. The residue was crystallized from ethanol yielding 0.034 g of **14** (*ca* 1%).

3-[4-(2-Hydroxy-naphthalen-1-ylazo)-phenyl]-2-thioxo-imidazolidin-4-one (**17**).

To diazonium salt **16a** (made as described above from 2 g of amine **16**) kept at 0 °C an equimolar amount of 2-naphthol (1.18 g) in 5.9 cm^3 of 10 % NaOH was quickly added with constant stirring. A precipitate formed immediately. Then 50 cm^3 of water was added and the mixture was stirred for 0.5 h. The precipitate was collected by filtration and washed with water until neutral. The precipitate was dried and crystallized from acetic acid yelding 2.65 g (89.1%) of **17**.

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