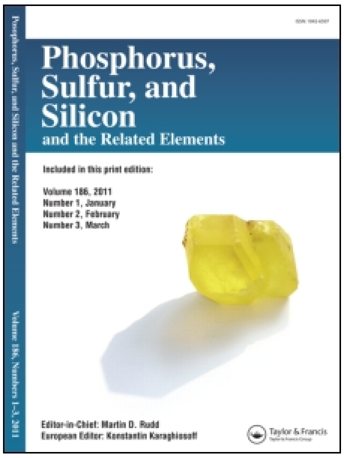

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Synthesis and Spectroscopic Properties of Fused 5-Arylidene-2-Thiohydantoin Derivatives

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SYNTHESIS AND SPECTROSCOPIC PROPERTIES OF FUSED 5-ARYLIDENE-2-THIOHYDANTOIN DERIVATIVES

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Imidazothiazole [(**1**)–(**12**)], imidazothiazine [(**13**)–(**20**)], and imidazothiazepine [(**21**), (**22**)] derivatives were obtained as the products of 1,2 or 2,3-dialkylation of 5-arylidene-2-thiohydantoin derivatives (ATH). The X-ray analysis of selected synthesized compounds showed their *Z*-configuration. The spectroscopic properties were described and examined for identification of 1,2-(type A) and 2,3-(type B)-substitution products. The reactivity of ATH was explained on the basis of X-ray analysis results and MNDO calculations.

Key words: Imidazothiazoles; imidazothiazines; imidazothiazepines; dialkylation of 5-arylidene-2-thiohydantoins; X-ray analysis.

INTRODUCTION

Searching for new structures with influence on the central nervous system (CNS) we have examined annelated 5,5-diphenyl-2-thiohydantoin (DPTH)[1–5] derivatives. Such compounds preliminarily pharmacologically tested have shown sedative properties.[6]

In continuation of our studies on structure—activity relationships we have obtained fused 5-arylidene 2-thiohydantoin (ATH) derivatives. The obtained compounds possess various influences on CNS. The antidepressant, anxiolytic and analgesic actions were attributed to imidazothiazole derivatives[7] while anticonvulsant properties were mostly connected with imidazothiazines.[8] The ATH derivatives have greater spatial flexibility of the aromatic substituent in comparison to DPTH ones. Presumably it is the cause of their pharmacological action.

We have performed spectral analyses (^1H, ^{13}C-NMR, IR, MS) of the obtained compounds looking for features with analytical value to distinguish the products of 1,2 (type A) or 2,3 (type B)-substitution. For some chosen compounds X-ray and conformational analyses were carried out.[9–11]

RESULTS AND DISCUSSION

Synthesis and Structures

Cyclization reactions of (ATH) with dibromoalkanes carried out in PTC conditions (solid-liquid) in acetone in the presence of potassium carbonate and TEBA as a phase-transfer catalyst, gave two kinds of isomeric products: the products of type A-1,2-substitution and type B-2,3-substitution of ATH (Scheme I).

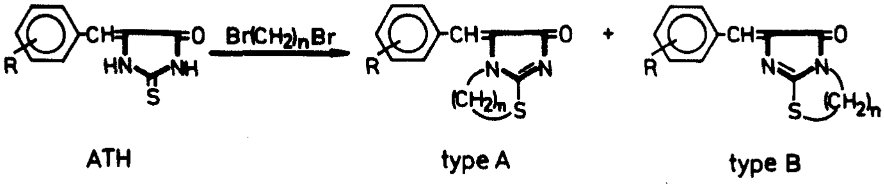
The alkylations with 1,2-dibromoethane were carried out with *o*-, *m*-, *p*-chloro- *p*-bromo-; *p*-methoxy-; *m*-, *p*-nitrobenzylidene and unsubstituted benzylidene 2-thiohydantoin. Mainly products of 2,3-substitution (type B) were obtained (yields and data on type of products formed are collected in Table I). In some cases column chromatography was carried out to isolate the products of 1,2-substitution. The products of type A were formed in low yields of range 3–4%.

The reactions with 1,3-dibromopropane were performed with benzylidene-; *p*-chloro-; *p*-bromo-; *p*-, *m*-nitro-; *o*-methoxy- and *p*-dimethylamino benzylidene 2-thiohydantoins giving exclusively the products of type B. Only in the reaction with *o*-methoxy ATH the product of 1,2-substitution was isolated with 1.3% yield.

Alkylations of benzylidene-, *p*- and *m*-chlorobenzylidene 2-thiohydantoins with 1,4-dibromobutane gave only products of 2,3-substitution with low yields 26 and 31%. In the reaction with *m*-chlorobenzylidene 2-thiohydantoin we could not isolate the bicyclic product, the only one obtained was the high melting disubstitution product of 1,4-dibromobutane with two 2-thiohydantoin moieties.

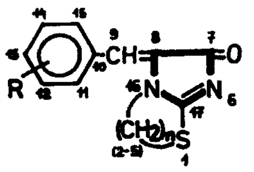
In our previous experiments[5] under similar conditions the products of 2,3-substitution of DPTH were formed in dominating amounts. However, when compared with DPTH, the alkylations of ATH with dibromoalkanes gave bicyclic products with lower yields[5] and the by-products were formed to a larger extent. In particular such process was observed in the reactions with dibromobutane, where the bicyclic products were obtained only with 20–30% yields.

As indicated in Table I, the yields of both types of isomers obtained during the synthesis were very different. Previously, X-ray structure analysis[5] supplied the explanation of type B product formation in predominance, with rising size of the fused ring. With the increasing dimension of such a ring for the compounds of type A the steric hindrance grew larger (see Table II, the values of C6-N1-C5 angle as a function of *n*). It seemed interesting that, calculated by MNDO method, the charge distribution in the DPTH molecule didn't indicate the sequence of the nitrogen atom alkylation (the negative charges on both nitrogen atoms were similar (Scheme II)). Only the steric hindrance was responsible for the observed alkylation course. According to the data in Table II, one has to consider also the possibility

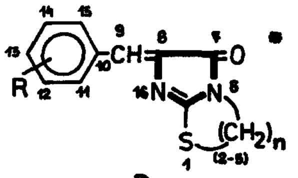


SCHEME I Synthesis of fused 5-arylidene 2-thiohydantoin derivatives.

TABLE I
Structures of fused 5-arylidene 2-thiohydantoin derivatives



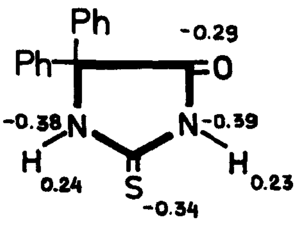
A



B

n	R	Type A		Type B	
		Compound	Yield (%)	Compound	Yield (%)
2	H	**1-A**	4.3	**2-B**	31
	p-Cl	**3-A**	4.4	**4-B**	48
	m-Cl			**5-B**	43
	o-Cl	**6-A**	3.1	**7-B**	46
	p-Br			**8-B**	51
	p-NO_2			**9-B**	51
	m-NO_2			**10-B**	40
	p-OCH_3	**11-A**	4.2	**12-B**	50
3	H			**13-B**	42
	p-Cl			**14-B**	45
	p-Br			**15-B**	40
	p-NO_2			**16-B**	35
	m-NO_2			**17-B**	60
	o-OCH_3	**18-A**	1.3	**19-B**	40
	p-$N(CH_3)_2$			**20-B**	35
4	H			**21-B**	31
	p-Cl			**22-B**	26

* Atoms description for spectral interpretations

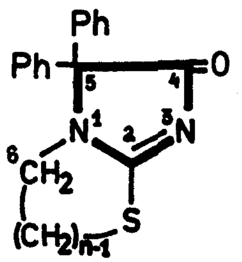


SCHEME II The charge distribution of DPTH calculated with MNDO method.

of two phenyl ring tightening in 1,2-substituted derivatives (angle Ph_1 towards Ph_2) with the increase of N1 substituent size.

For the explanation of the results given in Table I (for the ATH derivatives), the knowledge of the molecules conformations was required. As the steric position of benzylidene substituent was restricted by C=C bond the starting molecules of

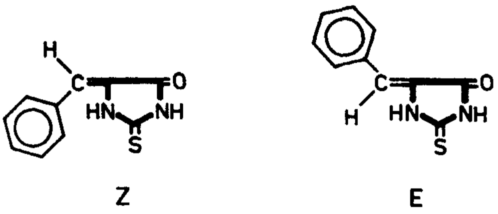
TABLE II
The angles illustrating the increase of steric hindrance in the molecules of fused DPTH derivatives of type A

	n	Compound	C 6-N 1-C 5 Angle	Ph_1/Ph_2 Angle between two phenyl rings
	2	**23-A**	131.6 (3)	79.4 (4)
	3	**24-A**	123.8 (2)	69.0 (4)
	4	**25-A**	123.6 (1)	62.5 (4)

ATH could occur in *E* or *Z*-forms (Scheme III). Therefore, the obtained bicyclic compounds (apart from A and B types) could be in *E* or *Z*-configuration. It could be presumed with great probability, that the product configuration should be the same as the respective ATH. However the isomerization process of arylidenehydantoin derivatives of *E* and *Z*-isomers was described.[12–14] In the cited papers it was established that, depending on the substitution pattern, in the equilibrium state one of the isomers occurred in dominating amount e.g. N1-substituted derivatives in the equilibrium state formed mixtures with *E*-isomers in predominance.[12,14] Then, it was obviously necessary to take into account the possibility of isomerization of N1-substituted ATH derivatives, e.g. the existence of 1,2-substituted derivatives (type A) in both *E* and *Z*-forms. However the X-ray structure analysis indicated *Z*-configuration of (**6-A**),[10] despite great steric crowding at N1 (Figure 1). The crystallographically examined molecules (**4-B**)[9] and (**10-B**)[11] were also *Z*-isomers. Furthermore from theoretical calculation (MNDO-method[15]) it was established that the *Z*-isomers of ATH were thermodynamically the more stable forms. Therefore, it could be expected that all cyclization products would also have *Z*-configuration.

Conformational analysis (molecular mechanics, MMX program[16]) in principle has shown the free rotation of the phenyl ring and shallow energy minima corresponding to the forms with the phenyl ring almost perpendicular to the thiohydantoin ring. Such analysis suggested a great decrease of steric hindrance in the neighborhood of N1 in the energy minimum conformations of ATH.

The charge distribution (MNDO method[15]) calculated for *o*-, *m*-, *p*-chloro and unsubstituted ATH (*Z*-forms in energy minimum conformation) differs from the distribution for DPTH (Scheme III) and to small degree depends on the place of the phenyl ring substitution. Scheme IV presents the charge distribution in the



SCHEME III Configuration of 5-arylidene 2-thiohydantoin derivatives.

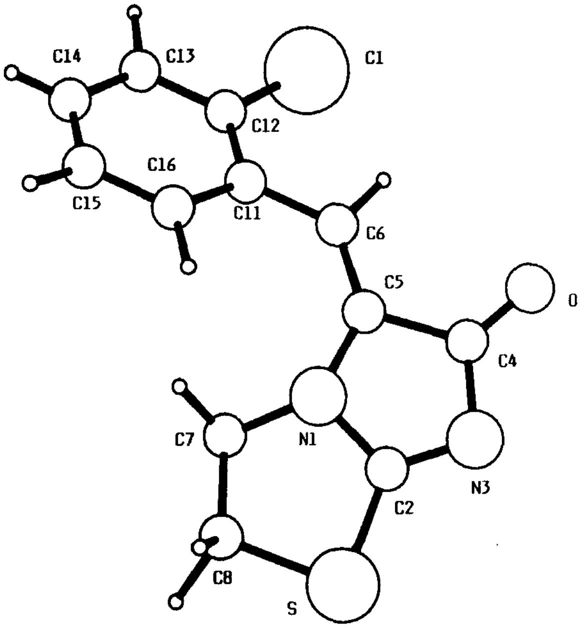
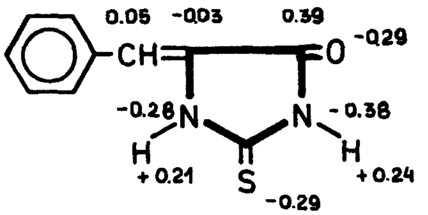


FIGURE 1 The structure of the *Z*-isomer of (**6-A**) molecule.



SCHEME IV The charge distribution of representative ATH calculated with MNDO method.

molecule of unsubstituted ATH. The negative charge on N3 is much higher than on N1. That is why the products of 2,3-substitution were mainly formed. With the increasing size of the formed ring, additionally the steric hindrance appeared in the N1-alkylation. It explained the decrease of the amount of 1,2-substituted product formation with the increase of the new ring size. As a sum of the charge distribution and steric hindrance effects the products of type A with 5-membered rings were obtained with yields of 3–4%, 6-membered rings (**18-A**) with about 1% yield and 7-membered ring products were not isolated.

The X-ray structure analysis provided also interesting data about the degree of planarity of the molecules with *Z*-configuration in the solid state. The flatness of "spatially overcrowded" (**6-A**) molecules was greater than for the N1-substituted hydantoin derivatives described by Drew *et al.*[17,18] The inclination of benzene and imidazolone rings in (**6-A**) equaled 34.8 (2)° while analogous angles for (*Z*)-1-methyl 5-benzylidene hydantoin[17] equalled 45.9(3)° and for (*Z*)-1-methyl (2,4,6-trimethyl benzylidene) hydantoin[18] 84.2(3)°. For 2,3-substituted ATH (type B) the dihedral angle was much smaller and equalled only 1.7(2)° for (**4-B**)[11] and 8.1(7)° for (**10-B**).[9]

Spectroscopic Properties

^{1}H-NMR Spectra. The ^{1}H-NMR spectra of 1,2 and 2,3-substituted derivatives show significant differences (Table III).

The main differences were found in the chemical shifts of the aliphatic and phenyl *ortho*-protons of both types of isomers. The signals from NCH_2 protons in *para*-substituted 5-membered derivatives of type A were shifted downfield (3.96–4.09

TABLE III

^{1}H Shifts

Compound, solvent	H-3 H-4	H-2	H-5	H-9	H-13	H-12 H-14	H-11 H-15	Others
1-A DMSO		3.85 (def.t, J 7.5Hz)	4.09 (def.t, J 7.5Hz)	6.73	7.36–7.45 (m)		8.18 (m)	
2-B DMSO		3.87 (m)		6.77	7.35–7.45 (m)		8.11 (m)	
3-A DMF		3.84 (def.t, J 6Hz)	3.95 (def.t, J 6Hz)	6.89		7.55 (def.d, J 8,6Hz	7.62 (def.d, J 8,6Hz)	
4-B DMF		4.02 (s)		6.79		7.54 (d J 8.5Hz)	8.23 (d J 8.5Hz)	
5-B DMSO		3.88 (s)		6.76	7.42 (m)		8.01 (m) 8.25 (s)	
6-A DMSO		3.69 (s)		6.77	7.45 (m)	7.54 (m)		
7-B DMSO		3.89 (br.s)		6.99	7.42 (m)	7.53 (m)	8.73 (m)	
8-B DMSO		3.87 (m)		6.73		7.60 (d J 8.5Hz)	8.05 (d J 8.5Hz)	
9-B DMSO		3.90 (m)		6.83		8.22 (d J 9Hz)	8.33 (d J 9Hz)	
10-B DMSO		3.91 (m)		6.85	8.44 (t,J 8Hz)	7.69 (dd,J 8Hz, J 1Hz)	8.18 (dt,J 8Hz, J 1.5Hz) 9.06 (t,J 2.1Hz)	
11-A DMF		3.84 (m)	4.01 (m)	6.88		7.06 (d J 8.6Hz)	7.55 (d J 8.6Hz)	3.88 (s,OCH_3)
12-B DMF		3.98 (s)		6.77		7.05 (d J 8.8Hz)	8.17 (d J 8.8Hz)	3.87 (s,OCH_3)
13-B DMSO	2.12–2.20 (m)	3.20–3.28 (m)	3.62 (t, J 6Hz)	6.82	7.32–7.45 (m)		8.12 (m)	
14-B $CDCl_3$	2.26 (m)	3.14 (def.t, J 5.7Hz)	3.73 (t, J 5.8Hz)	6.87		7.35 (d J 8.6Hz)	8.03 (d J 8.6Hz)	
15-B DMSO	2.17 (m)	3.25 (t, J 5.5Hz)	3.64 (t, J 5.8Hz)	6.82		7.64 (d, J 8.5Hz)	8.10 (d, J 8.5Hz)	
16-B $CDCl_3$	2.30 (m)	3.18 (t, J 5.6Hz)	3.76 (t, J 5.8Hz)	6.89		8.22 (s)		
17-B DMSO	2.14–2.22 (m)	3.25 (def.t, J 5.5Hz)	3.64 (def.t, J 6Hz)	6.92	8.44 (t, J 8.5Hz)	7.68 (dd J 8Hz, J 2.2Hz)	8.16 (dt J 8Hz, J 1.5Hz) 9.05 (t, J 2.5Hz)	
19-B $CDCl_3$	2.26 (m)	3.13 (t, J 5.6Hz)	3.74 (t, J 5.9Hz)	7.54	6.86 (d, J 7,6Hz)	7.32 (dt J 7.3Hz) 7.00 (t,J 7.5Hz)	8.70 (dd J 7.8Hz, J 1.7Hz)	3.87 (s,OCH_3)
20-B DMSO	2.15 (m)	3.21 (t, J 5.5Hz)	3.61 (t, J 6Hz)	6.76		6.74 (d, J 7,8Hz)	8.00 (d, J 7,8Hz)	3.00 (s,CH_3)
22-B DMSO	1.79 (br.s) 2.04 (br.s)	3.17 (def.t, J 5Hz)	3.75 (def.t, J 5Hz)	7.00		7.53 (d, J 7.5Hz)	8.22 (d, J 7.5Hz)	

ppm) in comparison with the signals of the SCH_2 (3.84–3.85 ppm) protons. The aliphatic proton signals of thiazole derivatives of type B were observed as singlets or non-separated multiplets.

The chemical shifts of the phenyl *ortho*-protons were different for type A and B derivatives.

In the analysis of spectroscopic properties of arylidene hydantoin derivatives Tan *et al.*[19,20] compared the *E* and *Z*-forms. Observed differences in *E* and *Z*-isomers for the *ortho*-proton chemical shifts were accounted for by the different spatial arrangement of the phenyl rings in *E*-forms (rather flat) than in *Z*-forms (rather twist). As it was explained, the spectral differences were caused by different possibilities of conjugation[19,20] of the phenyl ring with the hydantoin ring, easier for flat *E*-forms. (In the twisted *Z*-forms, unconjugated with the hydantoin rings, aromatic proton signals were not at all or poorly separated). Some of these spectral effects were connected also with the anisotropic effect of the carbonyl group, which in *E*-isomers caused the (H_0) peak to be shifted considerably downfield.

The *Z*-configuration of our examined compounds was established on the basis of X-ray analysis.[9–11] It was also found that the C6—C11 bond (see Figure 1) [1.460(5)–1.470(6)Å] in both types of isomers indicated no conjugation between the phenyl rings and the rest of the molecules. Additionally, the conformational analysis (MMX-program[16]) of the chosen bicyclic compounds showed[10,11] that (apart from some restricted positions in *ortho*-substituted derivatives) the phenyl rings had rotational freedom. Therefore we have presumed that the differences in the chemical shifts of *ortho*-protons of both types of isomers were connected with the anisotropic effect of the N1 atom. For compounds of type B it caused downfield chemical shifts of the *ortho*-protons (8.00–9.06 ppm) while for type A with the substituents at N1 such influence was impossible and the chemical shifts of the *ortho*-protons were in the 7.06–7.62 ppm ranges.

There is one exception however, the chemical shifts of the *ortho*-protons for both types of isomers **1-A** and **2-B** were similar. The explanation of this observation needs further experiments (e.g. X-ray analysis or additional spectral analyses of **1-A**).

^{13}C-NMR Spectra. The chemical shifts of aromatic carbons were ascribed by comparison with the values approximated by applying the principle of substituent additivity[21] (Table IV).

The ^{13}C-NMR spectra of 1,2- and 2,3-substituted derivatives have shown significant differences. The greatest differences were observed for the chemical shifts of the C-2, C-5, C-8, C-9, C-7 and C-17 carbons.

In the case of five membered isomers of type A greater differences of the C-2, C-5 carbon chemical shifts (in the proximity of phenyl ring) existed in comparison with the isomers of type B.

δ(ppm) 1,2-substituted (**3-A**), (**6-A**), (**11-A**) derivatives

C-2	C-5
32.13–32.62	47.32–49.07

δ(ppm) 2,3-substituted (**2-B**), (**4-B**), (**5-B**), (**7-B**)–(**10-B**), (**12-B**) derivatives

C-2	C-5
34.38–35.36	40.33–41.52

TABLE IV

^{13}C Shifts

No Solvent	C-2	C-3	C-4	C-5	C-9	C-8	C-10	C-11	C-12	C-13	C-14	C-15	C-7	C-17	Others
2-B DMSO	34.50			40.55	121.72	144.74	133.82	131.22	128.47	129.46			165.72	171.40	
3-A DMF	32.62			48.86	113.57	134.50	133.51	132.25	129.30	132.43			180.60	188.87	
4-B DMF	35.36			41.52	120.76	146.42	135.19	133.63	129.42	134.00			166.52	173.14	
5-B DMSO	34.63			40.63	119.89	146.06	136.29	130.13*	133.50	129.30	130.58*	130.43*	165.90	173.13	
6-A DMSO	32.13			47.32	110.37	133.60	133.33	130.95	130.72	129.64	127.23	131.79	179.52	188.75	
7-B DMSO	34.67			40.67	115.36	146.55	134.48	131.50	131.08	129.84	127.60	132.44	165.93	174.00	
8-B DMSO	34.54			40.57	120.16	145.22	133.09	132.95	131.49	122.91			165.55	172.04	
9-B DMSO	34.78			40.66	118.16	146.80	140.46	131.82	123.48	147.35			165.38	174.53	
10-B DMSO	34.71			40.33	118.57	146.50	137.16	124.88	148.01	123.44	129.94	135.57	165.37	173.62	
11-A DMF	32.42			49.07	115.65	132.12	125.62	132.28	114.76	160.97			180.63	187.95	55.76
12-B DMF	34.38			41.48	122.83	144.13	127.78	134.06	114.87	161.71			166.77	170.72	55.77
13-B DMSO	25.49	22.25		39.38	121.19	137.61	134.15	131.32	128.46	129.36			161.55	168.02	
14-B $CDCl_3$	26.79	23.64		40.51	123.02	138.61	136.28	133.66	129.49	133.41			161.03	169.45	
15-B DMSO	25.51	22.15		39.43	119.85	138.40	133.72	132.87	131.82	123.09			162.72	169.31	
16-B $CDCl_3$	26.88	23.51		40.57	120.49	140.84	141.33	132.78	124.29	148.19			163.94	169.18	
17-B DMSO	25.66	22.11		39.45	117.94	139.29	135.88	125.00	147.98	123.25	129.87	137.14	163.90	167.74	
19-B $CDCl_3$	26.78	23.72		40.48	118.88	137.86	124.12	159.56	111.23	131.93	121.54	133.40	159.56	169.68	56.25
20-B DMSO	22.45	22.59		39.44	123.85	134.00	122.05	133.73	111.95	151.49			157.10	168.45	39.44
22-B DMSO	31.00	26.70	29.93	40.54	123.24	139.10	134.61	133.30	128.72	132.81			166.44	168.57	

* The assignments are uncertain.

The vinyl carbon (C-9) signals of type A compounds were upfield shifted in relation to respective derivatives of type B.

The C-8 carbons of type A isomers resonating in the 132.12–134.83 ppm range were upfield shifted in comparison with type B isomers (144.13–146.80 ppm). In comparison of thiazole derivatives of type B with thiazine and thiazepine derivatives of the same type the values of the chemical shifts of the C-8 carbon decreased from 144.13–146.80 to 134.00–140.84 ppm.

The most significant differences (similarly as for DPTH derivatives) were observed in the chemical shifts of the C-7 and C-17 carbons. For the 1,2-substituted thiazoles, the signals of C-7 and C-17 were downfield shifted (179.52–180.63 and 187.50–188.87 ppm) in comparison with 2,3-substituted ones (165.37–166.77 and 170.72–174.53 ppm respectively). The same tendency was observed for all type B thiazine and thiazepine derivatives.

The pharmacological activity of the investigated compounds may be connected with the charge distribution in the molecules. The electron density distributions in differently substituted aromatic derivatives may be examined by means of the proton and carbon atom chemical shifts correlation with Hammett constants.

The substituent effects on the ^{13}C chemical shifts of the fused ATH derivatives were examined (Table V, Figure 2). It was stated that a correlation between the Hammett σ constants of the *para* and *meta* substituents and the chemical shifts of the C-10, C-9 and C-8 atoms of thiazole and thiazine type B isomers existed. The chemical shifts for C-9 and C-10 correlated with substituent effects in the same way for thiazole and thiazine derivatives, indicating that at these carbon atoms the differences between fused rings of the thiohydantoin thiazole and thiazine were not reflected. The substituent effects were reflected better at the C-9 carbon atom (excellent correlations) than at the C-8 (especially for thiazoles). The nature of aromatic substitution also influenced the C=O chemical shifts, although the correlation was only fairly good, (especially for thiazoles), suggesting a partial influence of the attached benzylidene ring on the internal part of imidazothiazole and imidazothiazines. Additionally, the C-17 chemical shifts of thiazole type B derivatives correlated well with the Hammett σ constants of *para* and *meta* substituents. This correlation was significant in view of the long distance of C-17 from the aryl substituents. However, for thiazine derivatives such correlation was rather poor denoting that the electron densities were changed by the substituents mainly in the part of the carbonyl group.

Also a correlation between ^{1}H (H-9) chemical shifts and Hammett σ constants existed, better for thiazine than for thiazole derivatives.

TABLE V

Correlation coefficients (γ), slopes (ρ) and intercepts (y) of chemical shifts (ppm) versus substituent constants σ

	CH=(6)	C-7(6)	C-10(6)	C-8(6)	C-9(6)	
γ	0.9341	0.9862	0.9374	0.9826	0.9948	
ρ	0.096	4.551	9.154	3.541	−3.837	
y	6.83	161.19	131.08	137.23	120.81	
			C-10(5)	C-8(5)	C-9(5)	C-17(5)
γ			0.9305	0.9090	0.9929	0.9502
ρ			9.894	2.476	−4.428	3.409
y			131.93	144.97	121.60	171.65

Compounds (**14-B**), (**16-B**) were not considered in the correlation calculations their spectra were exceptionally (because of their poor solubility in DMSO) measured in $CDCl_3$. The solvent influenced especially on C-9(6), C-7(6) chemical shifts. The C-8(6), C-10(6) and CH=(6) chemical shifts of (**14-B**), (**16-B**) agreed with correlations. The numbers in parentheses describe the rings size.

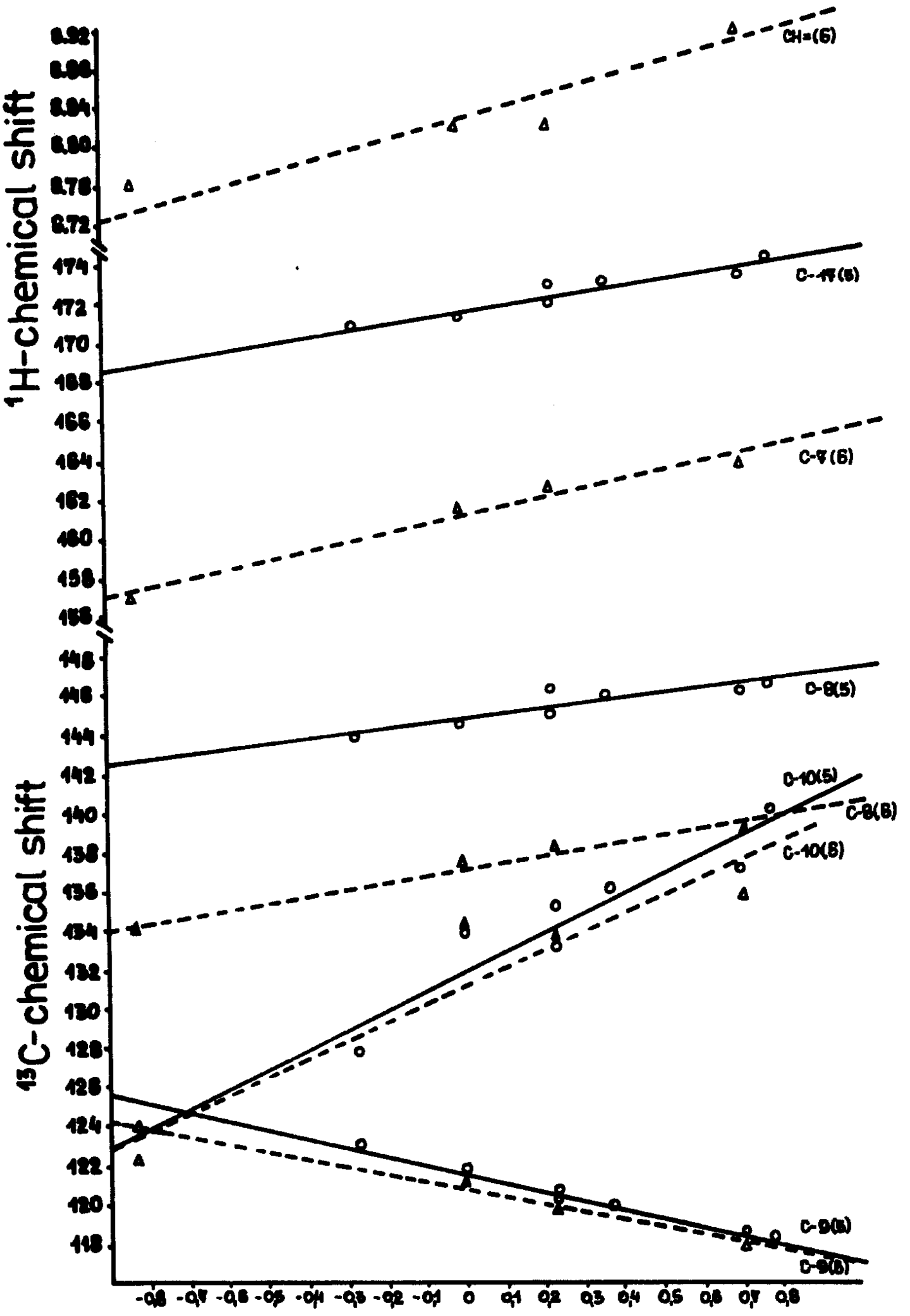


FIGURE 2 Correlation of ^{13}C chemical shifts para and meta substituent constants σ.

Mass Spectra. The examined compounds displayed the molecular ions, in some cases being the most intense peaks [(**4-B**), (**5-B**), (**8-B**)–(**10-B**), (**13-B**), (**15-B**), (**22-B**)]. Unlike the DPTH,[5] fused ATH derivatives of type A and B didn't show markedly pronounced differences in the fragmentation patterns in the electron impact mass spectra. The fragmentation ion with the diagnostic value for fused DPTH derivatives was M-CO, with greater intensity for type B derivatives. For ATH derivatives such ions appeared indeed with greater relative intensities for 2,3-substituted imidazothiazoles [with the exception of *ortho* substituted (**7-B**)]. The relative intensities of M-CO ions were for imidazothiazines markedly lower, or these ions were even impossible to detect [(**19-B**) and imidazothiazepines (**21-B**) and (**22-B**)].

The main fragmentation pathways of the examined compounds are presented in Table VI. The A^1 ions resulted from the loss of aromatic substituents, A^2 were a result of CO group cleavage, A^3 were the result of imidazolidinone ring decom-

TABLE VI

Characteristic fragment ions in the EI-mass spectra of compounds (**1**)–(**22**) m/z (relative intensity, %)

No	$M^{+\cdot}$	A^1	A^2	A^3	$A^{3'}$	A^4	$A^{4'}$	A^5	Others
1-A	230 (20)	-	202 (3)	116 (35)	-	89 (38)	-	86 (100)	
2-B	230 (57)	-	202 (58)	116 (100)	-	89 (48)	-	86 (21)	
3-A	264 (86)	229 (20)	236 (3)	150 (3)		123 (10)		86 (100)	
4-B	264 (100)		236 (65)	150 (65)	114 (8)	123 (10)		86 (13)	
5-B	264 (100)		236 (71)	150 (59)	114 (20)	123 (21)		86 (78)	
6-A	264 (1)	229 (100)		150 (8)	114 (6)	123 (8)		86 (55)	
7-B	264 (12)	229 (100)	236 (5)	150 (29)	114 (13)	123 (10)		86 (22)	
8-B	310 (100)		282 (64)	196 (24)	115 (41)	194 (24)		86 (58)	
9-B	275 (100)	229 (6)	247 (61)	161 (4)	115 (23)			86 (37)	
10-B	275 (100)	229 (2)	247 (48)	161 (9)	115 (25)		88 (8)	86 (39)	
11-A	260 (34)	229 (5)		146 (100)	117 (11)		91 (25)	86 (69)	
12-B	260 (38)		232 (32)	146 (100)	117 (3)		91 (12)	86 (14)	
13-B	244 (100)	-	216 (6)	116 (18)	-	89 (14)	-	100 (39)	
14-B	278 (24)		250 (3)	150 (13)	114 (6)	123 (9)		100 (55)	72 (100)
15-B	324 (100)	244 (4)	296 (3)	196 (8)	115 (13)		88 (7)	100 (93)	
16-B	289 (44)	243 (4)	260 (4)	162 (2)	115 (5)		88 (9)	100 (94)	72 (100)
17-B	289 (6)	243 (5)	260 (2)		115 (20)		88 (16)	100 (85)	72 (100)
18-A	274 (5)	243 (100)	246 (2)	146 (9)	116 (16)		91 (20)	100 (20)	
19-B	274 (13)	243 (4)		146 (11)	116 (30)		91 (25)	100 (12)	
20-B	287 (8)		259 (3)	159 (100)	116 (4)		88 (3)	100 (6)	
21-B	258 (67)	-		116 (36)	-	89 (26)	-	114 (54)	55 (100)
22-B	292 (100)			150 (11)		123 (3)		114 (60)	

position, A^4 were connected with the loss of the arylidene rest and A^5 reflected the presence of a fused heterocyclic ring. The fragmentation of the ions A^3 and A^4 by further cleavages with loss of aromatic substituents was also possible (especially for OCH_3 derivatives).

IR Spectra. The configuration of each type was supported for DPTH derivatives[5] as for as C=O and C=N stretching frequencies were concerned. For 1,2-substituted

TABLE VII

Analytical data for the fused arylidene 2-thiohydantoin derivatives (**1**)–(**22**)

Compound Formula	Solvent	Crystals	M.p./°C	Found (%) Required			ν/cm^{-1}		
				C	H	N	C=O	C=C	C=N
1-A $C_{12}H_{10}N_2OS$	$CHCl_3$:AcOEt 1:1	intensive yellow	197–199	62.8 62.6	4.3 4.4	12.4 12.2	1680	1608	1472
2-B $C_{12}H_{10}N_2OS$	dioxane	cream yellow	198–200	62.4 62.6	4.4 4.4	12.4 12.2	1710	1632	1516
3-A $C_{12}H_9N_2OSCl$	ethanol	cream white	219–220	54.5 54.4	3.4 3.4	10.6 10.6	1698	1640	1480
4-B $C_{12}H_9N_2OSCl$	ethanol+ dioxane	yellow	215–217	54.2 54.4	3.6 3.4	10.6 10.6	1702	1630	1526
5-B $C_{12}H_9N_2OSCl$	dioxane	citron yellow	186–188	54.4 54.4	3.4 3.4	10.7 10.6	1708	1636	1510
6-A $C_{12}H_9N_2OSCl$	ethanol	cream yellow	149–151	54.6 54.4	3.4 3.4	10.8 10.6	1712	1640	1480
7-B $C_{12}H_9N_2OSCl$	dioxane	citron yellow	207–209	54.2 54.4	3.3 3.4	10.5 10.6	1700	1632	1514
8-B $C_{12}H_9N_2OSBr$	ethanol+ dioxane	cream yellow	208–210	46.6 46.6	2.8 2.9	9.3 9.1	1698	1648	1492
9-B $C_{12}H_9N_3O_3S$	aq. dioxane	orange	249–251	52.3 52.3	3.4 3.3	15.4 15.3	1710	1640	1500
10-B $C_{12}H_9N_3O_3S$	CH_3COOH	citron yellow	252–254	52.2 52.3	3.4 3.3	15.3 15.3	1706	1648	1514
11-A $C_{13}H_{12}N_2O_2S$	ethanol	cream yellow	201–203	60.1 60.0	4.7 4.7	10.9 10.8	1694	1640	1476
12-B $C_{13}H_{12}N_2O_2S$	dioxane	citron yellow	192–194	60.2 60.0	4.7 4.7	10.9 10.8	1696	1648	1516
13-B $C_{13}H_{12}N_2O_2S$	dioxane (THF)	yellow	180–182	64.1 63.9	4.9 5.0	11.7 11.5	1715	1630	1520
14-B $C_{13}H_{11}N_2OSCl$	dioxane	citron yellow	200–202	56.1 56.0	4.2 4.0	10.2 10.2	1680	1610	1466
15-B $C_{13}H_{11}N_2OSBr$	dioxane	yellow	207–209	48.2 48.3	3.4 3.4	8.9 8.7	1690	1630	1520
16-B $C_{13}H_{11}N_3O_3S$	dioxane	orange	232–234	54.2 54.0	3.7 3.8	14.4 14.5	1720	1626	1476
17-B $C_{13}H_{11}N_3O_3S$	dioxane	citron yellow	228–230	54.1 54.0	3.8 3.8	14.6 14.5	1714	1648	1484
18-A $C_{14}H_{14}N_2O_2S$	ethanol	yellow	209–210	61.0 61.3	5.0 5.1	10.1 10.2	1660	1600	1480
19-B $C_{14}H_{14}N_2O_2S$	dioxane	citron yellow	204–206	61.3 61.3	5.0 5.1	10.5 10.2	1696	1624	1482
20-B $C_{15}H_{17}N_3OS$	dioxane	orange red	214–216	62.7 62.7	5.8 6.0	14.8 14.6	1690	1624	1520
21-B $C_{14}H_{14}N_2OS$	aq.dioxane	cream yellow	153–155	64.9 65.1	5.3 5.5	11.1 10.8	1698	1628	1526
22-B $C_{14}H_{13}N_2OSCl$	aq.dioxane	cream yellow	165–167	57.3 57.4	4.5 4.5	9.3 9.6	1692	1648	1488

isomers, where the conjugation of C=N and C=O groups occurred, the respective bands were observed at lower stretching frequencies (1685–1710 cm^{-1} and 1475–1490 cm^{-1}) than for 2,3-substituted isomers (1715–1720 cm^{-1} and 1550–1590 cm^{-1}).

In ATH derivatives such differences were not so significant (Table VII), because in any case there existed the conjugation of the C=N group either with C=O in type A isomers, or with exocyclic C=C in type B isomers.

EXPERIMENTAL

M.ps were determined on Boetius apparatus and are uncorrected. E.I. mass spectra at 70 eV: Finnigan MAT CH 7 A spectrometer, IR spectra in KBr pellets: Specord 71 IR spectrophotometer. ^1H and ^{13}C-NMR: Bruker WM 300 spectrometer or Varian Gemini 200 spectrometer in $CDCl_3$ [(**14-B**), (**16-B**), (**19-B**), in DMF-d_7 [(**3-A**), (**4-B**), (**11-A**), (**12-B**)], remaining samples in DMSO-d_6 with TMS as int. stand. J(Hz)—apparent coupling constants. Carbon multiplicities: APT technique. Column chromatography: Kieselgel 60 (70–230 mesh ASTM), Tlc: Kieselgel 60 GF_{254} plates. Spots on Tlc were detected by their absorption under UV light. The starting ATH derivatives were obtained with the method previously reported.[22] The new compound was 5-(2-chlorobenzylidene)-2-thiohydantoin m.p. 266–268°C (from ethanol). (Anal. calc. for $C_{10}H_7N_2OSCl$: C = 50.29; H = 2.97; N = 11.72; Found: C = 50.07; H = 2.99; N = 11.92). The yields for the syntheses of the bicyclic compounds were not optimized.

2,3-dihydro-6-(4-chlorobenzylidene)-imidazo-[2,1b]-thiazol-5(6H)-one (**4-B**) *and 2,3-dihydro-5-(4-chlorobenzylidene)-imidazo-[2,1-b]-thiazol-6(5H)-one* (**3-A**). To the stirred suspension of 5-(4-chlorobenzylidene)-2-thiohydantoin, 2.38 g (0.01 mol), K_2CO_3 (4.0 g) and triethylbenzylammonium chloride 0.3 g, (0.001 mol) in acetone (50 ml), the solution of 1,2-dibromoethane, 1.87 g, (0.01 mol) in acetone (10 ml) was added dropwise. The mixture was stirred at room temperature for two days. The precipitate was removed, washed with water and 1% NaOH solution. The remaining solid was suspended in chloroform (150 ml), stirred for 0.5 h and the suspension was filtered. The solid (0.9 m.p. ~240°C was discarded.

The chloroform filtrate was evaporated to dryness. The remaining solid was identified as (**4-B**) (0.9 g, 34%) m.p. 215–217°C (from ethanol). R_f – 0.57 (chloroform : ethyl acetate 1:1).

The acetone filtrate was evaporated to dryness, the residue dissolved in chloroform was washed with water and 1% NaOH, then evaporated to dryness. Chromatography on silica gel with benzene : acetone (20 : 1.5) as the eluent gave firstly imidazothiazole (**4**) of type B m.p. 215–217°C (from ethanol 0.37 g, 14%).

The further elution gave imidazothiazole (**3**) of type A m.p. 219–220°C (from ethanol 116 mg, 4.4%).

The compounds (**1-A**), (**6-A**), (**11-A**), (**18-A**) were purified by chromatography on silica gel with chloroform : ethyl acetate as eluent.

Analytical data of the compounds (**1**)–(**22**) are listed in Table VII.

In the reaction of 5-(3-chlorobenzylidene)-2-thiohydantoin with 1,4-dibrombutane the only product obtained with 54% yields was a high melting substance which was identified as the substitution product of 1.4-dibromobutane with two molecules of the thiohydantoin derivative m.p. 279–280°C (from DMF). Anal. calc. for $C_{24}H_{20}H_4O_2Cl_2S_2$: C = 54.23; H = 3.80; N = 10.54); Found: C = 54.17; H = 3.64; N = 10.37. R_f – 0.79 (chloroform : ethyl acetate 1 : 1) IR [cm^{-1}]: 3132 and 3064(NH), 1698(C=O), 1632(ArCH=), 1552 and 1500(C=N); MS(m/z): 530(M^+, 1%), 497(0.3), 442 (1), 326(2), 292(36), 264(7), 238(26), 151(28), 116(14), 89(23), 55(100).

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