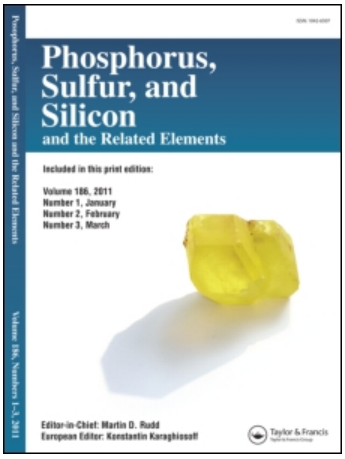


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

REACTION OF 2-THIOHYDANTOINS WITH SOME DIAZOALKANES AND SOME AMINES

Ahmed A. El-barbary[a]; Youssef L. Aly[b]; Abdel-Fatah M. Hashem[a]; Ashraf A. El-shehawy[b]
[a] Chemistry Department Faculty of Science, Tanta University Tanta, Egypt [b] Chemistry Department, Faculty of Education, Kafr El-Sheikh, Tanta University, Egypt

To cite this Article El-barbary, Ahmed A. , Aly, Youssef L. , Hashem, Abdel-Fatah M. and El-shehawy, Ashraf A.(2000) 'REACTION OF 2-THIOHYDANTOINS WITH SOME DIAZOALKANES AND SOME AMINES', Phosphorus, Sulfur, and Silicon and the Related Elements, 160: 1, 77 — 91
To link to this Article: DOI: 10.1080/10426500008043673
URL: http://dx.doi.org/10.1080/10426500008043673

Phosphorus, Sulfur and Silicon, 2000, Vol. 160, pp. 77-91
Reprints available directly from the publisher
Photocopying permitted by license only

REACTION OF 2-THIOHYDANTOINS WITH SOME DIAZOALKANES AND SOME AMINES

AHMED A. EL-BARBARY[a*], YOUSSEF L. ALY[b],
ABDEL-FATAH M. HASHEM[a] and ASHRAF A. EL-SHEHAWY[b]

[a]*Chemistry Department Faculty of Science, Tanta University Tanta, Egypt and*
[b]*Chemistry Department, Faculty of Education, Kafr El-Sheikh, Tanta University, Egypt*

(Received July 20, 1999; In final form November 05, 1999)

Reaction of 2-thiohydantoin derivatives with diazoalkanes as diazomethane. diphenyldiazomethane and/or 9-diazofluorene was investigated. Several 2-thio- and 2-methylthiohydantoins (**IIa,b**), (**IIIa,b**), (**XI**) and (**XII**) were prepared via the reaction of 2-thiohydantoins (**Ia,b**) and (**X**) with diazomethane. 2-Morpholino- and/or 2-piperidino- glycocyamidines (**VIIa,b**) and (**XVa,b**) were prepared by reacting 2-alkylthiohydantoins (**IIIa**) and (**XII**), respectively, with morpholine and/or piperidine. Moreover, treating of two equivalents of **XIVa-d** with one equivalent of piperazine afforded 1,4[di-(5-phenylmethylene-hydantoinyl)]-piperazines (**XVIa,b**). The behaviour of 2-alkylthiohydantoins towards alanine and anthranilic acid was also investigated. The structure of the products was established by correct analytical and spectral data as well as by chemical evidencies.

Keywords: Thiohydantoins; alkylthiohydantoins; diazoalkanes; glycocyamidines

Hydantoin derivatives have found use in medicine, they have mainly been considered as anticonvulsant agent[1]. 5,5-Disubstituted hydantoins were used as drugs in which penetrated the blood-brain barrier in a significant concentration[2]. Authors reported that 2-deoxyuridines with 5-methylene-2-thiohydantoin as the heterocycle in the 5-position showed cytotoxicity against MT-4 cells at 100 mM[3]. These results would be of great interest and prompted us to prepare some new hydantoin derivatives.

In this paper we first examined the reaction of 1-acetyl-2-thiohydantoins (**Ia,b**) with diazomethane. Treatment of **Ia,b** with diazomethane afforded 1-acetyl-3-methyl-2-thiohydantoins (**IIa,b**) and 1-acetyl-2-methylthiohydantoins (**IIIa,b**), respectively. Arenal et al.[4] have reported that the reac-

* Corresponding Author.

tion of **Ia** with diazomethane proceeded differently under the same reaction conditions; the reaction resulted in the formation of **IIa** and 3-methyl-2-acetylthiohydantoin (**VI**). The structure of the products **II** and **III** were supported by correct analytical and spectral data. Infrared spectra of compounds **II** and **III** exhibited no bands in the region of 3300 cm^{-1}, confirming the absence of NH groups. ^{1}H-NMR spectra of **IIIa,b** ($CDCl_3$) showed a singlet at 2.29, 2.37 corresponding to 3H (S-CH_3) and a singlet at 2.50, 2,58 ppm corresponding to 3H (N-CO-CH_3), respectively. Moreover, ^{13}C-NMR[5,6] of **IIIb** exhibited peaks of 17.69 (S-CH_3) and 167.24 ppm (C=N-3,C-2 in IIIa) with the lack of absorption at ~44 ppm characteristic of (C=N-1, C-2 inVI) as should be obtained from the structure of compound **VI** proposed by Arenal[4].

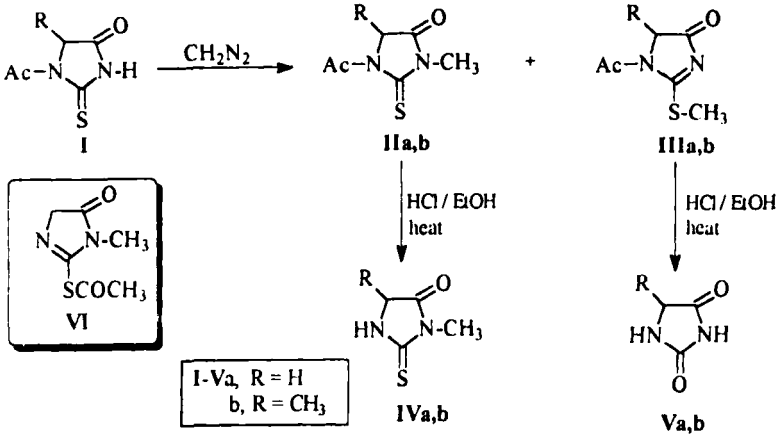
The structure of compounds **II** and **III** were further supported by chemical evidencies. Thus, acid hydrolysis of **IIa,b** and **IIIa,b** afforded the products which proved to be identical with authentic specimen of the corresponding hydantoin derivatives of the type **IVa,b**[5–7] and **Va,b**[5–7]. Moreover, fusion of **IIIa** with morpholine and/or piperidine yields the corresponding 2-morpholino- or 2-pieridino- glycocyamidine derivatives (**VIIa,b**), respectively, accompanied by the elimination of alkylthiols as well as the deacetylation of **IIIa** affected by the reacting base. These results make more evidence for the postulated structures and make no doubt about it.

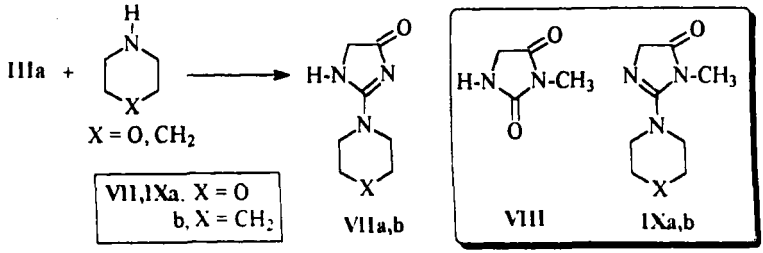
It is worth to mention that if the structure **VI**, postulated by Arenal et al.[4], is the correct, acid hydrolysis of **VI** should give 3-methyl-hydantoin (**VIII**) and its reaction with morpholine and/or piperidine should also give the corresponding 3-methyl-2-morpholino- or 2-piperidino-glycocyamidine derivatives (**IXa,b**), respectively, which is not the case in our hands.

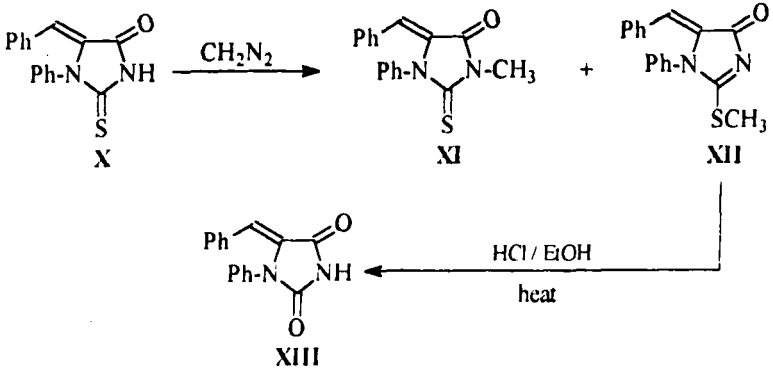
5-Benzylidene-1-phenyl-2-thiohydantoin (**X**) also reacted smoothly with diazomethane to yield the corresponding 5-benzylidene-1-phenyl-3-methyl-2-thiohydantoin (**XI**) and 5-benzylidene-1-phenyl-2-methylthiohydantoin (**XII**).

Acid hydrolysis of **XII** yields the corresponding 5-benzylidene-1-phenylhydantoin (**XIII**). Melting points and mixed melting points determinations of compounds **XI-XIII** with authentic samples of the corresponding ylidene derivatives of the same type gave no depression[8,9])

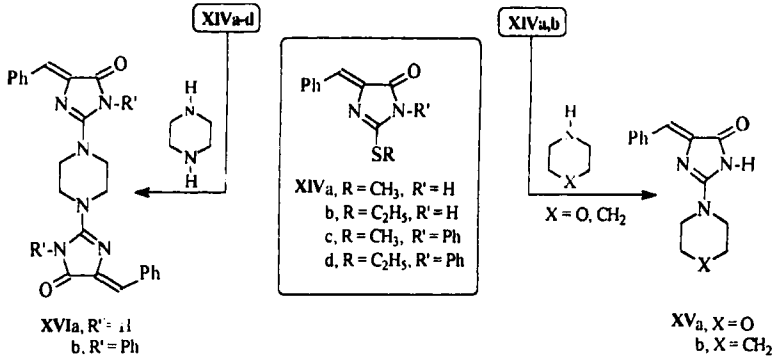
Reaction of 5-benzylidene-2-alkylthiohydantoins (**XIVa,b**) with secondary amines as morpholine, piperidine and/or piperazine was also investigated. Reaction of (**XIVa,b**) with morpholine and/or piperidine yielded the corresponding 2-morpholino- and/or 2-piperidino-glycocyamidines



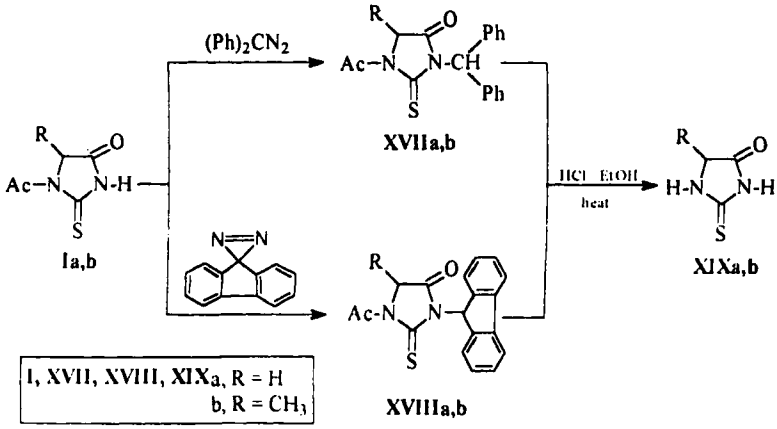


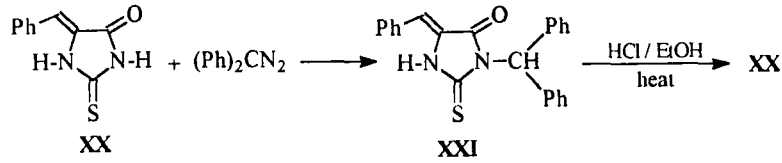


(**XVa,b**). Treating of two equivalents of comp-ounds **XIVa-d** with one equivalent of piperazine in refluxing ethanol afforded the corresponding 1,4[di-(5-benzylideneglycocyamidinyl)]piperazine (**XVIa**) and 1,4[di-(5-benzylidene-3-phenylglycocyamidinyl)]piperazine (**XVIb**).



1-Acetyl-2-thiohydantoins (**Ia,b**) also reacted with diphenyldiazomethane and/or 9-diazofluorene in boiling dry benzene to yield 1-acetyl-3-diphenylmethyl-2-thiohydantoins (**XVIIa,b**) and 1-acetyl-5-methyl-3-(9-fluorenyl)-2-thiohydantoins (**XVIIIa,b**), respectively. Similarly, the reaction of 5-benzylidene-2-thiohydantoin (**XX**) with diphenyldiazomethane furnished 5-benzylidene-3-diphenylmethyl-2-thiohydantoin (**XXI**). The structure of the products was supported on the basis of analytical and spectral data and by chemical evidencies as well.

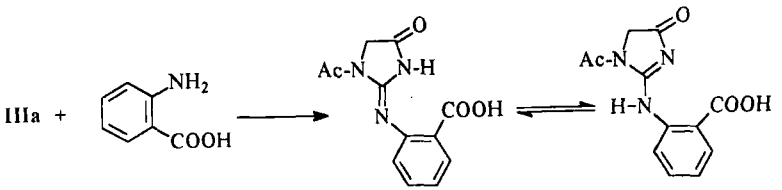




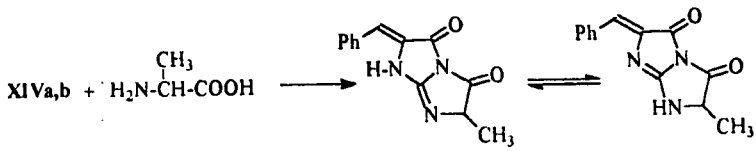
XX XXI

Thus, ^{13}C-NMR spectra of compounds **XVIIa,b, XVIIIa,b** and **XXI**showed the presence of C=S of 2-thiohydantoin derivatives within the range of δ = 170.19–186.03 ppm. Moreover, ^{1}H-NMR spectra showed no absorption for protons corresponding to N^3-H (see Table II). Acid hydrolysis of compounds **XVIIa,b, XVIIIa,b** and **XXI** yielded 2-thiohydantoin (**XIXa,b**) and (**XX**), respectively. Melting points and mixed melting points of compounds **XIXa,b** and **XX** with authentic samples of 2-thiohydantoin[8], 5-methyl-2-thiohydantoin[8] and 5-benzylidene-2-thiohydantoin[9], respectively, gave no depression.

The behaviour of 2-alkylthiohydantoin derivatives towards alanine and anthranilic acid was also investigated[10,11]. It has been found that reacting of 1-acetyl-2- methylthiohydantoin (**IIIa**) with anthranilic acid in refluxing ethanol afforded 1-acetyl-N^2-(o-carboxyphenyl)-glycocyamidine (**XXII**) with the elimination of methane thiol. Moreover, when compounds **XIVa,b** fused with alanine at 160–170°C, 3-benzylidene-2,3,5,6-tetrahydro-6-methyl-1H-imidazo-[1,2-a]-imidazol-2,5-dione (**XXIII**) was obtained. It is worthy to mention that compounds **XIVa,b** failed to react with alanine by refluxing in either ethanol or glacial acetic acid. The structure of compounds **XXII** and **XXIII** was established on the basis of analytical and spectral data.

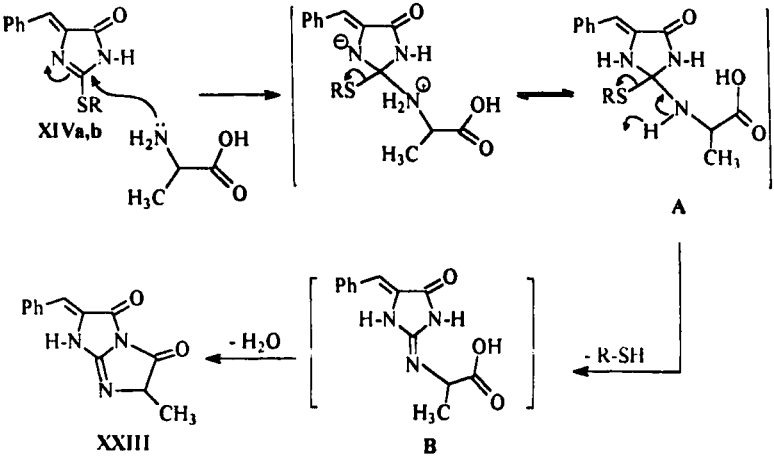


XXII



XXIII

The formation of **XXIII**, for example, may be obtained through the elimination of alkyl thiol followed by cyclization with elimination of water as proposed by the following mechanism. As to the formation of **XXIII**, a nucleophilic attack of 5-benzylidene-2-alkylthiohydantoins (**XIVa,b**) by the amino group of alanine to afford the intermediate **A** which eliminated alkyl thiol to afford the intermediate **B** Internal nucleophilic attack by the NH at the position 3 of hydantoin moiety on the COOH afforded the final product **XXIII** through the elimination of one mole of water.



EXPERIMENTAL

All melting points are uncorrected Microanalyses were performed by microanalytical center at Cairo University. Infra-red spectra were recorded on Perkin-Elmer 1420 spectrophotometer using KBr Wafer Technique.

The ^{1}H-NMR spectra were recorded using a Brücker 250 MHz spectrophotometer using $CDCl_3$ and DMSO as solvents and TMS as internal standard. Chemical shift values are expressed in δ ppm units. ^{13}C-NMR spectra were recorded on a BrÜcker 200 MHz spectrophotometer. TMS was used to determine the carbon chemical shifts and expressed in ppm.

All analytical samples were homogeneous by thin-layer chromatography, which was performed on EM silica gel 60F sheet (0.2 mm) with $C_6H_6/CHCl_3$ (2:5, V/V) and in ether/benzene (2:1, V/V) as the developing solvent. The spots were detected with U.V. Model UVGL-58. The experimental results are reported in Table I, and the spectral data (I.R., ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy) are reported in Tables II, III.

Action of diazomethane on 1-acetyl-2-thiohydantoins (Ia,b) and 5-benzylidene-1-phenyl-2-thiohydantoin (X)

General procedure

An ethereal diazomethane solution (prepared from 10 g nitrosomethylurea) was added to 0.01 mole of each **Ia,b** and **X** suspended in 30 ml of dry ether. The reaction mixture was kept in ice bath with vigorous stirring until the starting material was consumed (TLC). The reaction mixture was evaporated to dryness under vacuum and the solid product was chromatographed on silica gel (100/200 mech) by using ether/benzene (2:1) as an eluent to yield **IIa,b, IIIa,b, XI** and **XII**. The products **IIa** and **XI-XIII** gave no depression when admixed with authentic samples prepared by reported methods[4–7].

Reaction of 1-acetyl-2-methylmercaptohydantoin (IIIa) and/or 5-benzylidene-2-alkylthiohydantoins (XIVa,b) with morpholine or piperidine

General procedure

A mixture of morpholine or piperidine (5 ml) and each of **IIIa** or **XIVa,b** (0.01 mole) was heated under reflux until the starting material was consumed (TLC). The reaction mixture was evaporated to dryness under vaccum and the oily residue was crystallized from methanol to yield the products **VIIa,b** and **XVa,b**, respectively.

TABLE I Experimental data of the newly prepared compounds

Compd. No.	*Time (hour)*	*M P (°C)*	*Yield (%)*	*Mol. Formula Mol. Weight*	*% Analysis (Calcd/Found)*			
					C	*H*	*N*	*S*
IIb	3	50	64.5	$C_7H_{10}N_2O_2S$	45.16	5.37	15.05	17.20
				(186.23)	45.00	5.32	14.90	17.10
IIIa	2	197	32	$C_6H_8N_2O_2S$	41.86	4.65	16.28	18.60
				(172.21)	41.80	4.60	16.25	18.40
IIIb	2.5	123	29.5	$C_7H_{10}N_2O_2S$	45.16	5.37	15.05	17.20
				(186.23)	45.00	5.30	15.00	17.10
VIIa	4	207	83	$C_7H_{11}N_3O_2$	49.70	6.51	24.85	---
				(169.18)	49.81	6.53	24.83	---
VIIb	6	153	86	$C_8H_{13}N_3O$	57.48	7.78	25.15	---
				(167.21)	57.51	7.93	24.96	---
XVa	8	231	94	$C_{14}H_{15}N_3O_2$	65.37	5.84	16.34	---
				(257.29)	65.39	5.53	16.34	---
XVb	12	221	87.5	$C_{15}H_{17}N_3O$	70.59	6.67	16.47	---
				(255.32)	70.40	6.55	16.40	---
XVIa	6	216	91	$C_{24}H_{22}N_6O_2$	67.61	5.17	19.72	---
				(426.48)	67.82	5.21	19.71	---
XVIb	7	207	93	$C_{36}H_{30}N_6O_2$	74.74	5.19	14.53	---
				(578.67)	74.70	5.20	14.51	---
XVIIa	8	227	93	$C_{18}H_{16}N_2O_2S$	66.66	4.94	8.64	9.87
				(324.40)	66.50	4.89	8.63	9.50
XVIIb	5	201	94	$C_9H_{18}N_2O_2S$	67.45	5.32	8.28	9.46
				(338.42)	67.40	5.30	8.24	9.40
XVIIIa	120	168	88.5	$C_{18}H_{14}N_2O_2S$	67.08	4.35	8.69	9.94
				(322.38)	66.90	4.30	8.65	9.70
XVIIIb	50	159	91	$C_{19}H_{16}N_2O_2S$	67.85	4.76	8.33	9.52

Compd. No.	Time (hour)	M P (°C)	Yield (%)	Mol. Formula Mol. Weight	% Analysis (Calcd/Found)			
					C	H	N	S
				(336.41)	67.65	4.70	8.30	9.50
XXI	12	205	64	$C_{23}H_{18}N_2OS$	74.59	4.86	7.57	8.65
				(370.47)	74.60	4.70	7.40	8.60
XXII	6	205	89	$C_{12}H_{11}N_3O_4$	55.23	4.09	16.18	---
				(261.24)	55.17	4.22	16.09	---
XXIII	3	266	82	$C_{13}H_{11}N_3O_2$	64.73	4.56	17.43	---
				(241.25)	64.70	4.50	17.20	---

Reaction of 5-benzylidene-2-alkylthohydantoins (XIVa-d) with piperazine

General procedure

A mixture of **XIVa-d** (0.01 mole) and piperazine (0.0055 mole) in absolute ethanol (50 ml) was refluxed until the starting material was consumed. The reaction mixture was evaporated to half of its volume. cooled and then filtered off. The solid product was recrystallized from glacial acetic acid to yield **XVIa,b**.

Reaction of 1-acetyl-2-thiohydantoins (Ia,b), 5-benzylidene-2-thiohydantoin (XX) with diphenyldiazomethane or 9-diazofluorene

General procedure

Diphenyldiazomethane and/or 9-diazofluorene (0.011 mole) was added to a suspension of each of compounds **1a,b**or **XX** in 50 ml anhydrous benzene. The reaction mixture was refluxed until the starting material was consumed (TLC). The solvent was evaporated to dryness under vaccum and the obtained solid was crystallized from ethanol to give 1-acetyl-3-diphenylmethyl-2-thiohydantoins (**XVIIa,b**), 1-acetyl-5-methyl-3-(9-fluorenyl)-2-thiohydantoins (**XVIIIa,b**) and 5-benzylidene-3-diphenylmethyl-2-thiohydantoin (**XXI**).

TABLE II Infra-red and ^{1}H-NMR spectral data of the newly prepared compounds

I.R. (Cm^{-1})	*^{1}H-NMR (δppm)*
1740 (C=O of acetyl); 1710 (C=O of hydantoin); 1440 (C=S).	1.58 (d, 3H, CH_3 at C_5); 2.84 (s, 3H, N^3-CH_3); 3.28 (s, 3H, CH_3-CO (q, 1H, CH at position 5).
1760 (C=O of acetyl); 1720 (C=O of hydantoin); 1565 (C=N); 670 (C-S-C).	2.29 (s, 3H, S-CH_3); 2.50 (s, 3H, CH_3-CO); 4.61 (s, 2H, CH_2 at posi
1740 (C=O of acetyl); 1710 (C=O of hydantoin); 1570 (C=N); 680 (C-S-C).	1.63 (d, 3H, CH_3 at position 5); 2.37 (s, 3H, S-CH_3); 2.58 (s, 3H, CH 4.37 (q, 1H, CH at position 5).
3200 (NH); 1680 (C=O); 1580 (C=N).	3.50 (s, 4H, $2CH_2$-N); 3.63 (s, 4H, $2CH_2$-O); 3.73 (s, 2H, CH_2 at posi 7.94 (s, 1H, NH at position 1).
3200 (NH); 1680 (C=O); 1580 (C=N).	1.63 (s, 6H, $3CH_2$-N of piprazine); 3.39 (s, 4H, CH_2-N- CH_2); 3.93 (CH_2at position 5); 8.18 (s, 1H, N-H at position 1).
3150 (NH); 1700 (C=O); 1570 (C=N); 1450 (CH aromatic).	3.68 (t, 4H, 2C-CH_2-O); 3.70 (t, 4H, 2C-CH_2-O); 6.37 (s, 1H, Ph-CH 7.20–8.05 (m, 5H, aromatic protons); 11.25 (s, 1H, NH, at position 3
3150 (NH); 1720 (C=O); 1580 (C=N); 1440 (CH, aromatic).	2.52 (t, 4H, $2CH_2$-N of piprazine); 3.56–4.24 (t, 4H, $2CH_2$-N of piper 6.32 (s, 2H, 2 Ph-CH=C); 7.18–8.07 (m, 10H, aromatic protons); 10. 2H, 2NH, at position 3).
1720 (C=O of hydantoin); 1590 (C=N); 1450 (CH, aromatic).	2.80 (s, 4H, $2CH_2$-N of piprazine), 3.32 (s, 4H, 2 CH_2- N of piprazine (s, 2H, Ph-CH=C); 7.25–8.13 (m, 20H, aromatic protons).
3150 (NH); 1760 (C=O of acetyl); 1715 (C=O of hydantoin); 1340 (C=S).	1.56 (d, 3H, CH_3 at position 5); 2.27 (s, 3H, CH_3-CO); 4.19 (q, 1H, C position 5); 6.34 (s, 1H, N^3-CH); 7.20–7.44 (m, 10H, aromatic proto

I.R. (Cm^{-1})	*^{1}H-NMR (δppm)*
1755 (C=O, acetyl); 1715 (C=O of hydantoin); 1440 (CH, aromatic); 1320 (C=S).	2.26 (s, 3H, CH_3-CO); 4.41 (s, 2H, CH_2 at position 5); 6.36 (s, 1H, N[illegible] 7.01–7.75 (m, 8H, aromatic protons).
1760 (C=O, acetyl); 1720 (C=O of hydantoin); 1430 (CH, aromatic); 1320 (C=S).	1.67 (s, 3H, CH_3 at position 5); 2.28 (s, 3H, CH_3-CO); 4.39 (q, 1H, C position 5); 6.38 (s, 1H, N^3-CH); 7.25–7.75 (m, 8H, aromatic protons
3150 (NH); 2950; 1710 (C=O); 1450 (CH, aromatic); 1315 (C=S).	6.39 (s, 1H, N^3-CH); 6.73 (s, 1H, Ph-CH=C); 7.05- 8.04 (m, 15H, aro protons); 11.89 (s, 1H, N^3-H).
3335 (OH); 3150 (NH); 1760 (C=O of acetyl); 1720 (C=O of hydantoin); 1690 (C=O of anthranilic); 1585 (C=N).	2.29 (s, 3H, CH_3-CO); 4.39 (s, 2H, CH_2 at position 5 covered by 1H, COOH); 7.28–8.51 (4d, 1H, aromatic protons); 12.97 (s, 1H, N-H, at tion 3).
3100 (NH); 1760 (C=O of alanine); 1720 (C=O of hydantoin); 1590 (C=N).	1.45 (d, 3H, CH_3); 4.49 (q, 1H, N-CH-C=O); 6.35 (s, 1H, Ph-CH=C) 7.97 (m, 5H, aromatic protons); 10.86 (s, 1H, N-H at position 1).

TABLE III ^{13}C-NMR and mass spectral data of the newly prepared compounds

^{13}C-NMR data in δppm	*Compd. No.*	*Mass spectral data*
5.50 (CH_3 at C_5); 27.78 (N^3-CH_3); 28.21 (CH_3 of acetyl oup); 57.17 (C_5); 169.89 (C=O of acetyl group); 17241 C=O of hydantoin); 181.06 (C=S).	**IIIa**	M^+ 172 (41%, $C_6H_8N_2O_2S$); m/e – 130 (71%, $C_4H_6N_2OS$); (75%; CH_3NS); 43 (100%; CH_3CO or HNCO).
5.18 (CH_3 at C_5); 17.69 (S-CH_3); 23.35 (CH_3 of acetyl oup); 59.27 (C_5); 167.24 (C=N); 184.47 (C=O of acetyl); 5.59 (C=O of hydantoin).	**XVb**	M^+ 255 (98%; $C_{15}H_{17}N_3O$); m/e = 266 (25%; $C_{14}H_{16}N_3^+$); (12%; $C_9H_8N^+$); 117 (37%; C_8H_7N); 116 (30%; $C_8H_6N^+$); 8 (29%; $C_5H_{11}N$); 43 (39%; HNCO).

^{13}C-NMR data in δppm	Compd. No.	Mass spectral data
4.79, 65.49 ($2CH_2$-N, $2CH_2$-O of morpholine moiety); 71.42, 186.31, 50.17 (C_2, C_4, C_5 of hydantoin).	**XVIb**	M^+ 578 (32%; $C_{36}H_{30}N_6O_2$); m/e = 232 (14%; $C_{20}H_{19}N_4O$) (70%; $C_{18}H_{15}N_3O$); 131 (90%; C_9H_9N); 116 (100%; C_8H_6N (97.5%; $C_6H_5^+$).
3.74, 25.27 (2C, CH_2-N-CH_2 and 3C CH_2-CH_2- CH_2 of piperidine moiety); 170.59, 188.72, 51.05 (C_2, C_4, C_5 of hydantoin).	**XVIIb**	M^+ 338 (4%; $C_{19}H_{18}N_2O_2S$); m/e – 296 (4%; $C_{12}H_{16}N_2OS$) (14%; $C_{13}H_{12}$); 167 (100%; $C_{13}H_{11}^+$); 43 (47%; CH_3CO^+).
4.93, 65.46 (CH_2-N, CH_2-O of morpholine moiety); 159.10–167.90, 140.43 (C_2, C_4, C_5 of hydantoin); 111.80, 135.68, 128.19, 129.97, 127.23 (C_7, C_8, C_9, C_{10} of benzylidene moiety).	**XVIIIa**	M^+ 232 (50%; $C_{18}H_{14}N_2OS$); m/e – 280 (23%; $C_{16}H_{12}N_2OS$ (16%; $C_{13}H_{16}$); 165 (99%; $C_{13}H_9^+$); 43 (16%; CH_3CO.).
4.05, 45.08 (C_2, C_3 of piprazine moiety); 159.49, 172.77, 140.59 (C_5, C_7, C_8 of hydantoin); 110.80, 135.86, 127.06, 130.35, 129.22, 130.00, 129.85 (aromatic carbon atoms).	**XVIIIb**	M^+ 336 (14%; $C_{19}H_{16}N_2O_2S$); m/e = 294 (34%; $C_{17}H_{14}N_2C$ 166 (15%; $C_{13}H_{10}$); 165 (100%; $C_{13}H_9^+$); 43 (41%; CH_3CO
4.10, 48.03 (C_2, C_3 of piprazine moiety); 158.80, 170.50, 137.95 (C_5, C_7, C_8 of hydantoin); 118.53, 135.17, 126.20, 131.04, 128.26, 130.88, 128.31 (aromatic carbon atoms).	**XXI**	M^+ 370 (4%; $C_{17}H_{18}N_2OS$); m/e = 204 (7%; $C_{10}H_8N_2OS$); (100%; $C_{13}H_{11}^+$); 144 (30%; $C_9H_5NO^+$); 117 (12%; C_8H_7N
23.84 (CH_3 of acetyl group); 23.49 (CH_3 at C_5); 55.36 (C_5 of hydantoin); 59.14 (N^3-CH); 167.21 (C=O of hydantoin); 183.60 (C=O of acetyl group); 185.01 (C=S of hydantoin); 139.75, 127.47, 128.54, 128.48, 139.55, 127.41, 128.51, 128.17 (aromatic carbon atoms of other two rings).		

^{13}C-NMR data in δppm	Compd. No.	Mass spectral data
3.70 (CH_3 of acetyl group); 50.10 (C_5 of hydantoin); 58.35 (N^3-CH); 169.97 (C=O of acetyl group); 181.20 (C_4 of hydantoin), 186.03 (C=S); 142.38, 120.29, 125.86, 128.73, 127.42, 140.71, 140.07, 127.23, 127.62, 123.32, 119.94, 140.88 (carbon atoms of fluorene).		
1.91 (CH_3 at position 5); 23.41 (CH_3 of acetyl group); 50.18 (C_5 of hydantoin); 167.37 (C=O of acetyl group); 185.05 (C=O of hydantoin); 185.57 (C=S of hydantoin); 59.64 (N^3-CH); 142.69, 119.96, 125.86, 128.75, 127.66, 140.79, 140.71, 125.95, 128.71, 119.98, 142.41 (carbon atoms of fluorene).		
2.76 (N^3-CH); 121.43 (CH of benzylidene); 140.40 (C_5 of hydantoin); 162.67 (C=O of hydantoin); 170.19 (C=S S of hydantoin); 133.96, 128.63, 131.59, 130.10, 140.30, 127.46, 129.50, 128.42, 128.97, 121.49, 129.01, 127.94 (aromatic carbon atoms of other two rings).		
7.47 (CH_3); 49.72 (CH); 135.57 ($C_5$of hydantoin moiety); 141.50 (C=N); 157.90, 173.80 (C=O of hydantoin and C=O of amino acid, respectively); 111.70, 132.80, 127.34, 129.88, 128.28 (aromatic carbon atoms).		

Acid hydrolysis of compounds IIa,b, IIIa,b, XII, XVIIa,b, XVIIIa,b, and/or XXI

General procedure

A mixture of each of compounds **IIa,b, IIIa,b, XII, XVIIa,b, XVI-IIa,b**and/or **XXI** (0.01 mole) in ethanol (30 ml) and concentrated hydrochloric acid (8 ml) was refluxed for two hours. The reaction mixture was concentrated to half of its volume, cooled and filtered off. The resulting solid was recrystallized from the appropriate solvent to yield **IVa,b, Va,b, XIII, XIXa,b** and **XX**. The products **IVa,b, Va,b, XIII, XIXa,b** and **XX** gave no depression when admixed with authentic samples prepared by reported methods[4–9].

Reaction of 1-acetyl-2-methylthiohydantoin (IIIa) with anthranilic acid

A mixture of **IIIa** (0.01 mole) and anthranilic acid (0.011 mole) was heated under reflux in absolute ethanol (30 ml) until the starting material was consumed (TLC). The reaction mixture was cooled, filtered off and the solid product was recrystallized from glacial acetic acid to give 1-acetyl-N^2-(o-carboxyphenyl)-glycocyamidine (**XXII**).

Reaction of 5-benzylidene-2-alkylthiohydantoins (XIVa,b) with alanine

A mixture of compound **XIVa,b** (0.01 mole) and alanine (0.011 mole) was grinded together and fused in an oil bath at 160–170°C for 3 hours. The reaction mixture was allowed to cool to room temperature. The obtained solid was dissolved in a solution of NaOH (10%) and then acidified by dilute HC (20%). The solid formed was filtered off and crystallized from glacial acetic acid to give 3-benzylidene-2,3,5,6-tetrahydro-6-methyl-1H-imidazo- [1,2-a]-imidazol-2,5-diones (**XXIII**).

References

1. Sinks A. and Waring W.S., Prog Med. Chem. **3**, 313, 1963.
2. Firemark H., Barlow C.F., and Rath L.J., Int. J. neuropharmacol. **2**, 25, 1963.
3. EL-Barbary A.A., Khodair A.I., Pedersen E.B., and Nielson C., Monatshefte fur Chemie, **125**, 593, 1994.

4. Arenal I., Bernabe M, Fernadez alvarez, An Quin. E., Ser. C. **80**., (2), 109, 1984 (spain); C.A., **102**, 131962n (1985).
5. Edward J.T. and Nielsen S., J. Chem. Soc., 5075, 1975 and 2327, 1959.
6. Stuckey R.E., Nature, **160**, 189, 1947.
7. Johnson T.B., and Ticknor A.A., J. Amer. Chem. Soc., **40**, 636, 1918.
8. Edward J.T., Chem. Org. Sulfur Comp., **287**, 1966.
9. Villemin D. and Ricard M., Synthetic Comm., 17 (3), 283, (1987).
10. Daboun A. and Abdel-Aziz M.A., Heterocycles, **19**, 1375, 1982.
11. Daboun H.A., Abd-Elfattah A.M., Hussien M.M., and Shalaby A.F.A., Z. Naturforsch, **366**, 1981.