Preparation and Chemical Properties of 5-Dialkylaminomethylhydantoins and 2-Thio-Analogues

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An efficient procedure for the preparation of 5-dialkylaminomethylhydantoins 3, which are easily obtained from cyclization of the corresponding urea derivatives 2 starting with β-aminoalanines 1, is described. Methylenehydantoin and the corresponding 2-thio analogue (4a, 4b) were obtained from hydantoins 3a and 3b, respectively. Some new chemical properties of these hydantoin derivatives are reported.

Key words hydantoin; methylenehydantoin; β-aminoalanine; dimerization; elimination

Much interest has been shown in hydantoins and related compounds from synthetic and biological points of view.[1—6] In connection with our studies on synthetic applications of a new type of amino acid β-aminoalanines **1**[7—10] and our search for biologically active compounds, we have already reported that the compounds **1** are useful starting materials to prepare 5-dialkylaminomethylhydantoins (**3**: X=O, Y=CH) *via* cyclization of corresponding urea derivatives **2**, which are easily prepared by the addition of a primary amino group in compounds **1** to aryl isocyanates.[7] We carried out further preparation of new analogues of 5-dialkylaminomethylhydantoins and 2-thio-analogues. In this paper, we report the synthesis of these new derivatives **3** and the chemical properties observed in the synthesized compounds.

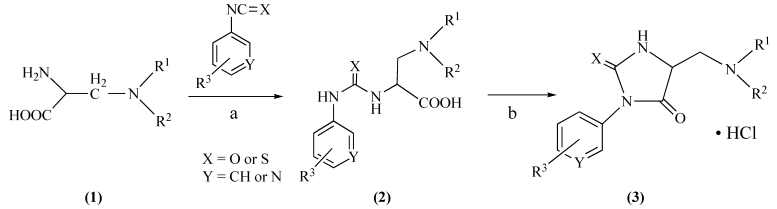
The desired compounds **3** were obtained in good yields by cyclization of the corresponding urea derivatives **2** prepared by condensation of aryl(thio)isocyanates with β-aminoalanines **1** (Chart 1). Since purification of the intermediates urea derivatives (**2b** and **2h**—**j**) was difficult, compound **3b** and the 2-thio-analogues **3h**—**j** were prepared by a "one-pot" procedure (**1**→**3**) without further purification of the corresponding intermediate urea derivatives. The results of the reaction stages (**1**→**2** and **2**→**3**) are summarized in Tables 1 and 2, respectively. The structures of these new products were established by spectroscopic and elemental analyses. All of the assignments were confirmed by two-dimensional (2D) -NMR spectroscopic analysis.

By treatment with a large excess amount of H_2O, deamination (elimination of dialkylamines **5**) of 2-thiohydantoin derivative **3b** took place to give 5-methylene-2-thiohydantoin **4b** (Chart 2). This behavior was easily confirmed by ^{1}H-NMR spectroscopic analysis. Thus, by ^{1}H-NMR (in DMSO) monitoring, easily detectable and characteristic signals for two 5-methylene protons in the compound **4b** (δ 5.18, and 5.35 ppm) are observed, and a remarkable signal for ^{13}C resonance (δ 97.6 ppm) of an exo-methylene carbon (>C=$\underline{C}H_2$) is also confirmed by the ^{13}C-NMR spectrum. We observed that this deamination of 2-thiohydantoin **3b** to give 5-methylene-2-thiohydantoin **4b** proceeded more easily than that of corresponding hydantoin (**3a**→**4a**)[7] through the above NMR experiments. 5-Methylene-2-thiohydantoin analogue **4b** could be isolated in good yield (76%, see Experimental). Throughout our repeated trials for the isolation of compound **4b**, we found that 5-methylene-2-thiohydantoin is not a stable species at elevated temperatures (over 80 °C in solution), giving unknown polymerized products. Methylenehydantoin **4a** or the 2-thio-analogue **4b** (by retro-Michael addition of **3a** or **3b**) is formed probably *via* a 6-membered tautomeric intermediacy state (**A**) (shown in Chart 2).

In ^{1}H-NMR spectra of 5-methylene-2-thiohydantoin **4b**, the N–H proton of the hydantoin ring was easily deuterated by treatment with D_2O. Interestingly, two 5-methylene protons were further deuterated smoothly at room temperature. This result obviously indicates that 5-methylene-2-thiohydantoin **4b** exists in an equilibrium state through keto-enol tautomerism of a thioamido functionality conjugated with a 5-methylene group in the 2-thiohydantoin ring (**4b-I**⇄**4b-II**⇄**4b-III**⇄**4b-IV**) (see Chart 3).

The 5-dialkylaminomethylhydantoin system **3** may exist as many constituted tautomers that are in equilibrium with each other and that differ in the location of hydrogen atoms and double bonds. Because of the contribution of these tautomeric isomers, compounds **3** show a variety of chemical behaviors depending on the reaction conditions (summarized in Chart 4).

Thus, in the case of **3a**, the fact that treatment with a large excess amount of methylamine in MeOH gave 5-methyl-5-methylamino hydantoin derivative **6** (9%) also supports the



Reaction conditions: a) 3 N-NaOH aq., rt *ca.* 50 °C, 1—3 h. b) concentarated HCl for several days, rt.

Chart 1

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above tautomerism (shown in Chart 3). In this reaction, *N*-phenylurea **7**[11] was also isolated (8%) together with recovery of the starting material **3a** (49%) (Chart 5). The formation of *N*-phenylurea **7** may be ascribable to the hydrolysis of a tautomeric form **E** shown in Chart 4.

In contrast, by treatment of hydantoin **3a** with methylamine in water, we also obtained *N*-phenylurea **7** by scission of the original amino acid C–N bond in 25% yield in addition to the β-substituted ring-opened urea derivative **8** (Chart 6) represented as the general structure **2′** shown in Chart 4 (see Experimental). This fact apparently indicates the contribution of a tautomeric isomer **E** and formation of **4** in equilibrium.

The fragment β-amino-α-ketoaldehyde such as **9** shown in brackets in Chart 4 could not be isolated in our repeated trials for isolation. This α-ketoaldehyde **9** is probably an unstable reactive material that gives unknown polymerized compounds. The formation stages of the ring-opened urea derivative **8** arising from two subsequent pathways [*via* path **b** from a precursor **4** or path **a** from a tautomeric form **G** of methyl-

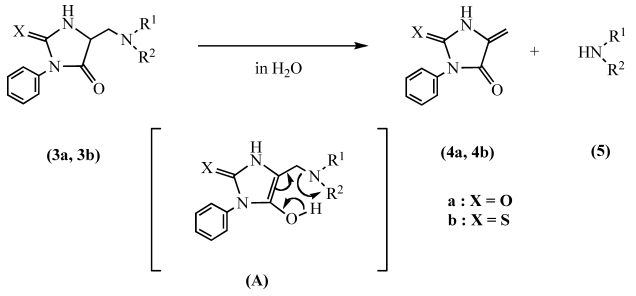


Chart 2

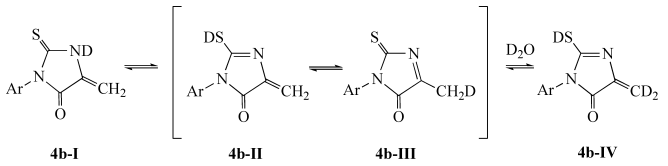


Chart 3

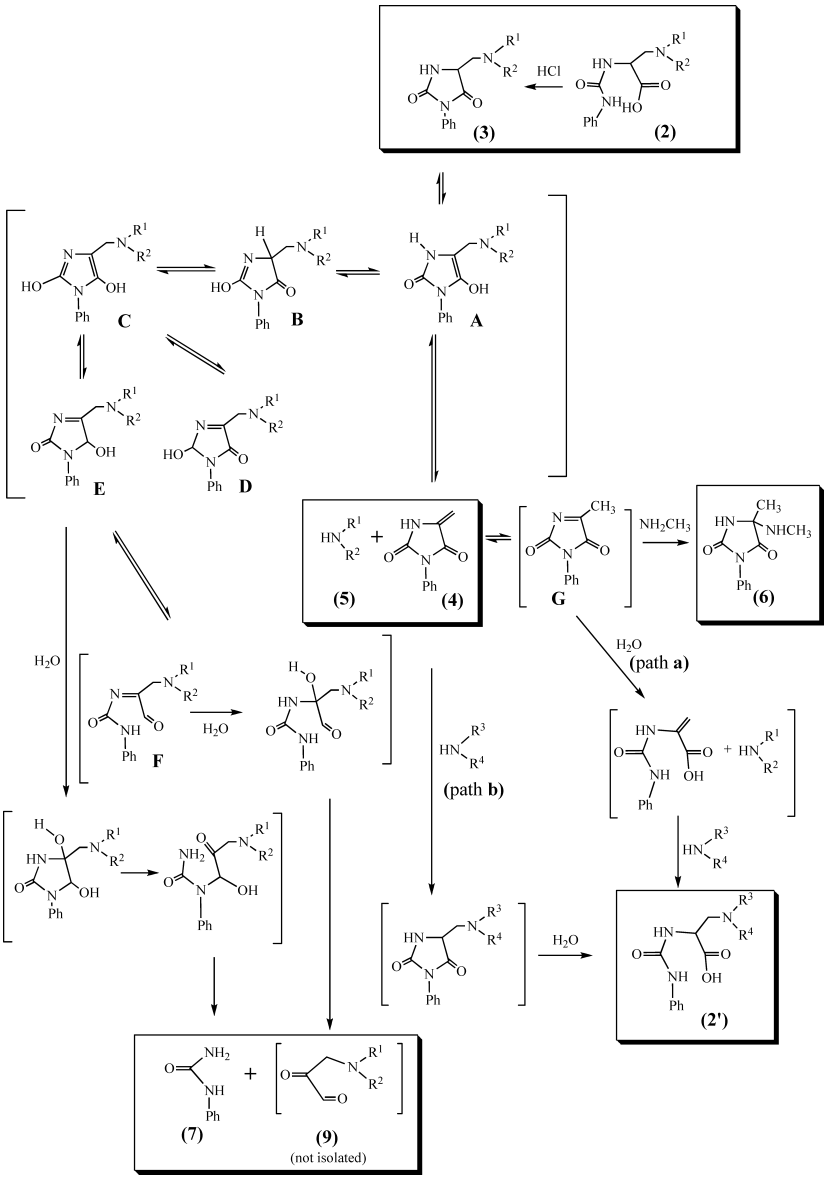


Chart 4

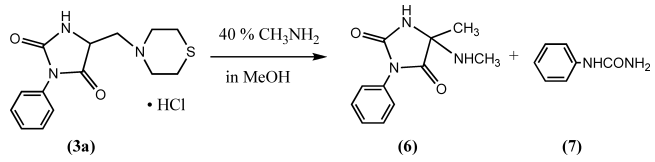


Chart 5

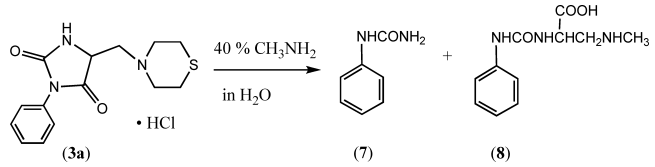


Chart 6

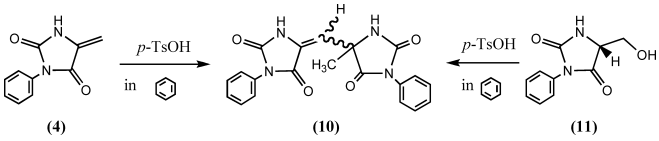


Chart 7

enehydantoin, including hydrolysis by water and addition of $MeNH_2$] can be considered in either of two ways (see Chart 4).

These results clearly indicate the contribution of the N(1)C(5) double bond in this hydantoin ring system **3** such as tautamers **D** and **E** in Chart 4. The contribution of the tautomers **E** or a ring-opened intermediate **F** was substantiated by the frequent formation of *N*-phenylurea **7** in many runs under hydrolytic conditions.

Regarding isolated methylenehydantoin **4a**, we found that compound **4a** shows an interesting chemical behavior. Treatment of **4a** with *p*-TsOH in benzene gave a dimeric hydantoin derivative **10** as an *E*/*Z* isomeric mixture in excellent yield (90%). The ratio of *E*/*Z* isomers of **10** was *ca.* 1/5 by ^{1}H-NMR spectroscopic analysis (see Experimental). This dimerized compound **10** was also obtained in good yield from a similar treatment of 5-hydroxymethylhydantoin **11** prepared by starting with D-serine methyl ester (see Chart 7 and Experimental). The formation of dimerized product **10** is the first observation as a chemical property of **4a**. This dimerization process can be considered to be an analogous manner of dimerization of enamines.[12,13]

On the basis of the above chemical information, further detailed synthetic studies of molecular modification and a search for biologically active new leads in the above hydantoin-relating derivatives are underway.

Experimental

Melting points are uncorrected. IR spectra were measured by a Shimadzu FT/IR-8100 spectrometer. The ^{1}H- and ^{13}C-NMR spectra were obtained by a JEOL JNM A-500 at 35 °C. The chemical shifts were expressed in δ ppm downfield from an internal tetramethylsilane (TMS) signal. The signal assignments were confirmed by ^{1}H–^{1}H two-dimensional (2D) correlation spectroscopy (COSY), ^{1}H–^{13}C heteronuclear multiple quantum coherence (HMQC), and ^{1}H–^{13}C heteronuclear multiple-bond connectivity (HMBC) spectra. High FAB-MS spectra were obtained by a JEOL JMS-HX110 mass spectrometer. The following abbreviations in parentheses were used for the thiomorpholine ring (Thi), pyrrolidine ring (Pyr), piperidine ring (Ppd), and hydantoin ring (Hyd).

Preparation of β-Aminoalanines (1) All of the starting compounds **1** were prepared according to the procedures reported previously. Physical and spectroscopic data have already been reported in our previous paper.[10]

General Procedure for Urea Derivatives (2) These compounds were prepared from β-aminoalanines **1** and phenyl isocyanates or phenyl isothiocyanates according to the procedure reported previously.[7] The preparations of **2b** and **2h**—**j** were carried out at elevated temperatures (*ca.* 50 °C).

New urea derivatives **2** prepared in this study are shown in Table 1. IR, FAB-MS, and elemental analysis are also shown in Table 1. Synthesis of 2-(3-phenylureido)-3-thiomorpholinopropanoic acid **2a** has already been reported.[7]

2-(3-Phenylthioureido)-3-thiomorpholinopropanoic Acid (**2b**): ^{1}H-NMR (DMSO-d_6) δ: 2.57—2.87 (10H, m, Thi-H and C$\underline{H}_2$N=), 3.00—4.50 (1H, br, COO$\underline{H}$), 4.89 (1H, br, C$\underline{H}$CH$_2$), 7.10—7.14 (1H, m, Ar H-4), 7.31—7.35 (2H, m, Ar H-3, H-5), 7.49—7.51 (2H, m, Ar H-2, H-6), 7.81—7.82 (1H, br, Ar–NHCSN$\underline{H}$), 10.01 (1H, br, Ar–N$\underline{H}$CSNH). ^{13}C-NMR (DMSO-d_6) δ: 26.7 (Thi C-2, C-6), 54.4 (Thi C-3, C-5) 54.7 (C$\underline{H}$CH$_2$N=), 58.3 (C$\underline{H}_2$N=), 122.8 (Ar C-4), 124.2 (Ar C-2, C-6), 128.3 (Ar C-3, C-5), 139.1 (Ar C-1), 172.6 (C$\underline{O}$OH), 180.0 (C$\underline{=}$S).

3-(Dimethylamino)-2-(3-phenylureido)propanoic Acid (**2c**): ^{1}H-NMR (D_2O) δ: 2.97 (6H, s, N(C$\underline{H}_3$)$_2$), 3.40 (1H, dd, *J*=13.0, 8.5 Hz, C$\underline{H}$HN=), 3.54 (1H, dd, *J*=13.0, 6.0 Hz, CH$\underline{H}$N=), 4.52—4.55 (1H, m, C$\underline{H}$CH$_2$), 7.18—7.21 (1H, m, Ar–H), 7.35—7.43 (4H, m, Ar–H). ^{13}C-NMR (D_2O) δ: 46.2 (N(CH$_3$)$_2$), 53.4 (C$\underline{H}$CH$_2$), 62.5 (C$\underline{H}_2$N=), 124.1 (Ar C-2, C-6), 127.1 (Ar C-4), 132.1 (Ar C-3, C-5), 140.7 (Ar C-1), 160.4 (NH$\underline{C}$ONH), 177.7 (C$\underline{O}$OH).

2-{3-(4-Chlorophenyl)ureido}-3-(dimethylamino)propanoic Acid (**2d**): ^{1}H-NMR (DMSO-d_6) δ: 2.66 (6H, s, N(C$\underline{H}_3$)$_2$), 2.89—2.93 (1H, m, C$\underline{H}$HN=), 3.12—3.16 (1H, m, CH$\underline{H}$N=), 3.5—5.0 (1H, br, COO$\underline{H}$), 4.06—4.08 (1H, m, C$\underline{H}$CH$_2$), 6.61—6.62 (1H, m, Ar–NHCONH), 7.24—7.26 (2H, m, Ar H-3, H-5), 7.44—7.46 (2H, m, Ar H-2, H-6), 9.36 (1H, s, Ar–N$\underline{H}$CONH). ^{13}C-NMR (DMSO-d_6) δ: 43.2 (N=(CH$_3$)$_2$), 48.8 (C$\underline{H}$CH$_2$), 59.2 (C$\underline{H}_2$N=), 118.9 (Ar C-2, C-6), 124.5 (Ar C-4), 128.4 (Ar C-3, C-5), 139.4 (Ar C-1), 154.9 (NH$\underline{C}$ONH), 171.9 (C$\underline{O}$OH).

2-{3-(4-Chlorophenyl)ureido}-3-(pyrrolidin-1-yl)propanoic Acid (**2e**): ^{1}H-NMR (HMPA-d_{18}) δ: 1.65—1.67 (4H, m, Pyr H-3, H-4), 2.50—2.58 (4H, m, Pyr H-2, H-5), 2.72—2.80 (2H, m, C$\underline{H}_2$N=), 3.3—5.1 (1H, br, COO$\underline{H}$), 4.38—4.42 (1H, m, C$\underline{H}$CH$_2$N=), 6.55—6.57 (1H, m, Ar–NHCONH), 7.19—7.22 (2H, m, Ar H-3, H-5), 7.50—7.52 (2H, m, Ar H-2, H-6), 9.90 (1H, s, Ar–N$\underline{H}$CONH). ^{13}C-NMR (HMPA-d_{18}) δ: 24.0 (Pyr C-3, C-4), 53.1 (C$\underline{H}$CH$_2$N=), 54.6 (Pyr C-2, C-5), 58.4 (C$\underline{H}_2$N=), 118.9 (Ar C-2, C-6), 124.4 (Ar C-4), 128.6 (Ar C-3, C-5), 141.2 (Ar C-1), 155.0 (NH$\underline{C}$ONH), 172.8 (C$\underline{O}$OH).

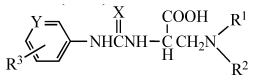
2-{3-(2,4-Dichlorophenyl)ureido}-3-(pyrrolidin-1-yl)propanoic Acid (**2f**): ^{1}H-NMR (DMSO-d_6) δ: 1.83—1.86 (4H, m, Pyr H-3, H-4), 2.98—3.00 (1H, m, C$\underline{H}$HN=), 3.01—3.04 (4H, m, Pyr H-2, H-5), 3.11—3.15 (1H, m, CH$\underline{H}$N=), 3.3—5.1 (1H, br, COO$\underline{H}$), 4.06—4.10 (1H, m, C$\underline{H}$CH$_2$), 7.29—7.31 (1H, m, Ar H-5), 7.44—7.45 (1H, m, Ar–NHCONH), 7.52 (1H, d, *J*=2.7 Hz, Ar H-3), 8.13—8.15 (1H, m, Ar H-6), 8.65 (1H, br, Ar–N$\underline{H}$CONH). ^{13}C-NMR (DMSO-d_6) δ: 22.9 (Pyr C-3, C-4), 50.7 (CHCH$_2$N=), 53.2 (Pyr C-2, C-5), 56.5 (C$\underline{H}_2$N=), 122.0 (Ar C-6), 122.2 (Ar C-2), 125.3 (Ar C-4), 127.2 (Ar C-5), 128.3 (Ar C-3), 135.9 (Ar C-1), 154.4 (NH$\underline{C}$ONH), 171.9 (C$\underline{O}$OH).

2-{3-(4-Methylphenyl)ureido}-3-(pyrrolidin-1-yl)propanoic Acid (**2g**): ^{1}H-NMR (DMSO-d_6) δ: 1.87—1.89 (4H, m, Pyr H-3, H-4), 2.21 (3H, s, Ar–C$\underline{H}_3$), 3.03—3.08 (1H, m, C$\underline{H}$HN=), 3.10—3.16 (4H, m, Pyr H-2, H-5), 3.21—3.25 (1H, m, CH$\underline{H}$N=), 3.3—4.8 (1H, br, COO$\underline{H}$), 4.00—4.03 (1H, m, C$\underline{H}$CH$_2$), 6.50—6.51 (1H, m, Ar–NHCONH), 7.00—7.02 (2H, m, Ar H-3, H-5), 7.28—7.30 (2H, m, Ar H-2, H-6), 9.00 (1H, s, Ar–N$\underline{H}$CONH). ^{13}C-NMR (DMSO-d_6) δ: 20.2 (Ar–C$\underline{H}_3$), 22.8 (Pyr C-3, C-4), 50.0 (C$\underline{H}$CH$_2$), 53.2 (Pyr C-2, C-5), 56.7 (C$\underline{H}_2$N=), 117.5 (Ar C-2, C-6), 128.9 (Ar C-3, C-5), 129.7 (Ar C-4), 137.8 (Ar C-1), 155.1 (NH$\underline{C}$ONH), 171.9 (C$\underline{O}$OH).

2-{3-(2,4-Dichlorophenyl)ureido}-3-(piperidin-1-yl)propanoic Acid (**2h**): ^{1}H-NMR (DMSO-d_6) δ: 1.45—1.48 (2H, m, Ppd H-4), 1.58—1.61 (4H, m, Ppd H-3, H-5), 2.71—2.75 (1H, m, C$\underline{H}$HN=), 2.77—2.87 (4H, m, Ppd H-2, H-6), 2.96—3.00 (1H, m, CH$\underline{H}$N=), 3.5—5.3 (1H, br, COO$\underline{H}$), 4.15—4.19 (1H, m, C$\underline{H}$CH$_2$), 7.29—7.31 (1H, m, Ar H-5), 7.38—7.39 (1H, m, Ar–NHCONH), 7.52 (1H, d, *J*=2.4 Hz, Ar H-3), 8.12—8.14 (1H, m, Ar H-6), 8.62 (1H, br, Ar–N$\underline{H}$CONH). ^{13}C-NMR (DMSO-d_6) δ: 22.5 (Ppd C-4), 24.3 (Ppd C-3, C-5), 49.0 (CHCH$_2$N=), 52.7 (Ppd C-2, C-6), 58.3 (C$\underline{H}_2$N=), 122.1 (Ar C-6), 125.3 (Ar C-2), 127.2 (Ar C-5), 128.3 (Ar C-3), 135.9 (Ar C-4), 143.8 (Ar C-1), 154.4 (NH$\underline{C}$ONH), 172.3 (C$\underline{O}$OH).

2-(3-Phenylthioureido)-3-(pyrrolidin-1-yl)propanoic Acid (**2i**): ^{1}H-NMR (DMSO-d_6) δ: 1.90—1.93 (4H, m, Pyr H-3, H-4), 2.00—5.00 (1H, br, COO$\underline{H}$), 3.14—3.19 (1H, m, C$\underline{H}$HN=), 3.26—3.27 (4H, m, Pyr H-2, H-5), 3.51—3.55 (1H, m, CH$\underline{H}$N=), 4.58—4.60 (1H, m, C$\underline{H}$CH$_2$N=), 7.10—7.12

Table 1. Preparation and Physical Data of Urea Derivatives (**2a**—**k**)

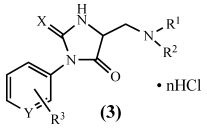


(2)

Compd. No.	X	Y	R^1	R^2	R^3	Yield (%)	mp (°C)	Formula	FAB-MS $(M+H)^+$	IR (KBr) cm^{-1}	*Anal.*[c] Found (Calcd)
2a[a]	O	CH	$-(CH_2)_2-S-(CH_2)_2-$		H	87	170—173 (dec.)	$C_{14}H_{19}N_3O_3S$	310	3326 1622	54.13 6.40 13.30 (54.35 6.19 13.58)
2b	S	CH	$-(CH_2)-S-(CH_2)_2-$		H	58	130—133 (dec.)	$C_{14}H_{19}N_3O_2S_2$	326	3286 1632	326.0993 (326.0997)
2c	O	CH	Me	Me	H	43	206.5 (dec.)	$C_{12}H_{17}N_3O_3$	252	3336 1627	57.21 6.64 16.58 (57.36 6.82 16.72)
2d	O	CH	Me	Me	4-Cl	49	178.8—180 (dec.)	$C_{12}H_{16}N_3O_3Cl\cdot 0.4H_2O$	286	3303 1615	49.18 5.59 14.61 (49.20 5.78 14.34)
2e	O	CH	$-(CH_2)_4-$		4-Cl	43	194—196 (dec.)	$C_{14}H_{18}N_3O_3Cl$	312	3313 1614	53.90 5.64 13.35 (53.94 5.82 13.48)
2f	O	CH	$-(CH_2)_4-$		2,4-Cl	10	167.2 (dec.)	$C_{14}H_{17}N_3O_3Cl_2\cdot 2H_2O$	346	3314 1614	44.00 5.26 10.94 (43.99 5.54 10.29)
2g	O	CH	$-(CH_2)_4-$		$4\text{-}CH_3$	35	189—191 (dec.)	$C_{15}H_{21}N_3O_3\cdot 0.6H_2O$	292	3357 1618	59.68 7.22 13.94 (59.63 7.41 13.91)
2h	O	CH	$-(CH_2)_5-$		2,4-Cl	98	—[b]	$C_{15}H_{19}N_3O_3Cl_2$	360	3322 1619	360.0883 (360.0882)
2i	S	CH	$-(CH_2)_4-$		H	57	140—142.5 (dec.)	$C_{14}H_{19}N_3O_2S$	294	3141 1619	294.1278 (294.1276)
2j	S	CH	$-(CH_2)_5-$		H	81	168 (dec.)	$C_{15}H_{21}N_3O_2S\cdot HCl$	308	3444 1624	308.1433 (308.1433)
2K	S	N	$-(CH_2)_4-$		H	65	155 (dec.)	$C_{13}H_{18}N_4O_2S\cdot 0.6H_2O$	453	3248 1612	51.22 6.21 18.23 (51.16 6.34 18.36)

a) Data were taken from ref. 7. *b*) Hygroscopic amorphous white powder. *c*) Elemental analysis of compounds **2b**, **2h**—**j** was carried out by high-resolution MS spectra.

Table 2. Preparation and Physical Data of Hydantoin Derivatives (**3a**—**k**)



(3)

Compd. No.	X	Y	R^1	R^2	R^3	Yield (%)	mp (°C)	Formula	FAB-MS $(M+H)^+$	IR (KBr) cm^{-1}	*Anal.* Found (Calcd)
3a[a]	O	CH	$-(CH_2)_2-S-(CH_2)_2-$		H	85	193—196	$C_{14}H_{18}N_3O_2ClS$	292	1779 1704	51.52 5.54 12.76 (51.29 5.53 12.82)
3b	S	CH	$-(CH_2)_2-S-(CH_2)_2-$		H	(84)[b]	168—170 (dec.)	$C_{14}H_{18}N_3OClS_2\cdot 0.2H_2O$	308	1759 1726	48.43 4.28 12.06 (48.39 5.34 12.09)
3c	O	CH	Me	Me	H	98	—[c]	$C_{12}H_{16}N_3O_2Cl\cdot 0.2H_2O$	234	1789 1725	52.78 6.01 15.34 (52.73 6.05 15.37)
3d	O	CH	Me	Me	4-Cl	97	180—182	$C_{12}H_{15}N_3O_2Cl_2$	268	1781 1733	47.34 4.98 13.84 (47.48 4.97 13.81)
3e	O	CH	$-(CH_2)_4-$		4-Cl	44	195—197 (dec.)	$C_{14}H_{17}N_3O_2Cl_2\cdot 0.4H_2O$	294	1775 1713	49.83 5.19 12.38 (49.83 5.32 12.45)
3f	O	CH	$-(CH_2)_4-$		2,4-Cl	52	183—185 (dec.)	$C_{14}H_{16}N_3O_2Cl_3\cdot 0.2H_2O$	328	1974 1726	45.66 4.39 11.43 (45.66 4.49 11.41)
3g	O	CH	$-(CH_2)_4-$		$4\text{-}CH_3$	99	188—189	$C_{15}H_{20}N_3O_2Cl$	274	1774 1712	58.09 6.54 13.54 (58.16 6.51 13.56)
3h	O	CH	$-(CH_2)_5-$		2,4-Cl	(79)[b]	193—195 (dec.)	$C_{15}H_{18}N_3O_2Cl_3$	342	1797 1729	47.55 4.74 11.13 (47.58 4.79 11.10)
3i	S	CH	$-(CH_2)_4-$		H	(74)[b]	189 (dec.)	$C_{14}H_{18}N_3OClS$	276	1757	53.72 5.90 13.42 (53.92 5.82 13.48)
3j	S	CH	$-(CH_2)_5-$		H	(79)[b]	198 (dec.)	$C_{15}H_{20}N_3OClS\cdot 0.3H_2O$	290	1757	54.30 6.08 12.66 (54.38 6.27 12.68)
3k	S	N	$-(CH_2)_4-$		H	94	180 (dec.)	$C_{13}H_{18}N_4OSCl_2\cdot 1.3H_2O$	277	1760	41.93 5.80 15.15 (41.89 5.57 15.03)

a) Data were taken from ref. 7. *b*) The yield was based on the starting amino acid (**1**). *c*) Hygroscopic amorphous white powder.

(1H, m, Ar H-4), 7.30—7.33 (2H, m, Ar H-3, H-5), 7.53—7.55 (2H, m, Ar H-2, H-6), 7.90 (1H, br, Ar–NHCSNH), 10.25 (1H, s, Ar–NHCSNH). ^{13}C-NMR (DMSO-d_6) δ: 22.8 (Pyr C-3, C-4), 53.3 (Pyr C-2, C-5), 53.4 (CHCH$_2$N=), 55.3 (CH$_2$N=), 122.7 (Ar C-2, C-6), 124.1 (Ar C-4), 128.5 (Ar C-3, C-5), 139.2 (Ar C-1), 171.3 (COOH), 179.8 (C=S).

2-(3-Phenylthioureido)-3-(piperidin-1-yl)propanoic Acid Hydrochloride (**2j**): ^{1}H-NMR (DMSO-d_6) δ: 1.49—1.65 (6H, m, Ppd H-3, H-4, H-5), 2.78—3.03 (5H, m, Ppd H-2, H-6 and CHHN=), 3.37—3.60 (1H, m, CHHN=), 4.68—4.71 (1H, m, CHCH$_2$N=), 3.50—6.00 (2H, br, COOH+Ar–NHCSNH), 7.10—7.13 (1H, m, Ar H-4), 7.31—7.34 (2H, m, Ar H-3, H-5), 7.49—7.51 (2H, m, Ar H-2, H-6), 7.73 (1H, br s, NH$^+$), 10.05 (1H, br, Ar–NHCSNH). ^{13}C-NMR (DMSO-d_6) δ: 22.0 (Ppd C-4), 23.7 (Ppd C-3, C-5), 52.1 (CH$_2$N=), 52.3 (Ppd C-2, C-6), 56.6 (CHCH$_2$N=), 122.3 (Ar C-2, C-6), 124.1 (Ar C-4), 128.5 (Ar C-3, C-5), 139.0 (Ar C-1), 171.6 (COOH), 179.9 (C=S).

2-(3-Pyridin-3-ylthioureido)-3-(pyrrolidin-1-yl)propanoic Acid (**2k**): ^{1}H-NMR (DMSO-d_6) δ: 1.91—2.17 (4H, m, Pyr H-3, H-4), 3.09—3.45 (5H, m, Pyr H-2, H-5 and CHHN=), 3.51—3.52 (1H, m, CHHN=), 3.00—4.60 (1H, br, COOH), 4.56 (1H, br, CHCH$_2$N=), 7.32—7.35 (1H, m, Pyridine H-5), 8.11—8.12 (2H, m, Pyridine H-4, H-6), 8.27—8.29 (1H, m, Pyridine H-2), 8.69 (1H, d, J=2.0 Hz, Pyridine-NHCSNH), 10.53 (1H, br, Pyridine-NHCSNH). ^{13}C-NMR (DMSO-d_6) δ: 22.8 (Pyr C-3, C-4), 53.3 (Pyr C-2, C-5), 53.7 (CHCH$_2$N=), 55.3 (CH$_2$N=), 123.2 (Pyridine C-5), 129.6 (Pyridine C-2), 136.4 (Pyridine C-3), 144.0 (Pyridine C-6), 144.6 (Pyridine C-4), 171.3 (COOH), 180.4 (C=S).

Preparation of Hydantoin and 2-Thiohydantoin Derivatives (3) Using the same method as that described in our previous paper,[7] hydantoin derivatives **3** were prepared from corresponding urea derivatives **2**. Hydantoins (**3b**, **3h**—**j**) were prepared from urea derivatives (**2b**, **2h**—**j**) obtained by the general procedure without purification. Hydantoin **3a** has been reported in our preliminary paper.[7] The results for new hydantoin and 2-thio analogues derivatives (**3b**—**k**) are summarized in Table 2.

3-Phenyl-5-(thiomorpholinomethyl)-2-thiohydantoin Hydrochloride (**3b**): In the NMR spectroscopic operation (in DMSO-d_6), formation of 2-thiomethylenehydantoin (25%) was observed after 10 min together with compound **3b**. The ratio of this product was based on the methylene signals of **4b** at δ 5.18 and δ 5.35 against a methyne proton at δ 5.24 of compound **3b**. In the spectrum of ^{1}H- and ^{13}C-NMR (DMSO-d_6), two compounds (**4b** and thiomorpholine) were observed in an equilibrium state. ^{1}H-NMR (DMSO-d_6) δ: 2.50—3.96 (10H, m, Thi H-2, H-3, H-5, H-6 and CH$_2$-Thi), 5.24 (1H, br, Hyd H-5), 7.30—7.52 (5H, m, Ar H), 10.58 (1H, s, Hyd N(1)-H), 11.64 (1H, br, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 23.7 (Thi C-2, C-6), 44.5 (Thi C-3, C-5), 54.8 (Hyd C-5), 57.6 (CH$_2$-Thi), 128.6, 128.7 (Ar C-2—C-6), 133.1 (Ar C-1), 171.0 (C=O), 182.5 (C=S). Thiomorpholine was also detected in this spectrum at δ: 2.86—2.89 (4H, m, Thi H-2, H-6), 3.24 (4H, br, Thi H-3, H-5), 9.29 (2H, br s, NH$_2^+$ in Thi), ^{13}C-NMR (DMSO-d_6) δ: 23.4 (Thi C-2, C-6), 44.5 (Thi C-3, C-5),

5-(Dimethylamino)methyl-3-phenylhydantoin Hydrochloride (**3c**): ^{1}H-NMR (DMSO-d_6) δ: 2.88 [6H, s, N(CH$_3$)$_2$], 3.57—3.58 [2H, m, CH$_2$N(CH$_3$)$_2$], 4.87—4.89 (1H, m, Hyd H-5), 7.36—7.43 (3H, m, Ar H-3, H-4, H-5), 7.48—7.51 (2H, m, Ar H-2, H-6), 8.72 [1H, s, Hyd N(1)-H], 10.97 (1H, br, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 42.1, 43.4 (CH$_3$×2), 52.6 (Hyd C-5), 58.1 [CH$_2$N(CH$_3$)$_2$], 126.6 (Ar C-2, C-6), 128.0 (Ar C-4), 128.7 (Ar C-3, C-5), 131.8 (Ar C-1), 155.2 (Hyd- C-2), 170.6 (Hyd C-4).

3-(4-Chlorophenyl)-5-(dimethylamino)methylhydantoin Hydrochloride (**3d**): ^{1}H-NMR (DMSO-d_6) δ: 2.88 [6H, s, N(CH$_3$)$_2$], 3.57 [2H, d, J=6.0 Hz, CH$_2$N(CH$_3$)$_2$], 4.88 (1H, td, J=6.0, 1.0 Hz, Hyd H-5), 7.43 (2H, d, J=8.5 Hz, Ar H-2, H-6), 7.57 (2H, d, J=8.5 Hz, Ar H-3, H-5), 8.80 [1H, s, Hyd N(1)-H], 11.2 (1H, br, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 42.1, 43.4 (CH$_3$×2), 52.7 (Hyd C-5), 58.1 [CH$_2$N(CH$_3$)$_2$], 128.2 (Ar C-2, C-6), 128.7 (Ar C-3, C-5), 130.7 (Ar C-4), 132.3 (Ar C-1), 154.8 (Hyd C-2), 169.8 (Hyd C-4).

3-(4-Chlorophenyl)-5-(pyrrolidin-1-ylmethyl)hydantoin Hydrochloride (**3e**): ^{1}H-NMR (DMSO-d_6) δ: 1.92, 2.04 (each 2H, br, Pyr H-3, H-4), 3.09 (2H, br, Pyr H-2, H-5), 3.64—3.69 (4H, m, CH$_2$-Pyr and Pyr H-2, H-5), 4.81—4.83 (1H, m, Hyd H-5), 7.42—7.45 (2H, m, Ar H-2, H-6), 7.55—7.58 (2H, m, Ar H-3, H-5), 8.78 [1H, s, Hyd N(1)-H], 11.13 (1H, br, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 22.4, 22.7 (Pyr C-3, C-4), 53.4, 54.1 (Pyr C-2, C-5), 53.7 (Hyd C-5), 55.0 (Pyr-CH$_2$), 128.3 (Ar C-2, C-6), 128.7 (Ar C-3, C-5), 130.7 (Ar C-4), 132.3 (Ar C-1), 154.9 (Hyd C-2), 167.8 (Hyd C-4).

3-(2,4-Dichlorophenyl)-5-(pyrrolidin-1-ylmethyl)hydantoin Hydrochloride (**3f**): ^{1}H-NMR (DMSO-d_6) δ: 1.92, 2.50 (each 2H, br, Pyr H-3, H-4), 3.11 (2H, br, CH$_2$-Pyr), 3.65—3.72 (4H, m, Pyr H-2, H-5), 4.91 (0.5H, d, J=9.0 Hz, Hyd- H-5), 5.04 (0.5H, d, J=7.5 Hz, Hyd H-5), 7.86—7.87 (1H, m, Ar H-3), 8.91—8.92 [1H, s, Hyd N(1)-H], 11.23 (1H, br, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 22.3, 22.5, 22.6, 22.7 (Pyr C-3, C-4), 53.0, 53.3, 53.8, 54.3, 54.9, 55.4 (Pyr C-2, C-5 and Pyr–CH$_2$), 53.9, 54.4 (Hyd C-5), 128.3, 128.4, 128.4, 129.4, 129.4, 132.3 (Ar C-3, C-5, C-6), 132.3, 132.3, 133.0, 133.0, 134.8, 134.9 (Ar C-1, C-2, C-4), 153.8, 154.2 (Hyd C-2), 169.2,169.4 (Hyd C-4).

3-(4-Methylphenyl)-5-(pyrrolidin-1-ylmethyl)hydantoin Hydrochloride (**3g**): ^{1}H-NMR (DMSO-d_6) δ: 1.91 — 2.04 (4H, m, Pyr H-3, H-4), 2.34 (3H, s, CH$_3$), 3.08—3.10 (2H, m, Pyr H-2, H-5), 3.63—3.70 (4H, m, CH$_2$-Pyr and Pyr H-2, H-5), 4.82 (1H, td, J=6.0, 1.5 Hz, Hyd H-5), 7.23—7.25 (2H, m, Ar H-2, H-6), 7.28—7.29 (2H, m, Ar H-3, H-5), 8.70 [1H, s, Hyd N(1)-H], 11.22 (1H, br, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 20.6, 22.7 (Pyr C-3, C-4), 53.3, 54.1 (Pyr C-2, C-5), 53.7 (Hyd C-5), 55.2 (Pyr–CH$_2$), 126.5 (Ar C-2, C-6), 129.1 (Ar C-3, C-5), 129.2 (Ar C-1), 137.5 (Ar C-4), 155.3 (Hyd C-2), 170.0 (Hyd C-4).

3-(2,4-Dichlorophenyl)-5-(piperidin-1-ylmethyl)hydantoin Hydrochloride (**3h**): ^{1}H-NMR (DMSO-d_6) δ: 1.37—1.42 (1H, m, Ppd H-4), 1.72—1.93 (5H, m, Ppd H-3, H-4, H-5), 2.97—3.09 (2H, m, Ppd H-2, H-6), 3.40—3.67 (4H, m, Ppd H-2, H-6 and CH$_2$-Ppd), 5.04 (0.5H, dd, J=9.5, 1.5 Hz, Hyd H-5), 5.18 (0.5H, d, J=1.5 Hz, Hyd H-5), 7.55—7.63 (2H, m, Ar H-5, H-6), 7.86—7.87 (1H, m, Ar H-3), 9.04—9.05 [1H, s, Hyd N(1)-H], 10.9 (1H, br, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 21.0 (Ppd C-4), 22.0, 22.1, 22.2, 22.2 (Ppd C-3, C-5), 51.6, 52.0, 53.4, 53.7 (Ppd C-2, C-6), 52.4, 53.0 (Hyd C-5), 57.9, 53.0 (Ppd–CH$_2$), 127.5, 128.3, 128.4, 129.5, 132.2, 133.0 (Ar C-3, C-5, C-6), 134.8, 134.9, 134.9 (Ar C-1, C-2, C-4), 153.7, 154.0 (Hyd C-2), 169.4, 169.6 (Hyd C-4).

3-Phenyl-5-(pyrrolidin-1-ylmethyl)-2-thiohydantoin Hydrochloride (**3i**): In the case of pyrrolidine derivative (**3i**), formation of 85% of 2-thiomethylenehydantoin was observed in ^{1}H-NMR spectra (in DMSO-d_6) after 10 min. ^{1}H-NMR (DMSO-d_6) δ: 1.92—2.05 (4H, m, Pyr H-3, H-4), 3.05—3.10 (2H, m, Pyr H-2, H-5), 3.67—3.77 (4H, m, Pyr H-2, H-5, and CH$_2$-Pyr), 5.05—5.07 (1H, m, Hyd H-5), 7.31—7.32 (2H, m, Ar H), 7.32—7.33 (3H, m, Ar H), 10.56 [1H, s, Hyd N(1)-H], 11.22 (1H, s, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 22.5 (Pyr C-3, C-4), 53.1 (Pyr C-2, C-5), 54.2 (Pyr–CH$_2$), 56.4 (Hyd C-5), 128.6, 128.7 (Ar C-2—C-6), 133.0 (Ar C-1), 170.9 (C=O), 182.7 (C=S).

3-Phenyl-5-(piperidin-1-ylmethyl)-2-thiohydantoin Hydrochloride (**3j**): In the case of piperidine derivative **3j**, formation of 82% of 2-thiomethylenehydantoin was observed in ^{1}H-NMR spectra (in DMSO-d_6) after 1 h. ^{1}H-NMR (DMSO-d_6) δ: 1.75—1.86 (6H, m, Ppd H-3, H-4, H-5), 3.39—3.60 (6H, m, Ppd H-2, H-6 and CH$_2$-Ppd), 5.50 (1H, br, Hyd H-5), 7.13—7.51 (5H, m, Ar H), 8.42 [1H, s, Hyd N(1)-H], 10.34 (1H, br s, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 21.2, 22.2, 22.2 (Ppd C-3, C-4, C-5), 52.4 (Hyd C-5), 52.7 (Ppd C-2, C-6), 56.3 (Ppd–CH$_2$), 123.0, 124.5, 128.6 (Ar C-2—C-6), 138.8 (Ar C-1), 170.3 (Hyd C=O), 180.7 (Hyd C=S).

3-(Pyridin-3-yl)-5-(pyrrolidin-1-ylmethyl)-2-thiohydantoin Dihydrochloride (**3k**): ^{1}H-NMR (CD$_3$OD) δ: 2.02—2.22 (4H, m, Pyr H-3, H-4), 3.25—3.32 (2H, m, Pyr H-2, H-5), 3.85—3.90 (4H, m, Pyr H-2, H-5, and CH$_2$-Pyr), 5.12—5.14 (1H, m, Hyd H-5), 8.28—8.31 (1H, m, Pyridine H-5), 8.92—8.94 (1H, m, Pyridine H-4), 8.96—8.98 (1H, m, Pyridine H-6), 9.22—9.29 (1H, m, Pyridine H-2). ^{13}C-NMR (CD$_3$OD) δ: 24.1, 24.2 (Pyr C-3, C-4), 56.9, 56.4 (Pyr C-2, C-5), 55.4 (Pyr–CH$_2$), 58.2 (Hyd C-5), 128.7 (Pyridine C-5), 134.6 (Pyridine C-1), 142.4 (Pyridine C-6), 143.0 (Pyridine C-2), 147.8 (Pyridine C-4), 171.5 (C=O), 182.9 (C=S).

5-Methylene-3-phenyl-2-thiohydantoin (4b) A suspension of compound **3b** (0.134 g, 0.39 mmol) in water (10 ml) was kept at room temperature for 3 d. The solid material in the reaction mixture was extracted with Et$_2$O. The organic layer was washed with 1N-HCl (×2) and then brine and dried over anhydrous MgSO$_4$. Concentration of the solvent gave a yellow solid material **4b** (60 mg, 76%), mp>200 °C (dec). IR (KBr) cm^{-1}: 3228, 1716 1657. MS (positive) m/z: 205. ^{1}H-NMR (DMSO-d_6) δ: 5.18 (1H, d, J=1.8 Hz, Hyd=CHH), 5.35 (1H, d, J=1.8 Hz, Hyd=CHH), 7.34—7.52 (5H, m, Ar H), 12.47 [1H, br s, N(1)-H], ^{13}C-NMR (DMSO-d_6) δ: 97.6 (Hyd=CHH), 126.6, 128.6, 128.6, 128.7, 128.7 (Ar C-2—C-6), 132.9 (Ar C-1), 135.2 (Hyd C-5), 162.3 (Hyd C-4), 178.0 (Hyd C-2). *Anal*. Calcd for C$_{10}$H$_8$N$_2$OS: C, 58.8; H, 3.95; N, 13.72. Found: C, 58.80; H, 4.25; N, 13.43.

Treatment of Compound (3a) with Methylamine in Methanol A solution of hydantoin hydrochloride **3a** (0.3 g, 9.1×10^{-4} mol) and methylamine (0.43 g, 40% in H$_2$O, 5.5×10^{-3} mol) in methanol (15 ml) was refluxed for 15 min. After evaporation of the solvent, water (*ca.* 7 ml) was added to the mixture and mixture was extracted with AcOEt. The extract was evaporated to give a brownish material. Purification by column chromatography with SiO$_2$ (with AcOEt–Hexane=5 : 1 as a solvent) gave three main products [**3a** (as a free base), 5-methyl-5-methylamino-1-phenylhydantoin **6**, and

1-phenylurea **7**] in 49%, 9%, and 8% yields, respectively. 1-Phenylurea **7**[11] was shown to be identical to a commercially available authentic sample by ^{1}H-, ^{13}C-NMR and IR spectroscopic analysis.

5-Methyl-5-methylamino-1-phenylhydantoin (**6**): mp 117—118 °C. IR (KBr) cm^{-1}: 3311, 1721, 1713 1696. FAB-MS (positive) *m*/*z*: 220 (M+H$^+$). ^{1}H-NMR (DMSO-d_6) δ: 1.45 (3H, m, C$\underline{H}_3$), 2.17 (3H, d, J=5.0 Hz, NHC$\underline{H}_3$), 2.93 (1H, br, N$\underline{H}$CH$_3$), 7.32—7.48 (5H, m, Ar H), 8.44 [1H, br, N(1)-H]. ^{13}C-NMR (DMSO-d_6) δ: 23.6 (CH$_3$), 28.2 (NHC$\underline{H}_3$), 73.9 (Hyd C-5), 126.6 (Ar C–2, C-6), 127.7 (Ar C-4), 128.6 (Ar C-3, C-5), 132.0 (Ar C-1), 154.1 (Hyd C-2), 174.5 (Hyd C-4). *Anal*. Calcd for $C_{11}H_{13}N_3O_2\cdot 0.1H_2O$: C, 59.77; H, 6.02; N, 19.01. Found: C, 59.77; H, 5.90; N, 18.82.

Treatment of Compound (3a) with Methylamine in Water Methylamine (0.43 g, 40% in H_2O, 5.5×10^{-3} mol) was added to a solution of 0.3 g of **3a** (9.1×10^{-4} mol) in H_2O (10 ml). The mixture was stirred for 40 min at room temperature. After evaporation of the solvent *in vacuo*, H_2O (2—3 ml) was added to the residue. The resulting crystallized material was collected by filtration to give 1-phenylurea **7** (28—32%). After evaporation of the mother filtrate, purification of the products gave the compound **8** (25—40%).

3-(Methylamino)-2-(3-phenylureido)propanoic Acid (**8**): mp 188—189 °C (dec.). IR (KBr) cm^{-1}: 1701, 1648, 1603. FAB-MS (positive) *m*/*z*: 238 (M+H)$^+$. ^{1}H-NMR (D$_2$O) δ: 2.79 (3H, s, NHC$\underline{H}_3$), 3.28—3.32 (1H, m, NHCHC$\underline{H}$HNHCH$_3$), 3.45—3.48 (1H, m, NHCHCH$\underline{H}$NHCH$_3$), 4.43—4.46 (1H, m, NHC$\underline{H}$CHHNHCH$_3$), 7.17—7.42 (5H, Ar H). ^{13}C-NMR (D$_2$O) δ: 36.0 (NHCH$_3$), 54.2 (NHCH$\underline{C}$H$_2$), 54.6 (NH$\underline{C}$HCH$_2$), 124.0 (Ar C-2, C-6), 127.0 (Ar C-4), 132.1 (Ar C-3, C-5), 140.7 (Ar C-1), 160.5 (NHCONH), 177.6 ($\underline{C}$OOH). *Anal*. Calcd for $C_{11}H_{15}N_3O_3\cdot 0.5H_2O$: C, 53.65; H, 6.55; N, 17.06. Found: C, 53.86; H, 6.37; N, 16.96.

Formation of Dimerized Methylenehydantoin (10) from Methylenehydantoin (4a) A solution of methylenehydantoin **4a** (12 mg, 0.06 mmol) in the presence of *p*-toluenesulfonic acid (50 mg) in anhydrous benzene (6 ml) was refluxed for 10 min. After evaporation of the solvent, the residue was dissolved in AcOEt. The resulting solution was washed with aq.-NaHCO$_3$ (5%, 1 ml×2), washed with brine, and then dried over anhydrous MgSO$_4$. Evaporation of the solvent gave dimerized product **10** in 90% yield, mp 161—162 °C. ^{1}H- and ^{13}C-NMR spectroscopic results were consistent with an *E*/*Z* isomeric mixture of **10**. This isomeric ratio (*E*/*Z*=*ca.* 1/5) was easily estimated by integration values of corresponded vinyl protons at δ 5.62 ppm (*E*) and at δ 5.77 ppm (*Z*), respectively. This stereochemistry of the two stereo isomers (*E*/*Z*) could be determined on the basis of data reported by Tan *et al.*[14] and by careful analysis of 2D-NMR spectroscopic data. IR (KBr) cm^{-1}: 3305, 1777, 1713 1680. FAB-MS (positive) *m*/*z*: 377 (M+H$^+$). ^{1}H-NMR (DMSO-d_6) δ: 1.67, 1.73 [3H, m, C$\underline{H}_3$ (*E* and *Z*, respectively)], 5.62, 5.77 [1H, s, Hyd=C$\underline{H}$–(*E* and *Z*, respectively)], 733—7.52 (10H, m, Ar H), 8.72, 10.43 (each 1H, br, NH). ^{13}C-NMR (DMSO-d_6) δ: 24.0, 27.6 [CH$_3$, (*Z* and *E*, respectively)], 60.0, 58.2 [Hyd C-5 (*Z* and *E*, respectively)], 108.9, 113.8 [methyleneHyd (C-5)=$\underline{C}$H–(*Z* and *E*, respectively)], 126.6 126.7, 126.7, 128.0, 128.5, 128.6, 128.7, 128.8, 128.8, 128.9 (Ar C2—C-6), 131.1, 131.2, 131.4, 131.8, 131.8, 132.3 [methyleneHyd C-5 and Ar C-1 (×2)], 153.3, 152.4 [methyleneHyd C-2 (*Z* and *E*, respectively)], 154.2, 154.5 [Hyd C-2 (*Z* and *E*, respectively)], 162.3, 160.6 [methyleneHyd C-4 (*Z* and *E*, respectively)], 173.4, 174.1 [Hyd C-4 (*Z* and *E*, respectively)]. *Anal*. Calcd for $C_{20}H_{16}N_4O_4\cdot 0.3H_2O$: C, 62.92; H, 4.38; N, 14.68. Found: C, 62.94; H, 4.54; N, 14.41.

5-Hydroxymethyl-3-phenylhydantoin (11) Phenyl isocyanate (1.15 g, 9.66 mmol) was added dropwise to a solution of D-serine methyl ester hydrochloride (1 g, 6.43 mmol) in 3 M-sodium hydroxide (3 ml) with vigorous stirring at 50 °C for 90 min. After evaporation of the solvent, conc HCl was added to the residue and the resulting mixture was allowed to stand for 4 d at room temperature. After evaporation of the solvent, the residue was triturated with AcOEt and the separated crystal material was filtered to give 5-hydroxymethylhydantoin derivative **11** (0.98 g in 74% yield). An analytical sample was obtained by recrystallization from EtOH, mp 167—168 °C (Lit[15] mp 166—167 °C). IR (KBr) cm^{-1}: 3262, 1767, 1693. FAB-MS (positive) *m*/*z*: 207 (M+H$^+$). ^{1}H-NMR (DMSO-d_6) δ: 3.67—3.70 (1H, m, C$\underline{H}$H–OH), 3.75—3.80 (1H, m, CH$\underline{H}$–OH), 4.22 (1H, t, J=3.0 Hz, Hyd H-5), 5.15 (1H, t, J=5.0 Hz, OH), 7.35—7.38 (3H, m, Ar H), 7.44—7.48 (2H, m, Ar H), 8.33 (1H, br s, NH). ^{13}C-NMR (DMSO-d_6) δ: 59.0 (Hyd C-5), 60.1 (CH$_2$–OH), 126.4 (Ar C-2, C-6), 127.5 (Ar C-4), 128.6 (Ar C-3, C-5), 132.3 (Ar C-1), 156.0 (Hyd C-2), 171.9 (Hyd C-4). *Anal*. Calcd for $C_{10}H_{10}N_2O_3\cdot 0.1H_2O$: C, 57.74; H, 4.94; N, 13.47. Found: C, 57.74; H, 4.90; N, 13.45.

Formation of Dimerized Methylenehydantoin (10) from 5-Hydroxymethyl-3-phenylhydantoin (11) A solution of 5-hydroxymethyl-3-phenylhydantoin **11** (0.51 g, 2.48 mmol) obtained above and *p*-toluenesulfonic acid (2.5 g, 14.5 mmol) in anhydrous benzene was refluxed for 7 h with a water separator. After evaporation of the solvent, the residue was dissolved in AcOEt and washed with water (×4), washed with brine, and dried over MgSO$_4$. Evaporation of the solvent gave dimerized methylenehydantoin derivative **10**, 0.42 g in 90% yield. The product was identical to a sample obtained from the reaction starting with methylenehydantoin **4a**. The isomeric ratio (*E*/*Z*) of the products in this reaction was also *ca.* 1/5.

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