HETEROCYCLES, Vol. 78, No. 1, 2009, pp. 213 - 220. © The Japan Institute of Heterocyclic Chemistry
Received, 8th August, 2008, Accepted, 18th September, 2008, Published online, 22nd September, 2008.
DOI: 10.3987/COM-08-11519

A SYNTHETIC APPLICATION OF β-AMINOALANINES TO SOME NEW 5-DIALKYLAMINOMETHYL-3-PHENYLHYDANTOIN DERIVATIVES

Fumiko Fujisaki, Kaori Shoji, and Kunihiro Sumoto*

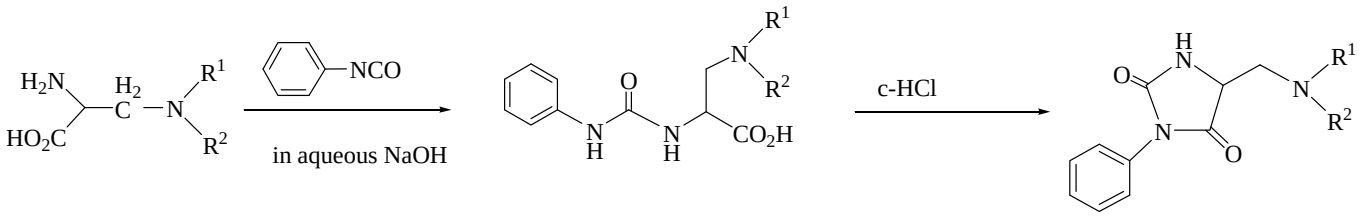
Faculty of Pharmaceutical Sciences, Fukuoka University, Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. E-mail: kunihiro@cis.fukuoka-u.ac.jp

Abstract — 5-Dialkylaminomethylhydantoins (**3**) were synthesized from β-aminoalanines (**1**) as the starting materials in two stages. Intermediate urea derivatives (**2**) prepared from the addition reaction of β-aminoalanines to phenyl isocyanate are easily cyclized to 5-dialkylaminomethylhydantoins (**3**) with good yields. The deamination reaction of some of the hydantoin derivatives (**3a**, **3b**) in water were observed and resulted in the formation of 3-phenyl-5-methylenehydantoin (**4**). The hydantoin derivative (**3b**) regenerated a urea derivative (**2c**, **d**) by treatment with excess amounts of pyrrolidine or piperidine.

Hydantoins (imidazolizine-2,4-diones) and related compounds are attracting considerable attention because of their chemical and biological properties. Indeed, a large number of hydantoins which frequently demonstrate biological activity have been prepared for various biological applications.[1-4] For example, recent studies regarding hormone receptor antagonists[2-4] have been reported which are based on a hydantoin scaffold.

In connection with studies on β-aminoalanines,[5-8] the synthetic application of these novel β-aminoalanines for the preparation of hydantoin derivatives was investigated. This report describes the successful application for the new conventional procedure of 5-dialkylaminomethylhydantoin derivatives and some chemical properties of 5-dialkylaminomethylhydantoins.

The synthetic procedure for the new 5-dialkylaminomethyl substituted hydantoin derivatives (**3**) by using racemic β-aminoalanines (**1**)[8] as starting materials is shown in Scheme 1. The first stage is a nucleophlic

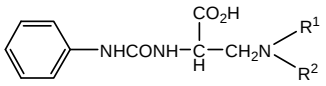


(**1a-e**) (**2a-e**) (**3a-e**)

Scheme 1. Preparation of 5-Dialkylaminomethylhydantoins

addition of free *β*-aminoalanines to phenyl isocyanates to yield *N*-phenylcarbamoyl-*β*-aminoalanines derivatives (**2**). This addition reaction was easily achieved in H_2O. The facile cyclization to the target hydantoins (**3**) also occurred with good yields by treatment of the adducts (**2**) with concentrated HCl at room temperature. The results for the addition products urea derivatives (**2**) and hydantoins (**3**) are summarized in Tables 1 and 2, respectively. For the preparation of hydantoin derivatives (**3**), one-pot synthesis is more conventional than the two-stage procedure (see EXPERIMENTAL).

Table 1. Synthesis of Compounds (2a-e)

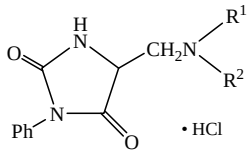


Compd. No	R^1	R^2	Yield (%)	mp (°C)	Formula	FAB-MS $(M+H)^+$	IR(KBr) cm^{-1}	Anal. Found (Calcd)
2a	$-(CH_2)_2-O-(CH_2)_2-$		90	188 (decomp) (H_2O)	$C_{14}H_{19}N_3O_4 \cdot 0.3\ H_2O$	294	3323 1621	56.16 6.43 14.00 (56.29 6.61 14.07)
2b	$-(CH_2)_2-S-(CH_2)_2-$		87	170—173 (EtOH)	$C_{14}H_{19}N_3O_3S$	310	3326 1622	54.13 6.40 13.30 (54.35 6.19 13.58)
2c	$-(CH_2)_4-$		66	202 (decomp) (H_2O)	$C_{14}H_{19}N_3O_3 \cdot 0.2\ H_2O$	278	3335 1624	59.89 7.07 15.03 (59.93 6.97 14.97)
2d	$-(CH_2)_5-$		83	194 (decomp) (C_2H_5OH)	$C_{15}H_{21}N_3O_3$	292	3316 1628	61.75 7.34 14.24 (61.84 7.26 14.42)
2e	Et	Et	59	168—173 (H_2O)	$C_{14}H_{21}N_3O_3$	280	3314 1632	60.06 8.01 8.54 (59.82 8.07 8.83)

The structures of these products were easily confirmed by both the spectroscopic data and elemental analyses. Therefore, characteristic absorption bands at 3314-3337 (urea NH) and 1621-1634 cm^{-1}(urea C=O) were observed in the IR spectra (KBr) for all compounds (**2a-2e**). In the ^{1}H-NMR spectra, all of the observed signals were characteristic of the represented structures (**2a-2e**). All of the IR spectra of the hydantoins (**3a-3e**) showed two distinct hydantoin ring amide C=O absorptions at 1779-1789 and

1704-1725 cm^{-1} (Table 2) and the ^{1}H-NMR data for compounds (**3c-3e**) were consistent with the corresponding hydantoin structures (see EXPERIMENTAL).

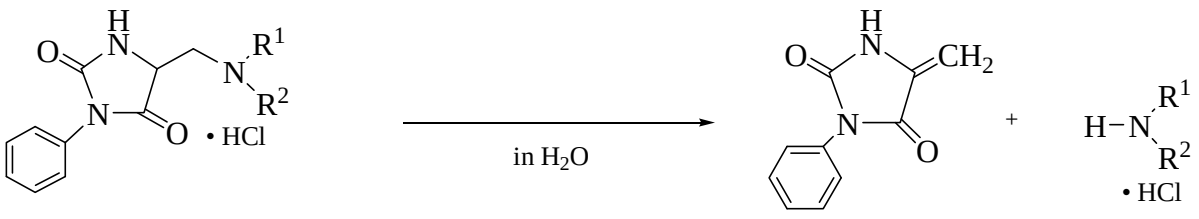
Table 2. Synthesis of New Hydantoin Derivatives (3a-e)



Compd. No	R^1	R^2	Yield (%)	mp (°C)	Formula	FAB-MS $(M+H)^+$	IR(KBr) cm^{-1}	Anal. Found (Calcd)
3a	$-(CH_2)_2-O-(CH_2)_2-$		87	201.5—205 (decomp)	$C_{14}H_{18}N_3O_3Cl$	276	1780 1716	53.90 5.93 13.46 (53.94 5.82 13.48)
3b	$-(CH_2)_2-S-(CH_2)_2-$		85	193.1—196 (decomp)	$C_{14}H_{18}N_3O_2ClS$	292	1779 1704	51.52 5.54 12.76 (51.29 5.53 12.82)
3c	$-(CH_2)_4-$		100	176—179(decomp)	$C_{14}H_{18}N_3O_2Cl$ • 0.1 H_2O	260	1781 1716	56.40 6.26 14.05 (56.85 6.13 14.21)
3d	$-(CH_2)_5-$		94	190.5—193.7 (decomp)	$C_{15}H_{20}N_3O_2Cl$ • 0.1 H_2O	274	1782 1708	57.75 6.41 13.49 (58.16 6.51 13.56)
3e	Et	Et	100	amorphous[a] (hygroscopic)	$C_{14}H_{20}N_3O_2Cl$ • 0.5 H_2O	262	1783 1720	54.89 6.90 13.75 (54.81 6.90 13.70)

a) Hygroscopic amorphous powder.

The 5-dialkylaminomethyl substituted hydantoin (**3**) synthesized in this study showed an interesting chemical behavior. Therefore, the treatment of product hydantoins (**3**) with large excess amount of water yielded easily deaminated 5-methylenehydantoin (**4**).[9] Interestingly, during NMR spectroscopic examination in DMF/H_2O, the compounds (**3a** and **3b**) having a morpholino or thiomorpholino group as a



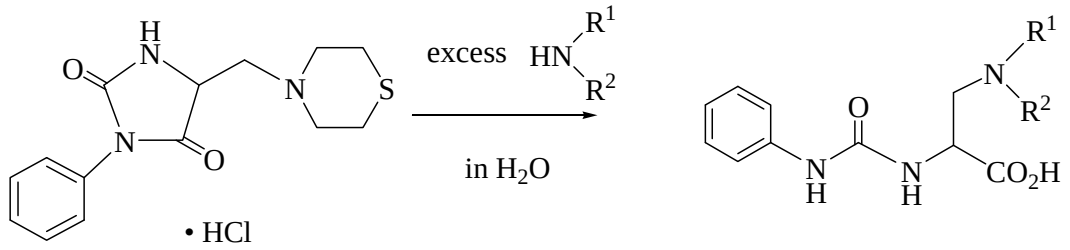
(3a, b) **(4)**

Scheme 2. Elimination of 5-Dialkylaminomethylhydantoin **(3)**

part of dialkylamino functionality were found to be a mixture of 5-methylenehydantoin (**4**) and a corresponding secondary amine (morpholine or thiomorpholine) (see EXPERIMENTAL: Scheme 2). No original 5-substituted hydantoins (**3a** and **3b**) could be detected by NMR analysis. Evaporation of the

solvent yielded the original 5-dialkylmethylamino hydantoin (**3a** and **3b**) quantitatively. On the other hand, after dissolving (**3a**) in excess amounts of H_2O (1 g per 100 mL), filtration of the precipitated crystallized materials produced 5-methylenehydantoin (**4**)[9] with a 73% yield, the structure of which was determined by an elemental analysis and NMR spectroscopic data. The eliminated product (**4**) showed the theoretical integrational values characteristic of two vinyl protons at δ: 4.94 and 5.24 ppm (^{1}H-NMR). In contrast, the compounds (**3c-3e**) having simple 5-dialkylaminomethyl groups at C-5 on hydantoin nucleus were stable in solution (MeOH/DMF or DMSO) at room temperature and no elimination process was observed during the NMR spectroscopy analysis.

Further study of these hydantoin derivatives showed the compound (**3**) to be easily converted to the original urea derivatives. The exchange reaction of a dialkylamine moiety can be also applied to the preparation of **2**. For instance, when the compound (**3b**) was treated with excess of pyrrolidine or piperidine it produced the ring-opened urea derivative (**2c**) or (**2d**) with a 63% or a 53% yield, respectively (Scheme 3).



(3b) **(2c, d)**

Scheme 3

This is the first report of the elimination process (retro-Michael addition observed above) and the reversibility of such process of the 5-dialkylaminomethyl functionality of hydantoin nucleus. On the basis of the characteristic reversible processes of these 5-dialkylaminomethylhydantoins, further investigations on molecular modification of such 5-substituted hydantoin derivatives including 5-methylenehydantoin are currently underway to identify biologically active compounds.

EXPERIMENTAL

The melting points are uncorrected. The IR spectra were measured with a Shimadzu FT/IR-8100 spectrometer. The ^{1}H- and ^{13}C-NMR spectra were obtained on a JEOL JNM A-500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) at 35 °C. The chemical shifts are expressed as δ ppm downfield from an internal tetramethylsilane (TMS) signal. The signal assignments were confirmed with ^{1}H-^{1}H two-dimensional (2D) correlation spectroscopy (COSY), ^{1}H-^{13}C heteronuclear multiple quantum coherence (HMQC),

^{1}H-^{13}C heteronuclear multiple-bond connectivity (HMBC) spectra. FAB-MS spectra were obtained with a JEOL JMS-HX110 mass spectrometer. The following abbreviations in the brackets were used for the morpholine ring (Mor), thiomorpholine ring (Thi), pyrrolidine ring (Pyr), piperidine ring (Ppd) and for hydantoin ring (Hyd), respectively.

General procedure for the preparation of compounds (2a-e)

A solution of a *β*-aminoalanine dihydrochloride (**1**)[8] (0.02 mol) in 10 mL of H_2O was added to 14 mL of aqueous 3*N* sodium hydroxide (0.042 mol). Phenyl isocyanate (0.03 mol) was added to the resulting solution dropwise under vigorous stirring at rt. When half the phenyl isocyanate had been introduced, a second portion of 20 mL of sodium hydroxide (0.06 mol) was added dropwise in order to keep the reaction mixture strongly basic (ca. pH 13) throughout the overall reaction. Next, the reaction mixture was stirred for another 1 h and the resulting mixture was filtered under a reduced pressure. The desired (phenylureido)propanoic acids (**2**) precipitated from the filtrate by addition of ammonium chloride were collected. The physical data and elemental analysis are summarized in Table 1. The ^{1}H-and ^{13}C-NMR spectroscopic data of the isolated products are shown below.

3-Morpholino-2-(3-phenylureido)propanoic acid (2a)

^{1}H-NMR (D_2O) *δ:* 3.18-3.39 (6H, m, Mor H-3, H-5 and C$\underline{H}_2$Ph), 3.94-3.97 (4H, m, Mor H-2, H-6), 4.52-4.58 (1H, m, C$\underline{H}$COOH), 7.18-7.22 (1H, m, *p*-Ar H), 7.34-7.43 (4H, m, *o* and *m*-Ar H). ^{13}C-NMR (D_2O) *δ:* 53.3 (C$\underline{H}$COOH), 55.1 (Mor C-2, C-6), 62.4 (C$\underline{H}_2$-Mor), 67.1 (Mor C-3, C-5), 124.2 (*o*-Ar C), 127.1 (*p*-Ar C), 132.5 (*m*-Ar C), 140.7 (Ar C-1), 160.6 (NHCONH), 178.1 (COOH).

2-(3-Phenylureido)-3-thiomorpholinopropanoic acid (2b)

^{1}H-NMR (D_2O) *δ:* 2.93-3.01 (4H, m, Thi H-2, H-6), 3.28-3.59 (6H, m, Thi H-3, H-5 and C$\underline{H}_2$-Thi), 4.50-4.53 (1H, m, C$\underline{H}$COOH), 7.17-7.22 (1H, m, *p*-Ar H), 7.33-7.61 (4H, m, *o* and *m*-Ar H). ^{13}C-NMR (D_2O) *δ:* 27.9 (Thi C-2, C-6), 51.5 (C$\underline{H}_2$-Thi), 55.7 (Thi C-3, C-5), 60.2 (C$\underline{H}$COOH), 118.5 (*o*-Ar C), 122.0 (*p*-Ar C), 128.6 (*m*-Ar C), 141.3 (Ar C-1), 155.8 (NHCONH), 174.0 (COOH).

2-(3-Phenylureido)-3-(pyrrolidin-1-yl)propanoic acid (2c)

^{1}H-NMR (D_2O) *δ:* 2.09-2.12 (4H, m, Pyr H-3, H-4), 3.45-3.63 (6H, m, Pyr H-2, H-5 and C$\underline{H}_2$-Pyr), 4.49-4.53 (1H, m, C$\underline{H}$COOH), 7.18-7.1 (1H, m, *p*-Ar H), 7.35-7.43 (4H, m, *o* and *m*-Ar H), ^{13}C-NMR (D_2O) *δ:* 25.5 (Pyr C-3, C-4), 54.8 (C$\underline{H}$COOH), 57.6 (Pyr C-2, C-5), 60.0 (C$\underline{H}_2$-Pyr), 124.1 (*o*-Ar C), 127.1 (*p*-Ar C), 132.1 (*m*-Ar C), 140.7 (Ar C-1), 160.4 (NHCONH), 177.8 (COOH).

2-(3-Phenylureido)-3-(piperidin-1-yl)propanoic acid (2d)

^{1}H-NMR (D_2O) *δ:* 1.66 (2H, br s, Ppd H-4), 1.85-1.86 (4H, m, Ppd H-3, H-5), 3.05-3.40 (4H, m, Ppd H-2, H-6), 3.34 (1H, dd, *J* = 13.0, 9.0 Hz, C$\underline{H}$H-Ppd), 3.49 (1H, dd, *J* = 13.0, 5.5 Hz, CH$\underline{H}$-Ppd), 4.56 (1H, dd, *J* = 9.0, 5.5 Hz, C$\underline{H}$COOH), 7.17-7.22 (1H, m, *p*-Ar H), 7.34-7.43 (4H, m, *o* and *m*-Ar H),

^{13}C-NMR (D_2O) *δ:* 24.0 (Ppd C-4), 25.7 (Ppd C-3, C-5), 53.3 (CHCOOH), 56.6 (Ppd C-2, C-6), 61.9 (CH_2-Ppd), 124.2 (*o*-Ar C), 127.1 (*p*-Ar C), 132.1 (*m*-Ar C), 140.6 (Ar C-1), 160.6 (NHCONH), 177.8 (COOH).

3-(Diethylamino)-2-(3-phenylureido)propanoic acid (2e)

^{1}H-NMR (D_2O + DMF-d_7) *δ:* 1.36 (6H, t, *J*= 7.5 Hz, CH_2CH_3 x 2), 3.22 [1H, dd, *J* = 12.5, 9.0 Hz, CHHN$(Et)_2$], 3.36 (4H, ddd, *J* = 7.5, 6.0, 1.0 Hz, CH_2CH_3 x 2), 3.46 [1H, dd, *J* = 12.5, 6.0 Hz, CHHN$(Et)_2$], 4.25 (1H, dd, *J* = 9.0, 6.0 Hz, CHCOOH), 6.94-6.98 (1H, m, *p*-Ar H), 7.26-7.29 (2H, m, *m*-Ar H), 7.53-7.55 (2H, m, *o*-Ar H). ^{13}C-NMR (D_2O + DMF-d_7) *δ:* 9.43 (CH_2CH_3 x 2), 48.2 (CH_2CH_3 x 2), 49.9 (CHCOOH), 55.4 [$CH_2N(Et)_2$], 118.6 (*o*-Ar C), 122.3 (*p*-Ar C), 129.3 (*m*-Ar C), 141.1 (Ar C-1), 156.8 (NHCONH), 172.7 (COOH).

General procedure for the preparation of 5-(dialkylaminomethyl)imidazolidine -2,4-dione (3a-e)

A solution of (phenylureido)propanoic acid (**2**) (1.0 mmol) in concentrated hydrochloric acid (5 mL) was allowed to stand at rt for 1 to 2 d. Evaporation of the solvent gave a compound (**3c-e**). In case of (**3a**) and (**3b**), a crystalline precipitate was separated from the solution. The physical data and the findings of an elemental analysis are summarized in Table 2.

5-(Morpholinomethyl)-3-phenylimidazolidine-2,4-dione hydrochloride (3a)

^{1}H-NMR (D_2O + DMF-d_7) *δ:* 3.31-3.33 (4H, m, Mor H-2, H-6), 3.96-3.98 (4H, m, Mor H-3, H-5), 5.27 (1H, d, *J* = 2.0 Hz, 5-methylenehydantoin =CHH), 5.53 (1H, d, *J* = 2.0 Hz, 5-methylenehydantoin =CHH), 7.42-7.54 (3H, m, Ar H-3, H-4, H-5), 7.58-7.61 (2H, m, Ar H-2, H-6). ^{13}C-NMR (D_2O + DMF-d_7) *δ:* 45.9 (Mor C-3, C-5), 66.3 (Mor C-2, C-6), 100.7 (5-methylenehydantoin =CHH), 129.3 (Ar C-2, C-6), 131.6 (Ar C-4), 132.0 (Ar C-3, C-5), 133.5 (Ar C-1), 136.7 (Hyd C-5), 157.0 (Hyd C-2), 166.2 (Hyd C-4).

3-Phenyl-5-(thiomorpholinomethyl)imidazolidine-2,4-dione hydrochloride (3b)

The NMR spectroscopic data (in D_2O) of this compound also showed a mixture of methylenehydantoin and thiomorpholine hydrochloride.

3-Phenyl-5-(pyrrolidin-1-ylmethyl)imidazolidine-2,4-dione hydrochloride (3c)

^{1}H-NMR (CD_3OD+DMF-d_7) *δ:* 2.10, 2.20 (each 2H, br s, Pyr H-3, H-4), 3.29-3.30 (2H, br, Pyr H-2, H-5), 3.73-3.77 (1H, m, CHHN=), 3.81-3.82 (1H, m, CHHN=), 3.84-3.85 (2H, br, Pyr H-2, H-5), 4.82-4.84 (1H, m, $CHCH_2N$=), 7.40-7.43 (3H, m, Ar H-3, H-4, H-5), 7.47-7.51 (2H, m, Ar H-2, H-6). ^{13}C-NMR (CD_3OD+DMF-d_7) *δ:* 23.9, 24.2 (Pyr C-3, C-4), 55.1 ($CHCH_2N$=), 56.5 ($CHCH_2N$=), 56.6 (Pyr C-2, C-5), 127.7 (Ar C-2, C-6), 129.4 (Ar C-4), 130.0 (Ar C-3, C-5), 133.2 (Ar C-1), 157.6 (Hyd C-2), 171.8 (Hyd C-4).

3-Phenyl-5-(piperidin-1-ylmethyl)imidazolidine-2,4-dione hydrochloride (3d)

^{1}H-NMR (DMSO-d_6) *δ:* 1.41 (1H, br, Ppd H-4), 1.72-1.74 (1H, m, Ppd H-4), 1.83 (4H, br, Ppd H-3, H-5),

2.99-3.03 (2H, m, Ppd H-2, H-6), 3.45-3.64 (4H, m, Ppd H-2, H-6, and C$\underline{H}_2$N=), 4.94 (1H, s, C$\underline{H}$CH$_2$N=), 7.36-7.42 (3H, m, Ar H-3, H-4, H-5), 7.47-7.51 (2H, m, Ar H-2, H-6), 8.78 (1H, s, N$\underline{H}$). ^{13}C-NMR (DMSO-d_6) δ: 21.0, 22.2, 22.3 (Ppd C-3, C-4, C-5), 52.1, 53.5 (Ppd C-2, C-6), 52.3 ($\underline{C}$HCH$_2$N=), 57.9 (CH$\underline{C}$H$_2$N=), 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), 170.2 (Hyd C-4).

5-{(Diethylamino)methyl}-3-phenylimidazolidine-2,4-dione hydrochloride (3e)

^{1}H-NMR (DMSO-d_6) δ: 1.27-1.30 [6H, m, N(CH$_2$C$\underline{H}_3$)$_2$], 3.29-3.34 [4H, m, N(C$\underline{H}_2$C$\underline{H}_3$)$_2$], 3.47-3.51 (1H, m, C$\underline{H}$HN=), 3.59-3.64 (1H, m, CH$\underline{H}$N=), 4.90 (1H, d, J = 8.5 Hz, C$\underline{H}$CH$_2$N=), 7.37-7.42 (3H, m, Ar H-3, H-4, H-5), 7.48-7.51 (2H, m, Ar H-2, H-6), 8.74 (1H, s, N$\underline{H}$), 10.66 (1H, br, NH$^+$). ^{13}C-NMR (DMSO-d_6) δ: 8.3, 8.4 [N(CH$_2$$\underline{C}H_3$)$_2$], 46.9, 47.5 [N($\underline{C}H_2CH_3$)$_2$], 52.4 ($\underline{C}HCH_2$N=), 52.9 ($\underline{C}H_2$N=), 126.6 (Ar C-2, C-6), 127.9 (Ar C-4), 128.7 (Ar C-3, C-5), 131.8 (Ar C-1), 155.2 (Hyd C-2), 170.2 (Hyd C-4).

5-Methylene-3-phenylimidazolidine-2,4-dione (4).

(Method A)

A solution of (**3a**) (1g, 3.21 mmol) in water (ca. 100 mL) was heated in a water bath and allowed to stand at rt for 6 h. Filtration of the precipitated material gave 0.32 g (53%) of **4**. Two further filtrations of the precipitate from the mother liquors at intervals of 24 h afforded an additional 0.12 g (20%) of the product (**4**). The total yield was 73 %, mp >255 °C (decomp).[9a] IR (KBr) cm^{-1}: 1773, 1715, 1669. FAB-MS (positive) *m/z*: 189 (M+H$^+$). ^{1}H-NMR (DMSO-d_6) δ: 4.93 (1H, d, J = 1.5 Hz, =C$\underline{H}$H), 5.24 (1H, d, J = 1.5 Hz, =CH$\underline{H}$), 7.40-7.42 (3H, m, Ar H-3, H-4, H-5), 7.47-7.50 (2H, m, Ar H-2, H-6), 10.8 (1H, br, N$\underline{H}$). ^{13}C-NMR (DMSO-d_6) δ: 94.6 (=CH$_2$), 126.6 (Ar C-2, C-6), 127.9 (Ar C-4), 128.7 (Ar C-3, C-5), 131.6 (Ar C-1), 134.9 (Hyd C-5), 152.9 (Hyd C-2), 161.9 (Hyd C-4). *Anal*. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found. C, 63.74; H, 4.41; N, 14.87.

(Method B)

A solution of (**3a**) (1g, 3.21 mmol) in water (ca. 30 mL) was extracted continuously for 3 h with AcOEt. Concentration of the solvent yielded 0.49 g (82%) of **4**, mp 200 °C (decomp).[9b] The spectroscopic data (IR, FAB-MS and NMR) were identical with those of the compound obtained by Method A. *Anal*. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found. C, 63.68; H, 4.37; N, 14.89.

One-pot synthesis of compound (3a)

A solution of amino acid dihydrochloride (**1a**) (5 g, 0.02 mol) in 10 mL of H_2O was combined with 14 mL of aqueous 3*N* sodium hydroxide (0.042 mol). Phenyl isocyanate (3.6 g, 0.03 mol) was added dropwise to the resulting solution with vigorous stirring at rt. When half the phenyl isocyanate had been introduced, a second portion of 20 mL of sodium hydroxide (0.06 mol) was added dropwise to keep the reaction mixture strongly basic (ca. pH 13). After the addition of phenyl isocyanate, the mixture was stirred for another 1 h and then filtered under reduced pressure. The filtrate was neutralized (pH 7) by the

addition of 20% hydrochloric acid and concentrated *in vacuo*. The residue was combined with concentrated hydrochloric acid (80 mL) and the insoluble by-product was removed by filtration under reduced pressure. The filtrate was allowed to stand for 1 d and the precipitated material (**3a**) was collected by filtration. The yield was 75%.

Conversion of 5-thiomorpholinomethylhydantoin derivative (3b) to ureido derivative (2c)

A solution of thiomorpholine-hydantoin (**3b**) (0.3 g, 0.963 mmol) in H_2O (30 mL) was heated on a water bath for 5 min. To this solution pyrrolidine (1.2 mL) was added and the mixture was stirred for 3 min. After concentration of the solvent, the residue was washed with Et_2O. The residue was combined with H_2O and the insoluble material was collected by filtration to give **2c** (0.03 g). After the concentration of the filtrate *in vacuo,* the crystallized product **2c** (0.13 g) was then obtained by addition of a small amount of MeOH (63%). The compound (**2d**) was also obtained from the reaction of piperidine with the compound (**3b**) in 53% yield.

REFERENCES

1. O. Ninoslav, B. Monika, Z. Branka, C. Mario, N. Ante, F. Danijel, K. Marijeta, P. Kresimir, B. Jan, A. Graciela, S. Robert, C. De Erik, R-M. Silvana, and M. Mladen, *J. Med. Chem.*, 2005, **48**, 475.
2. X. Zhang, G. F. Allan, T. Sbriscia, O. Linton, S. G. Lundeen, and Z. Sui, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5763.
3. F. Balavoine, P. Malabre, T. Alleaume, A. Rey, V. Cherfils, O. Jeanneton, S. Seigneurin-Venin, and F. Revah, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3754.
4. L. G. Hamann, M. C. Manfredi, C. Sun, S. R. Krystek, Jr., Y. Huang, Y. Bi, D. J. Augeri, T. Wang, Y. Zou, D. A. Betebenner, A. Fura, R. Seethala, R. Golla, J. E. Kuhns, J. A. Lupisella, C. J. Darienzo, L. L. Custer, J. L. Price, J. M. Johnson, S. A. Biller, R. Zahler, and J. Ostrowski, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1860.
5. F. Fujisaki, M. Oishi, and K. Sumoto, *Chem. Pharm. Bull*., 2007, **55**, 124.
6. F. Fujisaki, N. Abe, and K. Sumoto, *Chem. Pharm. Bull*., 2004, **52**, 1238.
7. F. Fujisaki, N. Abe, and K. Sumoto, *Chem. Pharm. Bull*., 2002, **50**, 129.
8. N. Abe, F. Fujisaki, and K. Sumoto, *Chem. Pharm. Bull*., 1998, **46**, 142.
9. a) M. Bergmann and D. Delis, *Ann.*, 1927, **458**, 76. b) S. Murahashi, H. Yuki, K. Kosai, and F. Doura, *Bull. Chem., Soc. Japan*, 1966, **39**, 1563.