One-Step Synthesis of 3-Amino-2,4-imidazolinediones (3-Aminohydantoins) From α-Amino Acids

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α-Amino acids melted with ethyl or *t*-butyl carbazate or, preferably, refluxed with *t*-butyl carbazate in quinoline gave high yields of 3-amino-2,4-imidazolidinediones (3-aminohydantoins).

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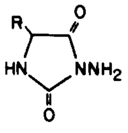
Recently, the structure assignment of hexahydro-1,2,4-triazine-3,6-diones (**3**), isomeric with 3-amino-2,4-imidazolidinediones (3-aminohydantoins) (**2**) has come under question [1-3]. It has been shown [2,3] that hexahydro-1,2,4-triazine-3,6-dione (**3**) prepared by the reaction of phenylthiocarbonylglycine carbobenzoxyhydrazide with lead acetate in ethanol as reported by Lindemann, *et al.* [4] was in fact 3-amino-2,4-imidazolidinedione (**2**). Similarly, the cyclization product of ethyl semicarbazinoacetate with sodium ethoxide [5] was found to be **2** rather than **3**.



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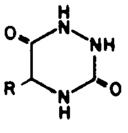

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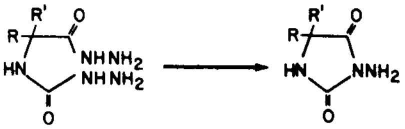
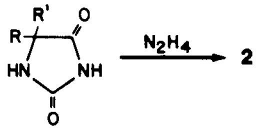
5-Substituted and 5,5-disubstituted 3-aminohydantoins **2** were prepared in a multi-step reaction by heating solutions of *N*-carboxy-α-amino acid dihydrazides **1** in water [5], alcohol [6] or dimethyl formamide [8].



1 **2**

Another reported synthesis of compounds **2** restricted to 5,5-disubstituted series is the reaction of refluxing hydrazine hydrate and 5,5-disubstituted hydantoins (**4**) [7].



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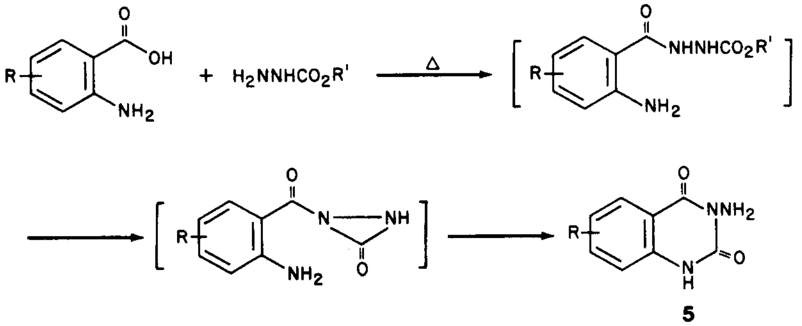
The ring contraction of 1,2,4-triazin-5-ones to imidazolin-2-ones by the reaction of hydroxylamino-*O*-sulfonic acid and to 1,2,3-triazoles by the reaction of chloramine was studied by Rees and Sales [9]. However, the proposed mechanisms of these ring transformations are not applicable to compound **3**. In fact, the alleged hexahydro-1,2,4-triazine-3,6-diones **3** [10] was reassigned to 3-amino-2,4-imidazolidinediones **2**. This is supported by rapid deamination of compounds **2** to the well-established 2,4-imidazolidinediones **4** under mild conditions [6a].

We have recently reported [11] that *ortho* amino acids react with ethyl or *t*-butyl carbazate in refluxing quinoline to give the corresponding 3-amino-2,4(1*H*,3*H*)-quinazolinediones (**5**). The proposed mechanism of this reaction is outlined in Scheme I.

Continuing our interest in using natural products for the synthesis of heterocyclic compounds [12-15], we now report a one-step synthesis of 3-amino-2,4-imidazolidinediones (3-aminohydantoins) **2** from α-amino acids. Mixtures of phenylalanine or tyrosine and *t*-butyl carbazate were heated for a short time at melt or reflux to give high yields of **2** rather than the isomeric hexahydro-1,2,4-triazine-3,6-diones **3** (Method A) (See Scheme II).

The yields were moderate or low with non-aromatic α-amino acids. However, using quinoline at reflux as the re-

Scheme I



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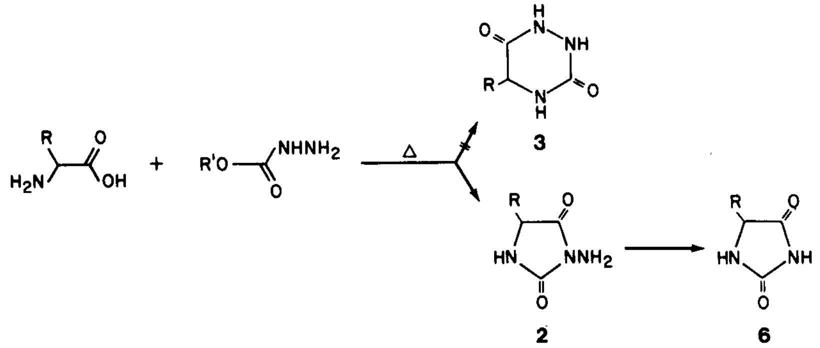
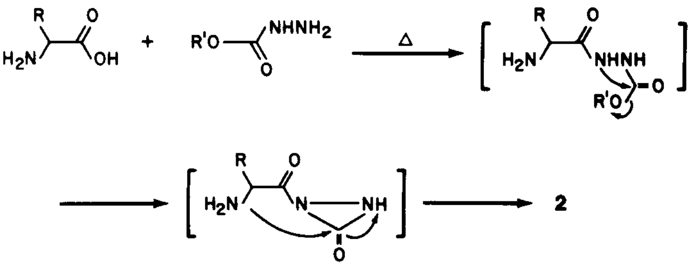
Scheme II



action solvent, good yields of compounds **2** were obtained (Method B). In the case of glycine, a mixture of unidentified compounds along with 22% unsubstituted **2** was obtained.

Substitution of quinoline by undecane, benzyl alcohol or dimethylformamide resulted in the formation of only small or trace amounts of **2**.

Scheme III



The structure assignment of the compounds **2** was based on comparison with known derivatives prepared by alternative methods [4,5,8] through infrared spectroscopy. The compounds were also deaminated with nitrous acid to the corresponding well-known hydantoins **4** [6a].

All optically active α-amino acids used led to the formation of racemized 3-aminoimidazolidinediones **2**. Racemization may be attributed to the nucleophilicity of carbazate and quinoline at elevated reaction temperature.

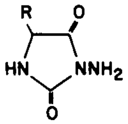
A possible mechanism for this reaction is described (See Scheme III).

EXPERIMENTAL

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-9 instrument. Specific rotations were measured using a Rudolph Photoelectric Polarimeter Model 200.

Table I

3-Amino-2,4-imidazolidinediones



Compound	R	Mp °C	Yield %	Method (hours)	Formula	C %		H %		N %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
1	H	195-198 [a]	22	B (7)	$C_3H_5N_3O_2$	31.30	31.22	4.37	4.50	36.41	36.41
2	CH_3	133-134 [b]	40	B (3)	$C_4H_7N_3O_2$	37.20	37.31	5.46	5.41	32.53	32.60
			5	A (10)							
3	C_2H_5	102-104	56	B (24)	$C_5H_9N_3O_2$	41.95	42.05	6.33	6.11	29.37	29.29
4	C_3H_7	123-125	86	B (6)	$C_6H_{11}N_3O_2$	45.85	45.95	7.05	6.89	26.73	26.81
5	C_4H_9	137-138	66	B (6)	$C_7H_{13}N_3O_2$	49.11	49.19	7.63	7.62	24.54	24.55
6	$(CH_3)_2CH$	144-145 [c]	51	B (6)	$C_6H_{11}N_3O_2$	45.85	46.09	7.05	7.11	26.73	26.60
			2	A (2)							
7	$(CH_3)_2CH_2CH$	150-152 [d]	58	B (10)	$C_7H_{13}N_3O_2$	49.11	49.41	7.63	7.59	24.54	24.75
8	$C_6H_5CH_2$	204-205 [e]	96	B (4)	$C_{10}H_{11}N_3O_2$	58.52	58.52	5.40	5.30	20.47	20.29
			88	A (0.25)							
9	*p*-$HOC_6H_4CH_2$	215-216 [f]	82	B (3)	$C_{10}H_{11}N_3O_3$	54.29	54.31	5.01	4.79	18.99	19.09
			63	A (4)							

A, No solvent, B, In quinoline. [a] Ref [8] 195-196°. [b] Ref [8] 133-135°. [c] Ref [8] 140-141.5°. [d] Ref [6b] 150-153. [e] Ref [6b] 205-206. [f] Ref [8] 212-214°.

5-(4-Benzyl)-3-amino-2,4-imidazolidinedione (**8**). Method A.

A mixture of 825 mg (5 mmoles) of L-phenylalanine and 1.045 g (10 mmoles) of ethyl carbazate heated on a hot plate to melt and kept 15 minutes at the melt temperature. After cooling, the solid mass was recrystallized twice from 2-propanol containing 20% water giving 900 mg (88%) of **8**.

Identical results were obtained when ethyl carbazate was substituted by *t*-butyl carbazate.

Method B.

A solution of 660 mg (4 mmoles) of L-phenylalanine and 665 mg (5 mmoles) of *t*-butyl carbazate in 7.5 ml redistilled quinoline was refluxed for four hours. After cooling, 10 ml of ether and 30 ml of hexane were added and the almost pure crystals were filtered and recrystallized from 2-propanol-water to give 787 mg (96%) of **8**.

All other compounds **2** were prepared similarly.

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