Ring Transformations of 1,3,4-Oxadiazol-2(3*H*)-one Derivatives into 1-Amino and 1,3-Diamino-2,4-imidazolidinedione (Hydantoin) Derivatives

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Some ethyl 5-aryl(or benzyl)-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetates were prepared and treated with ammonia, primary amines or hydrazine to give 1-amino-2,4-imidazolidinedione or 1,3-diamino-2,4-imidazolidinedione derivatives. The 1,3-bis(benzylideneamino)-2,4-imidazolidinedione was obtained by reacting ethyl bromoacetate with the 1,5-dibenzylidenecarbonohydrazide sodium salt.

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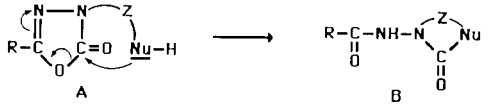
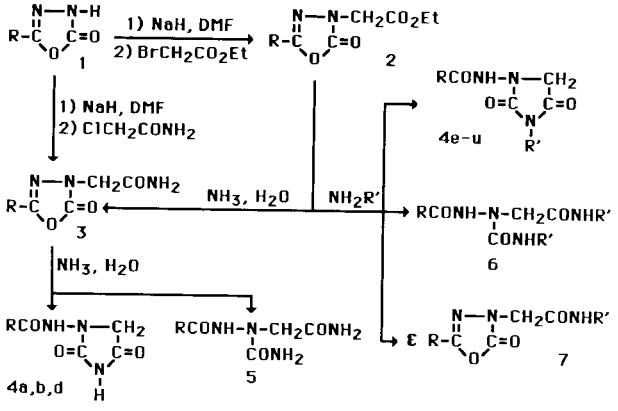
The ring opening ability of 3-unsubstituted 1,3,4-oxadiazol-2(3*H*)-ones **1** towards various nucleophiles (water [1], alcohols [1], ammonia [1-4], primary and secondary amines [1-7] and hydrazines [1,2,8,9]) gave semicarbazides, carbonohydrazides and heterocyclic compounds.

In a recent paper, we reported the ring transformation of 5-aryl-3-carbazoyl-1,3,4-oxadiazol-2(3*H*)-ones into 4-benzamido-1,2,4-triazolidine-3,5-diones [10]. Other 3-substituted 1,3,4-oxadiazol-2(3*H*)-one derivatives of general structure **A** could be used to prepare various heterocyclic compounds of the general formula **B** by a general intramolecular reaction pathway (Scheme 1). "Z" represents a chain of 2 or 3 carbon or heteroelement units. The nucleophilic center NuH could be obtained by *N*-alkylation of oxadiazolone **1** or formed as an intermediate in a reaction of a functionalized N-3 substitutent with a nucleophilic reagent.

Scheme 1



Scheme 2



In this second report, we describe reactions of ethyl 5-aryl(or benzyl)-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetates **2** with ammonia, primary amines (Scheme 2) or hydrazine (Scheme 4). Esters **2** were obtained in good yields (Table I) by treatment of oxadiazolones **1** with sodium hydride in dry dimethylformamide, followed by ethyl bromoacetate.

When esters **2** were allowed to react for some hours in the presence of an aqueous ammonia solution at room temperature, amides **3** were predominantly formed (Table I) besides the corresponding hydantoins **4a,b** or **d** except for compound **2c** (R = 4-chlorophenyl) which gave **4c** (Table II) in one step. When the reaction time was as long as a day, amides **3** were transformed into 1-acylamino-2,4-imidazolidinediones **4a,b,d** in good yields. Besides these compounds, greasy by-products (probably semicarbazides **5**) were present but were not isolated. Amides **3** were identical to compounds synthesized by alkylation of oxadiazolone **1** sodium salts with chloroacetamide.

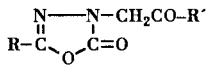
As expected, esters **2** also reacted with primary alkylamines and benzylamine. The reaction gave 1-acylamino-3-alkyl(or benzyl)-2,4-imidazolidinediones **4e-u**, 1,2,4-trisubstituted semicarbazides **6** and amides **7**. The amine/ester molar ratio was an important parameter with pure amine (propylamine, butylamine,...) to obtain only compounds **4** or **6** in refluxing methanol. Amides **7** were often present in traces in the reaction mixture, except for the reaction with **2c**. At a 4:1 molar ratio, hydantoins **4** were predominantly formed besides some quantity of **6**. When the molar ratio was higher than 6:1, compounds **6** were exclusively present.

With aqueous methylamine or ethylamine solutions and at a 6:1 amine/ester molar ratio, the corresponding hydantoins **4** were obtained at room temperature when the reaction mixture was stirred in methanol for 12 hours.

With ammonia or primary amines, the reaction mechanism could proceed *via* a nucleophilic attack of the NH_2 amino group on the ester carbonyl group with amide **3** or **7** formation. A subsequent nucleophilic attack of the NH amido group on the cyclic carbonyl group with oxadiazolone ring opening could convert to hydantoin **4** formation.

Table I

1,3,4-Oxadiazol-2-one Derivatives 2,3,7

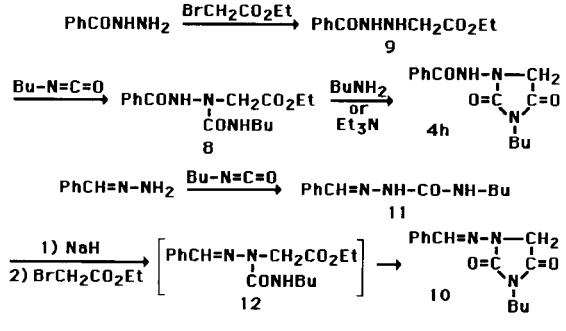


No.	R	R′	Yield % [a]	Mp °C	Formula	Analyses, % Calcd./Found C	H	N	IR, ν cm^{-1}	^{1}H NMR [b] δ ppm
2a	Ph	OEt	72	91 [c]	$C_{12}H_{12}N_2O_4$ (248.23)	58.06	4.87	11.29	1780, 1740, 1610	1.2 (t, 3H), 4.2 (q, 2H), 4.75 (s, 2H) 7.5-7.95 (m, 5H)
						58.01	4.89	11.32		
2b	4-MePh	OEt	66	140 [d]	$C_{13}H_{14}N_2O_4$ (262.26)	59.53	5.38	10.68	1790, 1740, 1610	1.2 (t, 3H), 2.35 (s, 3H), 4.2 (q, 2H), 4.7 (s, 2H), 7.4 and 7.75 (2d, 4H)
						59.61	5.35	10.71		
2c	4-ClPh	OEt	78	132 [e]	$C_{12}H_{11}ClN_2O_4$ (282.67)	50.98	3.92	9.91	1795, 1740, 1610	1.2 (t, 3H), 4.2 (q, 2H), 4.75 (s, 2H) 7.65 and 7.85 (2d, 4H)
						51.07	3.87	9.95		
2d	Ph-CH_2	OEt	86	43 [d]	$C_{13}H_{14}N_2O_4$ (262.26)	59.53	5.38	10.68	1780, 1740, 1630	1.15 (t, 3H), 4 (s, 2H), 4.15 (q, 2H), 4.6 (s, 2H), 7.35 (s, 5H)
						59.45	5.42	10.70		
3a	Ph	NH_2	61 [f] 55 [i]	243 [g,h]	$C_{10}H_9N_3O_3$ (219.19)	54.79	4.14	19.17	3400, 3320, 3160 1760, 1685	4.4 (s, 2H), 7.45 (bs, 2H), 7.5-8 (m, 5H)
						54.84	4.11	19.21		
3b	4-MePh	NH_2	57 [f] 35 [i]	259 [e,j]	$C_{11}H_{11}N_3O_3$ (233.22)	56.65	4.75	18.02	3410, 3300, 3200 1760, 1680	2.35 (s, 3H), 4.35 (s, 2H), 7.5-7.8 (m, 6H)
						56.72	4.76	17.96		
3d	Ph-CH_2	NH_2	55	140 [g]	$C_{11}H_{11}N_3O_3$ (233.22)	56.65	4.75	18.02	3390, 3290, 3190 1775, 1690	3.95 (s, 2H), 4.25 (s, 2H), 7.1-7.75 (m, 7H)
						56.56	4.79	18.00		
7a	Ph	NHMe	[k]	200 [d]	$C_{11}H_{11}N_3O_3$ (233.22)	56.65	4.75	18.02	3310, 1780, 1655	2.6 (d, 3H), 4.4 (s, 2H), 7.5-7.95 (m, 5H), 8.15 (q, 1H)
						56.58	4.73	18.06		
7b	4-MePh	NHMe	[k]	214 [d]	$C_{12}H_{13}N_3O_3$ (247.25)	58.29	5.30	17.00	3300, 1785, 1660	2.35 (s, 3H), 2.6 (d, 3H), 4.4 (s, 2H), 7.35 and 7.7 (2d, 4H), 8.15 (q, 1H)
						58.34	5.27	17.05		
7c	4-MePh	NHEt	[k]	234 [d]	$C_{13}H_{15}N_3O_3$ (261.27)	59.76	5.79	16.08	3295, 1785, 1660	1 (t, 3H), 2.4 (s, 3H), 3.2 (q, 2H), 4.4 (s, 2H), 7.4 and 7.7 (2d, 4H), 8.2 (t, 1H)
						59.66	5.76	16.07		
7d	4-ClPh	NHEt	[k]	230 [d]	$C_{12}H_{12}ClN_3O_3$ (281.69)	51.16	4.29	14.92	3305, 1790, 1655	1.05 (t, 3H), 3.15 (q, 2H), 4.4 (s, 2H), 7.65 and 7.85 (2d, 4H), 8.2 (t, 1H)
						51.12	4.32	14.97		

[a] Non optimized yields. [b] In DMSO-d_6. [c] 1-Butanol. [d] 1-Propanol, [e] Ethanol. [f] Obtained with *N*-alkylation of oxadiazolone. [g] Ethyl acetate. [h] Petroleum ether 40-60. [i] Obtained by reacting **2a** with ammonia. [j] Water. [k] Obtained in traces.

However, compound **8** (Scheme 3), which could be another intermediate of the ring opening in the reaction of **2a** with butylamine and was prepared by treatment of ethyl 2-benzoylhydrazinoacetate (**9**) with butyl isocyanate, was easily cyclized into hydantoin **4h** at room temperature in a few minutes under the experimental conditions of formation of hydantoin **4h** from ester **2a**. Compound **8** was also cyclized into **4h** in the presence of triethylamine (pK_α = 11) with heating but no cyclization occurred in the presence of pyridine (pK_α = 5.2).

Scheme 3



A method similar to that used to obtain 1-amino-3-arylhydantoins [11,12] was also employed to prepare in one step hydantoin **10** by reacting ethyl bromoacetate with the sodium salt of the benzaldehyde 4-butylsemicarbazone (**11**). The intermediate **12**, similar to compound **8**, was not isolated. These results show a second possible way for the reaction mechanism of esters **2** with amines by, at first, nucleophilic attack at the cyclic carbonyl group.

Scheme 4

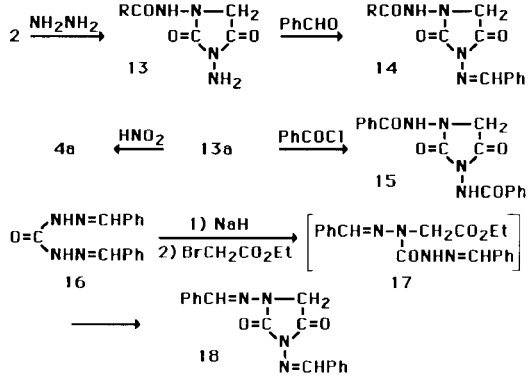
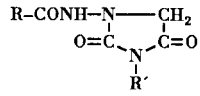


Table II

2,4-Imidazolidinedione Derivatives **4,13,14,15**



No.	R	R′	Yield % [a]	Mp °C	Formula	Analyses, % Calcd./Found C H N	IR, ν cm^{-1}	^{1}H NMR [b] δ ppm
4a	Ph	H	85	238 [c,d]	$C_{10}H_9N_3O_3$ (219.19)	54.79 4.14 19.17 54.63 4.11 19.24	3240, 3150, 1800, 1720, 1645	4.2 (s, 2H), 7.5-8.1 (m, 5H), 10.9 (bs, 2H)
4b	4-MePh	H	62	264 [c,d]	$C_{11}H_{11}N_3O_3$ (233.22)	56.65 4.75 18.02 56.55 4.74 18.08	3320, 3210, 1790 1720, 1685	2.35 (s, 3H), 4.15 (s, 2H), 7.35 and 7.8 (2d, 4H), 10.8 (bs, 1H), 11.7 (bs, 1H)
4c	4-ClPh	H	82	258 [c,d]	$C_{10}H_8ClN_3O_3$ (253.64)	47.35 3.18 16.57 47.22 3.20 16.65	3310, 3200, 1780, 1720, 1685	4.15 (s, 2H), 7.6 and 7.95 (2d, 4H), 11.1 (bs, 2H)
4d	$PhCH_2$	H	35	158 [d]	$C_{11}H_{11}N_3O_3$ (233.22)	56.65 4.75 18.02 56.75 4.71 18.05	3275, 3200, 1795, 1745, 1660	3.5 (s, 2H), 4.05 (s, 2H), 7.3 (s, 5H), 10.4 (bs, 1H), 11.1 (bs, 1H)
4e	Ph	Me	41	194 [c,d]	$C_{11}H_{11}N_3O_3$ (233.22)	56.65 4.75 18.02 56.57 4.79 18.07	3300, 1780, 1700, 1655	2.95 (s, 3H), 4.2 (s, 2H), 7.45-8.05 (m, 5H), 11 (s, 1H)
4f	Ph	Et	43	143 [c,d]	$C_{12}H_{13}N_3O_3$ (247.25)	58.29 5.30 17.00 58.26 5.27 17.06	3320, 1790, 1715, 1670	1.1 (t, 3H), 3.5 (q, 2H), 4.2 (s, 2H), 7.5-8 (m, 5H), 10.95 (s, 1H)
4g	Ph	Pr	55	162 [c,d]	$C_{13}H_{15}N_3O_3$ (261.27)	59.76 5.79 16.08 59.80 5.77 16.04	3320, 1785, 1720, 1670	0.85 (t, 3H), 1.35-1.75 (m, 2H), 3.45 (t, 2H), 4.25 (s, 2H), 7.4-8 (m, 5H), 11 (s, 1H)
4h	Ph	Bu	53	125 [c,d]	$C_{14}H_{17}N_3O_3$ (275.30)	61.08 6.22 15.26 61.17 6.18 15.30	3290, 1785, 1715, 1670	0.85 (t, 3H), 1.05-1.65 (m, 4H), 3.45 (t, 2H), 4.2 (s, 2H), 7.4-8 (m, 5H), 10.95 (s, 1H)
4i	Ph	iBu	43	134 [c,d]	$C_{14}H_{17}N_3O_3$ (275.30)	61.08 6.22 15.26 61.00 6.25 15.28	3290, 1790, 1720, 1645	0.85 (d, 6H), 1.8-2.2 (m, 1H), 3.3 (d, 2H), 4.25 (s, 2H), 7.4-8 (m, 5H), 11 (s, 1H)
4j	Ph	CH_2Ph	50	140 [c,d]	$C_{17}H_{15}N_3O_3$ (309.31)	66.01 4.89 13.59 66.11 4.86 13.64	3300, 1790, 1710 1670	4.3 (s, 2H), 4.65 (s, 2H), 7.35 (s, 5H), 7.45-8 (m, 5H), 11 (bs, 1H)
4k	4-MePh	Me	40	206 [c,d]	$C_{12}H_{13}N_3O_3$ (274.25)	58.29 5.30 17.00 58.40 5.27 17.06	3260, 1780, 1710, 1655	2.35 (s, 3H), 2.95 (s, 3H), 4.2 (s, 2H), 7.35 and 7.85 (2d, 4H), 10.9 (s, 1H)
4l	4-MePh	Et	66	161 [c,d]	$C_{13}H_{15}N_3O_3$ (261.27)	59.76 5.79 16.08 59.65 5.82 16.04	3280, 1780, 1710, 1660	1.1 (t, 3H), 2.35 (s, 3H), 3.5 (q, 2H), 4.2 (s, 2H), 7.35 and 7.8 (2d, 4H), 10.9 (s, 1H)
4m	4-MePh	Pr	71	186 [c,d]	$C_{14}H_{17}N_3O_3$ (275.30)	61.08 6.22 15.26 60.96 6.26 15.32	3300, 1780, 1715, 1660	0.85 (t, 3H), 1.3-1.7 (m, 2H), 2.35 (s, 3H), 3.4 (t, 2H), 4.2 (s, 2H), 7.3 and 7.8 (2d, 4H), 10.9 (s, 1H)
4n	4-MePh	Bu	50	148 [c.d]	$C_{15}H_{19}N_3O_3$ (289.32)	62.27 6.62 14.52 62.27 6.59 14.59	3290, 1785, 1710, 1660	0.9 (t, 3H), 1.05-1.65 (m, 4H), 2.35 (s, 3H), 3.45 (t, 2H), 4.2 (s, 2H), 7.35 and 7.8 (2d, 4H), 10.9 (s, 1H)
4o	4-ClPh	Me	76	200 [c,d]	$C_{11}H_{10}ClN_3O_3$ (267.66)	49.36 3.77 15.70 49.28 3.79 15.75	3260, 1785, 1710, 1660	2.95 (s, 3H), 4.2 (s, 2H), 7.65 and 7.95 (2d, 4H), 11 (bs, 1H)
4p	4-ClPh	Et	63	190 [c,d]	$C_{12}H_{12}ClN_3O_3$ (281.69)	51.16 4.29 14.92 51.29 4.26 14.94	3265, 1785, 1705, 1660	1.1 (t, 3H), 3.5 (q, 2H), 4.2 (s, 2H), 7.65 and 7.95 (2d, 4H), 11.1 (s, 1H)
4q	4-ClPh	Pr	40	166 [c,d]	$C_{13}H_{14}ClN_3O_3$ (295,71)	52.80 4.77 14.21 52.73 4.78 14.24	3280, 1790, 1710 1660	0.9 (t, 3H), 1.4-1.9 (m, 2H), 3.45 (t, 2H), 4.25 (s, 2H), 7.65 and 7.95 (2d, 4H), 11.05 (s, 1H)
4r	4-ClPh	Bu	55	175 [c,d]	$C_{14}H_{16}ClN_3O_3$ (309.74)	54.28 5.21 13.57 54.20 5.25 13.54	3280, 1790, 1710, 1660	0.9 (t, 3H), 1-1.7 (m, 4H), 3.5 (t, 2H), 4.2 (s, 2H), 7.6 and 7.9 (2d, 4H), 11 (s, 1H)
4s	$PhCH_2$	Me	21	139 [e,f]	$C_{12}H_{13}N_3O_3$ (247.25)	58.29 5.30 17.00 58.14 5.28 17.04	3300, 3190 [g] 1790, 1720, 1665	2.9 (s, 3H), 3.5 (s, 2H), 4.1 (s, 2H), 7.3 (s, 5H), 10.55 (bs, 1H)
4t	$PhCH_2$	Et	57	134 [e,f]	$C_{13}H_{15}N_3O_3$ (261.27)	59.76 5.79 16.08 59.75 5.79 16.12	3280, 1780, 1725, 1670	1.05 (t, 3H), 3.4 (q, 2H), 3.5 (s, 2H), 4.1 (s, 2H), 7.3 (s, 5H), 10.55 (bs, 1H)
4u	$PhCH_2$	Pr	38	84 [e,f]	$C_{14}H_{17}N_3O_3$ (275.30)	61.08 6.22 15.26 61.10 6.18 15.21	3280, 1775, 1720, 1670	0.8 (t, 3H), 1.3-1.65 (m, 2H), 3.3 (t, 2H), 3.5 (s, 2H), 4.05 (s, 2H), 7.3 (s, 5H), 10.5 (s, 1H)

Table II (continued)

No.	R	R'	Yield % [a]	Mp °C	Formula	Analyses, % Calcd./Found C H N	IR, ν cm^{-1}	^{1}H NMR [b] δ ppm
13a	Ph	NH_2	45	201 [h]	$C_{10}H_{10}N_4O_3$ (234.21)	51.28 4.30 23.92 51.35 4.27 23.96	3340, 3310, 3220, 1785, 1710, 1660	4.2 (s, 2H), 5 (s, 2H), 7.3-8 (m, 5H), 10.9 (s, 1H)
13b	4-MePh	NH_2	52	200 [d]	$C_{11}H_{12}N_4O_3$ (248.23)	53.22 4.87 22.57 53.35 4.85 22.65	3350, 3330, 3280, 3200, 1790, 1720, 1655	2.4 (s, 3H), 4.15 (s, 2H), 5 (s, 2H), 7.35 and 7.85 (2d, 4H), 10.85 (s, 1H)
13c	4-ClPh	NH_2	60	218 [c,d]	$C_{10}H_9ClN_4O_3$ (268.65)	44.71 3.38 20.86 44.59 3.41 20.83	3350, 3340, 3290, 3210, 1780, 1715, 1690	4.15 (s, 2H), 5 (s, 2H), 7.6 and 7.9 (2d, 4H), 11.05 (s, 1H)
13d	$PhCH_2$	NH_2	30	180 [e,f]	$C_{11}H_{12}N_4O_3$ (248.23)	53.22 4.87 22.57 53.06 4.90 22.51	3300, 3220, 3180, 1785, 1720, 1680	3.5 (s, 2H), 4.05 (s, 2H), 4.9 (s, 2H), 7.3 (s, 5H), 10.5 (s, 1H)
14a	Ph	N=CHPh	75	202 [i]	$C_{17}H_{14}N_4O_3$ (322.31)	63.35 4.38 17.38 63.38 4.35 17.43	3240, 1780, 1720, 1650	4.34 (s, 2H), 7.35-8.1 (m, 10H), 9.3 (s, 1H), 11.15 (bs, 1H)
14b	4-MePh	N=CHPh	73	212-270 [j]	$C_{18}H_{16}N_4O_3$ (336.34)	64.28 4.80 16.66 64.43 4.84 16.70	3220, 1790, 1740 1655	2.4 (s, 3H), 4.35 (s, 2H), 7.4 (d, 2H), 7.5-8 (m, 7H), 9.3 (s, 1H), 11.05 (s, 1H)
14c	4-ClPh	N=CHPh	75	249 [c]	$C_{17}H_{13}ClN_4O_3$ (356.75)	57.23 3.67 15.71 57.36 3.70 15.66	3260, 1775, 1720, 1660	4.35 (s, 2H), 7.5-8.1 (m, 9H), 9.3 (s, 1H), 11.3 (s, 1H)
14d	$PhCH_2$	N=CHPh	80	161 [k]	$C_{18}H_{16}N_4O_3$ (336.34)	64.28 4.80 16.66 64.28 4.77 16.70	3320, 1780, 1730, 1690	3.55 (s, 2H), 4.2 (s, 2H), 7.3 (s, 5H), 7.45-7.9 (m, 5H), 9.2 (s, 1H), 10.7 (bs, 1H)
15	Ph	NHCOPh	72	280 [k]	$C_{17}H_{14}N_4O_4$ (338.31)	60.35 4.17 16.56 60.30 4.20 16.61	3220, 1815, 1750, 1655	4.5 (s, 2H), 7.45-8.1 (m, 10H), 11.15 (s, 1H), 11.3 (s, 1H)

[a] Non optimized yields. [b] In DMSO-d_6. [c] Ethanol. [d] Water. [e] Ethyl acetate. [f] Petroleum ether 40-60. [g] The ir spectra of compound **4s** showed one broad N-H band at 3300 cm^{-1} when it was recrystallized from ethanol-water and two N-H bands at 3300 and 3190 cm^{-1} when it was recrystallized from ethyl acetate-petroleum ether (same mp and ^{1}H nmr spectra). [h] 1-Butanol. [i] Methanol. [j] The compound **14b** melted at 212° and after solidification melted again at 270° (same compound). [k] 1-Propanol.

No reaction occurred between esters **2** and arylamines. Vigorous conditions (high boiling solvents) and the presence of catalysts (triethylamine, pyridine or sodium ethylate) gave no results.

Treatment of esters **2** with hydrazine hydrate in boiling ethanol conducted to diamino derivatives **13** of hydantoin besides some very greasy products which were not isolated (Scheme 4).

The diamino compounds **13** reacted with benzaldehyde to give the 3-benzylideneamino derivatives **14**. The 1,3-dibenzamido-2,4-imidazolidinedione **(15)** was prepared by reaction of benzoyl chloride with hydantoin **13a**. A nitrous deamination was effected with **13a** and conducted to **4a**. Few examples of 1,3-diaminohydantoin derivatives have been described in the literature. They were synthesized by action of chloramine with the sodium salt of hydantoin derivatives [13] or through the reaction of hydrazinopyridinium salts in a basic medium [14]. With the aim to prepare the unsubstituted 1,3-diamino-2,4-imidazolidinedione, the sodium salt of the 1,5-dibenzylidenecarbonohydrazide **(16)** was reacted with ethyl bromoacetate. The expected intermediate **17** was not isolated but the 1,3-bis(benzylideneamino)-2,4-imidazolidinedione **(18)** was obtained in good yield. Attempts to prepare the free amino compound by acid hydrolysis or hydrazinolysis was unsuccessful up to now.

Assignment for the structures of new products was provided by elemental analysis and ir and ^{1}H-nmr spectra. Most of their physicochemical data are listed in Tables I and II.

EXPERIMENTAL

Melting points (uncorrected) were determined with a Buchi oil heated apparatus. The ir spectra were recorded on a Perkin Elmer 1310 spectrophotometer as potassium bromide disks. The ^{1}H-nmr spectra were obtained in DMSO-d_6 on a Brucker WP 80 spectrometer and are reported as δ values (ppm) relative to tetramethylsilane as an internal standard.

Oxadiazolones **1**.

These compounds were prepared by the classical method by reaction of phosgene with the corresponding hydrazides [15].

Ethyl 5-Aryl(or benzyl)-2-oxo-1,3,4-oxadiazole-3(2*H*)-acetates **2**.

To a stirred solution of 10 mmoles of **1** in 40 ml of dry dimethylformamide at 0°, 0.24 g (10 mmoles) of sodium hydride was added. When hydrogen gas evolution ceased, the mixture was heated at 60-80° for 10 minutes. After cooling at 0°, a solution of 1.67 g (10 mmoles) of ethyl bromoacetate in 10 ml of dry dimethylformamide was added slowly at 0°. The reaction mixture was stirred for 30 minutes at room temperature, then for 30 minutes

at 60°. After cooling, it was poured onto 100 ml of ice-water. Compound **2** precipitated, was filtered and recrystallized from adequate solvent (Table I).

2-(5-Aryl(or benzyl)-2-oxo-1,3,4-oxadiazole-3(2*H*))-acetamides **3**.

The experimental procedure is identical to that used for esters **2** but ethyl bromoacetate was replaced by chloroacetamide (Table I).

1-Acylamino-2,4-imidazolidinediones **4a-d**.

A suspension of 10 mmoles of ester **2** in 20 ml of 28% aqueous ammonia solution and 20 ml of ethanol was stirred at 25° for 24 hours (**2a** and **2c**), 48 hours (**2b**) or 72 hours (**2d**). Solvents were evaporated and the resulting solid **4** was recrystallized from ethanol-water (Table II). When the reaction was stopped after 12 hours, amide **3** was often obtained as the major product in the resulting crop, except for **3c**.

1-Acylamino-3-alkyl-2,4-imidazolidinediones **4e-u** and Semicarbazides **6**.

To a suspension of 10 mmoles of ester **2** in 20 ml of methanol was added 40 mmoles of primary amine (propylamine, butylamine, isobutylamine or benzylamine). The mixture was stirred at reflux for 8 hours. Compound **7** was filtered (Table I) and the filtrate was evaporated. The resulting crude solid **4g-j,m,n,q,r** or **u** was washed with some ml of water, then recrystallized from adequate solvent (Table II). When amine was added at an amine/ester molar ratio higher than 6:1, compound **6** was obtained.

With methylamine or ethylamine, 60 mmoles of aqueous solution of amine were added to 10 mmoles of ester **2** in 5 ml of methanol and the reaction mixture was stirred for 12 hours at 25°. The solution was evaporated and the solid **4e,f,k,l,o,p,s** or **t** was recrystallized (Table II).

2-(2-Benzoyl-1-(*N*-methylcarbamoyl)hydrazino)-*N*-methylacetamide (**6a**).

This compound was recrystallized from ethyl acetate giving 1.06 g (40%), mp 140°; ir: 3340, 3300, 3210, 1650 (broad) cm^{-1}; nmr (DMSO-d_6): δ 2.55 and 2.6 (2d, 6H), 4 (s, 2H), 6.7-7.05 (m, 1H), 7.35-8.2 (m, 6H), 10.6 (bs, 1H).

Anal. Calcd. for $C_{12}H_{16}N_4O_3$ (264.28): C, 54.53; H, 6.10; N, 21.20. Found: C, 54.48; H, 6.12; N, 21.17.

2-(2-Benzoyl-1-(*N*-ethylcarbamoyl)hydrazino)-*N*-ethylacetamide (**6b**).

This compound was recrystallized from ethyl acetate giving 1.03 g (35%), mp 158°; ir: 3340, 3280, 1700, 1645 (broad) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1 and 1.05 (2t, 6H), 2.85-3.25 (m, 4H), 4 (s, 2H), 6.8-7.05 (m, 1H), 7.4-8.2 (m, 6H), 10.55 (bs, 1H).

Anal. Calcd. for $C_{14}H_{20}N_4O_3$ (292.33): C, 57.52; H, 6.90; N, 19.17. Found: C, 57.46; H, 6.92; N, 19.21.

2-(1-(*N*-Methylcarbamoyl)-2-phenylacetylhydrazino)-*N*-methylacetamide (**6c**).

This compound was recrystallized from water giving 1.45 g (52%), mp 162°; ir: 3380, 3300, 1690, 1655 (broad) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.55 and 2.6 (2d, 6H), 3.5 (s, 2H), 3.9 (s, 2H), 6.6-6.85 (m, 1H), 7.3 (s, 5H), 7.8-8 (m, 1H), 10.1 (bs, 1H).

Anal. Calcd. for $C_{13}H_{18}N_4O_3$ (278.30): C, 56.10; H, 6.52; N, 20.13. Found: C, 56.18; H, 6.50; N, 20.17.

Ethyl 2-Benzoyl-1-(*N*-butylcarbamoyl)hydrazinoacetate (**8**).

To a solution of 0.2 g (0.9 mmole) of compound **9** in 10 ml of dry ethyl acetate was added a solution of 0.1 g (1 mmole) of butyl isocyanate in 1 ml of ethyl acetate. The mixture was stirred at reflux for 1 hour. After removal of the solvent, **8** was obtained as an oily product which crystallized some time later. It was recrystallized from ethyl acetate-petroleum ether giving 0.2 g (69%), mp 110°; ir: 3370, 3200, 1745, 1650 (broad) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 0.8 (t, 3H), 1.1-1.4 (m, 7H), 3 (t, 2H), 4.15 (q, 2H), 4.25 (s, 2H), 6.8 (t, 1H), 7.35-8.05 (m, 5H), 10.55 (s, 1H).

Anal. Calcd. for $C_{16}H_{23}N_3O_4$ (321.37): C, 59.79; H, 7.21; N, 13.08. Found: C, 59.72; H, 7.24; N, 13.07.

Cyclization of Compound **8**.

To a solution of 64 mg (0.2 mmole) of **8** in 5 ml of methanol were added 2 drops of butylamine as a catalyst. Some minutes later and after removal of methanol, a greasy compound was obtained. It was recrystallized from ethanol-water and was identical to hydantoin **4h** prepared by reaction of ester **2a** with butylamine.

Ethyl 2-Benzoylhydrazinoacetate (**9**).

To a solution of 4.1 g (30 mmoles) of benzohydrazide in 30 ml of ethanol and 30 ml of dimethylformamide were added 1.26 g (15 mmoles) of sodium bicarbonate and 1.67 g (10 mmoles) of ethyl bromoacetate. The mixture was stirred at room temperature for 48 hours. After removal of solvents under reduced pressure, the resulting crop was treated with 200 ml of water and extracted with diethyl ether. The organic solution was washed with water, dried over magnesium sulfate and evaporated to give **9** with traces of benzohydrazide. It was purified by column chromatography on silica gel 60 0.05-0.2 mm (Macherey-Nagel) using ethyl acetate-petroleum ether (3:1) as the eluent and recrystallized from 1-propanol giving 1.3 g (59% from ethyl bromoacetate), mp 104° [16]; ir: 3250, 3210, 1740, 1620 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 1.15 (t, 3H), 3.6 (s, 2H), 4.15 (q, 2H), 5.3-5.55 (m, 1H), 7.4-7.9 (m, 5H), 10.5 (s, 1H).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$ (222.24): C, 59.45; H, 6.35; N, 12.61. Found: C, 59.42; H, 6.34; N, 12.56.

1-Benzylideneamino-3-butyl-2,4-imidazolidinedione (**10**).

To a solution of 5.48 g (25 mmoles) of benzaldehyde 4-butylsemicarbazone (**11**) (prepared from benzaldehyde hydrazone and butyl isocyanate in dry dimethylformamide, mp 163°, lit [20] mp 160-162°) in 100 ml of dry dimethylformamide was added 0.6 g (25 mmoles) of sodium hydride. The mixture was stirred at 80° for 40 minutes (end of hydrogen evolution). After cooling at 0°, a solution of 4.17 g (25 mmoles) of ethyl bromoacetate in 30 ml of dimethylformamide was added slowly. After heating at 60-80° for 45 minutes, the reaction mixture was poured onto 200 ml of ice-water. Hydantoin **10** precipitated. It was filtered, washed with 20 ml of water, essored and recrystallized from cyclohexane giving 2.72 g (42%), mp 127°; ir: 3100 (broad), 1770, 1710 (broad) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 0.85 (t, 3H), 1.1-1.65 (m, 4H), 3.45 (t, 2H), 4.4 (s, 2H), 7.35-7.85 (m, 5H), 7.9 (s, 1H).

Anal. Calcd. for $C_{14}H_{17}N_3O_2$ (259.30): C, 64.84; H, 6.61; N, 16.21. Found: C, 64.88; H, 6.63; N, 16.18.

1-Acylamino-3-amino-2,4-imidazolidinediones **13a-d**.

To a suspension of 10 mmoles of ester **2** in 40 ml of ethanol was added 0.75 g (15 mmoles) of hydrazine hydrate. The mixture was stirred at reflux for 24 hours. After cooling at 0°, compound **13** crystallized. It was filtered and the filtrate was evaporated to

give a greasy mixture. By addition of 5 ml of water, a new quantity of **13** precipitated and was filtered. Compounds **13** were recrystallized from adequate solvent (Table II).

Nitrous Deamination of **13a**.

To 50 ml of water, 50 ml of acetic acid and 1 ml of hydrochloric acid was added 2.34 g (10 mmoles) of **13a** and then dropwise at 5° a solution of 0.69 g (10 mmoles) of sodium nitrite in 5 ml of water. The mixture was stirred at 5° for 1 hour and the solvents were evaporated under reduced pressure. The resulting solid was recrystallized from water giving 1.55 g (71%) of **4a** (Table II).

1-Acylamino-3-benzylideneamino-2,4-imidazolidinediones **14a-d**.

A solution of 10 mmoles of hydantoin **13** and 1.06 g (10 mmoles) of benzaldehyde in 30 ml of ethanol and 1 ml of acetic acid was stirred at reflux for 24 hours. After removal of the solvent, the crude product **14** was obtained and recrystallized from adequate solvent (Table II).

1,3-Dibenzamido-2,4-imidazolidinedione (**15**).

To a suspension of 0.47 g (2 mmoles) of hydantoin **13a** in 10 ml of dry ethyl acetate and 0.5 ml of pyridine was added at 0° a solution of 0.28 g (2 mmoles) of benzoyl chloride in 2 ml of ethyl acetate. The mixture was heated at 60-80° for one hour with stirring. After removal of the solvent, the resulting crop was treated with 10 ml of water. The insoluble compound **15** was filtered and recrystallized (Table II).

1,3-Bis(benzylideneamino)-2,4-imidazolidinedione (**18**).

In 50 ml of dry dimethylformamide, 5.4 g (20 mmoles) of 1,5-dibenzylidenecarbonohydrazide (**16**) were treated with 0.48 g (20 mmoles) of sodium hydride at 80° for 20 minutes (end of hydrogen evolution). After cooling at 0°, a solution of 3.4 g (20 mmoles) of ethyl bromoacetate in 20 ml of dimethylformamide was added slowly. The resulting mixture was heated with stirring in a water bath for 20 minutes, then cooled at 25° and poured onto 200 ml of ice-water. Compound **18** precipitated. It was filtered and recrystallized from 1-butanol giving 3.25 g (53%), mp 214°; ir: 1780, 1730 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 4.55 (s, 2H), 7.35-8 (m, 10H), 8 (s, 1H), 9.3 (s, 1H).

Anal. Calcd. for $C_{17}H_{14}N_4O_2$ (306.31): C, 66.65; H, 4.61; N, 18.29. Found: C, 66.72; H, 4.60; N, 18.27.

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