α,β-Unsaturated Carboxylic Acid Derivatives. IX. The Cyclization of α-(*N*-Acyl-hydroxyamino) Acid Esters with Ammonia or Hydroxylamine[1]

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A new type of cyclization reaction of α-(*N*-acyl-hydroxyamino) acid esters to imidazolidine-4-one derivatives and the synthesis of several 2,5-piperazinedione derivatives are described. The treatment of β-methoxy-α-(*N*-chloroacetyl- or *N*-phthaloylglycyl-hydroxyamino) acid esters with ammonia gave 2-carbamoyl-2-(1-methoxy)alkyl- or aralkyl-imidazolidine-4-ones, while a similar cyclization of α-(*N*-haloacetylamino) or α-(*N*-haloacyl-hydroxyamino) acid esters with ammonia or hydroxylamine gave 2,5-piperazinedione, 1-hydroxy-2,5-piperazinedione or 1,4-dihydroxy-2,5-piperazinedione derivatives. The difference in the formation mechanisms between the imidazolidine-4-one and 2,5-piperazinedione and their structural assignment were discussed.

In previous papers, we have reported that the cyclization of newly synthesized ethyl α-(*N*-chloroacetylamino)-α-alkenoate (**8**)[2] with alcoholic ammonia generally gave 3-alkylidene- or 3-arylidene-2,5-piperazinediones,[3] while a similar cyclization of ethyl β-methoxy-α-(*N*-chloroacetyl- or *N*-phthaloylglycyl-hydroxyamino)alkanoates (**4**) with ammonia afforded 2-carbamoyl-2-(1-methoxy)alkyl-imidazolidine-4-ones (**10**).[4] However, it was later found that the same cyclization of the *O*-acetyl derivative of **4d** (**5d**; ethyl 2-(*O*-acetyl-*N*-chloroacetyl-hydroxyamino)-3-methoxy-3-phenylpropanoate)[5] gave the normal cyclization products, 3-(1,1-dialkoxy)benzyl-2,5-piperazinediones (**15** and **16**).

In this paper, we wish to report in detail on the conversion of **4** into **10**, and on the difference in the mode of cyclization between **4** and **5**. Moreover, it has been confirmed that the cyclization of ethyl 2-(*N*-bromoacetyl-hydroxyamino)-3-phenylpropanoate (**3d**), which has no methoxy group in the alkyl moiety, with ammonia and hydroxylamine gives the corresponding 1-hydroxy and 1,4-dihydroxy-2,5-piperazinediones (**17** and **18**), as reported by Cook and Slater.[6]

Results and Discussion

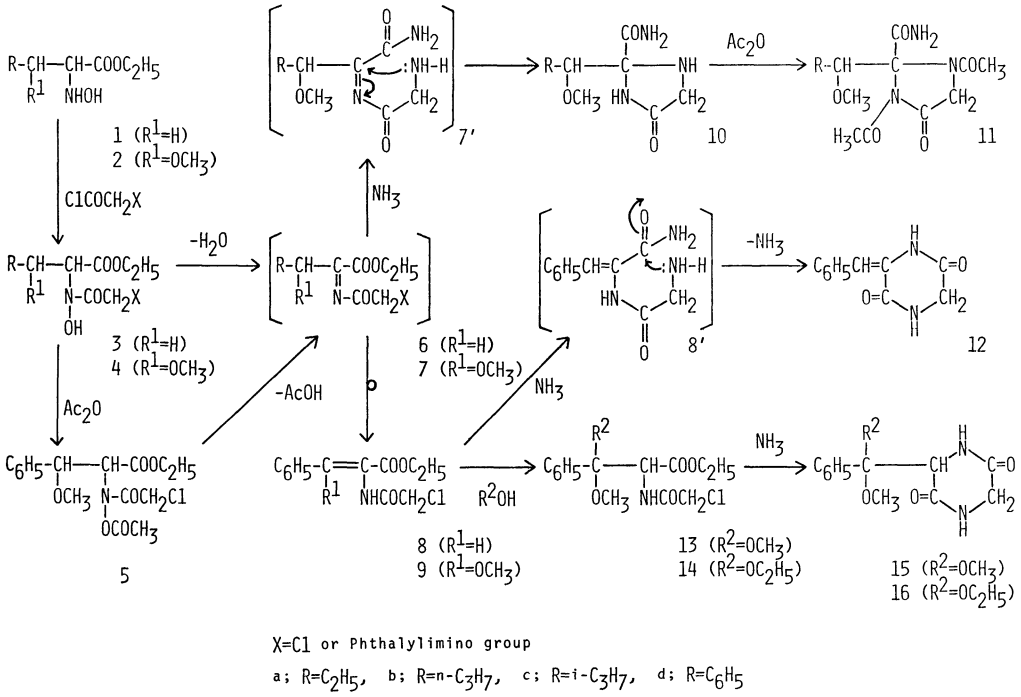
As the starting materials, ethyl α-(*N*-haloacetyl-hydroxyamino)-β-phenylpropanoate (**3d**; X=Cl and X=Br) and **4** (X=phthalylimino: **a**; R=C_2H_5, **b**; R=*n*-C_3H_7, **c**; R=*i*-C_3H_7, **d**; R=C_6H_5. X=Cl: **d**; R=C_6H_5) were synthesized by the acylation of ethyl α-hydroxyaminoalkanoate (**1**) or ethyl α-hydroxyamino-β-methoxyalkanoate (**2**)[7] with haloacetyl halide or phthaloylglycyl chloride respectively.

When an ethanol solution of **4** was saturated with ammonia at room temperature, an unexpected compound, **10** was obtained in a 23—51% yield. The structure of **10** was confirmed by elementary analysis, by the spectral data, and by the acetylation of **10**. The infrared spectrum showed the absorption bands of the amide and cyclic imino groups in the 3180—3360 region and that of the carbonyl groups in the 1665—1700 cm^{-1} region. The acetylation of **10** with acetic anhydride under reflux afforded 2-carbamoyl-1,3-diacetyl-2-(1-methoxy)alkyl-imidazolidine-4-one (**11**) in a good yield.

A similar treatment of ethyl 2-(*N*-chloroacetyl-hydroxyamino)-3-phenylpropanoate (**3d**; X=Cl) with ammonia yielded 3-benzylidene-2,5-piperazinedione (**12**) in a 30% yield, instead of the expected **17** or 2-benzyl-2-carbamoyl-imidazolidine-4-one. On the other hand, the same reaction of the **5** obtained by the acetylation of **4** with acetic anhydride[2] with methanolic or ethanolic ammonia gave 3-(1,1-dimethoxy) (**15**)- or 3-(1-ethoxy-1-methoxy)benzyl-2,5-piperazinedione (**16**) respectively, though the yields were poor.

In a previous paper,[5] we have reported that the treatment of **5** with alkali in benzene gave ethyl 2-(*N*-chloroacetylamino)-3-methoxy-3-phenyl-2-propenoate (**9**) *via* the corresponding imino derivative (**7**). Consequently, the formation of **15** and **16** indicates that ethyl 2-(*N*-chloroacetylamino)-3,3-dimethoxy (**13**)- or 3-ethoxy-3-methoxy-3-phenylpropanoate (**14**) is formed by the addition of alcohols to **9** and that it subsequently cyclizes to give **15** or **16** respectively. In fact, the treatment of **5** with methanol or ethanol in the presence of 3 M-potassium hydroxide at room temperature gave **13** or **14** respectively in a good yield. When the cyclization of the **13** or **14** isolated with alcoholic ammonia was performed at room temperature, the expected **15** or **16** was also obtained in a good yield.

From the above facts, it seems that the cyclization reaction of the β-methoxy compound (**4**) may proceed through an imino intermediate (**7**→**7'**) formed by the dehydration of **4** to give **10**, while, in the case of **3**, the corresponding imino intermediate (**6**) readily isomerizes to the tautomeric enamine (**8**→**8'**)[8] and then cyclizes to give **12**. It may be deduced that **7** is more stable, because of the influence of the methoxy group in the 3-position, than **6**, the prototropy of which readily takes place from the carbon in the 3-position to the nitrogen atom. Furthermore, on the other hand, it may be postulated that the difference in the reaction products between **4** and **5** depends upon their relative rate of dehydration from **4** and the elimination of acetic acid from **5**.[5] It may safely be concluded that the structures of the products in these cyclization are determined by the relative rate of elimination (**3,4**→



Scheme 1.

6,7 and **5**→**7**), the substitution of the halogen atom (X) with ammonia (X→NH_2), and the addition of alcohol to enamine (**8** and **9**). If the substitution of the halogen atom is faster than the elimination of water, as in the case of **4**, the newly formed amino group easily attacks the electron-deficient imino carbon to give a five-membered imidazolidine derivative. Even though the isomerization from **6** or **7** into **8** and **9** proceeds smoothly, **15** and **16** will be produced when the addition of alcohols to enamines (**8** and **9**) proceeds readily.

The infrared spectra of **13** and **14** showed the absorption band of NH at 3380 and the carbonyl group at 1700 cm^{-1}, while that of **15** and **16** showed them at 3080 and 3200 and in the 1680—1695 and 1660—1670 cm^{-1} regions, essentially as in ordinary 2,5-piperazinedione derivatives.

The physical constants, the yield, and the spectral data of the **10** and **11** and of **12**, **15**, and **16** obtained above are summarized in Tables 1 and 2 respectively.

When a solution of **3d** (X=Br) in ethanol was

Table 1. 2-Carbamoylimidazolidine-4-one derivatives (**10** and **11**)

Compd.	Yield (%)	Mp (°C)	Formula	Found, %			Calcd, %			IR spectrum, cm^{-1}, in KBr
				C	H	N	C	H	N	
10a	48	185—186	$C_8H_{15}N_3O_3$	47.80	7.66	21.00	47.75	7.51	20.88	3240, 3200, 1700
10b	31	192—194	$C_9H_{17}N_3O_3$	50.29	8.09	19.28	50.22	7.96	19.52	3350, 3180, 1690
10c	23	181—182	$C_9H_{17}N_3O_3$	49.98	8.22	19.74	50.22	7.96	19.52	3350, 3180, 1670
10d	51[a]	190—191	$C_{12}H_{15}N_3O_3$	57.88	6.06	16.59	57.82	6.07	16.86	3360, 3180, 1665
11a	75	169—170	$C_{12}H_{19}N_3O_5$	50.10	6.54	14.90	50.52	6.71	14.73	3410, 3250, 1705, 1690, 1570
11c	82	138—140	$C_{13}H_{21}N_3O_5$	51.97	6.93	14.08	52.16	7.07	14.08	3400, 3300, 1715, 1665, 1510
11d	95	191—193	$C_{16}H_{19}N_3O_5$	57.61	5.63	12.90	57.65	5.75	12.61	3425, 3225, 1670, 1665, 1545

a) Compound **10d** was also obtained in 46% yield from **4d** (X=Cl).

Table 2. 3-Benzylidene- and 3-benzyl-2,5-piperazinedione derivatives

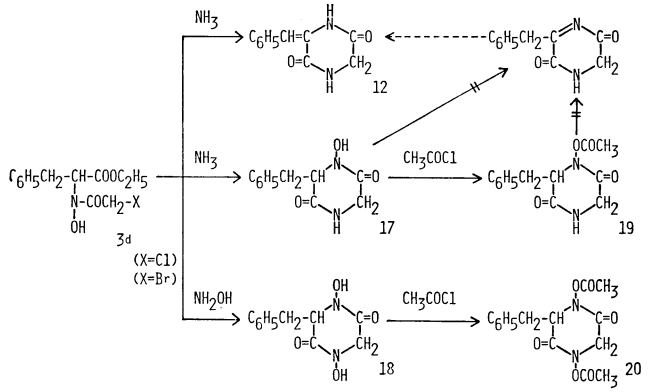
Compd.	Yield (%)	Mp (°C)	Formula	Found, %			Calcd, %			IR spectrum, cm^{-1} in KBr
				C	H	N	C	H	N	
12	30	278—280[a]								
15	44	238—239	$C_{13}H_{16}N_2O_4$	58.98	6.51	10.32	59.08	6.10	10.60	3200, 3080, 1680, 1660
16	39	243—244	$C_{14}H_{18}N_2O_4$	60.43	6.43	10.05	60.42	6.52	10.07	3200, 3080, 1695, 1670
17	54	247—248	$C_{11}H_{12}N_2O_3$	59.94	5.54	12.88	59.99	5.49	12.72	3150, 3060 1650
18	70	250—251	$C_{11}H_{12}N_2O_4$	55.69	5.14	11.80	55.93	5.12	11.86	3075, 2870, 1660
19	84	134—136	$C_{13}H_{14}N_2O_4$	59.63	5.20	10.32	57.53	5.38	10.68	3200, 1800, 1700, 1680
20	72	165—167.5	$C_{15}H_{16}N_2O_6$	56.33	4.99	8.66	56.25	5.04	8.75	1810, 1790, 1710

a) Ref. 3.

saturated with ammonia at room temperature, according to the Cook and Slater method,[6] Compound **17** was obtained, while the reaction with hydroxylamine gave **18** in a good yield. However, as has been mentioned above, Compound **17** and **18** could not be derived from **3d** (X=Cl).

From the above results and from facts previously reported,[6] it is evident that **3d** (X=Cl) reacts with ammonia to give **12** after dehydration into **6**, whereas **3d** (X=Br) cyclizes without the dehydration to give **17** and **18**. These results indicate the difference in the reactivity of chlorine and bromine atoms with ammonia or hydroxylamine.

Compounds **17** and **18** gave a deep violet coloration with methanolic ferric chloride, indicating the presence of the cyclic hydroxamino-acid structure. Moreover, for the purposes of the structural assignment, **17** or **18** was treated with excess acetyl chloride under reflux to give 3-benzyl-4-acetoxy (**19**)- or 3-benzyl-1,4-diacetoxy-2,5-piperazinedione (**20**) respectively, in a good yield; the characteristic coloration with the ferric chloride was not found. The attempted conversion of **17** or **19** into **12** by the dehydration or the elimination of acetic acid in methanolic ammonia *via* the pyrazine derivative was unsuccessful.



Scheme 2.

Experimental

All the melting points are uncorrected. The IR spectra were recorded with a Hitachi EPI-S2 Spectrometer. The NMR spectra were measured with a JNM-4H-100 Spectrometer (Japan Electron Optics Laboratory Co., Ltd.), using tetramethyl silane as the internal standard.

Materials. The ethyl 2-hydroxyamino-3-phenylpropanoate (**1d**)[5] and ethyl α-hydroxyamino-β-methoxyalkanoate (**2**)[7] were prepared by the methods previously reported.

Ethyl α-(N-Haloacetyl-hydroxyamino)-β-phenylpropanoate (3d). Into a solution of **1d** (0.027 mol) and pyridine (0.027 mol) in dry benzene (40 ml), we stirred, drop by drop, a solution of acetyl chloride or bromide (0.027 mol) in dry benzene (15 ml) at room temperature. After stirring for 3 hr, the resulting solution was washed successively with water, an aqueous solution of sodium hydrogencarbonate, 3 M-hydrochloric acid, and then finally with water. The benzene layer was dried over anhydrous magnesium sulfate and then evaporated. The reddish residual syrup was purified by chromatography on a silica gel column using benzene–ethyl acetate (X=Cl; 10: 1 or X=Br; 20: 1 in v/v) and the effluent solvent was evaporated under reduced pressure to give a pale yellow syrup (**3d**; X=Br) or colorless crystals (**3d**; X=Cl), which were then recrystallized from benzene–petroleum ether to give colorless needles. Ethyl 2-(*N*-chloroacetyl-hydroxyamino)-3-phenylpropanoate: yield, 41%; mp 64—65 °C. IR (KBr): 3200, 1730, 1640 cm^{-1}. NMR ($CDCl_3$): δ 7.54 (1H, bs, OH), 7.33 (5H, s, aromatic H), 5.42 (1H, t, J=8.2 Hz, $-CH_2-\underline{C}\underline{H}-$), 4.23 (2H, s, $-COCH_2-$), 3.22 (2H, d, J=8.2 Hz, $-C\underline{H}_2-\underline{C}\underline{H}-$). Found: C, 54.79; H, 5.67; N, 4.85%. Calcd for $C_{13}H_{16}NO_4Cl$: C, 54.64; H, 5.65; N, 4.90%. Ethyl 2-(*N*-bromoacetyl-hydroxyamino)-3-phenylpropanoate: yield, 46%. IR (KBr): 3200, 1730, 1620 cm^{-1}. Found: C, 47.58; H, 5.02; N, 4.11%. Calcd for $C_{13}H_{16}NO_4Br$: C, 47.29; H, 4.89; N, 4.24%.

Ethyl α-(N-Chloroacetyl- or Phthaloylglycyl-hydroxyamino)-β-methoxyalkanoate (4). Compound **4** was prepared by the methods previously reported.[5,7] Ethyl 2-(*N*-chloroacetyl-hydroxyamino)-3-methoxy-3-phenylpropanoate (**4d**; X=Cl); colorless needles from benzene–petroleum ether; yield, 58%; mp 108—109°C. IR (KBr): 3100, 1740, 1640 cm^{-1}. NMR ($CDCl_3$): δ 7.40 (1H, s, OH), 7.27 (5H, s, aromatic H), 5.35 (1H, d, J=7.0 Hz, $-\underline{C}\underline{H}-OCH_3$), 4.88 (1H, d, J=7.0 Hz, $-\underline{C}\underline{H}-\underline{N}-$), 4.22 (2H, s, $-COCH_2-$). Found: C, 53.10; H, 5.73; N, 4.30%. Calcd for $C_{14}H_{18}NO_5Cl$: C, 53.25; H, 5.71; N, 4.44%.

2-Carbamoyl-2-(1-methoxy)alkyl-imidazolidine-4-ones (10). When a solution of **4a—d** (0.02 mol) in ethanol (20 ml) was saturated with dry gaseous ammonia under cooling and then allowed to stand overnight at room temperature, colorless crystals were separated out. The crystals were collected and washed with methanol twice. Recrystallization from methanol gave **10a—d** as colorless needles. The melting points of all the new compounds decomposed.

In an analogous manner, **4d** (X=Cl) also reacted with ammonia to give **10d** (Table 1).

2-Carbamoyl-1,3-diacetyl-2-(1-methoxy)alkyl-imidazolidine-4-ones (11). A suspension of **10a, c, d** (0.002 mol) in acetic anhydride (4 ml) was heated at 120—130 °C until the crystals dissolved. The reaction solution was then concentrated under reduced pressure to dryness, giving a crystalline residue. The crystalline product was collected and recrystallized from boiling water to give **11a, c,** and **d** as colorless prisms (Table 1).

Ethyl α-(N-Chloroacetylamino)-β,β-dialkoxy-β-phenylpropanoate (13 and 14). To a solution of **5d** (0.005 mol, an unstable syrup, which was assigned by means of the IR spectrum (the $OCOCH_3$ band appeared at 1800 cm^{-1}) and which had no coloration with methanolic ferric chloride, derived by the reaction of **4d** (X=Cl) with excess acetic anhydride by a method previously reported[5]) in methanol (20 ml), with stirring, we added, drop by drop, a solution of potassium hydroxide (0.23 g) in methanol (10 ml) at room temperature. After continuous stirring for a day, the reaction solution was poured into benzene (20 ml) and washed with 3M-hydrochloric acid twice and with water. The benzene layer was dried over anhydrous magnesium sulfate and then evaporated under reduced pressure. The residual syrup thus obtained gradually crystallized. The crystalline product was collected and recrystallized from di-*n*-butyl ether to give **13** as colorless prisms; yield, 58%; mp 92—94 °C. IR (KBr): 3380, 1740, 1700, 1505 cm^{-1}. Found: C, 54.62; H, 6.06; N, 4.38%. Calcd for $C_{15}H_{20}NO_5Cl$: C, 54.64; H, 6.11; N, 4.25%.

In an analogous manner, Compound **14** was also obtained as a colorless syrup by the reaction of **5d** with ethanol, its structure was confirmed by means of the IR spectrum and by its conversion into **16**. Yield, 75%. IR (KBr): 3380, 1740, 1700, 1505 cm^{-1}.

Reaction of 13 or 14 with Ammonia. A solution of **13** (0.005 mol) in ethanol (20 ml) was saturated with dry gaseous

ammonia under cooling. When the resultant solution was allowed to stand at room temperature, a crystalline substance was precipitated. The ethanol was evaporated under reduced pressure, and the residual crystals were collected and washed successively with water and with ethanol. Subsequent recrystallization from glacial acetic acid gave **15** as colorless needles.

In an analogous manner, Compound **14** also reacted with ammonia to give **16** as colorless needles from acetic acid.

*Reaction of **4d** (X=Cl) with Ammonia.* A solution of **4d** (0.005 mol) in ethanol (20 ml) was saturated with dry gaseous ammonia under cooling. When the resultant solution was allowed to stand at room temperature for a day, colorless crystals were precipitated. The crystals were collected, washed with ethanol, and then recrystallized from glacial acetic acid to give **16** as colorless needles. The product was identical, in melting point and IR spectrum, with the sample obtained from **14**. Yield, 28%.

*Reaction of **3d** (X=Cl) with Ammonia.* When a solution of **3d** (0.005 mol) in ethanol (20 ml) was saturated with dry gaseous ammonia under cooling and then allowed to stand overnight at room temperature, colorless crystals were separated out. These crystals were collected and washed successively with water and with ethanol. Subsequent recrystallization from glacial acetic acid gave **12**. The product was identical, in melting point and IR spectrum, with the sample obtained by the method previously reported.[2]

*Reaction of **3d** (X=Br) with Ammonia.* A solution of **3d** (0.005 mol) in ethanol (30 ml) was saturated with dry gaseous ammonia under cooling. When the resultant solution was allowed to stand at room temperature overnight at room temperature, a crystalline product was precipitated. The precipitates were collected and washed with ethanol. The ethanol filtrate was condensed under reduced pressure to give a colorless powder, which was consistent with the first crystals obtained. Subsequent recrystallization from methanol gave **17** as colorless needles.

*Acetylation of **17** with Acetyl Chloride.* A mixture of **17** (0.001 mol) and acetyl chloride (3 ml) was refluxed at *ca.* 80 °C for 30 min until the crystals dissolved. The reaction solution was concentrated under reduced pressure to give a crystalline residue, which was collected and then washed with dry benzene twice. Recrystallization from benzene gave **19** as colorless needles. NMR ($CDCl_3$): δ 7.02—7.38 (6H, m, aromatic H and NH), 4.49 (1H, t, J=3.7 Hz, $-CH_2-\underline{C}\underline{H}-$), 3.23 (2H, d, J=3.7 Hz, $-C\underline{H}_2-CH-$), 2.58, 3.07 (2H, AB q, J=17.5 Hz, $-C\underline{H}_2-NH-$), 2.25 (3H, s, $-OCOCH_3$).

*Reaction of **3d** (X=Br) with Hydroxylamine.* A solution of **3d** (0.0066 mol) and hydroxylamine (made from hydroxylamine hydrochloride (0.6 g) and sodium (1.8 g)) in ethanol (150 ml) was refluxed for 3 hr. The reaction solution was then concentrated under reduced pressure. The residual syrup was dissolved in water (10 ml), and the aqueous solution was acidified with 3M-hydrochloric acid and then allowed to stand overnight in a refrigerator. The colorless crystals which were then separated out were collected and washed successively with water and ethyl ether. Recrystallization from ethyl acetate gave **18** as colorless tablets.

*Acetylation of **18** with Acetyl Chloride.* A mixture of **18** (0.001 mol) and acetyl chloride (3 ml) was refluxed at *ca.* 80 °C for 1 hr. After the removal of an insoluble substance, the reaction solution was condensed under reduced pressure to give a crystalline residue. The crystalline product was collected, washed with petroleum ether, and then recrystallized from benzene–petroleum ether to give **20** as colorless prisms. NMR ($CDCl_3$): δ 7.10—7.45 (5H, m, aromatic H), 4.67 (1H, t, J=4.0 Hz, $-CH_2-\underline{C}\underline{H}-$), 3.33 (2H, d, J=4.0 Hz, $-C\underline{H}_2-CH-$), 3.21, 3.93 (2H, AB q, J=16.0 Hz, $-CH_2-\underline{N}-$), 2.21, 2.28 (6H, two s, $-OCOCH_3$).

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