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Studies of Nitriles. IX.[1] Reactions of 2-Acetylamino-3,3-dichloroacrylic Amide and -N-acylamide with Aliphatic Amines. (2). Syntheses of Some α,α-Diamino Acid Derivatives

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Reaction of 2-acetylamino-3,3-dichloroacrylic-N-acetylamide (**1**) with aliphatic primary amines gave 2-acetylamino-2-(substituted amino)-3,3-dichloropropionamides (**3**) as major products, which differs distinctly from the results of reaction of **1** with aliphatic secondary amines which leads to oxazole derivatives **2**. The **3** compounds were also prepared by addition of aliphatic primary and secondary amines to 2-acetylamino-3,3-dichloroacrylamide (**6**). Small amounts of 2-methyl-5-(substituted amino)oxazole-4-carboxamides (**5**) were obtained also. The mechanisms of these reactions are discussed.

In the previous paper,[1] we described the preparation of 2-substituted-5-(substituted amino)oxazole-4-N-acylcarboxamides (**2**) by the reaction of 2-acylamino-3,3-dichloroacrylic-N-acylamide (**1**) with aliphatic secondary amines (Chart 1). In the course of further studies of this cyclization, we found that the reaction of **1** with aliphatic primary amines affords 2-acetylamino-2-(substituted amino)-3,3-dichloropropionamides (**3**), novel α,α-diamino acid derivatives, as major products.

Based on these results, we examined also the reactions of 2-acetylamino-3,3-dichloroacrylamide (**6**) and methyl 2-acetylamino-3,3-dichloroacrylate (**7**), derived readily[3] from 2-amino-3,3-dichloroacrylonitrile (ADAN), with aliphatic primary and secondary amines.

More recently, after completion of our experiments, B.S. Drach and co-workers reported[4] similar addition of aliphatic secondary amines to 2-benzoylamino-3,3-dichloroacrylamide.

Results and Discussion

Reaction of **1** with 3 molar eq. of *n*-propylamine under conditions similar to those for the preparation of 2-methyl-5-(substituted amino)oxazole-4-N-acetylcarboxamides (**2**) from **1** and aliphatic secondary amines, gave colorless crystals, mp 115—117° (decomp.), as the main product.

Elemental analysis ($C_8H_{15}O_2N_3Cl_2$) and the mass spectrum (*m/e* (rel. intensity); 215, 213, 211 (1:6:9, M^+-44, 59%), with no molecular ion) showed that two chlorine atoms remained. The nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) revealed the presence of an *n*-propylamino moiety (δ 0.92 (3H, t, J=7.0 Hz), 1.30—1.70 (2H, m), 2.15—2.60 (2H, m), and 2.86 (1H, br), exchangeable with deuterium)), one methyl group (δ 2.06 (3H, s)), three protons exchangeable with deuterium (δ 7.33 (1H, br), and 7.60—7.95 (2H, broad two peaks)) and an isolated methine proton (δ 6.47 (1H, s)).

1) Part VIII: K. Matsumura, T. Saraie, and N. Hashimoto, *Chem. Pharm. Bull.* (Tokyo), **24**, 924 (1976).
2) Location: *Jusohonmachi, Yodogawa-ku, Osaka, 532, Japan.*
3) Part VII: K. Matsumura, T. Saraie, and N. Hashimoto, *Chem. Pharm. Bull.* (Tokyo), **24**, 912 (1976).
4) B.S. Drach and G.N. Mis'kevich, *Zh. Org. Khim.*, **10**, 2315 (1974) [*J. Org. Chem. USSR* (Eng. Transl.), **10**, 2329 (1974)].

These data, especially the characteristic sharp singlet due to a methine proton, confirmed the structure to be 2-acetylamino-2-*n*-propylamino-3,3-dichloropropionamide (**3d**), which was produced apparently by addition of *n*-propylamine to the C=C bond of **1** at the α-position, followed by deacetylation of the imido group.

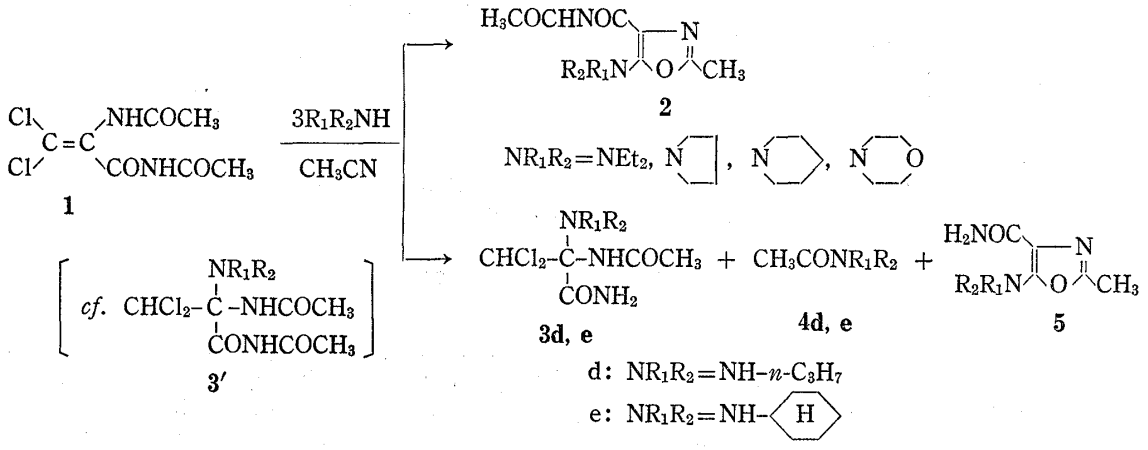


Chart 1

Similar treatment of **1** with 3 molar eq. of cyclohexylamine gave the addition product **3e** in 63% yield. In both cases, N-substituted acetamides **4d, e** and small amounts of oxazoles **5d, e** were also isolated. However, products which still retained the imido group were not detected.

In order to confirm the stage in which deacetylation of the imido group occurs, the reaction of **1** with 1 molar eq. of *n*-propylamine was examined under similar conditions. Consumption of **1** was 57% and formation of **3d** was only minute, barely appearing in the NMR spectrum. The main constitutent was 2-acetylamino-3,3-dichloroacrylamide (**6**), the deacetylation product of the imido group of **1**, and isolated in 32% yield (56% yield based on **1** consumed). Traces of N-*n*-propylacetamide **4d** and 2-methyl-5-*n*-propylaminooxazole-4-carboxamide **5d** were also detected.

In spite of our efforts, 2-acetylamino-2-*n*-propylamino-3,3-dichloro-N-acetylpropionamide (**3'**, $R_1R_2N=CH_3CH_2CH_2NH$), a possible intermediate of **3d**, was not detected. This result suggested that **3d** might be produced by addition of *n*-propylamine to the C=C bond of **6**, not to the C=C bond of **1** followed by deacetylation of the imido group. In fact, we found that, when treated with 3 molar eq. of *n*-propylamine in acetonitrile, **6** yielded **3d** in 77% yield together with a small amount of oxazole **5d** (9%). This novel addition was found to be fairly general with aliphatic primary and secondary amines (Table I).

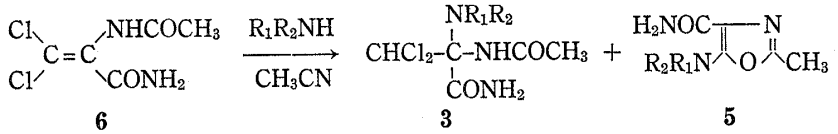
The reactions proceeded with ease at room temperature except for the cases with ammonia and benzylamine. As a by-product, oxazole **5** was formed in every case, but the yield was generally less than 10%.

Very recently, B.S. Drach and co-workers reported the reaction of 2-benzoylamino-3,3-dichloroacrylamide with aliphatic primary amines (CH_3NH_2 and $C_2H_5NH_2$) isolating similar addition products,[4] but did not describe the formation of the corresponding oxazoles.

In an attempt to obtain similar addition products, we treated methyl 2-acetylamino-3,3-dichloroacrylate (**7**) with aliphatic amines under similar conditions. The reaction of **7** with morpholine exclusively gave a cyclization product, methyl 2-methyl-5-morpholinooxazole-4-carboxylate (**9a**), in 94% yield. This result is in accord with those[1] of reactions of 2-acylamino-3,3-dihalogenoacrylonitriles (**10**) or **1** with the same amine. However, when treated with *n*-propylamine, **7** yielded **8b** and **9b** in 43% and 55% yield, respectively (Chart 2).

These and previously reported results[1] clearly show that the nucleophilic attack by amine on the 2-acylamino-3,3-dichloroacrylic system ($\begin{pmatrix}Cl\\Cl\end{pmatrix}C=C\begin{pmatrix}NHCOR\\R_3\end{pmatrix}$) can occur at both α- and β-

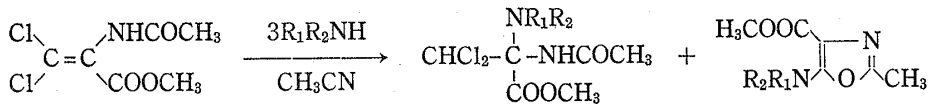
Table I. Preparation of 2-Acetylamino-2-(substituted amino)-3,3-dichloropropionamides (3)



6 **3** **5**

NR_1R_2	Compd. 3 No.	Yield (%)	mp (°C)	Recryst. solvent[a]	Compd. 5 No.	Yield (%)	mp (°C)	Recryst. solvent[a]
NH_2	**3a**	43	96— 98[b] (decomp.)	C	**5a**	10	125—127[c]	W
$NHCH_3$	**3b**	76	123—124 (decomp.)	B	**5b**	20	233—234 (decomp.)	W
$NHCH_2CH{=}CH_2$	**3c**	67[d]	125—126 (decomp.)	B	**5c**	8[d]	150—151	W
$NHCH_2CH_2CH_3$	**3d**	77	115—117 (decomp.)	B-H	**5d**	9	170—172	W
NH-⟨H⟩	**3e**	65	118—119 (decomp.)	B-H	**5e**	2	—	—
$NHCH_2$-C_6H_5	**3f**	45	123—124[e] (decomp.)	B	**5f**	8	167—168	E
⟨N O⟩	**3g**	56	153—155 (decomp.)	A	**5g**	5	147—149	A
⟨N ⟩	**3h**	60	127—128 (decomp.)	B	**5h**	7	122—123	B

a) A=acetonitrile B=benzene C=chloroform E=ethanol H=*n*-hexane W=water
b) Monohydrate
c) lit. mp 127—128° (*cf.* reference 7)
d) Based on **6** consumed
e) $C_{12}H_{15}O_2N_3Cl_2 \cdot C_6H_6$



7

8a : NR_1R_2=⟨N O⟩ ····· **9a** : 94%
8b : NR_1R_2=NH-*n*-C_3H_7 43% **9b** : 55%

Chart 2

carbons, giving an addition product and oxazole, respectively, and that the ratio of α-attack/β-attack is strongly dependent upon the kind of R_3, the value of the ratio decreasing in the order R_3=$CONH_2$>CONHCOR>COOR>CN.

The different reactivity of the substrate is explained by the existence of an equilibrium between the enamino (A)- and imino (B)-forms, the value of the equilibrium constant depending on the nature of R_3. That A and B react with an amine to give oxazole and an addition product, respectively, is rather straight-forward (Chart 3).

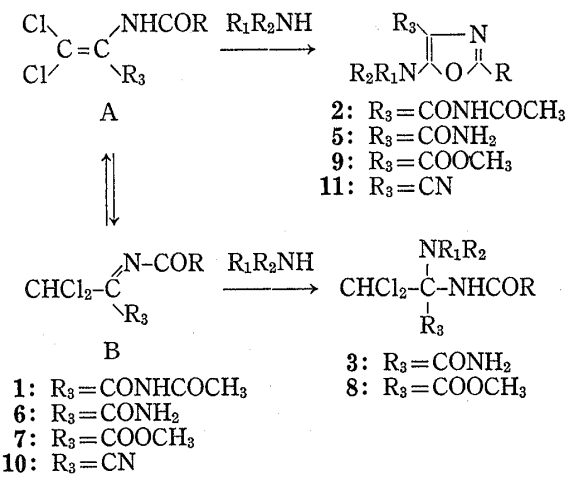
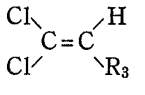


Chart 3

NMR measurement under ordinary conditions did not give any direct evidence for the presence of the imino form B of the compounds used. However, the values of chemical shift[5]

5) J.B. Ellern and H.B. Gray, *J. Org. Chem.*, 37, 4485 (1972).

Table II. Chemical Shifts of α-Hydrogen Atoms of 3,3-Dichloroacrylic Acid Derivatives **12**

		δ ppm	Solvent
 **12**	**12a** : R_3=CN	5.89[a]	$CDCl_3$
	12b : R_3=$CONHCOCH_3$	6.99[b]	$CDCl_3$
	12c : R_3=$CONH_2$	6.52[b]	$CDCl_3$
	12d : R_3=$COOCH_3$	6.29[c]	neat
	12e : R_3=$COCH_3$	6.42[c]	neat
	12f : R_3=COCl	6.72[c]	neat
	12g : R_3=CHO	6.25[c]	neat

a) *cf.* reference 6)
b) *cf.* reference 1)
c) *cf.* reference 5)

of the α-proton of 3,3-dichloroacrylic acid derivatives (**12**) shown in Table II suggest that electron density of the α-carbon of this conjugate system is markedly affected by the interactions of electronic effects of the dichloromethylene and R_3 groups.

Comparison of the chemical shift of **12a**, **c**, and **d** with each other shows that the electron density of the α-carbon atom is largest in **12a** and smallest in **12c**. The fact that the α-proton signal of **12b** appears at an unusually low field compared with those of other compounds can be understood as the result of a deshielding effect of the N-acetyl carbonyl group in the α-position.

Applying this information to the 2-acetylamino-3,3-dichloroacrylic system **1**, **6**, **7**, and **10**, we conclude that **10**, being made definitely electron deficient at the β-carbon atom by the presence of a strongly electron-withdrawing cyano group, reacts with amines only at the β-position yielding oxazoles **11** (R_3=CN).[1]

Since the electron-withdrawing power of the $CONH_2$ group is less than that of the CN group, the β-carbon atom of **6** becomes relatively electron rich due to the electron-withdrawing effect of the β-chlorine atoms and, therefore, **6** reacts with amines mainly at the α-position giving α,α-diamino acid derivatives **3**.

Since **7** has a β-carbon atom of intermediate electrophilic reactivity, the reaction of **7** with amines seems to be greatly influenced by a subtle difference in nucleophilicity of the attacking amine, giving oxazoles **9** with more nucleophilic secondary amines and α,α-diamino acid derivatives **3** with less nucleophilic primary amines.

In the reaction of imidic compound **1** with amines, both cyclization to oxazoles and aminolysis of the imido group followed by the addition can occur simultaneously (Chart 4).

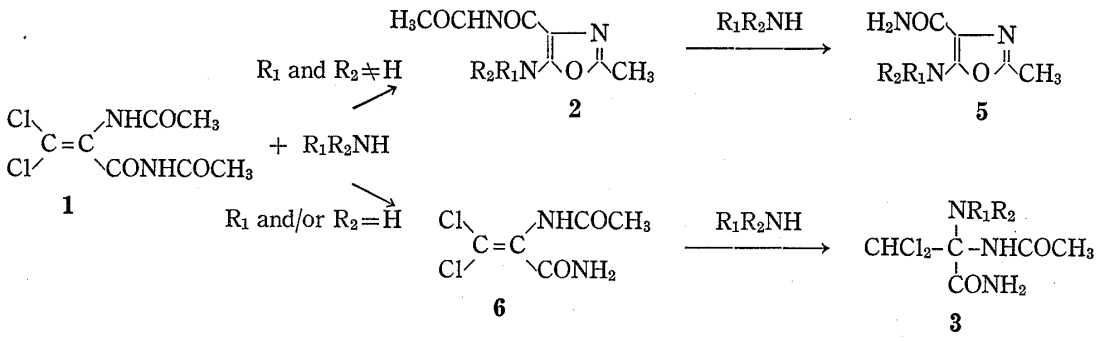


Chart 4

Secondary amines, being good nucleophiles, attack the β-carbon of **1** to give oxazoles **2** (and further **5**). Primary amines, being less nucleophilic, no longer attack the β-carbon as readily and attack the N-acylamino group, leading to production of **6** which, in turn, yields addition product **3**.

From these results, we conclude that this addition reaction is fairly general and a simple route to α,α-diamino acids, novel alanine derivatives.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi EPI-S2 spectrophotometer. NMR spectra were recorded on a Varian A-60 or T-60 spectrometer. Chemical shifts are given in parts per million (δ) down field from tetramethylsilane (TMS) as an internal standard. Ultraviolet (UV) spectra were obtained with a Perkin-Elmer 450 spectrophotometer. Mass spectra were obtained at 70 eV with a Hitachi RMU-6D mass spectrometer. The following abbreviations are used: sh=shoulder, s=singlet, d=doublet, t=triplet, m=multiplet, and br=broad.

Reactions of 2-Acetylamino-3,3-dichloroacrylic-N-acetylamide (1) with Aliphatic Amines——a) With *n*-Propylamine: To a suspension of 4.78 g (20 mmoles) of **1** in 300 ml of anhydrous CH_3CN, 4.72 g (80 mmoles) of *n*-propylamine was added in one portion and the mixture was stirred at room temperature for 2 days. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel with $CHCl_3$–10% acetone to give 3.60 g (70.3%) of 2-acetylamino-2-*n*-propylamino-3,3-dichloropropionamide (**3d**), 0.18 g (5%) of 2-methyl-5-*n*-propylaminooxazole-4-carboxamide (**5d**) and N-acetyl-*n*-propylamine (**4d**). A trace of 2-methyl-5-*n*-propylaminooxazole-4-N-acetylcarboxamide (**2d**) was also detected by the NMR spectrum ((CDCl$_3$) δ: 2.30 (3H, s, 2–CH_3), 2.46 (3H, s, $CONHCOCH_3$)). **3d**: IR ν_{max}^{Nujol} cm^{-1}: 3435, 3280, 3190, 3140 sh, 1707, 1660 sh, 1640, 1593, and 1512. NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.0 Hz), 1.30—1.70 (2H, m), 2.06 (3H, s), 2.15—2.60 (2H, m), 2.86 (1H, br), 6.47 (1H, s), 6.53 (1H, br), and 6.80—7.36 (2H, br 2 peaks). Mass Spectrum *m/e* (rel. intensity): 215, 213, 211 (1: 6: 9, M^+–$CONH_2$, 59%), 201, 199, 197 (1: 6: 9, M^+–$NHCOCH_3$, 2%) 173, 171, 169 (1: 6: 9, M^+–$CONH_2$–CH_2=C=O, 100%), 130 (9%), 131, 129, 127 (1: 6: 9, 17%), 70 (10%), 58 (10%), 43 (59%). *Anal.* Calcd. for $C_8H_{15}O_2N_3Cl_2$: C, 37.52; H, 5.90; N, 16.41. Found: C, 37.40; H, 5.90; N, 16.40. **5d**: IR ν_{max}^{Nujol} cm^{-1}: 3350, 3200, 1670, 1640, 1610, 1575, and 1555. NMR (d_6-DMSO) δ: 0.90 (3H, t, J=7.0 Hz), 1.25—1.90 (2H, m), 2.28 (3H, s), 2.90—3.60 (2H, m), and 6.72 (3H, br). Mass Spectrum *m/e* (rel. intensity): 184 (M^++1, 10%), 183 (M^+, 100%), 166 (M^+−17, 4%), 165 (M^+−18, 4%), 154 (M^+–C_2H_5, 54%), 141 (M^+−42, 20%), 137 (M^+–C_2H_5–OH, 40%), 125 (M^+–$NHCH_2CH_2CH_3$, 61%), 124 (29%), 99 (38%), 43 (98%). *Anal.* Calcd. for $C_8H_{13}O_2N_3$: C, 52.45; H, 7.15; N, 22.94. Found: C, 52.10; H, 7.42; N, 22.67.

b) With Cyclohexylamine: To a suspension of 4.78 g (20 mmoles) of **1** in 300 ml of anhydrous CH_3CN, 7.92 g (80 mmoles) of cyclohexylamine was added in one portion and the mixture was stirred at room temperature for 2 days. After the insoluble material had been removed by filtration, the filtrate was evaporated *in vacuo* to dryness. The residue was chromatographed on silica gel with $CHCl_3$ to give 3.70 g (62.6%) of 2-acetylamino-2-cyclohexylamino-3,3-dichloropropionamide (**3e**) and *ca.* 1.60 g (57%) of N-acetylcyclohexylamine (**4e**) together with a trace of 2-methyl-5-cyclohexylaminooxazole-4-acetylcarboxamide (**2e**, NMR (CDCl$_3$) δ: 2.32 (3H, s, 2–CH_3), 2.50 (3H, s, $COCH_3$)), which has an almost identical Rf value with that of **3e**. **3e**: IR ν_{max}^{Nujol} cm^{-1}: 3340, 3300, 1710 sh, 1690, 1675, 1660, 1643, 1570, and 1530. NMR ($CDCl_3$) δ: 0.80—2.0 (10H, br), 2.05 (3H, s), 2.30—2.80 (2H, br), 6.40—7.20 (2H, br 2 peaks), 6.60 (1H, s), and 7.45 (1H, br). Mass Spectrum *m/e* (rel. intensity): 255, 253, 251 (1: 6: 9, M^+–$CONH_2$, 100%), 241, 239, 237 (1: 6: 9, M^+–$NHCOCH_3$, 2%), 213, 211, 209 (1: 6: 9, 48%), 203, 201, (1: 3, 19%), 173, 171, 169 (1: 6: 9, M^+–$CONH_2$–C_6H_{10}, 18%), 131, 129, 127 (1: 6: 9, 79%), 99 (6%), 98 (11%), 83 (45%), 56 (38%), 55 (39%), 43 (78%), 41 (32%). *Anal.* Calcd. for $C_{11}H_{19}O_2N_3Cl_2$: C, 44.61; H, 6.47; N, 14.19. Found: C, 44.54; H, 6.57; N, 14.48.

Reactions of 2-Acetylamino-3,3-dichloroacrylamide (6) with Ammonia and Aliphatic Amines——a) With Ammonia: A suspension of 1.97 g (10 mmoles) of **6** in a mixture of 4.3 ml of 28% ammonium hydroxide and 150 ml of CH_3CN was placed in a 300 ml steel bomb. The vessel was closed, then the mixture was magnetically stirred at 80° for 20 hr. The vessel was cooled to 0° and then opened. The volatiles were removed *in vacuo* and the residual solid was chromatographed on silica gel with $CHCl_3$–10% MeOH to give 0.71 g (42.5%) of 2-acetylamino-2-amino-3,3-dichloropropionamide (**3a**) and 0.14 g (9.9%) of 2-methyl-5-aminooxazole-4-carboxamide[6] (**5a**). **3a**: IR ν_{max}^{Nujol} cm^{-1}: 3430, 3370, 3330 sh, 3220, 3050, 1700, 1664, 1640 sh, 1600, and 1560. NMR ($CDCl_3$) δ: 2.02 (3H, s), 2.92 (2H, br), 6.50 (1H, s), 6.98 (1H, br), and 7.40—7.90 (2H, br). *Anal.* Calcd. for $C_5H_9O_2N_3Cl_2 \cdot H_2O$: C, 25.72; H, 4.37; N, 18.30. Found: C, 25.88; H, 4.78; N, 18.11. **5a**: NMR (d_6-DMSO) δ: 2.19 (3H, s), 3.65 (2H, br), and 9.06 (2H, br).

b) With Methylamine: To a suspension of 3.94 g (20 mmoles) of **6** in 300 ml of CH_3CN, 6.2 g (60 mmoles) of 30% methylamine was added, then the mixture was stirred at room temperature for 2 days. The solent was evaporated *in vacuo* to dryness and a mixture of 90 ml of $CHCl_3$ and 10 ml of acetone was added to the residue. The resulting precipitate was collected by filtration to yield 1.20 g of brown powder which was recrystallized from water to afford 0.08 g of 2-methyl-5-methylaminooxazole-4-carboxamide (**5b**). The filtrate was concentrated to a volume of about 20 ml *in vacuo* and the resulting solid was collected by filtration to give 0.30 g of **5b**. This filtrate was chromatographed on silica gel with $CHCl_3$–acetone to give 3.45 g (75.7 %) of 2-acetylamino-2-methylamino-3,3-dichloropropionamide (**3b**) and 0.24 g of **5b**. The total yield of **5b**

6) M. Sekiya and J. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **18**, 2242 (1970).

amounted to 0.62 g (20.0%). **3b**: IR ν_{max}^{Nujol} cm^{-1}: 3410, 3250, 3200 sh, 3130, 1702, 1650 sh, 1636 sh, 1623, 1600, and 1510. NMR ($CDCl_3$) δ: 2.10 (3H, s), 2.26 (3H, s), 3.02 (1H, br), 6.52 (1H, br), 6.54 (1H, s), and 6.82—7.60 (2H, br 2 peaks). *Anal.* Calcd. for $C_6H_{11}O_2N_3Cl_2$: C, 31.60; H, 4.86; N, 18.42. Found: C, 31.33; H, 5.08; N, 18.57. **5b**: IR ν_{max}^{Nujol} cm^{-1}: 3370, 3300, 3160, 1690, 1673, 1660, 1610, 1570, and 1550. NMR ($CDCl_3$) δ: 2.31 (3H, s), 3.00 (3H, d, J=5.5 Hz), 5.55 (1H, br), and *ca.* 6.60 (2H, br). *Anal.* Calcd. for $C_6H_9O_2N_3$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.22; H, 5.71; N, 27.21.

c) With Allylamine: A mixture of 3.94 g (20 mmoles) of **6** and 3.42 g (60 mmoles) of allylamine was stirred at room temperature for 5 days. The solvent was evaporated to dryness *in vacuo* and 150 ml of $CHCl_3$–10% acetone was added to the residue. The suspension obtained was allowed to stand at 0—5° for 3 hr and the resulting solid was collected by filtration to give 1.43 g of powder which was recrystallized from water to give 0.56 g of recovered starting material **6**. The filtrate was evaporated *in vacuo* and the residue was chromatographed on silica gel with $CHCl_3$–acetone to give 2.85 g (56.1% based on **6** consumed) of 2-acetylamino-2-allylamino-3,3-dichloropropionamide (**3c**) and 0.23 g (6.3% based on **6** consumed) of 2-methyl-5-allylaminooxazole-4-carboxamide (**5c**) together with 0.09 g of starting material **6**. The total amount of **6** recovered was 0.65 g. **3c**: IR ν_{max}^{Nujol} cm^{-1}: 3410, 3250, 3110, 1705, 1640 sh, 1630, and 1510. NMR ($CDCl_3$) δ: 2.06 (3H, s), 3.05 (1H, br), 5.00—6.30 (5H, m), 6.37 (1H, br), 6.55 (1H, s), and 6.85—7.60 (2H, br 2 peaks). *Anal.* Calcd. for $C_8H_{13}O_2N_3Cl_2$: C, 37.81; H, 5.16; N, 16.54. Found: C, 37.58; H, 5.07; N, 16.60. **5c**: IR ν_{max}^{Nujol} cm^{-1}: 3300, 3150, 1655, 1603, 1580 sh, and 1560. NMR (d_6-DMSO) δ: 2.30 (3H, s), 3.72—4.10 (2H, m), 4.98—5.40 (2H, m), 5.63—6.30 (1H, m), and 6.60—7.10 (3H, br). *Anal.* Calcd. for $C_8H_{11}O_2N_3$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.60; H, 6.12; N, 23.15.

d) With *n*-Propylamine: A mixture of 3.94 g (20 mmoles) of **6** and 4.72 g (80 mmoles) of *n*-propylamine in 300 ml of CH_3CN was stirred at room temperature for 3 days. After removal of the insoluble material, the solvent was evaporated *in vacuo* to dryness. The residue was chromatographed on silica gel with $CHCl_3$–10% acetone yielding 3.92 g (76.6%) of **3d** and 0.34 g (9.3%) of **5d**.

e) With Cyclohexylamine: A mixture of 3.94 g (20 mmole) of **6** and 5.94 g (60 mmole) of cyclohexylamine in 300 ml of CH_3CN was stirred at room temperature for 3 days. A work up similar to that described above gave 3.86 g (65.3%) of **3e** and *ca.* 0.1 g (2.3%) of **5e**.

f) With Benzylamine: A suspension of 3.94 g (20 mmoles) of **6** and 6.42 g (60 mmoles) of benzylamine in 300 ml of CH_3CN was stirred at room temperature for 6 days. Thin-layer chromatography (TLC) analysis of the reaction mixture showed that a considerable amount of **6** still remained. After addition of an additional 2.14 g (20 mmoles) of benzylamine, the mixture was stirred under reflux for 5 hr. The solvent was evaporated *in vacuo* and 50 ml of $CHCl_3$ was added to the residue. The resulting precipitate was filtered to afford colorless crystals (2.60 g) which were found to be cyclohexylamine hydrochloride. The filtrate was concentrated and chromatographed on silica gel yielding 2.71 g (44.6%) of 2-acetylamino-2-benzylamino-3,3-dichloropropionamide (**3f**) and 0.364 g (7.9%) of 2-methyl-5-benzylaminooxazole-4-carboxamide (**5f**). **3f**: IR ν_{max}^{Nujol} cm^{-1}: 3440, 3290, 3200, 1708, 1650, 1600, and 1510. NMR ($CDCl_3$) δ: 2.10 (3H, s), 3.02—3.90 (3H, m), 6.23 (1H, br), 6.57 (1H, s), and 6.90—7.65 (2H+5H, s and br 2 peaks). *Anal.* Calcd. for $C_{12}H_{15}O_2N_3Cl_2 \cdot C_6H_6$: C, 56.55; H, 5.54; N, 11.00. Found: C, 56.55; H, 5.28; N, 11.00. **5f**: IR ν_{max}^{Nujol} cm^{-1}: 3300, 3170, 1668, 1609, 1580, 1560, and 1503. NMR (d_6-DMSO) δ: 2.25 (3H, s), 4.48 (2H, d, J=6.0 Hz), 6.80 (2H. br), and 7.05—7.80 (1H+5H, br). *Anal.* Calcd. for $C_{12}H_{13}O_2N_3$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.19; H, 5.47; N, 18.20.

g) With Morpholine: A suspension of 1.97 g (10 mmoles) of **6** and 2.61 g (30 mmoles) of morpholine in 200 ml of CH_3CN was stirred at room temperature for 3 days. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel with $CHCl_3$–10% acetone yielding 1.60 g (56.3%) of 2-acetylamino-2-morpholine-3,3-dichloropropionamide (**3g**) and *ca.* 0.1 g (4.7%) of 2-methyl-5-morpholinooxazole-4-carboxamide (**5g**). **3g**: IR ν_{max}^{Nujol} cm^{-1}: 3450, 3300, 3200, 3140, 1710, 1665, 1650 sh, 1598. NMR (d_6-DMSO) δ: 2.00 (3H, s), 2.40—2.75 (4H, m), 3.43—3.80 (4H, m), 7.10—7.70 (2H, br 2 peaks), 7.36 (1H, s), and 7.97 (1H, br). Mass Spectrum *m/e* (rel. intensity): 287, 285, 283 (1: 6: 9, M^+, 0.3%), 243, 241, 239 (1: 6: 9, M^+–$CONH_2$, 87%), 229, 227, 225 (1: 6: 9, M^+–$NHCOCH_3$, 4%), 201, 199, 197 (1: 6: 9, M^+–$CONH_2$–42, 100%), 158 (18%), 88 (9%), 87 (9%), 86 (19%), 57 (13%). 43 (49%). *Anal.* Calcd. for $C_9H_{15}O_2N_3Cl_2$: C, 38.04; H, 5.32; N, 14.79. Found: C, 37.99; H, 5.31; N, 14.64. **5g**: IR ν_{max}^{Nujol} cm^{-1}: 3370, 3250, 3150, 1668, 1633, 1610, and 1570. NMR (d_6-DMSO) δ: 2.27 (3H, s), 3.42—3.76 (8H, m), and 6.90 (2H, br). Mass Spectrum *m/e* (rel. intensity); 211 (M^+, 44%), 194 (M^+–OH, 9%), 193 (M^+–H_2O, 56%), 151 (15%), 141 (11%), 140 (19%), 135 (12%), 125 (M^+–C_4H_8NO, 100%), 123 (14%), 110 (10%), 86 (20%), 85 (14%), 70 (12%), 69 (28%), 57 (13%), 56 (13%), 55 (14%), 54 (17%), 43 (39%), 42 (19%). *Anal.* Calcd. for $C_9H_{13}O_3N_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 51.13; H, 6.06; N, 20.01.

h) With Piperidine: A similar treatment of 3.94 g (20 mmoles) of **6** with 5.10 g (60 mmoles) of piperidine in 300 ml of CH_3CN gave 3.38 g (60.0%) of 2-acetylamino-2-piperidino-3,3-dichloropropionamide (**3h**) and 0.3 g (7.2%) of 2-methyl-5-piperidinooxazole-4-carboxamide (**5h**) after purification by silica gel chromatography. **3h**: IR ν_{max}^{Nujol} cm^{-1}: 3420, 3320, 3260, 3200, 1710, 1666 and 1590. NMR (d_6-DMSO) δ: 1.54 (6H, br), 2.06 (3H, s), 2.40—3.00 (4H, br), 6.70—7.80 (3H, br), and 7.40 (1H, s). Mass Spectrum *m/e* (rel. intensity): 241, 239, 237 (1: 6: 9, M^+–$CONH_2$, 63%), 227, 225, 223 (1: 6: 9, M^+–$NHCOCH_3$, 5%), 199, 197, 195 (1: 6: 9, M^+–$CONH_2$–42, 83%), 189, 187 (1: 3, 11%), 156 (15%), 85 (19%), 84 (85%), 44 (17%), 43

(100%), 42 (18%), 41 (20%). *Anal.* Calcd. for $C_{10}H_{17}O_2N_3Cl_2$: C, 42.57; H, 6.07; N, 14.89. Found: C, 42.31; H, 6.09; N, 14.52. **5h**: IR ν_{max}^{Nujol} cm^{-1}: 3340, 3250, 3200, 1668, 1648, 1620, and 1560. NMR (d_6-DMSO) δ: 1.55 (6H, br), 2.23 (3H, s), 3.03—3.60 (4H, br), and 6.70 (2H, br). Mass Spectrum *m/e* (rel. intensity): 209 (M^+, 100%), 192 (M^+-17, 21%), 177 (M^+-32, 8%), 164 (M^+-45, 19%), 151 (20%), 125 ($M^+-C_5H_{10}N$, 21%), 110, (10%), 99 (10%), 84 ($C_5H_{10}N^+$, 70%), 83 (43%), 69 (21%), 55 (15%), 43 (28%), 41 (23%). *Anal.* Calcd. for $C_{10}H_{15}O_2N_3$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.48; H, 7.41; N, 20.36.

Reactions of Methyl 2-Acetylamino-3,3-dichloroacrylate (7) with Amines——a) With Morpholine: To a stirred solution of 2.12 g (10 mmoles) of 7 in 100 ml of CH_3CN, 2.61 g (30 mmoles) of morpholine was added dropwise, then the mixture was stirred overnight at room temperature. After evaporation of the solvent *in vacuo*, the residual oil was chromatographed on silica gel with $CHCl_3$ yielding 2.13 g (94.2%) of methyl 2-methyl-5-morpholinooxazole-4-carboxylate (**9a**) as a colorless solid. Recrystallization from benzene-*n*-hexane afforded colorless needles, mp 98—101°. IR ν_{max}^{Nujol} cm^{-1}: 1692, 1635, and 1572. NMR ($CDCl_3$) δ: 2.33 (3H, s), 3.46—4.00 (8H, m), and 3.80 (3H, s). Mass Spectrum *m/e* (rel. intensity): 227 (M^++1, 10%), 226 (M^+, 85%), 208 (M^+-18, 5%), 195 (M^+–OCH_3, 22%), 182 (M^+-44, 6%), 155 (16%), 141 (9%), 140 (M^+–C_4H_8NO, 100%), 126 (16%), 112 (16%), 110 (31%), 86 (24%), 85 (17%), 84 (16%), 70 (15%), 55 (28%), 43 (42%), 42 (22%). *Anal.* Calcd. for $C_{10}H_{14}O_4N_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.98; H, 6.23; N, 12.52.

b) With *n*-Propylamine: To a stirred solution of 1060 mg (5 mmoles) of 7 in 100 ml of CH_3CN, 890 mg (15 mmoles) of *n*-propylamine was added and the mixture was further stirred overnight at room temperature. After removal of the insoluble material by filtration, the solvent was evaporated *in vacuo*. The residue was extracted with 300 ml of ether and the extract was washed with water, then dried ($MgSO_4$). The solvent was evaporated *in vacuo* to dryness affording 1130 mg of a solid. The solid was a mixture of methyl 2-methyl-5-*n*-propylaminooxazole-4-carboxylate (**9b**) and methyl 2-acetylamino-2-*n*-propylamino-3,3-dichloropropionate (**8b**) in the ratio of 56: 44 according to its NMR spectrum. An attempt to separated them by silica gel column chromatography failed. But fractional recrystallization from benzene–*n*-hexane yielded pure **8b** and **9b**, both as colorless needles. **8b**: mp 69—71° (from benzene–*n*-hexane). IR ν_{max}^{Nujol} cm^{-1}: 3250, 3050, 1760, 1675 sh, 1660, 1610 sh, 1540. NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.0 Hz), 1.32—1.74 (2H, m), 2.08 (3H, s), 2.20—2.70 (2H, m), 3.05 (1H, br), 3.86 (3H, s), 6.29 (1H, s), and 6.68 (1H, br). Mass Spectrum *m/e* (rel. intensity): 215, 213, 211 (1: 6: 9, M^+–$COOCH_3$, 42%), 187 (M^+–$CHCl_2$, 31%), 173, 171, 169 (1: 6: 9, M^+–$COOCH_3$–CH_2=C=O, 75%), 145 (M^+–$CHCl_2$–CH_2=C=O, 77%), 127 (7%), 58 (20%), 43 (100%), 42 (14%), 41 (21%). *Anal.* Calcd. for $C_9H_{16}O_3N_2Cl_2$: C, 39.87; H, 5.95; N, 10.33. Found: C, 40.08; H, 5.86; N, 10.48. **9b**: mp 77—80° (from benzene–*n*-hexane). IR ν_{max}^{Nujol} cm^{-1}: 3450—3340, 1690 sh, 1660, and 1610. NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.0 Hz), 1.34—1.92 (2H, m), 2.32 (3H, s), 3.15—3.56 (2H, q, J=7.0 Hz), 3.80 (3H, s), and 6.10 (1H, br). Mass Spectrum *m/e* (rel. intensity): 198 (M^+, 100%). *Anal.* Calcd. for $C_9H_{14}O_3N_2$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.04; H, 7.70; N, 14.02.

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