Synthesis of 2-(Pyrimidin-1-yl)- and 2-(Purin-9-yl)-2-amino Acids

Takashi Nishitani, Tameo Iwasaki, Yoshitaka Mushika, and Muneji Miyoshi*

Department of Synthetic Chemistry, Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co. Ltd., 16-89, Kashima-3-chome, Yodogawa-ku, Osaka, Japan

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2-(Pyrimidin-1-yl)-2-amino acid derivatives were synthesized in excellent yields by the substitution reactions of 2-acetoxy-2-amino acid derivatives with a variety of naturally occurring pyrimidine bases in the presence of triethylamine or sodium hydride. Silyl Hilbert–Johnson procedure gave nearly the same results in the substitution reactions. This method was applied to a preparation of amino acids containing 5-fluorouracil. 2-(Purin-9-yl)-2-amino acid derivatives were also obtained in good yields by the use of purine bases under basic conditions.

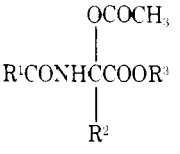
Amino acids containing nucleic acid bases such as N^1-pyrimidylamino acids and N^9-purinylamino acids are of interest as a class of unconventional nucleoside analogues[1] in which nucleic acid bases are attached onto nonsaccharidal residues. A number of this class of amino acids have been synthesized systematically and the biological evaluation of these amino acids has recently been provided.[2] Almost all of these studies, however, are still confined to a synthesis of amino acids having the bases either at the side chains or at the amino and/or carboxylic acid groups of the amino acids.[3a-c] Although amino acids containing nucleic acid bases at the 2-positions are recognized to be possibly involved in biological processes,[4] these 2-substituted-2-amino acids possessing labile geminal diamine moieties[5] have not yet been synthesized. This is presumably due to the difficulty encountered in the direct introduction of the nucleic acid bases to the 2-position of amino acids.

On the other hand, 2-functionalized-2-amino acid derivatives[6a-c] have recently been noted with special interest as potent intermediates in a preparation of 2-substituted-2-amino acids.[7a,b] Most recently, the synthetic versatility of 2-acetoxy-2-amino acids[8] in amino acid chemistry has been demonstrated by us[9] and by Olsen et al.;[10] the 2-acetoxy-2-amino acids undergo substitution reactions with a variety of nucleophiles under either basic or Lewis acid catalyzed conditions to afford physiologically interesting 2-substituted-2-amino acids. We now wish to report a synthesis of a novel class of amino acids, 2-(pyrimidin-1-yl)-2-amino acids and 2-(purin-9-yl)-2-amino acids, by the substitution reactions of several 2-acetoxy-2-amino acids with a variety of pyrimidines and purines, respectively.

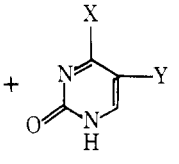
Pyrimidylamino Acids. A synthesis of the pyrimidylamino acid derivatives was carried out according to Scheme I. The reaction of uracil **2a** with *N*-acetyl 2-acetoxyglycinate (**1a**) in dimethylformamide in the presence of 1 molar equiv of triethylamine at room temperature afforded the 2-substitution product, ethyl *N*-acetyl-2-(uracil-1-yl)glycinate (**3a**), in 57% yield. Thymine (**2b**) and cytosine (**2c**) also reacted with the acetoxyglycinate **1a** to give the corresponding 2-substituted-2-amino acids **3b,c** in good yields. In these reactions, substitution at the N^1-position of the pyrimidine bases took place exclusively without any formation of byproducts. The use of sodium hydride instead of triethylamine, however, resulted in the formation of the N^1,N^3-disubstitution product along with the N^1-substitution product; treatment of thymine with the acetoxyglycinate **1a**, for example, afforded the N^1,N^3-disubstitution product (24%) and the N^1-substitution one (56%).

On the other hand, in the reaction of the pyrimidine bases with the 2-acetoxyamino acid derivatives other than the 2-acetoxyglycinate **1a**, sodium hydride was found to be preferable over triethylamine for selective formation of the N^1-substitution product; in the case of triethylamine, only the elimination product, α,β-dehydroamino acid, was observed.

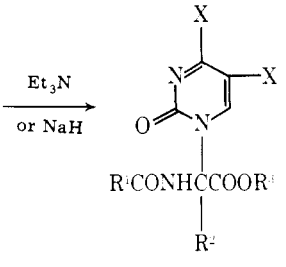
Scheme I



1a, $R^1 = CH_3$; $R^2 = H$; $R^3 = C_2H_5$
b, $R^1 = CH_3(CH_2)_2$; $R^2 = H$; $R^3 = C_2H_5$
c, $R^1 = PhCH_2O$; $R^2 = H$; $R^3 = C_2H_5$
d, $R^1 = R^2 = CH_3$; $R^3 = C_2H_5$
e, $R^1 = R^2 = CH_3$; $R^3 = CH_2Ph$
f, $R^1 = CH_3$; $R^2 = CH_2Ph$; $R^3 = C_2H_5$
g, $R^1 = CH_3$; $R^2 = CH_2CH{=}CH_2$; $R^3 = C_2H_5$



2a, X = OH; Y = H
b, X = OH; Y = CH_3
c, X = NH_2; Y = H
d, X = OH; Y = F



3a, $R^1 = CH_3$; $R^2 = H$; $R^3 = C_2H_5$; X = OH; Y = H
b, $R^1 = CH_3$; $R^2 = H$; $R^3 = C_2H_5$; X = OH; Y = CH_3
c, $R^1 = CH_3$; $R^2 = H$; $R^3 = C_2H_5$; X = NH_2; Y = H
d, $R^1 = R^2 = CH_3$; $R^3 = C_2H_5$; X = OH; Y = H
e, $R^1 = R^2 = CH_3$; $R^3 = C_2H_5$; X = OH; Y = CH_3
f, $R^1 = CH_3$; $R^2 = CH_2Ph$; $R^3 = C_2H_5$; X = OH; Y = CH_3
g, $R^1 = CH_3(CH_2)_2$; $R^2 = H$; $R^3 = C_2H_5$; X = OH; Y = F
h, $R^1 = PhCH_2O$; $R^2 = H$; $R^3 = C_2H_5$; X = OH; Y = F
i, $R^1 = R^2 = CH_3$; $R^3 = C_2H_5$; X = OH; Y = F
j, $R^1 = R^2 = CH_3$; $R^3 = CH_2Ph$; X = OH, Y = F
k, $R^1 = CH_3$; $R^2 = CH_2CH{=}CH_2$; $R^3 = C_2H_5$; X = OH; Y = F

On treatment of ethyl *N*-acetyl-2-acetoxyalaninate (**1d**) with uracil **2a** in dimethylformamide at 5–10 °C for 30 min using sodium hydride as a base, ethyl *N*-acetyl-2-(uracil-1-yl)alaninate (**3d**) was obtained in 76% yield. The other pyrimidine bases were also treated with the 2-acetoxyalaninate **1d** and 2-acetoxyphenylalaninate **1f** under the same conditions to give the corresponding pyrimidylamino acids in satisfactory yields

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Table I. Yields and Characterization of the 2-Pyrimidyl and 2-Purinyl-2-amino Acids[a]

compd	base	% yield	mp, °C	UV, λ_{max}[b], nm ($\epsilon \times 10^{-3}$)	NMR (Me_2SO-d_6), δ
3a	Et_3N	57	202–204	259 (10.13)	1.20 (t, 3 H), 1.98 (s, 3 H), 4.19 (q, 2 H), 5.64 (d, 1 H), 6.33 (d, 1 H), 7.67 (d, 1 H), 9.17 (d, 1 H), 11.44 (s, 1 H)
3b	Et_3N	72	187–189	264 (9.57)	1.20 (t, 3 H), 1.80 (s, 3 H), 1.97 (s, 3 H), 4.18 (q, 2 H), 6.30 (d, 1 H), 7.55 (s, 1 H), 9.15 (d, 1 H), 11.44 (s, 1 H)
3c	Et_3N	91	174 dec	238 (7.49) 269 (7.44)	1.18 (t, 3 H), 1.97 (s, 3 H), 4.14 (q, 2 H), 5.75 (d, 1 H), 6.19 (d, 1 H), 7.30 (s, 2 H), 7.67 (d, 1 H), 9.05 (d, 1 H)
3d	NaH	76	190 dec	259 (10.13)	1.19 (t, 3 H), 1.92 (s, 3 H), 1.97 (s, 3 H), 4.18 (q, 2 H), 5.57 (d, 1 H), 7.89 (d, 1 H), 8.53 (s, 1 H), 11.39 (s, 1 H)
3e	NaH	79	189 dec	264 (9.91)	1.18 (t, 3 H), 1.84 (s, 3 H), 1.92 (s, 3 H), 1.99 (s, 3 H), 4.17 (q, 2 H), 7.75 (s, 1 H), 8.44 (s, 1 H), 11.36 (s, 1 H)
3f	NaH	57	219 dec	264 (11.36)	1.12 (t, 3 H), 1.87 (s, 3 H), 1.99 (s, 3 H), 3.04 and 4.55 (ABq, 2 H), 4.04 (q, 2 H), 6.8–7.4 (m, 5 H), 8.03 (s, 1 H), 8.14 (s, 1 H), 11.02 (s, 1 H)
3g	NaH	48	150–152	266 (8.71)	0.85 (t, 3 H), 1.20 (t, 3 H), 1.3–1.9 (m, 2 H), 2.24 (t, 2 H), 4.19 (q, 2 H), 6.33 (d, 1 H), 8.02 (d, 1 H), 9.12 (d, 1 H), 12.01 (s, 1 H)
3h	Et_3N	53	syrup	265 (7.29)	1.20 (t, 3 H), 4.18 (q, 2 H), 5.12 (s, 2 H), 6.30 (d, 1 H), 7.35 (s, 5 H), 7.92 (d, 1 H), 8.57 (d, 1 H)
3i	NaH	68	171 dec	266 (8.51)	1.18 (t, 3 H), 1.92 (s, 3 H), 1.96 (s, 3 H), 4.18 (q, 2 H), 8.27 (d, 1 H), 8.58 (d, 1 H), 11.96 (s, 1 H)
3j	NaH	71	118 dec	265 (7.90)	1.93 (t, 3 H), 1.98 (s, 3 H), 5.15 (s, 2 H), 7.32 (s, 5 H), 8.21 (d, 1 H), 8.63 (s, 1 H), 11.95 (s, 1 H)
3k	NaH	40	178 dec	266 (8.47)	1.18 (t, 3 H), 1.95 (s, 3 H), 2.4–4.1, (ABm, 2 H), 4.17 (q, 2 H), 4.9–5.9 (m, 3 H), 8.35 (d, 1 H), 8.42 (s, 1 H), 12.01 (d, 1 H)
6a	NaH	51[c]	145–146	264 (8.97)	1.19 (t, 3 H), 1.99 (s, 3 H), 4.13 (q, 2 H), 6.83 (d, 1 H), 8.63 (s, 1 H), 8.75 (s, 1 H), 9.63 (d, 1 H)
6b	NaH	79	197 dec	259 (14.50)	1.14 (t, 3 H), 2.01 (s, 3 H), 2.31 (s, 3 H), 4.15 (q, 2 H), 7.25 (s, 2 H), 8.11 (s, 1 H), 8.16 (s, 1 H), 9.37 (s, 1 H)
6c	NaH	72	144–145	265 (9.02)	1.17 (t, 3 H), 2.08 (s, 3 H), 2.31 (s, 3 H), 4.19 (q, 2 H), 8.64 (s, 1 H), 8.81 (s, 1 H), 9.61 (s, 1 H)
6d	NaH	41	191 dec	324 (23.86)	1.14 (t, 3 H), 2.03 (s, 3 H), 2.25 (s, 3 H), 4.14 (q, 2 H), 8.19 (s, 2 H), 9.42 (s, 1 H), 13.78 (s, 1 H)
6e	NaH	57	197 dec	257 (15.13)	1.11 (t, 3 H), 1.92 (s, 3 H), 3.9–4.5 (m, 4 H), 6.8–7.5 (m, 7 H, Ph + NH_2), 8.21 (s, 1 H), 8.46 (s, 1 H), 9.03 (s, 1 H)
8	[d]	38	142–143	260 (10.70)	1.27 (t, 3 H), 2.15 (s, 3 H), 2.21 (s, 3 H), 3.27 (s, 3 H), 4.26 (q, 2 H), 5.58 (d, 1 H), 8.09 (d, 1 H), 9.6–9.9 (br, 1 H)

[a] Satisfactory elemental analyses were obtained for all new compounds listed above. [b] Measured in MeOH. [c] N^7-substitution product was formed in 9% yield. [d] $SnCl_4$ was used as a catalyst.

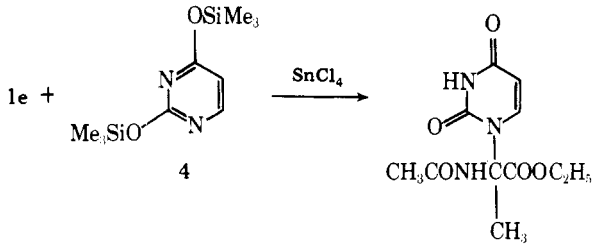
(see Table I). In the above reactions, N^1-substitution products were formed predominantly with entire exclusion of byproducts such as N^3-substitution products and N^1,N^3-disubstitution products, though concomitant formation of such byproducts was usually observed in the alkylation of the pyrimidine bases.[11]

An appreciable amount of α,β-dehydroamino acids was detected in the above substitution reactions by the use of sodium hydride as a base. It has already been reported that 2-functionalized-2-amino acids such as 2-acetoxyamino acids[9] and 2-methoxyamino acids[5b,12] undergo competitive elimination reaction as well as the substitution reaction when a feeble nucleophile is used. In the initial stage of the reactions under the conditions employed here, however, the α,β-dehydroamino acids were not detected at all but only the substitution products were observed. Furthermore, prolonged reaction time caused a conspicuous decrease of the substitution products with increase of the α,β-dehydroamino acids; the reaction of thymine with acetoxyphenylalaninate **1f** for 5 h, for example, resulted in 5% yield of the substitution product **3f** and 88% yield of the α,β-dehydroamino acid. Accordingly, the formation of the α,β-dehydroamino acids seems likely to take place via the elimination reaction of the products, pyrimidylamino acids, by the action of sodium acetate formed during the reaction. Indeed, on treatment of the pyrimidylalaninates or pyrimidylphenylalaninates with sodium acetate in dimethylformamide at 0–5 °C for 10 h, the corresponding α,β-dehydroamino acids formed quantitatively.

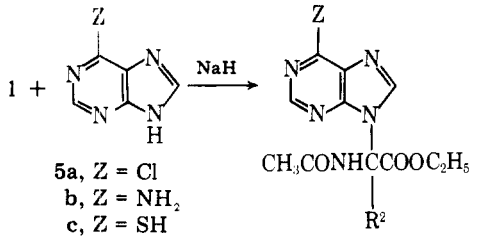
It was also found that the silyl Hilbert–Johnson reaction[13] could be used to effect the preparation of these pyrimidylamino acids. 2-Acetoxyalaninate **1d**, for example, reacted with 2,4-bis(trimethylsilyl)uracil (**4**) in acetonitrile in the presence of 0.25 molar equiv of stannic chloride at −10 °C to afford the corresponding coupling product **3d** in 72% yield (Scheme II). In this case, the reaction should be quenched carefully by using 1 molar equiv of sodium hydrogen carbonate to that of stannic chloride; the use of an excess amount of sodium hydrogen carbonate caused the decomposition of the product.

The above substitution reaction has been extended in a synthesis of amino acids containing 5-fluorouracil, which is well-known to exhibit a strong antitumor activity. The 2-

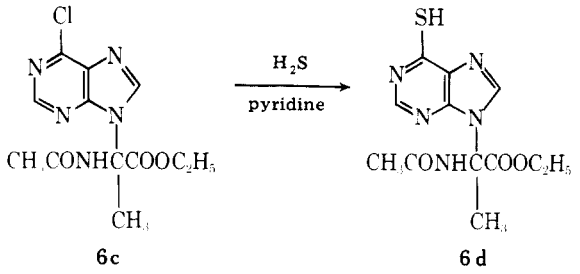
Scheme II



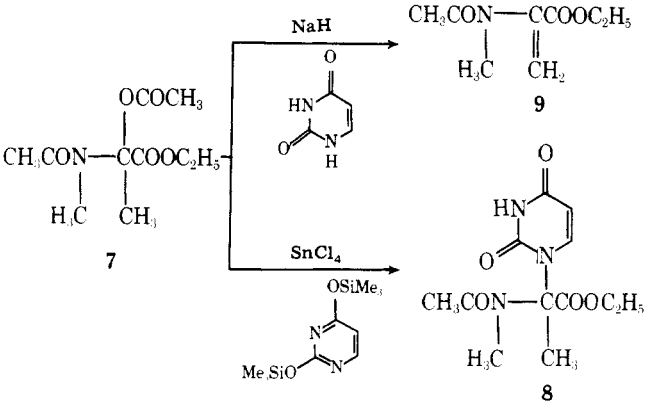
Scheme III



Scheme IV



Scheme V



acetoxyamino acid derivatives **1b–e,g** were allowed to react with 5-fluorouracil in the presence of triethylamine or sodium hydride as described above to afford the corresponding amino acids **3g–k** containing 5-fluorouracil in 40–71% yields. Benzyl *N*-acetyl-2-(5-fluorouracil-1-yl)alaninate (**3j**) thus obtained was reduced by the use of palladium on charcoal to give *N*-acetyl-2-(5-fluorouracil-1-yl)alanine in a quantitative yield. Attempts were made to convert ethyl *N*-(benzyloxycarbonyl)-2-(5-fluorouracil-1-yl)glycinate (**3h**) into the amino acid ester by hydrogenolysis using palladium on charcoal under various conditions. In this reaction, however, no amino acid ester was obtained but 5-fluorouracil was isolated in a quantitative yield. This fact indicates that the amino acid ester is so unstable as to isolate at least at room temperature.

The position of substitution of the pyrimidylamino acids was determined by the UV spectra. It is generally recognized[14] that UV spectra of N^1-alkylated pyrimidines show absorption maxima at almost the same wavelengths in neutral and alkaline media, whereas the absorption maxima of N^3-alkylated pyrimidines exhibit significantly higher wavelengths in alkaline medium than those in neutral medium. The pyrimidylamino acids obtained here have UV spectra characteristic of N^1-alkylated pyrimidines.

The yields and characterization of these amino acids are summarized in Table I.

Purinylamino Acids. It has been reported that direct alkylation of purine bases such as adenine[15] or 6-chloropurine[16] leads to isomeric mixtures of the purinyl derivatives. The position of alkylation on the purine bases is determined by reactivity of alkyl halides, solvents, and the presence or absence of a proton acceptor.[17]

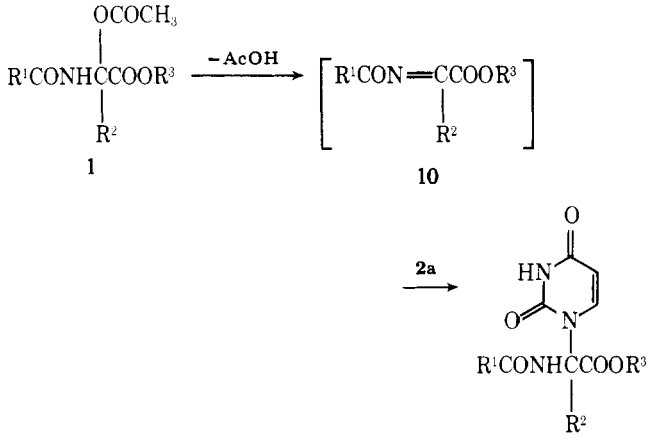
Initially, the reaction of the 2-acetoxyglycinate **1a** with 6-chloropurine (**5a**) was carried out under the same conditions as those employed for the preparation of the pyrimidylamino acids **3**, and the desired N^9-substitution product **6a** was obtained in 51% yield (Scheme III). In this reaction, the N^7-substitution product was formed in 9% yield. Although a variety of reaction conditions have been examined, the reaction conditions described here seem to be best to minimize the formation both of the substitution products other than the N^9-substitution ones and of the elimination products, α,β-dehydroamino acids. The other purine bases were also allowed to react with the acetoxyamino acids to give the corresponding purinylamino acids in good yields. The 6-thiol group of the purine **5c** did not participate[18] in the substitution reaction with the acetoxyamino acids. 2-(6-Mercaptopurin-9-yl)alaninate **6d** was also derived from the corresponding 6-chloropurine derivative **6c**. Treatment of compound **6c** with hydrogen sulfide in pyridine[19] afforded compound **6d** in 60% yield without cleavage of the geminal diamine skeleton (Scheme IV). The physical constants of compound **6d** thus obtained were identical with those prepared above.

The yields and the spectral data are listed in Table I. The position of substitution of the purinylamino acids **6** were confirmed by the spectral data.[14]

The biological activity of the amino acids reported herein is currently under investigation.

Reaction Intermediate. It has been documented that amidoalkylation reactions under neutral or basic conditions proceed through either S_N1 or S_N2 processes. Recently, S_N1 process resulting in the formation of transient intermediates, *N*-acylimines,[6c,10,20] has been suggested to be involved in nucleophilic substitution reactions on 2-functionalized-2-amino acids. In such reactions, however, the reaction mechanism is considered to be dominated by the structural features of the 2-functionalized-2-amino acids and/or by nucleophilicity of attacking reagents.[21a,b] In order to get an insight into the mechanism in the reactions of the 2-acetoxy-2-amino acids with the nucleic acid bases, the *N*-methyl analogue **7**, in which an *N*-acylimine cannot form, was treated with uracil under base-catalyzed conditions. In this reaction, no substitution product **8** was detected, but the elimination product **9** formed quantitatively. On the other hand, to exclude the possibility that the elimination product **9** may form from the substitution product **8** by the action of sodium acetate formed during the reaction, compound **8** was synthesized by silyl Hilbert-Johnson procedure and treated with sodium acetate in dimethylformamide at a temperature of 0–80 °C (Scheme V). Surprisingly, compound **8** was quite stable in the above basic medium. Accordingly, the elimination product **9** would be

Scheme VI



formed from the acetoxyamino acid **7**. These results strongly suggest that the formation of the *N*-acylimine intermediate is essential in such nucleophilic substitution reactions on 2-acetoxy-2-amino acids. As shown in Scheme VI, the *N*-acylimine **10** is probably formed in the incipient process by elimination of acetic acid from the acetoxyamino acid **1**, and then the addition reaction of uracil to the reactive carbon–nitrogen double bond of the *N*-acylimine **10** would take place to afford the substitution product.

Experimental Section

Equipment. Melting points were measured using the Yamato melting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu IR-27 infrared spectrophotometer. NMR spectra were obtained using a Hitachi Perkin-Elmer R-20 high-resolution NMR spectrometer with tetramethylsilane as internal standard. UV spectra were measured on a Hitachi EPS-3T spectrometer. Mass spectra were taken by a Hitachi M-60 mass spectrometer.

Preparation of *N*-Acyl-2-acetoxy-2-amino Acid Esters 1a–g. The acetoxyamino acids **1a–g** were prepared according to the method described previously.[8] Compounds **1a,c,d,f,g** showed the same physical constants as those reported. Compound **1b**, which was obtained in 85% yield by the electrolysis of butanamidemalonic acid monoester, showed mp 33–35 °C: NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.28 (t, 3 H), 1.4–2.0 (m, 2 H), 2.10 (s, 3 H), 2.1–2.5 (m, 2 H), 4.24 (q, 2 H), 6.38 (d, 1 H), 7.66 (d, 1 H). Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 52.20; H, 7.33; N, 6.14. The electrolysis of monobenzyl methylacetamidomalonate afforded compound **1e** (98% yield): mp 67–69 °C; NMR ($CDCl_3$) δ 1.96 (s, 3 H), 2.00 (s, 3 H), 5.17 (s, 2 H), 7.30 (s, 5 H), 7.38 (s, 1 H). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.13; N, 5.02. Found: C, 60.34; H, 6.08; N, 5.05.

Preparation of Compound 7. Benzyl ethyl methyl(*N*-acetyl-*N*-methylamino)malonate (6.22 g, 20.3 mmol), which was prepared by the reported method,[8] was dissolved in 60 mL of dioxane and the solution was subjected to hydrogenolysis over 10% Pd–C (0.6 g). After a theoretical amount of hydrogen was absorbed, the catalyst was filtered off and the filtrate was evaporated to dryness in vacuo. The resulting crystals were recrystallized with ethyl acetate–*n*-hexane to afford 4.31 g (98% yield) of monoethyl methyl(*N*-acetyl-*N*-methylamino)malonate as prisms: mp 91–92 °C dec; IR (Nujol) 2600, 1741, 1610 cm^{-1}; NMR (Me_2SO-d_6) δ 1.15 (t, 3 H), 1.56 (s, 3 H), 2.03 (s, 3 H), 2.90 (s, 3 H), 4.08 (q, 2 H). This compound is unstable and should be kept below 0 °C. When, for example, the compound was allowed to stand at room temperature for 72 h, it was converted quantitatively to ethyl *N*-acetyl-*N*-methylalaninate.

The monoester (3.03 g, 14 mmol) was electrolyzed[8] in a mixture of acetic acid (60 mL) and tetrahydrofuran (20 mL) containing 0.4 g of sodium acetate to afford compound **7** (2.92 g, 90% yield) as a colorless syrup: NMR ($CDCl_3$) δ 1.28 (t, 3 H), 1.86 (s, 3 H), 2.07 (s, 3 H), 2.10 (s, 3 H), 3.19 (s, 3 H), 4.26 (q, 2 H); mass spectrum *m/e* 231 (M^+), 188, 186, 173, 172, 171, 159, 158, 144, 131, 130, 129, 117, 116, 102, 85, 74, 56.

Reactions of Acetoxyamino Acids 1 with Pyrimidine Bases 2 in the Presence of Triethylamine (Typical Procedure). Ethyl *N*-acetyl-2-acetoxyglycinate (**1a**; 2.23 g, 11 mmol) and uracil 1.12 g (10 mmol) were dissolved in 20 mL of dimethylformamide. To this was added dropwise 1.01 g of triethylamine at room temperature and the reaction mixture was stirred for 2 days at the same temperature. The solvent was evaporated to dryness in vacuo. To the residue was added 10 mL of water and the product was extracted with three 100-mL portions of ethyl acetate. The combined ethyl acetate solution was dried over magnesium sulfate and evaporated to dryness in vacuo. The resulting colorless crystals were recrystallized from water to afford 1.45 g (57% yield) of compound **3a** as leaflets. Melting points and NMR data are given in Table I. Compound **3a**: IR (Nujol) 3270, 3160, 3020, 1741, 1690, 1657, 1549 cm^{-1}; UV λ_{max} (MeOH) 259 nm (ϵ 1.01 $\times$ 10^4); λ_{min} (MeOH) 229 nm (ϵ 2.17 $\times$ 10^3); λ_{max} (0.1 N HCl[22]) 259 nm (ϵ 1.01 $\times$ 10^4); λ_{min} (0.1 N HCl) 230 nm (ϵ 2.33 $\times$ 10^3); λ_{max} (0.01 N NaOH[23]) 263 nm (ϵ 7.08 $\times$ 10^3); λ_{min} (0.01 N NaOH) 243 nm (ϵ 4.85 $\times$ 10^3). Anal. Calcd for $C_{10}H_{13}N_3O_5$: C, 47.06; H, 5.13; N, 16.46. Found: C, 46.95; H, 5.08; N, 16.64.

Compound **3b** was similarly prepared by the reaction of acetoxyglycinate **1a** and thymine.

When acetoxyglycinate **1a** (2.23 g, 11 mmol) was treated with thymine (1.26 g, 10 mmol) at 5–10 °C for 30 min in the presence of 65% sodium hydride (0.37 g, 10 mmol), two products were observed on TLC of the reaction mixture. These were separated by silica gel chromatography using chloroform–methanol (20:1) as eluent to give N^1-substitution product **3b** and the N^1,N^3-disubstitution product in 56 and 24% yields, respectively. The physical constants of the N^1-substitution product obtained here were the same as those described above. The N^1,N^3-disubstitution product shows mp 182–194 °C; IR (Nujol) 3260, 1767, 1750, 1720, 1686, 1670, 1655, 1607 cm^{-1}; NMR (Me_2SO-d_6) δ 1.14 (t, 3 H), 1.18 (t, 3 H), 1.87 (s, 3 H), 1.93 (s, 3 H), 1.98 (s, 3 H), 4.11 (q, 2 H), 4.16 (q, 2 H), 6.31 and 6.33 (d d, 1 H), 7.07 (d, 1 H), 7.65 (s, 1 H), 8.58 and 8.61 (d d, 1 H), 9.14 and 9.21 (d d, 1 H); UV λ_{max} (MeOH) 267 nm (ϵ 9.37 $\times$ 10^3); λ_{min} (MeOH) 236 nm (ϵ 2.32 $\times$ 10^3); λ_{max} (0.1 N HCl) 268 nm (δ 9.13 $\times$ 10^3); λ_{min} (0.1 N HCl) 237 nm (ϵ 2.16 $\times$ 10^3); λ_{max} (0.01 N NaOH) 273 nm (ϵ 8.97 $\times$ 10^3); λ_{min} (0.01 N NaOH) 239 nm (ϵ 1.77 $\times$ 10^3). Anal. Calcd for $C_{17}H_{24}N_4O_8$: C, 49.51; H, 5.86; N, 13.59. Found: C, 49.62; H, 5.87; N, 13.52.

Reaction of Acetoxyamino Acids 1 with Pyrimidine Bases 2 in the Presence of Sodium Hydride (Typical Procedure). Ethyl *N*-acetyl-2-(uracil-1-yl)alaninate (**3d**) was prepared as follows. Uracil (0.56 g, 5 mmol) was dissolved in 20 mL of dimethylformamide. To this was added 65% sodium hydride (0.18 g) in one portion. The reaction mixture was stirred at 60 °C for 20 min and then cooled to 5–10 °C. To this was added portionwise ethyl *N*-acetyl-2-acetoxyalaninate (**1d**; 1.09 g, 5 mmol) at 5–10 °C under vigorous stirring. The stirring was continued for an additional 30 min and then 300 mL of ethyl acetate was added to the reaction mixture. The insoluble materials were filtered and the filtrate was washed with three 100-mL portions of water. The organic layer was separated, dried over magnesium sulfate, and evaporated in vacuo. The resulting residue was washed with 100 mL of petroleum ether, followed by 100 mL of isopropyl ether. The residue was crystallized by addition of ether. The crystals were collected by filtration and recrystallized with ethyl acetate–petroleum ether to afford 1.02 g (76%) of compound **3d** as colorless needles: IR (Nujol) 3410, 3210, 3110, 1758, 1710, 1678, 1620 cm^{-1}; UV λ_{max} (MeOH) 259 nm (ϵ 1.01 $\times$ 10^4); λ_{min} (MeOH) 230 nm (ϵ 2.43 $\times$ 10^3); λ_{max} (0.1 N HCl) 259 nm (ϵ 1.02 $\times$ 10^4); λ_{min} (0.1 N HCl) 231 nm (ϵ 2.72 $\times$ 10^3); λ_{max} (0.01 N NaOH) 260 nm (ϵ 7.05 $\times$ 10^3); λ_{min} (0.01 N NaOH) 243 nm (ϵ 5.32 $\times$ 10^3). Anal. Calcd for $C_{11}H_{15}N_3O_5$: C, 49.07; H, 5.62; N, 15.61. Found: C, 49.06; H, 5.68; N, 15.59. The melting point and other spectral data are described in Table I.

The compounds **3c,e–k** were also synthesized by the same procedure as above.

Silyl Hilbert–Johnson Procedure (Typical Procedure). 2,4-Bis(trimethylsilyl)uracil (**4**; 1.28 g, 5 mmol) and ethyl *N*-acetyl-2-acetoxyalaninate (**1d**; 1.09 g, 5 mmol) were dissolved in 20 mL of acetonitrile. To this was added dropwise stannic chloride (0.12 mL, 1.0 mmol) at 5–10 °C under vigorous stirring. The stirring was continued for 45 min at the same temperature. The reaction was quenched by addition of 5 mL of water containing 0.67 g of sodium hydrogen carbonate. The organic layer was separated, dried over magnesium sulfate, then evaporated to dryness in vacuo. To the resulting residue was added 50 mL of chloroform and the insoluble materials were filtered off. The filtrate was evaporated to dryness in vacuo. To the resulting residue was added ether and the crystals were collected by filtration to afford ethyl *N*-acetyl-2-(uracil-1-yl)alaninate (**3d**) in 72% yield. The physical constants were the same as those described above.

Reaction of Acetoxyamino Acids 1 with Purine Bases 5 (Typical Procedure). Ethyl *N*-acetyl-2-(adenin-9-yl)alaninate (**6b**) was prepared as follows. Adenine (**5b**; 0.67 g, 5 mmol) was dissolved in 20 mL of dimethylformamide. To this was added 65% sodium hydride (0.18 g, 5 mmol) in one portion and the reaction mixture was

stirred at 60 °C for 30 min. To this was added ethyl *N*-acetyl-2-acetoxyalaninate (**1d**; 1.09 g, 5 mmol) at 5–10 °C under vigorous stirring. The stirring was continued for additional 30 min at the same temperature. Water (100 mL) was added to the reaction mixture and the solution was adjusted to about pH 6 with acetic acid. The product was extracted with five 100-mL portions of ethyl acetate. The combined organic layer was washed with two 50-mL portions of water, dried over magnesium sulfate, and evaporated to dryness in vacuo. The resulting residue was washed with two 100-mL portions of *n*-hexane and crystallized by addition of ether. The crystals were collected by filtration and recrystallized from ethanol–*n*-hexane to afford 1.15 g (79% yield) of compound **6b** as colorless plates: IR (Nujol) 3390, 3290, 3120, 1746, 1692, 1669, 1607 cm^{-1}; UV λ_{max} (MeOH) 259 nm (ϵ 1.45 × 10^4); λ_{min} (MeOH) 227 nm (ϵ 2.21 × 10^3); λ_{max} (0.1 N HCl) 257 nm (ϵ 1.45 × 10^4); λ_{min} (0.1 N HCl) 229 nm (ϵ 3.21 × 10^3); λ_{max} (0.01 N NaOH) 261 nm (ϵ 1.41 × 10^4); λ_{min} (0.01 N NaOH) 230 nm (ϵ 2.78 × 10^3). Anal. Calcd for $C_{12}H_{16}N_6O_3$: C, 49.31; H, 5.52; N, 28.75. Found: C, 49.31; H, 5.53; N, 28.93.

The melting points and other spectral data are shown in Table I.

In the reaction of ethyl *N*-acetyl-2-acetoxyglycinate (**1a**) with 6-chloropurine (**5a**), two products were observed on TLC of the reaction mixture. These were separated by preparative thin-layer chromatography (Merck Kieselgel 60 F_{254}) with chloroform–methanol (20:1) as developing solvent to give the N^9-substitution product **6a** and the N^7-substitution product in 51 and 9% yields, respectively. Ethyl *N*-acetyl-2-(6-chloropurin-7-yl)glycinate: mp 120–121 °C; IR (Nujol) 3290, 3130, 3060, 1742, 1669, 1601 cm^{-1}; NMR (Me_2SO-d_6) δ 1.19 (t, 3 H), 2.03 (s, 3 H), 4.25 (q, 2 H), 7.12 (d, 1 H), 8.87 (s, 2 H), 9.63 (d, 1 H); UV λ_{max} (MeOH) 269 nm (ϵ 7.85 × 10^3); λ_{min} (MeOH) 228 nm (ϵ 2.59 × 10^3); λ_{max} (0.1 N HCl) 268 nm (ϵ 7.86 × 10^3); λ_{min} (0.1 N HCl) 228 nm (ϵ 2.10 × 10^3); λ_{max} (0.01 N NaOH) 272 nm (ϵ 8.18 × 10^3); λ_{min} (0.01 N NaOH) 234 nm (ϵ 1.75 × 10^3). Anal. Calcd for $C_{11}H_{12}N_5O_3Cl$: C, 44.38; H, 4.06; N, 23.53; Cl, 11.91. Found: C, 44.52; H, 4.18; N, 23.61; Cl, 11.83.

Conversion of Compound 6c to Compound 6d. Compound **6c** (100 mg) was dissolved in 10 mL of pyridine. H_2S gas was passed through the solution for 6 h at room temperature. The reaction mixture was allowed to stand overnight at room temperature and then concentrated to dryness in vacuo. The resulting residue was triturated with ether and the crystals were collected by filtration. Recrystallization of the product with ethanol–*n*-hexane afforded 60 mg (60% yield) of compound **6d** as colorless needles. The physical constants of compound **6d** thus prepared were in complete agreement with those obtained by the reaction of ethyl *N*-acetyl-2-acetoxyalaninate (**1d**) with 6-mercaptopurine (**5c**).

Preparation of Ethyl *N*-Acetyl-*N*-methyl-2-(uracil-1-yl)-alaninate (8). 2,4-Bis(trimethylsilyl)uracil (0.77 g, 3 mmol) and the acetoxyamino acid **7** (0.69 g, 3 mmol) were dissolved in 20 mL of acetonitrile. To this was added dropwise stannic chloride (0.07 mL, 0.6 mmol) dissolved in 2 mL of dichloromethane at −10 °C under vigorous stirring. After stirring for 1 h at the same temperature, the reaction mixture was poured into 5 mL of water containing 0.2 g of sodium hydrogen carbonate. The organic layer was separated, dried over magnesium sulfate, and evaporated to dryness in vacuo. The resulting residue was treated with silica gel chromatography using chloroform–methanol (20:1) as eluent to afford compound **8**. Recrystallization of the product with ethyl acetate–petroleum ether gave 0.32 g (38% yield) of pure compound **8** as colorless plates. The physical constants are shown in Table I.

When the acetoxyamino acid **7** was subjected to reaction with uracil in the presence of sodium hydride, ethyl *N*-acetyl-*N*-methyl-2,3-dehydroalaninate (**9**) was formed quantitatively. Compound **9**: bp 79–80 °C (1.5 mmHg); IR (film) 2930, 2860, 1728, 1667, 1653, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (t, 3 H), 1.90 (s, 3 H), 3.01 (s, 3 H), 4.22 (q, 2 H), 5.68 and 6.19 (s and s, 2 H); mass spectrum *m/e* 172 (M + 1), 171 (M^+), 156, 129, 126, 100, 85, 57, 56, 55, 43.

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Registry No.—**1a,** 62183-05-5; **1b,** 69706-77-0; **1c,** 62183-04-4; **1d,** 62183-00-0; **1e,** 69706-78-1; **1f,** 59223-92-6; **1g,** 62183-03-3; **2a,** 66-22-8; **2b,** 65-71-4; **2c,** 71-30-7; **2d,** 51-21-8; **3a,** 69706-79-2; **3b,** 69706-80-5; **3c,** 69706-81-6; **3d,** 69706-82-7; **3e,** 69706-83-8; **3f,** 69706-84-9; **3g,** 69706-85-0; **3h,** 69706-86-1; **3i,** 69706-87-2; **3j,** 69706-88-3; **3k,** 69706-89-4; **4,** 10457-14-4; **5a,** 87-42-3; **5b,** 73-24-5; **5c,** 50-44-2; **6a,** 69706-90-7; **6b,** 69706-91-8; **6c,** 69706-92-9; **6d,** 69706-93-0; **6e,** 69706-94-1; **7,** 69706-95-2; **8,** 69706-96-3; **9,** 69706-97-4; benzyl ethyl methyl(*N*-acetyl-*N*-methylamino), 69706-98-5; monoethyl methyl(*N*-acetyl-*N*-methylamino)malonate, 69706-99-6; diethyl α,α'-bis(acetylamino)-5-methyl-2,4-dioxo-1,3(2*H*,4*H*)-pyrimidinediacetate, 69707-00-2; ethylbutanamidemalonic acid monoester, 69707-01-3; monobenzyl methylacetamidomalonate, 16047-58-8; ethyl *N*-acetyl-2-(6-chloropurin-7-yl)glycinate, 69707-02-4.

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