[Chem. Pharm. Bull. 34(11)4516—4522(1986)]

Useful Syntheses of β-Amino-γ-ketobutyric Acid Derivatives from Aspartic Acid[1)]

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(Received April 21, 1986)

C-Acylation of α-isocyanosuccinate having an aspartic acid skeleton, Dakin–West and Friedel–Crafts reactions with 2-oxazolin-5-oneacetate (aspartic acid azlactone) were found to be efficient methods for the preparation of various β-amino-γ-ketobutyric acid derivatives.

Keywords——aspartic acid; β-amino-γ-ketobutyric acid; α-aminoketone; α-isocyanosuccinate; isonitrile; aspartic acid azlactone; Dakin–West reaction; Friedel–Crafts reaction

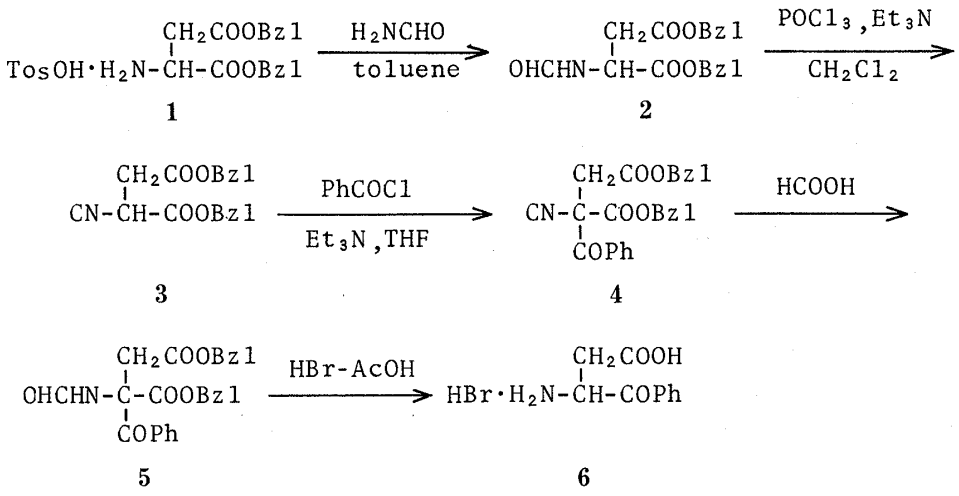
α-Functionalized amino acids are of great interest as versatile key intermediates for the preparation of biologically active compounds. In this context, we have studied α-isocyanoacetic acid derivatives as anionic amino acid synthons[2)] and α-acetoxy-α-amino acid derivatives as cationic amino acid synthons.[3)] β-Functionalized amino acids are also valuable compounds: for example, β-acylamino-γ-ketobutyric acid derivatives (**12**) are important intermediates for the preparation of oxazoleacetic acid derivatives (hypolipidemic agents).[4)] For the synthesis of **12**, we have employed α-(*N*-acylamino)ketone compounds as starting materials; the process involves the introduction of an acetate moiety into the α-aminoketone skeleton.[4)] For the preparation of β-amino-γ-ketobutyric acid derivatives, however, a starting compound with an aspartic acid skeleton, including an α-acetate group, is to be preferred in practice.

Here, we wish to describe useful methods for the synthesis of the title compounds, starting from aspartic acid derivatives.

Results and Discussion

Three synthetic methods were examined: one involves α-isocyanosuccinate (**3**) as an anionic reactive species and the others employ ethyl 2-aryl-2-oxazolin-5-oneacetate (aspartic acid azlactone) (**9**) as an anionic or cationic synthon.

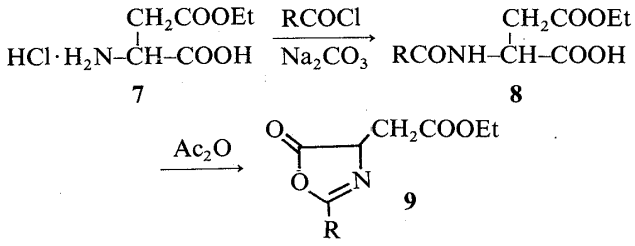
Firstly, we carried out α-*C*-acylation of dibenzyl α-isocyanosuccinate (**3**) according to our previously described procedures.[5)] The coupling reaction product (**4**) isolated as a syrup was converted by hydration with 98% formic acid to the *N*-formyl derivative (**5**), which was obtained in crystalline form. Subsequent deformylation, debenzylation and decarboxylation of the α-carboxyl group were simultaneously effected by the use of 33% hydrogen bromide–acetic acid to yield the desired β-amino-γ-ketobutyric acid hydrobromide in 30% yield. Such an inferior yield at this step may be due to poorly performed debenzylation. In an alternative route, **5** was saponified with 1 N sodium hydroxide and subsequent treatment with 4 N hydrochloric acid was attempted for decarboxylation. Contrary to expectation, the desired



1 2 3 4 5 6

Chart 1

TABLE I. Synthesis of Aspartic Acid Azlactones (**9a—c**)



7 8 9

	R	Yield (%)	
		8	**9**
a	Ph	—[a]	88[b]
b	4-F-Ph	—[a]	99[b]
c	4-Cl-Ph	70	93

a) Used for the subsequent reaction without isolation. *b*) Yield based on 7.

product was not obtained, but several side reactions occurred.

Secondly, to establish a more efficient method, the Dakin–West reaction with aspartic acid azlactone (**9**) as an anionic synthon was undertaken. The azlactones (**9a—c**) were obtained as stable crystals in good yields by dehydrative cyclization of the corresponding β-ethyl *N*-acyl aspartates (**8a—c**) as shown in Table I.

Azlactones derived from several amino acids have been successfully applied to the synthesis of α-acylaminoketones by means of the Dakin–West reaction.[6] The mechanism of this reaction has already been established by Steglich and others with alanine azlactone; it involves *O*-acylation and subsequent conversion to the *C*-acyl azlactone followed by decarboxylation.[7] We therefore investigated the Dakin–West reaction of **9** as exemplified in Chart 2. The reaction was carried out by two methods (A and B).

Method A employed stepwise procedures, for example, isolation of an intermediate at the first stage of the synthesis was carried out from the reaction mixture of **9c**, 2-furoyl chloride and triethylamine as described in the experimental section. The *O*-acyl azlactone (**10**) was isolated as crystals in 67% yield. The intermediate (**10**) was pure enough for the subsequent conversion without further crystallization. The crude **10** was then treated with pyridine at 60—70 °C. At this stage, **10** was converted to the *C*-acyl azlactone (**11**), which was not isolated

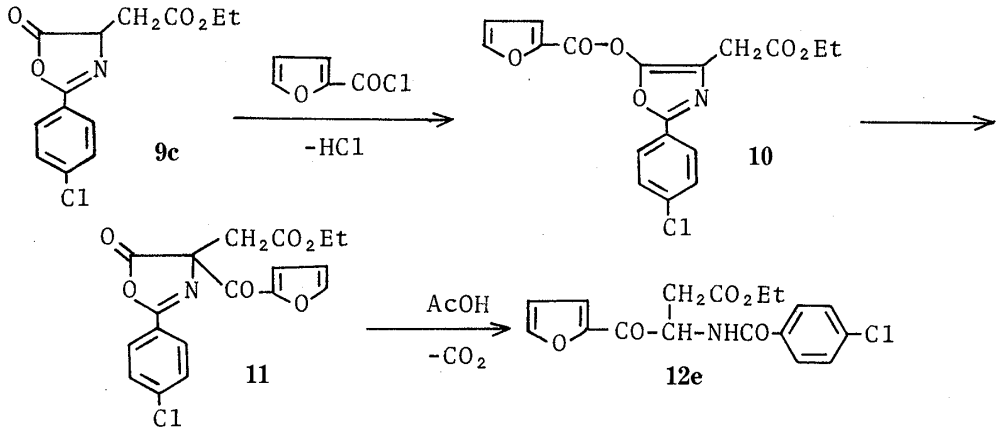
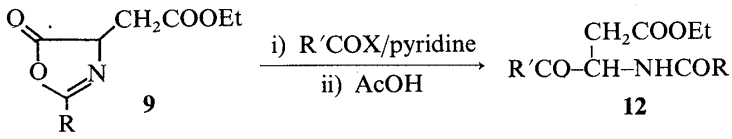


Chart 2

TABLE II. Preparation of β-Acylamino-γ-ketoesters (**12a—j**) by Means of the Dakin–West Reaction



12	R′	R	Yield (%)	mp (°C)
a	Ph	Ph	85	85—87[a]
b	Ph	4-F-Ph	77	97—98[a]
c	Ph	4-Cl-Ph	75	85—87[a]
d	4-Cl-Ph	Ph	80	134—135[a]
e	2-Furyl	4-Cl-Ph	70	104—105
f	2-Thienyl	4-Cl-Ph	78	112—113[a]
g	3-Pyridyl	4-Cl-Ph	70	105—106
h	iso-Pr	4-Cl-Ph	74	61—63
i	*n*-Heptyl	4-Cl-Ph	85	55—56
j	Cyclopentyl	4-Cl-Ph	87	72—74

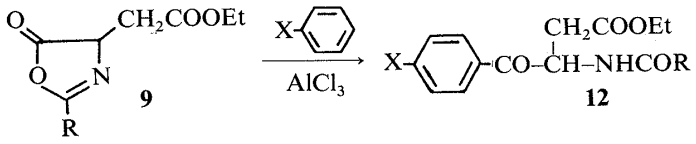
a) In accordance with the value in ref. 4.

in the present work, but was monitored by thin-layer chromatography (TLC). The intermediate (**11**) was treated with acetic acid at 90 °C to form the title compound (**12e**) in 58% yield based on **9c**.

Method B was a one-pot procedure; pyridine alone served as both base and solvent. The reaction of **9** with furoyl chloride in pyridine proceeded smoothly to produce the *C*-acyl azlactone (**11**) in good yield *via* the formation of the *O*-acyl intermediate (**10**). Similarly, the *C*-acyl intermediate (**11**) was easily converted by treatment with acetic acid to the desired product (**12e**). The results of the conversion of aspartic acid azlactone (**9**) to the β-acylamino-γ-ketoester (**12**) by method B are summarized in Table II.

The preparation of the title compounds through Friedel–Crafts reaction of aspartic acid azlactone may also be attractive, because degradative decarboxylation is unnecessary. From this standpoint, it is generally known that azlactones derived from some amino acids such as glycine and phenylalanine undergo Friedel–Crafts acylation with aromatic nuclei inter-[8] or intramolecularly[9] to produce the corresponding α-(*N*-acylamino)ketones in good yields. Furthermore in our preceding paper, we reported that Friedel–Crafts acylation is an effective method for the preparation of the title compound in optically active form, using *N*-methoxycarbonyl-α-L-aspartyl chloride β-ethyl ester as an electrophile.[10] Thus we applied the

TABLE III. Preparation of β-Acylamino-γ-ketoesters (**12**) by Friedel–Crafts Reaction



9 **12**

12	R	X	Solvent	Yield (%)	mp (°C)
b	4-F-Ph	H	Benzene	70	97—98[a]
c	4-Cl-Ph	H	Benzene	66	85—87[a]
k	4-Cl-Ph	Me	Toluene	49	93—95

a) Referred to **12b** and **12c** in Table II.

Friedel–Crafts reaction to the aspartic acid azlactone (**9**) with benzene, toluene or furan and aluminum chloride in the present work. With benzene and toluene, the desired products were obtained in 49—70% yields, as shown in Table III. When furan was used as the nucleophile, some side reactions such as self-condensation of furan were observed and the desired product was not obtained.

Thus, aspartic acid azlactone was found to be an efficient synthon for the preparation of β-*N*-acylamino-γ-ketoacid derivatives. α-Isocyanosuccinate was also found to be advantageous for the synthesis of the title compound bearing a free amino group.

Experimental

Melting points were measured on a Yamato melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-27 infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained using a Hitachi Perkin-Elmer R-20 high-resolution NMR spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were taken with a Hitachi M-60 mass spectrometer. Column chromatography was carried out with Kieselgel 60 (230—400 mesh, E. Merk) and analytical TLC was performed with precoated Kieselgel 60 F_{254} plates (0.25 mm thickness, E. Merk).

***N*-Formylaspartic Acid Dibenzylester (2)**——A suspension of **1** (128 g, 0.264 mol) and formamide (13.1 g, 0.29 mol) in toluene (400 ml) was refluxed for 8 h. Insoluble materials were filtered off and the filtrate was washed with water, dried over anhydrous magnesium sulfate and evaporated to afford **2** as a viscous oil (88.5 g, 98.4%). IR (Nujol): 3300, 1730, 1670 cm^{-1}. NMR ($CDCl_3$) δ: 2.72—3.25 (2H, m), 4.80—5.10 (1H, m), 5.00 (2H, s), 5.08 (2H, s), 6.55—6.90 (1H, br), 7.05—7.50 (10H, m), 8.10 (1H, s).

Dibenzyl α-Isocyanosuccinate (3)——Phosphoryl chloride (28.9 ml, 0.31 mol) was added dropwise to a solution of **2** (88.3 g, 0.259 mol) and triethylamine (151 ml, 1.09 mol) in methylene chloride (600 ml) at −5 to 5 °C. After being stirred at 10 °C for 2 h, the reaction mixture was chilled to −10 °C and poured into a solution of potassium carbonate (43 g) in water (250 ml). The aqueous layer was extracted with methylene chloride. The combined methylene chloride solution was washed with water, dried over anhydrous magnesium sulfate and evaporated. The residue was chromatographed on silica gel with methylene chloride to give **3** (71 g, 85%) as an oil. IR (Nujol): 2150, 1735 cm^{-1}. NMR ($CDCl_3$) δ: 3.00 (2H, d, J=6 Hz), 4.65 (1H, t, J=6 Hz), 5.08 (2H, s), 5.14 (2H, s), 7.15—7.50 (10H, m).

Dibenzyl α-Benzoyl-α-formylaminosuccinate (5)——Benzoyl chloride (2.8 g, 0.02 mol) was added dropwise to a solution of **3** (6.5 g 0.02 mol) and triethylamine (6 ml, 0.043 mol) in tetrahydrofuran (15 ml) at 27—34 °C under vigorous stirring. After being stirred at room temperature for 2 h, the mixture was evaporated to dryness. The residue was dissolved in ethyl acetate and the solution was washed with water, dried over anhydrous magnesium sulfate and evaporated. The residue was taken up in 98% formic acid (20 ml) and the mixture was stirred at 40—50 °C for 3 h. After evaporation of the formic acid, the residue was dissolved in ethyl acetate. The solution was washed with water, dried over anhydrous magnesium sulfate and evaporated. The residue was crystallized by adding *n*-hexane to give **5** (6.66 g, 75%). mp 104—106 °C. IR (KBr): 3350, 1740, 1690, 1640 cm^{-1}. NMR ($CDCl_3$) δ: 3.58 (1H, d, J=18 Hz), 3.82 (1H, d, J=18 Hz), 4.97 (2H, s), 5.10 (2H, s), 6.90—7.60 and 7.70—7.95 (15H, m). MS m/z 446 ($M^+ + 1$). *Anal.* Calcd for $C_{26}H_{23}NO_6$: C, 70.10; H, 5.20; N, 3.14. Found: C, 69.56; H, 5.18; N, 3.19.

3-Amino-4-oxo-4-phenylbutyric Acid Hydrobromide (6)——The formylamino derivative **5** (2 g, 4.5 mmol) was treated with 33% hydrogen bromide–acetic acid (13 ml), and the mixture was stirred at room temperature overnight

and at 50 °C for 3 h. After evaporation to dryness, the residue was dissolved in water and washed with ethyl acetate. The aqueous solution was evaporated and the residual crystalline product was recrystallized from methanol–ether to give **6** (0.39 g, 30%). mp 177—180 °C. IR (Nujol): 1730, 1690 cm^{-1}. NMR (DMSO-d_6) δ: 2.89 (2H, d, J=6 Hz), 5.10—5.30 (1H, m), 7.30—8.00 (5H, m), 8.10—9.10 (3H, br). *Anal.* Calcd for $C_{10}H_{12}BrNO_3$: C, 43.82; H, 4.41; Br, 29.15; N, 5.11. Found: C, 43.47; H, 4.37; Br, 29.30; N, 5.13.

***N*-(4-Chlorobenzoyl)aspartic Acid *β*-Ethyl Ester (8c)**——Aspartic acid *β*-ethyl ester hydrochloride (**7**) (98.8 g, 0.5 mol) was treated with sodium carbonate (185 g, 1.75 mol) at 5 °C in water (1000 ml) and acetone (100 ml). 4-Chlorobenzoyl chloride (105 g, 0.6 mol) was added dropwise at 5 °C for 1 h under vigorous stirring. After further stirring at 20 °C for 1 h, the mixture was washed with toluene and adjusted to pH 3—4 by adding conc. hydrochloric acid. The product was extracted with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate, evaporated and crystallized from diisopropyl ether to give **8c** (122 g, 81%). mp 101.5—102.5 °C. IR (Nujol): 3420, 1735, 1635, 1595, 1570 cm^{-1}. NMR (DMSO-d_6) δ: 1.13 (3H, t, J=7.5 Hz), 2.55—3.10 (2H, m), 4.00 (2H, q, J=7.5 Hz), 4.57—4.90 (1H, m), 7.40 and 7.75 (2H each, A_2B_2, J=9 Hz), 8.68 (1H, d, J=7.5 Hz). MS *m/z*: 299 (M^+). *Anal.* Calcd for $C_{13}H_{14}ClNO_5$: C, 52.10; H, 4.71; Cl, 11.83; N, 4.67. Found: C, 52.14; H, 4.57; Cl, 12.01; N, 4.46.

Compounds **8a** and **b** were used for the following reaction without purification.

2-(4-Chlorophenyl)-4-ethoxycarbonylmethyl-5-oxo-2-oxazoline (9c)——The crystalline product **8c** (7.2 g, 0.07 mol) was suspended in acetic anhydride (42 ml) and toluene (12 ml). The mixture was stirred at 50 °C for 2 h. After evaporation of the solvent, the residue was crystallized from *n*-hexane to afford **9c** as colorless crystals (9.2 g, 93%). mp 97—100 °C. IR (Nujol): 1820, 1725, 1650 cm^{-1}. NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7.5 Hz), 2.80—3.35 (2H, m), 4.08 (2H, q, J=7.5 Hz), 4.56 (1H, t, J=4.5 Hz), 7.35 and 7.85 (2H each, A_2B_2, J=9 Hz). MS *m/z*: 281 (M^+). *Anal.* Calcd for $C_{13}H_{12}ClNO_4$: C, 55.43; H, 4.29; Cl, 12.59; N, 4.97. Found: C, 55.20; H, 4.32; Cl, 12.21; N, 5.01. TLC *Rf*: 0.4 ($CHCl_3$: *n*-hexane : AcOEt = 5 : 5 : 1).

Compounds **9a** and **b** were prepared by a similar procedure from crude **8a** and **b**, respectively.

4-Ethoxycarbonylmethyl-5-oxo-2-phenyl-2-oxazoline (9a)——Yield 88% based on **7**. mp 68—69 °C. IR (Nujol): 1815, 1725, 1650 cm^{-1}. NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7.5 Hz), 2.85—3.34 (2H, m), 4.14 (2H, q, J=7.5 Hz), 4.62 (1H, t, J=5 Hz), 7.30—8.30 (5H, m). MS *m/z*: 247 (M^+). *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.90; H, 5.41; N, 5.50.

4-Ethoxycarbonylmethyl-2-(4-fluorophenyl)-5-oxo-2-oxazoline (9b)——Yield 99% based on **7**. mp 73—74 °C. IR (Nujol): 1820, 1730, 1655 cm^{-1}. NMR ($CDCl_3$) δ: 1.2 (3H, t, J=7.5 Hz), 2.87—3.35 (2H, m), 4.17 (2H, q, J=7.5 Hz), 4.65 (1H, t, J=5 Hz), 7.05—7.35 (2H, m), 7.93—8.25 (2H, m). MS *m/z*: 265 (M^+). *Anal.* Calcd for $C_{13}H_{12}FNO_4$: C, 58.87; H, 4.56; F, 7.16; N, 5.28. Found: C, 58.59; H, 4.50; F, 7.15; N, 5.31.

Ethyl 2-(4-Chlorophenyl)-4-furoyloxy-4-oxazoleacetate (10)——Triethylamine (15.4 ml, 0.11 mol) was added dropwise to a solution of **9a** (28.2 g, 0.1 mol) and 2-furoyl chloride (15.7 g, 0.12 mol) in ethyl acetate (250 ml) at 0 °C, and the mixture was stirred for 1 h. After removal of the insoluble materials by filtration, the filtrate was evaporated. The residue was crystallized from a mixture of diisopropyl ether and *n*-hexane (3 : 2, 50 ml). The crystals were recrystallized from diisopropyl ether to afford **10** (26 g, 67%). mp 59.5—60.5 °C. IR (Nujol): 1770, 1735, 1665, 1250, 1230 cm^{-1}. NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz), 3.63 (2H, s), 4.18 (2H, q, J=7 Hz), 6.67 (1H, dd, J=2 and 4 Hz), 7.43 and 7.93 (2H each, A_2B_2, J=9 Hz), 7.52 (1H, d, J=4 Hz), 7.77 (1H, d, J=2 Hz). *Anal.* Calcd for $C_{18}H_{14}ClNO_6$: C, 57.54; H, 3.76; Cl, 9.43; N, 3.73. Found: C, 57.22; H, 3.50; Cl, 9.40; N, 3.78. TLC *Rf*: 0.5 ($CHCl_3$: *n*-hexane : AcOEt = 5 : 5 : 1).

Ethyl 3-(4-Chlorobenzoylamino)-4-(2-furyl)-4-oxobutyrate (12e) (Dakin–West Reaction)——Method A: Triethylamine (32.72 g, 0.324 mol) was added to a solution of **9c** (84.51 g, 0.3 mol) and 2-furoyl chloride (43.08 g, 0.33 mol) in ethyl acetate (840 ml) at −2 to 5 °C, and the mixture was stirred at 10 to 15 °C for 30 min. Insoluble materials were filtered off and the filtrate was evaporated to dryness. Pyridine (240 ml, 3.0 mol) was added to the residue, and the mixture was stirred at 25 °C for 30 min and then at 60—70 °C for 2 h. Conversion of the *O*-acyl intermediate (**10**) to the succeeding intermediate (**11**) was monitored by TLC: change of *Rf* value 0.5 to 0.7 ($CHCl_3$: *n*-hexane : AcOEt = 5 : 5 : 1). Then, after addition of acetic acid (90 ml, 1.5 mol), the mixture was stirred at 80—90 °C for 3 h, and evaporated *in vacuo*. The residue was crystallized from ethanol (105 ml). The crude crystals were collected and washed successively with cold ethanol and diisopropyl ether to give **12e** (60.85 g, 58.0%). mp 104—105 °C. TLC *Rf*: 0.3 ($CHCl_3$: *n*-hexane : AcOEt = 5 : 5 : 1). IR (Nujol): 3300, 3100, 1738, 1680, 1630, 1595 cm^{-1}. NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz), 3.07 (2H, d, J=5 Hz), 4.20 (2H, q, J=7 Hz), 6.60—6.70 (1H, m), 7.30—8.00 (7H, m). *Anal.* Calcd for $C_{17}H_{16}ClNO_5$: C, 58.38; H, 4.61; Cl, 10.14; N, 4.00. Found: C, 58.33; H, 4.50; Cl, 9.86; N, 4.03.

Method B: 2-Furoyl chloride (3.6 g, 0.028 mol) was added dropwise to a mixture of **9c** (7.05 g, 0.025 mol) in pyridine (9.9 g, 0.125 mol) under cooling with ice. The mixture was stirred at room temperature for 1 h and at 50—60 °C for a further 2 h. Acetic acid (3.8 g) was added at 55 °C and the mixture was stirred at the same temperature for 2 h. The reaction mixture was poured into brine (50 ml) and extracted with ethyl acetate. The organic layer was separated, washed successively with 5% hydrochloric acid, water, sat. aq. sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate and evaporated. Crystallization was carried out by adding ethanol (9 ml). The crystals were collected and washed with cold ethanol and diisopropyl ether to afford **12e** (6.07 g, 70%) mp 104—105 °C.

Compounds **12a—d, f—j** were similarly prepared by method B. In the cases of **12h** and **i**, acid anhydrides were used as the acylating reagents instead of the acid chlorides.

Ethyl 3-(4-Chlorobenzoylamino)-4-oxo-4-(3-pyridyl)butyrate (12g)——Yield 70%. mp 105—106 °C. IR (Nujol): 3200, 1740, 1690, 1660, 1595 cm^{-1}. NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz), 3.00 (2H, d, J=5 Hz), 4.14 (2H, q, J=7 Hz), 5.80—6.05 (1H, m), 7.36 and 7.74 (2H each, A_2B_2, J=9 Hz), 7.2—8.0 (2H, br), 8.32 (1H, ddd, J=1, 1, 6 Hz), 8.77 (1H, dd, J=1, 5 Hz), 9.21 (1H, d, J=1 Hz). *Anal.* Calcd for $C_{18}H_{17}ClN_2O_4$: C, 59.92; H, 4.75; Cl, 9.83; N, 7.76. Found: C, 59.72; H, 4.82; Cl, 9.93; N, 7.50.

Ethyl 3-(4-Chlorobenzoylamino)-4-oxo-4-(2-propyl)butyrate (12h)——Yield 74%. mp 61—63 °C. IR (Nujol): 3290, 3050, 1780, 1725 cm^{-1}. NMR ($CDCl_3$) δ: 0.92 (6H, d, J=6 Hz), 1.24 (3H, t, J=7 Hz), 1.90—2.60 (1H, m), 2.46 (2H, m), 2.92 (2H, dq, J=3, 6 Hz), 4.12 (2H, q, J=7 Hz), 4.88 (1H, m), 7.20—7.80 (1H, m), 7.34 and 7.70 (2H each, A_2B_2, J=9 Hz). *Anal.* Calcd for $C_{16}H_{20}ClNO_4$: C, 58.99; H, 6.19; Cl, 10.88; N, 4.30. Found: C, 58.97; H, 6.32; Cl, 10.92; N, 4.52.

Ethyl 3-(4-Chlorobenzoylamino)-4-heptyl-4-oxobutyrate (12i)——Yield 85%. mp 55—56 °C. IR (Nujol): 3320, 1720, 1640, 1530 cm^{-1}. NMR ($CDCl_3$) δ: 0.50—2.00 (16H, m), 2.40—2.80 (2H, m), 2.80—3.20 (2H, m), 4.27 (2H, q, J=7 Hz), 4.80—5.20 (1H, m), 7.41 and 7.79 (2H each, A_2B_2, J=9 Hz), 7.20—7.60 (1H, br). *Anal.* Calcd for $C_{20}H_{28}ClNO_4$: C, 62.90; H, 7.39; Cl, 9.28; N, 3.67. Found: C, 62.85; H, 7.39; Cl, 9.35; N, 3.65.

Ethyl 3-(4-Chlorobenzoylamino)-4-cyclopentyl-4-oxobutyrate (12j)——Yield 87%. mp 72—74 °C. IR (Nujol): 3330, 1720, 1640, 1545 cm^{-1}. NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz), 1.40—2.10 (8H, m), 2.92 (1H, d, J=4 Hz), 2.98 (1H, d, J=4 Hz), 2.90—3.40 (1H, m), 4.14 (2H, q, J=7 Hz), 4.95—5.25 (1H, m), 7.41 and 7.78 (2H each, A_2B_2, J=9 Hz), 7.30—7.70 (1H, br). *Anal.* Calcd for $C_{18}H_{22}ClNO_4$: C, 61.45; H, 6.30; Cl, 10.08; N, 3.98. Found: C, 61.24; H, 6.27; Cl, 10.00; N, 3.95.

Ethyl 3-(4-Chlorobenzoylamino)-4-oxo-4-phenylbutyrate (12c) (Friedel–Crafts Reaction)——Aluminum chloride (15.1 g, 0.113 mol) was added in one portion to a solution of **9c** (10.7 g, 0.038 mol) in benzene (50 ml). The mixture was stirred at room temperature overnight and poured into ice-dil. hydrochloric acid. The product was extracted with ethyl acetate. The extract was washed successively with brine, sat. aq. sodium hydrogencarbonate and brine, dried over anhydrous magnesium sulfate and evaporated. The residue was chromatographed on silica gel ($CHCl_3$: *n*-hexane : AcOEt=5 : 5 : 1) to afford **12c** (9 g, 66%). mp 85—87 °C.

Compound **12b** was obtained by a similar procedure. In the case of **12k**, toluene was used as the solvent to produce the corresponding toluoyl derivative by an otherwise similar procedure.

Ethyl 3-(4-Chlorobenzoylamino)-4-oxo-4-(4-tolyl)butyrate (12k)——Yield 49%. mp 93—95 °C. IR (Nujol): 3300, 1740, 1675, 1620 cm^{-1}. NMR (DMSO-d_6) δ: 1.17 (3H, t, J=7 Hz), 5.60—6.00 (1H, m), 7.20—7.70 (4H, m), 7.70—8.00 (4H, m), 9.18 (1H, d, J=8 Hz). MS m/z: 373 (M^+). *Anal.* Calcd for $C_{20}H_{20}ClNO_4$: C, 64.26; H, 5.39; Cl, 9.48; N, 3.75. Found: C, 64.07; H, 5.35; Cl, 8.99; N, 3.79.

Acknowledgement We express our thanks to Dr. I. Chibata, Research and Development Executive, Dr. M. Kisumi, Director of the Research Laboratory of Applied Biochemistry and Dr. S. Ohshiro, Director of the Pharmaceutical Technics Division, for encouragement and interest. Thanks are also extended to Dr. N. Yoneda, Vice Director of the Research Laboratory of Applied Biochemistry for his valuable comments during the course of this study.

References and Notes

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