

[Chem. Pharm. Bull.]  
33(7)2731—2734(1985)]

## Studies on Amino Acid Derivatives. IV.<sup>1)</sup> Synthesis of 3-Amino-2(1*H*)-pyridone Derivatives Using 4-Ethoxymethylene-2-phenyl-5-oxazolone

TAKUO CHIBA\* and TAKUMI TAKAHASHI

*Pharmaceutical Institute, Tohoku University  
Aobayama, Sendai 980, Japan*

(Received October 8, 1984)

The reaction of 4-ethoxymethylene-2-phenyl-5-oxazolone (**1**) with 3-amino-2-butenates (**2a—2c**) gave 1-substituted 3-benzamido-5-ethoxycarbonyl-6-methyl-2(1*H*)-pyridones (**4a—4c**) in 56—77% yields. Similarly, compound **1** reacted with 3-amino-2-butenamides (**3a** and **3b**) to yield 1-substituted 3-benzamido-5-carbamoyl-6-methyl-2(1*H*)-pyridones (**7a** and **7b**). In the reaction of compound **1** with arylaminobutenamides (**3c** and **3d**), 5-carbamoyl-2(1*H*)-pyridones (**7c** and **7d**) and 5-cyano-2(1*H*)-pyridones (**8c** and **8d**) were obtained.

**Keywords**—hippuric acid; 3-benzamido-2-pyridone derivative; 4-ethoxymethylene-2-phenyl-5-oxazolone; 3-amino-2-butenate; 3-amino-2-butenamide; ring transformation

4-Ethoxymethylene-2-phenyl-5-oxazolone (**1**), which can be easily prepared from hippuric acid, is known to react with active methylene compounds and with amino heterocycles to give pyrones<sup>2)</sup> and bicyclic heterocycles,<sup>3)</sup> respectively.

We now wish to report the synthesis of 3-amino-2(1*H*)-pyridone derivatives by the reaction of **1** with either 3-amino-2-butenates (**2**) or 3-amino-2-butenamides (**3**). Both of the latter compounds are also useful synthons for various heterocyclic compounds.<sup>4)</sup> Thus, heating of a mixture of **1** and ethyl 3-amino-2-butenate (**2a**) in dioxane in the presence of triethylamine resulted in the formation of 3-benzamido-5-ethoxycarbonyl-6-methyl-2(1*H*)-pyridone (**4a**) in 64% yield. When the same mixture was heated at 80 °C without solvent or base, the pyridone **4a** and tetrahydropyridine **5** were obtained in 59% and 11% yields, respectively. In the nuclear magnetic resonance (NMR) spectrum of **5**, the H<sub>4</sub> proton appeared at 4.80 ppm as a doublet and the H<sub>3</sub> proton at 5.03 ppm as a double doublet. These spectral data confirmed the tetrahydropyridine structure of **5**. Compound **5** was transformed into the pyridone **4a** with elimination of ethanol by heating at an elevated temperature.

3-Substituted amino-2-butenates (**2b** and **2c**) also reacted with **1** to afford 1-substituted 3-benzamido-2(1*H*)-pyridones (**4b** and **4c**) in 77% and 56% yields, respectively. When the reaction of **1** with **2c** was carried out at 80—90 °C in dioxane in the presence of triethylamine, 4-methylene-5-oxazolone **6** was obtained in 42% yield. Heating of compound **6** regenerated the pyridone **4c**.

The same reaction also proceeds if 3-amino-2-butenamides are used instead of 3-amino-2-butenates. Thus, the reaction of **1** with 3-amino- and 3-benzylamino-2-butenamide (**3a** and **3b**) gave rise to 3-benzamido-5-carbamoyl-2(1*H*)-pyridone derivatives (**7a** and **7b**) in 70% and 45% yields, respectively.

Two pathways, a and b, are suggested for the formation of the 2-pyridone derivatives **4** and **7**. In pathway a, Michael addition of **2a—2c** or **3a—3d** to the oxazolone **1** gives intermediate A, which cyclizes to the tetrahydropyridine B. Elimination of ethanol from B yields the final products **4a—4c** and **7a—7d**.

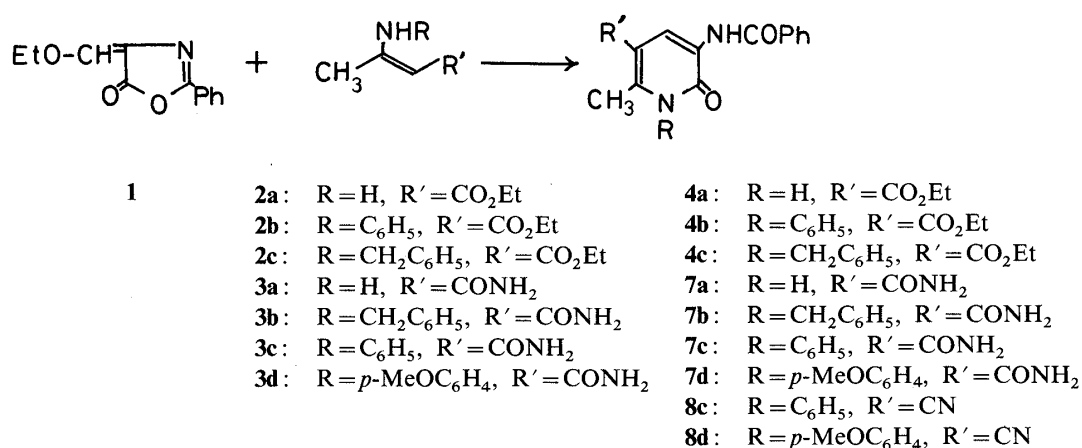
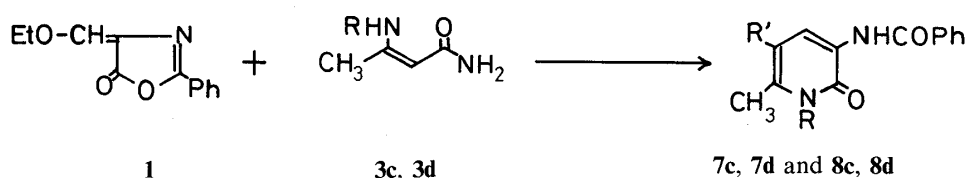


Chart 1

TABLE I. Reaction of **1** with **3c** and **3d**

<b>1</b>	3-Arylamino-2-butenamide	Reaction conditions	Solvent [Catalyst]	Yield of product	
				R' = CONH <sub>2</sub>	R' = CN
0.5 g	<b>3c</b> (0.41 g) (R = C <sub>6</sub> H <sub>5</sub> )	Reflux 5.5 h	Dioxane (0.3 ml) [Triethylamine (0.3 ml)]	<b>7c</b> (0.10 g, 13%)	<b>8c</b> (0.26 g, 34%)
0.5 g	<b>3c</b> (0.41 g) (R = C <sub>6</sub> H <sub>5</sub> )	130 °C 6.5 h	—	<b>7c</b> (0.28 g, 35%)	<b>8c</b> (0.14 g, 18%)
0.5 g	<b>3d</b> (0.47 g) (R = <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> )	Reflux 9 h	Dioxane (0.5 ml) [Triethylamine (0.5 ml)]	<b>7d</b> (0.14 g, 16%)	<b>8d</b> (0.32 g, 39%)
0.5 g	<b>3d</b> (0.47 g) (R = <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> )	120 °C 6 h	—	<b>7d</b> (0.34 g, 39%)	<b>8d</b> (0.02 g, 2%)

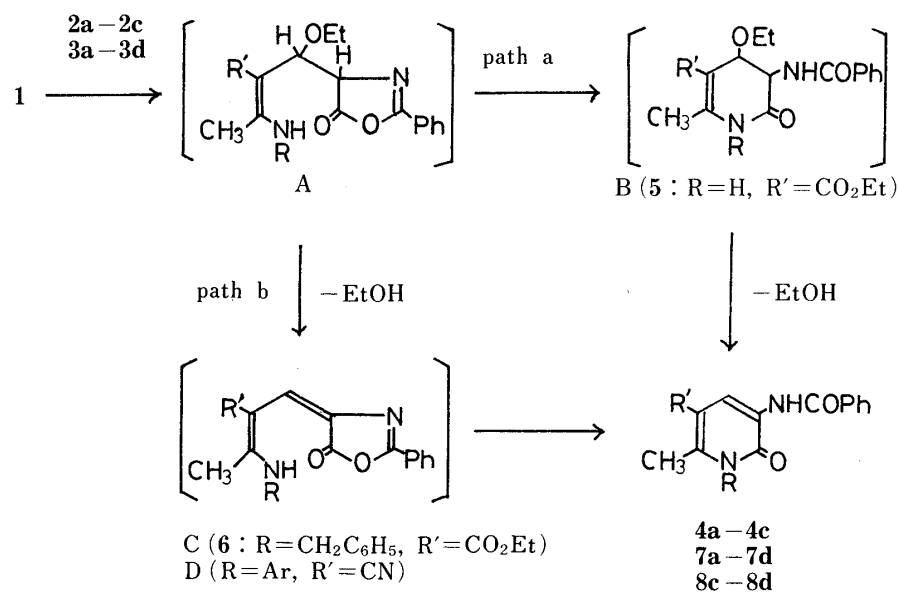


Chart 2

If the elimination of ethanol occurs prior to the cyclization to the tetrahydropyridine, intermediate C might be formed to give 2-pyridones by ring transformation as shown in pathway b. While we could not prove which pathway is actually operating, the following results strongly suggest that the reaction proceeds by pathway b (at least partly). Thus, 3-arylamino-2-butenamides (**3c** and **3d**) were reacted with **1** to give 1-aryl-3-benzamido-5-carbamoyl-2(1*H*)-pyridones (**7c** and **7d**) and 5-cyano-2(1*H*)-pyridones (**8c** and **8d**). The ratio of **7c**, **7d** and **8c**, **8d** depended on the reaction conditions as shown in Table I. The mechanism of the dehydration giving the 5-cyano-2(1*H*)-pyridone **8** is not clear at present, but it seems reasonable to assume that **1** acts as a dehydrating agent. However, since treatment of compound **7** with **1** did not give compound **8**, a pathway in which the dehydration of intermediate C gives intermediate D, which would then afford compound **8** by ring transformation, seems probable. This argument, as well as the isolation of the oxazolone derivative **6**, strongly suggests the participation of pathway b.

### Experimental<sup>5)</sup>

**3-Benzamido-5-ethoxycarbonyl-6-methyl-2(1*H*)-pyridone (4a)**—a) A mixture of 4-ethoxymethylene-2-phenyl-5-oxazolone (**1**) (1.0 g) and ethyl 3-amino-2-butenate (**2a**) (0.7 g) in dioxane (0.5 ml) was heated in the presence of triethylamine (0.4 ml) at 80–85 °C until compound **1** was no longer detectable on thin layer chromatography (silica gel) (about 2.5 h). The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography using CH<sub>2</sub>Cl<sub>2</sub>–AcOEt as an eluant to give needles (**4a**). Yield 0.89 g (64%), mp 252–253 °C (from MeOH). *Anal.* Calcd for C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.28; H, 5.35; N, 9.46. IR, (Nujol): 3325, 1710, 1665 (sh), 1640 cm<sup>-1</sup>. NMR (DMSO-*d*<sub>6</sub>) δ: 1.33 (3H, t, *J* = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 2.60 (3H, s, CH<sub>3</sub>), 4.30 (2H, q, *J* = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 7.50–8.17 (5H, m, arom-H), 8.78 (1H, s, 4-H), 9.25 (1H, br s, NH), 12.27–12.80 (1H, br s, NH).

b) A mixture of **1** (2.0 g) and **2a** (1.2 g) was heated at 80 °C for 6 h to give the tetrahydropyridine **5** (0.38 g) which was transformed into a mixture of **4a** and **5** on being purified by recrystallization. Compounds **4a** and **5** were separated by fractional recrystallization from CH<sub>2</sub>Cl<sub>2</sub>–hexane in 54% and 11% yields, respectively. 3-Benzamido-4-ethoxy-5-ethoxycarbonyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine (**5**): mp 177–178 °C. IR (CHCl<sub>3</sub>): 3450 (sh), 3420, 1720 (sh), 1700, 1655, 1640 cm<sup>-1</sup>. NMR (CDCl<sub>3</sub>) δ: 1.13 (3H, t, *J* = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 1.30 (3H, t, *J* = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 2.40 (3H, s, CH<sub>3</sub>), 3.63 (2H, q, *J* = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 4.23 (2H, q, *J* = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 4.80 (1H, d, *J* = 4 Hz, 4-H), 5.03 (1H, dd, *J* = 4, 8 Hz, 3-H), 7.00 (1H, d, *J* = 8 Hz, NH), 7.43–7.65 (3H, m, arom-H), 7.77–8.05 (2H, m, arom-H), 8.63 (1H, br s, NH). Heating of **5** at 180 °C for 5 min gave **4a** quantitatively.

**3-Benzamido-5-ethoxycarbonyl-6-methyl-1-phenyl-2(1*H*)-pyridone (4b)**—A mixture of **1** (1.0 g) and ethyl 3-anilino-2-butenate (**2b**) (1.0 g) in dioxane (0.3 ml) was heated at 80–90 °C for 6 h in the presence of triethylamine (0.3 ml) to give needles (**4b**). Yield 0.77 g (77%), mp 200–201 °C (from MeOH). *Anal.* Calcd for C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.03; H, 5.39; N, 7.32. IR (CHCl<sub>3</sub>): 3375, 1710, 1665 (sh), 1640 cm<sup>-1</sup>. NMR (CDCl<sub>3</sub>) δ: 1.50 (3H, t, *J* = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 2.48 (3H, s, CH<sub>3</sub>), 4.45 (2H, q, *J* = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 7.17–8.20 (10H, m, arom-H), 9.12 (1H, br s, NH), 9.20 (1H, s, 4-H).

**3-Benzamido-1-benzyl-5-ethoxycarbonyl-6-methyl-2(1*H*)-pyridone (4c)**—a) Compound **1** (1.0 g) and ethyl 3-benzylamino-2-butenate (**2c**) (1.0 g) were heated in dimethylformamide (0.5 ml) at 140 °C for 2 h. The reaction mixture was concentrated to dryness to give prisms (**4c**). Yield 0.46 g (56%), mp 131–132 °C (from MeOH). *Anal.* Calcd for C<sub>23</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.67; H, 5.78; N, 6.94. IR (CHCl<sub>3</sub>): 3380, 1710, 1660 (sh), 1635 cm<sup>-1</sup>. NMR (CDCl<sub>3</sub>) δ: 1.38 (3H, t, *J* = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 2.70 (3H, s, CH<sub>3</sub>), 4.33 (2H, q, *J* = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 5.50 (2H, s, CH<sub>2</sub>), 7.00–8.17 (10H, m, arom-H), 9.10 (2H, s, NH and 4-H).

b) A mixture of **1** (1.0 g) and **2c** (1.0 g) in dioxane (0.5 ml) was heated in the presence of triethylamine (0.3 ml) at 90 °C for 9.5 h. Ether (5 ml) was added to the reaction mixture. The precipitates obtained were filtered off and recrystallized from methanol to give 4-(3-benzylamino-2-ethoxycarbonyl-2-butenylidene)-2-phenyl-5-oxazolone (**6**) as orange prisms. Yield 0.76 g (42%), mp 145–146 °C. IR (CHCl<sub>3</sub>): 3600, 1760, 1680, 1630 cm<sup>-1</sup>. NMR (CDCl<sub>3</sub>) δ: 1.33 (3H, t, *J* = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 2.40 (3H, s, CH<sub>3</sub>), 4.22 (2H, q, *J* = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>O), 4.68 (2H, d, *J* = 6 Hz, CH<sub>2</sub>), 7.20–7.55 (8H, m, arom-H), 7.71 (1H, s, CH), 7.70–8.17 (2H, m, arom-H), 11.30–11.77 (1H, br, NH). Compound **6** was quantitatively led to **4c** by heating in dimethylformamide at 140 °C for 1 h.

**3-Benzamido-5-carbamoyl-6-methyl-2(1*H*)-pyridone (7a)**—A mixture of **1** (1.0 g) and 3-amino-2-butenamide (**3a**) in dioxane (0.3 ml) was heated in the presence of triethylamine (0.2 ml) at 85–90 °C for 20 min to give needles (**7a**). Yield 0.42 g (70%), mp 329–331 °C (dec.) (from CH<sub>2</sub>Cl<sub>2</sub>–MeOH). *Anal.* Calcd for C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>: C, 61.98; H, 4.83; N, 15.49. Found: C, 61.84; H, 4.62; N, 15.59. IR (Nujol): 3400, 3300, 3200, 1655, 1645 (sh) cm<sup>-1</sup>. NMR

(DMSO- $d_6$ )  $\delta$ : 2.45 (3H, s, CH<sub>3</sub>), 6.93—8.23 (7H, m, arom-H and NH<sub>2</sub>), 8.45 (1H, s, 4-H), 9.28 (1H, br s, NH), 12.10—12.40 (1H, br, NH).

**3-Benzamido-1-benzyl-5-carbamoyl-6-methyl-2(1H)-pyridone (7b)**—Compound **1** (0.5 g) and 3-benzylamino-2-butenamide (**3b**) (0.44 g) were heated at 140 °C for 6 h to give needles (**7b**). Yield 0.37 g (45%), mp 258—259 °C (from MeOH). *Anal.* Calcd for C<sub>21</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.86; H, 5.27; N, 11.78. IR (Nujol): 3400, 3330, 3210, 1670, 1635 cm<sup>-1</sup>. NMR (DMSO- $d_6$ )  $\delta$ : 2.33 (3H, s, CH<sub>3</sub>), 5.37 (2H, s, CH<sub>2</sub>), 6.93—8.08 (12H, m, arom-H and NH<sub>2</sub>), 8.37 (1H, s, 4-H), 9.30 (1H, br s, NH).

**1-Aryl-3-benzamido-5-carbamoyl-6-methyl-2(1H)-pyridones (7c and 7d) and 1-Aryl-3-benzamido-5-cyano-6-methyl-2(1H)-pyridones (8c and 8d)**—Following the procedure given for **4a**, **1** was allowed to react with 3-arylamino-2-butenamides (**3c** and **3d**) to give products **7c**, **7d**, **8c** and **8d**. Reaction conditions and yields are shown in Table I.

**3-Benzamido-5-carbamoyl-6-methyl-1-phenyl-2(1H)-pyridone (7c)**: Needles, mp 267—268 °C (from MeOH). *Anal.* Calcd for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.29; H, 5.04; N, 12.09. IR (CHCl<sub>3</sub>): 3525, 3475, 3420, 3380, 1670, 1640 cm<sup>-1</sup>. NMR (DMSO- $d_6$ )  $\delta$ : 2.10 (3H, s, CH<sub>3</sub>), 7.15—8.15 (12H, m, arom-H and NH<sub>2</sub>), 8.52 (1H, s, CH), 9.32 (1H, br s, NH).

**3-Benzamido-5-cyano-6-methyl-1-phenyl-2(1H)-pyridone (8c)**: Needles, mp 263—264 °C (from CH<sub>2</sub>Cl<sub>2</sub>–MeOH). *Anal.* Calcd for C<sub>20</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 72.93; H, 4.59; N, 12.76. Found: C, 73.30; H, 4.74; N, 12.79. IR (CHCl<sub>3</sub>): 3380, 2220, 1645 cm<sup>-1</sup>. NMR (CF<sub>3</sub>CO<sub>2</sub>H)  $\delta$ : 2.37 (3H, s, CH<sub>3</sub>), 7.12—8.00 (10H, m, arom-H), 8.88 (1H, s, CH), 9.20 (1H, br s, NH).

**3-Benzamido-5-carbamoyl-1-(4-methoxyphenyl)-6-methyl-2(1H)-pyridone (7d)**: Needles, mp 281—282 °C (from MeOH). *Anal.* Calcd for C<sub>21</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>: C, 66.83; H, 5.07; N, 11.14. Found: C, 66.86; H, 5.03; N, 11.19. IR (Nujol): 3360, 3200, 1660, 1640 cm<sup>-1</sup>. NMR (DMSO- $d_6$ )  $\delta$ : 2.10 (3H, s, CH<sub>3</sub>), 3.87 (3H, s, CH<sub>3</sub>O), 6.93—8.33 (11H, m, arom-H and NH<sub>2</sub>), 8.50 (1H, s, CH), 9.31 (1H, br s, NH).

**3-Benzamido-5-cyano-1-(4-methoxyphenyl)-6-methyl-2(1H)-pyridone (8d)**: Prisms, mp 246—247 °C (from AcOEt). *Anal.* Calcd for C<sub>21</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>: C, 70.18; H, 4.77; N, 11.70. Found: C, 69.86; H, 4.77; N, 11.53. IR (CHCl<sub>3</sub>): 3380, 2220, 1640 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>)  $\delta$ : 2.27 (3H, s, CH<sub>3</sub>), 3.88 (3H, s, CH<sub>3</sub>O), 7.07—8.03 (9H, m, arom-H), 8.68 (1H, s, CH), 9.03 (1H, br s, NH).

**Acknowledgement** The authors are grateful to Prof. Kaneko for valuable advice and encouragement, and to the Central Analysis Room of this institute.

#### References and Notes

- 1) Part III: T. Chiba, J. Sakaki, and T. Kato, *Yakugaku Zasshi*, **104**, 587 (1984).
- 2) H. Behringer and K. Falkenberg, *Chem. Ber.*, **96**, 1428 (1963).
- 3) O. Tsuge and M. Noguchi, *Heterocycles*, **16**, 2149 (1981).
- 4) T. Kato, *Heterocycles*, **3**, 413 (1975).
- 5) Melting points are uncorrected. IR spectra were taken on a JASCO IR-S spectrometer. <sup>1</sup>H-NMR spectra were recorded on a JEOL JNM-PMX 60 spectrometer with tetramethylsilane or 3-(trimethylsilyl)propanesulfonic acid sodium salt as an internal standard.