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

Studies on Amino Acid Derivatives. IV.[1] 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-butenoates (**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 drivative; 4-ethoxymethylene-2-phenyl-5-oxazolone; 3-amino-2-butenoate; 3-amino-2-butenamide; ring transformation

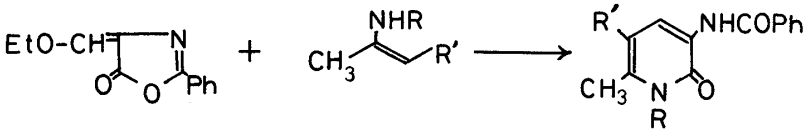
4-Ethoxymethylene-2-phenyl-5-oxazolone (**1**), which can be easily prepared from hippuric acid, is known to react with active methylene compounds and with amino heterocycles to give pyrones[2] and bicyclic heterocycles,[3] respectively.

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-butenoates (**2**) or 3-amino-2-butenamides (**3**). Both of the latter compounds are also useful synthons for various heterocyclic compounds.[4] Thus, heating of a mixture of **1** and ethyl 3-amino-2-butenoate (**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_4 proton appeared at 4.80 ppm as a doublet and the H_3 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-butenoates (**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-butenoates. 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**.



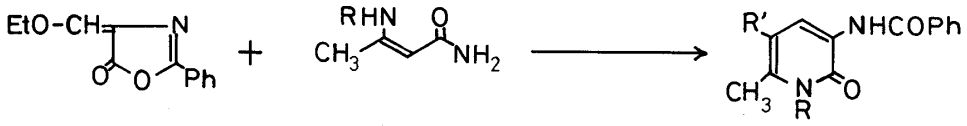
1

2a: R=H, R′=CO_2Et
2b: R=C_6H_5, R′=CO_2Et
2c: R=$CH_2C_6H_5$, R′=CO_2Et
3a: R=H, R′=$CONH_2$
3b: R=$CH_2C_6H_5$, R′=$CONH_2$
3c: R=C_6H_5, R′=$CONH_2$
3d: R=*p*-$MeOC_6H_4$, R′=$CONH_2$

4a: R=H, R′=CO_2Et
4b: R=C_6H_5, R′=CO_2Et
4c: R=$CH_2C_6H_5$, R′=CO_2Et
7a: R=H, R′=$CONH_2$
7b: R=$CH_2C_6H_5$, R′=$CONH_2$
7c: R=C_6H_5, R′=$CONH_2$
7d: R=*p*-$MeOC_6H_4$, R′=$CONH_2$
8c: R=C_6H_5, R′=CN
8d: R=*p*-$MeOC_6H_4$, R′=CN

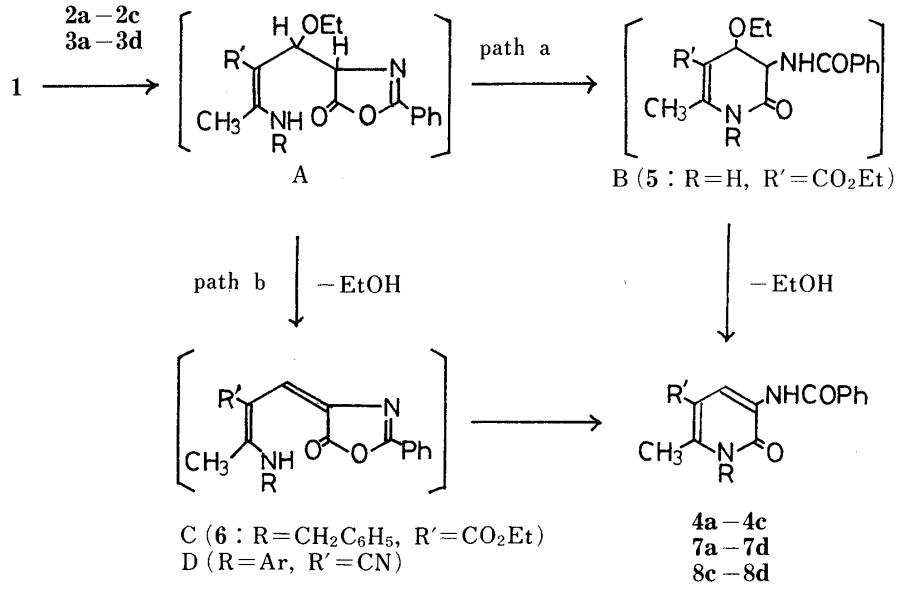
Chart 1

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



1 **3c**, **3d** **7c**, **7d** and **8c**, **8d**

1	3-Arylamino-2-butenamide	Reaction conditions	Solvent [Catalyst]	Yield of product R′=$CONH_2$	Yield of product R′=CN
0.5 g	**3c** (0.41 g) (R=C_6H_5)	Reflux 5.5 h	Dioxane (0.3 ml) [Triethylamine (0.3 ml)]	**7c** (0.10 g, 13%)	**8c** (0.26 g, 34%)
0.5 g	**3c** (0.41 g) (R=C_6H_5)	130 °C 6.5 h	—	**7c** (0.28 g, 35%)	**8c** (0.14 g, 18%)
0.5 g	**3d** (0.47 g) (R=*p*-$MeOC_6H_4$)	Reflux 9 h	Dioxane (0.5 ml) [Triethylamine (0.5 ml)]	**7d** (0.14 g, 16%)	**8d** (0.32 g, 39%)
0.5 g	**3d** (0.47 g) (R=*p*-$MeOC_6H_4$)	120 °C 6 h	—	**7d** (0.34 g, 39%)	**8d** (0.02 g, 2%)



A

B (**5**: R=H, R′=CO_2Et)

C (**6**: R=$CH_2C_6H_5$, R′=CO_2Et)
D (R=Ar, R′=CN)

4a–4c
7a–7d
8c–8d

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[5]

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-butenoate (**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_2Cl_2–AcOEt as an eluant to give needles (**4a**). Yield 0.89 g (64%), mp 252—253 °C (from MeOH). *Anal.* Calcd for $C_{16}H_{16}N_2O_4$: 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^{-1}. NMR (DMSO-d_6) δ: 1.33 (3H, t, J=7 Hz, CH_3CH_2O), 2.60 (3H, s, CH_3), 4.30 (2H, q, J=7 Hz, CH_3CH_2O), 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_2Cl_2–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 ($CHCl_3$): 3450 (sh), 3420, 1720 (sh), 1700, 1655, 1640 cm^{-1}. NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7 Hz, CH_3CH_2O), 1.30 (3H, t, J=7 Hz, CH_3CH_2O), 2.40 (3H, s, CH_3), 3.63 (2H, q, J=7 Hz, CH_3CH_2O), 4.23 (2H, q, J=7 Hz, CH_3CH_2O), 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-butenoate (**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 $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.03; H, 5.39; N, 7.32. IR ($CHCl_3$): 3375, 1710, 1665 (sh), 1640 cm^{-1}. NMR ($CDCl_3$) δ: 1.50 (3H, t, J=7 Hz, CH_3CH_2O), 2.48 (3H, s, CH_3), 4.45 (2H, q, J=7 Hz, CH_3CH_2O), 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-butanoate (**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 $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.67; H, 5.78; N, 6.94. IR ($CHCl_3$): 3380, 1710, 1660 (sh), 1635 cm^{-1}. NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7 Hz, CH_3CH_2O), 2.70 (3H, s, CH_3), 4.33 (2H, q, J=7 Hz, CH_3CH_2O), 5.50 (2H, s, CH_2), 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 ($CHCl_3$): 3600, 1760, 1680, 1630 cm^{-1}. NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7 Hz, CH_3CH_2O), 2.40 (3H, s, CH_3), 4.22 (2H, q, J=7 Hz, CH_3CH_2O), 4.68 (2H, d, J=6 Hz, CH_2), 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_2Cl_2–MeOH). *Anal.* Calcd for $C_{14}H_{13}N_3O_3$: 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^{-1}. NMR

(DMSO-d_6) δ: 2.45 (3H, s, CH_3), 6.93—8.23 (7H, m, arom-H and NH_2), 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(1*H*)-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 $C_{21}H_{19}N_3O_3$: 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^{-1}. NMR (DMSO-d_6) δ: 2.33 (3H, s, CH_3), 5.37 (2H, s, CH_2), 6.93—8.08 (12H, m, arom-H and NH_2), 8.37 (1H, s, 4-H), 9.30 (1H, br s, NH).

1-Aryl-3-benzamido-5-carbamoyl-6-methyl-2-(1*H*)-pyridones (7c and 7d) and 1-Aryl-3-benzamido-5-cyano-6-methyl-2(1*H*)-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(1*H*)-pyridone (**7c**): Needles, mp 267—268 °C (from MeOH). *Anal.* Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.29; H, 5.04; N, 12.09. IR ($CHCl_3$): 3525, 3475, 3420, 3380, 1670, 1640 cm^{-1}. NMR (DMSO-d_6) δ: 2.10 (3H, s, CH_3), 7.15—8.15 (12H, m, arom-H and NH_2), 8.52 (1H, s, CH), 9.32 (1H, br s, NH).

3-Benzamido-5-cyano-6-methyl-1-phenyl-2(1*H*)-pyridone (**8c**): Needles, mp 263—264 °C (from CH_2Cl_2–MeOH). *Anal.* Calcd for $C_{20}H_{15}N_3O_2$: C, 72.93; H, 4.59; N, 12.76. Found: C, 73.30; H, 4.74; N, 12.79. IR ($CHCl_3$): 3380, 2220, 1645 cm^{-1}. NMR (CF_3CO_2H) δ: 2.37 (3H, s, CH_3), 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(1*H*)-pyridone (**7d**): Needles, mp 281—282 °C (from MeOH). *Anal.* Calcd for $C_{21}H_{19}N_3O_4$: 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^{-1}. NMR (DMSO-d_6) δ: 2.10 (3H, s, CH_3), 3.87 (3H, s, CH_3O), 6.93—8.33 (11H, m, arom-H and NH_2), 8.50 (1H, s, CH), 9.31 (1H, br s, NH).

3-Benzamido-5-cyano-1-(4-methoxyphenyl)-6-methyl-2(1*H*)-pyridone (**8d**): Prisms, mp 246—247 °C (from AcOEt). *Anal.* Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.70. Found: C, 69.86; H, 4.77; N, 11.53. IR ($CHCl_3$): 3380, 2220, 1640 cm^{-1}: NMR ($CDCl_3$) δ: 2.27 (3H, s, CH_3), 3.88 (3H, s, CH_3O), 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 Analaysis Room of this institute.

References and Notes

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