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Studies on Amino Acid Derivatives. V.[1] Synthesis of Pyridobenzazoles

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Ethyl 2-benzimidazoleacetate (**2a**) reacted with 4-ethoxymethylene-2-phenyl-5-oxazolone (**1**) to give 2-benzamido-4-ethoxycarbonyl-1-oxo-1,5-dihydropyrido[1,2-*a*]benzimidazole (**5a**). Similar reactions of ethyl 2-benzoxazoleacetate (**3a**) or ethyl 2-benzothiazoleacetate (**4a**) with compound **1** gave the corresponding pyridobenzazoles, *i.e.*, pyrido[2,1-*b*]benzoxazole (**6a**) and pyrido[2,1-*b*]-benzothiazole (**7a**), respectively.

2-Cyanomethyl- (**2b**, **3b**, and **4b**) and 2-acetonyl-benzazole derivatives (**2c**, **3c**, and **4c**), if used in the above reactions instead of 2-ethoxycarbonyl derivatives (**2a**, **3a**, and **4a**), gave the corresponding pyridobenzazole derivatives (**5b**, **6b**, **7b**, **5c**, **6c**, and **7c**).

Keywords——4-ethoxymethylene-2-phenyl-5-oxazolone; ethyl 2-benzazoleacetate; 2-cyanomethylbenzazole; 2-acetonylbenzazole; pyrido[1,2-*a*]benzimidazole; pyrido[2,1-*b*]benzoxazole; pyrido[2,1-*b*]benzothiazole; intramolecular acylation

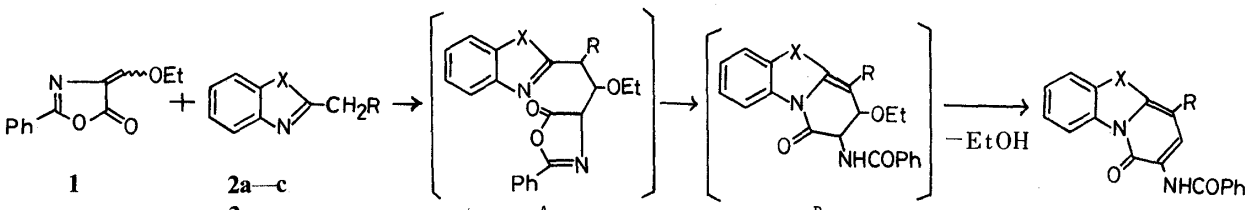
It was reported that 4-ethoxymethylene-2-phenyl-5-oxazolone (**1**) is a useful synthon for the synthesis of heterocyclic compounds, such as pyrones,[2] pyrimidoazoles,[3] and pyrimidoazines.[3] Previously, we reported that the reaction of compound **1** with enamine derivatives such as 3-amino-2-butenoates and 3-amino-2-butenamides gave the corresponding 3-benzamido-2-pyridone derivatives.[1] Further, 2-benzimidazoleacetate and 2-pyridineacetonitrile, which have a cyclic enamine structure, reacted with diketene to give pyridobenzimidazole[4] and quinolizine,[5] respectively. As a continuation of our study on the synthesis of nitrogen-containing heterocycles using 4-ethoxymethylene-2-phenyl-5-oxazolone (**1**), which is easily prepared from hippuric acid and triethyl orthoformate,[6] we now wish to report the reaction of compound **1** with benzazoleacetates, 2-cyanomethylbenzazoles, and 2-acetonylbenzazoles.

Thus, heating of a mixture of **1** and ethyl 2-benzimidazoleacetate (**2a**) resulted in the formation of 2-benzamido-4-ethoxycarbonyl-1-oxo-1,5-dihydropyrido[1,2-*a*]benzimidazole (**5a**) in 76% yield. In the infrared spectrum of **5a**, α-pyridone and amido carbonyl absorptions were observed at 1655 and 1630 cm^{-1}, respectively, instead of the oxazolone carbonyl absorption (1788 cm^{-1}) of the starting material (**1**). The nuclear magnetic resonance spectrum of **5a** showed a signal due to the C_3 proton at 8.62 ppm as a singlet. These spectral data confirmed the pyridobenzimidazole structure of **5a**. Similarly, benzoxazole (**3a**) and benzothiazole (**4a**) reacted with **1** upon heating to give the corresponding pyridobenzazoles, *i.e.*, 2-benzamido-4-ethoxycarbonyl-1-oxopyrido[2,1-*b*]benzoxazole (**6a**) and 2-benzamido-4-ethoxycarbonyl-1-oxopyrido[2,1-*b*]benzothiazole (**7a**), in 73% and 76% yields, respectively. Structure assignments of these products were made on the basis of elemental analyses and spectral measurements.

When benzazole-2-acetonitriles (**2b**, **3b** and **4b**) were used instead of benzazoleacetates (**2a**, **3a** and **4a**) in the reaction with **1**, the corresponding pyridoazole derivatives were also obtained. Thus, heating of **1** with benzimidazole-2-acetonitrile (**2b**) afforded 2-benzamido-4-cyano-1-oxo-1,5-dihydropyrido[1,2-*a*]benzimidazole (**5b**) in 84% yield. Similarly, the reaction of either benzoxazole-2-acetonitrile (**3b**) or benzothiazole-2-acetonitrile (**4b**) with **1** gave rise to

the corresponding pyridoazoles, *i.e.*, 2-benzamido-4-cyano-1-oxopyrido[2,1-*b*]benzoxazole (**6b**) and 2-benzamido-4-cyano-1-oxopyrido[2,1-*b*]benzothiazole (**7b**), in 78% and 63% yields, respectively. 4-Acetyl-2-benzamido-pyridobenzazoles (**5c**, **6c**, and **7c**) were obtained by the reaction of 2-acetonylbenzazoles (**2c**, **3c**, and **4c**) with compound **1**. Elemental analyses and spectral data of these products were consistent with pyridobenzazole structures (**5b**—**5c**, **6b**—**6c**, and **7b**—**7c**).

The formation of the pyridobenzazoles can be rationalized as follows: addition of active methylene groups of benzazoles (**2**, **3**, and **4**) to the ethoxymethylene of the oxazolone **1** would form the intermediate (A). Intramolecular acylation at the nitrogen atom of the benzazole nucleus with cleavage of the oxazolone ring of A then gives the intermediate (B), which finally yields the pyridobenzazole by elimination of ethanol.



1 **2a—c** **3a—c** **4a—c** A B **5a—c** **6a—c** **7a—c**

2, **5**: X=NH **a**: R=CO_2Et
3, **6**: X=O **b**: R=CN
4, **7**: X=S **c**: R=$COCH_3$

Chart 1

TABLE I. Reaction of Compound **1** with Benzazoles

No.	Product X	R	Conditions	Yield (%)	mp (°C)
5a	NH	CO_2Et	90 °C, 1 h	76	275—276
6a	O	CO_2Et	150 °C, 17 h	73	199—200
7a	S	CO_2Et	140 °C, 2 h	76	248
5b	NH	CN	190 °C, 10 min	84	335—336 (dec.)
6b	O	CN	140 °C, 2 h	78	261—262
7b	S	CN	140 °C, 1 h	63	260
5c	NH	$COCH_3$	140 °C, 2 h	82	304—305 (dec.)
6c	O	$COCH_3$	140 °C, 3 h	64	235—236
7c	S	$COCH_3$	140 °C, 30 min	75	266

Experimental[7]

Reaction of 4-Ethoxymethylene-2-phenyl-5-oxazolone (1) with Benzazoles——General Procedure: A mixture of equimolar amounts of **1** and a benzazole (**2**, **3**, or **4**) was heated until **1** was no longer detectable on thin layer chromatography (TLC) (preparative thin layer chromatography (PLC) plates, Silica gel 60 F_{254}); after being cooled, the resulting solid was washed with an appropriate organic solvent (ether for **5a**, **7a**, **5b**, **6b**, and **7b**; acetone for **6a**; hexane for **6a** and **7c**) and purified by recrystallization. Reaction conditions, yields, and melting points are shown in Table I.

2-Benzamido-4-ethoxycarbonyl-1-oxo-1,5-dihydropyrido[1,2-*a*]benzimidazole (5a)——The reaction of the oxazolone **1** (0.5 g) with ethyl 2-benzimidazoleacetate (**2a**) (0.47 g) gave **5a**. Needles (from acetone). *Anal.* Calcd for $C_{21}H_{17}N_3O_4$: C, 67.19; H, 4.57; N, 11.20. Found: C, 67.13; H, 4.62; N, 11.59. IR ν_{max}: 3400, 3350, 1675, 1655, and 1630 cm^{-1}. NMR (DMSO-d_6) δ: 1.32 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.35 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.22—8.25 (8H, m, aromatic-H), 8.45—8.78 (1H, m, C_9-H), 8.62 (1H, s, C_3-H), 9.29 (1H, br s, N$\underline{H}$COPh), 12.27—12.82 (1H, br, ring NH).

2-Benzamido-4-ethoxycarbonyl-1-oxopyrido[2,1-*b*]benzoxazole (6a)——The reaction of the oxazolone **1** (0.5 g) with ethyl 2-benzoxazoleacetate (**3a**) (0.47 g) gave **6a**. Needles (from AcOEt). *Anal.* Calcd for $C_{21}H_{16}N_2O_5$; C, 67.01;

H, 4.29; N, 7.45. Found: C, 66.76; H, 3.92; N, 7.23. IR ν_{max}: 3390, 1710, 1655, and 1635 cm^{-1}. NMR ($CDCl_3$) δ: 1.45 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 4.44 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 7.33—8.17 (8H, m, aromatic H), 8.37—8.70 (1H, m, C_9-H), 8.83 (1H, br s, NH), 9.33 (1H, s, C_3-H).

2-Benzamido-4-ethoxycarbonyl-1-oxopyrido[2,1-*b*]benzothiazole (7a)——The reaction of the oxazolone **1** (0.43 g) with ethyl 2-benzothiazoleacetate (**4a**) (0.44 g) gave **7a**. Needles (from benzene). *Anal.* Calcd for $C_{21}H_{16}N_2SO_4$: C, 64.27; H, 4.11; N, 7.14; S, 8.17. Found: C, 64.25; H, 4.19; N, 6.90; S, 8.48. IR ν_{max}: 3400, 1685 (sh), 1670, and 1635 cm^{-1}. NMR ($CDCl_3$) δ: 1.45 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 4.45 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 7.20—8.17 (9H, m, aromatic H), 8.88—9.40 (1H, br, NH), 9.28 (1H, s, C_3-H).

2-Benzamido-4-cyano-1-oxo-1,5-dihydropyrido[1,2-*a*]benzimidazole (5b)——The reaction of the oxazolone **1** (0.43 g) with 2-benzimidazoleacetonitrile (**2b**) (0.31 g) gave **5b**. Needles (from CH_2Cl_2–MeOH). High-resolution MS: M^+ Calcd for $C_{19}H_{12}N_4O_2$; 328.0959. Found: 328.0952. IR ν_{max}: 3400, 3175, 2210, 1660, and 1625 cm^{-1}. NMR (DMSO-d_6) δ: 7.32—8.25 (8H, m, aromatic H), 8.40 (1H, s, C_3-H), 8.55—8.83 (1H, m, C_9-H), 9.52 (1H, br s, NH), 12.17—14.88 (1H, br, ring NH).

2-Benzamido-4-cyano-1-oxopyrido[2,1-*b*]benzoxazole (6b)——The reaction of the oxazolone **1** (0.43 g) with 2-benzoxazoleacetonitrile (**3b**) (0.32 g) gave **6b**. Needles (from CH_2Cl_2–MeOH). *Anal.* Calcd for $C_{19}H_{11}N_3O_3$: C, 69.30; H, 3.37; N, 12.76. Found: C, 69.49; H, 3.50; N, 12.96. IR ν_{max}: 3300, 2220, 1670, and 1640 cm^{-1}. NMR (DMSO-d_6) δ: 7.37—8.67 (9H, m, aromatic H), 8.57 (1H, s, C_3-H), 9.70 (1H, br s, NH).

2-Benzamido-4-cyano-1-oxopyrido[2,1-*b*]benzothiazole (7b)——The reaction of the oxazolone **1** (0.43 g) with 2-benzothiazoleacetonitrile (**4b**) (0.35 g) gave **7b**. Needles (from CH_2Cl_2–MeOH). *Anal.* Calcd for $C_{19}H_{11}N_3O_2S$; C, 66.08; H, 3.21; N, 12.17; S, 9.28. Found: C, 65.87; H, 3.12; N, 11.98; S, 9.28. IR ν_{max}: 3380, 2210, 1670, and 1640 cm^{-1}. NMR ($CDCl_3$) δ: 7.36—8.00 (8H, m, aromatic H), 8.92 (1H, s, C_3-H), 9.02 (1H, br s, NH), 8.80—9.22 (1H, m, C_9-H).

4-Acetyl-2-benzamido-1-oxo-1,5-dihydropyrido[1,2-*a*]benzimidazole (5c)——The reaction of the oxazolone **1** (0.43 g) with 2-acetonylbenzimidazole (**2c**) gave **5c**. Needles (from $CHCl_3$). *Anal.* Calcd for $C_{20}H_{15}N_3O_3$: C, 69.56; H, 4.38; N, 12.17. Found: C, 69.59; H, 4.15; N, 12.08. IR ν_{max}: 3400, 3210, 1705, 1670 (sh), 1655, and 1625 (sh) cm^{-1}. NMR (DMSO-d_6) δ: 2.50 (3H, s, $COCH_3$), 7.32—8.20 (8H, m, aromatic H), 8.52—8.83 (1H, m, C_9-H), 8.68 (1H, s, C_3-H), 9.45 (1H, br s, NH), 13.03—13.33 (1H, br, ring NH).

4-Acetyl-2-benzamido-1-oxopyrido[2,1-*b*]benzoxazole (6c)——The reaction of the oxazolone **1** (0.37 g) with 2-acetonylbenzoxazole (**3c**) (0.30 g) gave **6c**. Needles (from CH_2Cl_2–MeOH). *Anal.* Calcd for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.52; H, 4.07; N, 7.84. IR ν_{max}: 3400, 1715, 1670, and 1640 cm^{-1}. NMR ($CDCl_3$) δ: 2.87 (3H, s, $COCH_3$), 7.18—8.03 (9H, m, aromatic H), 8.68 (1H, br s, NH), 9.12 (1H, s, C_3-H).

4-Acetyl-2-benzamido-1-oxopyrido[2,1-*b*]benzothiazole (7c)——The reaction of the oxazolone **1** (0.43 g) with 2-acetonylbenzothiazole (**4c**) (0.38 g) gave **7c**. Needles (from benzene). *Anal.* Calcd for $C_{20}H_{14}I_3N_2S$: C, 66.28; H, 3.89; N, 7.73; S, 8.85. Found: C, 66.49; H, 3.96; N, 7.56; S, 9.05. IR ν_{max}: 3390, 1705, 1665 (sh), 1655, and 1630 cm^{-1}. NMR (CF_3CO_2H) δ: 2.80 (3H, s, $COCH_3$), 7.45—8.18 (8H, m, aromatic H), 8.97—9.48 (3H, m, C_3-H, C_9-H, and NH).

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References and Notes

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7) Melting points are uncorrected. Infrared (IR) spectra were taken on a JASCO IR-S spectrometer, and nuclear magnetic resonance (NMR) spectra on a JEOL JNM-PMX 60 spectrometer with tetramethylsilane or 3-(trimethylsilyl)propanesulfonic acid sodium salt as an internal standard.