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Syntheses of Heteroaromatic Carboxylic Acids Closely Related to Fusaric Acid

HIROSHI YAMANAKA,*,[a] MICHINAO MIZUGAKI,[a] TAKAO SAKAMOTO,[a] MATAICHI SAGI,[a] YOSHIO NAKAGAWA,[a] HIDEKI TAKAYAMA,[b] MASATAKA ISHIBASHI,[b] and HIROSHI MIYAZAKI[b]

Pharmaceutical Institute, Tohoku University,[a] Aobayama, Sendai 980, Japan and Research Laboratories, Pharmaceutical Division, Nippon Kayaku Co.,[b] Shimo, Kita-ku, Tokyo 115, Japan

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In order to investigate the generality of a chain-elongation reaction observed in the metabolism of fusaric acid (5-butyl-2-pyridinecarboxylic acid) and its derivatives, various heteroaromatic (diazine, 1,3-azole, and 1,2-azole) carboxylic acids with a normal alkyl side-chain were synthesized.

Keywords——palladium-catalyzed condensation; terminal acetylene; regio-selective ring formation; drug metabolism; pyrazine; pyridazine; imidazole; oxazole; pyrazole; isoxazole

In connection with the metabolism[1] of 5-butyl-2-pyridinecarboxylic acid (fusaric acid), we have reported[2] the synthesis and metabolism of 5-alkyl-2-pyrimidinecarboxylic acids. That is, 2-pyrimidinecarboxylic acids having a propyl, butyl, pentyl, or hexyl group at the 5-position, like fusaric acid, underwent a chain-elongation reaction in rat liver to give the corresponding 2-pyrimidineacrylic acids and 2-pyrimidine propanoic acids as major metabolites.

In order to explore the limitations of this unique metabolic chain-elongation reaction, our attention was next directed to the behavior of further *N*-heteroaromatic acids having structures closely related to that of fusaric acid. The present paper deals with the syntheses of esters of these acids for use as substrates in the investigation of the above metabolic reaction.

Firstly, methyl 6-pentyl-3-pyridazinecarboxylate (**3**) and methyl 5-pentyl-2-pyrazinecarboxylate (**6**) were synthesized by means of palladium-catalyzed condensation of chloroheteroaromatics with terminal acetylenes[3] as a key reaction. Namely, 6-chloro-3-pyridazinecarboxylate (**1**)[4] reacted with 1-pentyne in the presence of a catalytic amount of a palladium–triphenylphosphine complex to afford methyl 6-(1-pentynyl)-3-pyridazinecarboxylate (**2**). The unsaturated methyl ester (**2**) was readily hydrogenated to give **3** in an overall yield from **1** of 77%.

The synthesis of methyl 5-pentyl-2-pyrazinecarboxylate (**6**) was also accomplished by a route similar to that used for the synthesis of **3**. Methyl 5-chloro-2-pyrazinecarboxylate (**4**)[5] was allowed to react with 1-pentyne under similar conditions to give methyl 5-(1-pentynyl)-2-pyrazinecarboxylate (**5**). Upon being shaken in a hydrogen stream over palladium on charcoal, **5** was smoothly reduced to methyl 5-pentyl-2-pyrazinecarboxylate (**6**) in 71% overall yield from **4**.

Secondly, in the azole series, four compounds with structures corresponding to that of fusaric acid were prepared.

According to the reported method for the synthesis of ethyl 5-methyl-2-imidazolecarboxylate,[6] ethyl thio-oxamate[7] was ethylated with the Meerwein reagent to give ethyl (ethylthio)iminoacetate (**8**). Then, 1-amino-2-heptanone hydrochloride (**7**)[8] was allowed

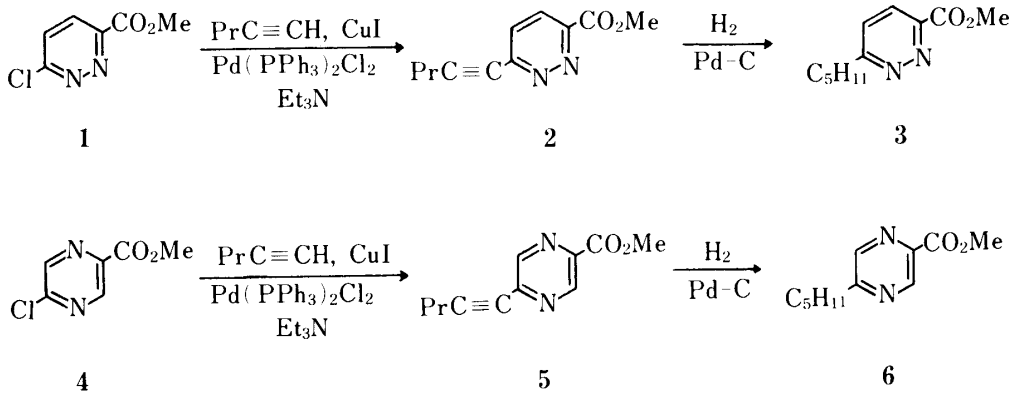

Chart 1

to react with **8** under basic conditions to give ethyl 5-pentyl-2-imidazolecarboxylate (**9**) in 73% yield.

When ethyl *N*-(2-oxoheptyl)oxamate (**10**) prepared by the acylation of **7** with ethoxalyl chloride was treated with phosphoryl chloride, a cyclization with dehydration proceeded to give ethyl 5-pentyl-2-oxazolecarboxylate (**11**) in 72% yield.

Ethyl 3-pentyl-5-pyrazolecarboxylate (**13**) and ethyl 5-pentyl-3-isoxazolecarboxylate (**14**) were both prepared from ethyl 2,4-dioxononanoate (**12**).[9] Namely, on treatment with an equimolecular amount of hydrazine hydrate, **12**, smoothly underwent the usual pyrazole cyclization, and **13** was isolated without contamination by the corresponding carboxyhydrazide.

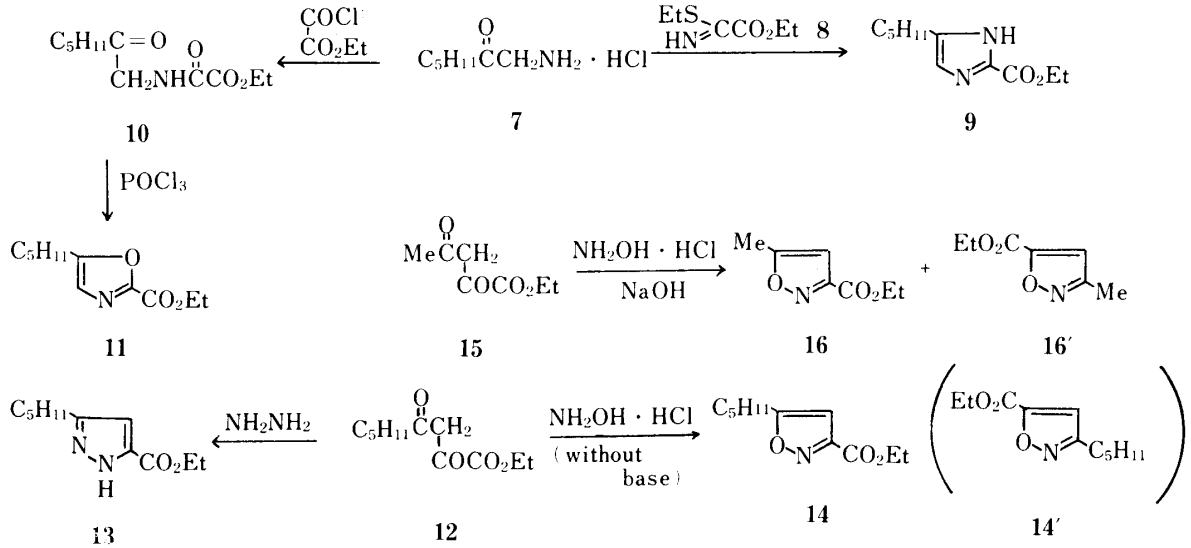

Chart 2

On the other hand, the synthesis of **14** from **12** was somewhat complicated. It is well known[10] that an unsymmetrical 1,3-diketone reacts with hydroxylamine hydrochloride to give a mixture of two positional isomers of the corresponding 3,5-disubstituted isoxazole. In fact, when **12** was allowed to react with hydroxylamine hydrochloride in ethanol in the

presence of sodium hydroxide, **14** was formed together with an equal amount of ethyl 3-pentyl-5-isoxazolecarboxylate (**14'**), and attempts to separate the two compounds were unsuccessful. In connection with this, it has been reported[11] that the reaction of ethyl 2,4-dioxopentanoate (**15**) with hydroxylamine hydrochloride alone in ethanol afforded **14** exclusively. According to the above procedure, the regio-selective synthesis of our desired compound (**14**) was accomplished in good yield. The structure of the product was confirmed by comparison of its proton magnetic resonance (^{1}H-NMR) spectrum with those of **16** and **16'**.

The esters (**3**, **6**, **9**, **11**, **13**, and **14**) thus obtained were converted to their free acids by treatment with aq. sodium (or potassium) hydroxide at room temperature. In the case of the imidazole and the oxazole, sodium 5-pentyl-2-imidazolecarboxylate and potassium 5-pentyl-2-oxazolecarboxylate were used for the subsequent investigation, because the free acid could not be easily isolated due to its high solubility in water, and the free acid of **11** was not purified because it was subject to ready decarboxylation.

Metabolic conversion of these acids together with 5-butyl-2-thiazolecarboxylic acid[12] in rats was tested,[13] and the results will be reported in detail and discussed elsewhere.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were taken with a JASCO IRA-1 spectrometer. ^{1}H-NMR spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ values using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

Methyl 6-(1-Pentynyl)-3-pyridazinecarboxylate (2)——A mixture of methyl 6-chloro-3-pyridazinecarboxylate[4] (**1**) (5.2 g, 30 mmol), 1-pentyne (4.5 g, 66 mmol), Pd $(PPh_3)_2Cl_2$ (180 mg, 0.26 mmol), CuI (30 mg), and Et_3N (30 ml) was heated at 50 °C for 20 h. After removal of the Et_3N under reduced pressure, 3 N HCl was added to the residue. The resulting mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extract was purified by silica gel column chromatography using C_6H_6 as an eluent to give pale yellow needles, mp 104—105.5 °C, which were recrystallized from hexane–C_6H_6. Yield 5.0 g (80%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240, 1740. ^{1}H-NMR ($CDCl_3$): 1.08 (3H, t, J=7 Hz), 1.33—2.00 (2H, m), 2.53 (2H, t, J=7 Hz), 4.07 (3H, s), 7.57 (1H, d, J=9 Hz), 8.13 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.49; H, 5.92; N, 13.72. Found: C, 64.41; H, 5.84; N, 13.48.

Methyl 6-Pentyl-3-pyridazinecarboxylate (3)——A solution of **2** (4.1 g, 20 mmol) in MeOH (70 ml) was shaken in an H_2 stream in the presence of 5% Pd-charcoal (2 g) until the absorption of H_2 stopped. The catalyst was removed by filtration, and the filtrate was concentrated to dryness under reduced pressure. A small amount of H_2O was added to the residue, and the resulting aqueous solution was extracted with CH_2Cl_2. The CH_2Cl_2 extract was recrystallized from hexane to give colorless needles, mp 83—84 °C. Yield 4.0 g (96%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740. ^{1}H-NMR ($CDCl_3$): 0.90 (3H, t, J=6 Hz), 1.20—2.20 (6H, m), 3.07 (2H, t, J=7 Hz), 4.03 (3H, s), 7.47 (1H, d, J=9 Hz), 8.17 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.32; H, 8.00; N, 13.39.

A suspension of **3** (2.0 g, 10 mmol) in 3 N NaOH (20 ml) was stirred at room temperature until the suspension became homogeneous. The resulting solution was acidified to pH 3.2 with conc. HCl to give a colorless precipitate which was collected by filtration. Recrystallization from hexane–C_6H_6 gave the free acid of **3** as colorless needles, mp 104—106 °C.

Methyl 5-(1-Pentynyl)-2-pyrazinecarboxylate (5)——A mixture of methyl 5-chloro-2-pyrazinecarboxylate (**4**)[5] (2.3 g, 13 mmol), 1-pentyne (2.1 g, 31 mmol), Pd $(PPh_3)_2Cl_2$ (100 mg, 0.14 mmol), CuI (20 mg), and Et_3N (30 ml) was heated at 50 °C for 24 h. After removal of the Et_3N under reduced pressure, 3 N HCl was added to the residue. The resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was purified by silica gel column chromatography using hexane and C_6H_6 as eluents. The crude product obtained from the C_6H_6 eluate was distilled under reduced pressure to give a yellow liquid, bp 142—145 °C (1 mmHg). Yield 2.02 g (76%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240, 1740. ^{1}H-NMR ($CDCl_3$): 1.06 (3H, t, J=7 Hz), 1.33—2.03 (2H, m), 2.53 (2H, t, J=7 Hz), 4.00 (3H, s), 8.65 (1H, d, J=1 Hz), 9.20 (1H, d, J=1 Hz). *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.43; H, 5.95; N, 13.64.

Methyl 5-Pentyl-2-pyrazinecarboxylate (6)——A solution of **5** (2.0 g, 10 mmol) in MeOH (70 ml) was shaken in an H_2 stream over 5% Pd-charcoal (200 mg) until the absorption of H_2 stopped. The reaction mixture was treated as in the case of **3**, and the crude product was purified by distillation under reduced pressure to give a colorless liquid, bp 122—125 °C (2 mmHg). Yield 1.9 g (94%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740. ^{1}H-NMR ($CDCl_3$): 0.93 (3H, t, J=6 Hz), 1.10—2.10 (6H, m), 2.93 (2H, t, J=7 Hz), 4.09 (3H, s), 8.53 (1H, d, J=1 Hz), 9.20 (1H, d, J=1 Hz). *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.18; H, 7.65; N, 13.65.

An emulsion of **6** (1.0 g 5 mmol) in 3 N NaOH (10 ml) was stirred at room temperature until the oily substance disappeared. The resulting homogeneous mixture was acidified to pH 2.6 with conc. HCl to give a colorless solid which was collected by filtration and washed with a small amount of H_2O. Recrystallization of the solid from hexane gave the free acid of **6** as colorless needles, mp 65—67 °C.

Ethyl 5-Pentyl-2-imidazolecarboxylate (9)——Triethyloxonium tetrafluoroborate (5.8 g, 30 mmol) was added to a stirred solution of ethyl thioxamate (2.7 g, 20 mmol) in freshly distilled CH_2Cl_2 at room temperature in several portions during 4 h. After the mixture had been stirred for a further 2 h at room temperature, the CH_2Cl_2 was evaporated off under reduced pressure. The residue was dissolved in AcOH (20 ml), then 1-amino-2-heptanone hydrochloride (**7**) (3.31 g, 20 mmol) and AcONa (1.7 g, 40 mmol) were added. The resulting mixture was heated 90—100 °C for 3 h with vigorous stirring. The precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure to give a residue, which was dissolved in H_2O. The solution was extracted with ether, and the ether extract was purified by distillation under reduced pressure to give a colorless liquid, bp 199—200 °C (1 mmHg). Yield 3.1 g (74%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1700. ^{1}H-NMR ($CDCl_3$): 0.86 (3H, t, J=6 Hz), 1.33 (3H, t, J=7 Hz), 1.06—2.26 (6H, m), 2.65 (2H, t, J=7 Hz), 4.93 (2H, q, J=7 Hz), 6.97 (1H, s), 8.00—10.00 (1H, br). *Anal.* Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 63.04; H, 8.74; N, 13.39.

A mixture of **9** (1.05 g, 5 mmol) and 5 N NaOH (1 ml) was stirred at room temperature for 3 h. After removal of the H_2O under reduced pressure, the residue was washed with MeOH and ether to give sodium 5-pentyl-2-imidazolecarboxylate as a colorless solid, mp > 200 °C.

Ethyl *N*-(2-Oxoheptyl)oxamate (10)——Ethoxalyl chloride (12.3 g, 90 mmol) was added dropwise to a suspension of **7** (5 g, 30 mmol) in dry C_6H_6 for 4 h under reflux. After removal of the C_6H_6 under reduced pressure, the residue was made alkaline with 3 N Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from hexane to give colorless scales, mp 57—59 °C. Yield 6.87 g (72%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380, 1700. ^{1}H-NMR ($CDCl_3$): 0.88 (3H, t, J=6 Hz), 1.37 (3H, t, J=7 Hz), 1.00—2.00 (6H, m), 2.50 (2H, t, J=7 Hz), 4.23 (2H, d, J=5 Hz), 4.36 (2H, q, J=7 Hz), 7.50—8.10 (1H, br). *Anal.* Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.33; H, 8.55; N, 5.99.

Ethyl 5-Pentyl-2-oxazolecarboxylate (11)——A mixture of **10** (4.0 g, 17.5 mmol) and $POCl_3$ (50 ml) was refluxed for 3 h. After removal of excess $POCl_3$ under reduced pressure, the residue was poured into ice-water. The aqueous layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid, bp 128—132 °C (2 mmHg). Yield 3.3 g (90%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$): 0.90 (3H, t, J=6 Hz), 1.45 (3H, t, J=7 Hz), 1.10—2.00 (6H, m), 2.75 (2H, t, J=7 Hz), 4.45 (2H, q, J=7 Hz), 6.97 (1H, s). *Anal.* Calcd for $C_{11}H_{17}NO_3$: C, 62.65; H, 8.34; N, 6.71. Found: C, 62.54; H, 8.11; N, 6.63.

A mixture of **11** (1.1 g, 5.2 mmol), KOH (720 mg, 130 mmol), and MeOH (10 ml) was stirred at room temperature for 1 h. The resulting solid was filtered off and washed with MeOH and ether to give potassium 5-pentyl-2-oxazolecarboxylate as a colorless solid, mp > 200 °C.

Ethyl 3-Pentyl-5-pyrazolecarboxylate (13)——A solution of ethyl 2,4-dioxononanoate (**12**) (2.1 g, 10 mmol) and $NH_2NH_2 \cdot H_2O$ (0.5 g, 10 mmol) in EtOH (10 ml) was refluxed for 2 h. The mixture was poured into H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 extract was distilled under reduced pressure to give a colorless liquid, bp 148 °C (1 mmHg). Yield 1.8 g (86%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 1710. ^{1}H-NMR ($CDCl_3$): 0.85 (3H, t, J=6 Hz), 1.33 (3H, t, J=7 Hz), 1.10—2.00 (6H, m), 2.67 (2H, t, J=7 Hz), 4.33 (2H, q, J=7 Hz), 5.56 (1H, s), 10.00—11.50 (1H, br). *Anal.* Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.83; H, 9.01; N, 13.06.

A mixture of **13** (1.8 g, 8.6 mmol) and 3 N NaOH (20 ml) was stirred at room temperature overnight, acidified to pH 2.8 with conc. HCl, and extracted with ether. The ether extract was recrystallized from C_6H_6 to give the free acid of **13** as colorless needles, mp 175—176 °C.

5-Pentyl-3-isoxazolecarboxylic Acid——A mixture of ethyl 5-pentyl-3-isoxazolecarboxylate (**14**) (2.0 g, 9 mmol) [bp 128—130 °C (2 mmHg)], prepared according to the literature,[11] and 3 N NaOH (20 ml) was stirred overnight at room temperature, then acidified to pH 2.6 with conc. HCl, and extracted with ether. The ether extract was recrystallized from hexane–ether to give the free acid of **14** as colorless needles, mp 175—176 °C.

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