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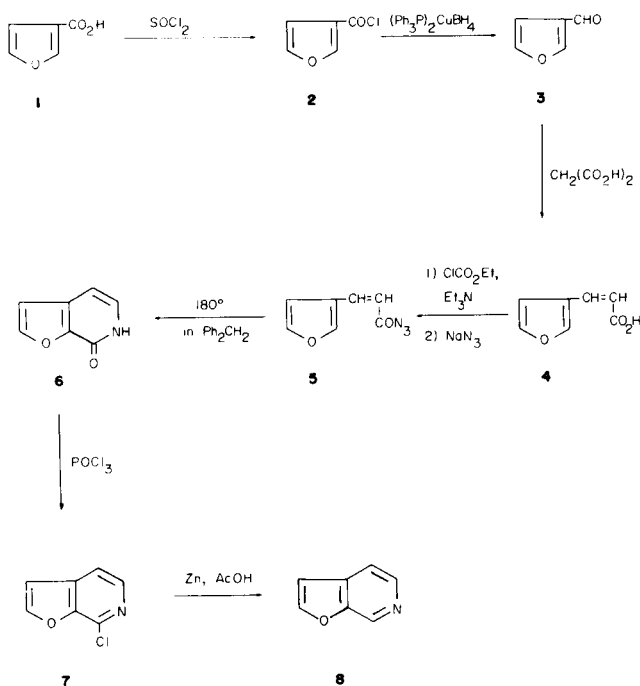
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The parent framework of furo[2,3-c]pyridine has been synthesized. 3-Furoic acid chloride (**2**) was reduced with bis(triphenylphosphine) copper(I) tetrahydroborate to afford 3-furaldehyde (**3**) which was condensed with malonic acid to give β -(3-furyl)acrylic acid (**4**). The acrylic acid **4** was converted to the acid azide (**5**), which in turn was cyclized to give furo[2,3-c]pyridin-7(6*H*)-one (**6**) by heating at 180° in diphenylmethane. The pyridone **6** was chlorinated with phosphorus oxychloride, followed by reduction with zinc and acetic acid to give furo[2,3-c]pyridine (**8**).

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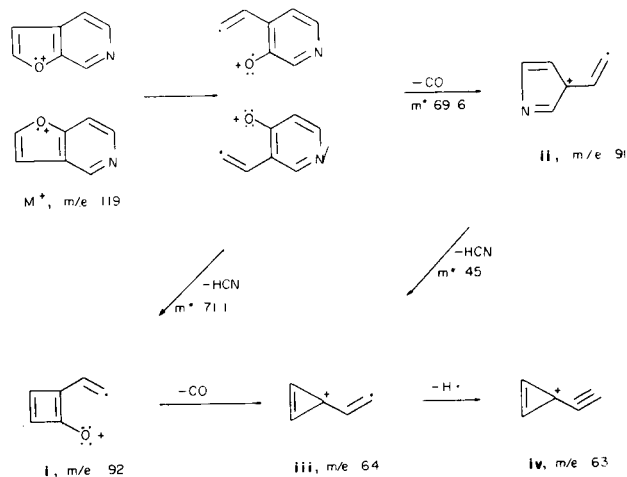
Among the six possible furopyridines, the unsubstituted furo[2,3-*b*]pyridine (**1**), furo[3,2-*b*]pyridine (**2**), furo[3,2-*c*]pyridine (**3**) and furo[3,4-*c*]pyridine (**4**) had been synthesized. However, the synthesis of the parent framework of furo[2,3-*c*]pyridine has not yet been reported. The ready availability of 3-furoic acid (**1**) prompted an attempt to use this compound as a convenient starting material for the synthesis of furo[2,3-*c*]pyridine by the method of Eloy and Deryckere (**3a**) by which furo[3,2-*c*]pyridine was synthesized from furfural and malonic acid.

Scheme 1



The conversion of 3-furoic acid to 3-furaldehyde (**3**) was achieved by the reduction of 3-furoic acid chloride (**2**) with bis(triphenylphosphine) copper(I) tetrahydroborate (**5**) in 60-70% yield. Condensation of the aldehyde **3** with malonic acid afforded β -(3-furyl)acrylic acid (**4**). The acrylic acid **4** was treated with ethyl chloroformate and

Scheme 11



triethylamine in acetone to give a mixed acid anhydride which was converted to the acid azide (**5**) by the reaction with sodium azide. The azide **5** was heated in diphenylmethane at 180° to give furo[2,3-*c*]pyridin-7(6*H*)-one (**6**). The structure of compound **6** was confirmed by spectroscopic data. The ir spectrum of **6** exhibits ν C=O of lactam at 1660 cm⁻¹ and ν NH at 3160 and 3000 cm⁻¹. In the nmr spectrum (Table I), the signals of protons attached to the furan ring appeared at δ 6.72 (H-3) and 7.78 (H-2), those to the pyridine ring at δ 6.58 (H-4) and 7.28 (H-5), the signal of NH at δ 12.60.

The furopyridone **6** was transformed to 7-chlorofuro[2,3-*c*]pyridine (**7**) by refluxing with phosphorus oxychloride. Reduction of the chloro compound **7** with zinc and acetic acid afforded furo[2,3-*c*]pyridine (**8**) as a colorless oil distillable under reduced pressure. The nmr spectrum of **8** (Table I) showed in addition to the expected spin-spin coupling, long-range coupling occurred between H-4 and H-7 and also between H-3 and H-7. This long-range coupling H-3 to H-7 is consistent with the so-called "zig-zag" path hypothesis and had also been reported in furo[3,2-*c*]pyridine (**3**) and furo[3,2-*b*]pyridine (**2a**). The chemical shift of each of the protons of **8** is much similar

Table I

		NMR Assignment (δ values) for the Furo[2,3- <i>c</i>]pyridines and Furo[3,2- <i>c</i>]pyridine					
		H-2	H-3	H-4	H-5	H-7	NH
6		7.78 d	6.72 d	6.58 d	7.28 d	—	12.60
		$J_{2,3} = 1.8$ Hz	$J_{2,3} = 1.8$ Hz	$J_{4,5} = 7.0$ Hz	$J_{4,5} = 7.0$ Hz		broad s
7		7.78 d	6.86 d	7.46 d	8.19 d	—	—
		$J_{2,3} = 2.1$ Hz	$J_{2,3} = 2.1$ Hz	$J_{4,5} = 5.3$ Hz	$J_{4,5} = 5.3$ Hz		
8		7.70 d	6.75 dd	7.48 dd	8.37 d	8.87 dd	—
		$J_{2,3} = 2.4$ Hz	$J_{2,3} = 2.4$ Hz	$J_{4,5} = 5.4$	$J_{4,5} = 5.4$ Hz	$J_{4,7} = 1.0$ Hz	
			$J_{3,7} = 0.8$ Hz	$J_{4,7} = 1.0$ Hz		$J_{3,7} = 0.8$ Hz	
		H-2	H-3	H-7	H-6	H-4	
Furo [3,2- <i>c</i>]- pyridine		7.58 d	6.76 dd	7.39 dt	8.45 d	8.90 d	—
		$J_{2,3} = 2.3$ Hz	$J_{2,3} = 2.3$ Hz	$J_{3,7} = 1.0$ Hz	$J_{6,7} = 5.8$ Hz	$J_{4,7} = 1.0$ Hz	
			$J_{3,7} = 1.0$ Hz	$J_{4,7} = 1.0$ Hz			
				$J_{6,7} = 5.8$ Hz			

s: singlet, d: doublet, dd: double doublet, dt: double triplet. Spectra were determined in deuteriochloroform.

to that of the corresponding proton of furo[3,2-*c*]pyridine (7) (H-4 of **8** corresponds to H-7 of furo[3,2-*c*]pyridine, H-5 to H-6, and H-7 to H-4, respectively), which would suggest these two furopyridines are similar in electron density on the corresponding carbon atoms and in chemical properties.

In the mass spectrum, both compound **8** and furo[3,2-*c*]pyridine (7) exhibited the molecular ion at m/e 119 as the base peak and intense peaks were observed at m/e 92, 91, 64 and 63 (Scheme II). Elimination of HCN from the molecular ion gives rise to the ion **i** at m/e 92 while loss of CO gives ion **ii** at m/e 91. Ion **i** subsequently fragments by loss of CO to ion **iii** at m/e 64 which can be also formed from ion **ii** by successive loss of HCN. Fragmentation of ion **iii** by loss of H• gives rise to the species **iv** at m/e 63.

The uv spectrum of **8** (methanol λ max in nm, log ϵ): 209.6 (3.89), 244.5 (3.90), 265 (3.63), 272.3 (3.63) and 280.7 (3.47) is analogous with that of furo[3,2-*c*]pyridine (7): 207.5 (4.13), 241 (3.95), 269 (3.30) and 276 (3.08).

EXPERIMENTAL

Melting points were obtained using a Yanagimoto micro melting point apparatus and were reported uncorrected. The ir spectra were recorded on a JASCO A-102 spectrometer. The nmr spectra were recorded on a JEOL JNM-PMX 60 spectrometer with tetramethylsilane as an internal reference. Mass spectra were obtained on a Hitachi RMU-6MG mass spectrometer. The uv spectra were recorded on a JASCO UVIDECE-505 spectrometer. Microanalyses were performed by the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University.

3-Furaldehyde (3).

A mixture of 3-furoic acid (20 g, 179 mmoles) and thionyl chloride (65.5 g 550 mmoles) in benzene (200 ml) was refluxed for 7 hours. The benzene and excess thionyl chloride were removed by distillation and the residue was distilled under reduced pressure to give 21.3 (91.5%) of

3-furoyl chloride (**2**), bp 68-74° (48 mm Hg) (lit (5), bp 65° (47 mm Hg)).

Bis(triphenylphosphine) copper(I) tetrahydroborate (89 g, 148 mmoles) was added to a stirred solution of 3-furoyl chloride (17.5 g, 134 mmoles) and triphenylphosphine (77 g, 294 mmoles) in acetone (300 ml) at room temperature. The reaction mixture was stirred for 1 hour and the precipitate was removed filtration. The filter cake was washed with ether and the solvents removed from the combined filtrates under reduced pressure below 40°. The residue was extracted with methanol, filtered, and the methanol removed under reduced pressure. The residue was dissolved in chloroform (100 ml) and stirred at room temperature over finely powdered copper(I) chloride (20 g) for 30 minutes in order to remove free triphenylphosphine. The mixture was filtered, the chloroform filtrate evaporated under reduced pressure and the residue extracted with ether. The ethereal extract was evaporated under reduced pressure and the residue distilled to give 8.62 g (67%) of furaldehyde (**3**), bp 68-76° (48 mm Hg) (literature (5), bp 70-72° (43 mm Hg)); ir (liquid film): 3150, 3000 (CH), 2840, 2750 (CH=O), 1690 (C=O), 1565, 1515, 875 and 745 (furan ring) cm^{-1} , nmr (deuteriochloroform): δ 6.73 (1H, dd, $J = 2.0$ Hz, $J' = 0.8$ Hz, H-4), 7.33 (1H, td, $J = 2.0$ Hz, $J' = 1.6$ Hz, $J'' = 0.6$ Hz, H-5), 8.04 (1H, dd, $J = 1.6$ Hz, $J' = 0.8$ Hz, H-2), 9.86 (1H, d, $J = 0.6$ Hz, -CHO).

β -(3-Furyl)acrylic Acid (4).

3-Furaldehyde (3.35 g, 34.9 mmoles) was heated with malonic acid (5 g, 48 mmoles) in pyridine (4 ml) on a water bath for 2 hours. The reaction mixture was poured onto 100 g of ice, acidified with hydrochloric acid, filtered, and the filter cake recrystallized from water to yield 3.36 g (70%) of **4**, mp 153-155°; ir (potassium bromide): 3100-2500 (OH) and 1680 (C=O) cm^{-1} , nmr (deuteriochloroform): δ 6.17 (1H, d, $J = 16.0$ Hz, H- α), 6.62 (1H, dd, $J = 2.0$ Hz, $J' = 0.8$ Hz, H-4), 7.46 (1H, dd, $J = 2.0$ Hz, $J' = 1.6$ Hz, H-5), 7.69 (1H, dd, $J = 1.6$ Hz, $J' = 0.8$ Hz, H-2), 7.70 (1H, d, $J = 16.0$ Hz, H- β), 11.05 (1H, broad s, CO₂H).

Anal. Calcd. for C₇H₆O₃: C, 60.87; H, 4.38. Found: C, 61.15; H, 4.47.

Furo[2,3-*c*]pyridin-7(6H)-one (6).

To a mixture of β -(3-furyl)acrylic acid (10 g, 72.5 mmoles) and triethylamine (8.6 g, 85.4 mmoles) in acetone (100 ml) was added dropwise ethyl chloroformate (10.5 g, 96.7 mmoles) at 0°. After stirring for 30 minutes at this temperature, a solution of sodium azide (7.0 g, 107.7 mmoles) in water (30 ml) was added to the reaction mixture at 0°, and stirred for 1 hour. The reaction mixture was diluted with 300 ml of ice-water, and the acid azide (**5**) formed was extracted with benzene. The

dried benzene solution was added dropwise to a stirred mixture of diphenylmethane (80 ml) and tributylamine (14 ml) and 180°. During the addition, the temperature of the mixture was kept at 175-185° by controlling the addition of the azide solution, and the benzene evaporated was distilled off. After addition was completed, the diphenylmethane and tributylamine were evaporated under reduced pressure, the residue extracted with boiling water, filtered with charcoal, the filtrate evaporated to dryness under reduced pressure to give 7.91 g (80.8%) of crude **6**, mp 145-150°. Recrystallization from acetone-water gave an analytically pure sample, mp 149-152°; ir (potassium bromide): 3160, 3000 (NH), 1660 (C=O) cm^{-1} .

Anal. Calcd. for $\text{C}_7\text{H}_5\text{NO}_2$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.18; H, 3.90; N, 10.32.

7-Chlorofuro[2,3-c]pyridine (**7**).

Furo[2,3-c]pyridin-7(6H)-one (6.74 g, 50 mmoles) was refluxed with phosphorus oxychloride (20 ml) for 3 hours. After cooling, the reaction mixture was poured slowly onto ice, basified with 10% aqueous sodium hydroxide, extracted with ether, dried over potassium carbonate. The oily residue of the ethereal solution was distilled under reduced pressure to afford 6.6 g (85.6%) of **7**, bp 128-138° (20 mm Hg) (mp 64-65.5).

Anal. Calcd. for $\text{C}_7\text{H}_4\text{ClNO}$: C, 54.74; H, 2.63; N, 9.12. Found: C, 54.38; H, 2.58; N, 9.09.

Furo[2,3-c]pyridine (**8**).

A solution of **7** (0.5 g, 3.26 mmoles) in acetic acid (7 ml) was refluxed with powdered zinc (1.2 g, 18.3 mmoles) for 5 hours. After cooling, the mixture was filtered, and the filtrate evaporated under reduced pressure.

The residue was dissolved in water, made alkaline with 20% aqueous sodium hydroxide, and extracted with chloroform. The extract was dried over potassium carbonate and evaporated under reduced pressure. The residual oil was distilled to give 0.37 g (95.5%) of **8**, bp 150° (40 mm Hg), as an almost colorless oil of isoquinoline-like odor. The Methiodide had mp 165-166° (from methanol-acetone) colorless prisms.

Anal. Calcd. for $\text{C}_8\text{H}_8\text{INO}$: C, 36.80; H, 3.09; N, 5.37. Found: C, 36.70; H, 3.19; N, 5.17.

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- (7) Furo[3,2-c]pyridine was prepared according to the method reported by F. Eloy and A. Deryckere (3a).