Intramolecularly Hydrogen-bonded 3-Phenacyl-1*H*-pyrido[3,4-*b*]-pyrazin-2-one and 2-Phenacyl-4*H*-pyrido[3,4-*b*]pyrazin-3-one [1]

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Twelve phenacyl derivatives of 1*H*-pyrido[3,4-*b*]pyrazin-2-ones and 4*H*-pyrido[3,4-*b*]pyrazin-3-ones have been synthesized. In these compounds, C=N double bonds at the 3 and 4 positions in the former compounds and those at the 1 and 2 positions in the latter compounds migrate onto the side chains to form phenacylidene structures. These migrations are facilitated by chelation between side chain carbonyl and the proton attached to the ring nitrogen atom which was generated by the migration. All the hydrogen-bonded structures appear to be stable as shown by their ir spectra in the crystalline state, and by their ^{1}H nmr spectra in solution.

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The condensation of 3,4-diaminopyridine (**1**) with ethyl *o*-, *m*- and *p*-substituted benzoylpyruvates **2-9** in acetic acid solution gave a series of compounds **10-17** (Table I), but in a sulfuric acid solution, this reaction afforded their isomers **18-21** (Table II).

To determine the pyrazin-2-one or the pyrazin-3-one ring structure possible for the two groups of isomers **10-17** and **18-21**, all the compounds were hydrolyzed with hydrochloric acid to yield the corresponding 3-methyl-1*H*-pyrido[3,4-*b*]pyrazin-2-one (**22**) and 2-methyl-4*H*-pyrido-[3,4-*b*]pyrazin-3-one (**23**), respectively. The latter compound showed exactly the same melting point and nmr spectral data [2] of **23** reported by Clark-Lewis and Singh [3].

It is of interest that similar condensations of 2,5,6-triamino-4-hydroxypyrimidine with the same ethyl benzoylpyruvates afforded only a single compound under acidic conditions as shown in an earlier paper [4].

Table I

1*H*-Pyrido[3,4-*b*]pyrazin-2-ones

Compound	R	Yield (%)	Mp(°C) (Recrystallized from)	Molecular Formula	Elemental Analyses(%) Calcd./Found			
					C	H	N	Br
10	H	59.9	> 300 (AcOH-EtOH)	$C_{15}H_{11}N_3O_2 \cdot 1H_2O$	63.60 63.81	4.63 4.44	14.83 15.04	
11	*p*-OCH_3	81.2	> 300 (AcOH)	$C_{16}H_{13}N_3O_3 \cdot 1/3CH_3COOH$	63.49 63.68	4.58 4.42	13.33 13.63	
12	*p*-OH	73.3	> 300 (Pyridine)	$C_{15}H_{11}N_3O_3$	64.05 64.28	3.94 4.08	14.94 15.11	
13	*p*-Br	64.0	> 300 (Pyridine)	$C_{15}H_{10}BrN_3O_2$	52.35 52.17	2.93 3.12	12.21 11.97	23.22 22.98
14	*p*-CH_3	35.1	273-274 (AcOH)	$C_{16}H_{13}N_3O_2 \cdot 1/3CH_3COOH$	66.80 66.80	4.83 4.80	14.04 14.26	
15	*m*-OH	22.6	> 300 (Pyridine)	$C_{15}H_{11}N_3O_3$	64.05 63.96	3.94 4.15	14.94 14.65	
16	*m*-OCH_3	67.1	243-245 (AcOH)	$C_{16}H_{13}N_3O_3 \cdot 1/3CH_3COOH$	63.49 63.53	4.58 4.45	13.33 13.68	
17	*o*-OCH_3	59.1	243-245 (AcOH-EtOH)	$C_{16}H_{13}N_3O_3$	65.08 65.02	4.44 4.59	14.23 13.99	

Table II

4*H*-Pyrido[3,4-*b*]pyrazin-3-ones

Compound	R	Yield (%)	Mp(°C) (Recrystallized from)	Molecular Formula	Elemental Analyses(%) Calcd./Found		
					C	H	N
18	H	55.0	252-253 (AcOH)	$C_{15}H_{11}N_3O_2 \cdot 1H_2O \cdot 1/2H_2SO_4$	64.05 63.96	3.94 4.15	14.94 14.65
19	*p*-OCH_3	59.3	243-245 (AcOH-EtOH)	$C_{16}H_{13}N_3O_3$	65.08 65.02	4.44 4.59	14.23 13.99
20	*p*-CH_3	82.4	273-274 (AcOH-EtOH)	$C_{16}H_{13}N_3O_2$	68.80 67.08	4.69 4.83	15.05 14.86
21	*m*-OH	23.3	> 300 (Pyridine)	$C_{15}H_{11}N_3O_3$	64.05 64.21	3.94 4.21	14.94 14.68

Scheme

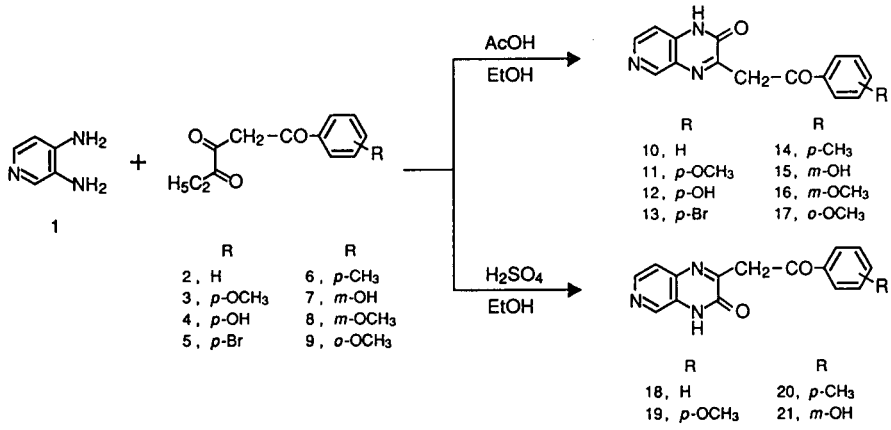


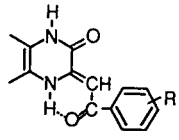
Table III

Nmr and Ir Spectra Data for Compounds 10-21

Compound	Side Chain(=CH)	^{1}H-Nmr δ (ppm) Ring (=CH) at			N-H at 1 or 4	Ir(cm^{-1})	
		5	7	8		C=O	C=C
	(s,1H)	(s,1H)	(d,1H)	(d,1H)	(br,1H,1H)		
10	6.88	8.83	8.45	7.20	12.5, 13.3	1630	1622
11	6.84	8.74	8.21	7.04	12.1, 13.3	1630	1610
12	6.82	8.70	8.20	7.00	12.1 13.3	1630	1610
13	6.84	8.79	8.20	7.06	12.2 13.4	1620	1605
14	6.85	8.73	8.23	7.05	12.1 13.3	1630	1620
15	6.80	8.76	8.20	7.05	12.1 13.3	1625	1610
16	6.84	8.76	8.15	7.05	12.2 13.4	1630	1610
17	6.84	8.72	8.20	7.05	12.9 13.3	1630	1610
18	7.06	8.96	8.31	7.81	12.3 13.3	1630	1610
19	6.82	8.91	8.17	7.50	12.1 13.3	1630	1620
20	7.04	8.90	8.21	7.81	12.1 13.3	1630	1615
21	6.82	8.86	8.18	7.88	12.2 13.4	1625	1610

The ^{1}H nmr spectra of these two types of compounds **10-17** and **18-21** were measured in dimethyl sulfoxide-d_6 (DMSO-d_6) (Table III).

In all cases, no methylene signals of the phenacyl group appear but methine and broad N-H signals are given. The secondary amino group cannot occur unless the nitrogen-carbon double bond has been displaced onto the side chain. Thus, all the compounds **10-21** exist in the "enamine form" which is facilitated by internal hydrogen bonding. The hydrogen-bonded structures obtained are supported by their ir spectra [5,6] (Table III). The structures consistent with these spectra data are designed as "3-phenacylidene-3,4-dihydro-1*H*-pyrido[3,4-*b*]pyrazin-2-ones" **10-17** and "2-phenacylidene-1,2-dihydro-4*H*-pyrido-[3,4-*b*]pyrazin-3-ones" **18-21**, respectively.



Figure

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded as potassium bromide disks using a Nippon Bunko IRA-1 spectrophotometer. The ^{1}H nmr spectra were obtained in DMSO-d_6 using a JEOL FX-90 spectrometer and are reported as δ values (ppm, TMS as an internal standard).

The starting materials, ethyl benzoylpyruvates, were prepared according to the method of Beyer and Claisen [4,7].

General Procedure for the Syntheses of 1*H*-Pyrido[3,4-*b*]pyrazin-2-ones **10-17**.

Into a solution of **1** (0.66 g, 6 mmoles) in ethanol (20 ml) and 50% aqueous acetic acid (20 ml), a solution of the ethyl benzoylpyruvates **2-9** (6 mmoles) in ethanol (10 ml) was added dropwise with stirring. The temperature of the reaction mixture was gradually raised to 100°. The mixture, which started to turn a deep orange with the formation of a reddish-yellow precipitate, was refluxed for 3 hours, and then allowed to stand overnight at room temperature. The crystals thus deposited were collected on a funnel and washed well with water and ethanol. The crude product was recyrstallized from a solvent as shown in Tables I and II.

Physical and spectral data of the products are shown in Tables I, II and III.

General Procedure for the Syntheses of 4*H*-Pyrido[3,4-*b*]pyrazin-3-ones **18-21**.

The above procedure was modified by using aqueous 1*M* sulfuric acid in place of 50% aqueous acetic acid.

Physical and spectral data of the products are shown in Tables I, II and III.

REFERENCES AND NOTES

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