Unambiguously Confirmed Structure of 2-Phenacylidene-1,2-dihydro-4*H*-pyrido[2,3-*b*]pyrazin-3-one and 3-Phenacylidene-3,4-dihydro-1*H*-pyrido[2,3-*b*]pyrazin-2-one

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To determine the structures of two isomeric products, 2-phenacylidene-1,2-dihydro-4*H*-pyrido[2,3-*b*]pyrazin-3-one (**2**) and 3-phenacylidene-3,4-dihydro-1*H*-pyrido[2,3-*b*]pyrazin-2-one (**3**) obtained by condensation of 2,3-diaminopyridine (**1**) with ethyl benzoylpyruvate [1-3], these compounds were hydrolyzed to give 2-methyl-4*H*-pyrido[2,3-*b*]pyrazin-3-one (**4**) and 3-methyl-1*H*-pyrido[2,3-*b*]pyrazin-2-one (**5**), respectively [4,5]. Both hydrolysates **4** and **5** were hydrogenated to afford 2-methyl-1,2-dihydro-4*H*-pyrido[2,3-*b*]pyrazin-3-one (**6**) and 3-methyl-3,4-dihydro-1*H*-pyrido[2,3-*b*]pyrazin-2-one (**7**). The latter compound was identical with an unequivocally synthesized compound providing proof for the structures of all these compounds.

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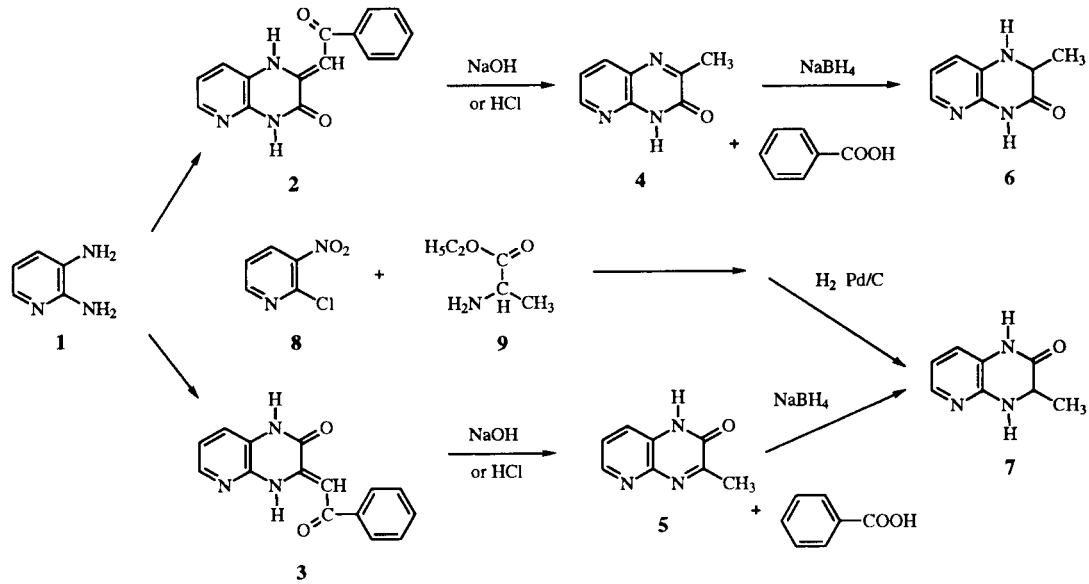
We previously reported [1] that condensation of **1** with ethyl benzoylpyruvate carried out in aqueous sulfuric acid solution afforded **2**, and in aqueous acetic acid solution gave **3**. The structures of these products were tentatively confirmed by their ^{1}H nmr spectral data.

On the other hand, Bodforss synthesized a compound which might be formulated either as **2** or **3**, but could not make a decision between these two isomeric structures [6]. Hence, we wished to obtain further structural evidence as follows.

Hydrolysis of **2** and **3** with aqueous sodium hydroxide or hydrochloric acid solution gave the corresponding hydrolysates **4** and **5**. Both hydrolysates showed identical ^{1}H nmr spectra with two methyl derivatives of pyrido[2,3-*b*]pyrazinone as reported by Abasolo *et al.* [5]. However, their melting points were different. These methyl derivatives of pyrido[2,3-*b*]pyrazinone were reported first by Leese and Rydone [4] who described the melting point for 2-methyl-4*H*-pyrido[2,3-*b*]pyrazin-3-one (**4**) as 240°, and that for 3-methyl-1*H*-pyrido[2,3-*b*]pyrazin-2-one (**5**) as 270° dec. Abasolo *et al.* reported the melting point 240° (254-256°) for the

Scheme



former, and 279° (300° dec) for the latter (the results of the present study are shown in parentheses).

As a further step to establish the structures, **4** and **5** were hydrogenated with sodium borohydride to give 2-methyl-1,2-dihydro-4*H*-pyrido[2,3-*b*]pyrazin-3-one (**6**) and 3-methyl-3,4-dihydro-1*H*-pyrido[2,3-*b*]pyrazin-2-one (**7**), respectively. The unambiguous synthesis of **7** was achieved by the reaction of 2-chloro-3-nitropyridine (**8**) with alanine ethyl ester (**9**) followed by catalytic hydrogenation. Two series of compounds **2, 4, 6** and **3, 5, 7** have thus been obtained in support for their structures by this synthetic proof.

EXPERIMENTAL

All melting points are uncorrected. The ^{1}H nmr spectra were obatained in dimethyl sulfoxide-d_6 (DMSO-d_6) using a JEOL FX-90 spectrometer, and are reported as δ values (ppm, TMS as an internal standard).

2-Methyl-4*H*-pyrido[2,3-*b*]pyrazin-3-one (**4**).

A suspension of **2** (0.5 g) in 2*M* aqueous sodium hydroxide solution (15 ml) was heated at 110° for 40 minutes. The reaction mixture quickly turned into a solution upon heating. Concentrated hydrochloric acid was dropped into the solution, after cooling with stirring until it remained slightly alkaline. The resulting crystals were collected by filtration, recrystallized from water to give **4**, mp 254-256° dec. The ^{1}H nmr spectral data agreed with those obtained by Abasolo *et al.* [5], δ 2.41 (s, 3H, CH_3), 7.33 (dd, 1H, H_7), 8.10 (dd, 1H, H_8), 8.46 (dd, 1H, H_6), 12.7 (br s, 1H, NH).

Anal. Calcd. for $C_8H_7N_3O$: N, 26.07. Found: N, 26.21.

The filtrate was acidified with aqueous 6*M* hydrochloric acid, and extracted with ether repeatedly. Ether was removed from the combined extracts, and the residue was recrystallized from ethanol to afford benzoic acid (0.2 g), mp 121-121.5°, undepressed on admixture with a commercial sample.

3-Methyl-1*H*-pyrido[2,3-*b*]pyrazin-2-one (**5**).

A suspension of **3** (0.50 g) in aqueous 2*M* hydrochloric acid (6 ml) was heated for 2 hours. After cooling, the mixture was extracted with ether three times. The extracts were dried (anhydrous sodium sulfate) and evaporated. The residue (0.20 g) was recrystallized from ethanol to afford bezoic acid (0.16 g), mp 121-122°, undepressed on admixture with a commercial sample. The acidity of the aqueous layer was alkalized with sodium bicarbonate (powder), and repeatedly extracted with ethyl acetate. From the combined extracts, the solvent was removed. The residue was recrystallized from water to give **5**, mp 300° dec. The ^{1}H nmr spectral data agreed with those obtained by Abasolo *et al.* [5], δ 2.41 (s, 3H, CH_3), 7.47 (dd, 1H, H_7), 7.70 (dd, 1H, H_8), 8.48 (dd, 1H, H_6), 12.7 (br s, 1H, NH).

Anal. Calcd. for $C_8H_7N_3O$: N, 26.07. Found: N, 25.80.

3-Methyl-3,4-dihydro-1*H*-pyrido[2,3-*b*]pyrazin-2-one (**7**).

A). Hydrogenation of 3-Methyl-1*H*-pyrido[2,3-*b*]pyrazin-2-one (**5**).

A mixture of sodium borohydride (0.02 g) and **5** (0.15 g) in 0.5*M* aqueous sodium hydroxide solution (2 ml) was allowed to stand at room temperature. After three days, 0.04 g of sodium borohydride was added. After one more day, the mixture was neutralized with concentrated hydrochloric acid, the resulting precipitate was collected by filtration and then recrystallized from ethanol to give **7** (0.07 g), mp 267-270°, ^{1}H nmr: δ 1.29 (d, 3H, CH_3), 3.90 (qq, 1H, H_3), 6.58 (dd, 1H, H_7), 6.93 (dd, 1H, H_8), 7.62 (dd, 1H, H_6).

Anal. Calcd. for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75. Found: C, 58.63; H, 5.71; N, 25.58.

B). Condensation of 2-Chloro-3-nitropyridine (**8**) and Alanine Ethyl Ester (**9**).

A mixture of **8** (0.48 g) and **9** (0.38 g) in ethanol (10 ml) was stirred at room temperature for 2 hours. The mixture was concentrated to give ethyl 2-(3-nitro-2-pyridyl)aminopropionate (0.46 g). The product in ethanol was shaken with hydrogen over 5% activated palladium on carbon at room temperature until absorbance of hydrogen stopped. After the catalyst was filtered off, the filtrate was evaporated *in vacuo* to give **7**, mp 268-270° (from ethanol); ^{1}H nmr: δ 1.29 (d, 3H, CH_3), 3.87 (qq, 1H, H_3), 6.58 (dd, 1H, H_7), 6.94 (dd, 1H, H_8), 7.63 (dd, 1H, H_6).

Anal. Calcd. for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75. Found: C, 59.16; H, 5.81; N, 25.88.

2-Methyl-1,2-dihydro-4*H*-pyrido[2,3-*b*]pyrazin-3-one (**6**).

This compound (0.03 g) was prepared from **4** (0.075 g) by hydrogenation similar to that described for the synthesis of **7**, mp 238-240°; ^{1}H nmr: δ 1.30 (d, 3H, CH_3), 3.86 (qq, 1H, H_3), 6.77 (dd, 1H, H_7), 6.94 (dd, 1H, H_8), 7.53 (dd, 1H, H_6).

Anal. Calcd. for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75. Found: C, 58.62; H, 5.72; N, 25.48.

REFERENCES AND NOTES

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