Reaction Products of Dialkyl Acetylenedicarboxylates with 2,3-Diaminopyridine

Taketsugu Seki [1]

Department of Chemistry, Sasaki Institute, Kanda-Surugadai, Chiyodaku, Tokyo 101, Japan

Yasuo Iwanami* [2]

Department of Chemistry, Keio University, Hiyoshi 4-1, Yokohama 223, Japan

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The condensation of dialkyl acetylenedicarboxylates **1** and **2** with 2,3-diaminopyridine (**3**) or its 5-bromo derivative **4** in ethanol gave pyrido[2,3-*b*]pyrazinones with a common side chain -CH_2-COOR at their 2-position, **5-7**, but in the presence of sulfuric acid the reaction afforded their isomers with the same side chain at the 3-position, **8-10**. All of the products were shown to exist in enamine form, in which a ring double bond has been displaced onto their side chain (=CH-COOR) being facilitated by an internal chelation as demonstrated by their ir and ^{1}H nmr spectra.

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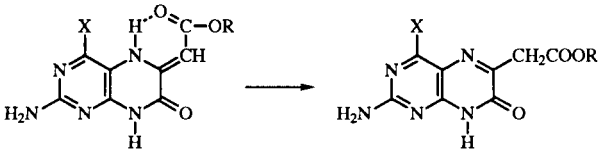
In imine-enamine tautomerism, the imine form is generally predominant over the enamine [3,4]. One of the authors has shown previously that some acetate derivatives of a naturally-occurring pteridine, *i.e.* alkyl isoxanthopterin-6-acetates consist exclusively of the imine form [5].

We were particularly interested in whether the same acetate derivatives of similar heterocycles with one nitrogen atom less in the ring, compared to isoxanthopterin, would also exist in the imine form.



enamine imine

X = O or NH
R = CH_3 or C_2H_5

When the condensation of **1** and **2** with **3** or **4** was carried out in ethanol, a series of compounds, **5-7**, were obtained. Isomers **8-10** were formed when the reaction was carried out in an ethanolic solvent acidified with aqueous sulfuric acid.

To determine their structures, compound **5** and its isomer **8** were hydrolyzed with aqueous sodium hydroxide or aqueous hydrochloric acid into **11** and **12**, respectively. The latter compound was shown to be identical to 3-methyl-1*H*-pyrido[2,3-*b*]pyrazin-2-one, which has been unequivocally synthesized previously by us [6]. Thus, the two series of compounds, **5-7** and **8-10**, were confirmed to be 2-acetates and 3-acetates, respectively. These structures were supported by the finding that bromo compounds **7** and **10** underwent debromination with hydrazine (Pd-C) to give **5** and **8**.

The ir and ^{1}H nmr spectra of **5-10** gave adequate information as to their existing modes, which are herein referred

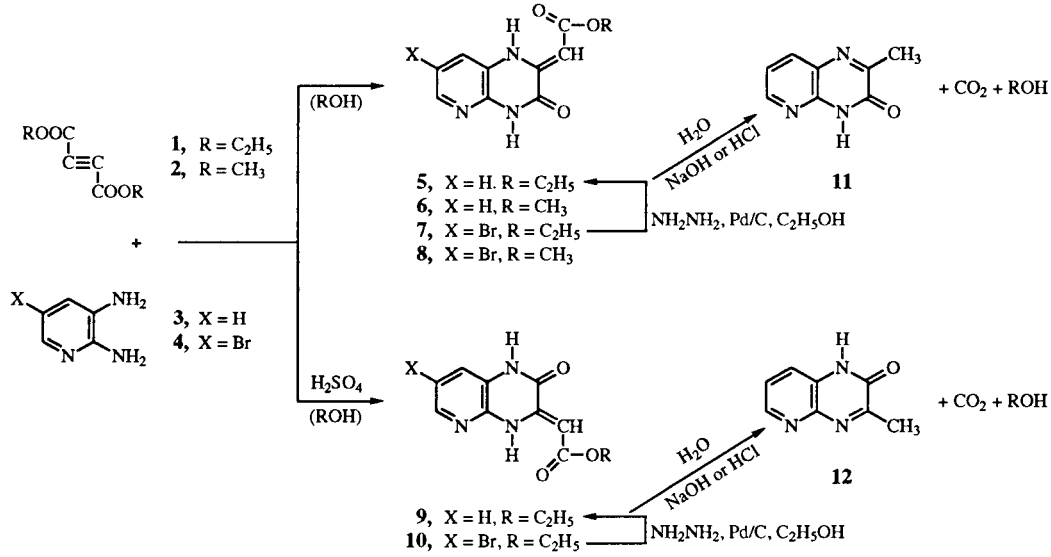


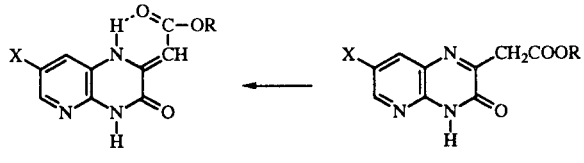
Table 1

NMR and IR Spectral Data for Compounds **5-10**

Compound	Side Chain (=CH) (s, 1H)	^{1}H NMR δ (ppm) Ring (=CH) at 6 (dd, 1H)	7 (dd, 1H)	8 (dd, 1H)	N-H at 1 or 4 (br, 1H, 1H)	IR (cm^{-1}) C=O	C=C
5	5.56	7.94	7.08	7.84	11.0, 12.1	1650	1630
6	5.57	7.93	7.09	7.85	11.0, 12.1	1648	1630
7	5.58	8.20		8.04	11.0, 12.3	1648	1625
8	5.61	8.21		8.03	11.0, 12.3	1650	1625
9	5.57	8.01	7.07	7.38	11.1, 11.8	1648	1620
10	5.54	8.05		7.50	11.1, 11.9	1648	1625

to as the imine and enamine forms, as mentioned above. The side chain carbonyls in the imine form should give a normal ester absorption, but they exhibited a band in the region 1630-1650 cm^{-1}. The shift to lower frequencies is consistent with the occurrence of an α,β-unsaturated ester C=O probably involved in hydrogen bonding (Table 1). This suggests their existence in the enamine form.

Their enamine structures were further supported by the ^{1}H nmr spectra. The signals of =CH-, instead of -CH_2- appeared together with those of the hydrogen-bonded -NH- at lower field (Table 1). The structure consistent with these data is designated as 2-ethoxycarbonylmethylene-1,2-dihydro-4*H*-pyrido[2,3-*b*]pyrazin-3-one (**5**) *etc.*



Thus, all of the compounds **5-10** exhibited structures in striking contrast with those of isoxanthopterin-6-acetates.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Nippon Bunko IRA-1 spectrometer. The ^{1}H nmr spectra were obtained on a JEOL FX-90 spectrometer in dimethyl sulfoxide-d_6 (DMSO-d_6) with TMS as the internal standard. Chemical shifts are reported in ppm (δ).

2-Ethoxycarbonylmethylene-1,2-dihydro-4*H*-pyrido[2,3-*b*]pyrazin-3-one (**5**).

Into a suspension of **3** (1.09 g) in ethanol (30 ml), a solution of **1** (1.70 g) in ethanol (10 ml) was added dropwise with stirring at room temperature. The mixture was stirred for a further 2 hours. The precipitated yellow crystals (1.50 g, 64%) were collected by filtration. The crude product was recrystallized from 70% aqueous ethanol to give **5**, mp 211-211.5° dec.

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.81; H, 4.61; N, 18.27.

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

This compound was prepared from **3** (0.33 g) and **2** (0.43 g) in a manner similar to that described for the synthesis of **5**, in a yield of 0.52 g (78%). An analytical sample was recrystallized from 70% aqueous methanol, mp 270-282° dec.

Anal. Calcd. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 55.02; H, 4.01; N, 19.33.

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

This compound was prepared from **4** [7-9] (0.56 g) and **1** (0.51 g) in a manner similar to that described for the synthesis of **5**, yielding 0.49 g (48%). An analytical sample was recrystallized from acetic acid-ethanol, mp 280° dec (lit [10] 240° dec).

Anal. Calcd. for $C_{11}H_{10}BrN_3O_3$: C, 42.33; H, 3.23; N, 13.46. Found: C, 42.50; H, 3.09; N, 13.35.

7-Bromo-2-methoxycarbonylmethylene-1,2-dihydro-4*H*-pyrido-[2,3-*b*]pyrazin-3-one (**8**).

This compound was prepared from **4** (0.94 g) and **2** (0.71 g) in a manner similar to that described for the synthesis of **5**, in a yield of 0.64 g (43%). An analytical sample was recrystallized from acetic acid-methanol, mp 280° dec.

Anal. Calcd. for $C_{10}H_8BrN_3O_3$: C, 40.29; H, 2.71; N, 14.10. Found: C, 40.50; H, 2.79; N, 14.35.

3-Ethoxycarbonylmethylene-3,4-dihydro-1*H*-pyrido[2,3-*b*]pyrazin-2-one (**9**).

Into a suspension of **3** (0.66 g) in ethanol (18 ml) and 1 *M* sulfuric acid (18 ml), a solution of **1** (1.03 g) in ethanol (3 ml) was added dropwise with stirring at room temperature under an argon atmosphere. After the mixture was stirred overnight, the precipitated yellow crystals (0.05 g) were removed by filtration and then further allowed to stand for 9 days at room temperature. The crystals thus deposited were collected on a funnel, in a yield of 0.33 g (24%). The crude product was recrystallized from 70% aqueous ethanol to give **9**, mp 225-227° dec.

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.93; H, 4.53; N, 17.98.

7-Bromo-3-ethoxycarbonylmethylene-3,4-dihydro-1*H*-pyrido-[2,3-*b*]pyrazin-2-one (**10**).

This compound was prepared from **4** (0.75 g) and **1** (0.68 g) in a manner similar to that described for the synthesis of **9**, yielding 0.45 g (36%). An analytical sample was recrystallized

from acetic acid-ethanol, mp 295° dec.

Anal. Calcd. for $C_{11}H_{10}BrN_3O_3$: C, 42.33; H, 3.23; N, 13.46. Found: C, 42.55; H, 3.38; N, 13.41.

Hydrogenation of **7** and **10**.

Into a suspension of **7** (0.35 g) in 40 ml of ethanol, 10% Pd-C (50 mg) and hydrazine hydrate (0.7 ml) was added, and the mixture was refluxed for 0.5 hours. After cooling, the catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The solid was recrystallized from ethanol to give 0.11 g (42%) of **5**.

A suspension of **10** (0.35 g), 10% Pd-C (50 mg) and hydrazine hydrate (0.7 ml) was refluxed for one hour, and 0.09 g (35%) of **3** was obtained after recrystallization from ethanol. The compounds **5** and **9** were identified by comparing their ir and ^1H nmr spectra with compounds obtained from condensation of **1** and **3**.

Hydrolysis of **5**.

A suspension of **5** (0.70 g) in 1 *M* aqueous sodium hydroxide (15 ml) was refluxed for 30 minutes. The reaction mixture became a solution upon heating, into which 6 *M* hydrochloric acid was added dropwise after cooling with stirring until it remained slightly alkaline. The resulting crystals were recrystallized from water to give **11** (0.32 g), mp 254-256° dec. The ^1H nmr spectral data agreed with those of an authentic sample reported in a previous paper [6].

The hydrolysis of **5** was also performed with 6 *M* hydrochloric acid.

Hydrolysis of **9**.

A suspension of **9** (0.41 g) in 6 *M* hydrochloric acid (10 ml) was refluxed for 2.5 hours. After cooling, the reaction mixture was alkalized with sodium bicarbonate (powder), and extracted with ethyl acetate repeatedly. Ethyl acetate was removed from the combined extracts, and the residue was recrystallized from water to give **12** (0.17 g), mp 300° dec. The ^1H nmr spectral data agreed with those of an authentic sample from a previous paper [6].

The hydrolysis of **9** was also performed in aqueous 2 *M* sodium hydroxide.

REFERENCES AND NOTES

[1] Present address: Research Laboratories, Nikken Chemicals Co. Ltd., Ohmiya, Saitama 330, Japan.

[2] To whom correspondence should be directed at the Department of Chemistry, Keio University, Hiyoshi 4-1, Yokohama 223, Japan.

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