The Reaction of Acetylenecarboxylic Acid with Amines. XVI.[1] Formation of Alkyl Isoxanthopterinacetates Possessing Imine Structure[2]

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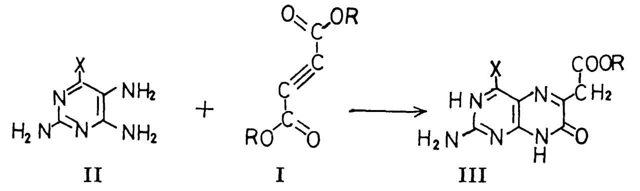
Methyl and ethyl isoxanthopterin-6-acetates and their 4-amino analogues have been prepared *via* a new route from acetylenedicarboxylate and 2,5,6-triamino-4-hydroxypyrimidine or 2,4,5,6-tetraaminopyrimidine. These compounds uniquely exist in the imine form as evidenced by NMR and IR spectral data. This is the only exceptional case so far examined, since a number of related compounds exist in enamine form. When dissolved in sulfuric acid, however, tautomerization of imine to enamine is observed. It was demonstrated by NMR inspection that the methylene hydrogen on the side chain is exchangeable with deuterium. The tautomerism in sulfuric acid is discussed.

The reactions of ethyl and methyl acetylenedicarboxylates (Ia and Ib) with 2,5,6-triamino-4-hydroxypyrimidine (IIa) or 2,4,5,6-tetraaminopyrimidine (IIb) gave the corresponding alkyl isoxanthopterin-6-acetates (IIIa and IIIb) or their 4-amino analogues (IIIc and IIId). Although the preparation of the ethyl ester (IIIa and IIIc) by a different route is known,[3] this procedure provides another route.

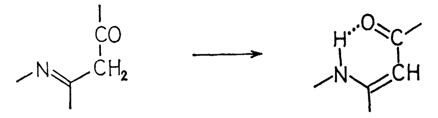


II
a : X=OH
b : X=NH$_2$

I
a : R=Et
b : R=Me

III
a : X=OH; R=Et
b : X=OH; R=Me
c : X=NH$_2$; R=Et
d : X=NH$_2$; R=Me

In a previous paper[4] we reported that the compound customarily called ethyl 2(1*H*)-quinoxalinone-3-acetate exists in the enamine form, *i.e.* in a structure to be named 3-ethoxycarbonylmethylene-3,4-dihydro-2(1*H*)-quinoxalinone. The enamine form is facilitated by an intramolecular hydrogen bonding. The preceding report was the first to present evidence for such a chelate structure. Since then, many examples of similar enamines possessing intramolecular hydrogen bonding have been reported from our laboratory in condensed[1,4–6] and noncondensed[1,4,6] nitrogen-containing heterocycles of five-,[5] six-,[1,4–6] and seven-membered[5] rings or even in simpler alkyl β-aminoacrylates.[1,5,7]



imine form enamine form

Because of their structural resemblance to the heterocycles,[1–4] compounds IIIa—d were expected to exist in the enamine form. Nevertheless, IR and NMR spectroscopic data have disclosed the predominancy of the imine form both in their solution and crystalline states.

The IR spectra of III exhibited ester carbonyl bands in the range 1747—1716 cm^{-1}, but not 1698—1644 cm^{-1}, which was expected for an intramolecularly hydrogen-bonded α,β-unsaturated ester carbonyl common to all the related compounds reported in the preceding papers. This suggests that the side chain of III exists in an alkyl acetate form rather than in chelated alkoxycarbonylmethylene form.

In order to obtain further evidences the NMR spectra of III were examined. Although solubility of III in the usual solvents was not high enough for the spectroscopy, we found that sulfuric acid was good solvent in which III was stable at ordinary temperature.

The NMR spectra of IIIa in sulfuric acid are shown in Fig. 1. A triplet at 1.78 ppm and a quartet at 4.75 ppm are observed besides two broad signals due to NH protons at 5.24 and *ca.* 8.00 ppm. The profile of the quartet appears deformed. The relative intensity of the quartet represents 4: 3 to the triplet due to methyl protons of the ethoxyl group. This can be explained by the overlapping of a quartet due to methylene protons of the ethoxyl group with a singlet due to the other methylene protons adjacent to the pteridine ring. In deuteriosulfuric acid, the coinciding singlet has disappeared together with amino proton signals, and the intensity of the remaining quartet diminishes to two-thirds that of the triplet. Namely, the triplet and quartet turn out typical bands of an ethoxyl group.

The spectrum of IIIa in deuteriodimethyl sulfoxide is essentially the same as that in sulfuric acid. Similar phenomena have been observed in the spectra of IIIb—d.

From these results except those in deuteriosulfuric acid, it is evident that this compound exists as ethyl isoxanthopterin-6-acetate (IIIa) but not as 6-ethoxy-

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[1] Part XV: Y. Iwanami, This Bulletin, **44**, 1311 (1971).

[2] Presented in part at the IVth International Symposium on Pteridines, Toba, July, 1969, and also partially described in The Symposium Proceedings, "Chemistry and Biology of Pteridines," International Academic Printing Co., Yamabuki-cho Shinjuku-ku, Tokyo (1970), p. 129.

[3] A. G. Renfrew, P. C. Piatt, and L. H. Cretcher, *J. Org. Chem.*, **17**, 467 (1952).

[4] Y. Iwanami, *Nippon Kagaku Zasshi*, **82**, 778, 780 (1961).

[5] Y. Iwanami, *ibid.*, **83**, 100, 161, 316, 593, 597 (1962); H. Sasaki, H. Sakata, and Y. Iwanami, *ibid.*, **85**, 704 (1964).

[6] Y. Iwanami, Y. Kenjo, K. Nishibe, M. Kajiura, and S. Isoyama, This Bulletin, **37**, 1740 (1964); Y. Iwanami, S. Isoyama, and Y. Kenjo, *ibid.*, **37**, 1745 (1964).

[7] Y. Iwanami, *Nippon Kagaku Zasshi*, **82**, 632, 634 (1961); **83**, 600 (1962).

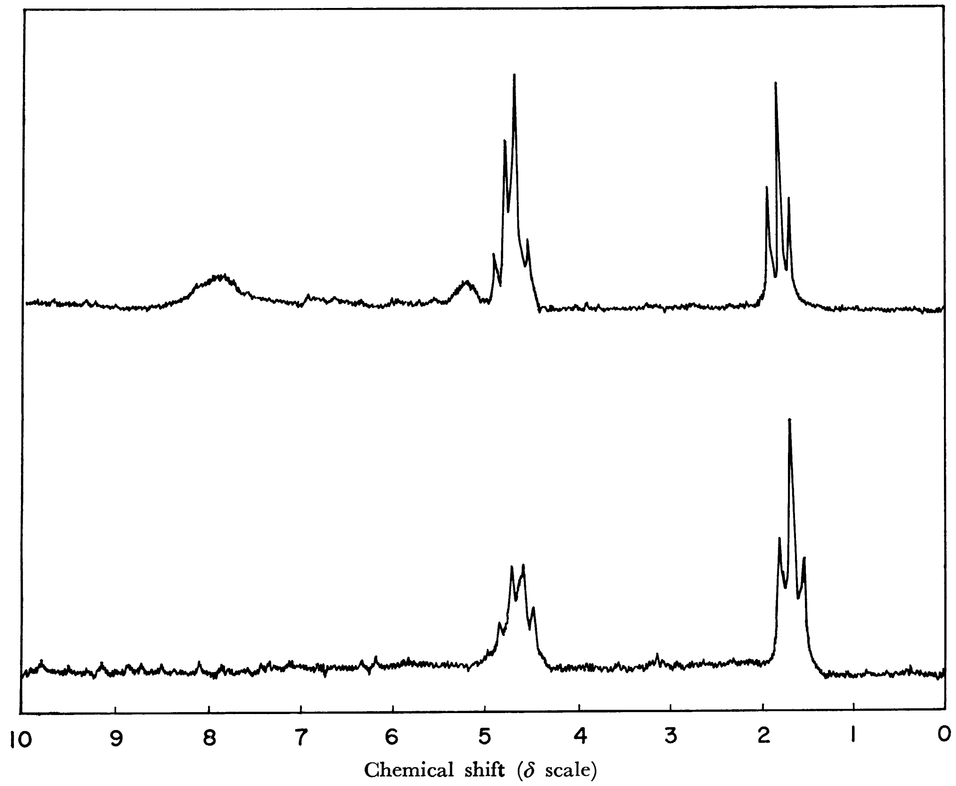
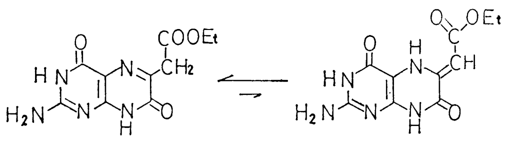


Fig. 1. NMR spectra (60 MHz) of ethyl isoxanthopterin-6-acetate (IIIa) in sulfuric acid (above) and deuteriosulfuric acid (below).

carbonylmethylene-5,6-dihydroisoxanthopterin (IVa).

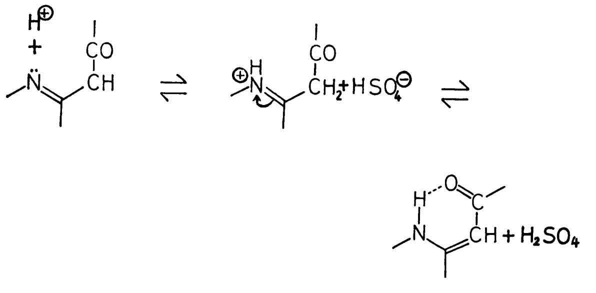


IIIa IVa

However, tautomerization between IIIa and IVa is not excluded as shown by the fact that the methylene protons adjacent to the ring are exchangeable with deuterium of the solvent. This exchange is fully explained by tautomerization which causes direct and repeated additions of deuterium to the carbon bearing an olefinic proton in another tautomeric (enamine) form or replacements occuring stepwise to exchange an amino proton with deuterium and then to transfer it onto olefinic carbon, in deuteriosulfuric acid.

Thus, the structure of III in solution and crystalline state has been estableished by NMR and IR spectra, respectively.

Indication of imine-enamine tautomerism is given only when the spectrum in sulfuric acid is compared with that in deuteriosulfuric acid. This was the only successful experiment to detect tautomerism. Unfortunately, we could not see whether or not the interconversion of imine to enamine occurs in inert solvents, because of low solubility. On the basis of our previous observation,[1] however, we deduce that III would exclusively exist in the imine form under ordinary circumstances (for example, in crystalline state or in an inert solvent). When III is dissolved in sulfuric acid or other protic solvents, protonation by the acids would cause the interconversion of imine to enamine as follows:



This mechanism is well explained by the above deuterium exchange. Probably, concerted reaction[1] of the solvent cation and anion equilibrate both tautomeric forms.

It is of interest that an isomer of IIIa, ethyl xanthopterin-7-acetate,[8] exists in the enamine form[9] in deuteriodimethyl sulfoxide, in contrast to III, while the compound exists as a 1: 1 mixture of imine and enamine forms in trifluoroacetic acid. The tautomerism occurring in trifluoroacetic acid can also be accounted for the above hypothetical mechanism.

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[8] L. Merlini, W. von Philipsborn, and M. Viscontini, *Helv. Chim. Acta*, **46**, 2592 (1963).

[9] Recently, we have examined the structures of 6-phenacylisoxanthopterines and 7-phenacylxanthopterins, which possess β-carbonyl groups in their side chains as do III and above mentioned ethyl xanthopterin-7-acetate.[8] It was found that both phenacylpterins exist in the enamine form, and the interconversion of enamine to imine is evidenced by NMR spectra in deuteriosulfuric acid. The results will be reported elsewhere.

Experimental

IR spectra were measured for potassium bromide disks on a Nippon Bunko DS-301 spectrophotometer. NMR spectra were determined with a Hitachi H-60 spectrometer and recorded in δ values with tetramethylsilane as external standard.

Ethyl Isoxanthopterin-6-acetate (*IIIa*). Into a suspension of IIa sulfate (0.4 g) in an aqueous solution (10 m*l*) of sodium acetate (0.8 g), a solution of Ia (0.35 g) in ethanol (10 m*l*) was added dropwise with stirring at room temperature. After the mixture was stirred for further 3 hr, it was allowed to stand overnight. The precipitated crystals (0.5 g) were collected by filtration and recrystallized repeatedly from dimethyl sulfoxide. The crystals were washed well with water and ethanol successively on a glass filter and kept *in vacuo* over phosphorus pentoxide at an elevated temperature (100°C) for a few hours in order to eliminate completely the solvent to give IIIa as dark yellow powders; mp>300°C.

Found: C, 41.08; H, 4.55; N, 23.45%. Calcd for $C_{10}H_{11}O_4N_5 \cdot 3/2H_2O$: C, 41.12; H, 4.79; N, 23.94%.

Methyl Isoxanthopterin-6-acetate (*IIIb*). In a similar manner to IIIa, the crude product of IIIb (0.15 g) from IIa sulfate (0.2 g) and Ib (0.15 g) was recrystallized from dimethyl sulfoxide to afford IIIb; mp>300°C.

Found: C, 39.10; H, 4.10; N, 25.22%. Calcd for $C_9H_9O_4N_5 \cdot 3/2H_2O$: C, 38.87; H, 4.32; N, 25.10%.

Ethyl 2,4-Diamino-7(*8*H)*-pteridinone-6-acetate* (*IIIc*). Similarly, the crude product of IIIc (0.56 g) from IIb sulfate (1.2 g) and Ia (0.85 g) was recrystallized from dimethyl sulfoxide. The crystals collected on a glass filter were washed with a 1:1 mixture of dimethyl sulfoxide and 50% sulfuric acid, water, and ethanol, successively, and then kept *in vacuo* to give IIIc; mp>300°C.

Found: C, 40.97; H, 4.46; N, 28.71%. Calcd for $C_{10}H_{12}O_3N_6 \cdot 1/4H_2SO_4 \cdot 1/4H_2O$: C, 40.95; H, 4.47; N, 28.66%.

Methyl 2,4-Diamino-7(*8*H)*-pteridinone-6-acetate* (*IIId*). The crude product of IIId (0.73 g) from IIb sulfate (1.20 g) and Ib (1.14 g) was recrystallized from dimethyl sulfoxide; mp>300°C.

Found: C, 41.98; H, 4.47; N, 32.59%. Calcd for $C_9H_{10}O_3N_6 \cdot 1/2H_2O$: C, 41.70; H, 4.28; N, 32.42%..

I am indebted to Mr. T. Inagaki, Central Research Laboratories, Nitto Chemical Industry Co., for his determination of the NMR spectra, and to Mr. A. Norose for his technical assistance.