BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 49(4), 1161—1162 (1976)

## NMR Spectroscopic Studies on the Tautomerism in Schiff Bases of Tenuazonic Acid Analogs

Tatsuaki Yamaguchi, Kimitoshi Saito, Toshio Tsujimoto,\* and Hidetaka Yuki\*

Laboratory of Organic Chemistry, Chiba Institute of Technology, Narashino, Chiba 275

\*Faculty of Pharmaceutical Sciences, Osaka University, Yamadakami, Suita, Osaka 565

(Received October 13, 1975)

**Synopsis.** A NMR spectroscopic study of <sup>15</sup>N-enriched Schiff bases of such tenuazonic acid analogs as 3-acetyltetramic acid, 3-acetyltetronic acid, and 3-acetylthiotetronic acid showed the predominance of ketamine forms in their tautomeric equilibria in CDCl<sub>3</sub>. The ratios of "external tautomers" between two different ketamine forms, as calculated from the <sup>15</sup>N-H signal intensities, were compared favorably with the ratios obtained from the ring methylene signals.

In connection with the study¹) of the antitumor activities of Schiff bases of tenuazonic acid analogs,²) their tautomeric structures were examined by means of NMR spectroscopy. These Schiff bases³) may exist in a solution in any form of "external tautomers" ( $B_N$ ,  $B_0 \rightleftharpoons C_N$ ,  $C_0$ ), besides "internal tautomers" ( $B_N \rightleftharpoons B_0$ ,  $C_N \rightleftharpoons C_0$ ), as Forsén and coworkers have suggested for unsymmetrical  $\beta$ , $\beta$ '-triketones.⁴) They have also estimated the ratios of the "external tautomers" of unsymmetrical cyclic  $\beta$ , $\beta$ '-triketones from the intensities of the split NMR signals of the ring methylene.

$$(B_{N}) \xrightarrow{R} (B_{0})$$

$$(B_{N}) \xrightarrow{(B_{0})} (B_{0})$$

$$(C_{N}) \xrightarrow{(C_{0})} (C_{0})$$

$$(C_{N}) \xrightarrow{(C_{0})} (C_{0})$$

$$(C_{N}) \xrightarrow{(C_{0})} (C_{0})$$

$$(C_{N}) \xrightarrow{(C_{0})} (C_{0})$$

## Results and Discussion

The presence of "external tautomers" in the Schiff bases of these tenuazoinc acid analogs was detected from the splitting of the ring methylene (5-position) signals (3.70—4.53 ppm) in their NMR spectra. The counterpart in the higher field of the split methylene signals can be assigned to the tautomeric pair of  $B_N$  and  $B_0$ , and the lower one, to the pair of  $C_N$  and  $C_0$ , since the anisotropic effect<sup>5)</sup> of the neighboring carbonyl group (4-position) can be expected to be more pronounced in the forms of  $C_N$  and  $C_0$  than in  $B_N$  and  $B_0$ , in which the carbonyl groups are hydrogen-bonded  $(B_N)$  or enolized  $(B_0)$ . The ratios of the "external tautomers",  $B_N + B_0$  to  $C_N + C_0$ , for these Schiff bases

were calculated from intensities of the corresponding signals (Table 1).

The observed NMR spectra of these Schiff bases showed a broad doublet arising from the active hydrogen in the region of 11.66-13.67 ppm (Table 2). In order to elucidate the exact assignment of these signals to the tautomeric structures, the Schiff bases of tenuazonic acid analogs were synthesized using commercially available aniline- $^{15}N$ , since sharp signals can be expected for protons bonded to the  $^{15}N$ -nucleus (I=1/2), and the  $^{15}N$ -H spin coupling constant of ca. 90 Hz makes possible a ready detection of any "internal" tautomerization between N-H and O-H.<sup>6)</sup>

The spectrum of the <sup>15</sup>N-substituted Schiff base (IA) from 3-acetyltetramic acid contained two pair of sharp doublets at nearly the same position relative to the corresponding <sup>14</sup>N-compound (Fig. 1). The observed <sup>15</sup>N-H spin coupling constant was 90.0 Hz for each doublet at 34 °C in CDCl<sub>3</sub>. Upon raising the sample temperature to +60 °C or lowering it to -70 °C, no changes were observed in the chemical shifts, signal intensities, or coupling constants of this compound. Therefore, it can be concluded that IA primarily exists in the ketoamine forms, B<sub>N</sub> and C<sub>N</sub>. The intensity ratio of the higher-field doublet to the lower one showed a good coincidence with the ratio of "external tautomers" calculated from the intensities of the ring methylene signals (Table 1). Accordingly, the higher-field doublet can be ascribed

Table 1. Ratios of "external tautomers" calculated from the intensity ratios of ring methylene signals and  $^{15}{\rm NH}$  signals

No.	Compounds		$B_N + B_O/C_N + C_O$	$\mathrm{B_{N}/C_{N}}$
	$\mathbf{X}$	R	(from CH <sub>2</sub> )	(from <sup>15</sup> NH)
IA	NH	H	1.13	1.17
IB	NH	$\mathrm{CH_2C_6}$	$H_5 1.39$	1.41
II	Ο	H	0.37	0.36
III	S	Н	0.34	0.32

Table 2. Chemical shifts of active hydrogens

No.	$\delta^{14}_{ m NH}$ (ppm)	(ppm)	$(J^{{\scriptscriptstyle 15}}{}_{{\scriptscriptstyle \mathrm{N-H}}}) \atop (\mathrm{Hz})$
	(PPIII)	$\mathbf{B_{N}}$ form	$C_N$ form
IA	12.09 12.44	12.17 (90.0)	12.52 (90.0)
IB	12.08 12.40	12.11 (90.0)	12.48 (90.0)
II	11.66 12.44	11.61 (90.0)	12.57 (91.8)
III	12.89 13.67	12.86 (90.9)	13.66 (86.4)

to the  $B_{\scriptscriptstyle N}$  form, and the lower one to the  $C_{\scriptscriptstyle N}$  form. The observed spectra of the other compounds showed patterns similar to that of IA and indicated the same conclusion in the assignment of the signals. However, the observed 15N-H coupling constant (86.4 Hz) of the  $C_N$  form in the Schiff base (III) of 3-acetylthiotetronic acid is found to be markedly smaller than the values for the others. This suggests that ca. 5% of the Co form is present at 34 °C in the CDCl<sub>3</sub> solution of this compound. The presence of the  $C_0$  form in III is also supported by the results for the <sup>13</sup>C-NMR spectrum of III, which showed an additional small signal of enolic carbon at 193.88 ppm (from TMS) besides two signals at 195.18 and 198.81 ppm arising from free carbonyl carbon and hydrogen-bonded carbonyl carbon respectively. The exceptional feature of III could be explained by the geometry of the molecule. Simple molecular orbital calculation are in progress to obtain further insights in this field.

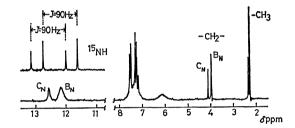


Fig. 1. NMR spectrum of 3-(1'-anilinoethylidene)-pyrrolidine-2,4-dione (IA) in CDCl<sub>3</sub> at 90 MHz.

## **Experimental**

Materials. The IA,<sup>7)</sup> IB,<sup>7)</sup> II,<sup>8)</sup> and III<sup>9)</sup> were prepared according to the procedures described in the literature cited. Aniline- $^{15}N$  (95% isotopic purity) was obtained from Prochem BOC, Ltd.

Measurements. The NMR spectra were measured with a Hitachi Perkin-Elmer R-22 spectrometer at 90 MHz at 34 °C,

using TMS as the internal standard. Solutions were made so as to contain  $1.5 \times 10^{-4}$  mol of compounds in 0.4 ml of CDCl<sub>3</sub>.

The <sup>13</sup>C-NMR spectra measured on a JNM-FX60 spectrometer equipped with a PFT-100 Fourier transform accessory at 25.1 MHz, using TMS as the internal reference and a 10-mm-diameter NMR tube. The spectra were obtained by 5000-times accumulations measured on a broad-band proton decoupler. The solution contained 200 mg of the sample in 2 ml of CDCl<sub>3</sub>.

The authors are grateful to Mr. Muneki Ohuchi of the Japan Electron Optics Laboratory for the <sup>13</sup>C-NMR measurement.

## References

- 1) (a) H. Yuki, E. Kitanaka, A. Yamao, and Y. Hashimoto, *GANN*, **62**, 199 (1971). (b) H. Yuki, K. Kariya, and Y. Hashimoto, *Chem. Pharm. Bull.*, **15**, 727 (1967). (c) H. Yuki, Y. Kaizu, S. Yoshida, and K. Takiura, *ibid.*, **19**, 1664 (1971).
- 2) Common names were consciously introduced for these compounds in order to express the mixed systems of complicated tautomers.
- 3) Although the ketoimine form (A) is another possible tautomer, there is no evidence for its presence in any of these Schiff bases.
- 4) (a) S. Forsén and M. Nilsson, "The Chemistry of the Carbonyl Group," Vol. 2, J. Zabicky, ed., John Wiley & Sons, London (1970), p. 157. (b) S. Forsén, F. Merényi, and M. Nilsson, *Acta Chem. Scand.*, **21**, 620 (1967).
- 5) Z. Bankowsa and I. Zadrozna, Rocz. Chem. Ann. Soc., 45, 183 (1971).
- 6) a) G. O. Dudek and E. P. Dudek, J. Am. Chem. Soc., **86**, 4283 (1964). (b) G. O. Dudek and G. P. Volpp, J. Org. Chem., **30**, 50 (1965). (c) G. O. Dudek and E. P. Dudek, J. Am. Chem. Soc., **88**, 2407 (1966). (d) G. O. Dudek and E. P. Dudek., J. Chem. Soc., B, **1971**, 1356. (e) B. Sunners, L. H. Pitte, and W. G. Schneider, Can. J. Chem., **38**, 681 (1960).
  - 7) R. N. Lacey, J. Chem. Soc., 1954, 832.
  - 8) R. N. Lacey, J. Chem. Soc., 1954, 850.
- 9) D. M. O'Mant, J. Chem. Soc., C, 1968, 1501.