Investigation in Tetronic Acid Ketoxime Derivatives. Structure and Beckmann Rearrangement. Synthesis of 3-Acetamidotetronic Acids

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The structure and tautomeric equilibria of 3-(1-hydroxyiminoethylidene)tetronic acids have been investigated by ^1H and ^{13}C nmr spectroscopy. These oximes are convertible into 3-acetamidotetronic acids.

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Because of our interest in tetronic acid chemistry, we studied the Beckmann rearrangement of the ketoximes of acetyltetronic acids, as a possible route to the 3-acetamidotetronic acids.

Formally, the acetyltetronic acids **1**, possess two sites of oximation. As early as 1910 Benary had reported that the acetyltetronic acid (**1a**) led to 3-(1-hydroxyiminoethylidene)tetronic acid (1). It has been further reported that the Beckmann rearrangement of this oxime gave the 3-acetamidotetronic acid (**3a**), when treated with phosphorus pentachloride in phosphorus trichloride (2). In our hands, this method led to no useful result. Furthermore, evidence for the structures of these compounds was not presented. Therefore, we decided to explore the stereochemistry of the ketoximes of acetyltetronic acids (**1a** and **1b**) and to find out the best experimental conditions for their Beckmann rearrangement.

Treatment of potassium enolates tetronic acid **1** with hydroxylamine hydrochloride, as previously reported (1), afforded the crystalline oximes **2**, which were recrystallized from water. The ^1H nmr spectra of compounds **2a** and **2b**, at 20° in DMSO-d_6 are indicative of a single compound. Conclusive evidence in support of 3-(1-hydroxyiminoethylidene)tetronic acid came from the ^{13}C nmr data. The coupled spectrum of **2b**, provided a straightforward assignment of the carbon resonances. The signal at 195.8 ppm was assigned to C-4, this carbon is coupled with the H-5 proton (doublet ^2J = 4 Hz) and with the methyl group (^3J = 2 Hz). The C-2 resonance at 171.6 ppm appears as a doublet (^3J = 2 Hz). The quartet (^2J = 6 Hz) at 163.6 ppm arises from the C-6 carbon, this shift indicates a characteristic signal due to an oxime carbon (3-5). The remaining carbons C-5, C-3 and C-7 are consistent with the reported values for tetronic acid (see Table I).

It can be expected that the oximes **2** would have the preferred *E*-configuration, stabilized by an internal hydrogen bond, with an important contribution of a dipolar form. This structure is strongly suggested by a blue ferric test.

As anticipated, the acetamide derivatives **3a** and **b**, easily formed, in alkaline medium *via* the *o*-benzenesulfonyl oximes, can be related to an *E*-configuration of the oximes **2** according to the accepted mechanism of the Beckmann rearrangement. Compound **3b** was previously obtained, with an unspecified yield, by catalytic hydrogenation, in acetic medium of 5-methyl-3-phenylhydrazonotetronic acid (7) (Scheme I).

Structures of compounds **3** are supported by their ^1H nmr spectra which indicated the presence of characteristic methyl protons of the acetamides at 2.2 ppm and one enolic hydroxy group. No tautomeric equilibrium could be detected from the 350 MHz ^1H nmr and ^{13}C nmr studies, contrary to the acetyl tetronic acids **1** (6,8). The carbon resonances of compounds **3b** (Table I), secured from the gated decoupled spectrum δ 169.6 (d, ^3J = 2 Hz), 164.08 (d, ^2J = 4 Hz and q ^3J = 2 Hz), 172.7 (octuplet, ^2J = 3 Hz) for C-2, C-4 and C-6, respectively, are consistent with an enolic carbonyl at the C-4 position, accordingly with the values of the ascorbic acid (9).

Table I

^{13}C-Nmr Chemical Shifts of Compounds **2** and **3** (a) (δ ppm)

Compound No.	Temperature °C	C-2	C-3	C-4	C-5	C-6	C-7	C-8
2a	20	172.55	86.23	193.27	69.99	163.19	11.48	
2b	20	171.65	85.49	195.85	76.86	163.63	11.53	17.07
2b A 75%	55	171.79	85.63	195.96	76.88	163.83	11.47	17.04
2b B 25%	55	170.70	88.32	196.84	75.73	155.36	15.63	17.23
3b	(b)	169.60	100.61	164.08	74.46	172.70	22.22	17.75

(a) Recorded on a Brucker WP80 Spectrometer with respect to TMS in DMSO-d_6. (b) In deuteriochloroform.

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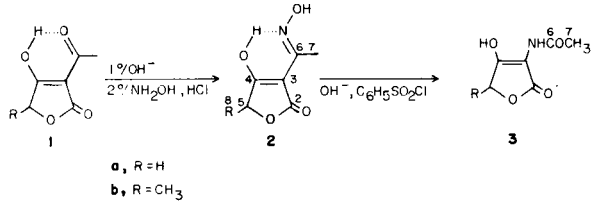
Table II

^{1}H-Nmr Chemical Shifts of the **A** and **B** Forms (δ ppm)

Compound No.	Solvent	CH_3 (C-7)	H (C-5)	CH_3 (C-5)	OH, NH
2a	DMSO-d_6 (a)	2.49 (2.35)	4.41 (4.58)		10
2b	DMSO-d_6 (b)	2.46 (2.31)	4.50 (4.62)	1.27 (1.32)	11 (12) (c)
2b	acetonitrile (a)	2.59 (2.41)	4.61 (4.65)	1.36 (1.41)	9-10 (c)

Numbers in parentheses are those in the **B** form. (a)Recorded on a Varian A60 Spectrometer. (b) Recorded on a 350 MHz Cameca Spectrometer. (c) A broad flat band is seen with ill-defined chemical shift.

Scheme I



a, R = H
b, R = CH_3

Tautomerism in Ketoximes of Acetyltetronic Acids **2**.

Crystallization of the crude oximes **2** from water gave a pure compound (**A** form) as evidenced from the ^{1}H nmr spectra in DMSO-d_6 solution at 20° by tlc after dissolution in ethanol at room temperature, one spot (ethyl acetate as eluent) was observed. However, the acetonitrile solution displayed two spots on tlc. There is formation of a less polar compound (**B** form). When the isomeric solution **A/B** is column chromatographed on silica gel, isomer **B** was first collected as single compound, but it returns to an isomeric mixture in solution. In the ^{1}H nmr spectra, separate resonance signals are observed for the protons of the **A** and **B** forms (Table II). The ratio **A/B** is found to be temperature and solvent dependant. However, it appears that the equilibrium is not rapidly reversible, since the composition of an isomeric mixture obtained at 70° in DMSO-d_6 remained unchanged after 24 hours at room temperature. The strong solvatation effect of this solvent could stabilize both forms by intermolecular bonding (Table III).

Scheme II

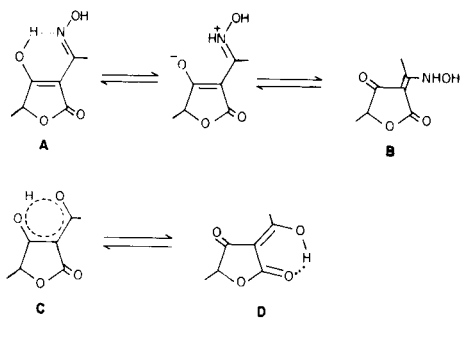


Table III

Composition of the Isomeric Mixture

Compound No.	Solvent	Temperature °C	% **A**	% **B**
2a	DMSO-d_6	20	100	
		35	85	15
2b	DMSO-d_6	20	100	
		35	85	15
		50	80	20
		70	70	30
2b	acetonitrile-d_3	30	70	30
		30 (a)	50	50

(a) After dissolution at reflux temperature then recorded at 30°.

Comparison of the ^{13}C nmr spectra (Table I) of compound **2b** recorded at 20° and 55° allows the assignment of the carbon resonances of the two forms **A** and **B**. The chemical shifts of C-7 and C-3 on going from the **A** form to the **B** form are shifted from δ 4.16 and 2.72, respectively, to lower field. Thus, there can be no *E/Z* isomerism, since the ability to distinguish between *syn* and *anti* oximes lies in the shielding effect of the oxime oxygen on the α-carbon when the hydroxy group is *syn* to that carbon (3-5). On the other hand, it is known, that the conversion of a carbonyl to an *E* or *Z* oxime is accompanied by a very consistent mean change in the carbon position. The large upfield shift of δ 8.5 observed for the C-6 carbon-oxime on going from the **A** to **B** form may have accounted for a major change of the C=N bond. The structure of **B** as an enehydroxylamine (Scheme II) is suggested by these findings. An isomeric structure of **B** is compatible with the ir data, because a collected isomeric mixture of a ratio 40:60 **A/B** (from **2b**, by column chromatography) exhibits, in the solid state, the carbonyl ketone and lactone stretchings at 1735 and 1750 cm^{-1}, respectively, whereas, compound **A** displays only a band at 1700 cm^{-1} attributable to an intermolecular-hydrogen bonded carbonyl lactone. Such a tautomerism resembles that of acetyl tetronic acids (1), in which the presence in solution of different species **C** and **D** had been demonstrated by nmr spectroscopy. The tautomer **D** exists as exo-enol form (Scheme II).

EXPERIMENTAL

Compounds **1** were prepared as previously described (10).

Preparation of Compounds **2**.

To a solution of acetyltetronic acids **1** (0.01 mole) in 1*N* aqueous potassium hydroxide (10 ml.) was added hydroxylamine hydrochloride (2.08 g., 0.03 mole) in water (10 ml.). The reaction mixture was stirred at room temperature for 24 hours. The precipitate oxime was filtered.

E-4-Hydroxy-3-(1-hydroxyiminoethylidene)-2-oxo-2,5-dihydrofurane (R = H) (**2a**).

The crude oxime was recrystallized from water, yield 80%, m.p. 149° (after drying by azeotropic distillation with toluene), lit. (1) m.p. 149°.

E-4-Hydroxy-3-(1-hydroxyiminoethylidene)-5-methyl-2-oxo-2,5-dihydrofurane (R = CH_3) (**2b**).

The crude oxime was recrystallized from water, yield 73%; m.p. 170°; uv (ethanol): λ max (ε) 231 (9,600), 294 (13,500); ir (potassium bromide): 3400-2400, 1700, 1690, 1650, 1520 cm^{-1}.

Anal. Calcd. for $C_7H_9NO_4$ (171.15): C, 49.12; H, 5.30; N, 8.18. Found: C, 48.85; H, 5.23; N, 8.23.

Isomerisation of the Oximes **2b**.

Compound **2b** (**A** form) (0.25 g.) and acetonitrile (15 ml.) was heated at reflux for 10 minutes. After cooling the resulting solution was chromatographed on silica gel (50 g.) through a column (39 cm × 24 mm) using ethyl acetate as eluent. The collected fraction from 75 to 150 ml. was reduced under vacuum. The solid residue (0.1 g.), analyzed by nmr, indicated an isomeric ratio of 40:60 **A/B**; ir (potassium bromide): 3400-2400, 1750, 1735, 1700, 1640, 1600, 1450.

Preparation of Compounds **3**.

To a solution of the oxime **2** (0.01 mole) and benzenesulfonyl chloride (0.01 mole, 1.46 g.) in tetrahydrofuran (50 ml.) was added drop by drop, with stirring, aqueous sodium hydroxide (1.2 g., 0.03 mole) in water (120 ml.) at 50°. The resulting mixture was refluxed for 1 hour and concentrated under vacuum to about 30 ml. The cooled solution was neutralized with cold dilute hydrochloric acid. The solution on cooling gave the crystalline compounds **3**.

3-Acetamido-4-hydroxy-2-oxo-2,5-dihydrofuran (R = H) (**3a**).

The separated solid was recrystallized from ethanol to give (0.67 g., 43%) of **3a**, m.p. 172°, lit. (2) m.p. 170°; uv (ethanol): λ nm (ε) 228 (5,600), 256 (5,800); ir (chloroform): 3400, 3300, 1760, 1700, 1650 cm^{-1}; ^1H nmr (deuteriochloroform): 2.20 (3H, s), 4.69 (2H, s), 9.7 (1H, broad), 12.9 (1H, broad).

Anal. Calcd. for $C_6H_7NO_4$ (157.12): C, 45.86; H, 4.49; N, 8.92. Found: C, 45.75; H, 4.32; N, 8.88.

3-Acetamido-4-hydroxy-5-methyl-2-oxo-2,5-dihydrofuran (R = CH_3) (**3b**).

The solid which separated was recrystallized from ethanol to give (0.85 g., 50%) of **3b**, m.p. 154°, lit. (3) m.p. 152°; uv (ethanol): λ nm (ε) 220 (7,100), 256 (5,000); ir (chloroform): 3400, 3300, 1760, 1700, 1655 cm^{-1}. ^1H nmr (deuteriochloroform): 1.50 (3H, d, J = 7 Hz), 2.20 (3H, s), 4.86 (1H, q, J = 7 Hz), 8.75 (1H, broad), 12.73 (1H, broad).

Anal. Calcd. for $C_7H_9NO_4$ (171.15): C, 49.12; H, 5.30; N, 8.18. Found: C, 48.85; H, 5.44; N, 8.10.

REFERENCES AND NOTES

(1) E. Benary, *Ber.*, **43**, 1065 (1910).

(2) W. Baker, K. D. Grice and A. B. A. Jansen, *J. Chem. Soc.*, 241 (1943).

(3) G. C. Levy and G. L. Nelson, *J. Am. Chem. Soc.*, **94**, 4897 (1972).

(4) G. E. Hawkes, K. Herwig and J. D. Roberts, *J. Org. Chem.*, **39**, 1017 (1974).

(5) J. H. Wikel, C. J. Paget, D. C. Delong, J. D. Nelson, C. Y. E. Wu, J. W. Paschal, A. Dinner, R. J. Templeton, M. O. Chaney, N. D. Jones and W. Chamberlin, *J. Med. Chem.*, **23**, 368 (1980).

(6) J. P. Jacobsen, T. Reffstrup and P. M. Boll, *Acta Chem. Scand.*, **31**, 756 (1977).

(7) J. Lecocq, *Bull. Soc. Chim. Fr.*, 183 (1951).

(8) S. Gelin and P. Pollet, *Tetrahedron Letters*, **21**, 4491 (1980).

(9) T. Radford, J. G. Sweeny and G. A. Iacobucci, *J. Org. Chem.*, **44**, 658 (1979).

(10) S. Gelin and A. Galliaud, *C. R. Acad. Sci. Paris*, **275**, 897 (1972).