Synthesis of 3-Formyltetronic Acid and Enamine Derivatives

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The first reported synthesis of 3-formyltetronic acid and its conversion to enamine derivatives is described. 3-Dimethylaminomethylene-2,4-dioxotetrahydrofuran derivatives were also prepared by treatment of tetronic acids with dimethylformamide diethyl acetal. Nmr spectral studies are included.

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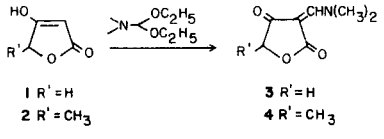
During our studies on tetronic acid derivatives, it was discovered that the 3-dimethylaminomethylenetetronic acid **3** possess antiinflammatory activity as potent as that of aspirin, without gastrointestinal irritation. Encouraged by these preliminary results, the synthesis of a series of β-aminoendione derivatives was undertaken in order to evaluate their activities.

Results and Discussion.

Dimethylaminomethylene tetronic acids **3** and **4** were synthetized by reacting dimethylformamide diethyl acetal with tetronic acids **1** and **2** (Scheme 1). Our general approach to the synthesis of enamine derivatives having various amino groups consisted of the preparation of 3-formyltetronic acid **5** from tetronic acid **1** and dimethoxymethyl acetate. Condensation of **5** with appropriate amines yielded compounds **6-10** (Scheme 2).

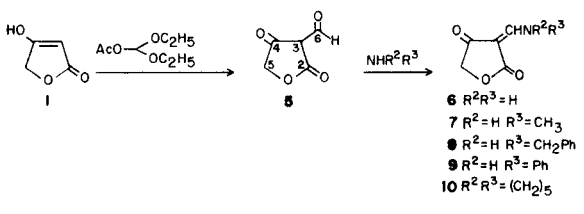
SCHEME 1



1 R' = H
2 R' = CH_3

3 R' = H
4 R' = CH_3

SCHEME 2



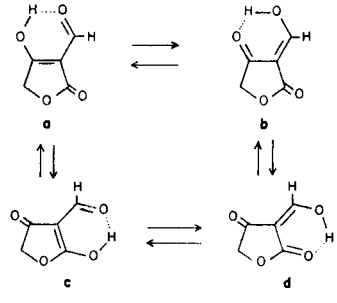
1

5

6 R^2R^3 = H
7 R^2 = H R^3 = CH_3
8 R^2 = H R^3 = CH_2Ph
9 R^2 = H R^3 = Ph
10 R^2R^3 = $(CH_2)_5$

Structure **5** is supported by its spectral data. This compound can occur in several enolic forms, the external (**a,b** ⇌ **c,d**) and the internal (**a** ⇌ **b**; **c** ⇌ **d**) tautomers. Internal tautomers are rapidly interconverted, whereas the external tautomers are generally slowly interconverted. The presence of tautomeric forms **c** and **d** was not evidenced by 350 MHz ^{1}H nmr, in contrast to the parent compound 3-acetyl tetronic acid (1). The population of the tautomers **a** and **b** can be estimated from the observed average chemical shift δ 8.83 (in deuteriochloroform) of the C-6 formyl proton [$\delta\mathbf{ab} = \delta\mathbf{a}(x_\mathbf{a}) + \delta\mathbf{b}(x_\mathbf{b})$]. Taking the δ 9.82 of salicylaldehyde (2) and δ 6.71 of formylcamphor (3) for the corresponding endo $H_\mathbf{a}$ and exo $H_\mathbf{b}$ enol forms, the **a**/**b** ratio could be approximately estimated to 68:32. Forsen, *et al.* (4) reported that 2-formylcyclopentan-1,3-dione exists in deuteriochloroform predominantly as 2-formyl-3-hydroxycyclopent-2-en-1-one on the basis of resonance field δ 9.59 for the aldehyde proton. In this case, the calculated ratio of **a**/**b** for the respective aldo enol and hydroxymethylene ketone is 92:8. These results revealed a marked difference due to replacement of a five cyclopentan-1,3-dione ring by a five 2,4-dioxofuran ring (Scheme 3).

SCHEME 3



a **b** **c** **d**

The structure of compounds **3,4 6-10** are in agreement with their microanalyses as well as with their spectroscopic data. The 350 MHz ^{1}H nmr spectra of compounds **6,7** and **8** display two sets of lines which established the presence in solution of both the *E* and *Z* isomers relative to the exocyclic C=C bond; the *E* isomer predominated. Such a stereoisomerism of β-aminoendione derivatives is known (6-8). ^{13}C Nmr spectra of compounds **6** and **9** give rise to two resonances for all the carbon atoms (see Experimental) in a 60:40 and 70:30 ratio, respectively. It is known that a hydrogen-bonded carbonyl resonates at lower field than a corresponding free carbonyl (5,6). Therefore, it can be assumed that the *E* isomer is predominant, which is in agreement with the relative chelating power of a carbonyl group which is ketone > ester (9). The assignments of the carbon resonances were accomplished by off resonance decoupling and chemical shift comparison with previous findings concerning the tetronic acid derivatives (1). From

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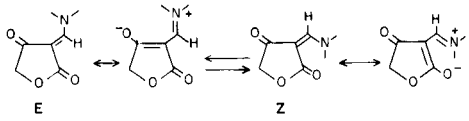
^{1}H nmr studies it can be established that the C-6 olefinic proton next to the carbonyl function (*Z* isomer) resonates at lower field compared to the corresponding proton next to the carboxyl function (*E* isomer). The chemical shift of the NH proton resonates at a lower field when it is chelated with the more electronegative carbonyl group (*E* isomer) than with the carboxyl group (*z* isomer).

The 80 MHz ^{1}H nmr spectra of compounds **3, 4** and **10** (*N*-disubstituted) at 35° in deuteriochloroform seem to be typical of unique species. Nevertheless, the 350 ^{1}H nmr spectrum of **3**, enregistred at 20° disclosed the presence of an *E*/*Z* isomeric mixture in a 80:20 ratio. The two pairs of signals coalesced at 50°. Fast rotation around the C-3 C-6 exocyclic bond from a dipolar resonance hybrid, over the nmr time scale, can explain the disappearance of the splittings (Scheme 4).

SCHEME 4



E Z

The results of antiinflammatory testing against carrageenan-induced foot edema in rats according to the method of Winter (10) showed that only compound **3** displayed significant reduction of swelling at ED_{30} = 130 mg./kg. (95% confidence limits), LD_{50} (mice) = 1200 mg./kg. The analgesic activity measured according to the acetic acid writhing method of koster (11) showed only an Ed_{50} = 208 mg./kg. (95% confidence limits). In this series of compounds, alterations to the basic structure of parent compound **3** are detrimental since all of the other compounds which were prepared have no activity in these tests.

EXPERIMENTAL

All melting points were determined on a Kofler block and are uncorrected. Infrared and ultraviolet spectra were obtained with Beckmann Model Acculab 2 and DB spectrophotometers. Nmr spectra were recorded on Brucker WP 80 and 350 MHz Cameca (^{1}H nmr) and Varian X-100-12 FT (^{13}C nmr) spectrometers, with respect to TMS. Elemental analyses were performed by Microanalytical laboratory, Centre National de la recherche scientifique, 69390 Vernaison, France. Tetronic acids **1** and **2** were prepared according to our previously reported procedure (12).

3-Dimethylaminomethylenetetronic Acid (**3**).

Diethylformamide diethyl acetal (1.31 g., 10 mmoles) was added to the tetronic acid (1 g., 10 mmoles). A vigorous reaction is soon over. The reaction mixture was allowed to stand at room temperature for 30 minutes. The solid which precipitated was collected, washed with ether and recrystallized from ethanol to yield 1.17 g. (77%) of the title compound, m.p. 149°; ir (potassium bromide): 1760, 1675 cm^{-1}; uv (ethanol): λ max 227 nm (ε 11,100), 301 (19,800); ^{1}H nmr (deuteriochloroform): 350 MHz at 20°, δ 3.39 (s, 3H, NCH_3), 3.79 (br, 3H, NCH_3), 4.38 (s, 0.8 H, CH_2, C-5), 4.49 (br, 0.2 H, CH_2, C-5), 7.42 (s, 0.8 H, olefinic), 7.54 (s, 0.2 H, olefinic); at 50°, 3.38 (s, 3H), 3.78 (s, 3H), 4.40 (s, 2H), 7.44 (s, 1H); ^{13}C nmr (DMSO-d_6): δ 172.99 (C-2), 89.11 (C-3), 191.14 (C-4), 70.47 (C-5), 155.91 (C-6), 47.61 (NCH_3), 43.48 (NCH_3).

Anal. Calcd. for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.30; H, 5.88; N, 8.83.

3-Dimethylaminomethylene-5-methyltetronic Acid (**4**).

Compound **4** was obtained in an analogous manner to that of **3**, giving 1.33 g. (79%) of product, m.p. 116°; ir (chloroform): 1750, 1675, 1625 cm^{-1}; uv (ethanol): λ max 227 nm (ε 11,200), 302 (19,000); ^{1}H nmr (deuteriochloroform): 80 MHz at 35°, δ 1.43 (d, J = 7 Hz, 3H, CH_3, C-5), 3.50 (s, 3H, NCH_3), 3.85 (s, 3H, NCH_3), 4.61 (q, J = 7 Hz, 1H, C-5), 7.65 (s, 1H).

Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.79; H, 6.55; N, 8.23. Found: C, 56.89; H, 6.58; N, 8.19.

3-Formyltetronic Acid (3-Formyl-2,4-dioxotetrahydrofuran) (**5**).

A mixture of tetronic acid **1** (1 g., 10 mmoles) and diethoxymethyl acetate (1.94 g., 12 mmoles) was heated at 50° for 10 minutes. The reaction mixture was cooled and filtered to give a solid which was washed with ether, then recrystallized from ethyl acetate with a trace of water to yield 0.9 g. (61%) of 3-formyltetronic acid, m.p. 90°; ir (potassium bromide): 1750, 1680 cm^{-1}; uv (ethanol): λ max 227 nm (ε 11,900), 270 (13,100); ^{1}H nmr (deuteriochloroform): 350 MHz, δ 4.50 (s, 2H, CH_2, C-5), 8.6 (br, exchangeable), 9.2 (s, 1H, CHO); 350 MHz ^{1}H-nmr (DMSO-d_6) 4.44 (s, 2H), 8.17 (br, exchangeable, 8.99 (s, 1H).

Anal. Calcd. for $C_5H_4O_4 \cdot H_2O$: C, 41.10; H, 4.14. Found: C, 40.99; H, 4.12.

3-Aminoalkylmethylenetetronic Acids. General Procedure.

To a solution of 3-formyltetronic acid (1.46 g., 10 mmoles, $C_5H_4O_4 \cdot H_2O$) in absolute ethanol (10 ml.) was added appropriate amine (28% aqueous ammonium hydroxide (1 ml., 14 mmoles), 33% aqueous methylamine (1 ml., 10 mmoles), benzylamine (1.07 g., 10 mmoles), aniline (0.93 g., 10 mmole) or piperidine (0.85 g., 10 mmoles). After stirring at room temperature for 1 hour, the reaction mixture was concentrated to 5 ml. The precipitate was filtered, then washed (ether) and recrystallized from ethanol to give the title compounds.

3-Aminomethylenetetronic Acid (**6**).

This compound was obtained in a yield of 50%, m.p. 220° dec.; ir (chloroform): 1750, 1690, 1645 cm^{-1}; uv (ethanol): λ max 221 nm (ε 11,400), 285 (16,700); ^{1}H nmr (DMSO-d_6): 350 MHz, mixture of *E* and *Z* isomers, 60:40, respectively, δ 4.408, 4.412 (2s, 2H, CH_2, C-5, *E,Z*), 7.68 (dd J = 16.9 and 8.9 Hz, 0.6 H olefinic *E*), 7.82 (dd J = 17.0 and 8.8 Hz, 0.4 H olefinic *Z*), 8.98 (br, 0.4 H, NH, *Z*), 9.47 (br, 0.6 H, NH, *E*), 9.55 (br, 1H, NH); ^{13}C nmr (DMSO-d_6): *E* isomer 60%, δ 170.25 (C-2), 91.53 (C-3), 195.40 (C-4), 70.30 (C-5), 155.10 (C-6, =CH), *Z* isomer 40%, δ 172.59 (C-2), 91.13 (C-3), 193.28 (C-4), 153.53 (=CH).

Anal. Calcd. for $C_5H_5NO_3$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.20; H, 4.05; N, 10.66.

3-Aminomethylmethylenetetronic Acid (**7**).

This compound was obtained in a yield of 80%, m.p. 180°; ir (chloroform): 1750, 1675, 1630 cm^{-1}; uv (ethanol): λ max 225 mn (ε 12,300), 294 (18,900); ^{1}H nmr (deuteriochloroform): 350 MHz, mixture of the *E* and *Z* isomers, 55:45, respectively, δ 3.29 (d, J = 5.5 Hz, 3H, $NHCH_3$), 4.468, 4.473 (2s, 2H, CH_2, C-5, *E,Z*), 7.70 (d, J = 14.5 Hz, 0.55 H, olefinic, *E*), 7.81 (d, J = 14.8 Hz, 0.45 H, olefinic, *Z*), 8.90 (br, 0.45 H, NH, *Z*), 9.60 (br, 0.55 H, NH, *E*).

Anal. Calcd. for $C_7H_7NO_3$: C, 51.06; H, 5.00; N, 9.93. Found: C, 51.11; H, 5.05; N, 9.91.

3-Benzylaminomethylenetetronic Acid (**8**).

This compound was obtained in a yield of 75%, m.p. 178°; ir (chloroform): 1750, 1680, 1630 cm^{-1}; uv (ethanol): λ max 224 nm (ε 12,900), 300 (22,600); ^{1}H nmr (deuteriochloroform): 350 MHz, mixture of the *E* and *Z* isomers, 55:45, respectively, δ 4.464, 4.472 (2s, 2H, CH_2, C-5, *E,Z*), 4.61 (d, J = 6 Hz, 2H, CH_2Ph), 7.22-7.48 (m, 5H, aromatic) 7.76 (d, J = 14.3 Hz, 0.55 H olefinic *E*), 7.88 (d, J = 14.8 Hz, 0.45 H, olefinic *Z*),

9.26 (br, 0.45 H, NH, *Z*), 9.90 (br, 0.55 H, NH, *E*).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.38; H, 5.16; N, 6.57.

3-Anilinomethylenetetronic Acid (9).

This compound was obtained in a yield of 50%, m.p. 174°, lit. (4) m.p. 174-176°; ^{1}H nmr (deuteriochloroform):350 MHz, mixture of the *E* and *Z* isomers, 70:30, respectively, δ 4.564, 4.573 (2s, 2H, CH_2, C-5, *E,Z*), 7.24-7.50 (m, 5H, aromatic), 8.23 (d, J = 13.4 Hz 0.7 olefinic *E*), 8.34 (d, J = 14.3 Hz, 0.3 H olefinic *Z*), 10.60 (br, 0.3 H, NH, *Z*), 11.30 (br, 0.7 H, NH, *E*), ^{13}C nmr (DMSO-d_6): *E* isomer 70%, δ 171.42 (C-2), 93.58 (C-3), 195.41 (C-4), 70.60 (C-5, 148.84 (CH=), 138.18 (C′-1), 118.83 (C′-2,6), 129.27 (C′-3,5), 126.29 (C′-4) (aromatic), *Z* isomer 30%, δ 172.42 (C-2), 93.12 (C-3), 193.53 (C-4), 71.94 (C-5), 147.94 (C-6).

3-Piperidinomethylenetetronic Acid (**10**).

This compound was obtained in a yield of 60%; m.p. 188°; ir (chloroform): 1740, 1670, 1600 cm^{-1}; uv (ethanol): λ max 227 nm (ε 11,600), 302 (21,300); ^{1}H nmr (deuteriochloroform): 80 MHz, δ 1.66-2.16 (br, 6H, CH_2), 3.61-4.03 (br, 2H, NCH_2), 4.35-4.80 (br, 4H, NCH_2 and CH_2, C-5), 7.68 (s, 1H, olefinic).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.30; H, 6.59; N, 7.05.

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