Synthesis of Tetronic Acid Enamine. Dienamine Derivatives from 3-(2*H*)Furanones

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The synthesis of 5-aryl (or alkyl) aminomethylene-3-(1-amino or 1-alkylaminoethylidene)-2,4-dioxo-(3*H*,5*H*)furans and 5-arylaminomethylene-3-(1-hydroxyethylidene)-2,4-dioxo-(3*H*,5*H*)furans (new 3-acetyltetronic acid derivatives) are described. The stereochemistry of these compounds from the ^{1}H nmr data is discussed.

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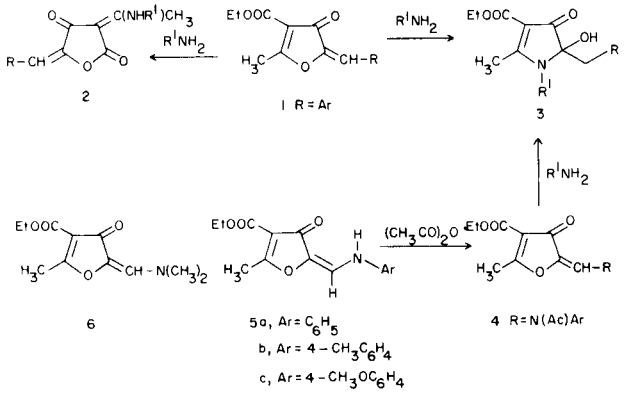
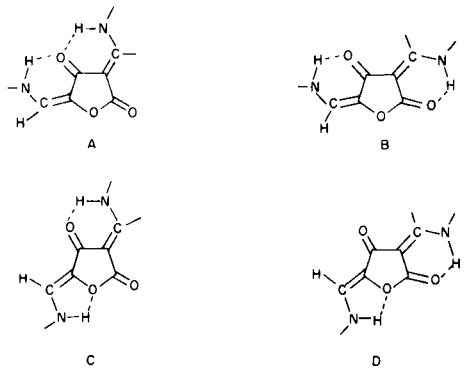
In preceding papers, our attention has been directed to the behaviour of 2-arylidene-4-ethoxycarbonyl-3-(2*H*)-furanones **1**, upon treatment with ammonia or primary aliphatic amines. The reaction afforded either the enamines of the tetronic acids **2** (1), or the 5-hydroxy-4-oxopyrroline derivatives **3** (2), depending on the reaction conditions. However, 2-*N*-acetyl-*N*-arylaminomethylene-3-(2*H*)furanones **4** (R = N(Ac)Ar) produced, under the same reaction conditions, only the corresponding hydroxypyrrolinones **3** (2) (Scheme I). As a continuation of our synthetic studies on 3-(2*H*)furanones and tetronic acids (3) we have investigated the reaction of compounds **5** and **6** with ammonia and primary aliphatic amines. This reaction provides an entry to the hitherto unknown tetronic acid dienamine and enamine derivatives **7-14**.

Scheme I



Treatment of compounds **5** with ammonia, cyclohexylamine and benzylamine in refluxing ethanol, resulted in complete conversion to the corresponding dienamines **7, 8** and **9**. The reaction of compounds **6** with an excess of amines (3 moles) in refluxing ethanol afforded the dienamines **10** and **11**, with an exchange reaction of the dimethylamino group. When this last reaction was carried out in water at room temperature, the compounds **12** and **13** were isolated, by merely filtering, from the reaction mixture. Attempts at substituting the dimethylamino group for compounds **10** or **11** with a cyclohexylamino or a benzylamino group were unsuccessful; the starting material was always recovered. This indicated that the dimethylamino exchange takes place before the lactonization (Scheme II).

The structure of the dienamines was assigned on the basis of their analytical, physical and spectral data (Table I and II). The ir spectra, in solid state or in solution of all these compounds **7-13** show they exist only as an enaminoketonic tautomeric structure, being characterized by the bands at 1720-1750 cm^{-1} (ν C=O lactone carbonyl) and 1675-1700 cm^{-1} (ν C=O ketone carbonyl). Although other possibilities could be expected, four major tautomeric species **A, B, C** and **D** could be considered for compounds **7-11**. In the ir spectra, the NH stretching vibrations at 3360-3110 cm^{-1} indicate extensive hydrogen bonding; however, the ir data do not allow positive elucidation of the stereochemical nature of these compounds.



The ^{1}H nmr data for all the compounds **7-13** display two sets of signals for the methyl groups, the vinyl protons and the NH protons which are unaltered by dilution. This fact, clearly show an *E/Z* isomeric mixture around the C-3 double bond. The stereochemistry can be assigned by assuming that the chemical shift of the NH proton resonates at a

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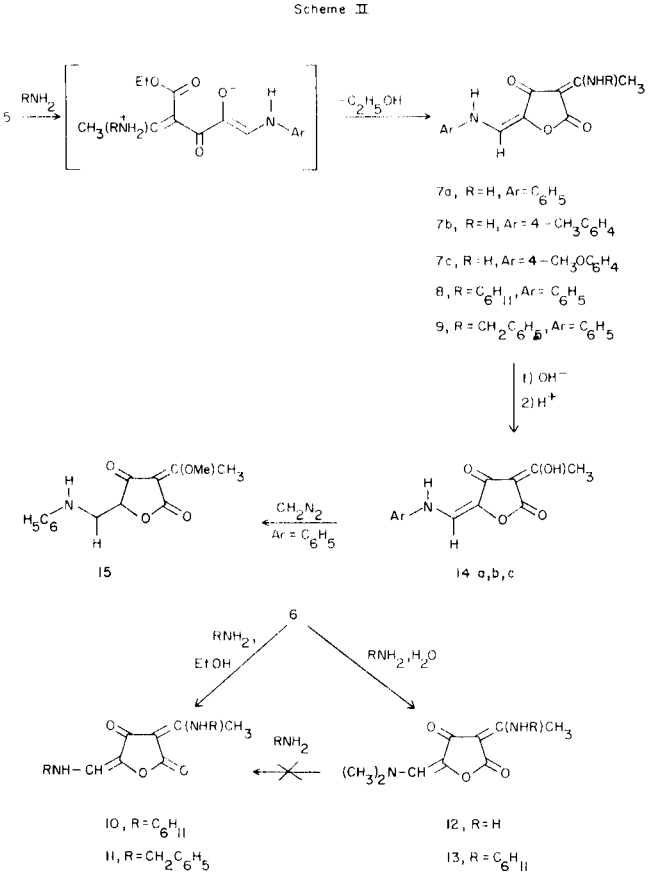
Scheme II



lower field when it is chelated with the more electronegative carbonyl group (*E* isomer) than with the carboxyl group (*Z* isomer). This interpretation is in agreement with the data available for analogous compounds (4). The *E/Z* tautomers exhibit a ratio of 65-80 to 35-20, which is not significantly influenced by a variation of the solvent (deuteriochloroform or DMSO-d_6) (Table II).

The nmr spectra of the 5-*N*-arylaminomethylene substituted compounds **7-9** in DMSO-d_6, exhibit a low field doublet for the NH-Ar proton at δ 8.95-9.15 ppm, which is unaffected by dilution, with a large coupling constant (^{3}J H-C-N-H = 12.5-13 Hz). This is typical of a strong intramolecular hydrogen bond in a chelated enaminoketonic structure (5,6). All these facts together show that compounds **7-9** exist principally as the tautomeric "double hydrogen bond" form **A**, accompanied by a minor amount of the tautomeric form **B**. Few examples of two protons which are simultaneously associated with one acceptor group have previously been described (7). The NH-Ar chelation disappears in deuteriochloroform at room temperature.

The 5-*N*-alkylaminomethylene compounds **10-11** show substantial differences as compared with the 5-*N*-arylaminomethylene compounds **7-9** in the nmr spectra. In DMSO-d_6 the NH proton of the C-5 substituent is not chelated. In deuteriochloroform the signal for this NH proton appeared at high field (δ 4.77-5.17 ppm) with a large coupling constant ^{3}J H_a-C-N-H_b = 13 Hz, thus indicating that H_a and H_b are held antiperiplanar to each other. The chemical shift of the NH proton is independent of the concentration, but its value is not consistent with previous reports of nmr investigations of chelated *N*-alkylenaminoketone derivatives (4,8-10). These findings could be explained either by the presence of a **C/D** isomeric mixture or by a weakening of the intramolecular bond in the **A/B** tautomeric structure in replacing an arylamino group by an alkylamino group, since various hydrogen bonding strengths could occur between the NH protons and the central oxygen atom. A choice between these alternatives cannot be made from the data in our hands.

The spectral analysis of compounds **12** and **13** (5-dimethylaminomethylene) did not enable a determination of the relative stereochemistry around the C-5 double bond.

Selective hydrolysis, under basic conditions, of the *N*-alkylamino or amino group of compounds **7-9** afforded the corresponding 3-acetyl tetronic acid derivatives **14**. Treatment of compounds **10-13** under the same reaction conditions failed to yield identifiable products. Compounds **14** possess acidic properties and are soluble in sodium hydrogen carbonate; they afford a green coloured ferric chloride solution and react with ethereal diazomethane to yield only one enol ether derivative **15**, as seen from the nmr spectrum.

The nmr spectra of tetronic acids **14**, in DMSO-d_6, show a doublet at low field (δ 10.15-10.2 ppm) with a large coupling constant (^{3}J H-C-N-H = 13-13.5 Hz), thus showing the NH chelated enamino-ketonic structure. The spectra further show a unique signal for the methyl protons and an enol proton at δ 7.2-11.1 ppm, which can be brought to higher field with dilution. These data are compatible with intermolecular hydrogen bonding between the enolic proton and the DMSO-d_6 molecule. A variation of the tautomeric equilibria in going from deuteriochloroform to DMSO-d_6 solution recently has been observed for 3-acetyltetronic acid by an nmr investigation (11). Unfortunately, the compounds **14** are extremely insoluble in any solvent (*eg.* chloroform). Thus, evidence to distinguish between the C-3 *E* or *Z* isomeric structure has not been found.

EXPERIMENTAL

All melting points were taken on a Kofler block. The ir and uv spectra were obtained with a Beckman Model Acculab 2 and DB spectrophotometers. The nmr spectra were measured using tetramethylsilane as the internal standard with a Varian A-60 spectrometer. Microanalyses were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, Villeurbanne, France.

Table I

Physical Data for Compounds **7-15**

Compound No.	Yield %	M.p. (°C) Solvent	Molecular Formula	Analyses Calcd./Found % C	H	N	UV (Ethanol) λ max (nm) (ε × 10^{-3}) (d)	Ir (cm^{-1}) ν NH and ν CO Potassium Bromide		Chloroform	
7a	84	318 dec Water	$C_{13}H_{12}N_2O_3$	63.92 63.68	4.95 5.05	11.47 11.15	246 (14.3), 292 (16.6) 376 (33.3)	3360 3300 3150	1725 1700 1675	(a)	
7b	82	312 (c)	$C_{14}H_{14}N_2O_3$	65.10 65.07	5.46 5.42	10.85 10.91	245 (17.6), 292 (19.5) 378 (33.9)	3360 3280 3140	1720 (sh) 1700 1675	(a)	
7c	86	309 (c)	$C_{14}H_{14}N_2O_4$	61.31 61.27	5.15 5.03	10.21 10.06	246 (14.7), 294 (16.0) 384 (30.6)	3360 3280 3140	1720 (sh) 1700 1675	(a)	
8	81	184 Acetonitrile	$C_{19}H_{22}N_2O_3$	69.92 70.10	6.79 6.96	8.58 8.62	254 (15.8), 297 (16.8) 378 (38.8)	3310	1725 1685	3420 3230 (w)	1740 1700
9	65	166 Acetone	$C_{20}H_{18}N_2O_3 \cdot H_2O$ (b)	68.17 68.25	5.72 6.08	7.95 8.05	254 (15.8), 298 (17.0) 381 (37.3)	3260 3110	1725 (sh) 1715 1690 (sh)	3420 3240 (w)	1740 1700
10	60	162 Acetonitrile	$C_{19}H_{28}N_2O_3$	68.64 68.60	8.49 8.44	8.43 8.44	250 (15.4), 296 (16.7) 358 (27.5)	3310	1725 1690	3420 3230 (w)	1725 1690
11	71	163 Acetonitrile	$C_{21}H_{20}N_2O_3$	72.39 72.27	5.79 5.96	8.04 8.24	250 (14.7), 298 (17.5) 358 (26.8)	3300	1725 1690	3420 3240 (w)	1720 1690
12	84	214 Water	$C_9H_{12}N_2O_3 \cdot H_2O$ (b)	50.46 50.50	6.59 6.47	13.08 13.01	242 (11.4), 288 (16.3) 352 (19.1)	3280 3130	1720 (sh) 1700 (sh) 1690 1650 (w)	(a)	
13	93	185 Acetonitrile	$C_{15}H_{22}N_2O_3$	64.72 64.78	7.97 8.16	10.07 9.98	248 (13.8), 297 (16.6) 361 (24.4)	3230	1725 1685	3230 (w)	1730 (sh) 1720 1685
14a	83	260 Ethanol	$C_{13}H_{11}NO_4$	63.67 63.50	4.52 4.53	5.71 5.72	242 (13.6), 273 (8.2) 363 (32.5)	3250 3180	1750 1690	(a)	
14b	76	264 Ethanol	$C_{14}H_{13}NO_4$	64.86 64.83	5.05 5.15	5.40 5.19	242 (13.5), 277 (9.0, sh) 368 (29.6)	3240 3190 (sh)	1750 1700	(a)	
14c	70	262 Ethanol	$C_{14}H_{13}NO_5$	61.09 60.85	4.76 4.87	5.09 4.94	245 (12.9), 275 (7.4, sh) 369 (27.0)	3200 (sh) 3180	1755 1700	(a)	
15	66	193 Ethanol	$C_{14}H_{13}NO_4$	64.86 64.86	5.05 5.20	5.40 5.31	243 (7.0), 408 (48.0)	3260	1740 1700	3400	1750 1685

(a) Insoluble. (b) The compound crystallizes with one molecule of water. (c) Washed with ethanol. (d) Absorptions: sh, shoulder; w, weak band.

Table II

Proton Magnetic Resonance Parameters of Compounds **7-15**

Compound No.	Solvent	Chemical Shifts (δ ppm) and Coupling Constants (Hz)
7a	DMSO-d_6	2.47 and 2.57 (2s, 3H), 6.8-7.6 (m, 5H), 7.12 (d, 1H, J = 12.5) (a), 8.95 (d, 1H, J = 12.5) (b), 8.7-9.7 (1.25H) (c) and 10.0 (0.75H) (c)
7b	DMSO-d_6	2.25 (s, 3H), 2.45 and 2.57 (2s, 3H), 7.12 (d, 1H) (a), 7.19 (s, 4H), 9.17 (d, 1H, J = 13) (b), 8.7-9.9 (1.35H) and 10.3 (0.65H) (c)
7c	DMSO-d_6	2.47 and 2.57 (2s, 3H), 3.78 (s, 3H), 6.8-7.5 (m, 5H), 9.10 (d, 1H, J = 12.5) (b), 8.7-9.9 (1.75H) and 10.3 (s, 0.25H) (c)
8	DMSO-d_6	1.1-2.3 (m, 10H), 2.58 (s, 3H), 3.5-4.2 (m, 1H) (c), 7.11 (d, 1H, J = 13) (c), 6.9-7.6 (m, 5H), 8.97 (d, 1H, J = 13), 9.3-10.0 (0.3H) (c), 11.35 (m, 0.7H) (c)
	Deuteriochloroform	1.1-2.3 (m, 10H), 2.60 and 2.74 (2s, 3H), 3.4-4.1 (m, 1H) (c), 6.7-7.7 (m, 7H), 9.8 (0.2H) and 11.4 (0.8H) (c)
9	DMSO-d_6	2.61 (s, 3H), 4.81 (d, 2H, J = 5), 6.7-7.7 (m, 10H), 7.12 (d, 1H, J = 13) (c), 9.07 (d, 1H, J = 13), 9.8-10.4 and 11.4 (1H) (c)
10	DMSO-d_6	0.8-2.3 (m, 20H), 2.55 and 2.68 (2s, 3H), 2.8-4.2 (2H) (c), 6.63 and 6.68 (2s, 2H), 9.6-10.4 (0.25H) (c), 11.8 (m, 0.75H)
	Deuteriochloroform	0.8-2.3 (m, 20H), 2.60 and 2.73 (2s, 3H), 3.17 (m, 1H) (c), 3.73 (m, 1H) (c), 4.77 (2d, 1H, J = 13, J = 7), 6.75 and 6.80 (d, 1H, J = 13), 9.73 (0.2H) and 11.45 (0.8H) (c)
11	DMSO-d_6	2.53 and 2.63 (2s, 3H), 4.40 (d, 2H, J = 5), 4.72 (d, 2H, J = 5), 6.68 (d, 1H, J = 12.5), 6.9-7.6 (m, 1H), 9.8-10.3 (0.3H) (c), 11.62 (m, 0.7H)
	Deuteriochloroform	2.55 and 2.67 (2s, 3H), 4.41 (d, 2H, J = 6), 4.65 (d, 2H, J = 6), 5.17 (m, 1H) (c), 6.73 and 6.80 (2d, 1H, J = 13), 7.2-7.6 (m, 10H), 10.0 (0.2H) (c), 11.6 (0.8H) (c)
12	DMSO-d_6	2.43 and 2.53 (2s, 3H), 3.08 (s, 6H), 6.50 (s, 1H), 8.7-9.5 (1.25H) and 10.1 (0.75H) (c)
13	Deuteriochloroform	1.1-2.2 (m, 10H), 2.61 and 2.73 (2s, 3H), 3.17 (s, 6H), 3.77 (1H) (c), 6.47 and 6.52 (2s, 1H), 9.8 (0.2H) (c) and 11.5 (0.8H) (c)
14a	DMSOd_6	2.38 (s, 3H), 6.9-7.6 (m, 5H), 7.65 (d, 1H, J = 13.5), 10.2 (d, 1H, J = 13.5), 11.1 (s, 1H)
14b	DMSO-d_6	2.27 (s, 3H), 2.38 (s, 3H), 7.0-7.5 (m, 4H), 7.65 (d, 1H, J = 13), 9.25 (s, 1H), 10.15 (d, 1H, J = 13)
14c	DMSO-d_6	2.39 (s, 3H), 3.76 (s, 3H), 6.95 (d, 2H, J = 8.5), 7.20 (s, 1H), 7.37 (d, 2H, J = 8.5), 7.62 (d, 1H, J = 13.5), 10.17 (d, 1H, J = 13.5)
15	DMSO-d_6	2.40 (s, 3H), 4.22 (s, 3H), 6.8-7.8 (m, 4H), 7.58 (d, 1H) (a), 10.06 (d, 1H, J = 13)

(a) Obscured by aromatic protons. (b) Obscured by NH_2 protons. (c) Broad signal.

Compounds **5** and **6** were prepared as previously described (12).

3-(1-Alkylaminoethylidene)-5-aryl (or alkyl) aminomethylene-2,4-dioxo-(3*H*,5*H*)furans (**7-11**).

Preparation of Compounds **7a-c**.

To a solution of **5a-c** (0.01 mole) in hot ethanol (50 ml.), 10 ml. of 28% aqueous ammonium hydroxide was added. The mixture was refluxed 10 minutes and then cooled, and the precipitated solid was filtered, washed with cold ethanol and dried.

Preparation of Compounds **8-11**.

A solution of **5** or **6** (0.01 mole) in ethanol (50 ml.) and cyclohexylamine or benzylamine (0.015 mole in the case of **5a** and 0.03 mole in the case of **6**) was refluxed for 30 minutes. After removal of the solvent under reduced pressure, the remaining oil was triturated with ether. The resulting product was then collected by filtration and recrystallized from the appropriate solvent (see Table I).

3-(1-Amino and Cyclohexylaminoethylidene)-5-dimethylaminomethylene-2,4-dioxo-(3*H*,5*H*)furans (**12** and **13**).

To a solution of **6** (2.25 g., 0.01 mole) in 20 ml. of water was added 6 ml. of 28% aqueous ammonium hydroxide or 2.5 ml. of cyclohexylamine. The mixture was stirred and the solid product which precipitated after a moment was collected by filtration, washed with water and recrystallized from water (in the case of **12**) or acetonitrile (in the case of **13**).

3-(1-Hydroxyethylidene)-5-arylaminoethylene-2,4-dioxo-(3*H*,5*H*)furans (**14a-c**).

A mixture of **7** (or **8,9**) (0.01 mole), ethanol (10 ml.) and 1*N* aqueous sodium hydroxide solution (10 ml.) was refluxed 15 minutes. The cooled reaction mixture was then acidified with concentrated hydrochloric acid. The solid which precipitated was collected, washed with water and dried. Analytical samples were obtained by recrystallization from ethanol.

3-(1-Methoxyethylidene)-5-anilinomethylene-2,4-dioxo-(3*H*,5*H*)furan (**15**).

The compound **14a** was treated with an excess of an ethereal-alcoholic solution of diazomethane overnight. After removal of the solvent, the enol ether was recrystallized from ethanol.

The yields and physical data are given in Table I.

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