Synthesis of some 3-Ethoxycarbonyl-5-hydroxy-4-oxo-2-pyrroline Derivatives from 3(2*H*)furanones

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A number of 3-ethoxycarbonyl-5-hydroxy-2-methyl-5-or-1,5-substituted 4-oxo-2-pyrrolines have been prepared, respectively, by the action of ammonium hydroxide or primary aliphatic amines on 2-arylidene or 2-*N*-acetyl-*N*-arylaminomethylene-4-ethoxycarbonyl-5-methyl-3(2*H*)furanones. The structures of these prepared compounds have been determined by spectroscopic data and chemical means.

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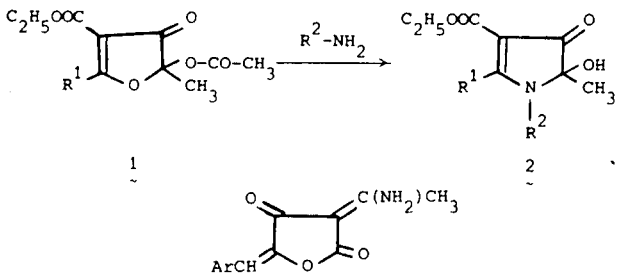
Previous papers from this laboratory have demonstrated the variety of ring transformations which ensue by the action of nucleophilic reagents on 3(2*H*)furanones (1-5). Thus, for example, 2-acetoxy-4-ethoxycarbonyl-3(2*H*)furanones **1** react with aliphatic and aromatic primary amines giving rise to *N*-substituted-3-ethoxycarbonyl-5-hydroxy-4-oxo-2-pyrroline derivatives **2** (4). Under the same conditions, ammonium hydroxide was found to afford the *N*-unsubstituted hydroxypyrrolinones (6). On the other hand, we have shown that the reaction of the ammonium hydroxide with various 2-arylidene-4-ethoxycarbonyl-3-(2*H*)furanones **4**, in refluxing ethanol, produced the enamines of the tetronic acid derivatives **3** (1). We now wish to report an additional study on compounds **4** and **5** in an effort to develop a synthetic route to hitherto unknown 5-hydroxypyrrolinones **6-12**. A few examples of these compounds are known (7-11).



1 2

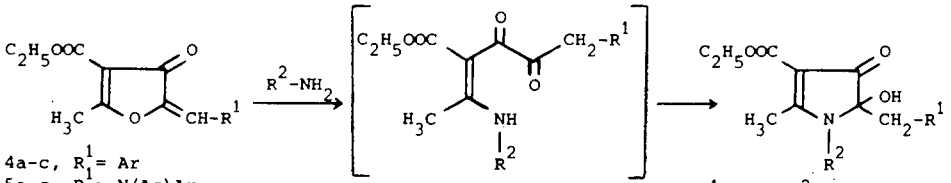
3

The action of ammonium hydroxide on compounds **4** can be directed to the formation of compounds **6** by proper choice of reaction conditions, in acetonitrile solution (0.1*M* in 3(2*H*)furanone) at low temperature (0°). At higher concentration, at room temperature, the reaction yielded a mixture of compounds **3** and **6**. These results indicate that lactonization of the open intermediate formed by nucleophilic addition does not occur under mild conditions and the heterocyclic enamino ketones, stable tautomeric forms of the acyclic diketo enamines, were obtained.

Similar behavior has been observed with primary aliphatic amines: methylamine, benzylamine, cyclohexylamine. Consequently, these reactions provide a simple route to 5-hydroxy-4-oxo-2-pyrrolines **6-12** (Scheme I). The aromatic primary amines do not react: the starting material was recovered.

The structure of compounds **6-12** is supported by elemental analysis and spectral data. The infrared spectra show strong OH stretching vibrations at ≃ 3680, 3550, 3300-3200 cm^{-1} and the characteristic absorption of the β-amino-enones, vinylogous of γ-lactams ν C=O ≃ 1680 and ν C=C-N ≅ 1500-1550 cm^{-1} (10). The ultraviolet absorption spectra disclose a peak at λ ≃ 306-334 nm. The cyclic nature of these compounds was particularly revealed in compounds **8** and **11** by their ^{1}H-nmr spectra which show that the signal of the methylene protons in the *N*-benzyl group appears as an AB quartet due to the

Scheme 1



4a-c, R^1 = Ar
5a-c, R^1 = N(Ac)Ar
a, Ar = C_6H_5
b, Ar = 4-$CH_3C_6H_4$
c, Ar = 4-$CH_3OC_6H_4$

6a-c, R^1 = Ar, R^2 = H
7a,b, R^1 = Ar, R^2 = H
8a-c, R^1 = Ar, R^2 = $CH_2C_6H_5$
9a,b, R^1 = Ar, R^2 = cyclo-C_6H_{11}
10a,b, R^1 = N(Ac)Ar, R^2 = H
11a-c, R^1 = N(Ac)Ar, R^2 = $CH_2C_6H_5$
12a-c, R^1 = N(Ac)Ar, R^2 = cyclo-C_6H_{11}

Table I

Physical Data for Compounds **6-12**

Compound	R^1	R^2	Yield %	M.p. °C Solvent	Molecular Formula	Analyses % Calcd. / Found C	H	N	Uv in Ethanol λ max (nm) (ε)		Ir (cm^{-1}) Chloroform
6a	C_6H_5	H	74	170 water	$C_{15}H_{17}NO_4$	65.44 65.72	6.22 6.20	5.09 5.21	211 (11300) 242 (17000) 307 (6800)	3690 3580 3420 3250	1725 1690 1525
6b	4-$CH_3C_6H_4$	H	70	144 water	$C_{16}H_{19}NO_4$	66.42 66.60	6.62 6.45	4.84 4.84	218 (10000) 242 (15200) 306 (6500)	3680 3570 3420 3250	1725 1690 1520
6c	4-$CH_3OC_6H_4$	H	75	154 water	$C_{16}H_{19}NO_5$	62.94 62.95	6.27 6.46	4.59 4.53	230 (14200) 243 (15200) 284 (5300) 306 (6100)	3680 3570 3420 3250	1725 1680 1520
7a	C_6H_5	CH_3	71	152 ethyl acetate	$C_{16}H_{19}NO_4$	66.42 66.67	6.62 6.64	4.84 4.91	211 (11000) 249 (15550) 326 (6720)	3680 3575 3300	1720 1680 1540
7b	4-$CH_3C_6H_4$	CH_3	70	159 ethyl acetate	$C_{17}H_{21}NO_4$	67.31 67.20	6.98 7.01	4.62 4.75	215 (10200) 248 (13000) 326 (6000)	3680 3575 3300	1720 1680 1540
8a	C_6H_5	$CH_2C_6H_5$	80	144 ethyl acetate-hexane 1:1	$C_{22}H_{23}NO_4$	72.31 72.12	6.34 6.37	3.83 3.84	210 (12200) 248 (13650) 326 (7420)	3680 3550 3300	1725 1670 1500
8b	4-$CH_3C_6H_4$	$CH_2C_6H_5$	85	169 ethyl acetate-hexane 1:1	$C_{23}H_{25}NO_4$	72.60 73.02	6.64 6.60	3.69 3.60	214 (14100) 248 (14400) 326 (7600)	3680 3550 3300	1725 1680 1520
8c	4-$CH_3OC_6H_4$	$CH_2C_6H_5$	88	158 acetonitrile	$C_{23}H_{25}NO_5$	69.85 69.57	6.37 6.34	3.54 3.49	210 (12600) 228 (12400) 248 (12800) 330 (7300)	3680 3550 3300	1725 1680 1520

9a	C_6H_5	cyclo-C_6H_{11}	70	175 ethyl acetate-hexane 1:1	$C_{21}H_{27}NO_4$	70.56 70.50	7.61 7.68	3.92 3.94	210 (8900) 250 (13500) 326 (7025)	3680 3550 3300	1720 1680 1500
9b	4-$CH_3C_6H_4$	cyclo-C_6H_{11}	60	176 ethyl acetate	$C_{22}H_{29}NO_4$	71.13 70.94	7.87 7.92	3.77 3.76	214 (9550) 248 (14000) 326 (6850)	3680 3550 3300	1720 1680 1500
10a	C_6H_5-N(Ac)	H	90	157 acetonitrile	$C_{17}H_{20}N_2O_5$	61.43 61.08	6.07 6.12	8.43 8.77	211 (9400) 238 (15900) 307 (5980)	3680 3530 3420 3290	1730 1690 1655 1500
10b	4-$CH_3C_6H_4$-N(Ac)	H	92	161 acetonitrile	$C_{18}H_{22}N_2O_5$	62.41 62.04	6.40 6.47	8.09 8.27	212 (10200) 239 (17080) 306 (6100)	3680 3540 3430 3300	1725 1685 1650 1500
11a	C_6H_5-N(Ac)	$CH_2C_6H_5$	90	198 ethanol	$C_{24}H_{26}N_2O_5$	68.23 67.82	6.20 6.23	6.63 6.54	210 (13070) 246 (13250) 330 (6440)	3680 3540 3200	1730 (sh), 1500 1700 (sh) 1680 1640 (sh)
11b	4-$CH_3C_6H_4$-N(Ac)	$CH_2C_6H_5$	94	192 acetonitrile	$C_{25}H_{28}N_2O_5$	68.79 68.71	6.47 6.41	6.42 6.51	211 (15650) 244 (15080) 331 (7200)	3680 3540 3220	1730 (sh), 1630 (sh) 1700 (sh), 1520 1680
11c	4-$CH_3OC_6H_4$-N(Ac)	$CH_2C_6H_5$	95	188 ethanol	$C_{25}H_{28}N_2O_6$	66.36 66.18	6.24 6.33	6.19 6.25	211 (14400) 235 (17200) 331 (6900)	3670 3540 3220	1720 (sh), 1640 (sh) 1700 (sh), 1500 1680
12a	C_6H_5-N(Ac)	cyclo-C_6H_{11}	73	134 ethyl acetate	$C_{23}H_{30}N_2O_5$, H_2O	63.87 64.02	7.46 7.48	6.48 6.62	209 (7960) 248 (13870) 332 (7020)	3680 3520 3200	1725 (sh), 1640 1700 (sh), 1500 1680
12b	4-$CH_3C_6H_4$-N(Ac)	cyclo-C_6H_{11}	88	169 ethyl acetate	$C_{24}H_{32}N_2O_5$	67.27 67.11	7.53 7.56	6.54 6.47	210 (10570) 246 (13550) 333 (6500)	3680 3520 3210	1725 (sh), 1635 1695 (sh), 1500 1680
12c	4-$CH_3OC_6H_4$-N(Ac)	cyclo-C_6H_{11}	70	135 acetonitrile	$C_{24}H_{32}N_2O_6$	64.84 64.63	7.26 7.25	6.30 6.24	211 (10470 234 (15390) 334 (6600)	3680 3530 3210	1730 (sh), 1640 1700 (sh), 1520 1690

Scheme 2

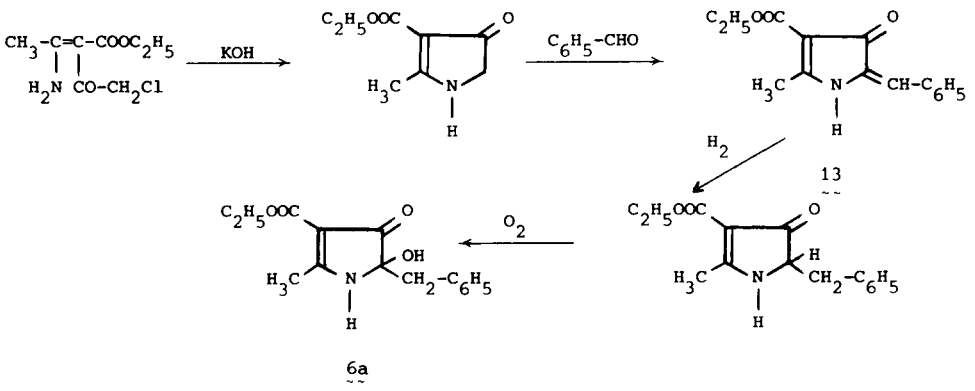


Table II

Proton Magnetic Resonance Parameters

Compound	Chemical Shift, ppm δ (deuteriochloroform)
6a	1.25 (t, 3H), 2.47 (s, 3H), 3.32 (br s, 2H), 4.22 (q, 2H), 5.55 (br s, 1H), 7.33 (s, 5H), 9.0 (br s, 1H)
6b	1.25 (t, 3H), 2.23 (s, 3H), 2.45 (s, 3H), 3.16 (br s, 2H), 4.18 (q, 2H), 5.75 (br s, 1H), 6.83-7.43 (m, 4H), 9.1 (br s, 1H)
6c	1.25 (t, 3H), 2.43 (s, 3H), 3.11 (br s, 2H), 3.55 (s, 3H), 4.20 (q, 2H), 5.63 (br s, 1H), 6.75 (d, 2H, J = 8 Hz), 7.16 (d, 2H, J = 8 Hz), 8.80 (br s, 1H)
7a	1.26 (t, 3H), 2.35 (s, 3H), 3.16 (s, 3H), 3.14 and 3.30 (2d, 2H, AB, J = 14 Hz), 4.20 (q, 2H), 6.08 (br s, 1H), 7.26 (m, 5H)
7b	1.25 (t, 3H), 2.30 (s, 3H), 2.35 (s, 3H), 3.16 (s, 3H), 3.09 and 3.25 (2d, 2H, AB, J = 14 Hz), 4.21 (q, 2H), 6.0 (br s, 1H), 7.08 (s, 4H)
8a	1.20 (t, 3H), 2.13 (s, 3H), 3.20 and 3.31 (2d, 2H, AB, J = 14 Hz), 4.16 (q, 2H), 4.51 and 4.91 (2d, 2H, AB, J = 16 Hz), 5.90 (br s, 1H), 7.17 (s, 5H), 7.30 (s, 5H)
8b	1.23 (t, 3H), 2.16 (s, 3H), 2.28 (s, 3H), 3.11 and 3.27 (2d, 2H, AB, J = 14 Hz), 4.16 (q, 2H), 4.51 and 4.91 (2d, 2H, AB, J = 16 Hz), 5.55 (br s, 1H), 6.98 (s, 4H), 7.30 (s, 5H)
8c	1.21 (t, 3H), 2.18 (s, 3H), 3.11 and 3.27 (2d, 2H, AB, J = 14 Hz), 3.76 (s, 3H), 4.15 (q, 2H), 4.55 and 4.92 (2d, 2H, AB, J = 16 Hz), 6.25 (br s, 1H), 6.73 (d, 2H, J = 8 Hz), 7.08 (d, 2H, J = 8 Hz), 7.35 (s, 5H)
9a	0.9-2.20 (m, 10H), 1.25 (t, 3H), 2.53 (s, 3H), 3.13 (br s, 2H), 4.16 (q, 2H), 5.76 (br s, 1H), 7.15 (s, 5H)
9b	0.9-2.2 (m, 10H), 1.28 (t, 3H), 2.3 (s, 3H), 2.6 (s, 3H), 3.15 (s, 2H), 4.25 (q, 2H), 5.70 (br s, 1H), 7-7.30 (m, 4H)
10a	1.28 (t, 3H), 1.85 (s, 3H), 2.52 (s, 3H), 3.83 and 4.17 (2d, 2H, AB, J = 14.5 Hz), 4.24 (q, 2H), 6.28 (br s, 1H), 7.0-7.6 (m, 5H)
10b	1.30 (t, 3H), 1.83 (s, 3H), 2.34 (s, 3H), 2.52 (s, 3H), 3.84 and 4.21 (2d, 2H, AB, J = 14.5 Hz), 4.25 (q, 2H), 6.10 (s, 1H), 7.11 (s, 4H), 8.75 (s, 1H)
11a	1.28 (t, 3H), 1.92 (s, 3H), 2.44 (s, 3H), 4.28 (q, 2H), 4.03 and 4.40 (2d, 2H, AB, J = 14 Hz), 4.80 and 5.13 (2d, 2H, AB, J = 18 Hz), 6.39 (br s, 1H), 7.0-7.7 (m, 10H)
11b	1.23 (t, 3H), 1.85 (s, 3H), 2.37 (s, 3H), 2.43 (s, 3H), 4.22 (q, 2H), 3.96 and 4.37 (2d, 2H, AB, J = 14 Hz), 4.76 and 5.09 (2d, 2H, AB, J = 18 Hz), 6.4 (br s, 1H), 6.9-7.6 (m, 10H)
11c	1.22 (t, 3H), 1.85 (s, 3H), 2.45 (s, 3H), 3.83 (s, 3H), 4.22 (q, 2H), 3.90 and 4.40 (2d, 2H, AB, J = 14 Hz), 4.78 and 5.10 (2d, 2H, AB, J = 18 Hz), 6.48 (br s, 1H), 6.93 (d, 2H, J = 9 Hz), 7.13 (d, 2H, J = 9 Hz), 7.41 (s, 5H)
12a	1.28 (t, 3H), 1.1-2.5 (m, 10H), 1.87 (s, 3H), 2.69 (s, 3H), 3.5-4.5 (br, 1H), 4.27 (q, 2H), 3.88 and 4.42 (2d, 2H, AB, J = 15 Hz), 6.68 (br s, 1H), 7.1-7.6 (m, 5H)
12b	1.32 (t, 3H), 1.1-2.5 (m, 10H), 1.88 (s, 3H), 2.38 (s, 3H), 2.70 (s, 3H), 3.5-4.5 (br, 1H), 4.30 (q, 2H), 3.79 and 4.48 (2d, 2H, AB, J = 15 Hz), 6.77 (s, 1H), 7.25 (s, 4H)
12c	1.30 (t, 3H), 1.1-2.5 (m, 10H), 1.87 (s, 3H), 2.70 (s, 3H), 3.5-4.5 (br, 1H), 3.87 (s, 3H), 4.29 (q, 2H), 3.79 and 4.46 (2d, 2H, AB, J = 15 Hz), 6.78 (s, 1H), 6.99 (d, 2H, J = 9 Hz), 7.29 (d, 2H, J = 9 Hz)

Coupling constants ethoxycarbonyl group CH_3-CH_2: 7 Hz; br: broad.

presence of an asymmetric center in the cyclic form. The methylene at C-5 also displayed an AB pattern in compounds **7**, **8**, and **10-12**. These findings are in agreement with published literature on the tautomerism of 4-oxo-2-pyrroline derivatives (7,10,12) (Tables I and II).

The structure of compound **6a** was securely established by chemical evidence, because it is known that the most striking property of some 2,5-dimethyl-4-oxopyrroline derivatives is their rapid autoxidation in air (10). The same compound **6a** (identity established by comparison of infrared and nmr spectra) was obtained by the series of transformations presented in Scheme 2: condensation of benzaldehyde with 3-ethoxycarbonyl-2-methyl-4-oxo-pyrroline and subsequent autoxidation of the resulting material after catalytic hydrogenation.

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. Compounds **4** (1) and **5** (5) were prepared as previously described.

3-Ethoxycarbonyl-5-hydroxy-2-methyl-4-oxo-2-pyrrolines.

Preparation of Compounds **6**, **7**, and **10**.

A suspension of furanones **4** or **5** (0.01 mole) in acetonitrile (100 ml.) was cooled to 0° with stirring and 2.7 ml. (0.04 mole) of 28% aqueous ammonium hydroxide or 3 ml. (0.03 mole) of 33% aqueous methylamine was added dropwise. After 1 hour at 0°, the mixture was kept at room temperature for a night. The solution was concentrated to dryness *in vacuo* and the residual solid was stirred with ether (50 ml.). After cooling, the precipitated solid was filtered, washed with ether and recrystallized.

Preparation of Compounds **8** and **9**.

Benzylamine or cyclohexylamine (0.02 mole) was added to a suspension of furanones **4** (0.01 mole) in acetonitrile (50 ml.), at room temperature. The reaction mixture was left overnight at room temperature and then poured over ice/water (100 ml.). The solution was acidified (*p*H 4) with 30% aqueous hydrochloric acid and the precipitate was extracted into chloroform. The chloroform solution was dried and evaporated to give the products which were purified by recrystallization.

Preparation of compounds **11** and **12**.

To a suspension of furanones **5** (0.01 mole) in ether (50 ml.) was added the appropriate amine (0.02 mole). The furanones dissolved and the reaction mixture was allowed to stand at room temperature for 2 hours. The precipitated product was collected, washed with ether and purified by crystallization.

Data on all compounds are summarized in Tables I and II.

5-Benzylidene-3-ethoxycarbonyl-2-methyl-4-oxo-2-pyrroline (**13**).

The condensation was carried out preparatively according to reference (13). A mixture of ethyl-2-methyl-4-oxo-2-pyrrolin-3-carboxylate (14), 1.68 g. (0.01 mole) and benzaldehyde, 2.12 g. (0.02 mole), was refluxed for 15 minutes. After the mixture was cooled, the solid was collected and crystallized from 95% ethanol, yield 1.9 g. (74%), m.p. 248° dec.; ir (chloroform): 3430, 3250, 1725, 1700, 1640, 1570; uv (ethanol) λ max (ε): 208 (5900), 251 (9100), 310 (10300), 402 nm (4500); nmr (DMSO-d_6): δ 1.27 (t, 3H, J = 7 Hz), 2.66 (s, 3H), 4.23 (q, 2H, J = 7 Hz), 6.6 (s, 1H), 7.38-7.71 (m, 3H), 7.74-8.0 (m, 2H), 11.0 (s, br., 1H).

5-Benzyl-3-ethoxycarbonyl-5-hydroxy-2-methyl-4-oxo-2-pyrroline (**6a**).

A solution of compound **13**, 2.57 g. (0.01 mole), in ethanol (50 ml.) was hydrogenated over 5% Pd/C (0.2 g.) at room temperature under 30 atm. of hydrogen. Uptake of the calculated amount required 45 minutes; the catalyst was filtered off and the solvent evaporated *in vacuo*. The crude residue was exposed to air in a thin film for two days being converted into solid mass from ethyl acetate, compound **6a** was obtained as white crystals, yield 0.25 g. (10%). The ir and nmr spectra of this compound were identical to the product of the reaction with ammonium hydroxide and furanone **4a**.

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