Synthesis of Some 4-Hydroxy-2-pyrrolin-5-one Derivatives via Acyloin Rearrangement

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The preparation of a number of new N-unsubstituted and N-substituted 3-(ethoxycarbonyl)-4-hydroxy-2,4-substituted-2-pyrrolin-5-ones is described. The reaction involves an acyloin rearrangement of corresponding 3-(ethoxycarbonyl)-5-hydroxy-2,5-substituted-2-pyrrolin-4-ones. Results from the chemical reduction and the isomerization of some compounds are presented.

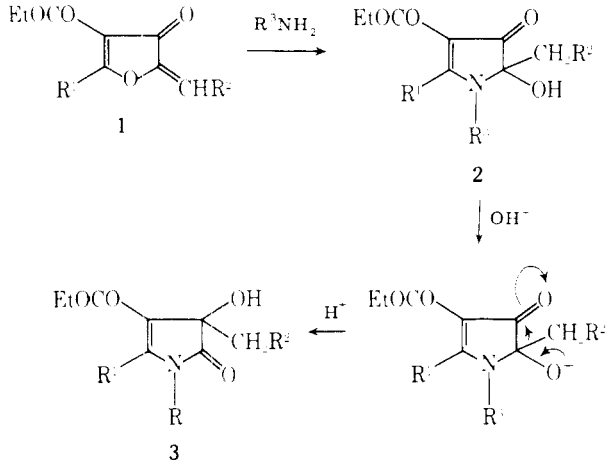
We have reported the synthesis of 5-hydroxy-2-pyrrolin-4-one derivatives **2** via ammonia or primary amine treatment of various 3(2*H*)-furanones **1**.[1,2] We wish to describe in this paper the synthesis of N-unsubstituted and N-substituted 3-(ethoxycarbonyl)-4-hydroxy-2,4-substituted-2-pyrrolin-5-ones **3** by an acyloin rearrangement of **2** under basic conditions. This reaction provides a new entry into the synthesis of this class of lactams, of which very few examples have been reported in the chemical literature.

Photooxidation of pyrrole derivatives has been shown to give 5-alkoxy- or 5-hydroxy-3-pyrrolin-2-ones.[3] Autoxidation of 3,5-diphenyl-1-methyl-3-pyrrolin-2-one gave simultaneous formation of two isomers: 3,5-diphenyl-3-hydroxy-1-methyl-2-pyrrolin-5-one and 3,5-diphenyl-5-hydroxy-1-methyl-3-pyrrolin-2-one.[4] The base-catalyzed conversion of 2-hydroxy-2-phenylindolin-3-one to 3-hydroxy-3-phenylindolin-2-one is known.[5,6]

Results and Discussion

Treatment of 5-hydroxylactams **2a–l** with aqueous potassium hydroxide at 25–65 °C (see Experimental Section) gave the 4-hydroxylactams **3a–l**. The mechanism of this reaction involves first the removal of the OH proton from **2** followed by an acyloin rearrangement of the anion (Scheme I).

Scheme I



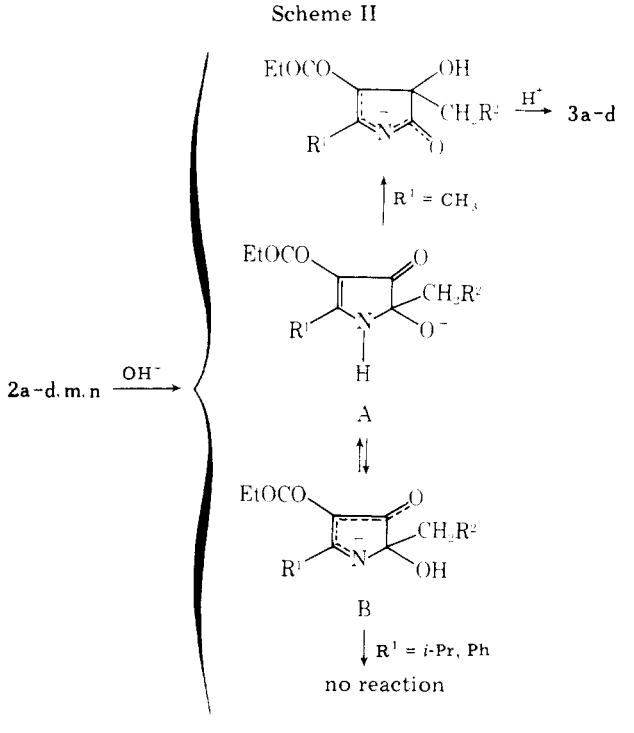
	R^1	R^2
1a	CH_3	C_6H_5
1b	CH_3	$4\text{-}CH_3C_6H_4$
1c	CH_3	$4\text{-}CH_3OC_6H_4$
1d	CH_3	furyl
1e	CH_3	$CH{=}CHCH_3$ (*E*)
1f	*i*-Pr	C_6H_5
1g	C_6H_5	C_6H_5

	R^1	R^2	R^3
2a, 3a	CH_3	C_6H_5	H
2b, 3b	CH_3	$4\text{-}CH_3C_6H_4$	H
2c, 3c	CH_3	$4\text{-}CH_3OC_6H_4$	H
2d, 3d	CH_3	furyl	H
2e, 3e	CH_3	C_6H_5	CH_3
2f, 3f	CH_3	C_6H_5	CH_2Ph
2g, 3g	CH_3	$4\text{-}CH_3C_6H_5$	CH_2Ph
2h, 3h	CH_3	$4\text{-}CH_3OC_6H_5$	CH_2Ph
2i, 3i	CH_3	furyl	CH_2Ph
2j, 3j	CH_3	$CH_3CH{=}CH$	CH_2Ph
2k, 3k	*i*-Pr	C_6H_5	CH_2Ph
2l, 3l	C_6H_5	C_6H_5	CH_2Ph
2m	*i*-Pr	C_6H_5	H
2n	C_6H_5	C_6H_5	H

The influence of the substituents at 1, 2, and 5 positions is particularly important regarding the possible rearrangement. The presence of a group of high migratory aptitude such as benzyl, furfuryl, and 2-butenyl in the 5 position is necessary. The reaction failed when R^2 = H. All of the compounds **2a–n** are soluble in aqueous potassium hydroxide at room temperature and can be regenerated by immediate acidification. The N-substituted 4-hydroxylactams **3e–l** precipitate in alkaline solution, while the N-unsubstituted compounds **3a–d** are soluble. The direction of the rearrangement suggests that the anions of these 4-hydroxypyrrolinones are thermodynamically more stable than those of the 5-hydroxypyrrolinones **2a–d.** Surprisingly, the compounds **2m,n** (R^1 = *i*-Pr and Ph, R^2 = Ph, R^3 = H) did not give the expected compounds **3m,n.** The fact that the unreacted compounds **2m,n** were recovered, on treatment with acid, in good yield while compounds **2a–d** reacted under the same conditions would suggest that the rearrangement must be reached by an equilibrium between the anions A and B. Hydrogen abstraction can take place at the nitrogen atom or at the oxygen atom. When R^1 = *i*-Pr and Ph, possibly, the equilibrium is displaced toward B (Scheme II).

The conversion of **2** into **3** is clearly supported by their IR, UV, and ^1H NMR spectra. In the IR spectra the characteristic

Scheme II



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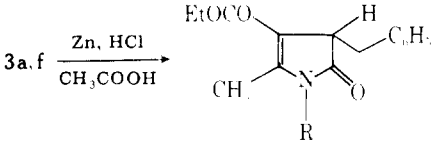
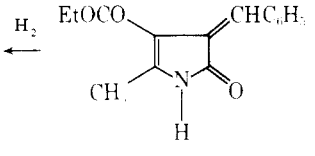
bands of α,β-unsaturated β-amino ketones at 1680–1690 and 1500–1520 cm^{-1} disappeared and bands at 1700 and 1640 cm^{-1} (ν C=O lactam and ν C=C, respectively) appeared. In addition, hydroxylic bands were observed. In the UV spectra, a hypsochromic shift takes place. Our data may be compared with those of the parent lactams.[7] The cyclic structure of compounds **3** is also supported by their ^1H NMR spectra, which show that the signal of the methylene protons at the C-4 position appears as an AB pattern due to the presence of an adjacent asymmetric center. Moreover, the chemical shifts of the protons of the alkyl substituents R^1 are shifted upfield on going from **2** to **3**.

The structure of compound **3a** was also established by chemical evidence. Chemical reduction of **3a,f** by a mixture of zinc dust, hydrochloric acid, and acetic acid gave **4a,f**. Physical and spectroscopic properties of **4a** were identical in all respect with those of the product obtained by catalytic hydrogenation of 4-benzylidene-3-(ethoxycarbonyl)-2-methyl-2-pyrrolin-5-one (**5**).[8]



4a, R^3 = H
f, R^3 = CH_2Ph



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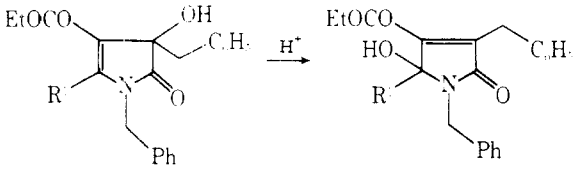
Attempts to dehydrate or to isomerize, in acidic conditions, the compounds **3a–j** (R^1 = CH_3) resulted in the formation of polymeric materials, from which we were not able to obtain any identifiable product. These experiments suggest the formation of the corresponding 2-methylene derivatives, which would polymerize. The NMR spectra of the crude products show the disappearance of the protons of the methyl group. In contrast, the compounds **3k,l**, with R^1 = *i*-Pr and Ph, are isomerized to 5-hydroxy-3-pyrrolin-2-ones **6k,l**.



3k,l **6k**, R^1 = *i*-Pr
l, R^1 = Ph

The structure of **6k,l** is supported by elemental analysis and spectral data. In particular, the ultraviolet absorption spectra disclose only a peak at λ 214 and 217 nm, respectively, because of the disappearance of the cyclic conjugated amide C=CNC=O.

One interesting physical property common to all 4-hydroxylactams **3** described in this investigation is the characteristic fluorescence they emit when illuminated by near-ultraviolet light. In contrast, the isomerized compounds **6k,l** are not fluorescent.

Experimental Section

Melting points determined on a Kofler hot plate are uncorrected. Infrared and ultraviolet spectra were obtained with Beckmann Model Acculab 2 and DB spectrophotometers. ^1H NMR spectra were recorded on a Varian A-60. Elemental analyses were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, Villeurbanne, France.

Compounds **1a–e**[9] and **2a–c,e–h**[2] were prepared as previously described.

2-Benzylidene-4-(ethoxycarbonyl)-5-isopropyl-3(2*H*)-furanone (1f). To a mixture of 5-isopropyl-4-(ethoxycarbonyl)-3(2*H*)-furanone[10] (1.98 g, 10 mmol) and benzaldehyde (1.38 g, 13 mmol) was added dropwise with stirring concentrated hydrochloric acid (0.8 mL). The resulting solution was allowed to stand at room temperature overnight and then cooled to 0 °C. The solid was filtered and washed with hexane, and the residual solid was recrystallized from cyclohexane to give 1.9 g (66%) of **1f**, mp 74 °C.

2-Benzylidene-4-(ethoxycarbonyl)-5-phenyl-3(2*H*)-furanone (1g). To dry ethanol (50 mL) acidified with acetyl chloride (8 mL) was added 5-phenyl-4-(ethoxycarbonyl)-3(2*H*)-furanone[10] (2.32 g, 10 mmol) and benzaldehyde (2.12 g, 20 mmol). The solution was allowed to stand at room temperature overnight. The resulting precipitate was filtered, washed with ether, and recrystallized from ethanol to yield 2 g (62%) of **1g**, 108 °C.

Preparation of N-Unsubstituted 5-Hydroxy-2-pyrrolin-4-ones (2d,m,n). A suspension of the appropriate furanone **1** (10 mmol) in acetonitrile (100 mL) was cooled to 0 °C with stirring, and 2.7 mL (40 mmol) of 28% aqueous ammonium hydroxide was added dropwise. After 1 h at 0 °C, 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 precipitate solid was filtered, washed with ether, and recrystallized (Table I).

Preparation of 1-Benzyl-5-hydroxy-2-pyrrolin-4-ones (2i–l). Benzylamine (2.14 g, 20 mmol) was added to a suspension of the appropriate furanone **1** (10 mmol) 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 (pH 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 (Table I).

Preparation of N-Unsubstituted 3-(Ethoxycarbonyl)-4-hydroxy-2,4-disubstituted-2-pyrrolin-5-ones (3a–d). General

Table I. Synthesis of 5-Hydroxy-2-pyrrolin-4-ones 2

compd	yield, %	mp, °C[a]
2d	60	148[b]
2i	86	148[c]
2j	60	124[c]
2k	50	174[d]
2l	35	164[e]
2m	60	165[c]
2n	33	157[c]

[a–e] Recrystallization solvent: [b] water, [c] ethyl acetate, [d] hexane–ethyl acetate (3:1), [e] hexane–ethyl acetate (1:2). Satisfactory analytical values (±0.3% for C, H, N) were reported for all compounds in this table.

Table II. Synthesis of 4-Hydroxy-2-pyrrolin-5-ones 3

compd	yield	mp, °C[a]
3a	65	169[b]
3b	60	165[b]
3c	67	130[b]
3d	60	132[b]
3e	60	119[c]
3f	78	148[d]
3g	75	142[e]
3h	75	138[e]
3i	64	132[e]
3j	60	114[e]
3k	60	128[f]
3l	60	135[e]

[a–f] Recrystallization solvent: [b] water, [c] hexane, [d] hexane–ethyl acetate (1:1), [e] hexane-ethyl acetate (2:1), [f] cyclohexane. Satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in this table.

Procedure. A solution of compound **2a–d** (10 mmol) in 5% aqueous potassium hydroxide (50 mL) was heated with stirring in a water bath. The temperature was kept at 65–70 °C for 10 min, and then the mixture was allowed to stand at room temperature for 1 h. After filtration, the resulting solution was acidified with 6 N aqueous hydrochloric acid. The precipitated hydroxypyrrolinone was extracted with two 40-mL portions of chloroform. The organic phase was washed with water and dried over sodium sulfate. The solvent was removed in vacuo, leaving a white solid which was recrystallized (Table II).

Preparation of 4-Benzyl-3-(ethoxycarbonyl)-4-hydroxy-1,2-dimethyl-2-pyrrolin-5-one (3e). A solution of **2e** (10 mmol) in 5% aqueous potassium hydroxide (30 mL) and chloroform (30 mL) was allowed to stir in a water bath at 65 °C for 10 min. After cooling to room temperature, the organic layer was washed with water and worked up as described above.

Preparation of 1-Benzyl-3-(ethoxycarbonyl)-4-hydroxy-2,4-disubstituted-2-pyrrolin-5-ones (3f–l). A solution of compound **2f–l** (10 mmol) in 5% aqueous potassium hydroxide (50 mL) was heated with stirring in a water bath. The temperature was kept in the range of 55 to 60 °C for **2f–h,k,** 30 to 35 °C for **2i,j,** and 25 to 30 °C for **2l** for 5 min. The reaction mixture was held at room temperature for 1 h. The precipitated hydroxypyrrolinone was extracted and worked up as described above (Table II).

Preparation of 4a from 5. A suspension of 4-benzylidene-3-(ethoxycarbonyl)-2-methyl-2-pyrrolin-5-one (**5**)[8] (1.28 g, 5 mmol) in ethyl acetate (25 mL) was hydrogenated with 5% palladium on carbon (0.75 g) at room temperature and 1 atm. After uptake of the calculated amount of hydrogen (1 h), the catalyst was filtered off and the solvent was evaporated under reduced pressure. The crude product was recrystallized to yield 78% of pure **4a.**

Preparation of 4a,f from 3a,f. To a stirred mixture of **3a,f** (3.6 mmol), zinc dust (1 g, 0.015 g-atom), and acetic acid (6 mL) was added concentrated hydrochloric acid (5 mL) in 10 equal portions of 0.5 mL over a period of 3 h. The temperature of the mixture rose from 25 to 50–70 °C. The mixture was cooled to room temperature and poured into 100 mL of ice water. The precipitated compound **4a,f** was collected by filtration, washed with water, dried, and recrystallized.

4-Benzyl-3-(ethoxycarbonyl)-2-methyl-2-pyrrolin-5-one (4a): 0.7 g, 75%; mp 150 °C (hexane–ethyl acetate, 1:1); IR ($CHCl_3$) 3660, 3440, 3200, 1735, 1700, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (3 H, t, J = 7 Hz), 2.18 (3 H, d, $J_{CH_3-H_4}$ = 1.5 Hz), 3.25–3.41 (2 H, m), 4.30 (2 H, q, J = 7 Hz), 7.08–7.33 (5 H, m), 8.68 (1 H, broad); UV (ethanol) nm (ϵ) 212 (7050), 285 (8500). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.43; H, 6.79; N, 5.49.

1,4-Dibenzyl-3-(ethoxycarbonyl)-2-methyl-2-pyrrolin-5-one (4f): 1 g, 80%; mp 104 °C (hexane); IR ($CHCl_3$) 1735, 1700, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (3 H, t, J = 7 Hz), 2.10 (3 H, d, $J_{CH_3-H_4}$ = 1.5 Hz), 3.33–3.53 (2 H, m), 3.57–3.80 (1 H, m), 4.35 and 4.85 (2 H, 2d, J_{AB} = 16 Hz), 4.28 (2 H, q, J = 7 Hz), 6.55–6.78 (2 H, m), 7.0–7.36 (8 H, m); UV (ethanol) nm (ϵ) 212 (10 500), 291 (8500). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.11; H, 6.62; N, 3.96.

1,3-Dibenzyl-4-(ethoxycarbonyl)-5-hydroxy-5-isopropyl-3-pyrrolin-2-one (6k). A solution of sulfuric acid (0.2 mL) in acetic acid (4 mL) was added to a stirred suspension of **3k** (1 g, 2.5 mmol) in acetic acid (8 mL). The reaction mixture cleared and was allowed to stand at room temperature overnight. It was poured into water (40 mL) and extracted with $CHCl_3$ (3 × 30 mL). The organic layer was neutralized with saturated $NaHCO_3$ solution and dried. The solvent was removed, and the solid residue was recrystallized to give 0.5 g (50%) of **6k**: mp 124 °C (cyclohexane); IR ($CHCl_3$) 3660, 3580, 1725 (sh), 1700 cm^{-1}; NMR ($CDCl_3$) δ 0.63 (3 H, d, J = 7 Hz), 0.86 (3 H, d, J = 7 Hz), 1.30 (3 H, t, J = 7 Hz), 2.33 (1 H, m), 3.75 (1 H, broad, exch.), 3.90 (2 H, s), 4.30 (2 H, q, J = 7 Hz), 4.53 (2 H, s), 7.05–7.60 (10 H, m); UV (ethanol) nm (ϵ) 214 (11 600). Anal. Calcd for $C_{14}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.40; H, 7.02; N, 3.61.

1,3-Dibenzyl-4-(ethoxycarbonyl)-5-hydroxy-5-phenyl-3-pyrrolin-2-one (6l). To a stirred solution of **3l** (1 g, 2.3 mmol) in acetic acid (10 mL) was added dropwise H_2SO_4 (1 mL) at room temperature; the precipitation began to take place in 30 min. The stirring was discontinued after 2 h. The resulting crystalline solid was filtered, washed with water, and recrystallized to give 3.3 g (80%) of **6l**: mp 170 °C (ethanol); IR ($CHCl_3$) 3660, 3580, 1725 (sh), 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.13 (3 H, t, J = 7 Hz), 3.98 and 4.56 (2 H, 2d, J_{AB} = 15 Hz), 4.08 (2 H, s), 7.13 (5 H, s), 7.22–7.50 (10 H, m), OH proton is not observed; UV (ethanol) nm (ϵ) 217 (14 400). Anal. Calcd for $C_{27}H_{21}NO_4$: C, 75.86; H, 5.90; N, 3.28. Found: C, 75.99; H, 5.91; N, 3.28.

Registry No.—**1d,** 60404-06-0; **1e,** 68682-69-9; **1f,** 68682-70-2; **1g,** 68682-71-3; **2a,** 68682-72-4; **2b,** 68682-73-5; **2c,** 68682-74-6; **2d,** 68682-50-8; **2e,** 68682-75-7; **2f,** 68682-76-8; **2g,** 68682-77-9; **2h,** 68682-78-0; **2i,** 68682-51-9; **2j,** 68682-52-0; **2k,** 68682-53-1; **2l,** 68682-54-2; **2m,** 68682-55-3; **2n,** 68682-56-4; **3a,** 68682-57-5; **3b,** 68682-58-6; **3c,** 68682-59-7; **3d,** 68682-60-0; **3e,** 68682-61-1; **3f,** 68682-62-2; **3g,** 68682-63-3; **3h,** 68682-64-4; **3i,** 68682-65-5; **3j,** 68682-66-6; **3k,** 68682-67-7; **3l,** 68682-68-8; **4a,** 68682-79-1; **4f,** 68682-80-4; **5,** 68682-81-5; **6k,** 68682-82-6; **6l,** 68682-83-7; benzaldehyde, 100-52-7; benzylamine, 100-46-9; 5-isopropyl-4-(ethoxycarbonyl)-3(2*H*)-furanone, 53252-35-0; 5-phenyl-4-(ethoxycarbonyl)-3(2*H*)-furanone, 67219-76-5; ammonium hydroxide, 1336-21-6.

Supplementary Material Available: Spectroscopic data (UV, IR, and ^1H NMR) for compounds **3a–l** (1 page). Ordering information is given on any current masthead page.

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