3-(2-Pyrrolidinyl)-2,4-furandione Analogs

Gary M. Coppola* and Robert E. Damon

Sandoz Research Institute, Chemistry Research Department,
Sandoz Pharmaceuticals Corporation,
Route 10, East Hanover, NJ 07936

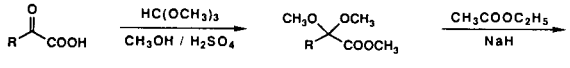
Received January 23, 1990

The reaction of 4,4-dimethyl-3-oxobutanoic (or pentanoic) acid esters with the lactim ether of 2-pyrrolidone in the presence of 2-hydroxypyridine produces condensation products **4** in 57-72% yield. Acidic hydrolysis of **4** affords the furandione system **5** in 75-81% yield.

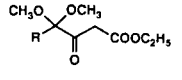
J. Heterocyclic Chem., **27**, 815 (1990).

In an earlier paper [1] we have reported the condensation of cyclic imino ethers with ethyl *o*-fluorobenzoyl acetate to produce fused quinoline derivatives. As an extension of that research, the interaction of cyclic imino ethers with an active methylene compound possessing an additional function, suitably positioned, capable of cyclization was investigated. Two such compounds which meet the requirements are the β-ketoesters **2a** and **2b**. Their preparations were readily accomplished (Scheme 1) similar to the procedure of Ross, *et al.* [2] by the condensation of the dimethoxyester **1** with ethyl acetate in the presence of either sodium or sodium hydride.

Scheme 1

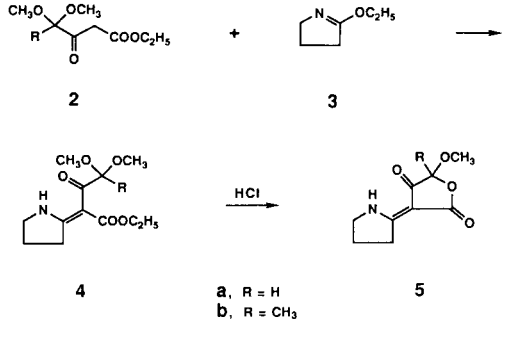


1



2 **a**, R = H
b, R = CH_3

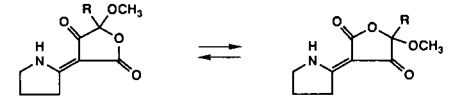
When **2** was allowed to react with the 5-membered lactim ether **3** in the presence of 2-hydroxypyridine, the expected product **4** was isolated in moderate yield. The treatment of **4** with dilute hydrochloric acid in dioxane did not result in the formation of an α-dione or any products derived from cyclization of the dione with the pyrrolidine nitrogen atom. Instead, the furan-2,4-dione was isolated in good yield (Scheme 2).



2 3 4 5

a, R = H
b, R = CH_3

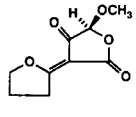
The infrared spectrum of **5a** exhibits an N-H absorption at 3310 cm^{-1} with additional absorptions at 1755 cm^{-1} (lactone C=O), 1680 cm^{-1} (ketone) and 1600 cm^{-1} (C=C). The nmr spectrum shows two exchangeable multiplets at δ 9.9 and 9.4 each of which integrates to approximately one-half of one proton. The dioxygenated methinyl proton (R = H) signal is also seen as two distinct singlets at δ 5.3 and 5.28 while the OCH_3 group falls as one singlet at δ 3.6. The occurrence of these dual signals suggest that the molecule exists as a mixture of *E* and *Z* isomers.



E isomer *Z* isomer

The chemistry leading to **5b** behaved in a similar manner to that of **5a** and readily furnished the corresponding 5-methyl analog. The N-H proton of **5b** was also seen as two multiplets of approximately equal intensity at δ 9.9 and 9.2 indicating the same isomeric ratio as that observed for **5a**.

The structure of **5** is of interest because, with minor variations in two skeletal functionalities, it closely resembles the naturally occurring carolic acid (**6**) [3] obtained as a metabolite from *Penicillium charlesii* [4,5].



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EXPERIMENTAL

Melting points were determined on a Thomas-Hoover unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian T-60 and EM-360 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multip-

let). The mass spectra were determined on an LKB 9000 spectrometer.

Unless otherwise stated, all solutions of organic compounds were washed with saturated sodium chloride solution then were dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

Dimethoxyacetic Acid Methyl Ester (**1a**).

A solution of 15 g (0.16 mole) of glyoxilic acid hydrate and 5 drops of concentrated sulfuric acid in a mixture of 50 ml of methanol and 50 ml of trimethyl orthoformate was refluxed for 18 hours. A solution of sodium methoxide in methanol was used to neutralize the sulfuric acid then the excess methanol was removed under reduced pressure in a 40° water bath. The residue was distilled at 20 mm to give 12.3 g (46%) of **1a**, bp 70-72° (lit bp 67° at 18 mm [6]); ir (chloroform): 1765 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.85 (s, 1H), 3.80 (s, 3H), 3.41 (s, 6H).

2,2-Dimethoxypropanoic Acid Methyl Ester (**1b**).

A solution of 50 g (0.57 mole) of pyruvic acid and 0.4 ml of concentrated sulfuric acid in a mixture of 160 ml of methanol and 160 ml of trimethyl orthoformate was refluxed for 18 hours. The methanol was removed under reduced pressure at 40° and the remainder of the mixture was poured into cold water and was basified with 10% sodium bicarbonate. The organic material was extracted (2x) into ether and, after drying over sodium sulfate, the solvent was removed under reduced pressure and the residue was distilled at 27 mm to give 47.1 g (56%) of **1b**, bp 81° (lit bp 62-63° at 12 mm [7]); ir (chloroform): 1740 cm^{-1}; nmr (deuteriochloroform): δ 3.8 (s, 3H), 3.3 (s, 6H), 1.55 (s, 3H).

4,4-Dimethoxy-3-oxobutanoic Acid Ethyl Ester (**2a**).

To a mixture of 9.0 g (0.067 mole) of **1a** and 9.0 g (0.1 mole) of ethyl acetate, heated in an oil bath at 70-75°, was added 1.55 g of sodium in small portions. After 10 minutes all of the sodium had dissolved, then an additional 9.0 g of ethyl acetate followed by 1.55 g of sodium were added. The mixture was stirred at 75° for 4 hours then at room temperature for 18 hours. The viscous red solution was poured into cold water and the mixture was washed with ether. The aqueous phase was acidified with 2*N* hydrochloric acid and the organic material was extracted into methylene chloride. After drying over sodium sulfate, the solvent was removed under reduced pressure and the residue was distilled at 0.5 mm to give 6.9 g (55%) of **2a**, bp 62-65°; ir (chloroform): 1765, 1740 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.6 (s, 1H), 4.2 (q, 2H), 3.6 (s, 2H), 3.4 (s, 6H), 1.25 (t, 3H).

4,4-Dimethoxy-3-oxopentanoic Acid Ethyl Ester (**2b**).

To 12.0 g (0.25 mole) of sodium hydride (50% in mineral oil, pentane washed) in a 300 ml flask was added 14.8 g (0.1 mole) of **1b** then 27 g (0.31 mole) of ethyl acetate. The mixture was stirred at 40-45° for 6 hours then at room temperature for 10 hours. Water was cautiously added and the resulting solution was washed with ether. The aqueous phase was acidified with 2*N* hydrochloric acid and the organic material was extracted into methylene chloride. After drying over sodium sulfate, the solvent was removed under reduced pressure and the residue was distilled at 0.35 mm to give 12.2 g (60%) of **2b**, bp 63-66°; ir (chloroform): 1760, 1736 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.21 (q, 2H), 3.6 (s, 2H), 3.25 (s, 6H), 1.4 (s, 3H), 1.3 (t, 3H).

Anal. Calcd. for $C_9H_{16}O_5$: C, 52.9; H, 7.9. Found: C, 53.1; H, 7.9.

4,4-Dimethoxy-3-oxo-2-(2-pyrrolidinylidene)butanoic Acid Ethyl Ester (**4a**).

A mixture of 5.2 g (0.027 mole) of **2a**, 3.3 g (0.029 mole) of **3** [8], and 2.6 g (0.027 mole) of 2-hydroxypyridine was stirred at 90° for 3 days. Approximately 5 ml of chloroform was added and the solution was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product, 4.0 g (57%) of **4a**. An analytical sample was crystallized from ether/pentane, mp 50-52°; ir (chloroform): 3205, 1692, 1612 cm^{-1}; ^1H nmr (deuteriochloroform): δ 11.3 (m, 1H, NH), 5.55 (s, 1H), 4.25 (q, 2H), 3.7 (t, 2H), 3.4 (s, 6H), 3.15 (t, 2H), 2.05 (m, 2H), 1.35 (t, 3H).

Anal. Calcd. for $C_{12}H_{19}NO_5$: C, 56.0; H, 7.4; N, 5.4. Found: C, 55.9; H, 7.2; N, 5.4.

4,4-Dimethoxy-3-oxo-2-(2-pyrrolidinylidene)pentanoic Acid Ethyl Ester (**4b**).

A mixture of 22.5 g (0.11 mole) of **2b**, 13.0 g (0.13 mole) of **3** [8], and 10.0 g (0.105 mole) of 2-hydroxypyridine was stirred at 90° for 10 days. Chloroform (5 ml) was added to the mixture and the solution was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product, 21.5 g (72%) of **4b**. An analytical sample was crystallized from ether/pentane, mp 93-95°; ir (chloroform): 3240, 1695, 1610, 1560 cm^{-1}; ^1H nmr (deuteriochloroform); δ 10.7 (m, 1H, NH), 4.2 (q, 2H), 3.7 (t, 2H), 3.2 (s, 6H), 2.9 (t, 2H), 2.35-1.85 (m, 2H), 1.55 (s, 3H), 1.3 (t, 3H).

Anal. Calcd. for $C_{13}H_{21}NO_5$: C, 57.5; H, 7.8; N, 5.2. Found: C, 57.1; H, 8.3; N, 4.8. Reanalysis of hydrogen did not improve the value.

5-Methoxy-3-(2-pyrrolidinylidene)-2,4(3*H*,5*H*)-furandione (**5a**).

A mixture of 3.0 g (0.017 mole) of **4a** and 0.4 ml of 2*N* hydrochloric acid in 40 ml of dioxane was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product, 1.7 g (75%) of **5a**. An analytical sample was crystallized from methylene chloride/ether, mp 150-151°; ir (chloroform): 3310, 1755, 1680, 1600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.9 (m, 0.5H), 9.4 (m, 0.5H), 5.3 (s, 0.5H), 3.9 (t, 2H), 3.6 (s, 3H), 3.35 (t, 2H), 2.6-2.1 (m, 2H).

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.8; H, 5.6; N, 7.1. Found: C, 54.8; H, 5.8; N, 7.0.

5-Methoxy-5-methyl-3-(2-pyrrolidinylidene)-2,4(3*H*,5*H*)-furandione (**5b**).

A mixture of 1.6 g (5.7 mmoles) of **4b** and 0.4 ml of 2*N* hydrochloric acid in 30 ml of dioxane was stirred at room temperature for 48 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product, 1.0 g (81%) of **5b**. An analytical sample was crystallized from methylene chloride/ether, mp 137-140°; ir (chloroform): 3330, 1740, 1665, 1595 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.9 (m, 0.5H), 9.2 (m, 0.5H), 3.85 (t, 2H), 3.25 (s, 3H), 3.25 (t, 2H), 2.55-2.0 (m, 2H), 1.5 (s, 3H); ms: (70 eV) m/z 211 (M^+).

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.9; H, 6.3; N, 6.6. Found: C, 57.2; H, 6.7; N, 6.5.

Acknowledgement.

The authors wish to thank Alicia Kahle and Sue DiCataldo for running the nmr spectra, Jackie Misuro for performing the microanalyses and Robert Clark for determining the mass spectra.

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