A LABORATORY SYNTHESIS OF 4-HYDROXY-2(5H)-FURANONE (β-TETRONIC ACID)

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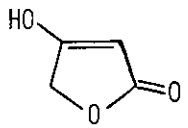
Abstract – A 'one pot'-fashioned preparation of 4-hydroxy-2(5H)-furanone (β-tetronic acid) was conducted in 38-40% overall yield starting from ethyl acetoacetate.

The α,β-unsaturated γ-lactone moiety, 2(5H)-furanone, occurs in a number of natural products.[1] The lactone hydroxylated at the β position is commonly known as β-tetronic acid (I), and biologically important activities have been examined for the analogs.[2]



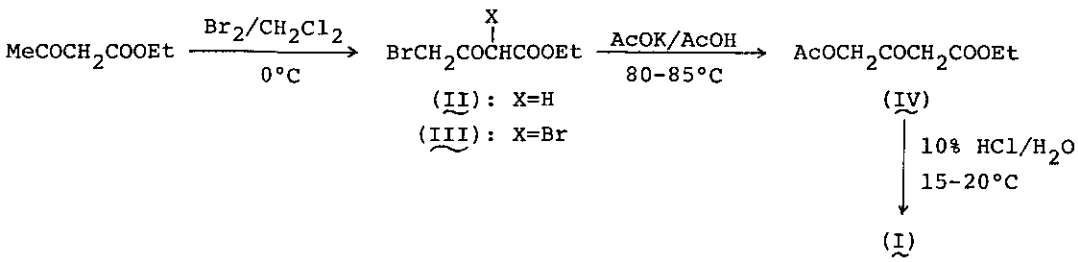
(I)

To date, a large number of synthetic routes to I have also been developed.[2c,3] Most of these, however, have shortcomings due either to low yields or to multistep procedures resulting in poor reproducibility. The need to prepare β-tetronic acid congeners and to examine their reactivity led us to devise a simple and reliable route to I.

Published routes to I can be divided into three categories;[4] one starting with the reaction of α-chloroacetyl[3a] or α-acetoxyacetyl chloride[3d] with a malonic ester and the other two with mono-[3b] and dibromination[3e] of an acetoacetic ester. Of the latter two, the one *via* a monobromoacetoacetate (II) involves alkaline hydrolysis of the ester followed by lactonization, and the other *via* a dibromo ester (III) involves pyrolytic lactonization and subsequent hydrogenolysis of the resulting bromo lactone; both seem simple in procedure but rather laborious in work-up, especially in the selective extraction of the highly hydrophilic lactone (I) from an aqueous mother liqour.

Meanwhile, effective transformation of the monobromide (II) into the acetoxy ester (IV) was reported in the pilocarpine synthesis,[5] and was followed by a report[6] describing a two-step route to I from II *via* this acetoxylation. Thus, a combination of the acetoxylation of ethyl acetoacetate *via* monobromination and acidic lactonization seems promising as a 'one pot'-fashioned procedure for I.

Actually, the procedure was found satisfactory.



In practice, bromination of ethyl acetoacetate was run in dichloromethane at 0°C, and subsequent transformation into the acetoxy ester (IV) was effected on treatment with potassium acetate in acetic acid[7] at 80-85°C, followed by treatment with 10% hydrochloric acid at room temperature to give β-tetronic acid (I) in 38-40% overall yield.

The procedure involves no extraction of I from any aqueous liqour with solvents and is more convenient for the preparation of a large size sample.

EXPERIMENTAL

A solution of bromine (48 g, 0.3 mol) in CH_2Cl_2 (15 ml) was added dropwise to a solution of ethyl acetoacetate (39 g, 0.3 mol) in CH_2Cl_2 (180 ml) at 0°C over a period of 50 min, and the mixture was stirred for additional 25 min at 15-20°C and then aerated by passage of dry air for 1 h.

Potassium acetate (90 g, 0.9 mol) and acetic acid (300 ml) were added to the reaction mixture, and the whole mixture was heated at 80-85°C for 5 h[8] with gradual distillation of CH_2Cl_2 (amounted to a distillate of 110 ml).

After cooling and subsequent filtration in order to remove the deposited KBr (weighed 34.0 g, 95.2% recovery), the mixture was diluted with 10% HCl (400 ml) and stirred at 15-20°C for 41 h.[8] The reaction mixture was evaporated under reduced pressure, and the resulting residue was washed with benzene (50 ml × 3) and then with ethyl acetate (AcOEt, 30 ml) and extracted with ethanol (50 ml × 3).

On evaporation of the ethanol extracts was obtained β-tetronic acid (I) (9.3 g, 31% yield) as pale yellow crystals, mp 139-140°C (lit.,[3e] mp 141-142°C). On evaporation of the AcOEt washings and subsequent trituration of the resulting residue with AcOEt (5 ml × 2) was obtained an additional crop of I (2.8 g, 9.3% yield).

The spectroscopic (IR and NMR[9]) data of the sample were in good accordance with those reported.[3e]

NOTES AND REFERENCES

1. For a recent review of butenolides, see Y.S. Rao, Chem. Rev., 1976, 76, 625.

2. a) K. Rehse, J. Wagenknecht, and N. Rietbrock, Arch. Pharm., 1978, 311, 986; b) A. Ibi, E. Taniguchi, and K. Maekawa, Agric. Biol. Chem., 1979, 43, 1641; c) Review: L.J. Haynes and J.R. Plimmer, Quart. Rev., 1960, 14, 292; d) Review: G. Pattenden, Fortschr. Chem. Org. Naturst., 1978, 35, 133.

3. For recent reports, see a) T.P.C. Mulholland, R. Foster, and D.B. Haydock, J. Chem. Soc., Perkin Trans. I, 1972, 1225; b) A. Svendsen and P.M. Boll, Tetrahedron, 1973, 29, 4251; c) J.V. Greenhill, M. Ramli, and T. Tomassini, J. Chem. Soc., Perkin Trans. I, 1975, 588; d) P. Pollet and S. Gelin, Tetrahedron, 1978, 34, 1453; e) D.G. Schmidt and H. Zimmer, Synth. Commun., 1981, 11, 385.

4. A route via the acid or alkaline hydrolysis of β-aminocrotonolactones has also been reported: a) Ref. 3c; b) K.J. Boosen, Ger. Offen. 2,025,570 (C. A., 1971, 74, 42273z); c) K.J.Boosen, U.S. 3,758,515 (C. A., 1973, 79, 126297b); d) K.J. Boosen, U.S. Reissue 28,242 (C. A., 1975, 82, 170652z). The reexamination by the present authors gave no satisfactory results.

5. J.I. Degraw, Tetrahedron, 1972, 28, 967.

6. T. Kato, M. Sato, and H. Kimura, J. Chem. Soc., Perkin Trans. I, 1979, 529.

7. Despite the procedure reported,[6] using sodium acetate in hot ethanol, the employment of potassium acetate in hot ethanol gave no good results.

8. Disappearance of the bromo or acetoxy ester on each stage of the reaction was readily monitored by TLC analysis on Merck pre-coated silica gel 60 F_{254} plates with the solvent phase benzene/acetone (20 : 1).

9. Measured for the solution in DMSO-d_6 on a JEOL JNM-FX 200 operating at 199.5 MHz for ^1H and 50.1 MHz for ^{13}C nuclei. The allylic coupling between C_3- and C_5-protons failed to be detected despite a value of $\sim$0.5[3b] or 1.2 Hz[3e] (60 MHz, in DMSO-d_6) reported. An analogous feature has been reported: ref. 3c.

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