A STUDY ON LACTONIZATION OF SOME BROMINATED DERIVATIVES OF β-BENZOYLPROPIONIC ACID

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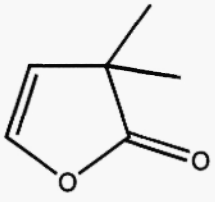
Abstract : The cyclodehydration of some brominated derivatives, on the methylene chain, of β-benzoylpropionic acid, to the corresponding 2(5H)-furanones or 2(3H)-furanones, depending on the substitution and reaction conditions, is described here.

Butenolides are unsaturated γ-lactones which may be also regarded as 2(3H)-furanones **1** or 2(5H)-furanones **2**. The 2(5H)-furanone ring occurs widely in nature but we found no isolated natural products containing the 2(3H)-furanone core. This is probably because the 2(5H)-furanones are more stable and hence more in abundance than the corresponding 2(3H)-isomers.



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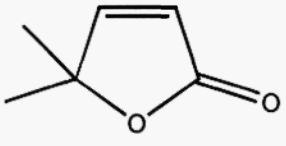

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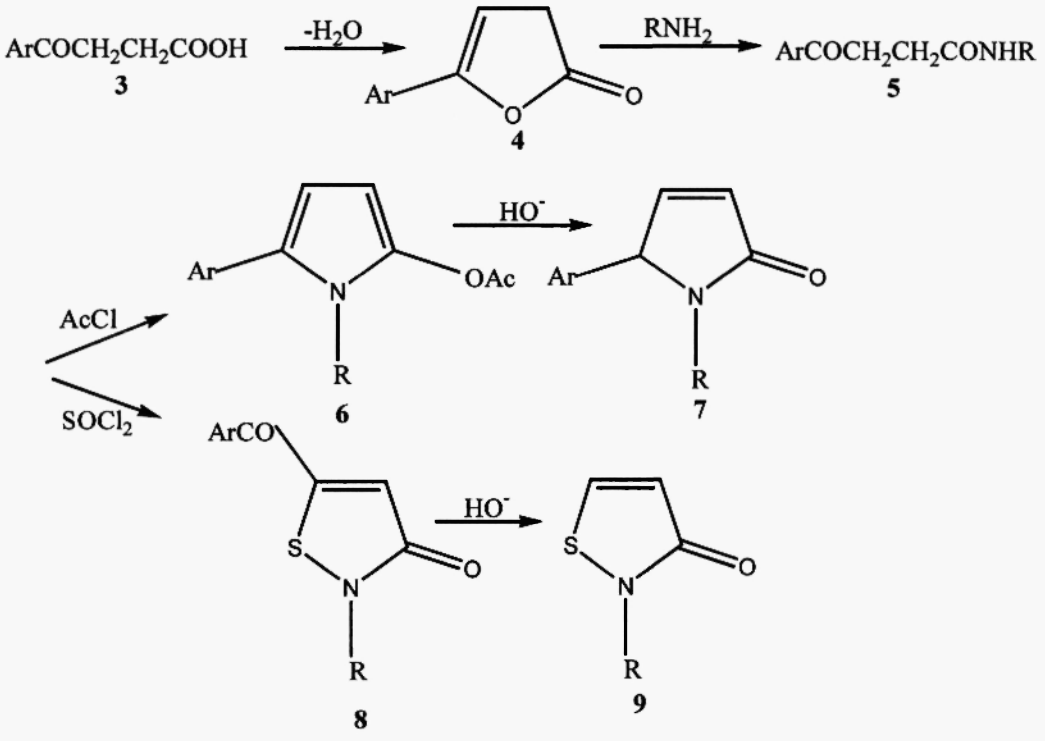
Several naturally occurring products exist in plants as glycosides of steroidal lactones, which are known as carbenolides. In either form, they exert a specific and powerful action on the cardiac muscle of human and animals. Four new butenolides, (of 2(5H)-form), have been isolated[1] from *streptomyces antibioticus* TÜ 99 showing, in preliminary tests, an antibiotic activity against *pseudomonas*. Four new 5-substituted α,β-unsaturated lactones[2] were also isolated from two marine *streptomyces* strains, B 5632 and B 3497. Chiral γ-substituted butenolides of type **2** are known to be useful synthons for the enantiocontrolled construction of a variety of biologically active natural and unnatural compounds.[3] Some naturally occurred γ-lactones have been also referred[4] to have strong herbicidal activity.
Therefore butenolides form an important class of compounds which appear as substructures in many natural products and also constitute pivotal building blocks for the synthesis of a wide range of biologically active products.
Among the synthetic methods used for the preparation of butenolides is the cyclodehydration of γ-keto acids which can be readily enolized usually giving the $\Delta^{\beta,\gamma}$-butenolides or 2(3H)-furanones, effected under dehydrating conditions. Among other reagents used for this lactonization are: acetic anhydride,[5] acetyl chloride,[6] acetic anhydride-sulfuric acid solution[7] and other dehydrated agents depending on the nature of substance to be lactonized. Yet another method for the preparation of butenolides consists of heating the γ-keto acid and distilling the lactone under reduced pressure.[8]

In the course of our studies on preparation of β-aroylpropionamides **5** and their reactions to different heterocycles, substituted pyrroles **6** and pyrrolinones[9] **7** or isothiazolones,[10] **8**, **9**, (Scheme-1), we used the 5-aryl-2(3H)-furanones **4**, prepared from the corresponding β-aroylpropionic acids **3**, on reaction with different amines (Scheme-1).



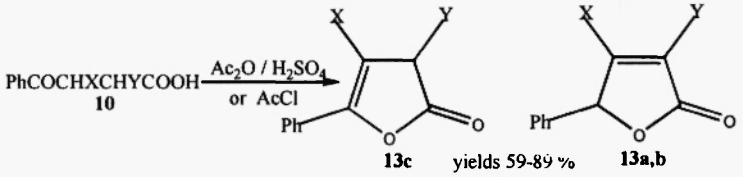
Scheme-1

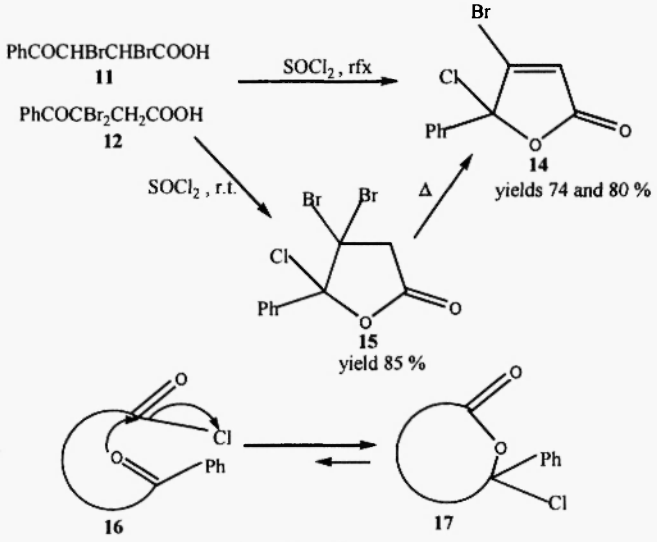
In a previous work,[11] we studied the lactonization of a series of β-aroylpropionic acids, using the reagents mentioned above under different conditions, and found that the ease of cyclodehydration reaction depends on the aryl group, the reagent used and to conditions. Thus acetic anhydride-sulfuric acid is more drastic reagent from acetic anhydride alone, and acetyl chloride is of intermediate reactivity.

In order to prepare bromosubstituted analogues to the products referred above, (see Scheme 1), we wish to report here the lactonization of some α and/or β brominated β-benzoylpropionic acids prepared from the β-benzoylpropionic acid or the β-benzoylacrylic acid. Except for a chemical interest in these lactonizations the resulting lactones, because of their general bioactivity, could be added to the corporate library, useful as prodrugs, especially the 2(5H)-furanones. Additionally, these new γ-lactones, except for their utility to the preparation of γ-keto amides **5**, could be used as intermediates for reactions with different nucleophiles or other syntheses.

The known[12] α-bromo- and α-chloro-β-benzoylpropionic acids **10a** and **10b** were prepared from the β-benzoylacrylic acid, (prepared according to a literature report,[13] via a Friedel-Crafts reaction of benzene and maleic anhydride), by addition of hydrogen bromide or hydrogen chloride using concentrated solutions of them instead

of gaseous acids.[12] The also known[14] β-bromo-β-benzoylpropionic acid **10c** was prepared by the classical substitution reaction on β-benzoylpropionic acid, using equimolar quantities of the acid and bromine in glacial acetic acid. The α,β-dibromo-β-benzoylpropionic acid **11** was prepared by an addition reaction[15] of bromine to an equimolar quantity of β-benzoylacrylic acid. The β,β-dibromo-β-benzoylpropionic acid **12** was also prepared from β-benzoylpropionic acid (see experimental).

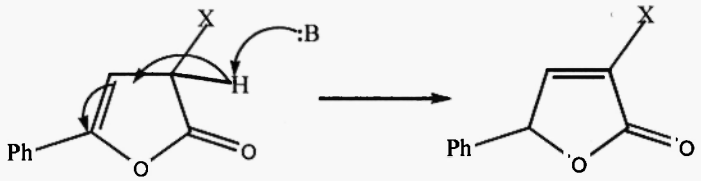




Scheme-2

The lactonization of the halo acids **10b** and **10c** was effected by acetic anhydride-sulfuric acid solution,[16] at room temperature, while the acid **10a** was lactonized using acetyl chloride at reflux conditions. The 2(5H)-furanones, **13a** and **13b**, were received from the acids, **10a** and **10b**, while the 2(3H)-furanone **13c**, from the acid **10c**. This difference can be explained by an isomerization of the initially formed 2(3H)-furanones through abstraction of the C3 carbon proton by a base present in the reaction's environment, (Scheme-3). The reagents used above were proved unsuccessful for lactonization of the dibro acids **11** and **12,** therefore the thionyl chloride was used instead. These acids gave under reflux conditions in thionyl chloride the same lactone **14,** (a $\Delta^{\alpha,\beta}$-butenolide), which corresponds to the dehydrobrominated cyclic tautomers of the corresponding, (open-chain), acid chlorides of the acids **11** and **12**.

Scheme 3



X=Br, Cl

Scheme-3

But when the reaction of the acid **12** with thionyl chloride took place at room temperature conditions the dibromo lactone **15** was received, which on heating, [37] melting point or in thionyl chloride solution, was converted by loss of hydrogen bromide to the lactone **14**. These results are consistent with the initially formation of the acycarboxyl chloride **16**, following the ring closure through an intramolecular nucleophilic addition of the ketonic oxygen to the carbonyl of the carboxyl chloride, forming the cyclic tautomer **17**, (Scheme 2). The stability of these cyclic tautomers is mainly due to the high electrophilicity of the –COCl group afforded by the –I-effect of the chlorine atom, and to the non-existent steric hindrance connecting the interacting groups and bromine atoms. The structure of these products was assigned on the basis of spectroscopic data and elemental analyses.
Finally, it must be pointed out that Bhatt[17] and co-workers, investigating kinetically the solvolysis reactions of levulinic and 2-benzoylbenzoic acid chlorides and some of their substituted derivatives, found no tautomeric equilibrium between the ring and chain forms of these chlorides

Conclusively, in this work we study the lactonization of some halogenated, (mainly brominated), derivatives on methylene chain of β-benzoylpropionic acid prepared from this acid and from the β-benzoylacrylic acid. For cyclodehydration of the α- and β-bromo-β-benzoylpropionic acids we used refluxing acetyl chloride conditions or acetic anhydride-containing trace of concentrated sulfuric acid at room temperature. The lactonization of α,β-dibromo-β-benzoylpropionic and β,β-dibromo-β-benzoylpropionic acids using the two above reagents was proved unsuccessful. Therefore, we tested the thionyl chloride for lactonization of these two acids, a reagent non selective for lactonization, but we found that these two acids were lactonized effectively through their conversion to the corresponding carboxyl chlorides, which then tautomerized to the cyclic γ-lactone form by the subsequent conversion to the stable 2(5H)-furanone-5-chloride by simultaneous dehydrobromination.
These γ-lactones, mainly the reactive 2(3H)-furanones, is likely to be useful synthons for the preparation of γ-keto amides also useful for synthesis of different heterocycles. The application of the method to other halogenated β-aroylpropionic acids and therefore their usage generally as electrophiles is in our immediate plan.

Experimental

General. NMR spectra were recorded at ambient temperature using a Varian Gemini 2000 300 MHz spectrometer. The data are reported as follows: chemical shift are quoted in ppm on the δ scale, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants are given in (Hz). Micro analyses were performed by microanalytical laboratory of CNRS (France). Melting points are reported uncorrected. IR spectra were obtained at a Nicolet Magna 560 spectrometer, as nujol mulls, and were calibrated against the polystyrene 1600 cm^{-1} band, and given in reciprocal centimetres. 70eV Electronic impact mass spectra were recorded on a Delsi-Nermag R-1010c spectrometer.

General procedure for the preparation of the haloacids **10a** and **10b**: A mixtue of β-benzoylacrylic acid 7 g and aqueous hydrobromic acid 48%, 35 ml was allowed under vigorous stirring at room temperature for three days. The solid product was filtered and washed well with water, 8.6 g of almost pure acid **10a** was received as was shown, (^{1}H NMR),. Recrystallization from benzene gave an analytical sample, (7.7 g, 75%), mp 123-124 ^{0}C, lit.[11] mp 124-125 ^{0}C. The acid **10b** was also prepared in an analogues manner, thus from 5 g of the β-benzoylacrylic acid, 4.9 g 81% yield of analytically pure acid **10b** were received, mp 119-120 ^{0}C, lit.[11] mp 121 ^{0}C.

β-Bromo-β-benzoylpropionic acid, 10c: A mixture of β-benzoylpropionic acid 3.47 g (19.47 mmol) and bromine 1 ml (19.52 mmol) in glacial acetic acid 15 ml was heated in a water bath at 60 ^{0}C under vigorous stirring. In few minutes the red colored solution formed disappeared, the acidic solution was poured in ice-water and the solid was filtered and washed with water to give 5 g of almost pure, (^{1}H NMR), acid **10c.** After recrystallization from carbon tetrachloride an analytical sample of the acid **10c** was received, (4.7 g, 94% yield), mp 118-119 ^{0}C, lit.[13] mp 120-121 ^{0}C.

β,β-Dibromo-β-benzoylpropionic acid, 12: To a refluxing solution of β-benzoylpropionic acid 3.47 g (19.47 mmol), in carbon tetrachloride 15 ml, bromine 2 ml (39.04 mmol) was added slowly and in few minutes a colorless solution was formed. After cooling in an ice bath the formed solid was collected and washed with cold carbon tetrachloride, which was shown to be, (^{1}H NMR), pure acid **12**. After recrystallization from carbon tetrachloride an analytical sample, (4.3 g, yield 66%), mp 115-116 ^{0}C, was received. Anal. Calcd for $C_{10}H_8Br_2O_3$: C, 35.73; H, 2.40; Br, 47.58. Found: C, 35.47; H, 2.46; Br, 47.63. IR: 3400, 1718, 1710. ^{1}H NMR ($CDCl_3$): 4.00 (s, 2H, -CH_2-), 7.33-7.70 (m, 3H, C3C4C5 arom.), 8.13-8.40 (m, 2H, C2C6 arom.), 13,30 (s 1H,-COOH).

3-Bromo-5-phenyl-2(5H)-furanone, 13a: A solution of the bromoacid **10a** 2 g in freshly distilled acetyl chloride 20 ml was refluxed for 4h. The solution was concentrated under vacuum to a reddish oily product, which after trituration with diethyl ether gave a solid product. After recrystallization from diethyl ether an analytical sample was received, (1.1 g, yield 59%), of the lactone **13a**, mp 78-79 ^{0}C. Anal. Calcd for $C_{10}H_7BrO_2$: C, 50.22; H, 2.95; Br, 33.44. Found: C, 50.11; H, 2.87; Br, 33.65. IR: 1785. and 1750. ^{1}H NMR ($CDCl_3$): 5.87 (d, J=5 Hz, 1H, C5), 6.93-7.33 (m, 5H, arom.), 7.60 (d, J=5 Hz, 1H, C4). ^{13}C NMR ($CDCl_3$): 89.87, 112.57, 127.20, 127.70, 129.00, 141.61, 142.12, 165.04. HRMS (EI) calcd for $C_{10}H_7BrO_2$: 239.0654. Found: 239.0647.

3-Chloro-5-phenyl-2(5H)-furanone, 13b: A solution of α-chloro-β-benzoylpropionic acid, **10b**, 2 g in a solution of acetic anhydride and concentrated sulfuric acid 15 ml was kept under stirring at room temperature for a day. This solution was added to ice-water under stirring, the solid formed was filtered and washed well with water. After recrystallization from benzene an analytical sample, (1.2 g, yield 65% yield), mp 91-92 ^{0}C, was received. Anal. Calcd for $C_{10}H_7ClO_2$: C, 61.70; H, 3.63; Cl, 18.23. Found: C, 61.63; H, 3.51; Cl, 18.20. IR: 1781 and 1750. ^{1}H NMR ($CDCl_3$): 5.90 (d, J=5 Hz, 1H, C5), 6.98-7.38 (m, 5H, arom.), 7.44 (d, J=5 Hz, 1H, C4). ^{13}C NMR ($CDCl_3$): 88.82, 127.20, 127.72, 129.00, 136.90, 141.60, 163.30. HRMS (EI) calcd for $C_{10}H_7ClO_2$: 194.6144. Found: 194.6140.

4-Bromo-5-phenyl-2(3H)-furanone, 13c. A solution of the bromoacid **10c** (4 g, 15.56 mmol), in a solution of acetic anhydride and concentrated sulfuric acid 16 ml was kept at room temperature for five days. This solution was added to ice-water 50 ml, the formed solid was filtered and washed well with water to give 3.8 g of a solid which was shown, (^{1}H NMR) to be an almost pure sample of the butenolide **13c**. After recrystallization from diethyl ether an analytical sample was received, (3.3 g, yield 89%), mp 87-88 ^{0}C, lit.[18] mp 88-89 ^{0}C. Anal. Calcd for $C_{10}H_7BrO_2$: C, 50.22; H, 2.95; Br, 33.44. Found: C, 50.34; H, 2.76; Br, 33.70. IR: 1812. ^{1}H NMR ($CDCl_3$): 3.66 (s, 2H, -CH_2-), 7.33-7.46 (m, 3H, C3C4C5 arom.), 7.80-8.15 (m, 2H, C2C6 arom.). ^{13}C NMR ($CDCl_3$): 42.85, 85.45, 126.40, 128.00, 128.70, 130.42, 145.90, 176.63. HRMS (EI) calcd for $C_{10}H_7BrO_2$: 239.0654. Found: 239.0646.

4-Bromo-5-chloro-5-phenyl-2(5H)-furanone, 14. Method (a): a solution of the α,β-dibromoacid **11** 2 g in freshly distilled thionyl chloride 15 ml was refluxed for 40 minutes. The solution was concentrated under vacuum to a solid residue which was shown, (^{1}H NMR), to be almost pure sample of the butenolide **14**. Recrystallization from diethyl ether gave an analytical sample, (1.2 g, 74% yield), mp 73-74 ^{0}C. Anal. Calcd for $C_{10}H_6BrClO_2$: C, 43.89; H, 2.21; Br, 29.23; Cl, 11.70. Found: C, 43.67; H, 1.98; Br, 29.33, Cl, 11.66. IR: 1825, 1772, 1602. ^{1}H NMR ($CDCl_3$): 6.38 (s, 1H, =CH), 7.33-7.81 (m, 5H, arom.). ^{13}C NMR ($CDCl_3$): 118.41, 127.00, 128.60, 128.80, 129.00, 130.72, 137.40, 173.40. HRMS (EI) calcd for $C_{10}H_6BrClO_2$: 273.5104. Found: 273.5110.

Method (b): a solution of the β,β-dibromo-β-benzoylpropionic acid **12** 2 g in freshly distilled thionyl chloride 20 ml was refluxed for 2.5h. The solution was concentrated under vacuum to a solid residue, pure sample as shown, (^{1}H NMR), of the butenolide **14**. After recrystallization from diethyl ether an analytical sample was received, (1.3 g, 80% yield), mp 73-74 ^{0}C.The melting point was unchanged on admixture with the lactone which was received from the lactonization of the α,β-dibroacid **11**.

4,4-Dibromo-5-chloro-5-phenyl-2(3H)-furanone, 15. A solution of the β,β-dibromo-β-benzoylpropionic acid, **12**, 2 g in freshly distilled thionyl chloride 20 ml was kept at room temperature under stirring for twenty hours. The solution was concentrated under vacuum, (without heating), to give an oily product which crystallized later to a solid which was shown, (^{1}H NMR), to be almost pure the lactone **15**. After recrystallization from carbon tetrachloride an analytical sample was received, (1.8 g, 85% yield), mp 102-103 ^{0}C. Anal. Calcd for $C_{10}H_7Br_2ClO_2$: C, 33.87; H, 1.99; Br, 45.10; Cl, 10.01. Found: C, 33.61; H, 1.87; Br, 44.91; Cl, 10.13. IR: 1841. ^{1}H NMR (CD_3COCD_3): 3.95 and 4.43 (dd, J=18 Hz, 2H, -CH_2-), 7.03-7.76 (m, 5H, arom.). ^{13}C NMR (CD_3COCD_3): 48.33, 67.11, 126.10, 128.20, 128.90, 130.42, 135.50, 176.14. HRMS (EI) calcd for $C_{10}H_7Br_2ClO_2$: 354.4224. Found: 354.4218.

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