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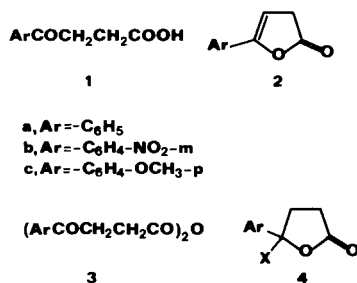
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The ease of lactonization of the  $\gamma$ -keto acids  $\text{ArCOCH}_2\text{CH}_2\text{COOH}$  is shown to depend on the nature of the aryl group: the presence of electron-releasing substituents on the aryl group results in a more rapid reaction as compared to the presence of electron-withdrawing substituents. The ease of this cyclodehydration reaction is also shown to depend on the reagent used: acetic anhydride-sulfuric acid is a more drastic reagent than acetic anhydride alone. Acetyl chloride, a reagent of intermediate reactivity in this reaction, is shown to yield easily the corresponding 5-arylfuran-2(3*H*)-ones in satisfactory yields.

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The lactonization of  $\gamma$ -keto acids can usually be effected by heating with acetic anhydride, with acetyl chloride, or with an acetic anhydride-sulfuric acid mixture [1,2]. In connection with other work, we have prepared a number of butenolides **2**, where Ar is a substituted phenyl group. We now wish to discuss some observations concerning the behaviour of the  $\gamma$ -keto acids **1** in the lactonization reaction, using a) acetic anhydride, b) an acetic anhydride-sulfuric acid mixture, and c) acetyl chloride.



#### A. Reaction with Acetic Anhydride.

Acetic anhydride has been widely used for the lactonization reaction of **1** to give **2** [3-7]. For instance, the butenolides **2**, where Ar = -C<sub>6</sub>H<sub>4</sub>-OCH<sub>3</sub>-*p*, -C<sub>6</sub>H<sub>4</sub>-CH<sub>3</sub>-*p* and -C<sub>6</sub>H<sub>4</sub>-Br-*p*, have been prepared by heating a mixture of the corresponding acids **1** and acetic anhydride at 100° [3]. However, different reaction times have been reported for the cyclization of the three acids (10, 30 and 60 minutes, respectively), while the bromo-substituted butenolide was reported to be of doubtful purity. The reactivity of these acids would thus seem to depend on the nature of the substituent on the phenyl ring.

Following this observation, we have examined the course of the lactonization reaction for three representative 3-aryolpropionic acids, *i.e.* the unsubstituted acid **1a**, the *m*-nitro-substituted acid **1b** and the *p*-methoxy-substituted acid **1c**.

The reaction of 3-benzoylpropionic acid (**1a**) and acetic

anhydride was clearly shown to proceed through the initial formation of the corresponding acid anhydride **3a**. Heating the mixture of the acid and acetic anhydride at 100° for 5 minutes resulted in the isolation of the acid anhydride, while the corresponding butenolide **2a** was obtained after heating the reaction mixture at 100° for 70 minutes [8].

It is also significant, that the anhydride **3b** of the nitro-substituted acid **1b** could be isolated after heating the reaction mixture at 100° for 15 minutes [10]. The lactonization of this acid is really a very slow reaction, since heating the reaction mixture at 100° for three hours resulted in the formation of only 20% of the butenolide **2b**.

On the other hand, the methoxy-substituted acid **1c** was shown to yield easily the corresponding butenolide **2c**, after heating the reaction mixture at 100° for only 15 minutes. In this case however, the butenolide formed was found to be gradually decomposed, since heating the reaction mixture at 100° for more than 15 minutes resulted in the isolation of a resinous material, containing progressively smaller amounts of the butenolide [13].

These observations disclose the influence of electron-withdrawing and electron-donating substituents of the phenyl group on the facility of the lactonization reaction of **1** to form **2** and the stability of the butenolides **2** under the lactonization conditions as well.

#### B. Reaction with Acetic Anhydride-Sulfuric Acid.

The mixed acetic anhydride and sulfuric acid cyclodehydration of simple 3-aryolpropionic acids has been recently reported [14] to yield the butenolides **2**, Ar = -C<sub>6</sub>H<sub>5</sub> and -C<sub>6</sub>H<sub>3</sub>(CH<sub>3</sub>)<sub>2</sub>-3,4, in high and reproducible yields.

The lactonization reaction of 3-benzoylpropionic acid (**1a**) in acetic anhydride containing a trace of sulfuric acid was actually found to be fast and quantitative (see Experimental). Even the nitro-substituted acid **1b** was easily lactonized at room temperature for 15 minutes. On the other

hand, the methoxy-substituted acid **1c** was immediately lactonized, in less than one minute at room temperature, but the butenolide formed was again found to be gradually decomposing, when the solution of the acid in the reagent was kept at room temperature for more than one minute.

The mixture acetic anhydride-sulfuric acid is thus shown to be a more drastic reagent than acetic anhydride alone in the lactonization reaction of **1** to form **2**. The trace of sulfuric acid probably assists in the enolization of the acid **1** prior to lactonization. This reagent should be useful in the lactonization of 3-arylpropionic acids with strong electron-withdrawing substituents on the aryl group. These acids are lactonized in lower yields by acetic anhydride alone (see above) and, moreover, the butenolides formed were found to be sufficiently stable in the acetic anhydride-sulfuric acid mixture.

### C. Reaction with Acetyl Chloride.

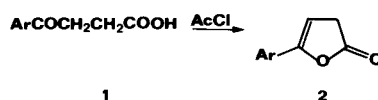
Acetyl chloride has been reported in various instances

to be an effective lactonization reagent for  $\gamma$ -keto acids [1,2]. This reagent has not however been used for the lactonization of 3-arylpropionic acids of the general formula **1**, with the exception of the acid **1a** [15] and the acid **1**, Ar =  $-\text{C}_6\text{H}_4\text{-Cl-}p$  [16].

3-Benzoylpropionic acid (**1a**) was shown (see Experimental) to be quantitatively lactonized in acetyl chloride solution after 10 minutes at room temperature, while the lactonization of the nitro-substituted acid **1b** required two hours under reflux. The methoxy-substituted acid **1c** was shown to be lactonized faster, in 6 minutes under reflux, but again the corresponding butenolide **2c** formed was gradually decomposed, when the reaction mixture was refluxed for more than 10 minutes.

Consequently, acetyl chloride is a lactonization reagent of intermediate reactivity as compared to acetic anhydride alone and to the acetic anhydride-sulfuric acid mixture. In this case, the lactonization of the acids **1** probably proceeds through a cyclic intermediate **4**, the acid chloride (X

Table 1  
5-Arylfuran-2(3H)-ones Obtained From the Reaction



Compound <b>2</b> - Ar	Reaction Conditions [a]	Mp (Yield) Recrystallization Solvent	Mp (lit)	PMR in Deuteriochloroform ( $\delta$ , ppm) [b,c]
$-\text{C}_6\text{H}_5$	1:10, 35 minutes	88-89° (83%) ethyl ether	91-92° [3]	3.40, d, $-\text{CH}_2$ 5.75, t, $=\text{C-H}$
$\text{C}_6\text{H}_4\text{-Br-}p$	1:10, 30 minutes	128-131° (70%) [d]	115-130° dec [3] 126-133° [26]	3.40, d, $-\text{CH}_2$ 5.78, t, $=\text{C-H}$
$-\text{C}_6\text{H}_4\text{-CH}_3\text{-}p$	1:20, 15 minutes	106-107° (77%) ethyl ether	111° [3]	2.36, s, $-\text{CH}_3$ 3.35, d, $-\text{CH}_2$ 5.66, t, $=\text{C-H}$
$-\text{C}_6\text{H}_4\text{-Cl-}p$	1:10, 30 minutes	105-106° (82%) ethyl ether	106-108° [9]	3.41, d, $-\text{CH}_2$ 5.76, t, $=\text{C-H}$
$-\text{C}_6\text{H}_4\text{-NO}_2\text{-}m$	1:10, 2 hours	131-133° (87%) methanol [f]	99° [7] [e]	3.50, d, $-\text{CH}_2$ 6.00, t, $=\text{C-H}$
$-\text{C}_6\text{H}_4\text{-OCH}_3\text{-}p$	1:20, 10 minutes	104-106° (76%) ethyl ether	110-111° [3]	3.38, d, $-\text{CH}_2$ 3.81, s, $-\text{OCH}_3$ 5.58, t, $=\text{C-H}$
$-\text{C}_6\text{H}_3(\text{CH}_3)_2\text{-}2,4$	1:10, 15 minutes	60-61° (60%) ethyl ether [g]		2.35, s, $-\text{CH}_3$ 2.43, s, $-\text{CH}_3$ 3.40, d, $-\text{CH}_2$ 5.51, t, $=\text{C-H}$
$-\text{C}_6\text{H}_3(\text{CH}_3)_2\text{-}3,4$	1:10, 15 minutes	105-108° (71%) ethyl ether	113.5-115.5° [14]	2.26, s, $-\text{CH}_3$ 3.35, d, $-\text{CH}_2$ 5.65, t, $=\text{C-H}$
$-\text{C}_6\text{H}_3(\text{NO}_2)_2\text{-}3,4$	1:20, 1 hour	164-165° dec (78%) ethyl ether [i]	154° [7]	3.55, d, $-\text{CH}_2$ [h] 3.95, s, $-\text{OCH}_3$ 6.21, t, $=\text{C-H}$

[a] Proportion of acid **1** (in g) to acetyl chloride (in ml) and reflux time of the mixture (see Experimental). [b] Aromatic proton absorptions are not reported. [c] The  $-\text{CH}_2$ - and  $=\text{C-H}$  proton signals appear as doublets and triplets respectively,  $J = 2.6$  cps. [d] This compound was obtained after treatment of the reaction product with a small amount of ethyl ether. The analytical sample, recrystallized from methanol, had mp 131-133°. *Anal.* Calcd. for  $\text{C}_{10}\text{H}_7\text{BrO}_2$ : C, 50.24; H, 2.95. Found: C, 50.09; H, 2.93. [e] *Cf.* also [10]. [f] This product had a pale pink colour. The analytical sample had mp 135-136°. *Anal.* Calcd. for  $\text{C}_{10}\text{H}_7\text{NO}_4$ : C, 58.54; H, 3.44; N, 6.83. Found: C, 58.54; H, 3.44; N, 6.87. [g] *Anal.* Calcd. for  $\text{C}_{12}\text{H}_{13}\text{O}_2$ : C, 76.57; H, 6.43. Found: C, 76.39; H, 6.50. [h] In  $\text{DMSO-d}_6$ . [i] *Anal.* Calcd. for  $\text{C}_{11}\text{H}_8\text{NO}_4$ : C, 56.17; H, 3.86; N, 5.96. Found: C, 56.19; H, 4.16; N, 5.96.

= -Cl) [17] or the acetoxy derivative ( $X = -OAc$ ), which would easily eliminate  $HX$  [19] to give the butenolide **2**.

Since the overall reaction of **1** to form **2** with acetyl chloride is sufficiently fast and experimentally simple, we have used it on a preparative scale with different 3-aryloxypropionic acids **1**, where Ar is a phenyl group bearing both electron-withdrawing and electron-releasing substituents. As shown in Table 1, the corresponding butenolides **2** could be easily prepared in satisfactory yields, better than 70% in recrystallized products. It should be noted that the acetyl chloride lactonization offers the possibility for a proper selection of reaction conditions, *i.e.* the proportion of acid **1** to acetyl chloride and the reaction time (see Table 1), depending on the substituents of the phenyl ring. For instance, an excess of acetyl chloride was used in the case of acids **1** with electron-releasing substituents; under these conditions, the butenolides **2** formed were found to be more stable (see Experimental). The reaction conditions reported in Table 1 are only indicative and no attempt was made to optimize the yields.

All butenolides **2** were recrystallized, when possible, from ether, since recrystallization from methanol or ethanol was observed to yield coloured products [21]. The isolation of pink coloured butenolides, resulting from the formation of "Pechmann dyes", has also been reported [3-5] in the lactonization of 3-aryloxypropionic acids when heated with acetic anhydride. No such coloured products were observed in the lactonization of the acids **1** with acetyl chloride, and this is another advantage of the method.

In agreement with their 5-arylfuran-2(3*H*)-one structure, all butenolides **2** show in the ir spectrum a strong carbonyl band at 1790-1800  $cm^{-1}$ , characteristic of  $\beta,\gamma$ -unsaturated five-membered ring lactones [23,24]. Their proton nmr spectra (see Table 1) show two characteristic signals: a doublet of the ring methylene protons at  $\delta$  3.35-3.50 ppm and a vinylic proton triplet at  $\delta$  5.50-6.00 ppm (in deuteriochloroform solution).

## EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ir spectra were obtained with a Perkin Elmer 267 spectrometer as nujol mulls. The pmr spectra were recorded on a Varian EM-360 60 MHz spectrometer; chemical shifts are given in ppm ( $\delta$ ) downfield from tetramethylsilane (internal standard) and are accurate to  $\pm 0.02$  ppm. Elemental analyses were obtained from the microanalytical laboratory of CNRS (France).

### A. Reactions with Acetic Anhydride.

All reactions described below were performed on mixtures of the acid **1** (1 g) and acetic anhydride (1 ml).

#### a. Acid **1a**.

The mixture of the acid **1a** and acetic anhydride was heated at 100° for 5 minutes and the excess anhydride was then evaporated *in vacuo*. The solid residue was shown (pmr in deuteriochloroform) to be mainly the acid anhydride **3a** containing a small amount (~6%, as evidenced

from the intensity of the vinylic proton triplet) of the butenolide **2a**. The solid residue was recrystallized from ethanol to give the acid anhydride **3a**, mp 100-103°, in 42% yield. A further recrystallization from ethanol gave an analytical sample, mp 103-105°, lit [25] mp 110°; ir: strong bands at 1818 and 1754 (anhydride CO), 1681 (ketone CO) and 1600  $cm^{-1}$  (phenyl); pmr: 2.95 and 3.36 (two t,  $J = 6$  cps, 8H,  $-CH_2CH_2-$  an  $A_2B_2$  system) and 7.36-8.06 ppm (m, 10H, aromatic protons).

Anal. Calcd. for  $C_{20}H_{16}O_5$ : C, 70.99; H, 5.36. Found: C, 70.88; H, 5.39.

#### b. Acid **1a**.

The mixture was heated at 100° for 70 minutes and the solid residue was shown (pmr) to be an almost pure sample of the butenolide **2a**. The residue was recrystallized from ether to give a 56% yield of the butenolide as a yellow solid, mp 85-87°, lit [3] mp 91-92°.

#### c. Acid **1b**.

The mixture with acetic anhydride was heated at 100° for 15 minutes and the semi-solid residue was shown (pmr) to be an almost pure sample of the acid anhydride **3b**. This was recrystallized from benzene to give the anhydride **3b**, mp 110-113°, in 32% yield. A further recrystallization gave an analytical sample, mp 118-120°; ir: strong bands at 1805 and 1750 (anhydride CO), 1702 (ketone CO) and 1620  $cm^{-1}$  (phenyl); pmr: 2.90 and 3.50 (two t,  $J = 6$  cps, 8H,  $-CH_2CH_2-$ ) and 7.65-8.60 ppm (m, 8H, aromatic protons).

Anal. Calcd. for  $C_{20}H_{16}N_2O_9$ : C, 56.08; H, 3.77; N, 6.54. Found: C, 56.27; H, 3.78; N, 6.44.

#### d. Acid **1b**.

The mixture with acetic anhydride was heated at 100° for three hours. The resulting red solution was shown (pmr in deuteriochloroform) to contain only 20% of the butenolide **2b**, as evidenced from the integration of the vinylic proton triplet versus the aromatic protons signal. The remaining signals of the spectrum are consistent with the presence of the acid anhydride **3b** as the major component of the mixture.

#### e. Acid **1c**.

The mixture was heated at 100° for 15 minutes and the solid residue was recrystallized from ether to give the butenolide **2c** in 70% yield as an almost colourless solid, mp 105-107°, lit [3] mp 110-111°. Heating the mixture of the acid **1c** with acetic anhydride at 100° for more than 15 minutes resulted, after evaporation of the excess acetic anhydride, in the isolation of a resinous material; this was shown (pmr) to contain a significantly lower proportion of the butenolide **2c**, as evidenced from the integration of the vinylic proton triplet versus the aromatic protons signal.

### B. Reactions with Acetic Anhydride-Sulfuric Acid.

All reactions described below were performed on solutions of 1 g of the acid **1** in 4 ml of an acetic anhydride-sulfuric acid solution (five drops of concentrated sulfuric acid were added to 100 ml of acetic anhydride).

#### a. Acid **1a**.

The solution of the acid in acetic anhydride-sulfuric acid was kept at room temperature for about one minute and the excess anhydride was then evaporated *in vacuo* at room temperature. The solid residue was shown (pmr in deuteriochloroform) to be a pure sample of the butenolide **2a**.

#### b. Acid **1b**.

The solution was kept at room temperature for 15 minutes and the colourless solid residue was shown (pmr) to be a pure sample of the butenolide **2b**. This was recrystallized from methanol to give the butenolide **2b** in 82% yield as a pale pink product, mp 132-134° (see Table 1). The same result was obtained when the solution of the acid was kept at room temperature for two hours.

#### c. Acid **1c**.

The solution was kept at room temperature for less than one minute and the residue was shown (pmr) to be a pure sample of the butenolide

**2c.** When the solution was kept at room temperature for 5 minutes, the residue was shown (pmr) to contain only 40% of the butenolide **2c**, as evidenced from the integration of the vinylic proton triplet versus the aromatic protons signal.

#### C. Reactions with acetyl chloride.

All reactions described below were performed on mixtures of the acid **1** (1 g) and acetyl chloride (10 ml).

##### a. Acid **1a**.

The mixture of the acid and acetyl chloride was stirred at room temperature. The acid was immediately dissolved and after 10 minutes the excess acetyl chloride was evaporated *in vacuo*. The essentially colourless solid residue was shown (pmr in deuteriochloroform) to be a pure sample of the butenolide **2a**. The same result was obtained when the solution in acetyl chloride was kept at room temperature for one hour or refluxed during 30 minutes. When however the mixture was refluxed for 12 hours (conditions reported in [15]), the yellow solid residue obtained after evaporating the excess acetyl chloride was shown (pmr) to contain about 60% of the butenolide **2a**, as evidenced from the integration of the vinylic proton triplet versus the aromatic protons signal.

##### b. Acid **1b**.

The mixture was refluxed for two hours and the essentially colourless solid residue was shown (pmr) to be a pure sample of the butenolide **2b**.

##### c. Acid **1c**.

The mixture was refluxed for 6 minutes and the essentially colourless solid residue was shown (pmr) to be an almost pure sample of the butenolide **2c**. When the mixture was refluxed for two hours, no vinylic proton triplet of the butenolide **2c** could be detected in the pmr spectrum of the resinous material obtained after evaporating the excess acetyl chloride. The same resinous material was obtained when a sample of pure butenolide **2c** was treated with acetyl chloride at reflux for two hours. The disappearance of the butenolide **2c** initially formed was then shown to proceed faster in a mixture of 1 g of the acid **1c** in 5 ml of acetyl chloride and much slower in a mixture of 1 g of the acid in 20 ml of acetyl chloride. When this last mixture was refluxed for 10 minutes, the residue was shown (pmr) to be a pure sample of the butenolide **2c**.

#### General Procedure for the Lactonization Reaction of **1** to form **2** Using Acetyl Chloride.

A mixture of acid **1** (2 g) and acetyl chloride (20 or 40 ml) was refluxed as indicated (see Table 1) and the excess acetyl chloride was then removed *in vacuo*. The residue, usually a colourless solid mass which was shown (pmr) to be an almost pure sample of the corresponding butenolide **2**, was rapidly washed with a small amount of ethyl ether and recrystallized, when possible, from this solvent. Physical characteristics of all butenolides **2** thus prepared are reported in Table 1.

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