Unstable 1,1,2-Enetriols as (Probable) Intermediates in the Decarboxylation of α,β-Diketo Acids

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During the acid hydrolyis of (hydrated) 4-aryl-2,3-diketobutyramide **2** (aryl = phenyl, *o*-chlorophenyl, *p*-methoxyphenyl), 3-aryllactic acid (**5**) is formed by rapid decarboxylation of the intermediate diketo acid (**3**). In the decarboxylation step, a further unstable intermediate is formed. The latter manifests itself by reducing 1 mol of added iodine during the hydrolysis–decarboxylation reaction, thereby forming 3-arylpyruvic acid (**6**), isolated instead of **5**. Thus, the oxidation of the unstable intermediate by iodine is more rapid than its ketonization. It is formulated as an 1,1,2-enetriol (**4**), more probable than an α-hydroxyketene.

The last years have witnessed a renewed interest in the classical subject of enol chemistry, through the work of Kresge,[1] Rappoport,[2] Capon,[3] and others.[4] Ynols[5] and enetriols[6] have been reported as transient species in flash photolyses. We present here results showing the probable intermediate formation of an 1,1,2-enetriol by a different way.[7]

It is well-known that enols are the first products formed in the facile decarboxylation of β-keto acids, which occurs in general via a cyclic mechanism.[8] Westheimer[9] has used this reaction to generate an enol that ketonizes sluggishly. On the other hand, α,β-diketo acids and their derivatives, like other vicinal tricarbonyl compounds,[10] are easily hydrated at the central carbonyl group. Combining these facts, one expects that during the decarboxylation of a hydrated α,β-diketo acid an 1,1,2-enetriol should be the first product formed. This unstable intermediate is expected to ketonize either to an α-hydroxy acid or to a glyoxal derivative; the former, stabilized by the resonance of the COOH group, would presumably prevail.[11]

$$R{-}CO{-}C(OH)_2{-}COOH \rightarrow R{-}C(OH){=}C(OH)_2 \rightarrow R{-}CHOH{-}COOH$$

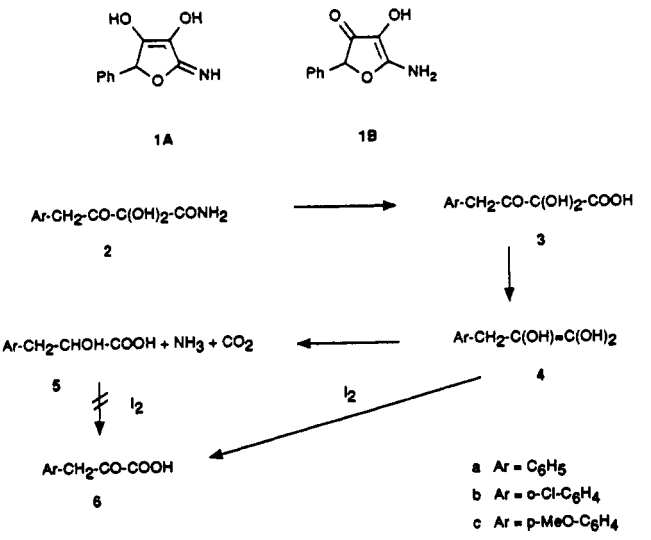
One might speculate that some reactions mentioned in the older literature proceed via this path, e.g.

$$Me{-}CO{-}C(OH)_2{-}COOEt \rightarrow Me{-}CHOH{-}COOH + CO_2 + EtOH \quad (1)[12]$$

$$HOOC{-}C(OH)_2{-}C(OH)_2{-}COOH \rightleftarrows HOOC{-}CO{-}C(OH)_2{-}COOH \rightarrow HOOC{-}CHOH{-}COOH + CO_2 \quad (2)[13]$$

However, it has to be taken into account that the same products can be formed via a benzilic acid type rearrangement involving migration of a COOR or COO^- group preceding decarboxylation; this path has been established for the reaction of the diketo ester of eq 1 in strong alkali[14]

Scheme I



and of related substrates.[15] To avoid the rearrangement reaction, acid conditions have to be applied.

$$Me{-}CO{-}C(OH)_2{-}COOEt \rightarrow Me{-}C(OH)(COOEt)COO^- \rightarrow Me{-}CHOH{-}COOH$$

We have tested this hypothesis while working with the easily accessible 4-aryl-2,3-diketobutyramide hydrates **2**, which are obtained by mild acid hydrolysis of **1**[16] (Scheme I). The latter compounds are prepared in one-step reactions at room temperature from aromatic aldehydes, glyoxal bisulfite, and cyanide ion.[17]

When **2a** (Ar = Ph) was submitted to acid hydrolysis of the amide group, molar quantities of NH_3 and CO_2 were liberated. The product isolated in good yield was 3-phenyllactic acid (**5a**). The CO_2 formed came exclusively from the carboxamide group, as demonstrated by using specifically labeled **2a**-1-^{14}C (prepared from K^{14}CN). (In contrast, during *alkaline* treatment of **2a**-1-^{14}C a benzilic acid type rearrangement with migration of the carboxamide group takes place forming $Ph{-}CH_2{-}C(OH)(CONH_2)COOH$, which by decarboxylation yields labeled phenyllactamide and *unlabeled* CO_2).[18] The *o*-chloro and

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p-methoxy compounds **2b,c**, treated with acid, reacted in the same way as **2a**. Kinetic experiments (by following the volume of CO_2 formed) showed that the rate of the reaction is practically unchanged by ring substitution (**2a** $k_{obs} = 3.2 \times 10^{-3}$ s^{-1}; **2b** 2.8×10^{-3} s^{-1}; **2c** 2.7×10^{-3} s^{-1}; 2 N H_2SO_4, 102.5 °C). The reaction is acid-catalyzed; up to 5.7 N acid, the rate constants are proportional to the stoichiometric acid concentration [H_3O^+] rather than to the Hammett acidity h_0. Both kinetic observations are in agreement with the view that the hydrolysis of the amide group is the rate-determining step of the reaction sequence and that the decarboxylation step of the diketo acid **3** is more rapid.

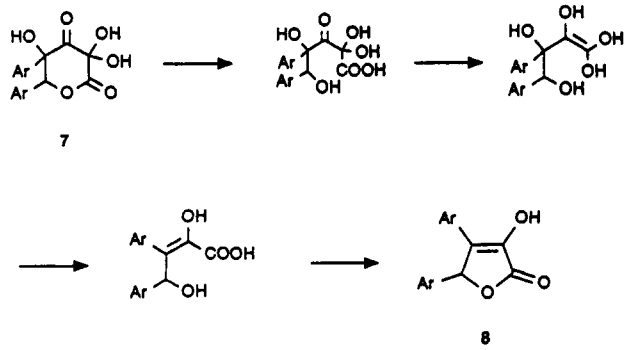
As anticipated, benzylglyoxal Ph—CH_2—CO—CHO, the alternative product of ketonization of **4**, was not found among the reaction products; it is not even an intermediate, for under the reaction conditions it is not transformed into the more stable product **5a**.

As **2** is prepared from **1** by mild treatment with acid and yields **5** under more drastic conditions, it is of course possible to convert **1** in one step into **5**. We found 89% yield for this transformation.

If an enol **4** is an intermediate in the decarboxylation, one could try to trap it by the action of a mild oxidant. I_2 is known to react very rapidly with simple enols to form α-iodo carbonyl compounds. With stabilized 1,2-enediols like ascorbic acid containing the group —C(OH)=C-(OH)—CO—, it reacts as a rapid oxidant yielding (hydrated) 1,2,3-tricarbonyl compounds.[19] 1,1-Enediols too are easily oxidized.[20] An unstable enetriol —C(OH)=C-$(OH)_2$ **4** would then form an α-keto acid —CO—COOH. When the hydrolysis–decarboxylation reaction of **2a** was run in the presence of an excess of iodine, 0.98 mol of I_2 per mol of **2a** was reduced to iodide; the product isolated in good yield was 3-phenylpyruvic acid (**6a**). In a kinetic experiment, I_2 practically did not change the overall reaction rate, showing that it does not intervene in the rate-determining step: $k_{obs} = 3.4 \times 10^{-3}$ s^{-1}.[21] Under the reaction conditions, the end product of hydrolysis **5a** is not oxidized, confirming that I_2 interferes with an intermediate. Ag^+, another oxidant of enediols, is not reduced during the hydrolysis–decarboxylation of **2a**, whereas selenious acid H_2SeO_3[22] is.

It is characteristic that the reaction of the enetriol with iodine is quantitative, without accompanying ketonization to **5**. It is known that the ketonization of simple enols, in spite of their great instability, is not a particularly rapid reaction;[3] for vinyl alcohol and related compounds the half-lives of ketonization at room temperature in the absence of catalysts are in the range of seconds or even minutes; in 2 N acid at 100 °C the reaction will be several orders of magnitude faster, without however reaching diffusion control. On the other hand, the reactions of the same enols with oxidants like I_2 are diffusion rate controlled, or at least nearly so.[23] This great difference in speed explains the absence of concurrent enolization of **4**. The reaction of hydrated Ag^+ with **4** is apparently slower, possibly because of the necessary desolvation of the ion, which is not required in the cases of I_2 and H_2SeO_3.

Scheme II



The results so far presented do not exclude the intermediacy of the nonhydrated α,β-diketo acid Ar—CH_2—CO—CO—COOH, which might be in equilibrium with the hydrate **3**. Decarboxylation of the unhydrated diketo acid could yield the hydroxyketene Ar—CH_2—C(OH)=C=O (instead of the enetriol **4**), which could then be hydrated to form **5**. Under certain conditions, the hydration would proceed via the formation of the 1,1,2-enetriol **4**, but a hydration mechanism avoiding this intermediate is also conceivable.[24,25] Until now, hydroxyketenes have not been characterized, but one cannot exclude that they are oxidized by I_2 as easily as other enols. A tentative distinction between the enetriol and the hydroxyketene as intermediates can be made, however, on the basis of the oxidation by H_2SeO_3: at room temperature, H_2SeO_3 reacts rapidly with stabilized 1,2-enediols like ascorbic acid, but very slowly with stabilized enols like that of acetylacetone. As in our case, the oxidation of the unstable intermediate formed by decarboxylation successfully competes with ketonization (in the case of an enetriol) or hydration (in the case of a hydroxyketene), which are both rather rapid reactions. It must be a rapid reaction too; this points to the rapidly reacting enetriol rather than the slow enol hydroxyketene. Further evidence should be available by increasing the lifetime of the intermediate through the decarboxylation of diketo acids formed under milder conditions, for instance, from *tert*-butyl esters and/or including steric hindrance from R of R—CO—$C(OH)_2$—COOH.

Acid hydrolyses followed by decarboxylation of other (hydrated) α,β-diketo acid derivatives have been reported to form products supposedly via 1,1,2-enetriols, e.g., the transformation of **7** into **8** (Scheme II), a reaction for which the absence of a rearrangement has been demonstrated,[26] and the transformation of α,β-diketobutyrolactone into pyruvic acid.[27] However, experimental support for the intermediates is lacking.

By the same mechanism, the known[28] decarboxylation of (hydrated) mesoxalic acid HOOC—$C(OH)_2$—COOH to glyoxylic acid HOOC—CHO would proceed via ethenetetrol $(HO)_2$—C=$C(OH)_2$. The related dibromomalonic acid HOOC—CBr_2—COOH consumes exactly 1 mol of bromine during decarboxylation, forming Br_3C—COOH,[29]

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(24) Simple ketenes are hydrated to 1,1-enediols under neutral or basic conditions; in the presence of acid catalysis, however, rate-determining protonation at C occurs without furnishing the enediol.[25] Whether hydroxyketenes are subject to the same pH conditions as simple ketenes is not known.
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presumably via bromination of an intermediate $Br_2C{=}C(OH)_2$.[29] The existence of unstable 1,1-enediol forms of carboxyl groups has recently been demonstrated.[30,20]

Experimental Section

5-Amino-4-hydroxy-2-phenylfuran-3-one (1B) or 3,4-Dihydroxy-5-phenyl-5*H*-furan-2-imine (1A)[17] was prepared in 95% crude yield by stirring benzaldehyde, glyoxal sodium bisulfite monohydrate and KCN at rt in dioxane-containing 2 N aqueous Na_2CO_3 and acidifying after 30 min. After crystallization from methanol: mp 173–178 °C dec; IR (KBr) 1700, 1620, 1560, 1520 cm^{-1}.

1a-1-^{14}C was prepared by the same method using K^{14}CN.

4-Phenyl-2,3-diketobutyramide hydrate 2a[16] was prepared in 72% crude yield by hydrolysis of 1a with Amberlite IR 120 (H^+ form) in water suspension at 70 °C. After crystallization from water: mp 108–110 °C dec, ^{1}H NMR (CD_3OD, 250 MHz) 4.02 (s, 2 H), 7.14–7.31 (m, 5 H).

4-(*o*-Chlorophenyl)-2,3-diketobutyramide hydrate 2b:[16] ^{1}H NMR (CD_3OD, 250 MHz) 4.25 (d, J = 1.5, 2 H), 7.17–7.38 (m, 4 H).

4-(*p*-Methoxyphenyl)-2,3-diketobutyramide hydrate 2c:[16] ^{1}H NMR (CD_3OD, 250 MHz) 3.76 (s, 3 H), 3.95 (s, 2 H), 6.81–7.09 (m, 4 H).

Hydrolysis–Decarboxylation of 2a. A mixture of **2a** (0.61 g, 2.9 mmol) and 2 N H_2SO_4 (50 mL) was refluxed during 90 min under a stream of N_2; the CO_2 formed was absorbed in NaOH and transformed into $BaCO_3$ (0.57 g, 99%). After being cooled, the solution was extracted continuously during 24 h by ether. The extract yielded by evaporation 0.46 g (95%) of crude **5a**: mp after recrystallization from benzene 95.5–96.5 °C (lit.[31] mp 97 °C); IR (Nujol) 1710, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) 3.01 (dd, J = 7.0, 14, 1 H, CH_2), 3.22 (dd, J = 4.2, 14, 1 H, CH_2), 4.53 (dd, J = 4.2, 7.0, 1 H, CHOH), 7.24–7.38 (m, 5 H).

In a parallel experiment, the CO_2 formed was measured by volume (95%).

Amide: mp 112–113 °C (from benzene; lit.[32] mp 112–113 °C); IR (KBr) 1640, 1595, 1495 cm^{-1}.

2a-1-^{14}C of specific activity 573 ± 5 ipm/mmol yielded 104% of $BaCO_3$ of 574 ± 5 ipm/mmol and **5a** (three times recrystallized) of 8 ± 5 ipm/mmol (=1.4% of the initial activity).

Direct Transformation of 1a to 5a. A mixture of **1a** (1.6 g, 8.3 mmol) and 2 N HCl (25 mL) was heated 1 h under reflux. The yellow solution was extracted with ether and the extract washed neutral with water, dried, and evaporated to give 1.23 g (89%) of **5a**; after two recrystallizations from benzene: mp 96 °C. Amide: mp 112–113 °C.

Hydrolysis–Decarboxylation of 2b. A mixture of **2b** (0.19 g, 0.79 mmol) and 2 N H_2SO_4 (10 mL) refluxed for 90 min yielded CO_2 (104% as $BaCO_3$, >95% by gas volume), NH_3 (92%, determined in aliquots of the reaction mixture by the diffusion method[33]), and 0.12 g (95%) of crude **5b**; mp (after recrystallization from benzene) 97–98 °C. Anal. Calcd for $C_9H_9ClO_3$: C, 53.86; H, 4.53. Found: C, 53.08; H, 4.77.

Methyl ester: mp 57–58 °C (from ether–petroleum ether). Anal. Calcd for $C_{10}H_{11}ClO_3$: C, 55.95; H, 5.17. Found: C, 56.14; H, 5.05. **Amide**: mp 164–165 °C (from benzene–methanol). Anal. Calcd for $C_9H_{10}ClNO_2$: C, 54.11; H, 5.01; N, 7.01. Found: C, 54.02; H, 5.38; N, 7.26.

Hydrolysis–Decarboxylation of 2c.[34] A mixture of **2c** (1.0 g, 4.5 mmol), alcohol (25 mL), and 8 N HCl (25 mL), refluxed during 4 h, yielded CO_2 (103% as $BaCO_3$, >97% by volume) and, after ether extraction of the concentrated solution and two recrystallizations from $CHCl_3$–petroleum ether, 0.60 g (68%) of **5c**; mp 104–105 °C (mp 85–87 °C, from ether–petroleum ether) (lit.[35] mp 88 °C (from ethyl acetate–petroleum ether)). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.18; H, 6.20.

Oxidative Hydrolysis–Decarboxylation. A mixture of **2a** (0.29 g, 1.4 mmol) and a 0.5 N solution of I_2 in 2 N H_2SO_4 (40 mL) was refluxed for 25 min. After the mixture was cooled, excess I_2 was reduced with sulfite. The solution was extracted 10 times with ether; the ether extract, washed with sulfite solution and water, dried, and evaporated, yielded 0.23 g (103%) of crude **6a**: mp (after recrystallization from $CHCl_3$) 148–150 °C (lit.[36] mp 154–155 °C); IR (nujol) 1690, 1615 cm^{-1} (identical with an authentic sample of phenylpyruvic acid).

In a parallel experiment, the consumption of I_2 was determined: 101; 96% (by titration). Controls showed that the total content ($I_2 + I^-$) did not change during the reaction; i.e., no I_2 was bound by substitution into organic compounds.

5a (3.7 mg, 0.022 mmol), heated 50 min at 100 °C with excess I_2 in 2 N H_2SO_4 (sealed tube), reduced 0.015 mequiv of I_2 (3%).

A mixture of **2a** (53 mg, 0.25 mmol) and H_2SeO_3 (33 mg, 0.25 mmol) in 2 N H_2SO_4 (10 mL) during 1 h at 95 °C reduced 1.05 mequiv of oxidant (iodometric titration). **5a** does not reduce H_2SeO_3.

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