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LACTONIZATION OF 3,5,7-TRIOXO-7-PHENYLHEPTANOIC ACID AND ITS 2-METHYL HOMOLOG*

T. M. HARRIS† and C. M. HARRIS

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37203

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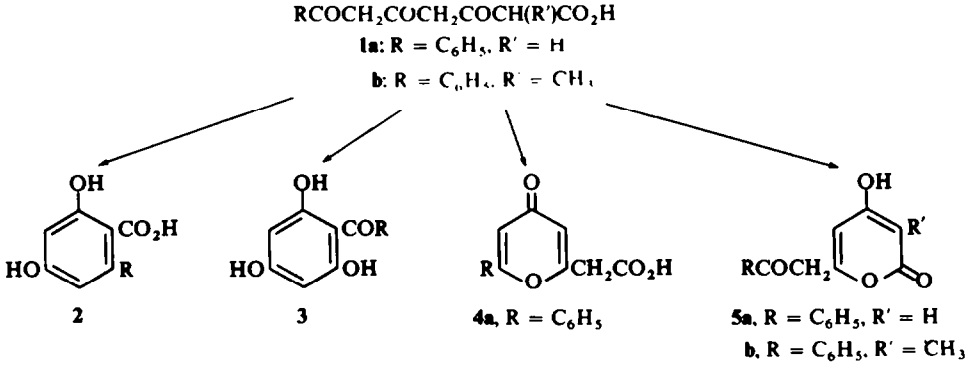
Abstract—3,5,7-Trioxo-7-phenylheptanoic acid and its 2-methyl homolog were cyclized by treatment with acetic anhydride to form the corresponding δ-lactones (or 4-hydroxy-2-pyrones). An alternative synthesis of this structural type was achieved by treatment of the trisodium salt of 1-phenyl-1,3,5-hexanetrione with carbonyl sulfide. The reaction apparently involved the corresponding triketo thiolacid, but spontaneous cyclization occurred to give the lactone. The biogenetic significance of these reactions is discussed.

3,5,7-TRIKETO acids **1** (R′ = H) are theoretically capable of cyclizing by four different dehydrative processes to form six-membered rings. Two of these cyclizations lead to phenols (**2** and **3**) and the other two to oxygen heterocyclic compounds (**4** and **5**) (see Scheme A). 3,5,7-Trioxo-7-phenylheptanoic acid (**1a**) and other triketo acids have been prepared in this laboratory and all of the cyclizations with the exception of lactone formation have been demonstrated with them and/or with the corresponding methyl esters.[1–3] The cyclizations were effected in a selective fashion leading to satisfactory yields of the individual products. We now wish to report two methods by which the fourth cyclization, lactonization, may be brought about.



SCHEME A

Lactonization of 3,5-diketo acids to form 4-hydroxy-2-pyrones has previously been accomplished by means of strong acids such as polyphosphoric acid[4] and anhydrous,

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liquid hydrogen fluoride.[5] 1,3,5-Triketones are also cyclized by strong acids, resulting in the formation of 4-pyrones.[4, 6–8] Strong acids could convert 3,5,7-triketo acids either to 4-hydroxy-2-pyrones **5** or to 4-pyrones **4**. The reaction of **1a** with anhydrous, liquid hydrogen fluoride has, in fact, been investigated and found to give entirely 4-pyrone **4a**.[2]

3,5-Diketo acids also have been lactonized by means of acetic anhydride.[9, 10] It was proposed that the reaction involves cyclization of a mixed acid anhydride.[10] A consequence of such a mechanism is that under these conditions a triketo acid should form mixed anhydride **6** which would undergo lactonization selectively.

$$RCOCH_2COCH_2COCH_2COOCOCH_3$$

6

Triketo acid **1a** was dissolved in acetic anhydride and stored for 1 hr at ambient temperature, during which time some crystals separated from the solution. The solution was cooled and the crystalline material was isolated by filtration and washed to give 74% of lactone **5a**. Crystalline **5a** existed in a number of tautomeric and/or crystalline modifications, the formation of which depended upon the solvent and method employed in crystallization. The various types of material showed little variation in melting points but wide variations in the IR spectra of potassium bromide pellets. The spectrum of a solution of **5a** in *tert.*-butanol was more informative; it showed absorption bands at 1560 and 1680 cm^{-1}. The latter is probably a composite of the stretching bands of the phenacyl and 2-pyrone carbonyl groups. The UV spectrum contained maxima at 284 (ε 9070) and 245 mμ (ε 14,400). These correspond satisfactorily to the maxima of 4-hydroxy-6-methyl-2-pyrone and acetophenone which occur at 283 (ε 6020)[11] and 242 mμ (ε 12,600),[12] respectively. The NMR spectrum showed the presence of one methylene group and two vinyl hydrogens, indicating that only one carbonyl group was enolized. The vinyl hydrogens were coupled to each other by 2 Hz.

Triketo acid **1b**, which had been prepared by carboxylation of the trianion of 1-phenyl-1,3,5-heptanetrione, was similarly treated with acetic anhydride to give pyrone **5b** in 53% yield. The structure of **5b** was substantiated by the NMR spectrum in which the methyl, the methylene, and the vinyl hydrogens appeared as singlets at appropriate chemical shifts.

The second synthesis of lactone **5a** was effected by treatment of the trianion of 1-phenyl-1,3,5-hexanetrione with carbonyl sulfide. The trianion was formed by treatment of the triketone with three equivalents of sodium amide in liquid ammonia (Scheme B). The ammonia was replaced with ether prior to addition of the carbonyl sulfide. Many years ago Weigert treated Grignard reagents with carbonyl sulfide to prepare thiolacids.[13] In the present case the thiolacid could not be detected; the only isolable product (35%) was a sulfur-free compound which was readily identified as lactone **5a**. It is probable that the thiolacid is an intermediate which spontaneously cyclizes to form the lactone either in the reaction mixture or during isolation.* The

* The other anionic sites of the trianion may also have reacted with carbonyl sulfide (i.e. to give **i**), but products resulting from this were not detected. Bis-β-ketocarboxylic acids decarboxylate spontaneously.

$$C_6H_5COCH(COSH)COCH(COSH)COCH_2COSH$$

i

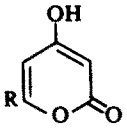
activity of thiolacids as acylating agents is much higher than that of the oxy analogs.[14]

$$C_6H_5COCH_2COCH_2COCH_3 \xrightarrow[\text{liq } NH_3]{3NaNH_2} C_6H_5CO\bar{C}HCO\bar{C}HCO\bar{C}H_2 \xrightarrow[\text{ether}]{COS} \xrightarrow[H_2O]{H^+}$$

$$[C_6H_5COCH_2COCH_2COCH_2COSH] \longrightarrow \mathbf{5a}$$

SCHEME B

The carbonyl sulfide reaction can be used for the preparation of lactones of 3,5-diketo acids. Treatment of the disodium salt of benzoylacetone with carbonyl sulfide afforded the corresponding lactone **7a** in 42% yield.*



7a, R = C_6H_5
b, R = n-C_4H_9

Although the yields of the carbonyl sulfide reactions are not high, the procedure may still be an attractive way to synthesize certain 4-hydroxy-2-pyrones. When comparisons are made between this method and the lactonization of diketo and triketo acids, it should be remembered that the latter reaction requires initial conversion of the diketone or triketone to the corresponding acid.

The carbonyl sulfide reaction is of particular interest with relation to biosynthesis of lactones of types **5** and **7**. In the current view, the poly-β-keto acids derived from acetic acid probably exist in living systems as thiol esters, either of coenzyme A or of protein thiols.[16] Our results suggest one possible manner in which the presence of a sulfur leaving group may influence the course of reactions of such compounds. The spontaneous cyclization of diketo and triketo thiolacids would appear to be a very good model for the reactions by which 4-hydroxy-6-methyl-2-pyrone,[17–20] 3,6-dimethyl-4-hydroxy-2-pyrone,[21] 6-acetonyl-4-hydroxy-2-pyrone[18] and related compounds are biosynthesized.

EXPERIMENTAL†

Lactonization of triketo acid **1a**

3,5,7-Trioxo-7-phenylheptanoic acid (**1a**)[1] (0·200 g, 0·00081 mole) was dissolved in 3 ml of acetic anhydride. After 1 hr at room temperature the solution was stored at −20° overnight. The light colored solid was separated by filtration and washed with water to give 0·138 g (74%) of 4-hydroxy-6-phenacyl-2-pyrone (**5a**), m.p. 179–181°. Recrystallization from ethanol–water gave m.p. 185·5–187·5°; NMR (CD_3SOCD_3–$CDCl_3$) δ 4·32 (2, s, 6-C$\underline{H}_2$), 5·35 (1, d, J = 2 Hz, 3-C$\underline{H}$), 6·13 (1, d, J = 2 Hz, 5-C$\underline{H}$), 7·3–8·1 ppm (5, m, $C_6\underline{H}_5$); UV (95% EtOH) 284 (ε 9070) and 245 mμ (ε 14,400). (Found: C, 67·63; H, 4·13. Calc. for $C_{13}H_{10}O_4$: C, 67·82; H, 4·38%).

The IR spectrum of the compound in potassium bromide was dependent upon the previous history of

* The reaction has also been employed for the preparation of **7b** from 2,4-octanedione in 48% yield as part of a synthesis that is described elsewhere.[15]

† Melting points were determined in open capillaries and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. IR spectra were determined with a Beckman IR-10 spectrophotometer; NMR spectra with a Varian A-60 spectrometer. Tetramethylsilane was employed as an internal standard in the NMR samples.

the sample and apparently reflected differing tautomers and crystalline modifications; (crystallization from ethanol–water) 1660, 1610–1560, 1430 cm^{-1}; (crystallization from methanol) 1700–1670, 1590, 1460 cm^{-1}. A spectrum of a solution in *tert.*-butanol showed maxima at 1680 and 1560 cm^{-1}.

Preparation of 2-methyl-7-phenyl-3,5,7-trioxoheptanoic Acid (**1b**)*

To a suspension of 0·15 mole of sodium amide in 800 ml of liquid ammonia was added 7·6 g (0·035 mole) of 1-phenyl-1,3,5-heptanetrione[22] in ethereal solution. After 3 hr, the ammonia was evaporated on the steam bath. Anhydrous ether was added simultaneously to maintain the volume of the reaction mixture. The ammonia-free, ethereal suspension was treated with lumps of dry ice causing it to change from brown to bright yellow. The mixture was added to cold, dilute HCl. The ethereal layer was separated and extracted several times with cold 5% $NaHCO_3$. The aqueous extracts were acidified immediately with cold, dilute HCl and the resulting suspension was extracted with ether. The ethereal solution was dried ($MgSO_4$) and evaporated to leave 5·1 g of a brown, crystalline solid. Recrystallization from hot chloroform–hexane gave 3·4 g (37%) of **1b** as pale yellow plates; m.p. 87·5–88°; IR (KBr) 1715, 1600, 1575 cm^{-1}. The NMR spectrum ($CDCl_3$) showed a mixture of tautomeric forms; relatively little enolization occurred at the 2-position. (Found: C, 64·30; H, 5·58. Calc. for $C_{14}H_{14}O_5$: C, 64·12; H, 5·38%).

Lactonization of triketo acid **1b**

2-Methyl-3,5,7-trioxo-7-phenylheptanoic acid (**1b**) (0·196 g, 0·00075 mole) was dissolved in 7 ml of acetic anhydride. The mixture was allowed to stand at room temperature for 16 hr and at −20° for 6 days. Filtration afforded 0·120 g (65%) of 4-hydroxy-3-methyl-6-phenacyl-2-pyrone (**5b**), m.p. 219–222°. Recrystallization was unsuccessful; however, satisfactory purification was achieved by dissolving in 5% $NaHCO_3$, filtering and acidifying with dilute HCl to give 0·097 g (53%) of **5b**; m.p. 217–219°; IR (KBr) 1670, 1635, 1570, 1405, 1255 cm^{-1}; NMR (CD_3SOCD_3–$CDCl_3$) δ 1·82 (3, s, C$\underline{H}_3$), 4·29 (2, s, C$\underline{H}_2$), 6·23 (1, s, 5-C$\underline{H}$), 7·4–8·2 ppm (5, m, $C_6\underline{H}_5$). (Found: C, 68·96; H, 5·00. Calc. for $C_{14}H_{12}O_4$: C, 68·85; H, 4·95).

Synthesis of **5a** *with carbonyl sulfide*

To a suspension of 0·130 mole of sodium amide (formed from 3·0 g of Na) in 300 ml of liquid ammonia was added 5·1 g (0·025 mole) of 1-phenyl-1,3,5-hexanetrione. The dark red solution was allowed to stir for 0·5 hr during which time some precipitation occurred. The ammonia was evaporated with the steam bath and anhydrous ether was added simultaneously. After the odor of ammonia was no longer detectable, carbonyl sulfide was bubbled into the brown suspension for 5 min, causing the reaction mixture to turn green. The ethereal slurry was poured into a mixture of ice and 30 ml of 12M HCl. The layers were separated and the ethereal layer was extracted several times with 5% $NaHCO_3$. The combined alkaline extracts were acidified quickly and filtered to yield 2·0 g (35%) of **5a** as a yellow solid, m.p. 165–167° and 186–187° after recrystallization from ethanol–water. The mixture melting point of this material with that prepared by the other method was undepressed; the NMR spectra were identical.

Synthesis of **7a** *with carbonyl sulfide*

By a comparable procedure 8·1 g (0·05 mole) of benzoylacetone was added to 0·178 mole of sodium amide in liquid ammonia to afford the dianion, which was treated (in ether) with carbonyl sulfide. The mixture was poured into a mixture of ice and 40 ml of 12M HCl. The layers were separated and the ethereal layer was extracted several times with 5% $NaHCO_3$. The alkaline extracts were acidified; filtration yielded 4·0 g (42%) of 4-hydroxy-6-phenyl-2-pyrone (**7a**), m.p. 252–254° (Lit.[5] m.p. 254–256°).

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