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Simple Preparation of Highly Pure Monomeric ω-Hydroxycarboxylic Acids

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Abstract:

Highly pure monomeric ω-hydroxycarboxylic acids (HCAs) with ≥C_6 are prepared from their corresponding lactones or alkyl ω-hydroxycarboxylates through saponification followed by H_2SO_4 acidification and treatment at 35−40 °C/8−12 mbar or by freeze-drying. The HCA is being formed through its sodium or potassium salt and is obtained in 80−85% yield with >99.5% purity, uncontaminated with dimers. This simple procedure excludes chromatographic purification.

Linear monomeric ω-hydroxycarboxylic acids containing 6−20 carbon atoms and their derivatives find multiple applications in dermopharmaceuticals and cosmetics owing to their sebum and rough skin controlling effect, in the chemical modification of surfaces as such bipolar substances form self-assembling monolayers, etc.[1] For instance, *trans*-10-hydroxy-2-decenoic and 10-hydroxydecanoic acids present in the honeybee (*Apis mellifera*) royal jelly possess anticancerous and antidiabetic properties.[2]

The most practical preparative routes of HCAs include reductive or oxidative double bond transformation (through the ozonide for example) of monounsaturated fatty acids or their corresponding alcohols, high-temperature catalytic hydrogenation of a mixture of saturated aliphatic dicarboxylic acids and the corresponding glycols,[3] mixed cross-electrochemical Kolbe condensation between ω-acyloxyacids and the monoester of a diacid,[4] synthesis from ω-chloro acids or alcohols via the malonation route, high-temperature reductive alkaline scission of fatty acids,[5] and catalyzed air oxidation of cyclohexanol and cyclohexanone in the preparation of ϵ-hydroxycaproic acid.[6]

However, as in most of these routes high temperature is often required during either the synthesis or the isolation step, the HCA is accompanied by its dimer or oligomer thus necessitating a purification step, e.g., column chromatography by gradient elution. In addition, several literature procedures regarding HCAs synthesis use Amberlite IR-120 (H^+) or aqueous HCl to acidify ω-hydroxycarboxylate salts, and they are not clear; for example, 6-hydroxycaproic acid is often mentioned to be an oil.[7] In fact, we found that heating 6-hydroxycaproic acid at 60 °C for 30 min results in the formation of 3.5% of its dimer. Also for the same HCA, different melting points are found in the literature with no NMR data proving the exclusion of dimers.

In this work,[8] we present a simple and up-scalable two-step synthesis of highly pure HCAs starting from the corresponding lactones or alkyl ω-hydroxycarboxylates, either through isolation of the ω-hydroxyacid potassium salt or in one-pot synthesis.

Pure ω-hydroxyacid potassium salt is obtained by saponification of the corresponding lactone or alkyl ω-hydroxycarboxylate with methanolic or aqueous KOH (<1 equiv) followed by concentration and rinsing of the salt. Pure HCA is then formed after acidification of the isolated potassium salt using <0.5 equiv of H_2SO_4. In one-pot synthesis, the pure HCA is obtained from the lactone using >1 equiv of base (without isolation of the potassium or sodium salt) followed by acidification with 0.5 equiv of H_2SO_4. The pure HCA is isolated after concentration of the mixture at 35−40 °C/8−12 mbar or by freeze-drying followed by extraction of the solid residue with an organic solvent. The use of H_2SO_4 is advantageous as it forms insoluble salt which does not accompany the extracted HCA (Scheme 1). The exclusion of dimers or oligomers is confirmed by ^1H and ^{13}C NMR (the characteristic signal in ^1H NMR for the dimer being at ∼4 ppm in $CDCl_3$).

Our process is attractive and up-scalable due to the ease of operating procedures excluding a chromatographic purification, involving instantaneous reactions (saponification, acidification), and easy isolation of the HCA in high yield (80−85%) and >99.5% chemical purity.

Experimental Section

Lactones C_6 and C_{15} are commercially available. Lactones C_7, C_8, and C_{12} were prepared from the corresponding ketones through Baeyer−Villiger oxidation.[9] Methyl 10-hydroxydecanoate was prepared from methyl 11-unde-

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Scheme 1

cenoate.[10] Lactone C_{11} was prepared from 11-bromoundecanoic acid.[11] Lactones were purified by distillation (>99.5% purity by GC). ICP-MS analysis of the HCAs showed a sulfur content <0.03%. Melting points were determined on a Kofler apparatus and are uncorrected. ^{1}H (299.94 MHz, internal Me_4Si) and ^{13}C NMR (75.43 MHz, internal $CDCl_3$) spectra were recorded for solutions in $CDCl_3$ or D_2O.

To determine the purity, ^{1}H NMR analysis was far more reliable than other used methods such as GC, HPLC, or titration. The use of 0.2 wt % of *p*-xylene as internal standard in ^{1}H NMR measurement has unequivocally proven the presence of HCA dimer to be well below this value. The signal of the aromatic protons of *p*-xylene in ^{1}H NMR is at δ 7.07 (s, 4 H) and is very well separated from the signals of HCAs and their dimers. ^{1}H NMR measurement with a relaxation delay $d_1 = 60$ s allows the quantitative determination of all compounds in the solution. It is noteworthy that the signal at δ 4.1 (t, 2 H) corresponding to the presence of HCA dimers was not detected in the pure samples; however, heating the pure samples at 60 °C for 30 min resulted in its appearance.

Preparation of 6-Hydroxycaproic Acid Potassium Salt: To a solution of KOH (224 g, min. 85%) in methanol (2.5 L) was added ϵ-caprolactone (456 g, 4 mol) under stirring. After addition, the mixture was concentrated to dryness on a rotary evaporator (35−40 °C/12 mbar), and the solid was washed with dry ether (2 × 1 L) to afford a white salt (586 g, 86%): mp 203−205 °C; ^{1}H NMR (D_2O) δ 1.34 (m, 2H, CH_2), 1.56 (m, 4 H, $CH_2CH_2CO_2K$, CH_2CH_2OH), 2.18 (t, $J = 7.4$ Hz, 2 H, CH_2CO_2K), 3.60 (t, $J = 6.6$ Hz, 2 H, CH_2OH).

Preparation of 6-Hydroxycaproic Acid. Method A: To a cold (0 °C) solution of 6-hydroxycaproic acid potassium salt (400 g, 2.34 mol) in water (450 mL) was added dropwise a solution of H_2SO_4 (114 g, 1.16 mol) in water (150 mL). The mixture was concentrated by freeze-drying or on a rotary evaporator (30 °C/8 mbar) and then further dried in vacuo over P_2O_5. The residue was extracted with dry ether. After concentration, a colorless solid (288 g, 93%) was obtained. Crystallin 6-hydroxycaproic acid could be obtained through recrystallization from ether/diisopropyl ether.

Method B: To a solution of KOH (276 g, min 85%) (or NaOH) in water (3.5 L) was added ϵ-caprolactone (456 g, 4 mol) under stirring. After addition, the solution was acidified at 0 °C with H_2SO_4 (114 g, 1.16 mol) in water (400 mL). The mixture was concentrated by freeze-drying and then further dried in vacuo over P_2O_5. The residue was extracted with dry ether. After concentration, a colorless solid (422 g, 80%) was obtained: mp 40−41 °C (ref 3a, mp 41.8−43.1 °C); ^{1}H NMR ($CDCl_3$) δ 1.41 (m, 2 H, CH_2), 1.63 (m, 4 H, $CH_2CH_2CO_2H$, CH_2CH_2OH), 2.36 (t, $J = 7.4$ Hz, 2 H, CH_2CO_2H), 3.65 (t, $J = 6.5$ Hz, 2 H, CH_2OH), 6. 99 (br s, 1 H, CO_2H); ^{13}C NMR ($CDCl_3$) δ 24.4, 25.1, 31.9, 33.9, 62.3, 178.8.

7-Hydroxyheptanoic Acid Potassium Salt. The product was prepared from heptanolactone: mp 210−214 °C; ^{1}H NMR (D_2O) δ 1.33 (m, 4 H, $(CH_2)_2$), 1.55 (m, 4 H, $CH_2CH_2CO_2K$, CH_2CH_2OH), 2.17 (t, $J = 7.4$ Hz, 2 H, CH_2CO_2K), 3.60 (t, $J = 6.6$ Hz, 2 H, CH_2OH).

7-Hydroxyheptanoic Acid. The product was prepared from its potassium salt: mp 43−44 °C (ref 12 appeared to be a syrup); ^{1}H NMR ($CDCl_3$) δ 1.39 (m, 4 H, $(CH_2)_2$), 1.53−1.71 (m, 4 H, $CH_2CH_2CO_2H$, CH_2CH_2OH), 2.36 (t, $J = 7.4$ Hz, 2 H, CH_2CO_2H), 3.65 (t, $J = 6.6$ Hz, 2 H, CH_2OH), 5.60 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.6, 25.3, 28.7, 32.3, 33.9, 62.8, 179.2.

8-Hydroxyoctanoic Acid Potassium Salt. The product was prepared from octanolactone: mp 227−230 °C; ^{1}H NMR (D_2O) δ 1.32 (m, 6 H, $(CH_2)_3$), 1.55 (m, 4 H, $CH_2CH_2CO_2K$, CH_2CH_2OH), 2.17 (t, $J = 7.4$ Hz, 2 H, CH_2CO_2K), 3.60 (t, $J = 6.6$ Hz, 2 H, CH_2OH).

8-Hydroxyoctanoic Acid. The product was prepared from its potassium salt: mp 60−61.5 °C (ref 13 57−58 °C); ^{1}H NMR ($CDCl_3$) δ 1.36 (m, 6 H, $(CH_2)_3$), 1.51−1.71 (m, 4 H, $CH_2CH_2CO_2H$, CH_2CH_2OH), 2.35 (t, $J = 7.3$ Hz, 2 H, CH_2CO_2H), 3.65 (t, $J = 6.6$ Hz, 2 H, CH_2OH), 5.88 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.6, 25.5, 28.9, 32.5, 34.0, 62.8, 179.3.

10-Hydroxydecanoic Acid Potassium Salt. The product was prepared from methyl 10-hydroxydecanoate. The salt was washed with dry tetrahydrofuran: mp 244−248 °C; ^{1}H NMR (D_2O) δ 1.29 (m, 10 H, $(CH_2)_5$), 1.53 (m, 4 H, $CH_2CH_2CO_2K$, CH_2CH_2OH), 2.16 (t, $J = 7.3$ Hz, 2 H, CH_2CO_2K), 3.58 (t, $J = 6.6$ Hz, 2 H, CH_2OH).

10-Hydroxydecanoic Acid. The acidification of 10-hydroxydecanoic acid potassium salt was carried out in water/tetrahydrofuran (2:1): mp 74−75 °C (ref 14 mp 75 °C); ^{1}H NMR ($CDCl_3$) δ 1.31 (m, 10 H, $(CH_2)_5$), 1.52−1.68 (m, 4 H, $CH_2CH_2CO_2H$, CH_2CH_2OH), 2.35 (t, $J = 7.3$ Hz, 2 H, CH_2CO_2H), 3.65 (t, $J = 6.6$ Hz, 2 H, CH_2OH); ^{13}C NMR ($CDCl_3$) δ 24.6, 25.6, 29.0, 29.1, 29.3 (2 s), 32.7, 33.9, 63.0, 179.3.

11-Hydroxyundecanoic Acid Potassium Salt. The product was prepared from undecanolactone. The salt was washed with dry tetrahydrofuran: mp 236−243 °C; ^{1}H NMR (D_2O) δ 1.30 (m, 12 H, $(CH_2)_6$), 1.54 (m, 4 H, $CH_2CH_2CO_2H$, CH_2CH_2OH), 2.17 (t, $J = 7.4$ Hz, 2 H, CH_2CO_2H), 3.59 (t, $J = 6.7$ Hz, 2 H, CH_2OH).

11-Hydroxyundecanoic Acid. The acidification of 11-hydroxyundecanoic acid potassium salt was carried out in water/tetrahydrofuran (2:1): mp 65−66 °C (ref 15 mp 62−63 °C); ^{1}H NMR ($CDCl_3$) δ 1.31 (m, 12 H, $(CH_2)_6$),

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1.52−1.71 (m, 4 H, $CH_2CH_2CO_2H$, CH_2CH_2OH), 2.36 (t, J = 7.4 Hz, 2 H, CH_2CO_2H), 3.66 (t, J = 6.6 Hz, 2 H, CH_2OH), 5.55 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.7, 29.0, 29.1, 29.3 (2 s), 29.4, 32.7, 33.9, 63.1, 179.2.

12-Hydroxydodecanoic Acid Potassium Salt. The product was prepared from dodecanolactone. The salt was washed with dry tetrahydrofuran: mp 231−233 °C; ^1H NMR (D_2O) δ 1.29 (m, 14 H, $(CH_2)_7$), 1.54 (m, 4 H, $CH_2CH_2CO_2H$, CH_2CH_2OH), 2.16 (t, J = 7.4 Hz, 2 H, CH_2CO_2H), 3.59 (t, J = 6.7 Hz, 2 H, CH_2OH).

12-Hydroxydodecanoic Acid. The acidification of 12-hydroxydodecanoic acid potassium salt was carried out in water/tetrahydrofuran (2:1): mp 84−85 °C (ref 16 84−85 °C); ^1H NMR ($CDCl_3$) δ 1.30 (m, 14 H, $(CH_2)_7$), 1.51−1.69 (m, 4 H, $CH_2CH_2CO_2H$, CH_2CH_2OH), 2.35 (t, J = 7.4 Hz, 2 H, CH_2CO_2H), 3.65 (t, J = 6.6 Hz, 2 H, CH_2OH); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.7, 28.9, 29.1, 29.3 (3 s), 29.4, 32.7, 33.9, 63.1, 179.3.

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15-Hydroxypentadecanoic Acid Potassium Salt. The product was prepared from cyclopentadecanolide. The salt was washed with dry tetrahydrofuran: mp 220−225 °C.

15-Hydroxypentadecanoic Acid. The acidification of 15-hydroxypentadecanoic acid potassium salt was carried out in water/tetrahydrofuran (2:1): mp 86−87 °C (ref 17 85−85.5 °C); ^1H NMR ($CDCl_3$) δ 1.23−1.41 (m, 20 H, $(CH_2)_{10}$), 1.52−1.68 (m, 4 H, $CH_2CH_2CO_2H$, CH_2CH_2OH), 2.35 (t, J 7.4 Hz, 2 H, CH_2CO_2H), 3.65 (t, J = 6.6 Hz, 2 H, CH_2OH); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.7, 29.0, 29.2, 29.3, 29.4, 29.5 (4 s), 32.8, 33.8, 63.1, 178.4.

Supporting Information Available

^1H and ^{13}C NMR spectra of C_6, C_7, C_8, C_{10}, C_{11}, C_{12}, and C_{15} ω-hydroxycarboxylic acids and of C_6 and C_{11} accompanied by their dimers. This material is available free of charge via the Internet at http://pubs.acs.org.

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