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Synthesis of ω-(4-hydroxyphenyl)alkanecarboxylic acids

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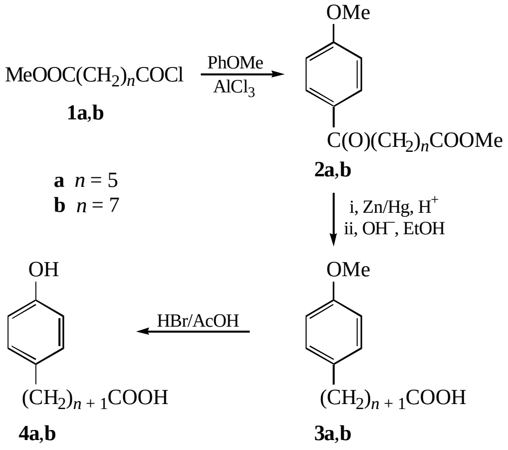
The title carboxylic acids were synthesised in six steps starting from α,ω-alkanedicarboxylic acids.

Alkylphenol ethoxylates are widely used nonionic surfactants, which are considered as extremely dangerous water pollutants. These compounds undergo degradation and biodegradation in the environment to form stable alkylphenols such as nonylphenol and octylphenol.[1] Nonylphenol exhibits high toxicity at concentrations as low as 0.04–5 mg dm^{-3}.[2–5] However, the estrogenic activity of alkylphenols is most hazardous because it is responsible for the reproductive toxicity towards aquatic organisms at much lower pollutant concentrations.[6,7]

Gas chromatography with mass-spectrometric detection (GC–MS)[8,9] and liquid chromatography[10–12] can detect nonionic surfactants and their metabolites at low concentrations. However, these sophisticated and expensive techniques are inappropriate for routine analysis. Immunoassay methods, which are in current use for monitoring environmental and biological materials, exhibit advantages over traditional analytical methods in terms of efficiency, rapidity and simplicity of performance. Immunoassay can be successfully used for the detection of environmental pollutants at a level of 0.005–0.01 ng cm^{-3} under field conditions. The key step in the development of an immunoassay procedure is the production of antibodies that recognize and bind the target analyte with high affinity and specificity.[13] The generation of antibodies to low-molecular-weight analytes, such as alkylphenols, is a challenge because small molecules are non-immunogenic and require conjugation to carrier proteins in order to elicit an immune response.[14] Because alkylphenols bear no functional groups capable of conjugation to a carrier, they should be subjected to derivatization. On the one hand, the derivatization protocol should provide an active group enabling the covalent linkage to amino acid side chains of the protein, and, on the other, it should keep free the important antigenic determinants of a target molecule. It was found that a linker between the target structure and the carrier is best to have a length of 3 to 6 methylene groups, which is optimal to avoid a shielding effect of the carrier and to expose the attached molecule to the immune system.[15,16] The most frequently used carrier proteins are keyhole limpet hemocyanin, bovine serum albumin (BSA), tyroglobulin, ovalbumin and conalbumin.[17,18]

In this work, we suggest a full synthetic route for alkylphenol derivatives, ω-(4-hydroxyphenyl)nonanoic and ω-(4-hydroxyphenyl)heptanoic acids. These compounds contain active terminal carboxyl groups and can be covalently attached to the ε-amino groups of BSA lysine residues, and the resulting conjugates can be used for the immunisation of rabbits and for the production of polyclonal antibodies to alkylphenol ethoxylates and alkylphenols as their metabolites. Because both the target compounds and the synthesised derivatives contain hydroxyphenyl rings, it may be expected that antibodies to the derivatives will bind specifically to the target compounds. The length of a linker of 6 to 8 methylene groups ensures that the target structure is physically distant from the carrier protein surface; moreover, it may also be expected that alkyl chains will contribute to the antibody recognition of target alkylphenols.

A retrosynthetic analysis of ω-(4-hydroxyphenyl)alkanecarboxylic acids leads to a reasonable procedure that involves the alkylation of anisole by a corresponding ω-haloalkanecarboxylic acid. Unfortunately, this procedure was unsuccessful because under conditions of the Friedel–Crafts reaction the alkyl group of the acid easily undergoes isomerization. Simultaneously, polysubstitution in anisole can also occur at different binding sites. Note that long-chain haloalkanecarboxylic acids are not easily available.



Scheme 1

Contrary to the alkylation, the acylation of anisole by appropriate carbonyl compounds followed by the reduction of the carbonyl group seems to be the most convenient procedure. This reaction sequence was used for the synthesis of 4-(4-hydroxyphenyl)butyric acid[19] and 7-(4-hydroxyphenyl)heptanoic acid[20] (no experimental details were published in the latter case).

The reaction between an α,ω-dicarboxylic acid and an equimolar amount of its dimethyl ester leads to the monomethyl ester of the dicarboxylic acid; the subsequent addition of $SOCl_2$ affords ω-methoxycarbonylalkanecarboxylic acid chlorides **1a**,**b**. Anisole was quantitatively acylated at the para position by compounds **1a**,**b**, which were used without special purification; alkyl chain isomerization was not observed.† The reduction of carbonyl groups in **2a**,**b** according to the modified Clemmensen method in a two-phase system resulted in partial hydrolysis of esters **2a**,**b**. A mixture of the above acids and their esters was refluxed in an alkaline medium to provide the full hydrolysis of the esters. ω-(4-Methoxyphenyl)alkanecarboxylic acids **3a**,**b** were obtained in good yields.‡

The protective methyl group of the 4-hydroxyphenyl moiety of **3a**,**b** was removed with the use of an HBr solution in glacial acetic acid, and compounds **4a**,**b** were obtained.§

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† *Methyl 7-(4-methoxyphenyl)-7-oxoheptanoate* **2a** *and methyl 9-(4-methoxyphenyl)-9-oxononanoate* **2b**. The methyl esters of dicarboxylic acid chlorides **1a**,**b** were synthesised by a well-known method[21] using monomethyl dicarboxylates and thionyl chloride in benzene. To a solution of 8.1 g of anisole (75 mmol) in dichloroethane (46 ml), 18 g of anhydrous $AlCl_3$ (0.24 mol) was added with stirring at 0 °C. Next, 68 mmol of **1a**,**b** in dichloroethane (10 ml) was added on cooling with stirring. The reaction mixture was allowed to stand for 3 h on cooling and then for 1 h at room temperature. Next, it was poured onto ice, and 50 ml of 6 M HCl was added. The solution was extracted with Et_2O (2×50 ml), and the organic layer was washed with H_2O (2×50 ml). The solvent was evaporated to dryness in a vacuum; H_2O (10 ml) was added to the residue and evaporated to dryness (this procedure was repeated three times).

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[‡] *7-(4-Methoxyphenyl)heptanoic acid* **3a** *and 9-(4-methoxyphenyl)-nonanoic acid* **3b**. To a suspension of Zn (30 g) in a 5% $(AcO)_2Hg$ solution (50 ml), 53.25 mmol of **2a**,**b** in toluene (30 ml), H_2O (22.5 ml) and HCl (52.5 ml) were added with stirring. The reaction mixture was refluxed for 6 h. Next, HCl (15 ml) was added, and the mixture was additionally refluxed for 6 h (this procedure was repeated three times). The solution was extracted with diethyl ether (3×50 ml), and the extract was dried with Na_2SO_4. The solvent was evaporated to dryness; toluene traces were evaporated with CCl_4. The residue (a mixture of **3a**,**b** and their methyl esters) was dissolved in 40 ml of EtOH, and a 10% NaOH solution (40 ml) was added. This slurry was refluxed for 6 h; EtOH was evaporated, and H_2O (40 ml) and HCl were added until the end of the precipitate formation. The precipitate was filtered off, washed with cold water and dried.

[§] *7-(4-Hydroxyphenyl)heptanoic acid* **4a** *and 9-(4-hydroxyphenyl)-nonanoic acid* **4b**. A mixture of **3a**,**b** (19 mmol), 48% HBr (15 ml) and glacial acetic acid (15 ml) was refluxed for 6 h. The solvent was evaporated to dryness; the residue was treated with a 5% NaOH solution (25 ml) and activated charcoal and refluxed for 0.5 h. The hot solution was filtered and treated with 3 ml of HCl. The precipitate formed was recrystallised from dilute EtOH.

NMR spectra were measured on a BS-467 spectrometer at 60 MHz with HMDS as an internal standard.

2a: yield 97%, mp 46 °C.[22] ^{1}H NMR ($CDCl_3$) δ: 8.15 (d, 2H, Ph, *o*-H, *J* 8 Hz), 7.13 (d, 2H, Ph, *m*-H, *J* 8 Hz), 4.18 (s, 3H, *Me*–O–Ph), 4.02 (s, 3H, AcO), 3.28 (t, 2H, CH_2–CO–Ph, *J* 6 Hz), 2.73 (t, 2H, CH_2COO), 1.90 [br. m, 6H, $(CH_2)_3$]. MS, *m*/*z*: 264 [M$^+$].

2b: yield 92%, mp 82 °C. ^{1}H NMR ($CDCl_3$) δ: 8.05 (d, 2H, Ph, *o*-H, *J* 8 Hz), 7.08 (d, 2H, Ph, *m*-H, *J* 8 Hz), 4.1 (s, 3H, *Me*–O–Ph), 3.90 (s, 3H, AcO), 3.20 (t, 2H, CH_2–CO–Ph, *J* 6 Hz), 2.70 (t, 2H, CH_2COO), 1.76 [br. m, 10H, $(CH_2)_5$]. MS, *m*/*z*: 292 [M$^+$].

3a: yield 83%, mp 81 °C. ^{1}H NMR ($CDCl_3$) δ: 10.80 (s, 1H, COOH), 7.33 (d, 2H, Ph, *m*-H, *J* 8 Hz), 7.15 (d, 2H, Ph, *o*-H, *J* 8 Hz), 4.1 (s, 3H, MeO), 2.65 (br. m, 4H, CH_2Ph, CH_2CO), 1.93 [br. m, 8H, $(CH_2)_4$]. MS, *m*/*z*: 236 [M$^+$].

3b: yield 85%, mp 50–52 °C. ^{1}H NMR ($CDCl_3$) δ: 10.60 (s, 1H, COOH), 7.23 (d, 2H, Ph, *m*-H, *J* 8 Hz), 6.96 (d, 2H, Ph, *o*-H, *J* 8 Hz), 4.1 (s, 3H, MeO), 2.75 (br. m, 4H, CH_2Ph, CH_2CO), 1.86 [br. m, 12H, $(CH_2)_6$]. MS, *m*/*z*: 264 [M$^+$].

4a: yield 70%, mp 84 °C. ^{1}H NMR ([$^2H_6$]acetone) δ: 7.53 (br. s, 1H, PhO*H*), 6.72 (d, 2H, Ph, *m*-H, *J* 8 Hz), 6.35 (d, 2H, Ph, *o*-H, *J* 8 Hz), 2.10 (br. m, 4H, CH_2Ph, CH_2CO), 1.24 [m, 8H, $(CH_2)_4$]. MS, *m*/*z*: 222 [M$^+$].

4b: yield 80.5%, mp 66 °C. ^{1}H NMR ([$^2H_6$]acetone) δ: 7.20 (br. s, 1H, PhO*H*), 6.66 (d, 2H, Ph, *m*-H, *J* 8 Hz), 6.43 (d, 2H, Ph, *o*-H, *J* 8 Hz), 2.40 (br. m, 4H, CH_2Ph, CH_2CO), 1.42 [m, 12H, $(CH_2)_6$]. MS, *m*/*z*: 250 [M$^+$].