Synthesis of 6- and 9-Ethyloctadecanoic Acids

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Summary

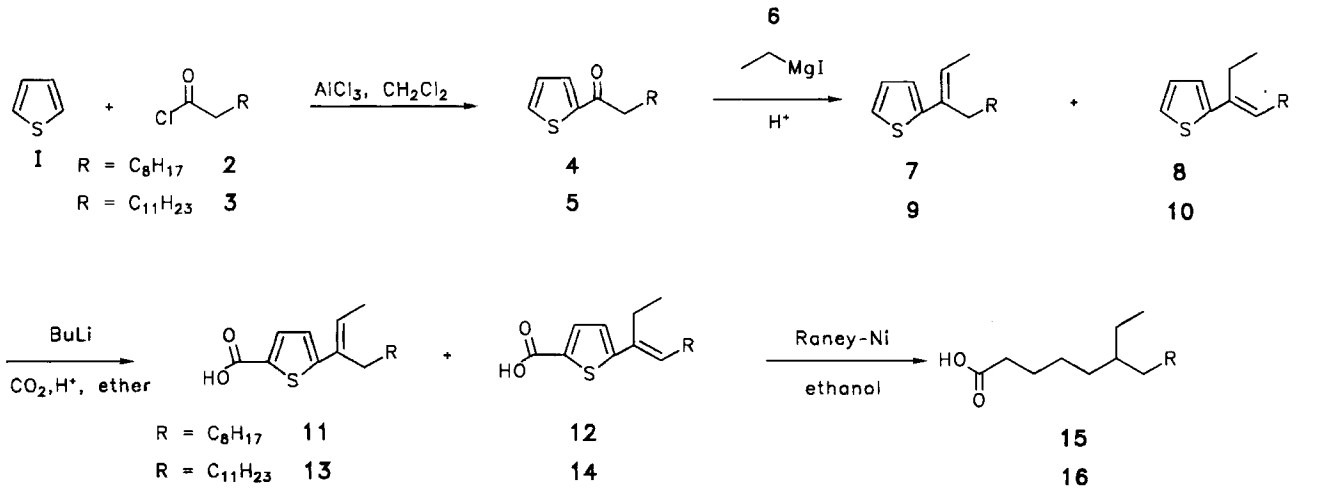
Specific branched fatty acids are of great interest in the search of a new type of drug penetration enhancers across human skin for transdermal drug delivery and in gaining an understanding of structure-activity relationships with skin lipids. A convenient synthesis has therefore been developed especially for ethyloctadecanoic acids. The successful syntheses of 6- and 9-ethyloctadecanoic acids are reported here.

Introduction

Studies on human skin aimed at improving transdermal drug delivery have been carried out, among other methods, by applying fatty acids to enhance the penetration of drugs, in view of the fact that various free fatty acids are substantial components of the skin. Branched chain alcohols (e.g. 2-octyl-dodecanol)[1], fatty acids (especially unsaturated, e.g. oleic acid)[2] and branched fatty acid esters (e.g. cetyl 2-ethylhexanoate)[3] have been used as skin penetration enhancers for a long time. It is, therefore, a logical step to investigate the permeation effects of branched fatty acids in dependence on their structural variations. There has been a report that certain branched fatty acids may have potential enhancing effects[4]. Since most branched fatty acids are not readily available in nature, it is necessary to develop convenient synthetic procedures for fatty acids branched at various positions.

Among the various pathways[5–8], an elegant procedure is developed specifically for ethyloctadecanoic acids, i.e. 6- and 9-ethyloctadecanoic acids (see Scheme 1). Thiophene (**1**) is frequently used as a precursor in the synthesis of long chain hydrocarbons and fatty acids[9–11]. Thiophene was acylated with decanoyl chloride (**2**) or tridecanoyl chloride (**3**) in a Friedel-Crafts reaction to yield 2-decanoyl thiophene (**4**) and 2-tridecanoyl thiophene (**5**), respectively. The catalyst used was $AlCl_3$[12]. The product was alkylated at the carbonyl function using the Grignard reagent of ethyl iodide (**6**). The resulted tertiary alcohol is dehydrated and two isomers were obtained from each reaction. The two isomers were 3-(2′-thienyl)-2-dodecene (**7**) and 3-(2′-thienyl)-3-dodecene (**8**), as well as 3-(2′-thienyl)-2-pentadecene (**9**) and 3-(2′-thienyl)-3-pentadecene (**10**).

In the next step the isomers were deprotonated by butyl-lithium at the 5′ position of thiophene, which is the most acidic one. The activated isomers were then brought into contact with dry ice to accomplish carboxylation. After work up 2-(dodec-2′-en-3′-yl)-thiophene-5-carboxylic acid (**11**) and 2-(dodec-3′-en-3′-yl)-thiophene-5-carboxylic acid (**12**), as well as 2-(pentadec-2′-en-3′-yl)-thiophene-5-carboxylic acid (**13**) and 2-(pentadec-3′-en-3′-yl)-thiophene-5-carboxylic acid (**14**), were obtained. At this point the thiophene ring can be opened by Raney-Nickel desulphuration and hydrogenation. The product ethyl ester was hydrolysed yielding 6-ethylpentadecanoic acid (**15**) and 6-ethyloctadecanoic acid (**16**) as end product. 6-Ethylpentadecanoic acid (**15**) underwent chain extension at the carboxyl function side in a radical



Scheme 1

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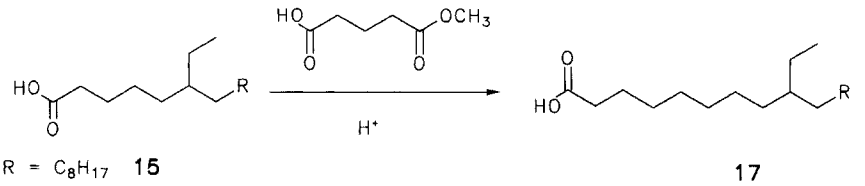

Scheme 2

type Kolbe reaction with monomethyl ester of glutaric acid by the application of current (see Scheme 2). The intermediate ester was hydrolysed yielding the other end product, 9-ethyloctadecanoic acid (**17**). Reaction products (intermediates) were purified either by distillation or by a column chromatography. Rough purity analysis was performed by NMR spectroscopy and the purity analysis of the final product was performed on its methyl ester derivative applying GC-MS.

Experimental

The ^{1}H NMR spectra were recorded on a JNM FX-200 NMR spectrometer (Jeol, Tokyo, Japan) on around 20 mg of material dissolved in 0.5 ml of 99% deuterated chloroform. The ^{13}C NMR spectra were also recorded on a JNM FX-200 (at 50 MHz) NMR spectrometer on around 50 mg of material dissolved in 0.5 ml of 99% deuterated chloroform. The IR spectra were recorded on a SP3-200 spectrophotometer. The mass spectrum for the methyl ester of 6-ethyloctadecanoic acid was recorded on an ITD 700 Mass Spectrometer equipped with a Packard Gas Chromatographic instrument.

*Tridecanoyl Chloride (**3**)*

Tridecanoic acid (24 g, 0.12 mol) and thionyl chloride (30 ml) were refluxed for 2 h in a 250 ml round-bottom flask. The escaping gasses were trapped in a bottle filled with water. The unreacted thionyl chloride was evaporated under reduced pressure. Yield: tridecanoyl chloride 24 g; 92%.

^{1}H NMR: δ(ppm) 2.88 (t, 2H, J = 7.2 Hz, H-2), 1.69 (m, 2H H-3), 1.27 (18H, CH_2's), 0.88 (t, 3H, J = 6.5 Hz, H-13).

*2-Decanoylthiophene (**4**)*

To $AlCl_3$ (44 g, 0.33 mol) in 260 ml dry CH_2Cl_2 cooled in an ice/salt-bath to –6 °C was quickly added decanoyl chloride(**2**) (38.2 g, 0.200 mol) and the mixture was stirred for 15 min. Thiophene (20.2 g, 0.240 mol) in 10 ml CH_2Cl_2 was slowly added while the ice bath was kept below –5 °C, followed by stirring for 30 min. For separation the mixture was poured into a mixture of 30 ml HCl (conc.), 300 ml water, and 120 g ice. The organic fraction was washed with water, brine and concentrated Na_2CO_3. After drying with $MgSO_4$ and evaporation of the solvent the crude product was distilled under reduced pressure.

Yield: 43 g 2-decanoyl thiophene (**3**); 90 %. b.p. 122 °C at 0.5 mm Hg.

^{1}H NMR: δ(ppm) 7.70 (dd, 1H, J = 3.78 Hz; 1.03 Hz, H-5′), 7.62 (dd, 1H, J = 4.79 Hz; 3.78 Hz, H-3′), 7.12 (dd, 1H, J = 4.79 Hz; 3.78 Hz, H-4′), 2.89 (t, 2H, J = 7.2 Hz, H-2), 1.72 (m, 2H, H-3), 1.27 (m, 12H, CH_2's), 0.87 (m, 3H, CH_3).

*2-Tridecanoylthiophene (**5**)*

To $AlCl_3$ (22 g, 0.17 mol) in 200 ml dry CH_2Cl_2 cooled in an ice/salt-bath to –6 °C was quickly added tridecanoyl chloride (**3**) (24 g, 0.10 mol) and the mixture was stirred for 15 min. Thiophene (11.0 g, 0.13 mol) in 10 ml CH_2Cl_2 was slowly added while the ice bath was kept below –5 °C, followed by stirring for 30 min. For separation, the mixture was poured into a mixture of 15 ml HCl (conc.), 150 ml of water, and 120 g ice. The organic fraction was washed with water, brine and concentrated Na_2CO_3. After drying with $MgSO_4$ and evaporation of the solvent the crude product was distilled under reduced pressure.

Yield: 27.2 g 2-tridecanoyl thiophene (**5**); 94 %. b.p. 140 °C at 0.5 mm Hg.

^{1}H NMR: δ(ppm) 7.70 (dd, 1H, J = 1.03 and 3.77 Hz, H-5′), 7.61 (dd, 1H, J = 1.37 and 5.15 Hz, H-3′), 7.12 (dd, 1H, J = 3.78 and 5.15 Hz, H-4′), 2.89 (t, 2H, J = 7.5 Hz, H-2), 1.74 (m, 2H, H-3), 1.26 (18H, CH_2's), 0.88 (t, 3H, H-13).

*3-(2′Thienyl)-2-dodecene (**7**) and 3-(2′Thienyl)-3-dodecene (**8**)*

2-Decanoyl thiophene (**4**) (42.9, 0.180 mol) in 50 ml diethyl ether was added slowly into the cooled flask containing freshly prepared Grignard reagent, ethylmagnesium iodide (**6**) and the mixture was vigorously stirred for 1 h at room temperature. The mixture was then poured into 350 ml saturated NH_4Cl and 220 g ice and stirred for 30 min. The water fraction was separated and extracted twice with diethyl ether. The extract was combined with organic fractions and the mixture was washed with water and brine, then dried with $MgSO_4$. The resulting tertiary alcohol was dehydrated by adding 1.7 g oxalic acid and a tiny amount of hydroquinone and heating for 30 min at 90 °C. The addition of hydroquinone was necessary to prevent polymerisation[8]. The product was taken up in diethyl ether and the organic fraction was washed with water and saturated Na_2CO_3 solution, dried with $MgSO_4$ and concentrated *in vacuo*. Distillation was carried out under reduced pressure again in the presence of a small amount of hydroquinone.

Yield: 37 g 3-(2′-thienyl)-2-dodecene and 3-(2′-thienyl)-3-dodecene both in *E* and *Z* configurations; 82%.

^{1}H NMR: δ(ppm) 7.23, 7.03 and 6.96 (m, 3H, thienyl hydrogens), 5.90 (m, 1H, H-4 **8**), 5.59 (m, 1H, H-2 **7**), 2.47 (m, 2H, H-5 **8**), 2.15 (m, 2H, H-4 **7**), 1.78 (m, 2H, H-2 **8**), 1.50 (m, 3H, H-1 **7**), 1.26 (12H, CH_2's), 1.09 (m, 4H, H-5 **7** and H-6 **8**), 0.85 (m, 6H, H-1 **8** and H-12).

*3-(2′-Thienyl)-2-pentadecene (**9**) and 3-(2′-Thienyl)-3-pentadecene (**10**)*

2-Tridecanoyl thiophene (**5**) (27 g, 0.10 mol) in 50 ml diethyl ether was added slowly to a cooled flask containing freshly prepared Grignard reagent, ethylmagnesium iodide (**6**) and the mixture was vigorously stirred for 1 h at room temperature. The mixture was then poured onto 200 ml saturated NH_4Cl and 130 g ice and stirred for 30 h. The water fraction was separated and extracted twice with diethyl ether. The extract was combined with organic fractions and the mixture was washed with water and brine and dried with $MgSO_4$. The resulting tertiary alcohol was dehydrated by adding 0.9 g oxalic acid and a tiny amount of hydroquinone and heating for 30 min at 90 °C. The product was taken up in diethyl ether and the organic fraction was washed with water and saturated Na_2CO_3 solution, dried with $MgSO_4$ and concentrated *in vacuo*. Distillation was carried out under reduced pressure again in the presence of a small amount of hydroquinone.

Yield: 23 g 3-(2′-thienyl)-2-pentadecene and 3-(2′-thienyl)-3-pentadecene; 81%.

^{1}H NMR: δ(ppm) 7.17, 7.06, 6.93 and 6.84 (m, 3H, thienyl hydrogens), 5.90 (m, 1H, H-4 **10**), 5.60 (m, 1H, H-2 **9**), 2.47 (m, 2H, H-5 **10**), 2.20 (m, 2H, H-4 **9**), 1.80 (m, 2H, H-2 **10**), 1.25 (15H, CH_2's and H-1 **9**), 1.09 (m, 4H, H-5 **9** and H-6 **10**), 0.85 (m, 6H, H-1 **10** and H-12).

*2-(Dodec-2′-en-3′-yl)-thiophene-5-carboxylic acid (**11**) and 2-(Dodec-3′-en-3′-yl)-thiophene-5-carboxylic Acid (**12**)*

The two isomeric products from the Grignard reaction (**7**) and (**8**) (in total 30 g, 0.120 mol) were dissolved in 200 ml dry diethyl ether under nitrogen and 100 ml butyl-lithium in hexane (0.16 mol) was slowly added at room temperature. The mixture was refluxed for 15 min. After cooling to room temperature, the mixture was gently brought into contact with dry ice submerged in 300 ml diethyl ether. Carbon dioxide reacts with the anionic carbon of the thienyl compound thus forming a carboxylate anion of the desired intermediate. After the mixture had reached 0 °C, 500 ml water was added. The organic fraction was separated and extracted with 120 ml 0.07 N NaOH, subsequently the extract was added into the first water fraction and acidified with 2 M H_2SO_4 to pH 1. The mixture was extracted thrice with

diethyl ether. The organic fraction was washed with brine and dried with $MgSO_4$ and concentrated *in vacuo*.

Yield: 21.5 g 2-(dodec-2′-en-3′-yl)-thiophene-5-carboxylic acid (**11**) and 2-(dodec-3′-en-3′-yl)-thiophene-5-carboxylic acid (**12**) both in *E* and *Z* configurations; 60%

^{1}H NMR: δ(ppm) **11**: 7.79 (d, 1H, *J* = 1.4 Hz, H-4′), 6.94 (d, 1H, H-3′), 5.70 (m, 1H, H-2), 2.17 (m, 2H, H-4), 1.40 (m, 3H, H-1), 1.26 (12H, CH_2's), 1.09 (m, 2H, H-5), 0.85 (3H, H-12).

^{1}H NMR: δ(ppm) **12**: 7.73 (d, 1H, *J* = 1.37 Hz, H-4′), 6.94 (d, 1H, H-3′), 6.07 (m, 1H, H-4), 2.46 (m, 2H, H-5), 1.81 (m, 2H, H-2), 1.26 (10H, CH_2's) 1.09 (m, 2H, H-6), 0.85 (6H, H-1 and H-12).

2-(Pentadec-2′-en-3′-yl)-thiophene-5-carboxylic Acid (**13**) *and 2-(Pentadec-3′-en-3′-yl)-thiophene-5-carboxylic Acid* (**14**)

The two isomeric products (**9**) and (**10**) from the Grignard reaction (in total 23 g, 0.08 mol) were dissolved in 100 ml dry diethyl ether under nitrogen and 80 ml butyl-lithium in hexane (0.13 mol) was slowly added at room temperature. The mixture was refluxed for 15 min. After cooled to room temperature, the mixture was gently brought into contact with dry ice submerged in 200 ml diethyl ether. After the mixture had reached 0 °C, 400 ml water was added. The organic fraction was separated and extracted with 120 ml 0.07 N NaOH, subsequently the extract was added into the water fraction and acidified with 2 M H_2SO_4 to pH 1. The mixture was extracted thrice with diethyl ether. The ether fraction was washed with brine and dried with $MgSO_4$ and concentrated in vacuo. Yield: 13.5 g 2-(pentadec-2′-en-3′-yl)-thiophene-5-carboxylic acid (**13**) and 2-(pentadec-3′-en-3′-yl)-thiophene-5-carboxylic acid (**14**); 51%

^{1}H NMR: δ(ppm) **13**: 7.79 (d, 1H, *J* = 1.4 Hz, H-4′), 6.95 (1H, H-3′) 5.67 (m, 1H, H-2), 2.17 (m, 2H, H-4), 1.40 (m, 3H, H-1), 1.26 (18H, CH_2's), 1.09 (m, 2H, H-5), 0.85 (3H, H-15).

^{1}H NMR: δ(ppm) **14**: 7.73 (d, 1H, *J* = 1.37 Hz, H-4′), 6.94 (d, 1H, H-3′), 6.07 (m, 1H, H-4), 2.46 (m, 2H, H-5), 1.81 (m, 2H, H-2), 1.26 (16H, CH_2's) 1.09 (m, 2H, H-6), 0.85 (6H, H-1 and H-15).

6-Ethylpentadecanoic Acid (**15**)

The carboxylation products (**11**) and (**12**) (12 g, 0.40 mol) dissolved in 300 ml dry ethanol were refluxed while 120 g of Raney-Nickel was added over a period of 2.5 h. Refluxing was continued for 2 h then the mixture was hot-filtered and the solid portion was washed thrice with 100 ml portions of boiling ethanol and once with 100 ml boiling ethanol:acetic acid (20:1). The fluid was concentrated to a volume of around 25 ml. A solution of 20 g NaOH in 50 ml water was added and this mixture refluxed for 3 h as to accomplish hydrolysis of the intermediate ethyl ester to 6-ethylpentadecanoic acid (**15**).

Yield: 6.4 g 6-ethylpentadecanoic acid; 58%.

^{1}H NMR: δ(ppm): 2.35 (t, 2H, *J* = 7.55 Hz, H-2), 2.00 (m, 1H, H-6), 1.60 (m, 2H, H-3), 1.26 (22H, CH_2's), .85 (6H, H-1 and H-15).

6-Ethyloctadecanoic Acid (**16**)

The carboxylation products (**13**) and (**14**) (12 g, 0.36 mol) and 250 ml dry ethanol were refluxed while 80 g of Raney-Nickel were added over a period of 2.5 h. Refluxing was continued for 2 h then the mixture was hot-filtered. The mixture was concentrated in vacuo. Hydrolysis was carried out in 20 ml water, 2 ml ethanol and 5 g sodium hydroxide.

Yield: 1.5 g 6-ethyloctadecanoic acid (**16**); 14%.

Purification was performed using preparative column chromatography eluted with petroleum ether:diethyl ether = 10:5, continued by dichloromethane:diethyl ether = 20:1. The product 6-ethyloctadecanoic acid was converted to its methyl ester for identification by mass spectrometry by reacting the acid with diazomethane[13].

^{1}H NMR: δ(ppm) 2.35 (t, 2H, *J* = 7.4 Hz, H-2), 1.98 (m, 1H, H-6), 1.60 (m, 2H, H-3), 1.26 (28H, CH_2's), 0.85 (6H, CH_3's). IR (film) ν = 3500–2400, 1705, 1460, 1410, 1380, 1285, 1240, 940, 715 cm^{-1}. GC: purity found 85.6%. m.p. 26.5°C; d_{20}^{20} 0.8675; n_{20}^{D} 1.453.

MS (EI) *m/e* (rel. int,.): 55(100), 74(68), 87(50), 97(42), 115(36), 130(35), 135(1), 149(10), 150(10), 157(14), 166(9), 180(3), 194(2), 208(2), 250(80), 265(10), 276(11), 297(10), 327(21)

9-Ethyloctadecanoic Acid (**17**)

6-Ethylpentadecanoic acid (**15**) (4.0 g, 0.015 mol), monomethyl ester of glutaric acid (4.2 g, 0.029 mol) and 0.24 g KOH in 90 ml methanol were refluxed at 55 °C while a current was applied through two platinum electrodes, each with an area of 0.6 cm^2 and placed at a distance of 2 cm from each other, at a voltage of 34 V and a current of 130 mA for 75 h. The pH of the mixture increased gradually to a value between 7 and 8. The mixture was then treated with a mixture of 50 ml diethyl ether, 50 ml CH_2Cl_2 and 10 ml HCl (conc.). After phase separation, the organic phase was washed with Na_2CO_3 solution and water, dried with $MgSO_4$ and concentrated in vacuo. Purification was performed using preparative column chromatography eluted with chloroform:diethyl ether = 15:1, followed by hexane:ethyl acetate = 20:1. Detection of different fractions was accomplished using an aqueous solution of 2.5% $CuSO_4$, 7.5% cupric acetate and 10% H_3PO_4. Yield: 1.2 g of methyl ester of 9-ethyloctadecanoic acid.

The ester was hydrolysed in 2.5 g NaOH, 20 ml water and 0.8 ml ethanol for 2.5 h at reflux temperature. After cooled to room temperature a mixture of 2.5 ml concentrated HCl, 4 ml diethyl ether and 3 ml dichloromethane was added. The water phase was discarded and the organic phase was dried and evaporated. Purification was performed using preparative column chromatography eluted with petroleum ether:diethyl ether = 9:1; 6:1; 4:1; and 3:1. The product 9-ethyloctadecanoic acid was converted to its methyl ester for identification by mass spectrometry by reacting the acid with diazomethane[13].

Yield: 0.7 g 9-ethyloctadecanoic acid (**17**); 15% on the basis that 4.0 g 6-ethylpentadecanoic acid was used. GC: purity found 80.4%. m.p. 20.0 °C; d_{20}^{20} 0.8525; n_{20}^{D}; 1.452.

^{1}H NMR: δ(ppm) 2.34 (m, 2H, H-2), 1.60 (m, 3H, H-3 and H-9), 1.26 (28H, CH_2's), 0.85 (6H, CH_3's). IR (film) ν = 3500–2400, 1705, 1460, 1410, 1380, 1280, 1110, 935, 715 cm^{-1}.

MS (EI) *m/e* (rel. int.): 55(100), 74(70), 87(53), 97(35), 115(18), 130(13), 149(21), 167(20), 177(3), 185(12), 199(38), 227(53), 247(14), 265(21), 283(6), 297(47), 326(15)

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