Synthesis of novel piperideine- and pyridine-containing long-chain fatty ester derivatives from methyl *iso*-ricinoleate

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COMMUNICATION

Oxidative rearrangement of methyl 9-azido-12,13-epoxystearate 2 with MeI, NaI and DMF and short-time concomitant ultrasonication at 120 °C yields exclusively 1,4- and 1,5-azido-oxo isomers 3 and 4, whereas prolonged heating furnishes pyrrole and pyridine derivatives 5 and 6; cyclization of 3 and 4 with Ph_3P gives pyrroline 7 and Δ^1-piperideine 8; and oxidative aromatization of 8 with PtO_2 yields compound 6 as an alternative route.

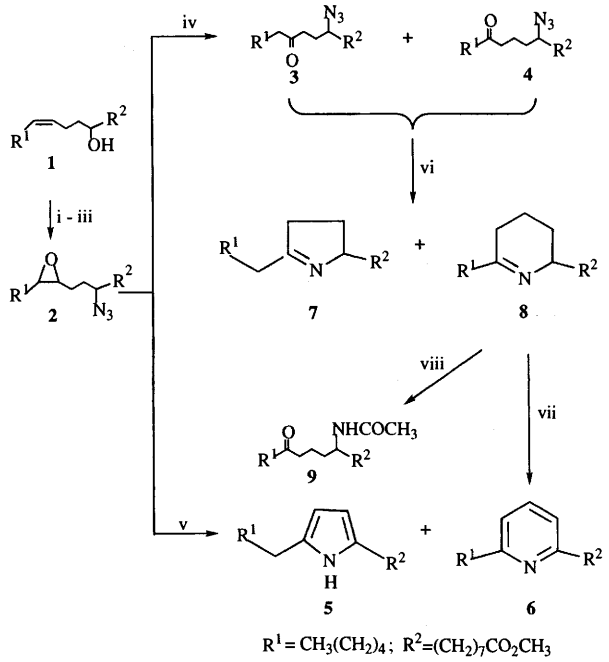
The biology and chemistry of heterocycles containing a piperideine† or pyridine nucleus have been the subject of numerous investigations.[1] 2,6-Dialkylated piperideine derivatives are found in the venom of the fire ant (*Solenopsis invicta*).[2] Such compounds display a diverse range of physiological actions, including the ability to cause histamine release from mast cells.[3–5] The chemistry of the ant venom from the genera *Solenopsis* and *Monomorium* has been reviewed.[6] Pyridines and their derivatives have attracted attention because of their bacteriocidal, fungicidal, antiviral and anti-inflammatory properties.[7,8] Pyridines containing an alkanoic acid substituent are formed during the metabolism of nicotinine and cotinine.[9]

We have recently reported the successful transformations of a large number of long-chain fatty esters (LCFE's) in water when such reactions are conducted under concomitant ultrasonic irradiation (20 kHz, 53 W cm^{-2}).[10,11] Here we describe the synthesis of novel 2,6-disubstituted pyridine and piperideine fatty ester derivatives from methyl *iso*-ricinoleate (methyl (*Z*)-9-hydroxyoctadec-12-enoate) as outlined in Scheme 1.

Methyl *iso*-ricinoleate **1** was converted into the corresponding azido derivative *via* the mesyloxy intermediate, which was subsequently epoxidized using *m*-chloroperoxybenzoic acid in water under ultrasonic irradiation to give the azidoepoxide **2** (90%).[10,12] Oxidative rearrangement of the epoxy system of compound **2** by using MeI, NaI and ultrasonic irradiation (20 kHz, 53 W cm^{-2}) in DMF[13] at 120 °C for 15 min furnished a mixture of methyl 9-azido-12-oxostearate **3** and 9-azido-13-oxostearate **4** in a ratio of 2 : 3 and in 95% yield. However, when compound **2** was heated with MeI and NaI in DMF at 120 °C for 20 h, the novel pyridine derivative methyl 8-(6-pentyl-2-pyridyl)octanoate **6** (59%) and a previously reported[14] 2,5-disubstituted pyrrole ester **5** (37%) were obtained in a ratio of about 3 : 2, respectively. From these results, it became evident that under short-period ultrasonic irradiation, the oxidative rearrangement of the epoxy system in compound **2** with NaI and MeI in DMF was product controlled and gave only the corresponding azido-oxo isomers **3** and **4** in high yield. In the absence of ultrasound, compound **2** remained unchanged when the same reaction was stirred at 120 °C for 15 min. Of further interest was the direct aromatization of the azidoepoxide **2** when subjected to prolonged heating (120 °C, 20 h). These experimental conditions demonstrate the unique effects of ultrasound *vs.* heat on a reactive epoxy intermediate such as that described. These reaction conditions and the results therefrom are unprecedented.

Treatment of the mixture of compounds **3** and **4** with Ph_3P and ultrasound in THF at ambient temperature gave a 1-pyrroline **7** (40%) and a novel 1-piperideine **8** (60%) derivative, which were readily separated by silica chromatography. The structure of the 1-pyrroline derivative **7** was identical to that derived from methyl *iso*-ricinoleate by a different route as described elsewhere.[12] Compound **8** was readily aromatized in the presence of PtO_2 in EtOH under ultrasound at ambient temperature to yield the 2,6-disubstituted pyridine derivative **6** (91%). Compound **6** was characterized from the shifts of the proton and carbon nuclei of the pyridine ring [δ_H 6.95 (2 H), 7.48 (1 H); δ_C 119.6 (2 C), 136.4 (1 C) and 161.8 (2 C)]. The position of the pyridine ring was confirmed by mass spectrometry from the ion fragments (*m*/*z*, intensity): 163 (base peak, 100%), 249 (49.9) and high resolution MS (calc. 305.2354 for $C_{19}H_{31}NO_2$, found 305.2356).

To determine the position of the double bond in compound **8**, the piperideine was ring-opened using acetic anhydride[15] and the structure of the resulting oxo acetamide **9** (methyl 9-acetamido-13-oxostearate) was confirmed by a combination of NMR and mass spectral analyses. The ^1H NMR spectrum of compound **9** exhibited a singlet at δ_H 1.95 (3 H) due to the methyl protons of the acetamido group ($NHCOCH_3$). A multiplet at δ_H 3.86 (1 H) and a doublet at δ_H 5.72 (1 H) were assigned to the 9-H and NH protons, respectively. The ^{13}C NMR spectrum displayed characteristic signals as follows: δ_C 23.4 ($NHCOCH_3$), 35.7 (C-8), 43.0 (C-14), 49.4 (C-9), 170.0 ($NHCOCH_3$) and 211.6 (C-13). The position of the amido



Scheme 1 *Reagents and conditions:* i, CH_3SO_2Cl, $(C_2H_5)_3N$, CH_2Cl_2, 0 °C, 30 min; ii, NaN_3, DMF, ultrasound, 20 °C, 30 min; iii, *m*-CPBA, H_2O, ultrasound, 20 °C, 30 min; iv, MeI, NaI, DMF, ultrasound, 120 °C, 15 min; v, MeI, NaI, DMF, 120 °C, stirring, 20 h; vi, Ph_3P, THF, ultrasound, 20 °C, 30 min; vii, PtO_2, EtOH, ultrasound, 20 °C, 30 min; viii, Ac_2O, 90 °C, 1 h.

† The IUPAC name for Δ^1-piperideine is 2,3,4,5-tetrahydropyridine.

group at C-9 was confirmed from the peaks at *m/z* 242 (base peak, 100%), 212 (81) and 228 (73), while the position of the oxo function at C-13 was identified from the ion fragments *m/z* 113 (11%) and 99 (15.7). As there were no significant ion fragments corresponding to *m/z* 298, 142, 100 and 89 in the mass spectrum of compound **9**, the possibility of the amido group being attached *to C-13* could be ruled out. Hence, it could therefore be inferred that the C=N bond in compound **8** was attached to the C-13 carbon atom of the parent long-chain fatty ester. The structure of compound **8** was further confirmed by the shifts of the proton and carbon nuclei of the piperideine system and by high resolution MS.

We conclude from these results that it is possible to exercise product control over the oxidative rearrangement of the epoxide in methyl 9-azido-12,13-epoxystearate with MeI and NaI in DMF, to obtain specifically the corresponding azido-oxo or aromatized (pyridine and pyrrole) products under ultrasound or thermal conditions.

Experimental

Reaction of methyl 9-azido-12,13-epoxystearate 2 with MeI, NaI, DMF under ultrasonic conditions

A mixture of methyl 9-azido-12,13-epoxystearate **2** (1.0 g, 2.8 mmol), sodium iodide (3.9 g, 26.0 mmol), methyl iodide (1.68 g, 11.8 mmol) and *N*,*N*-dimethylformamide (20 cm^3) was placed in an air-jacketed cell and the reaction mixture was sonicated for 15 min (using an ultrasound horn, 20 kHz, 53 W cm^{-2}, Sonoreactor, Undatim Ultrasonics, S.A., Louvain-la-Neuve, Belgium). The reaction temperature rose quickly within 3 min to 115–120 °C, at which it remained constant for the remaining 12 min. The reaction mixture was allowed to cool and water (200 cm^3) was added to the reaction mixture. The aqueous mixture was extracted with Et_2O (3 × 40 cm^3). The ethereal extracts were successively washed with aq. $Na_2S_2O_7$ (10% w/w, 50 cm^3) and water (30 cm^3), dried (Na_2SO_4) and filtered. The filtrate was evaporated under reduced pressure. The residue (0.99 g) was purified on a silica (15 g) column, using a mixture of hexane–Et_2O (4:1, v/v) as eluent, to give a mixture of methyl 9-azido-12-oxostearate **3** and methyl 9-azido-13-oxostearate **4** (0.95 g, 95%).

Reaction of methyl 9-azido-12,13-epoxystearate 2 with MeI, NaI and DMF under thermal conditions

A mixture of methyl 9-azido-12,13-epoxystearate **2** (1.0 g, 2.8 mmol), MeI (1.68 g, 11.8 mmol), NaI (3.9 g, 26.0 mmol) and DMF (20 cm^3) was stirred at 120 °C for 20 h under nitrogen. Water (200 cm^3) was added to the cooled reaction mixture and the latter was extracted with Et_2O (3 × 30 cm^3). The ethereal extracts were successively washed with aqueous $Na_2S_2O_7$ (10% w/w, 2 × 30 cm^3), dried (Na_2SO_4) and filtered. The filtrate was evaporated and the residue was chromatographed on a silica (20 g) column using a mixture of hexane–Et_2O as the eluent to give methyl 8-(5-hexylpyrrol-2-yl)octanoate **5**[14] (0.3 g, 37%) and methyl 8-(6-pentyl-2-pyridyl)octanoate **6** (0.52 g, 59%), $\delta_H(CDCl_3)$ 0.89 (t, 3 H, 18-H), 1.23–1.9 (m, 16 H), 2.29 (t, 2 H, 2-H), 2.74 (t, *J* 7.8,‡ 4 H, 8-H and 14-H), 3.66 (s, 3 H, CO_2CH_3), 6.95 (d, *J* 1.46, 2 H, 10-H and 12-H), 7.48 (t, *J* 7.7, 1 H, 11-H); $\delta_C(CDCl_3)$, 14.06 (C-18), 22.58 (C-17), 24.94 (C-3), 29.08, 29.14, 29.25, 29.72, 29.93, 30.13 (C-14), 31.68 (C-16), 34.09 (C-2), 38.55 (C-8), 51.45 (CO_2CH_3), 119.61 and 119.64 (ring C′-3/C′-5), 136.40 (ring C′-4), 161.77, 161.94 (ring C′-2/C′-6) and 174.33 (C-1) (Found: M^+, 305.2356. $C_{19}H_{31}NO_2$ requires *M*, 305.2354).

Cyclization of methyl azidooxostearates 3 and 4 with triphenylphosphine

A mixture of compounds **3** and **4** (1.13 g, 3.2 mmol), triphenylphosphine (1.34 g, 5.1 mmol) and anhydrous THF (20 cm^3) in a water-cooled jacketed cell was sonicated for 30 min. Water (100 cm^3) was added and the reaction mixture was extracted with Et_2O (3 × 40 cm^3). The ethereal extracts were washed with water (30 cm^3) and dried over anhydrous Na_2SO_4. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was separated by gradient elution using mixtures of hexane–Et_2O (95:5, v/v, 100 cm^3; 9:1, v/v, 200 cm^3; 85:15, v/v, 200 cm^3; 4:1, v/v, 400 cm^3 and 3:1, v/v, 400 cm^3) to give methyl 8-(5-hexyl-1-pyrrolin-2-yl)octanoate **7** (0.4 g, 40%)[14] and methyl 8-(2-pentyl-3,4,5,6-tetrahydro-6-pyridyl)-octanoate **8** (0.59 g, 60%) (Found: M^+, 309.2668. $C_{19}H_{35}NO_2$ requires *M*, 309.2665). $\delta_H(CDCl_3)$ 0.88 (t, 3 H, 18-H), 1.22–1.46 (m, 16 H) 1.46–1.74 (m, 6 H), 2.06 (m, 2 H, 10-H), 2.14 (t, 2 H, *J* 7, 12-H), 2.30 (t, 2 H, 2-H), 3.28 (br, 1 H, 9-H) and 3.66 (s, 3 H, CO_2CH_3); $\delta_C(CDCl_3)$ 14.06 (C-18), 18.69 (C-11), 22.57 (C-17), 24.99 (C-3), 26.13 (C-8), 26.68 (C-7), 26.95, 28.80 (C-10), 29.17, 29.28, 29.69, 31.74 (C-16), 34.14 (C-2), 37.56 (C-14), 41.20 (C-12), 51.45 (CO_2CH_3), 57.42 (C-9), 170.48 (C-13) and 174.37 (C-1).

Oxidative aromatization of methyl 8-(2-pentyl-3,4,5,6-tetrahydro-6-pyridyl)octanoate 8

A mixture of compound **8** (100 mg), PtO_2 (20 mg) and EtOH (20 cm^3) was sonicated for 30 min in a water-cooled jacketed cell. Water (100 cm^3) was added and the reaction mixture was extracted with Et_2O (3 × 30 cm^3). The ethereal extracts were washed with water (10 cm^3), dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated and the residue was chromatographed on silica to give pure methyl 8-(6-pentyl-2-pyridyl)octanoate **6** (90 mg, 91%). The ^1H and ^{13}C NMR spectra were consistent with those obtained for the same compound by the direct aromatization reaction as described above. The high resolution MS gave the following results. Found: M^+, 305.2355. $C_{19}H_{31}NO_2$ requires *M*, 305.2354.

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‡ *J* Values given in Hz.