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Synthesis of some carbamates of *myo*-inositol

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ABSTRACT

The syntheses are described of the 1-*O*-carbamoyl (**11**), 1-*O*-carbamoyl-2-*O*-stearoyl (**10**), 1-*O*-(acetylcarbamoyl)-2-*O*-stearoyl (**12**), 1-*O*-(heptylcarbamoyl) (**13**), 2-*O*-(heptylcarbamoyl) (**14**), 1,2-di-*O*-(heptylcarbamoyl) (**15**), and 1-*O*-(octadecylcarbamoyl) (**16**) derivatives of *myo*-inositol. None of these compounds had significant activity against phospholipase C.

INTRODUCTION

Recent research on the role of inositol phospholipids in cellular signalling pathways[1] has revived interest in the syntheses of inositol phosphates and phosphatidylinositol analogues[2] that can modulate the important intracellular signal transduction system based on the metabolism of phosphatidylinositol. Inositol-specific phospholipase C (PI-PLC) is a key enzyme in this system[1] which acts on phosphatidyl-*myo*-inositol 4,5-bisphosphate to yield the second messengers D-*myo*-inositol 1,4,5-trisphosphate (mediates the release of calcium ions from intracellular stores) and diacylglycerol (involved in the activation of protein kinase C). A complex pattern of events then occurs, many of which have been elucidated[3].

A specific and potent inhibitor of PLC could be a useful pharmacological tool, but, to date, only non-specific inhibitors are known[4]. Syntheses of analogues of natural *myo*-inositol phosphates and phosphatidyl-*myo*-inositol have been reported[2], but none is a potent and specific inhibitor of PLC[5].

We now describe the synthesis of some carbamates of *myo*-inositol designed as potential inhibitors of PLC.

RESULTS AND DISCUSSION

(±)-1,4,5,6-Tetra-*O*-benzyl-*myo*-inositol[6] (**1**) was reacted with sodium cyanate and trifluoroacetic acid in dichloromethane to give selectively the 3-carbamate

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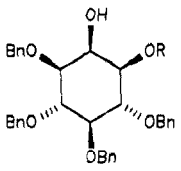

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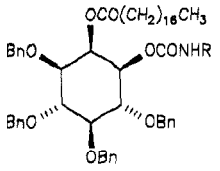

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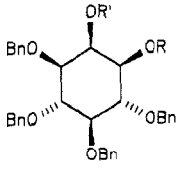
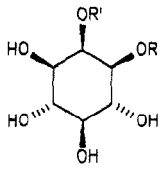
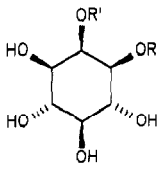
4 R = Ac



5 R = R' = $CONH(CH_2)_6CH_3$
6 R = $CONH(CH_2)_6CH_3$, R' = H
7 R = H, R' = $CONH(CH_2)_6CH_3$
8 R = H, R' = Bn
9 R = $CONH(CH_2)_{17}CH_3$, R' = Bn



10 R = $CONH_2$, R' = $CO(CH_2)_{16}CH_3$
11 R = $CONH_2$, R' = H
12 R = $CONHCOCH_3$, R' = $CO(CH_2)_{16}CH_3$



13 R = $CONH(CH_2)_6CH_3$, R' = H
14 R = H, R' = $CONH(CH_2)_6CH_3$
15 R = R' = $CONH(CH_2)_6CH_3$
16 R = $CONH(CH_2)_{17}CH_3$, R' = H

2 (85%). Treatment of **2** with butyl-lithium and stearoyl chloride gave (±)-1,4,5,6-tetra-*O*-benzyl-3-*O*-carbamoyl-2-*O*-stearoyl-*myo*-inositol (**3**) which, with acetic anhydride and 4-dimethylaminopyridine in toluene, yielded the *N*-acetyl derivative **4** (85%).

When **1** reacted with heptyl isocyanate[7] in dry ether, the 2- (**6**) and 3-heptylcarbamate (**7**) and the 1,2-di(heptylcarbamate) (**5**) were obtained and isolated in yields of 14%, 16%, and 46%, respectively. Likewise, when (±)-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol[6] (**8**) reacted with octadecyl isocyanate in dry ether, 60% of the 3-octadecylcarbamate **9** was obtained.

Hydrogenolysis (Pd/C) of **3** in acetic acid gave (±)-1-*O*-carbamoyl-2-stearoyl-*myo*-inositol (**10**). Likewise, hydrogenolysis (Pd/C) of **2**, **3**, **6**, **7**, **5**, and **9** in ethanol yielded, respectively, the 1-*O*-carbamoyl (**11**), 1-*O*-(acetylcarbamoyl)-2-*O*-stearoyl (**12**), 1-*O*-(heptylcarbamoyl) (**13**), 2-*O*-(heptylcarbamoyl) (**14**), 1,2-di-*O*-(heptylcarbamoyl) (**15**), and 1-*O*-(octadecylcarbamoyl) (**16**) derivatives of (±)-*myo*-inositol in almost quantitative yields.

It was hoped that the planar carbamate moiety of the above compounds might simulate the planar moiety of trigonal bipyramidal structures[8] of the phosphate group during the transition state of the enzymatic reactions. Some planar ions have been already proposed as inhibitors of creatine kinase[9]. However, when the above carbamates were tested against PI-PLC from human platelets, none showed intense activity[10].

EXPERIMENTAL

General methods. — Melting points were determined by a Reichert Thermovar apparatus and are uncorrected. T.l.c. and column chromatography were performed on silica gel (Merck), using hexane–EtOAc mixtures (*A* 1:1, *B* 3:1, *C* 3:2) and 3:2 light petroleum–Et_2O (*D*). The ^1H- and ^{13}C-n.m.r. spectra were recorded at 25° using a Varian XL-300 (300 MHz) or Bruker WP BSV (80 MHz) spectrometer with the appropriate internal standard. I.r. spectra were recorded for solutions of $CHCl_3$, using a Perkin–Elmer Infracord 298.

(±)-1,4,5,6-Tetra-O-*benzyl-3*-O-*carbamoyl*-myo-*inositol* (**2**). — To a solution of **1**[6] (10.8 g, 20 mmol) in CH_2Cl_2 (15 mL) was added sodium cyanate (2.6 g, 40 mmol). The suspension was stirred slowly, trifluoroacetic acid (3.1 mL, 42 mmol) was added dropwise, and stirring was continued overnight at room temperature. The mixture was treated with water, the organic layer was decanted, and the aqueous slurry was washed with two portions of CH_2Cl_2. The organic solutions were combined, washed with aqueous 5% sodium hydroxide and water, dried (Na_2SO_4), and concentrated. Column chromatography (solvent *A*) of the residue gave **2** (9.9 g, 85%), m.p. 158–160° (from hexane); ν_{max} 3680 (w), 3550 (m), 3420 (m), 2890–3100 (broad), 1910 (w), 1880 (w), 1815 (w), 1745 (s), 1590 (s), 1500 (m), 1460 (m), 1365 (s), 1345 (s), 1155–1020 (bs) cm^{-1}. ^1H-N.m.r. data (300 MHz, $CDCl_3$): δ 7.30 (m, 20 H, 4 Ph), 4.87–4.68 (m, 11 H, 4 PhCH_2, $CONH_2$, and H-3), 4.32 (t, 1 H, $J_{1,2}$ 0.9 Hz, H-2), 4.03 (t, 1 H, $J_{3,4}$ 10 Hz, H-4), 3.94 (t, 1 H, $J_{4,5}$ 10 Hz, H-5), 3.58–3.51 (m, 2 H, H-1,6), 2.52 (bs, 1 H, OH).

Anal. Calc. for $C_{35}H_{37}NO_7$: C, 72.02; H, 6.39; N, 2.40. Found: C, 71.96; H, 6.60; N, 2.38.

(±)-1,4,5,6-Tetra-O-*benzyl-3*-O-*carbamoyl-2*-O-*stearoyl*-myo-*inositol* (**3**). — To a solution of **2** (2.65 g, 4.54 mmol) in dry tetrahydrofuran (7 mL) under nitrogen was added, during several min, 1.6M butyl-lithium in hexane (3.15 mL). After 30 min, the mixture was treated dropwise with a solution of stearoyl chloride (1.65 mL, 4.54 mmol) in tetrahydrofuran (5 mL). The reaction was monitored by t.l.c. (solvent *A*) and, after 1 h, the solution was cooled to 0°, water (20 mL) was added, the aqueous phase was extracted with ether (3 × 25 mL), and the organic solutions were combined, dried (Na_2SO_4), and concentrated. Column chromatography (solvent *B*) of the oily residue gave **3** (723 mg, 19%), isolated as a syrup. ^1H-N.m.r. data (300 MHz, $CDCl_3$): δ 7.25 (s, 20 H, 4 Ph), 5.68 (t, 1 H, $J_{1,2}$ 3 Hz, H-2), 4.95–4.34 (m, 11 H, 4 PhCH_2, $CONH_2$, and H-3), 3.79 (m, 2 H), 3.50 (m, 2 H), 2.35 (t, 2 H, *J* 6 Hz, CH_2CO), 1.60 (m, 2 H, CH_2CH_2CO), 1.25 (m, 30 H, 15 CH_2), 0.85 (t, 3 H, *J* 6 Hz, CH_3).

Anal. Calc. for $C_{53}H_{71}NO_8$: C, 74.88; H, 8.42; N, 1.65. Found: C, 75.01; H, 8.40; N, 1.69.

(±)-1-O-*(Acetylcarbamoyl)-3,4,5,6-tetra*-O-*benzyl-2*-O-*stearoyl*-myo-*inositol* (**4**). — To a solution of **3** (100 mg, 0.18 mmol) and 4-dimethylaminopyridine (72 mg, 0.18 mmol) in toluene (0.3 mL) was added acetic anhydride (60 mg, 0.18 mmol). The mixture was stirred at room temperature for 1 h, then concentrated. Column chromatography (solvent *D*) of the residue gave **4** (136 mg, 85%), isolated as a syrup. ^1H-N.m.r.

data (300 MHz, Me_2SO-d_6): δ 7.25 (m, 20 H, 4 Ph), 5.60 (m, 1 H, H-2), 5.01 (m, 1 H, H-1), 4.81–4.45 (m, 9 H, 4 C*H*$_2$Ph and CONH), 3.88 (dd, 1 H, $J_{3,4}$ 10, $J_{2,3}$ 3 Hz, H-3), 3.77 (t, 1 H, $J_{4,5}$ 10 Hz, H-5), 3.69 (m, 2 H, H-4,6), 2.35 (t, 2 H, *J* 6 Hz, CH_2CO), 1.90 (s, 3 H, Ac), 1.55 (m, 2 H, C*H*$_2$$CH_2CO$), 1.13 (m, 30 H, 15 CH_2), 0.82 (t, 3 H, *J* 2 Hz, C*H*$_3$$CH_2$).

Anal. Calc. for $C_{55}H_{73}NO_9$: C, 74.04; H, 8.25; N, 1.57. Found: C, 74.09; H, 8.31; N, 1.60.

*(±)-1,4,5,6-Tetra-*O*-benzyl-*myo*-inositol heptylcarbamates.* — To a solution of **1** (1.5 g, 2.8 mmol) in dry Et_2O (60 mL) were added small pieces of sodium (64 mg, 2.8 mmol). The mixture was stirred under nitrogen overnight at room temperature. A solution of heptyl isocyanate[7] (780 mg, 5 mmol) in dry Et_2O (15 mL) was added dropwise. After 30 min, t.l.c. (solvent *A*) showed the absence of **1**. The mixture was poured into water and extracted with EtOAc, and the extract was washed with water, dried (Na_2SO_4), and concentrated. Column chromatography (solvent *C*) of the oily residue gave, first, (±)-1,4,5,6-tetra-*O*-benzyl-2,3-di-*O*-(heptylcarbamoyl)-*myo*-inositol (**5**; 1.06 g, 46%), isolated as a syrup. ^{1}H-N.m.r. data (80 MHz, $CDCl_3$): δ 7.41 (m, 20 H, 4 Ph), 5.69 (m, 1 H, H-2), 4.80 (m, 10 H, 4 C*H*$_2$Ph and 2 CONH), 3.70 (m, 6 H, 6 C*H*OH), 1.25 (m, 20 H, 10 CH_2), 0.80 (t, 6 H, *J* 2 Hz, 2 CH_3).

Anal. Calc. for $C_{50}H_{66}N_2O_8$: C, 72.96; H, 8.08; N, 3.40. Found: C, 73.06; H, 8.01; N, 3.45.

Eluted second was (±)-1,4,5,6-tetra-*O*-benzyl-3-*O*-(heptylcarbamoyl)-*myo*-inositol (**6**; 265 mg, 14%), isolated as a syrup. ^{1}H-N.m.r. data (80 MHz, $CDCl_3$): δ 7.21 (s, 20 H, 4 Ph), 4.70 (m, 9 H, 4 C*H*$_2$Ph and CONH), 4.30 (m, 1 H, H-1), 3.90 (m, 3 H), 3.50 (m, 2 H), 3.10 (m, 2 H, C*H*$_2$NH), 1.91 (m, 10 H, 5 CH_2), 0.80 (t, 3 H, *J* 2 Hz, CH_3).

Anal. Calc. for $C_{42}H_{51}NO_7$: C, 73.98; H, 7.54; N, 2.05. Found: C, 74.02; H, 7.44; N, 2.01.

Eluted third was (±)-1,4,5,6-tetra-*O*-benzyl-2-*O*-(heptylcarbamoyl)-*myo*-inositol (**7**; 303 mg, 16%), isolated as a syrup. ^{1}H-N.m.r. data (80 MHz, $CDCl_3$): δ 7.17 (m, 20 H, 4 Ph), 5.60 (m, 1 H, H-2), 4.85 (m, 9 H, 4 C*H*$_2$Ph and CONH), 3.70 (m, 5 H), 3.10 (m, 2 H, C*H*$_2$NH), 1.30 (m, 10 H, 5 CH_2), 0.85 (t, 3 H, *J* 2 Hz, CH_3).

Anal. Found: C, 74.04; H, 7.56; N, 2.06.

*(±)-1,2,4,5,6-Penta-*O*-benzyl-3-*O*-(octadecylcarbamoyl)-*myo*-inositol* (**9**). — To a solution of **8**[6] (0.8 g, 1.3 mmol) in dry Et_2O (25 mL) were added small pieces of sodium (35 mg, 1.5 mmol). The mixture was stirred under nitrogen overnight at room temperature. A solution of octadecyl isocyanate (381 mg, 1.3 mmol) in dry Et_2O (8 mL) was added dropwise. After 30 min, t.l.c. (solvent *D*) showed the absence of **8**. The mixture was poured into water and extracted with EtOAc, and the extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was crystallised from hexane to give **9** (710 mg, 60%), m.p. 83–86°; ν_{max} 3440 (w), 2920 (s), 2860 (s), 1745 (s), 1500 (m), 1455 (m), 1365 (m), 1140–1040 (bs) cm^{-1}. ^{1}H-N.m.r. data (300 MHz, Me_2SO-d_6): δ 7.27 (m, 25 H, 5 Ph), 4.70 (m, 12 H, 5 C*H*$_2$Ph, CONH, and H-3), 4.15 (t, 1 H, $J_{2,3}$ 3 Hz, H-2), 3.83 (m, 2 H, H-4,6), 3.70 (dd, 1 H, $J_{1,2}$ 3, $J_{1,6}$ 10 Hz, H-1), 3.59 (t, 1 H, $J_{4,5}$ 10 Hz, H-5), 2.99 (m, 2 H, C*H*$_2$NH), 1.40 (m, 2 H, C*H*$_2$$CH_2$NH), 1.14 (s, 30 H, 15 CH_2), 0.84 (t, 3 H, *J* 3 Hz, CH_3).

Anal. Calc. for $C_{60}H_{59}NO_7$: C, 79.53; H, 6.56; N, 1.55. Found: C, 79.64; H, 6.56; N, 1.56.

*(±)-1-*O*-Carbamoyl-2-*O*-stearoyl*-myo-*inositol* (**10**). — To a solution of **3** (500 mg, 0.59 mmol) in glacial acetic acid (180 mL) was added 10% Pd/C (250 mg). The mixture was shaken under hydrogen at atmospheric pressure for 1 h at room temperature, then filtered through a Celite pad, and the filter cake was washed with glacial acetic acid (50 mL). The filtrate and washings were combined, diluted with water (250 mL), and extracted with EtOAc (3 × 70 mL). The combined extracts were washed with water, dried (Na_2SO_4), and concentrated. The residue was crystallised from water to give **10** (263 mg, 91%), m.p. 115–118°. ^{1}H-N.m.r. data (300 MHz, Me_2SO-d_6): δ 5.30 (m, 1 H, H-2), 4.90 (m, 4 H, 4 OH), 4.56 (m, 1 H, H-1), 3.40 (m, 4 H, H-3,4,5,6), 2.25 (m, 2 H, CH_2CH_2CO), 1.50 (m, 2 H, CH_2CO), 1.20 (m, 30 H, 15 CH_2), 0.85 (m, 3 H, CH_3).

Anal. Calc. for $C_{25}H_{47}NO_8$: C, 61.62; H, 9.68; N, 2.86. Found: C, 61.65; H, 9.55; N, 2.91.

*(±)-1-*O*-Carbamoyl*-myo-*inositol* (**11**). — To a solution of **2** (480 mg, 0.82 mmol) in aqueous 95% ethanol (15 mL) was added 10% Pd/C (250 mg). The mixture was shaken under hydrogen at atmospheric pressure for 3 h at room temperature, then filtered through a Celite pad, and the filter cake was washed with ethanol, then water. The filtrate and washings were combined and concentrated, and the residue was recrystallised from water to yield **11** (164 mg, 90%), m.p. 186–190°. ^{1}H-N.m.r. data (300 MHz, Me_2SO-d_6): δ 6.42 (s, 2 H, NH_2), 4.23 (dd, 1 H, $J_{1,6}$ 10, $J_{1,2}$ 3 Hz, H-1), 3.78 (t, 1 H, 3 Hz, H-2), 3.52 (t, 1 H, $J_{5,6}$ 10 Hz, H-5), 3.34 (t, 1 H, $J_{4,5}$ 10 Hz, H-4), 3.13 (dd, 1 H, $J_{3,4}$ 10, $J_{2,3}$ 3 Hz, H-3), 2.95 (t, 1 H, H-6).

Anal. Calc. for $C_7H_{13}NO_7$: C, 37.67; H, 5.87; N, 6.27. Found: C, 37.52; H, 6.99; N, 6.18.

*(±)-1-*O*-(Acetylcarbamoyl)-2-stearoyl*-myo-*inositol* (**12**). — Using the same conditions as described for **11**, **4** (30 mg, 0.034 mmol) was converted in 24 h into **12** (17 mg, 92%), m.p. 134–137° (from water). ^{1}H-N.m.r. data (300 MHz, Me_2SO-d_6): δ 5.21 (t, 1 H, $J_{2,3}$ 2.6 Hz, H-2), 4.98 (d, 2 H, *J* 4.8 Hz, 2 OH), 4.85 (d, 1 H, *J* 4.4 Hz, OH), 4.54 (dd, 1 H, $J_{1,2}$ 2.6, $J_{1,6}$ 10.4 Hz, H-1), 3.50–3.05 (m, 4 H), 2.27 (t, 2 H, *J* 6 Hz, CH_2CO), 1.88 (s, 3 H, Ac), 1.50 (t, 2 H, *J* 6 Hz, CH_2CH_2CO), 1.21 (s, 30 H, 15 CH_2), 0.83 (t, 3 H, *J* 6 Hz, CH_3CH_2).

Anal. Calc. for $C_{27}H_{49}NO_9$: C, 60.99; H, 9.26; N, 2.63. Found: C, 61.11; H, 9.22; N, 2.69.

*(±)-1-*O*-(Heptylcarbamoyl)*-myo-*inositol* (**13**). — Using the same conditions as described for **11**, **6** (100 mg, 0.15 mmol) was converted in 24 h into **13** (47 mg, 97%), m.p. 169–171° (from water). ^{1}H-N.m.r. data (80 MHz, Me_2SO-d_6): δ 4.87 (m, 5 H, 5 OH), 4.35 (m, 1 H, H-1), 3.47 (m, 1 H, H-2), 3.10 (m, 2 H), 2.90 (m, 3 H), 1.25 (m, 10 H, 5 CH_2), 0.85 (t, 3 H, *J* 2 Hz, CH_3).

Anal. Calc. for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36. Found: C, 52.15; H, 8.48; N, 4.29.

*(±)-2-*O*-(Heptylcarbamoyl)*-myo-*inositol* (**14**). — Using the same conditions as described for **11**, **7** (200 mg, 0.3 mmol) was converted in 24 h into **14** (90 mg, 98%), m.p.

203–205° (from water). ^{1}H-N.m.r. data (80 MHz, Me_2SO-d_6): δ 4.95 (m, 1 H, H-2), 3.43 (m, 3 H), 3.26 (m, 2 H), 2.92 (m, 2 H, CH_2NH), 1.22 (m, 10 H, 5 CH_2), 0.84 (t, 3 H, *J* 2 Hz, CH_3).

Anal. Calc. for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36. Found: C, 52.33; H, 8.38; N, 4.39.

*(±)-1,2-Di-*O*-(heptylcarbamoyl)*-myo-*inositol* (**15**). — Using the same conditions as described for **11**, **5** (213 mg, 0.26 mmol) was converted in 24 h into **15** (108 mg, 90%), m.p. 185–187° (from water). ^{1}H-N.m.r. data (300 MHz, CD_3OD): δ 5.30 (m, 1 H, H-2), 4.90 (m, 1 H, H-1), 3.45 (m, 6 H), 1.30 (m, 20 H, 10 CH_2), 0.85 (t, 6 H, *J* 2 Hz, CH_3).

Anal. Calc. for $C_{22}H_{42}N_2O_8$: C, 57.12; H, 9.15; N, 6.05. Found: C, 56.99; H, 8.98; N, 5.99.

*(±)-1-*O*-(Octadecylcarbamoyl)*-myo-*inositol* (**16**). — Using the same conditions as described for **11**, **9** (710 mg, 0.78 mmol) was converted in 24 h into **16** (327 mg, 92%), m.p. 179–181° (from methanol). ^{1}H-N.m.r. data (300 MHz, Me_2SO-d_6): δ 4.24 (m, 1 H, H-1), 3.79 (m, 1 H, H-2), 3.61–3.12 (m, 4 H), 2.95 (t, 2 H, *J* 4.5 Hz, CH_2NH), 1.63 (m, 2 H, CH_2CH_2NH), 1.20 (s, 30 H, 15 CH_2), 0.85 (t, 3 H, *J* 3 Hz, CH_3).

Anal. Calc. for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42; N, 3.07. Found: C, 66.09; H, 6.40; N, 3.11.

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