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Note

Synthesis of some *myo*-inositol nitrates*

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Four selectively nitrated derivatives of *myo*-inositol have been synthesised for studies of hypotensive and cardiovascular activity[1]. Hydroxyl groups were converted into nitric esters by using nitric acid in acetic anhydride[2,3].

(±)-1,4,5,6-Tetra-*O*-allyl-*myo*-inositol (**3**) was prepared (20% from **1**) by allylation of (±)-1,2-*O*-isopropylidene-*myo*-inositol (**3**) followed by acid hydrolysis. Treatment of **3** with nitric acid in acetic anhydride at 0° gave the 1,2-dinitrate **4** (51%), the 2-nitrate **5** (18%), and the 1-nitrate **6** (15%), isolated by chromatography. Compounds **4–6** were each heated at 60° in 5:1 methanol–water in the presence of a trace of *p*-toluenesulfonic acid and a catalytic amount of Pd/C (ref. 5) to give the *O*-deallylated compounds **7** (85%), **8** (71%), and **9** (70%), respectively.

Likewise, 1,6:3,4-di-*O*-(tetraisopropyl-1,3-disiloxanediyl)-*myo*-inositol[6] (**10**) was reacted with an excess of nitric acid in acetic anhydride at 0° to give **11** (83%), treatment of which with tetrabutylammonium fluoride in dry tetrahydrofuran at room temperature gave the 2,5-dinitrate **12** (54% after chromatography and crystallisation).

EXPERIMENTAL

General methods. — Melting points were determined with a Reichert Thermovar apparatus and are uncorrected. T.l.c. and column chromatography were performed on silica gel (Merck) with hexane–EtOAc mixtures (*A*, 4:1; *B*, 3:2; *C*, 1:1), 95:5 light petroleum–Et_2O (*D*), and 4:1 $CHCl_3$–MeOH (*E*). The ^1H- and ^{13}C-n.m.r. spectra were recorded at 25° for solutions in $CDCl_3$ or D_2O with a Varian XL spectrometer with the appropriate internal standard.

(±)-1,4,5,6-Tetra-O-*allyl*-myo-*inositol* (**3**).— (±)-1,2-*O*-Isopropylidene-*myo*-

* Dedicated to Professor Alessandro Ballio in the year of his 70th birthday.
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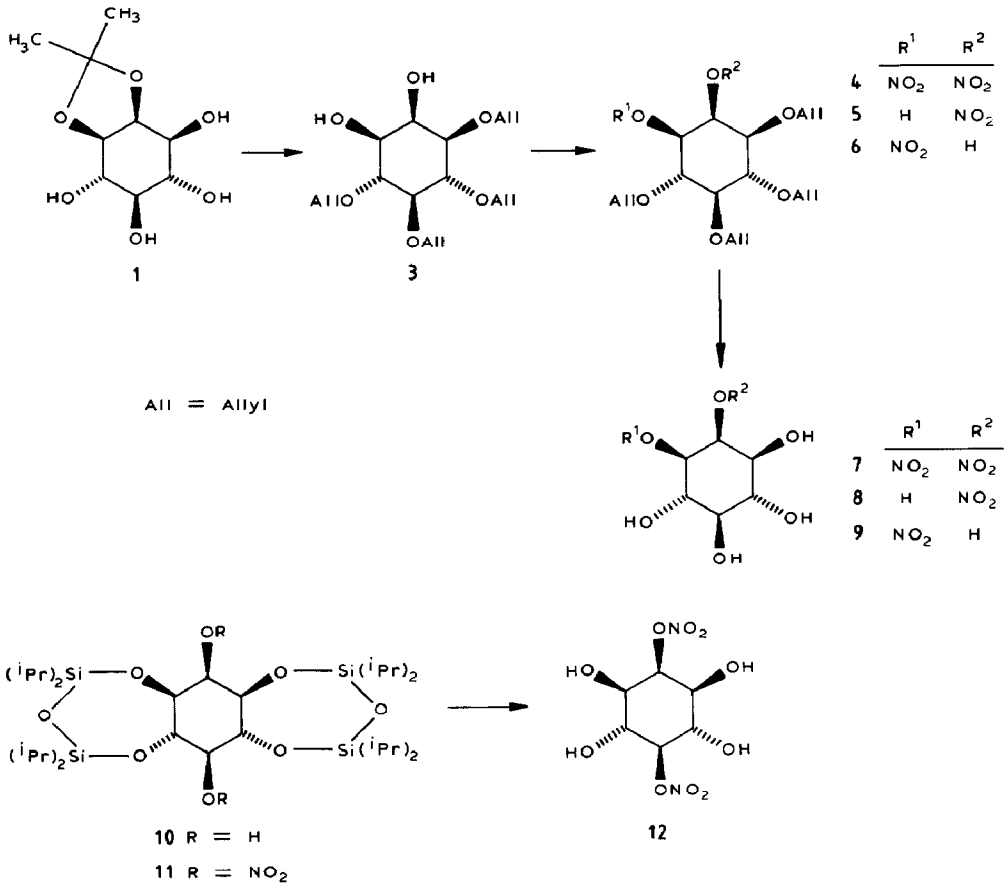

inositol[7] (**1**, 40 g) was stirred with powdered sodium hydroxide (200 g) and allyl bromide (500 mL) at 120° for 20 h. T.l.c. (solvent *A*) then showed almost complete conversion into the fully allylated product (R_F 0.5). The solution was diluted with ether, washed with water, dried (Na_2SO_4), and concentrated. Column chromatography (solvent *A*) of the residue gave (±)-3,4,5,6-tetra-*O*-allyl-1,2-*O*-isopropylidene-*myo*-inositol (**2**), a solution of which in methanol (500 mL) and conc. hydrochloric acid (40 mL) was heated under reflux for 15 min. Sodium hydrogen carbonate (60 g) was added, the methanol was evaporated, the residue was extracted with $CHCl_3$, and the extract was dried (Na_2SO_4) and concentrated to give **3** as a transparent oil (48 g, 77%). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.87 (m, 4 H, 4 C*H*=CH_2), 5.05–5.28 (m, 8 H, 4 OCH_2), 4.08–4.40 (m, 9 H, 4 CH=CH_2 and H-2), 3.60 (t, 1 H, $J_{5,6}$ 10 Hz, H-6), 3.52 (t, 1 H, $J_{4,5}$ 10 Hz, H-4), 3.35 (dd, 1 H, $J_{1,2}$ 3, $J_{1,3}$ 10 Hz, H-1), 3.18 (dd, 1 H, $J_{2,3}$ 3, $J_{3,4}$ 10 Hz, H-3), 3.12 (t, 1 H, H-5), and 2.95 (s, 2 H, 2 OH).

Anal. Calc. for $C_{18}H_{28}O_6$: C, 63.50; H, 8.29. Found: C, 63.37; H 8.44.

*(±)-1,4,5,6-Tetra-*O*-allyl-*myo*-inositol nitrates.* — Aqueous 65% HNO_3 (1 mL) and a solution of **3** (4.8 g) in Ac_2O (10 mL) were added dropwise and simultaneously to Ac_2O (12 mL) at 0°. After 30 min, t.l.c. (solvent *B*) showed the complete disappearance

of **3**. The mixture was poured into cold water and extracted with EtOAc, and the extract was washed with water, dried (Na_2SO_4), and concentrated. Column chromatography (solvent *B*) of the oily residue gave, first, (±)-3,4,5,6-tetra-*O*-allyl-*myo*-inositol 1,2-dinitrate (**4**; 3.1 g, 51%). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.71–6.98 (m, 4 H), 5.46 (t, 1 H, $J_{1,2}$ 3 Hz, H-2), 5.05–5.22 (m, 8 H), 4.68 (dd, 1 H, $J_{1,6}$ 10 Hz, H-1), 3.90–4.28 (m, 8 H), 3.59 (t, 1 H, $J_{5,6}$ 10 Hz, H-6), 3.52 (t, 1 H, $J_{4,5}$ 10 Hz, H-4), 3.35 (dd, 1 H, $J_{3,4}$ 10, $J_{2,3}$ 3 Hz, H-3), 3.20 (t, 1 H, H-5).

Anal. Calc. for $C_{18}H_{30}N_2O_{10}$: C, 49.76; H, 6.96; N, 6.44. Found: C, 49.86; H, 7.03; N, 6.48.

Eluted second was (±)-3,4,5,6,-tetra-*O*-allyl-*myo*-inositol 2-nitrate (**5**; 0.761 g, 14%). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.75–5.97 (m, 4 H), 5.62 (t, 1 H, $J_{1,2}$ 3 Hz, H-2), 5.05–5.35 (m, 8 H), 3.95–4.40 (m, 8 H), 3.30–3.55 (m, 4 H), 3.12 (t, 1 H, $J_{4,5}$ 10 Hz, H-5), 2.90 (s, 1 H, OH).

Anal. Calc. for $C_{18}H_{31}NO_8$: C, 55.51; H, 8.20; N, 3.59. Found: C, 55.48; H, 8.32; N, 3.67.

Eluted third was (±)-3,4,5,6-tetra-*O*-allyl-*myo*-inositol 1-nitrate (**6**; 0.544 g, 10%). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.81–6.43 (m, 4 H), 5.05–5.41 (m, 8 H), 4.86 (dd, 1 H, $J_{1,2}$ 3, $J_{1,6}$ 10 Hz, H-1), 4.5–4.35 (m, 9 H), 3.82 (t, 1 H, $J_{5,6}$ 10 Hz, H-6), 3.64 (t, 1 H, $J_{4,5}$ 10 Hz, H-4), 3.32 (dd, 1 H, $J_{3,4}$ 10, $J_{2,3}$ 3 Hz, H-3), 3.28 (t, 1 H, H-5).

Anal. Calc. for $C_{18}H_{31}NO_8$: C, 55.51; H, 8.20; N, 3.59. Found: C, 55.62; H, 8.02; N, 3.53.

(±)-myo-*Inositol 1,2-dinitrate* (**7**). — A solution of **4** (100 mg) in methanol (1 mL) and water (0.2 mL) was treated with 10% Pd/C (10 mg) and *p*-toluenesulfonic acid (10 mg), then boiled under reflux with stirring for 48 h, filtered through Celite, and concentrated. Recrystallisation of the residue from acetone–water gave **7** (50 mg, 85%), m.p. 170–173° (dec.). ^{1}H-N.m.r. data (D_2O): δ 5.96 (t, 1 H, $J_{2,3}$ 3 Hz, H-2), 5.40 (dd, 1 H, $J_{1,6}$ 10, $J_{1,2}$ 3 Hz, H-1), 3.46–3.96 (m, 4 H).

Anal. Calc. for $C_6H_{10}N_2O_{10}$: C, 26.67; H, 3.73; N, 10.37. Found: C, 26.80; H, 3.61; N, 10.40.

(±)-myo-*Inositol 2-nitrate* (**8**). — Using the conditions described for **7**, **5** (100 mg) was converted into **8** (44 mg, 71%), m.p. 197–199° (from acetone–water). N.m.r. data: ^{1}H, δ 5.62 (t, 1 H, $J_{2,3}$ 3 Hz, H-2), 3.75 [dd, 2 H, $J_{1,6}$ 10, $J_{1,2}$ 3 Hz, H-1(3)], 3.42 [t, 2 H, $J_{4,5}$ 10 Hz, H-4(6)], 3.19 (t, 1 H, $J_{5,6}$ 10 Hz, H-5); ^{13}C, δ 85.82, 76.50, 75.15, 71.91.

Anal. Calc. for $C_6H_{11}NO_8$: C, 29.88; H, 4.59; N, 5.80. Found: C, 30.01; H, 4.65; N, 6.04.

(±)-myo-*Inositol 1-nitrate* (**9**). — Using the conditions described for **7**, **6** (0.1 g) was converted into **8** (43 mg, 70%), m.p. 178–180° (from acetone–water). N.m.r. data: ^{1}H, δ 5.00 (dd, 1 H, $J_{1,6}$ 10, $J_{1,2}$ 3 Hz, H-1), 4.23 (s, 1 H, H-2), 3.76 (t, 1 H, $J_{4,5}$ 10 Hz, H-4), 3.57 (m, 2 H, H-5,6), 3.34 (m, 1 H, H-3); ^{13}C, δ 83.06, 74.80, 72.80, 71.35, 69.99, 69.85.

Anal. Calc. for $C_6H_{11}NO_8$: C, 29.88; H, 4.59; N, 5.80. Found: C, 29.61; H, 4.55; N, 5.83.

1,6:3,4-Di-O-(tetraisopropyl-1,3-disiloxanediyl)-myo-*inositol 2,5-dinitrate* (**11**). — To a stirred suspension of **10**[6] (1.28 g) in Ac_2O (15 mL) was added aqueous 65%

HNO_3 (0.60 mL) dropwise at room temperature. After 20 min, t.l.c. (solvent *D*) showed the complete disappearance of **10**. The mixture was poured into cold water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and concentrated. Trituration of the residue with water and then recrystallisation from MeOH gave **11** (1.19 g, 83%), m.p. 176–178°. ^{1}H-N.m.r. data ($CDCl_3$): δ 5.55 (t, 1 H, $J_{1,2}$ 2.1 Hz, H-2), 5.07 (m, 1 H, H-1), 3.91 (m, 4 H), 1.19 (m, 4 H), 1.01 (m, 4 H), 1.00 (d, 12 H, *J* 7.8 Hz), 0.89 (d, 12 H, *J* 7.4 Hz).

Anal. Calc. for $C_{30}H_{62}N_2O_{12}Si_4$: C, 47.67; H, 8.27; N, 3.71. Found: C, 47.80; H, 7.98; N,3.92.

myo-*Inositol 2,5-dinitrate* (**12**). — To a solution of **11** (0.98 g) in dry tetrahydrofuran (23 mL) was added tetrabutylammonium fluoride (12 mL, 1.1M in tetrahydrofuran) dropwise at room temperature. The reaction was monitored by t.l.c. (solvent *E*). After 45 min, the mixture was poured into water and washed with dichloromethane, and the aqueous phase was concentrated. Column chromatography (solvent *E*) of the residue and crystallisation from 5% MeOH in $CHCl_3$ gave **12** (0.189 g, 54%), m.p. 205–208° (dec.). N.m.r. data: ^{1}H, 5.70 (t, 1 H, $J_{1,2}$ 2.8 Hz, H-2), 5.05 (t, 1 H, $J_{4,5}$ 9.7 Hz, H-5), 3.93 (dd, 2 H, $J_{2,3}$ 3.2, $J_{3,4}$ 10.2 Hz, H-1,3), 3.72 (t, 2 H, $J_{1,6}$ 10 Hz, H-4,6); ^{13}C, δ 86.91, 85.22, 72.52, 71.81.

Anal. Calc. for $C_6H_{10}N_2O_{10}$: C, 26.68; H, 3.73; N, 10.37. Found: C, 26.53; H, 4.01; N, 10.02.

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