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Approach to the Synthesis of Homoinositols, a New Class of *myo*-Inositol Monophosphatase Inhibitors

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Abstract—A new class of structural analogues of inositol (polyhydroxycycloheptanes, homoinositols) is proposed. 2,3,4,4-Tetrachloro-8-octabicyclo[3.2.1]octadiene-2,6, the adduct of the Diels–Alder reaction between tetracyclopropene and furan, is suggested as the key compound in homoinositol synthesis. Its modification leads to the selective preparation of homoinositol stereomers and derivatives.

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Most of the currently known myo-inositol monophosphatase inhibitors, which are potential drugs for treating manic-depressive and other mental disorders, are polyhydroxycyclohexane derivatives (Scheme 1).

Of the other structural types of inhibitors, trihydroxycycloheptatrienone derivatives (Scheme 2) deserve special mention.

We have proposed a new class of potential *myo*-inositol monophosphatase inhibitors, namely polyhydroxycycloheptanes (homoinositols), which combine both types of structural elements (polyhydroxycyclohexane and trihydroxycycloheptatrienone derivatives). This work studies the possibility of synthesis of these compounds.

It is well known that [2 + 4]cycloaddition (the Diels–Alder reaction) produces unsaturated six-membered rings [1]. Tetrachlorocyclopropene, as a dienophile, enters this reaction with opening of its three-membered ring in an intermediate adduct, which generates a seven-membered ring [2] (Scheme 3).

2,3,4,4-Tetrachloro-8-oxabicyclo[3.2.1]octadiene-2,6 (**I**) is a convenient precursor for the synthesis of seven-membered inositol analogues, namely, homoinositols. The hydrolysis of compound **I** induced by concentrated sulfuric acid generates 3-chloro-8-oxabicyclo[3.2.1]oct-6-ene-2,4-dione (**II**). Partial hydrolysis of compound **I** by sulfuric acid (lasting less than 5 min) yields 2,3-dichloro-8-oxabicyclo[3.2.1]octadien-2,6-one-4 (**II**) in 60% yield.

It is stated for the first time that the reduction of diketone **II** by $LiAlH_4$ in THF at room temperature generates 8-oxabicyclo[3.2.1]octene-6-diol-1,3 (**III**) with simultaneous hydrodechlorination (Scheme 4).

Diol **III** contains latent oxy functionalities and can easily be converted to deoxyhomoinositol **IV** through OsO_4-enhanced oxidative dihydroxylation of the multiple bond and opening of the oxygen bridge as a result of acid hydrolysis or in the presence of boron tribromide.

The reduction of diketone **II** by sodium borohydride in alcohol at room temperature occurs at very slow rates (in our opinion, because of steric hindrances). During boiling of the reaction mixture, however, reduction is complete and diol **V** is formed with the halogen atom in the molecule being conserved (Scheme 5).

Thus, a new synthetic approach to the design of seven-membered structural analogues of inositol, homoinositols, has been found and in part implemented. A possibility of the diastereoselective reduction of type **II** bicyclic ketones to diols **III** and **IV** has been demonstrated.

EXPERIMENTAL

2,3,4,4-Tetrachloro-8-oxabicyclo[3.2.1]octadiene-2,6 (I). A mixture of tetrachlorocyclopropene (8.2 mL, 67 mmol), furan (8.8 mL, 120 mmol), and CCl_4 (16 mL) was heated in a sealed ampoule at 80°C for 18 h. The solvent was eliminated on a rotary evaporator. The residue was an oil, which rapidly crystallized. Recrystallization was from 40/70 petroleum ether; the yield was 14.7 g (89%). The compound had a pleasant smell. T_m = 68.0–68.5°C; T_m^{cast} = 59–60°C. R_f (silica gel/$CHCl_3$) = 0.75.

^{1}H NMR spectrum ($CDCl_3$), ppm: 6.89 (dd, 1H, HC=CH), 6.44 (dd, 1H, HC=CH), 5.40 (d, 1H, HCO), 4.91 (d, 1H, HCO).

^{13}C NMR spectrum, ppm: 139.17 (HC=CH), 129.79 (HC=CH), 89.95 (HCO), 82.18 (HCO).

For $C_7H_4OCl_4$ anal. calcd., %: C, 34.19; H, 1.64.

Found, %: C, 34.21; H, 1.61.

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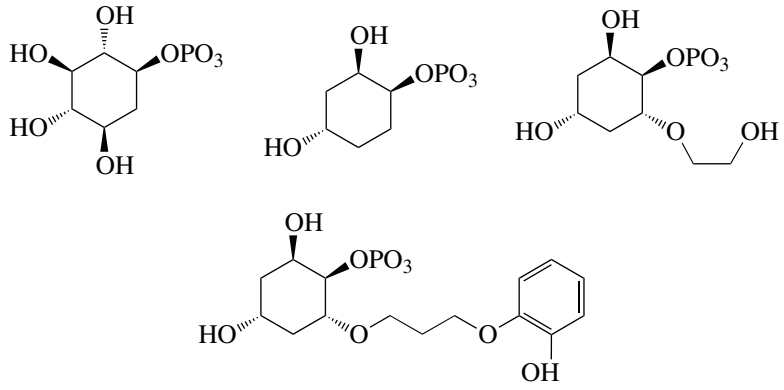
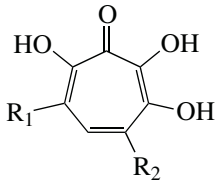
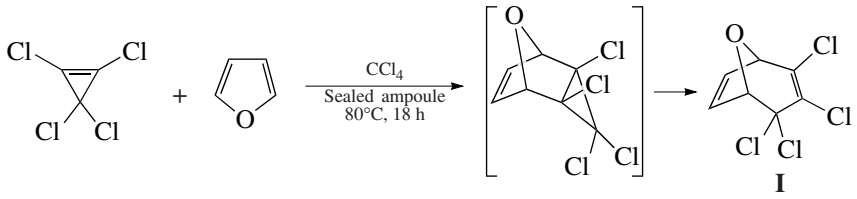


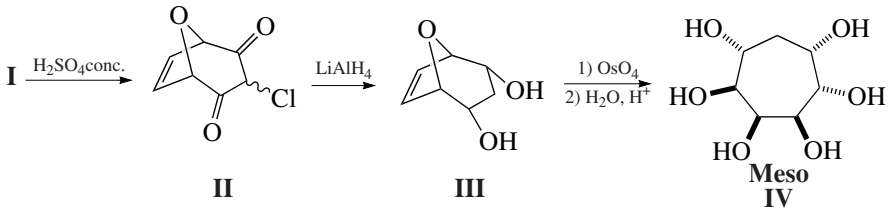
Scheme 1.



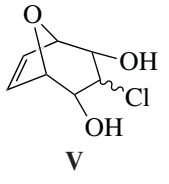
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

3-Chloro-oxabicyclo[3.2.1]oct-6-ene-2,4-dione (II). To compound **I** (9.2 g, 37 mmol), conc. H_2SO_4 (130 mL) was added, and the mixture was stirred on a water bath at 60°C for 35 min. The reaction mixture was poured onto ice, extracted with chloroform (5 × 20 mL), and dried over Na_2SO_4. The solvent was eliminated on a rotary evaporator. The yield of diketone **II** was 4.4 g (65%). R_f (diketone **II**, $CHCl_3$: MeOH = 10 : 1 = 0.5). T_m = 135–137°C. T_m^{cast} = 130–135°C.

^{1}H NMR spectrum ($CDCl_3$), ppm: 6.38 (s, 2H, HC=CH), 5.88 (s, 1H, HCCl), 5.46 (s, 2H, HCO).

^{13}C NMR spectrum ($CDCl_3$), ppm: 192.03 (C=O), 132.33 (C=C), 86.62 (HCO), 72.64 (HCCl).

IR spectrum: 1720 cm^{-1} (C=O).

8-Oxabicyclo[3.2.1]octene-6-diol-1,3 (III). To a solution of diketone **II** (0.1 g, 0.6 mmol) in absolute ether (2 mL), $LiAlH_4$ (50 mg) was added in increments with stirring and refluxing for 15 min. The mixture was stirred with reflux for 1 h. The reaction mixture was cooled with stirring; on a cold water bath, water (50 μL), 15% sodium hydroxide (50 μL), and water (150 μL) were added. The precipitate was filtered and washed with diether ether. The organic layer was separated; the aqueous layer was extracted with diethyl ether (3 × 3 mL) and dried over Na_2SO_4. The solvent was eliminated on a rotary evaporator. The yield of diol **III** was 55 mg (64%). R_f ($CHCl_3$: MeOH = 10 : 1) = 0.3.

^{1}H NMR spectrum (DMSO-d_6), ppm: 6.90 (s, 2H, HC=CH), 4.45 (s, 2H, HCO), 3.98 (s, 2H, HCOH), 1.81 (s, 2H, CH_2).

^{13}C NMR spectrum (DMSO-d_6), ppm: 134.11 (C=C), 85.65 (HCO), 71.28 (HCOH), 33.74 (CH_2).

IR spectrum: 3380 cm^{-1} (OH).

For $C_7H_{10}O_3$ anal. calcd., %: C, 59.14; H, 7.09.

Found, %: C, 58.97; H, 7.18

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