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THE RESOLUTION OF RACEMIC ALCOHOLS THROUGH THE ACID OXALATES. A NEW SYNTHESIS OF OPTICALLY ACTIVE MYO-INOSITOL 1-PHOSPHATES

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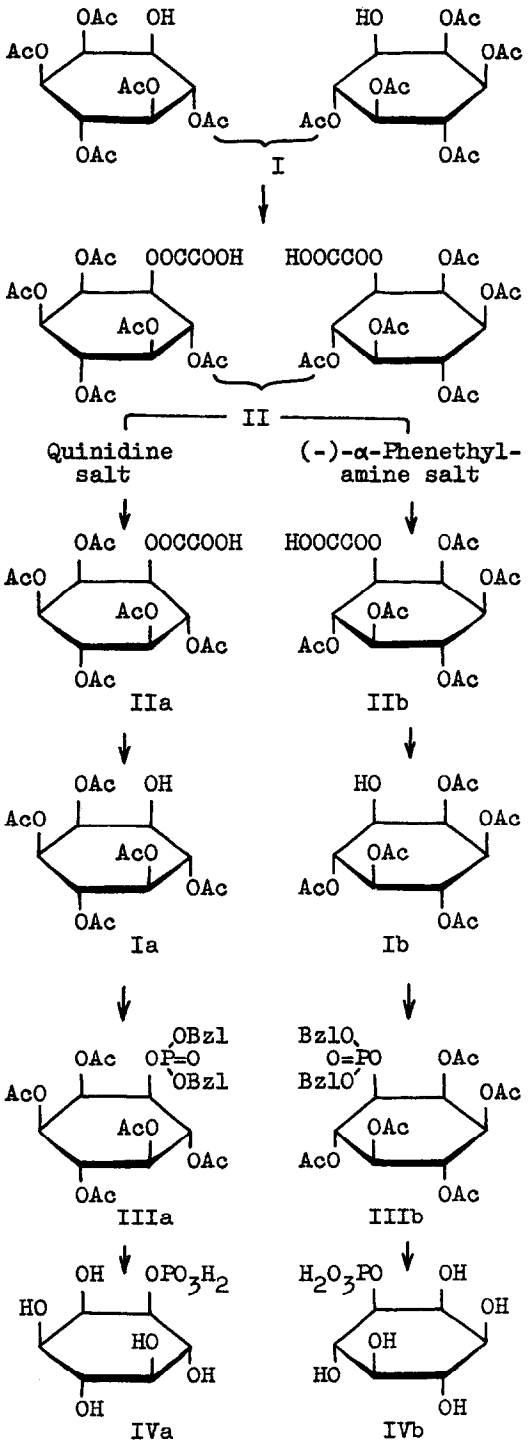
In the course of an investigation, directed towards the total synthesis of phosphatidyl inositol[1], we met with the need to resolve 1,2,4,5,6-penta-O--acetyl-myo-inositol (I)[2]. Known methods for the optical resolution of alcohols through acid succinates or phthalates[3], or through the orthoacetates of monosaccharides[4] were not suitable in our case because regeneration of the resolved alcohols requires acid or alkaline hydrolysis (alcoholysis) which may be accompanied by elimination and/or migration of acetyl groups.

In a search for more suitable derivatives of myo-inositol pentaacetate we turned to its acid oxalates. These seemed promising because the alcohols could be liberated under mild neutral conditions, e.g. by oxidation with lead tetraacetate. Attempts to accomplish the oxidation in the usual manner in ethyl acetate or benzene were unsuccessful: at room temperature the reaction did not take place whereas at elevated temperature complex mixtures of unidentified compounds were formed.

Much better results were obtained by a modification of the method developed by Bacha and Kochi[5] for decarboxylation of carboxylic acids. According to this method the lead tetraacetate oxidation is catalysed by cupric ions in boiling benzene-pyridine in an inert atmosphere (oxygen inhibits the reaction). We found that the above conditions allow the lead tetraacetate oxidation of myo-inositol pentaacetate acid oxalates to be carried out at even much lower temperatures. The oxidation is not accompanied by acetyl migration



or other side reaction and gives the desired myo-inositol pentaacetates in high yields.

Treatment of DL-1,2,4,5,6-penta-O-acetyl-myo-inositol* (I) with a 5-fold excess of oxalyl chloride in pyridine-chloroform at -10° and subsequent hydrolysis (dilution with water) gave the acid oxalate (II) in 83% yield, m.p. 191-3° (decomp.; from $CHCl_3$-ether)**.

Quinidine and (-)-α-phenethylamine were found to be the most suitable bases for the optical resolution of II (acid--amine ratio 1:0.75). After treatment of II with quinidine in dry methanol and a single recrystallization from the same solvent the quinidine salt of 1D-O-oxalyl--2,3,4,5,6-penta-O-acetyl-myo--inositol, m.p. 155-6° (decomp.), $[\alpha]_D$ +71° (c 2, dioxane), was obtained. Decomposition of the

* The recommended rules of cyclitol nomenclature[6] are used.

** Correct elementary analyses were obtained for all newly synthesized compounds.

salt with diluted HCl gave the D-antipode (IIa) in 21% yield (based on II), m.p. 190-2° (decomp., from $CHCl_3$-ether), $[\alpha]_D$ -4.7° (c 1.4, dioxane).

The salt of the 1L-antipode with (-)-α-phenethylamine was obtained by precipitation from dry ethanol and purified by 5-fold recrystallization from the same solvent, m.p. 190-2° (decomp., sintering at ca. 180°), $[\alpha]_D$ +5.5° (c 4.5, $CHCl_3$). Treatment with acid converted it into 1L-O-oxalyl-2,3,4,5,6--penta-O-acetyl-myo-inositol (IIb) with 22% yield (based on II), m.p. 190-2° (decomp., from $CHCl_3$-ether), $[\alpha]_D$ +4.6° (c 1.4, dioxane).

Since the oxalate (II) partly loses its oxalyl group during crystallization with bases, the mother liquors contain pentaacetate (I) and can not be used for isolation of the other antipode. However, the pentaacetate (I) is easily regenerated from these solutions and may be used again.

The acid oxalates IIa and IIb were oxidized with lead tetraacetate in the presence of cupric acetate in pyridine-dioxane under argon (30°, 5 hr) giving in 85-88% yield 1D-2,3,4,5,6-penta-O-acetyl-myo-inositol (Ia), m.p. 185-7° (from $CHCl_3$-ether), $[\alpha]_D$ -13.9° (c 1.6, dioxane), and 1L-2,3,4,5,6-penta-O-acetyl-myo-inositol (Ib), m.p. 185-7°, $[\alpha]_D$ +14.0° (c 1.6, dioxane), respectively.

Both antipodes were converted by successive treatment with phosphorus oxychloride and benzyl alcohol[1] into 1D-O-dibenzylphosphoryl-2,3,4,5,6-penta--O-acetyl-myo-inositol (IIIa), $[\alpha]_D$ -14.2° (c 2.8, dioxane), and its 1L-antipode (IIIb), $[\alpha]_D$ +14.5° (c 3, dioxane) (both substances were obtained as gums), respectively.

Debenzylation of the triphosphate (IIIa) by catalytic hydrogenolysis over palladium black followed by alkaline deacylation (0.5 MeONa in MeOH, 2 hr at room temperature) gave 1D-myo-inositol 1-phosphate isolated as the di-cyclohexylammonium salt, m.p. 194-6° (in capillary under argon, decomp.; from water-acetone), $[\alpha]_D$ +3.8° (c 3.1, water, pH 9); for the same salt obtained from natural phosphatidyl inositol Ballou and Pizer[7] gave $[\alpha]_D$ +3.4°; a specimen synthesized by Klyashchitskii et al.[4] had m.p. 202-4°, $[\alpha]_D$ +3.4° (c 1, water, pH 9).

In an analogous manner triphosphate IIIb was converted into 1L-myo--inositol 1-phosphate (IVb) isolated as the di-cyclohexylammonium salt, m.p. 190-2°, $[\alpha]_D$ -3.7° (c 3.8, water, pH 9); this substance synthesized from galactinol by Ballou and Pizer[7] had $[\alpha]_D$ -3.2° (water, pH 9); Mercier et al.[8] gave for the same compound synthesized from galactinol the data: m.p. 190-2°, $[\alpha]_D$ -4.9° ± 1.0 (c 5.7, water, pH 9).

The method described above for the optical resolution of myo-inositol pentaacetate may be extended to the preparation of other optically active labile alcohols.

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