[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

CYCLITOL DERIVATIVES. III. *EPI-* AND *MESO*-INOSITOL ESTERS OF *p*-AMINOBENZOIC AND *p*-AMINOSALICYLIC ACIDS

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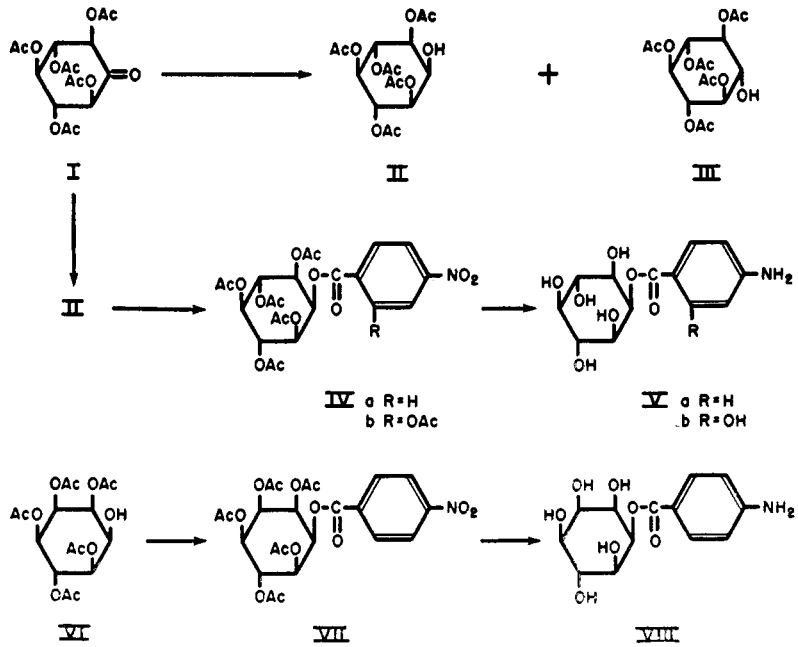
Previous communications in this series have dealt principally with N-containing cyclitols (1, 2) which were derived from *epi-* and *scyllo*-inosose. The present paper describes the synthesis of *epi-* and *meso*-inositol esters of *p*-aminobenzoic acid and *p*-aminosalicylic acid.

The desired starting compounds, *epi-* and *meso*-inositol pentaacetates (VI) and (II), were first reported by Posternak (3, 4). On repeating Posternak's procedure for the hydrogenation of *scyllo*-inosose pentaacetate (I) (platinum oxide, acetic acid) to II, Iselin (5) found the product (m.p. 161–162°) to be a practically inseparable 3:1 mixture of II and scyllitol pentaacetate (III). However, by using methanol instead of acetic acid Iselin was able to prepare pure II (m.p. 177–179°, corr.) in a yield of 84%. In our hands commercial, absolute ethanol proved to be a more satisfactory solvent than methanol and gave 60–75% yields of II as compared with the less-than-50% yields we obtained with methanol.[1]



The reaction of II and VI with *p*-nitrobenzoyl chloride in quinoline readily produced the nitro esters (IVa) and (VII) which were hydrogenated (Raney

[1] Hydrogenation of I in ethyl acetate gave a 70% yield of product which consisted of 90% of II and 10% of III as shown by acetylation and fractional crystallization of the resulting hexaacetate mixture. The 9:1 mixture of II and III could be separated by recrystallization from methanol.

nickel) to the corresponding amino esters. Deacetylation of the amino esters with methanolic ammonia gave *p*-aminobenzoyl-*meso*-inositol (Va) and *p*-aminobenzoyl-*epi*-inositol (VIII). In the deacetylation of *p*-aminobenzoyl-*epi*-inositol pentaacetate with methanolic sodium methoxide, methyl *p*-aminobenzoate and *epi*-inositol were formed instead of VIII, while VII, treated with either methanolic ammonia or methanolic sodium methoxide, yielded methyl *p*-nitrobenzoate and *epi*-inositol.

Attempts to condense II or VI with O-acetyl-*p*-nitrosalicylyl chloride in quinoline or pyridine resulted in the formation of intractable, amorphous powders which on alkaline hydrolysis yielded some *p*-nitrosalicylic acid. Similar results were obtained when O-benzyl-*p*-nitrosalicylyl chloride was used. The nitro ester (IVb) was finally isolated in a yield of 35%[2] after refluxing together II, O-acetyl-*p*-nitrosalicylyl chloride, and benzene.[3] Hydrogenation (platinum oxide) of IVb and deacetylation of the resultant amine gave *p*-aminosalicylyl-*meso*-inositol (Vb).

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EXPERIMENTAL[4]

p-Nitrosalicylic acid, m.p. 236–238°, was prepared by the sulfuric acid hydrolysis (9) of methyl 6-nitro-1,2-benzisoxazole-3-carboxylate (10) and converted to the *O-acetyl derivative* according to Viscontini and Pudles (11).

O-Benzyl-p-nitrosalicyclic acid. The procedure of Tarbell and Wystrach (12) for the benzylation of analogous compounds was used. Ethyl *p*-nitrosalicylate (13) (5 g.) gave 6.5 g. of ethyl O-benzyl-*p*-nitrosalicylate, m.p. 57–58°. The latter (6.0 g.), 12 ml. of Claisen's alkali (12), and 45 ml. of methanol, shaken periodically for 2.5 hours, diluted to 200 ml. with water and acidified, gave, after cooling overnight at 5°, a 100% yield of acid, m.p. 171–173°; long prisms from ethanol.

Anal. Calc'd for $C_{14}H_{11}NO_5$: C, 61.5; H, 4.1.

Found: C, 61.5; H, 4.1.

Hydrogenation of I. (*a*) *Ethanol as solvent.* One gram of I, m.p. 209–212° (4, 14), 0.2 g. of platinum oxide, and 30 ml. of commercial, absolute ethanol absorbed 1.6 moles of hydrogen during 20–25 hours. The filtered solution was concentrated *in vacuo* to 5–7 ml. to give 0.7 g. (70%) of needles of II, m.p. 174–177° (5).

(*b*) *Ethyl acetate as solvent.* I (1.0 g.), 0.1 g. of platinum oxide, and 12 ml. of ethyl acetate absorbed 1.3 moles of hydrogen during 1.5 hours. The filtered solution, diluted with 1–2 volumes of ligroin,[5] warmed, then cooled gradually to 5°, gave 0.7 g. of needles and prisms, m.p. 158–161°. Acetylation (5) of 0.1 g. gave 10 mg. of scyllitol hexaacetate (4, 5), m.p. 296–298° and 90 mg. of *meso*-inositol hexaacetate (4, 5), m.p. 213–215°. Recrystallization of the remaining 0.6 g. from methanol yielded 0.42 g. of II, m.p. 166–168°[6], which on acetylation

[2] In addition to the major product a low yield of an apparently isomeric nitro ester was obtained. Acyl group migration (6–8) in II during condensation might explain this, and alternative formulations for IVb as well as IVa and VII remain a possibility.

[3] An analogous experiment with VI failed to give tractable products.

[4] Melting points, observed in a capillary, are corrected for stem exposure. The microanalyses are from the Institutes service analytical laboratory under the direction of Dr. William C. Alford.

[5] B.p. 30–60°.

[6] This represents another crystalline modification of II. On recrystallization from ethanol it was reconverted to the needles of m.p. 177–179°.

gave a 100% yield of *meso*-inositol hexaacetate. From the methanol filtrate ellipsoids of m.p. 199–205°, separated. The analytical sample of this *scyllitol pentaacetate* (III) (from ethanol) melted at 211–213°.

Anal. Calc'd for $C_{16}H_{22}O_{11}$: C, 49.2; H, 5.7.
Found: C, 49.2; H, 5.7.

p-Nitrobenzoyl-epi-inositol pentaacetate (VII). Two grams of VI (3), 2.0 g. of *p*-nitrobenzoyl chloride, and 3 ml. of dry quinoline were heated on the steam-bath for 15–20 hours, dissolved in hot acetic acid, and the solution poured into ice-water. The yellow solid was digested with dilute sodium bicarbonate. The insoluble portion[7] was dried and recrystallized from ethanol-ligroin[5] to give 2.2 g. (80%) of VII, m.p. 148–151°. The analytical sample melted at 156–158°; oblong plates[8] from methanol or benzene-ligroin.[5]

Anal. Calc'd for $C_{23}H_{25}NO_{14}$: C, 51.2; H, 4.7.
Found: C, 51.1; H, 4.7.

Deacetylation of VII with either methanolic ammonia or sodium methoxide gave methyl *p*-nitrobenzoate, m.p. 93–95°, and *epi*-inositol, identified as the hexaacetate, m.p. 189–191°, alone or in mixture with authentic material.

p-Nitrobenzoyl-meso-inositol pentaacetate (IVa). This compound, prepared from II as described above, crystallized from ethanol or acetic acid in needles of m.p. 233–235°.

Anal. Calc'd for $C_{23}H_{25}NO_{14}$: C, 51.2; H, 4.7.
Found: C, 51.1; H, 4.6.

p-Aminobenzoyl-epi-inositol pentaacetate. One gram of VII, *ca.* 1 g. of Raney nickel, and 10 ml. of ethyl acetate absorbed 3.3 moles of hydrogen during 2.5 hours. The filtered solution, diluted with two volumes of ligroin,[5] gave 0.9 g. (95%) of amine, m.p. 198–202°; long needles from ethanol.

Anal. Calc'd for $C_{23}H_{27}NO_{12}$: C, 54.2; H, 5.3.
Found: C, 54.4; H, 5.4.

p-Aminobenzoyl-meso-inositol pentaacetate. The reduction of IVa as described for VII gave this compound in a yield of 90%; prisms from ethyl acetate-ligroin,[5] m.p. 201–203°.

Anal. Calc'd for $C_{23}H_{27}NO_{12}$: C, 54.2; H, 5.3.
Found: C, 53.9; H, 5.5.

p-Aminobenzoyl-epi-inositol (VIII) (NIH 4546).[9] *p*-Aminobenzoyl-*epi*-inositol pentaacetate (0.7 g.) and 7 ml. of saturated (at 25°) methanolic ammonia, shaken to solution and left for 15 hours at 25°, then for five hours at 5°, gave 0.3 g. (73%) of VIII. It crystallized from water as hemi-hydrated leaflets of m.p. 214–223°.

Anal. Calc'd for $C_{13}H_{17}NO_7 \cdot \frac{1}{2}H_2O$: C, 50.6; H, 5.9; H_2O, 2.9.
Found: C, 50.8; H, 5.9; loss (100°, 1 mm.) 2.3.

A sample, dried at 100° gave the following analysis.

Anal. Calc'd for $C_{13}H_{17}NO_7$: C, 52.2; H, 5.7.
Found: C, 52.2; H, 6.0.

Attempts to deacetylate the amine pentaacetate to VIII with 7% methanolic sodium methoxide gave only *epi*-inositol and methyl *p*-aminobenzoate, m.p. 112–113°.

p-Aminobenzoyl-meso-inositol (Va) (NIH 4545). This compound was prepared in 85% yield as described for VIII; leaflets from water, m.p. 249–254° (dec.).

Anal. Calc'd for $C_{13}H_{17}NO_7$: C, 52.2; H, 5.7.
Found: C, 52.4; H, 5.9.

O-Acetyl-p-nitrosalicylyl-meso-inositol pentaacetate (IVb). O-Acetyl-*p*-nitrosalicylic acid (11) (1.9 g.), 20 ml. of dry benzene, and 6 ml. of thionyl chloride were refluxed for four hours and evaporated to dryness *in vacuo*. Dry benzene (5 ml.) was added and the evaporation re-

[7] Acidification of the filtrate from this solid gave *p*-nitrobenzoic acid.

[8] Diamonds of m.p. 95° from ethanol.

[9] Compounds designated with NIH numbers have been tested *in vitro* (Dubos-Davis medium, H37Rv) by Dr. Bernard D. Davis, Tuberculosis Research Laboratory, Public Health Service, Cornell University Medical College, New York, N. Y.

peated. The residual sirup,[10] 1.5 g. of II, and 14 ml. of dry benzene were refluxed for 10–11 hours, the mixture was evaporated to dryness *in vacuo*, and the sirup dissolved in 25 ml. of warm, commercial, absolute ethanol. After 1–2 hours at 25° 0.8 g. (35%) of IVb, m.p. 197–200°, was obtained; prisms from acetone-ethanol, m.p. 202–203.5°, then 227–232°.[11]

Anal. Calc'd for $C_{25}H_{27}NO_{16}$: C, 50.3; H, 4.6.
Found: C, 50.7; H, 4.7.

The filtrate from the 0.8 g. of IVb gave, on warming, an additional 0.1 g. of IVb, then on long standing, 0.3 g. of an impure fraction which, on hydrogenation as described below for IVb, yielded 0.15 g. of an *amine* isomeric with the hexaacetate of Vb; prisms from ethyl acetate-ligroin,[5] m.p. 218° (rapid heating).[12]

Anal. Calc'd for $C_{25}H_{29}NO_{14}$: C, 52.9; H, 5.2.
Found: C, 52.9; H, 5.2.

O-Acetyl-p-aminosalicylyl-meso-inositol pentaacetate. Hydrogenation of 1.1 g. of IVb, 0.02 g. of platinum oxide, and 11 ml. of ethyl acetate required 0.5–1 hour. The filtered solution was evaporated to dryness *in vacuo* and the residual sirup crystallized from 2–3 ml. of ethanol (with addition of a few drops of ligroin)[5]; yield 0.9 g. (85%), needles from ethanol m.p. 177°.

Anal. Calc'd for $C_{25}H_{29}NO_{14}$: C, 52.9; H, 5.2.
Found: C, 52.8; H, 5.2.

p-Aminosalicylyl-meso-inositol (Vb) (NIH 4600). O-Acetyl-*p*-aminosalicylyl-*meso*-inositol pentaacetate (0.9 g.), and 10 ml. of saturated (at 25°) methanolic ammonia were shaken to solution (one hour) and left for 1.5–2 hours at 25°. Addition of 8 ml. of dry ether gave, after five hours at 25° and 15 hours at 5°, 0.22 g. of solid. An additional 0.03 g. (total yield 50%) was obtained on ether-dilution of the filtrate; needles from 70–80% ethanol-ether, m.p. 153–155°, to a froth.

Anal. Calc'd for $C_{13}H_{17}NO_8 \cdot 2H_2O$: C, 44.4; H, 6.0; N, 4.0; H_2O, 10.2.
Found: C, 44.9; H, 6.1; N, 4.0; loss (125°), 9.7.

SUMMARY

Starting from *epi-* and *meso*-inositol pentaacetates, *p*-aminobenzoyl-*epi*-inositol, *p*-aminobenzoyl-*meso*-inositol, and *p*-aminosalicylyl-*meso*-inositol have been synthesized and tested for *in vitro* activity in tuberculosis.

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[10] The preparation and characterization of this acid chloride (15) were reported shortly after the completion of the present work.

[11] Occasionally a third m.p. of *ca.* 280–290° was observed.

[12] The melt solidified instantaneously and did not remelt below 300°.