[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

CYCLITOL DERIVATIVES. II. DERIVATIVES OF *SCYLLO*-INOSOSE

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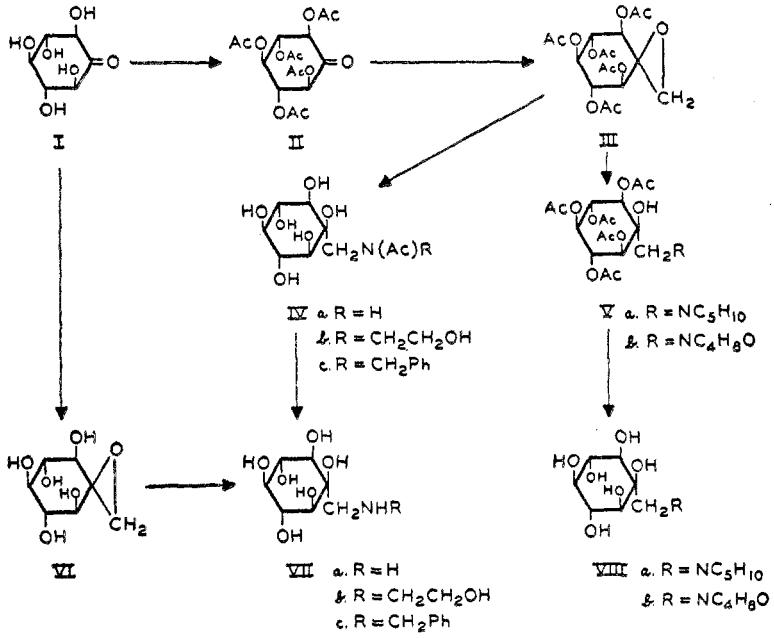
In the first communication (1) of this series we described various nitrogen-containing cyclitols derived from *rac.-epi*-inosose. The present paper deals with the conversion of *scyllo*-inosose (I) to N-substituted methylinositols.

Posternak (2) has shown that the reaction of I or its pentaacetate (II) with diazomethane yields the methyleneoxy derivative VI or III. He further found that treatment of III with reagents such as hydrogn bromide, sodium acetate, etc. resulted in cleavage of the oxirane ring with the formation of *meso*-inositol derivatives.[1]



We have subjected III to reaction with various amines in dry benzene or methanol. Piperidine or morpholine and III in boiling benzene gave the piperidinomethyl- or morpholinomethyl-*meso*-inositol pentaacetate (V)[2] which was deacetylated to VIII with methanolic ammonia. With benzylamine or ethanolamine the intermediate pentaacetates did not crystallize, but on treatment with

[1] Walden inversion apparently occurred in only one instance, namely in the reaction of III with boiling acetic anhydride (ferric or zinc chloride as catalyst).

[2] It is assumed that Walden inversion has not occurred in these additions.

methanolic ammonia they yielded the N-acetylaminomethyl-*meso*-inositols (IVb and c), one of the O-acetyl groups having migrated to the nitrogen (3, 4). Compounds IVb and IVc could also be prepared directly from III and the apropriate amine in boiling methanol, condensation, deacetylation, and acetyl group migration occurring in a single operation. Similarly III and methanolic ammonia gave the N-acetyl derivative (IVa) which was reported by Posternak (5) shortly after the completion of the present work. Hydrolysis of the N-acetyl compounds (IV) with hydrochloric acid afforded the aminomethylinositols (VII). Direct synthesis of VII was achieved starting from the methyleneoxy derivative (VI) of I.

Compounds designated by NIH numbers have been tested for *in vitro* activity against tuberculosis (Dubos-Davis medium, H37Rv). None appeared to be significantly effective.[3]

Acknowledgment; We are indebted to Dr. Laura C. Stewart for supervising the biochemical oxidation of *meso*-inositol to *scyllo*-inosose and to Mr. H. George Latham, Jr. for technical assistance. The microanalyses are from the Institutes service analytical laboratory under the direction of Dr. William C. Alford.

EXPERIMENTAL[4]

The *methyleneoxy derivatives* III and VI were prepared according to Posternak (2) in yields of 70% and 50% respectively. Usually most of the III crystallized directly from the reaction mixture in contrast to the experience of Posternak.

Piperidinomethyl-meso-inositol pentaacetate (Va). Piperidine (0.6 ml.), 1.5 g. of III, and 15 ml. of dry benzene, refluxed three hours, cooled and diluted slightly with ligroin (30–60°) gave a quantitative yield of Va; prisms, m.p. 197–199°, from ethanol.

Anal. Calc'd for $C_{22}H_{33}NO_{11}$: C, 54.2; H, 6.8.
Found: C, 54.3; H, 6.8.

Piperidinomethyl-meso-inositol (VIIIa) (NIH 4208). Methanolic ammonia[5] (10 ml.) and 1.5 g. of Va were shaken to solution, left at 25° overnight, and ice-cooled to give 0.6 g. (70%) of VIIIa. It was recrystallized from methanol (20 ml.)-water (3 ml.), then methanol; long plates, m.p. 227–229°.

Anal. Calc'd for $C_{12}H_{23}NO_6$: C, 52.0; H, 8.4.
Found: C, 51.9; H, 8.3.

Morpholinomethyl-meso-inositol pentaacetate (Vb). This compound was prepared as described for Va; yield 100%, needles or prisms, m.p. 199–200°.

Anal. Calc'd for $C_{21}H_{31}NO_{12}$: C, 51.5; H, 6.4.
Found: C, 51.5; H, 6.3.

Morpholinomethyl-meso-inositol (VIIIb) (NIH 4209). Deacetylation of Vb as described for Va gave 90% of VIIIb; needles or plates from water-ethanol, m.p. 232–234° (dec.).

Anal. Calc'd for $C_{11}H_{21}NO_7$: C, 47.3; H, 7.6.
Found: C, 47.3; H, 7.6.

The *picrate*, prepared with aqueous alcoholic picric acid, crystallized from water in yellow rods, m.p. 232–234° (dec.).

Anal. Calc'd for $C_{17}H_{24}N_4O_{14}$: C, 40.2; H, 4.8.
Found: C, 40.1; H, 4.8.

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[3] Testing was carried out in the Tuberculosis Research Laboratory, Public Health Service, Cornell University Medical College, New York, N. Y. under the direction of Dr. Bernard D. Davis.

[4] Melting points, observed in a capillary, are uncorrected.

[5] Saturated solution at room temperature.

N-Acetylaminomethyl-meso-inositol (IVa) (NIH 4215). Methanolic ammonia[5] (5 ml.) and 0.5 g. of III were left overnight at 25°, filtered, and concentrated to 2–3 ml. The resultant solid crystallized from water-alcohol in a yield of 0.2 g. (65%); needles, m.p. 215–216.5° (dec.); lit. (5), m.p. 219–220°.

Anal. Calc'd for $C_9H_{17}NO_7$: C, 43.0; H, 6.8; N, 5.6.
Found: C, 42.8; H, 7.0; N, 5.8.

N-Acetyl-2-hydroxyethylaminomethyl-meso-inositol (IVb) (NIH 4211). (a) One gram of III, 0.3 ml. of ethanolamine, and 10 ml. of methanol, refluxed 1–2 hours and cooled gave 0.55 g. (76%) of IVb; needles from water-ethanol or from methanol, m.p. 198–199.5°. A sample was dried at 78° for analysis.

Anal. Calc'd for $C_{11}H_{21}NO_8$: C, 44.7; H, 7.2; N, 4.7.
Found: C, 44.6; H, 7.5; N, 4.7.

(b) Ethanolamine (0.2 ml.), 0.5 g. of III, and 5 ml. of dry benzene was refluxed for two hours and cooled. The liquid was decanted, the resinlike material was dissolved in 5 ml. of methanolic ammonia,[5] and the solution filtered after one hour. From the filtrate 0.3 g. (80%) of IVb gradually separated; m.p. 198–200° alone or when mixed with IVb prepared as described above.

N-Acetylbenzylaminomethyl-meso-inositol (IVc) (NIH 4311). This compound was prepared in a yield of 84% (reaction time 3–4 hours) by either procedure (a) or (b) described above; needles from water, m.p. 230–232° (dec.).

Anal. Calc'd for $C_{16}H_{23}NO_7$: C, 56.3; H, 6.8; N, 4.1.
Found: C, 56.5; H, 6.9; N, 4.0.

Aminomethyl-meso-inositol (VIIa) *picrate.* (a) From IVa. A mixture of 0.8 g. of IVa and 24 ml. of 10% HCl was steam-heated for 1.5 hours and evaporated to dryness *in vacuo*. Trituration of the residue with hot methanol gave 0.5 g. of a hygroscopic hydrochloride. It was dissolved in 1–2 ml. of hot water and treated with 2–4 ml. of methanolic ammonia[5] to give 0.4 g. (60%) of VIIa (NIH 4324); ellipsoids from water-methanol, m.p. 163–175° or 198–200° (dec.); lit. (5), m.p. 160–162° (dec.). It was converted to the picrate (in aqueous alcohol) which crystallized from water-alcohol or aqueous methanol-ether in plates of m.p. 223–224° (dec.).

Anal. Calc'd for $C_{13}H_{18}N_4O_{13}$: C, 35.6; H, 4.1.
Found: C, 35.7; H, 4.2.

(b) *From VI.* Finely divided VI (0.1 g.) and 10 ml. of methanolic ammonia[5] were left at 25° for 70 hours (frequent shaking during the first seven hours). Concentration to 5 ml. and cooling at 5° gave a sticky solid which was dissolved in warm, aqueous picric acid. Addition of three volumes of 10% alcoholic picric acid and cooling gave 0.1 g. of picrate which was recrystallized from water-ethanol, then dissolved in 0.5 ml. of warm water, and the solution treated with 2 ml. of methanolic ammonia;[5] yield of base 0.03 g. (28%). This base (m.p. 163–165° or 198–200°) and its picrate (m.p. 222–224°) were identical with the VIIa and picrate prepared from IVa.

The *hydrochloride* of VIIa crystallized from water-methanol in needles, m.p. 231–234° (dec.) after drying for three hours at 78°.

Anal. Calc'd for $C_7H_{16}ClNO_6 \cdot \frac{1}{2}H_2O$: C, 33.0; H, 6.7; Cl, 13.9; H_2O, 3.5.
Found: C, 33.0; H, 6.5; Cl, 13.7; loss (117°), 3.0.

Posternak (5) reported this hydrochloride as anhydrous and decomposing, without melting, above 225°.

2-Hydroxyethylaminomethyl-meso-inositol (VIIb) *hydrochloride* (NIH 4325). Hydrolysis of IVb was effected as described for IVa. The resulting hydrated hydrochloride of VIIb (75% yield) crystallized from methanol-ether or water-alcohol in thin, rhombic prisms, m.p. 124–127°, to a froth. Drying at 117° *in vacuo* gave the anhydrous compound for analysis.

Anal. Calc'd for $C_9H_{20}ClNO_7$: C, 37.3; H, 7.0.
Found: C, 37.1; H, 7.2.

The *picrate*, prepared by adding excess alcoholic picric acid to an alcohol suspension of the hydrochloride, crystallized from water in needles of m.p. 78°, then 185–188°. After standing overnight or being dried at 78° it melted only at 187–189.5°.

Anal. Calc'd for $C_{15}H_{22}N_4O_{14}$: C, 37.4; H, 4.6.
Found: C, 37.4; H, 4.6.

Preparation of the hydrochloride of VIIb could also be effected in 75% yield by refluxing VI, ethanolamine, and methanol (2 hrs.), precipitating the amorphous base with ligroin (30–60°), and acidifying it (in methanol) to Congo Red with alcoholic HCl.

Benzylaminomethyl-meso-inositol (VIIc) *hydrochloride* (NIH 4312). This compound was prepared in a yield of 80% by hydrolysis of IVc as described above; needles from methanol-ether, m.p. 230–232° (dec.).

Anal. Calc'd for $C_{14}H_{22}ClNO_6$: C, 50.1; H, 6.6; Cl, 10.6.
Found: C, 49.7; H, 6.7; Cl, 10.3.

The *base*, prepared from the hydrochloride with dilute sodium hydroxide or from VI, benzylamine, and methanol (three hours refluxing, 90% yield), crystallized from water in plates, m.p. 213–215°.

Anal. Calc'd for $C_{14}H_{21}NO_6$: C, 56.2; H, 7.1.
Found: C, 56.1; H, 7.3.

SUMMARY

Reaction of the methyleneoxy derivative of *scyllo*-inosose pentaacetate (III) with morpholine and piperidine gave morpholinomethyl- and piperidinomethyl-*meso*-inositol pentaacetates (V) which were deacetylated to compounds VIII with methanolic ammonia.

Ammonia, ethanolamine, or benzylamine and III in methanol gave the N-acetylaminomethyl-*meso*-inositols (IV). Acid hydrolysis of IV gave the free amines (VII) which were also synthesized from the methyleneoxy derivative of *scyllo*-inosose (VI). The N-acetyl derivatives IVb and IVc could also be prepared from the appropriate amine and III in boiling benzene followed by treatment of the resinous mass with methanolic ammonia.

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REFERENCES

(1) MAY AND MOSETTIG, *J. Org. Chem.*, **14**, 1137 (1949).
(2) POSTERNAK, *Helv. Chim. Acta*, **27**, 457 (1944).
(3) FODOR AND KISS, *J. Am. Chem. Soc.*, **72**, 3495 (1950).
(4) ANDERSON AND LARDY, *J. Am. Chem. Soc.*, **72**, 3141 (1950).
(5) POSTERNAK, *Helv. Chim. Acta*, **33**, 1597 (1950).