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CYCLITOL DERIVATIVES. I. DERIVATIVES OF *RAC.-EPI*-INOSOSE

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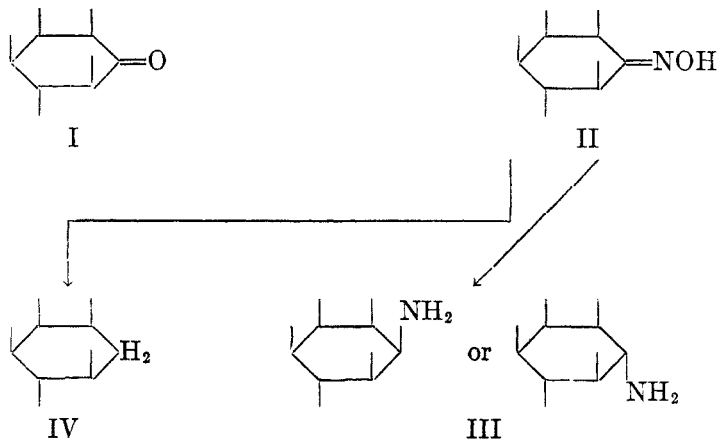
This is the first of a series of papers dealing with the synthesis of cyclitol derivatives.[1] It describes a number of nitrogen-containing compounds derived from *rac.-epi*-inosose (I).

The oxime (II) of *rac.-epi*-inosose could be obtained crystalline by adhering strictly to certain experimental conditions. Hydrogenation of II with platinum oxide in 70% methanol gave inosamine (III)[2] in a yield of 70%. When the hydrogenation was conducted in dilute acetic acid, a mixture consisting of *epi*-inositol and inosamine (III), was obtained in rather low yield; in dilute hydrochloric



acid only a desoxy-inositol (IV)[3] and very small amounts of *epi*-inositol (3) were formed. Catalytic hydrogenation of the semicarbazone of I gave a semicarbazide derivative in about 60% yield. From either compound, oxime or semicarbazone, only one of the two possible diastereomeric reduction products could be isolated. The inosamine III was readily N-methylated with formaldehyde in formic acid; it gave, with D-glucose, an amorphous, hygroscopic N-glucoside which failed to crystallize, and could not be reduced catalytically at room temperature and atmospheric pressure.

[1] The compounds are being tested for their action against *Mycobacterium tuberculosis* in the Tuberculosis Research Laboratory, U. S. Public Health Service, Cornell University Medical College, New York, N. Y., under the direction of Dr. Bernard D. Davis. An outline of the over-all plan of the cooperative project and methodological aspects will be given elsewhere.

[2] This compound has been prepared recently and independently by Carter, *et al.* (1). For the present we are naming this and analogous compounds inosamines as suggested by the authors.

[3] This compound was found to be identical with a desoxyinositol obtained recently by Magasanik and Chargaff (2) in the catalytic reduction of *rac.-epi*-inosose in acid solution.

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EXPERIMENTAL[4]

rac.-epi-Inosose (I) was prepared by the method of Posternak (3) whose procedure was adapted to 50-g. runs.[5] The optimal time for the nitric acid evaporation was found to be 10–15 minutes (1). The yield of I, purified through the phenylhydrazone, was 10–12%.

Oxime (II) of rac.-epi-inosose (NIH 3582).[6] A mixture of 8.0 g. of hydroxylamine hydrochloride, 11.2 g. of potassium acetate, 6 ml. of water, and 6 ml of absolute alcohol was shaken for ten minutes, cooled in ice, and filtered. The filtrate, diluted to 50 ml. with absolute ethanol, was added during 7–10 minutes to a 75°-solution of 10 g. of I in 75 ml. of water. After 1.5 hours at room temperature, 120 ml. each of absolute ethanol and ether were added. The solution was seeded[7] and left at room temperature for fifteen hours and at −3° for two days. The 7.9 g. of oxime resulting was dissolved in 25 ml. of warm water and 150 ml. of absolute ethanol and 40 ml. of ether were added; yield 7 g., m.p. 150–151° (dec.). For analysis it was recrystallized from 95% ethanol; needles.

Anal. Calc'd for $C_6H_{11}NO_5$: C, 37.3; H, 5.7.
Found: C, 37.5; H, 6.0.

Inosamine (III) hydrochloride (NIH 3489). A mixture of 1.2 g. of II, 0.1 g. of platinum oxide, 10 ml. of water,[8] and 20 ml. of methanol absorbed two moles of hydrogen during twelve hours. To the filtered, methanol-diluted solution was added 0.8 ml. of conc'd HCl and ether to turbidity: yield 0.9 g. (70%), m.p. 220–223° (dec.). It crystallized from water-methanol in prisms of m.p. 223–226° (evac. tube).

Anal. Calc'd for $C_6H_{14}ClNO_5$: C, 33.4; H, 6.6; Cl, 16.5.
Found: C, 33.4; H, 6.5; Cl, 16.5.

When mixed with a sample of *d,l*-inosamine-EA hydrochloride prepared by Carter, *et al.* (1) (m.p. 224–226°, evac. tube), the m.p. was unchanged.

The *free base* (plates, m.p. 204–208.5°, dec.) was prepared from the hydrochloride with aqueous alcoholic ammonia or directly from the filtered reduction mixture by ether-dilution. Attempts to purify it for analysis were attended by gradual decomposition.

The *picrate*, prepared from III with aqueous alcoholic picric acid-ether, crystallized from aqueous alcohol-ether containing a little picric acid, in yellow plates, m.p. 174–176°.

Anal. Calc'd for $C_{12}H_{16}N_4O_{12}$: C, 35.3; H, 4.0.
Found: C, 35.5; H, 3.9.

The *hexaacetate* melted at 188–189° alone or in mixture with that prepared by Carter, *et al.* (1).

The *N-acetyl derivative* had the m.p. 200–201.5° (dec.) (1).

N,N-Dimethylinosamine hydrochloride (NIH 3583). A mixture of 0.2 g. of III, 0.2 g. of 37% formaldehyde, and 0.28 g. of 98% formic acid was heated on the steam-bath for forty minutes, cooled, acidified with six drops of conc'd HCl, and diluted with methanol-ether.

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

[5] By H. George Latham, Jr.

[6] Compounds designated by an NIH number have been submitted for testing.

[7] Seed crystals were obtained by further dilution of a small sample with ethanol-ether, washing the precipitated oil with ethanol-ether and finally triturating it with methanol.

[8] With water alone as the solvent, highly colored solutions resulted from which no III could be obtained.

Gradually 0.15 g. (56%) of hydrochloride, m.p. 223–225° (dec.)[9] separated: prisms from aqueous methanol-ether.

Anal. Calc'd for $C_8H_{15}ClNO_5$: C, 39.4; H, 7.4.

Found: C, 39.5; H, 7.3.

The *picrate*, prepared from the hydrochloride with aqueous alcoholic picric acid-ether, was recrystallized from water-ethanol, then 95% ethanol; orange prisms, m.p. 182–184°.

Anal. Calc'd for $C_{14}H_{20}N_4O_{12}$: C, 38.5; H, 4.6.

Found: C, 38.7; H, 4.7.

Other hydrogenations of II. A mixture of 0.5 g. of II, 0.05 g. of platinum oxide, 3.5 ml. of water, and 0.5 ml. of conc'd HCl absorbed 2.6 moles of hydrogen during twenty hours. The filtered solution was evaporated to dryness *in vacuo* to give a partially crystalline residue which, from water-alcohol, gave 0.15% g. (35%) of *desoxyinositol* (IV),[10] m.p. 206–208°; prisms.

Anal. Calc'd for $C_6H_{12}O_5$: C, 43.9; H, 7.4.

Found: C, 43.8; H, 7.5.

A mixture of IV and the desoxyinositol (m.p. 204–206°) prepared by Magasanik and Chargaff (2) and termed by them *d,l-epi-quercitol*, melted at 205–207°.

The filtrate from the 0.15 g. of IV, evaporated to dryness, gave, from water-ethanol, a small yield of *epi*-inositol, m.p. 287–290° (evac. tube), identified by a mixed melting point with authentic material (3).

The *pentaacetate* of IV (acetic anhydride-H_2SO_4, steam-bath heat) crystallized from ethanol in plates, m.p. 123–124.5° or prisms, m.p. 142–143°. The two modifications were interconvertible.

Anal. Calc'd for $C_{16}H_{22}O_{10}$: C, 51.4; H, 5.9.

Found: C, 51.4; H, 5.9.

When II was hydrogenated in 25% aqueous acetic acid, 2.3 moles of hydrogen was absorbed to give *epi*-inositol (25%) and III in low yield.

1-Pentahydroxycyclohexylsemicarbazide (NIH 3518). A mixture of 1.0 g. of I semicarbazone (NIH 3517) (3a), 0.1 g. of platinum oxide, and 50 ml. of water absorbed 1.3 moles of hydrogen during sixty hours. The filtered solution was evaporated to dryness to give a sirup which crystallized from water-ethanol in a yield of 0.6 g.; rectangular plates, m.p. 208° (dec.).

Anal. Calc'd for $C_7H_{15}N_3O_6$: C, 35.4; H, 6.4.

Found: C, 35.4; H, 6.6.

Thiosemicarbazone of rac. epi-inosose (NIH 3788). A mixture of 1.0 g. of I, 0.6 g. of thiosemicarbazide, and 10 ml. of water was heated on the steam-bath for 15–20 minutes, let stand at room temperature for seven hours and at 5° overnight: yield 0.8 g., m.p. 197–198° (dec.): needles from water.

Anal. Calc'd for $C_7H_{13}N_3O_5S \cdot H_2O$: C, 31.2; H, 5.6; H_2O, 6.7.

Found: C, 31.3; H, 5.7; Loss in wt. (117°, high vac.), 6.7.

N-Glucoside of inosamine (NIH 3584). A mixture of 0.5 g. of anhydrous D-glucose, 0.5 g. of III, and 25 ml. of methanol was refluxed for two hours, diluted with ether, and left at 2° overnight to give 0.9 g. of an amorphous, hygroscopic solid. For analysis it was dissolved in boiling methanol (Norit), precipitated with dry ether (prolonged cooling), and dried at 75–80° *in vacuo*: m.p. 110–123° (froth), $[\alpha]_D^{20}$ −2.5° → 16° (*c*, 0.40, H_2O, 60 hrs.).

Anal. Calc'd for $C_{12}H_{23}NO_{10}$: C, 42.2; H, 6.8; N, 4.1.

Found: C, 42.4; H, 7.0; N, 4.1.

The change in rotation is apparently due principally to partial hydrolysis (5). When 0.3

[9] In the first experiment a lower-melting modification (m.p. 188–191°) was obtained. It was readily converted to the one of m.p. 223–225°.

[10] An isomeric desoxyinositol melting at 233–235° (pentaacetate, m.p. 190°) was obtained by Posternak (4) in the catalytic reduction (platinum oxide, dil. H_2SO_4) of *scyllo-meso*-inosose.

g. of N-glucoside was allowed to stand for three days in water, 0.05 g. of III was recovered as the hydrochloride. Attempts to hydrogenate the N-glucoside (methanol, platinum oxide, room temperature and pressure) were unsuccessful.

SUMMARY

The catalytic hydrogenation of the oxime of *rac.-epi*-inososе is described. Depending upon the conditions, an inosamine, a desoxyinositol, and *epi*-inositol were obtained in varying amounts.

An N-glucoside has been prepared from the above inosamine.

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