Anal. Calcd. for $C_{11}H_{15}ON$: N, 7.91. Found (Kjeldahl): N, 7.84.

Methylbenzylcarbinamine (Amphetamine) (II).—The distilled amide (15.4 g.) was boiled under reflux with 100 ml. of 15% hydrochloric acid for eleven hours. The mixture was then cooled, washed with benzene, and the aqueous layer separated and made alkaline with sodium hydroxide. The amine separated as an oil which was extracted with benzene, the extract dried (sodium sulfate), the benzene removed and the amine (7.0 g., 67%) boiling at 205–210° distilled at ordinary pressure. The benzoyl derivative melted at 134–135° alone or when mixed with an authentic sample prepared from phenylacetone.

N-(Dimethylbenzylcarbinol)-formamide.—Sodium cyanide (90%, 11 g., 0.2 mole) and 25 ml. of acetic acid were mixed with cooling and stirring. A solution of sulfuric acid (50 g.) in 25 ml. of acetic acid was then added with continued stirring at 20°. Dimethylbenzylcarbinol (30 g., 0.2 mole) was then added and the temperature permitted to rise spontaneously to 40–50° as the carbinol, insoluble at first, passed into solution. The mixture was then heated to 70° during one-half hour, stoppered, allowed to stand for two hours, diluted with 300 ml. of water, and neutralized with sodium carbonate. The formamide (21.5 g., 61%) separated as a viscous oil which was extracted with ether and distilled (b. p. 183–185° (15 mm.)) after drying (sodium sulfate) and removal of the ether.

Anal. Calcd. for $C_{11}H_{15}ON$: N, 7.81. Found (Kjeldahl): N, 7.55.

The formamide was also prepared by the same procedure with substitution of methallylbenzene and also 2-methyl-3-phenyl-2-propene for the dimethylbenzylcarbinol used above with practically identical result.

Dimethylbenzylcarbinamine (III).—The formamide (10 g.) obtained as in the preceding paragraph was refluxed for five hours with 85 ml. of 20% sodium hydroxide solution. The mixture was then steam distilled, the distilled amine dissolved in ether, dried (sodium sulfate) and the amine (7.5 g., 89%) distilled at 85–90° (10 mm.) after removal of the ether. Zenitz, Macks and Moore[10] reported the boiling point as 89–90° (10 mm.). The amine was dissolved in warm concentrated hydrochloric acid, the solution decolorized with carbon and allowed to cool to crystallize the hydrochloride, m. p. 198–198.5°. Zenitz, Macks and Moore[10] reported the melting point as 200–201°; Shelton and van Campen,[11] 195–196°.

Anal. Calcd. for $C_{10}H_{15}N$: N, 9.39. Found (Kjeldahl): N, 9.12.

Summary

A convenient general method for the preparation of *t*-carbinamines, and also a new synthesis of *β*-phenethylamines of interest as medicinals has been described.

[10] Zenitz, Macks and Moore, THIS JOURNAL, **70**, 955 (1948).

[11] Shelton and Van Campen, U. S. Patent 2,408,345 (Sept. 1946).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Identity of Müller's *iso*-Inositol with Racemic Inositol[1]

BY HEWITT G. FLETCHER, JR.,[2] AND GORDON R. FINDLAY[3]

In 1912 Hugo Müller[4] reported that the treatment of *meso*-inositol (m. p. 225°) or scyllitol with hydrogen halides in acetic acid solution at an elevated temperature gave a mixture from which, after hydrolysis with barium hydroxide, were isolated two hexahydroxycyclohexanes which he named *iso*- and *pseudo*-inositols. The marked similarity between the physical constants which Müller reported for *iso*-inositol and those which had previously been recorded for racemic inositol[5,6,7] has led to the suggestion[8] that the two cyclitols may be identical. It is the purpose of the present communication to present the evidence which verifies this identity.

Müller[4] described several processes leading to his *iso*- and *pseudo*-inositols. Hydrogen chloride, hydrogen bromide and hydrogen iodide were all employed and both *meso*-inositol and its hexaacetate as well as scyllitol were used; in each case the solvent was glacial acetic acid and the initial reaction product was treated with boiling aqueous barium hydroxide. For the present work *meso*-inositol was heated with glacial acetic acid which had been saturated with hydrogen chloride at room temperature. After sixty-nine hours at a temperature of 160° the solvent was removed *in vacuo* and the residue boiled with aqueous barium hydroxide. Removal of barium, deionization and finally concentration *in vacuo* yielded a residue which deposited from aqueous alcoholic solution a crude crystalline product representing twelve per cent. of the starting material. After recrystallization from water the substance was found to possess the same melting point as racemic inositol; a mixed melting point with authentic racemic inositol was undepressed. Comparison of the optical crystallographic properties of *iso*-inositol with those of racemic inositol showed the two to be identical. Further comparison of *iso*-inositol with racemic inositol was made through their hexaacetates and hexabenzoates. In both cases mixed melting points between the corresponding derivatives were undepressed.

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[1] A portion of the material of this paper is taken from a thesis submitted by Gordon R. Findlay to the Department of Chemistry of the Massachusetts Institute of Technology in October, 1944, in partial fulfillment of the requirements for the degree of Bachelor of Science.

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[4] H. Müller, *J. Chem. Soc.*, **101**, 2383 (1912).

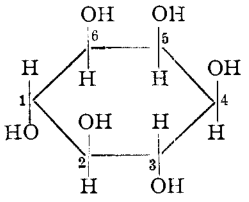
[5] L. Maquenne and C. Tanret, *Compt. rend.*, **110**, 86 (1890).

[6] G. Wyrouboff, *Bull. soc. franc. minéral.*, **25**, 165 (1902); *Chem. Zentr.*, **73**, II, 1498 (1902).

[7] G. Tanret, *Compt. rend.*, **145**, 1196 (1907).

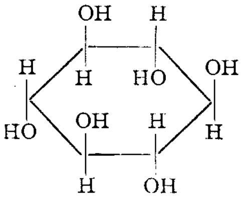
[8] H. G. Fletcher, Jr., *Advances in Carbohydrate Chem.*, **3**, 45 (1948).

As reviewed elsewhere,[8] the configurations of *meso*-inositol (I), scyllitol (II), *dextro*-inositol (III) and *levo*-inositol (IV) are now known with certainty. Inspection of the spatial formulas shows that the conversion of *meso*-inositol to racemic inositol necessitates that one Walden inversion take place at carbon atoms four or six. Since these two positions in *meso*-inositol are exactly equivalent (the molecule being symmetrical with respect to them) each of the two are attacked equally and a raceme results. On the other hand, it will be seen from the formulas that scyllitol has six planes of symmetry; all of its hydroxyl groups are equivalent and the inversion of any *one* of them produces *meso*-inositol. To obtain racemic inositol from scyllitol as Müller reported, it would be necessary to invert the configurations of *two* carbon atoms. While the mechanism of these inversions is as yet obscure it is interesting to observe that Müller reported the isolation of identical bromodesoxy- and dibromodidesoxy-inositols from both *meso*-inositol and scyllitol.



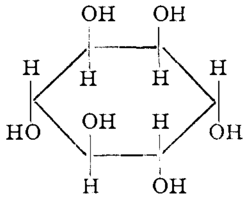
I

meso-Inositol



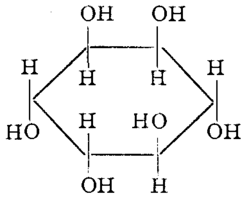
II

Scyllitol



III

dextro-Inositol



IV

levo-Inositol

Acknowledgment.—We wish to express our indebtedness to Professors J. M. Nelson and R. C. Elderfield for the gift of a sample of crude pinitol and to Dr. R. C. Hockett for a quantity of quebrachitol. Combustion analyses were carried out by Mrs. H. I. Fitz. We wish also to thank Mr. Joseph J. Fahey for optical crystallographic measurements.

Experimental[9]

iso-**Inositol from** *meso*-**Inositol.**—Ten grams of pure *meso*-inositol which had been dried at 120° was placed in a Pyrex pressure tube and covered with 55 ml. of glacial acetic acid which had previously been saturated with hydrogen chloride at 0°. The suspension was left at room temperature until hydrogen chloride evolution had become negligible; the tube was then sealed and heated at 160° for sixty-nine hours. The reddish-brown solution resulting from four such runs was diluted with 300 ml. of water and concentrated *in vacuo* to a stiff sirup. Three 300-ml. portions of water were successively evaporated *in vacuo* from this sirup in order to remove the bulk of the acid. The residual black tar was diluted with 250 ml. of water, treated with 140 g. of barium hydroxide octahydrate and then boiled under reflux for one hour. After cooling, the barium was removed from solution with 3 *N* sulfuric acid. Passage through a filter precoated with Filter-Cel and decolorizing carbon and then through a column of Amberlite IR-4 removed the major part of the colored impurities. The solution was then concentrated *in vacuo* at 45–55° to a stiff brownish sirup which was dissolved in 16 ml. of warm water and treated with 5 ml. of alcohol. After three weeks at 5° the solution had precipitated a pale, pink microcrystalline mass which weighed 4.8 g. (12%) and melted at 240–246°. Two recrystallizations from three parts of water gave clear quadrilateral plates melting at 252–253°; the molten material slowly darkened at this temperature. Müller[4] reported a value of 246–250° as the melting point of *iso*-inositol. A mixed melting point with authentic racemic inositol[10] gave the value of 252–254°.

Samples of *iso* and racemic inositol were submitted to Mr. Joseph J. Fahey of the United States Geological Survey for crystallographic comparison. He reported the constants for the two substances to be identical. The refractive indices n^{20}_D are $\alpha = 1.582$, $\beta = 1.584$ and $\gamma = 1.607$. The crystals are biaxial and positive in sign, the optical angle being 35° and the dispersion of violet is greater than red.

Anal. Calcd. for $C_6H_{12}O_6$: C, 39.99; H, 6.72. Found: C, 39.90; H, 6.67.

iso-**Inositol Hexaacetate.**—Pure *iso*-inositol (0.7089 g.) as prepared above was triturated with a boiling mixture of 5 ml. of dry pyridine and 3.5 ml. of acetic anhydride, one hour being required to effect solution. After standing overnight at 60° the reaction mixture was cooled, treated with finely divided ice and extracted with ethylene dichloride. Successive washings with water, 3 *N* sulfuric acid and aqueous sodium bicarbonate (all cold) served to remove pyridine and acid from the solution which was then dried over sodium sulfate. After removal of the desiccant the ethylene dichloride was removed *in vacuo* at 55°. Absolute alcohol (10 ml.) was distilled *in vacuo* from the residual sirup and it was then dissolved in 4 ml. of warm *n*-butanol. The stubby needles which formed at room temperature amounted to 1.43 g. (84%) and melted at 110–112°. Once recrystallized from a mixture of 8 parts of ether and 2 parts of pentane the product melted at 111–112° either alone or in admixture with a sample of racemic inositol hexaacetate prepared in a manner similar to the above from an authentic specimen of racemic inositol. Müller[4] reported a melting point of 112° for *iso*-inositol hexaacetate.

Anal. Calcd. for $C_{18}H_{24}O_{12}$: C, 49.99; H, 5.59. Found: C, 49.97; H, 5.48.

iso-**Inositol Hexabenzoate.**—*iso*-Inositol (0.4251 g.) was triturated with a mixture of 5 ml. of dry pyridine and 2.5 ml. of benzoyl chloride at approximately 105°; ten minutes sufficed for the solution of the solid. After three hours at 60° the excess acid chloride was decomposed with finely chipped ice and then extracted with ethylene dichloride. The non-aqueous layer was washed with water, 3 *N* sulfuric acid and finally aqueous sodium bicarbonate. After drying with sodium sulfate the solution was filtered through decolorizing carbon and concentrated *in vacuo* at 55°. Absolute alcohol was added and, after four hours at room temperature, the product was removed by filtration: 1.73 g. (91%). After recrystallization from a mixture of 3 parts of dioxane and 5 parts of absolute alcohol the *iso*-

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[9] Melting points over 220° were determined in a Berl and Kullmann copper block, the thermometer reading being corrected for stem exposure; below 220° a Hershberg-type apparatus having the thermometer completely immersed in the bath liquid was used.

[10] The demethylation of quebrachitol (*levo*-inositol monomethyl ether) and of pinitol (*dextro*-inositol monomethyl ether) was carried out according to the method of T. Posternak [*Helv. Chim. Acta*, **19**, 1007 (1936)] to give *levo*- and *dextro*-inositol, respectively. Recrystallization of a mixture of equal weights of the two enantiomorphs from a limited quantity of warm water gave racemic inositol melting at 252–254°. Maqenne and Tanret[5] reported a melting point of 253° in the Maquenne block.

inositol hexabenzoate melted at 216–217°. Mixed with a sample of racemic inositol hexabenzoate prepared in a similar fashion from authentic racemic inositol the material melted at 216–217°.[11]

Racemic inositol hexabenzoate is insoluble in pentane, very sparingly soluble in boiling alcohol and readily soluble in acetone and dioxane.

Anal. Calcd. for $C_{48}H_{36}O_{12}$: C, 71.63; H, 4.51. Found: C, 71.55; H, 4.48.

Müller[4] obtained a crystalline *iso*-inositol tetrabenzoate on heating *iso*-inositol with benzoyl chloride. Maquenne and C. Tanret[5] and later G. Tanret[7] reported a racemic inositol benzoate melting at 217°. Since our present hexabenzoate shows the same melting point it is presumed to be identical with theirs although their publications fail to give any details of preparation or analyses.

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[11] When heated rapidly to temperatures between 135 and 215° racemic inositol hexabenzoate melted and then resolidified. When heated slowly from 130 to 135° the clear prisms became opaque without losing their form and then melted at 216–217°.

Summary

The previously recorded observation that *meso*-inositol may be converted by the successive actions of hydrogen chloride in glacial acetic acid solution and hot aqueous barium hydroxide into an isomer has been confirmed.

Comparison of this isomer and its hexaacetate and hexabenzoate with racemic inositol and its corresponding derivatives has shown that the isomer, originally called *iso*-inositol is, in fact, racemic inositol.

CAMBRIDGE 39, MASSACHUSETTS

RECEIVED AUGUST 3, 1948

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

1,5-Anhydroribitol

BY R. JEANLOZ,[1] HEWITT G. FLETCHER, JR., AND C. S. HUDSON

Stereochemical theory predicts the possible existence of four 1,5-anhydro-pentitols: 1,5-anhydro-D-arabitol, 1,5-anhydro-L-arabitol, 1,5-anhydroxylitol and 1,5-anhydroribitol. The syntheses of 1,5-anhydro-D-arabitol[2] and 1,5-anhydroxylitol[3] have recently been reported by this Laboratory. This communication will describe the synthesis of the fourth member of the series, 1,5-anhydroribitol, and a group of related derivatives encountered in the course of the research.

In previous syntheses of 1,5-anhydrides of sugar alcohols[2,3,4] reductive desulfurization of acetylated aryl 1-thioglycosides has been the method of choice. However, in view of the ease of preparation and crystallinity of the pentose benzoates and tribenzoylpentosyl bromides[3,5] and considering the marked instability of triacetylribopyranosyl bromide,[6] the path to an aryl 1-thio-D-ribopyranoside tribenzoate appeared more attractive than that to the corresponding acetate. Low temperature benzoylation of D-ribose indeed readily gave in 35% yield crystalline β-D-ribopyranose tetrabenzoate (I); the substance is provisionally assigned to the β-series because of its strong levorotation and the dextrorotation (+8.6°) of the amorphous mixture remaining in the mother liquor which presumably contains the α-anomer. Both this crystalline tetrabenzoate and the sirup remaining after removal of solvent from its mother liquor gave, when treated with a solution of hydrogen bromide in glacial acetic acid, an easily crystallized 2,3,4-tribenzoyl-β-D-ribopyranosyl bromide (II) which was strongly levorotatory (−199°) and could therefore tentatively be classed in the β-series.

The stability of 2,3,4-tribenzoyl-β-D-ribopyranosyl bromide stands in marked contrast to that of its acetyl analog; a once-recrystallized sample showed no decomposition after storage for six months in a closed container at room temperature. Its condensation with potassium 2-thionaphtholate[7,2] yielded an amorphous mixture which was separated by chromatography on alumina. Rechromatography of a weakly adsorbed, sulfur-containing, levorotatory fraction gave in 42% yield (based on the bromide) a sirup having the analysis of a 2′-naphthyl 2,3,4-tribenzoyl-1-thio-β-D-ribopyranoside (III); its rotation of −59° permits its tentative classification in the β-series.

Reductive desulfurization of 2′-naphthyl 2,3,4-tribenzoyl-1-thio-β-D-ribopyranoside in alcoholic solution with Raney nickel led to the isolation of crystalline 2,3,4-tribenzoyl-1,5-anhydroribitol (IV). Catalytic debenzoylation of this product gave 1,5-anhydroribitol (V). The optical inactivity of this pentitol anhydride as well as that of its tribenzoate and triacetate affords conclusive proof of the presence of a *meso*-tetrahydropyran structure and confirms the supposition that the preceding three intermediates are all pyranose derivatives. Further proof was obtained through periodate oxidation of the free anhydride; as expected, 1,5-anhydroribitol consumed on a molar

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[2] H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **69**, 1672 (1947).

[3] H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **69**, 921 (1947).

[4] H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **70**, 310 (1948).

[5] H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **69**, 1145 (1947).

[6] R. A. Baxter, A. C. McLean and F. S. Spring, *J. Chem. Soc.*, **523** (1948).

[7] W. T. Haskins, R. M. Hann and C. S. Hudson, THIS JOURNAL, **69**, 1668 (1947).