brated at 24° had an $[\alpha]^{25}D$ −8° (*c* 3.1, water).[20] The sirupy acid was identified by conversion to its crystalline phenyl hydrazide, m.p. 98°.[20]

(20) J. W. E. Glattfeld and G. E. Miller, THIS JOURNAL, **42**, 2314 (1920).

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LAFAYETTE, IND.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

The Configuration of "α"-D-Glucosaccharinic Acid: 2-C-Methyl-D-*ribo*-pentonic Acid

BY JOHN C. SOWDEN AND DONALD R. STROBACH

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"α"-D-Glucosaccharinic acid has been converted, by Ruff degradation followed by reduction and acetylation, to 1-deoxy-D-arabinitol tetraacetate. Thus, the partial configuration of the acid at C-3 and C-4 is D-*erythro* and, since the partial configuration at C-2 and C-3 had been previously established as *erythro*, the acid is 2-*C*-methyl-D-*ribo*-pentonic acid.

Although "α"-D-glucosaccharinic acid was shown many years ago by Kiliani to be a 2-*C*-methyl-pentonic acid,[1] its configuration has not been rigorously established up to the present time.

Prior to the present work, the accumulated evidence bearing on the configuration of "α"-D-glucosaccharinic acid included the following. Nef[2] concluded, on the basis of his theory of the mechanism of saccharinic acid formation, that the acid was limited to the D-*arabino* or D-*ribo* configurations. Of these, he chose the former because of qualitative similarities between certain derivatives of the saccharinic acid and the corresponding derivatives of D-arabinonic acid. Isbell's modification[3] of the Nef mechanism did not change the conclusion that the saccharinic acid must possess either the D-*arabino* or D-*ribo* configuration, but the recent observation[4] that "α"-D-glucosaccharinic lactone forms a 2,3-*O*-isopropylidene derivative supports the assignment of the D-*ribo* configuration rather than the D-*arabino* configuration chosen by Nef. Adding uncertainty to either choice, however, was the fact that tracer experiments[4b] have revealed that fragment recombination plays an important role in the formation of "α"-D-glucosaccharinic acid and, hence, that the Nef–Isbell mechanism is not a safe basis for assigning configuration in this instance. Accordingly, a direct proof of the configuration at C-3 and C-4 of the acid was undertaken.

"α"-D-Glucosaccharinic acid (I) was converted by a Ruff degradation[5] to a sirupy product which, after reduction with sodium borohydride and acetylation, provided 1-deoxy-D-arabinitol tetraacetate (III). For comparison, the latter compound also was prepared unequivocally by applying the same sequence of reactions to D-fuconic acid (II). The products from the two sources were identical in melting point, optical rotation and X-ray diffraction pattern. Thus, the partial configuration of "α"-D-glucosaccharinic acid at C-3 and C-4 is D-*erythro* and, in view of the structure of its acetonated lactone, the acid is 2-*C*-methyl-D-*ribo*-pentonic acid.

The assignment of the *erythro* configuration to C-2 and C-3 of "α"-D-glucosaccharinic acid is based on the assumption that the hydroxyl groups at these positions must be *cis* to each other in the lactone to allow the formation of a cyclic ketal. This assumption is particularly acceptable if 2,3-*O*-isopropylidene-D-glucosaccharin is a γ-lactone. Accordingly,

(1) H. Kiliani, *Ber.*, **15**, 701, 2953 (1882); *Ann.*, **218**, 361 (1883). For a review of saccharinic acid chemistry, see J. C. Sowden, *Adv. in Carbohydrate Chem.*, **12**, 35 (1957).

(2) J. U. Nef, *Ann.*, **376**, 1 (1910).

(3) H. S. Isbell, *J. Research Natl. Bur. Standards*, **32**, 45 (1944).

(4) (a) L. M. Utkin and G. O. Grabilina, *Doklady Akad. Nauk (S.S.S.R.)*, **93**, 301 (1953); *C. A.*, **48**, 12676 (1954); (b) J. C. Sowden, M. G. Blair and D. J. Kuenne, THIS JOURNAL, **79**, 6450 (1957).

(5) O. Ruff, *Ber.*, **31**, 1573 (1898).

evidence for this structure was sought in the present work. The acetonated lactone was converted to its *p*-toluenesulfonate IV. The ester group in the latter readily underwent displacement when treated with sodium iodide in acetic anhydride or with sodium thiocyanate in acetonylacetone. Accordingly, the tosyl ester function is exocyclic[6] and hence the lactone ring is closed at C-4. The products from both of the displacement reactions were amorphous, but that from the treatment with sodium thiocyanate provided crystalline 5-deoxy-2,3-*O*-isopropylidene-2-*C*-methyl-D-*ribo*-pentonic γ-lactone (V) on treatment with Raney nickel. De-acetonation then yielded crystalline 5-deoxy-2-*C*-methyl-D-*ribo*-pentonic γ-lactone (VI).

Experimental

1-Deoxy-D-arabinitol Tetraacetate (III). (A) From "α"-D-Glucosaccharin.—One gram of "α"-D-glucosaccharin[1] in 15 ml of water was converted to the calcium saccharinate by brief boiling with a slight excess of calcium hydroxide. The solution then was cooled to room temperature, neutralized to phenolphthalein with dilute acetic acid, and subjected to the Ruff oxidation according to the general procedure described for calcium D-gluconate by Fletcher, Diehl and Hudson.[7] Four successive 2-ml. portions of 30% hydrogen peroxide were used for the oxidation. The sirupy product obtained from the degradation was dissolved in 5 ml. of water and treated with 0.2 g. of sodium borohydride. After standing overnight, the solution was acidified with acetic acid, de-ionized and concentrated at reduced pressure to a sirup. The latter then was concentrated with several portions of methanol to remove boric acid. The dried sirup was acetylated at room temperature overnight with a mixture of 5 ml. of acetic anhydride and 6 ml. of pyridine. The acetylation mixture was poured onto ice-water and extracted with chloroform. The extract was washed with dilute hydrochloric acid and water, dried over magnesium sulfate, and concentrated to a semi-crystalline mass. The crystals (0.18 g.) were collected with the aid of cold ethanol and recrystallized, first from aqueous ethanol and then from Skellysolve D. The resulting product showed m.p. 113–114° and $[\alpha]^{25}D$ + 25.5° in chloroform, *c* 2.6.

Anal. Calcd. for $C_{13}H_{20}O_8$: C, 51.3; H, 6.63. Found: C, 51.5; H, 6.56.

For 1-deoxy-D-arabinitol tetraacetate ("D-lyxomethylitol tetraacetate"), prepared from D-arabinose diethyl dithioacetal tetraacetate by desulfurization with Raney nickel, Bollenback and Underkofler[8] record m.p. 115–116° and $[\alpha]^{20}D$ + 27.3° in chloroform, *c* 1.

(B) **From D-Fucose.**—A solution of 10 g. of D-fucose (Nutritional Biochemicals Corporation, Cleveland, O.) in 500 ml. of water was treated with 25 g. of barium carbonate and 3.3 ml. of bromine. The mixture was shaken occasionally until the bromine dissolved (~30 min.) and then allowed to stand in the dark at room temperature for 40 hours. After removal of bromine by aeration, barium was removed by precipitation with a slight excess of sulfuric acid and filtration. The filtrate was passed over Duolite A-4 in the acetate form to remove hydrobromic and sulfuric acids and concentrated at reduced pressure, finally over potassium hydroxide to remove acetic acid. The resulting sirup was dissolved in 250 ml. of water and the solution was boiled with 2 g. of calcium hydroxide. After cooling, excess calcium was precipitated with carbon dioxide. The resulting solution of calcium D-fuconate was subjected to the Ruff oxidation as described above. Two successive 10-ml. portions of 30% hydrogen peroxide were used in the oxidation. The product was a sirup weighing 4.2 g. Two grams of the latter was reduced with sodium borohydride and then acetylated according to the general directions of Abdel-Akher, Hamilton and Smith.[9] The crude product thus obtained (1.3 g., m.p. 95–100°) was recrystallized first from ethanol and then from Skellysolve D to give 1-deoxy-D-arabinitol tetraacetate of m.p. 113–114° and $[\alpha]^{25}D$ + 25.6° in chloroform, *c* 2.4.

Anal. Calcd. for $C_{13}H_{20}O_8$: C, 51.3; H, 6.63. Found: C, 51.3; H, 6.66.

This product did not depress the melting point of that obtained from "α"-D-glucosaccharin, and the two preparations showed identical X-ray diffraction patterns.[10]

2,3-*O*-Isopropylidene-2-C-methyl-5-*O*-*p*-toluenesulfonyl-D-*ribo*-pentonic γ-lactone (IV).[11]—Ten grams of 2,3-*O*-isopropylidene-"α"-D-glucosaccharin[4] in 100 ml. of anhydrous pyridine was treated with 10.5 g. of *p*-toluenesulfonyl chloride at 0°. After 2 hours at 0° and 20 hours at room temperature, the solution was poured into ice-water. The resulting crystals (9 g.) were collected, washed with water, dried and recrystallized from ether–petroleum ether. The product (7.6 g.) showed m.p. 93–94° and $[\alpha]^{22}D$ +3.5° in chloroform, *c* 2.2.

Anal. Calcd. for $C_{16}H_{20}O_7S$: C, 53.9; H, 5.65. Found: C, 53.8; H, 5.43.

Refluxing 200 mg. of this product with 200 mg. of sodium iodide in 25 ml. of acetic anhydride for 1 hour resulted in the precipitation, after cooling, of 100 mg. (92%) of sodium *p*-toluenesulfonate. Filtration and concentration yielded an amorphous residue from which no crystalline product could be obtained.

5-Deoxy-2,3-*O*-isopropylidene-2-*C*-methyl-D-*ribo*-pentonic γ-Lactone (V).—A solution containing 4.6 g. of the above tosyl ester and 4.6 g. of sodium thiocyanate in 55 ml. of acetonylacetone was heated in an oven at 120° for 1 hour. Cooling and filtration then yielded 2.4 g. (96%) of sodium *p*-toluenesulfonate. The filtrate was concentrated in an air jet to a thin sirup. This was dissolved in ether, washed several times with water, dried over sodium sulfate and concentrated, finally at 0.1 mm. for several hours. The resulting sirup (3.6 g.) was refluxed in 200 ml. of absolute ethanol with about 50 g. of Raney nickel for 5 hours. The reaction solution was separated by decantation and filtration from the nickel and the latter was extracted four times with fresh, hot ethanol. Concentration of the combined filtrates, followed by concentration with Skellysolve B, yielded 275 mg. (11%) of crude V, m.p. 85–90°. Recrystallization from Skellysolve B gave pure V, m.p. 91–92° and $[\alpha]^{25}D$ −74° in chloroform, *c* 3.7.

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.4; H, 7.60. Found: C, 58.1; H, 7.58.

The observed low yield of V may be attributed, at least in part, to the surprisingly high volatility of this compound. An analytical sample being dried at room temperature and 0.1 mm. volatilized completely in 5 hours.

5-Deoxy-2-*C*-methyl-D-*ribo*-pentonic γ-Lactone (VI).—A solution containing 200 mg. of V in 1 ml. of ethanol and 6 ml. of 0.1 *N* hydrochloric acid was refluxed for 2 hours, cooled, de-ionized over Duolite A-4 and concentrated. The resulting crystals (m.p. 73–78°, 135 mg., 85%) were recrystallized from ether–petroleum ether to give pure VI, m.p. 77–78°, $[\alpha]^{25}D$ +68° in water, *c* 1.7.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.4; H, 6.89. Found: C, 49.3; H, 6.90.

ST. LOUIS, MO.

(6) R. S. Tipson, *Adv. in Carbohydrate Chem.*, **8**, 107 (1953).

(7) H. G. Fletcher, Jr., H. W. Diehl and C. S. Hudson, THIS JOURNAL, **72**, 4546 (1950).

(8) G. N. Bollenback and L. A. Underkofler, *ibid.*, **72**, 741 (1950).

(9) M. Abdel-Akher, J. K. Hamilton and F. Smith, *ibid.*, **73**, 4691 (1951).

(10) We are indebted to Mr. A. V. Guzzo of this Laboratory for the X-ray diffraction measurements.

(11) Abstracted from the Ph.D. dissertation of Dorothy J. Kuenne, Washington University, 1953.

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Cyclizations of Dialdehydes with Nitromethane. III.[1] Preparation of 3-Amino-3-deoxy-D-mannose

BY HANS HELMUT BAER[2a] AND HERMANN O. L. FISCHER[2b]

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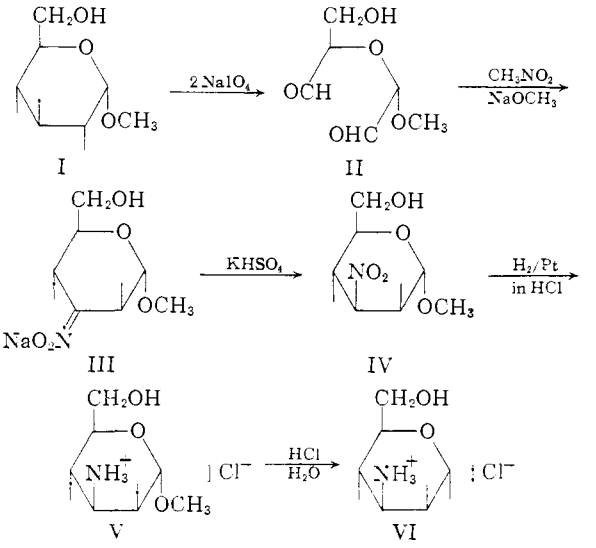
Cyclization, with nitromethane and sodium methoxide, of the dialdehyde produced by periodate cleavage of methyl α-D-glucopyranoside led to an *aci*-nitro condensation product (yield 80–85%) from which, upon acidification and hydrogenation, crystalline methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride could be prepared. This was hydrolyzed to give crystalline 3-amino-3-deoxy-α-D-mannose hydrochloride. The N-acetyl derivative of the latter was degraded to 2-acetamido-2-deoxy-D-arabinose.

Recently, a novel synthesis of 3-amino-3-deoxy sugars has been described.[1,3] The method has made possible the preparation of the D- and L-forms of 3-amino-3-deoxy-ribose hydrochloride in good yields with a reasonable outlay in time and materials. In addition, smaller amounts of 3-amino-3-deoxy-xylose derivatives are formed. The synthesis takes advantage of the well-known condensation reaction of nitroalkanes with aldehydes. As we have shown,[1,3] sugar "dialdehydes," formed by periodate cleavage of methyl glycosides, react with nitromethane and alkali in a twofold condensation involving *one* molecule of nitromethane with *both* aldehyde groups. The glycoside thus reconstituted then bears an *aci*-nitro group on carbon atom 3 and is obtained as the sodium salt. Acidification furnishes a mixture of epimeric methyl 3-nitro-glycosides, which can be hydrogenated to the corresponding methyl 3-amino-3-deoxy-glycosides. Conformational considerations have been employed for explaining the noteworthy fact that the stereospecificity of the condensation reaction is marked enough to permit the practical preparation of one favored product.

As already briefly mentioned,[3] this synthesis also proved to be applicable to the hexose series. The present paper reports the preparation of a new aminohexose, namely 3-amino-3-deoxy-α-D-mannose hydrochloride, using methyl α-D-glucopyranoside (I) as starting material. Periodate oxidation of I according to Jackson and Hudson gives D'-methoxy - D - hydroxymethyl - diglycolic aldehyde (II).[4] This sirupy dialdehyde, when treated with approximately equimolar amounts of nitromethane and sodium methoxide in methanolic solution at +4°, produced, in yields up to 85%, an amorphous powder which analyzed correctly for a methyl-*aci*-nitro-deoxy-hexoside sodium salt (III). The failure of this product to crystallize may be attributable to a lack in steric homogeneity. Support for this assumption came from a later stage of the synthesis. However, if the salt consisted of two or more stereoisomers, they were probably always formed in the same proportions since, in several parallel experiments and in successive fractions of an individual experiment, the products always exhibited, within narrow limits, the same rotational behavior. Immediately after dissolving III in water, the specific rotation was +52°. Thereafter a mutarotation was observed reaching a final value of about +100° after 5 days. The cause of this remarkable change is still unexplained.[5]

The methyl *aci*-nitro-hexopyranoside sodium salt (III) was acidified by means of solid potassium bisulfate. Ethyl acetate extraction of the dry salt mixture gave 90% of a methyl nitro-deoxy-hexopyranoside sirup ($[\alpha]_D$ +88°, in water). The results of the subsequent hydrogenation indicated that this sirup was a mixture. However, the methyl 3-nitro-3-deoxy-α-D-mannopyranoside (IV) appeared to represent a major part of it.



The hydrogenation of the nitrohexoside mixture (IV plus stereoisomers) was carried out with a platinum catalyst in the presence of one molecular equivalent of dilute hydrochloric acid. Three molecular equivalents of hydrogen was taken up readily at room temperature. From the reaction mixture, colorless needles of melting point 205° dec. and $[\alpha]_D$ +60° (water) could be separated in a yield of 32–36%, based on the nitrohexoside mixture. The analytical data proved the product to be

(1) Communication II, H. H. Baer and H. O. L. Fischer, THIS JOURNAL, **81**, 5184 (1959).

(2) (a) Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda 14, Md. (b) Deceased March 9, 1960.

(3) H. H. Baer and H. O. L. Fischer, *Proc. Natl. Acad. Sci.*, **44**, 991 (1958).

(4) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 994 (1937). The open chain dialdehyde formula as pertinent to the following reactions is depicted, although it is acknowledged that dialdehydes of this type are apt to assume cyclic hemiacetal structures; *cf.* F. Smith, *et al.*, *ibid.*, **79**, 691 (1957); **80**, 4681 (1958).

(5) The crystalline methyl 3-*aci*-nitro-3-deoxy-β-D-ribopyranoside sodium salt and its enantiomorph undergo analogous mutarotations.[1] An investigation thereon is being undertaken.