2,4-Dimethyl-3-amino-5-hydroxymethylpyridine hydriodide. A 1.0-g. portion of the aminodiol in 6.5 ml. of 7.6*M* hydriodic acid was heated just to boiling, then quickly cooled, and stored at 0–5° overnight. The dark oil which had separated was stirred with a little absolute ethanol, giving a mass of almost black, gummy crystals, weight 0.59 g. A sample of this material was crystallized from absolute ethanol for analysis, giving light yellow crystals, m.p. 190–196°. The analysis indicated that instead of producing the expected diiodide hydriodide, the reaction had given a product in which one of the hydroxymethyl groups was reduced down to methyl, with liberation of free iodine in the reaction mixture.

Anal. Calcd. for $C_8H_{11}N_2I_3$: C, 18.63; H, 2.15; N, 5.43; I, 73.79. Calcd. for $C_8H_{13}N_2OI$: C, 34.29; H, 4.98; N, 9.95; I, 45.30. Found: C, 34.27; H, 4.92; N, 10.06; I, 44.90.

From the original hydriodic acid filtrate on evaporation a second crop, 0.21 g. of crude product, m.p. 165–175°, was obtained, but has not been further purified.

Preparation of 4-deoxypyridoxine hydrochloride (New method). The 3-amine (50 mg.) was dissolved in 1.0 ml. of water, and silver chloride (43 mg.) was added. The mixture was heated with stirring for 5 min., during which time the white silver chloride was partly converted to yellow silver iodide. The mixture was filtered, and the residue washed with 1.0 ml. of water. The combined aqueous filtrate was acidified with 0.2 ml. of 12*M* hydrochloric acid. To this solution at 25° was added 23 mg. of sodium nitrite (dissolved in 1.0 ml. of water). Nitrogen bubbles appeared immediately. The solution was heated to near-boiling until effervescence ceased (10–15 min.).

The solution was vacuum-distilled to dryness, and 0.5 ml. of 12*M* hydrochloric acid was added to the residue. The distillation to dryness was repeated. The residue was then extracted with 2.0 ml. of absolute ethanol, cooled and filtered. To the filtrate was added ether, with stirring, until crystals began to separate. The crystals were collected and dried, giving about 10 mg. of material melting at 255° dec. The reported[13] m.p. for 4-deoxypyridoxine hydrochloride is 257°; for 5-deoxypyridoxine hydrochloride[11] it is 143°.

The infrared spectrum of 4-deoxypyridoxine hydrochloride so prepared was found to be identical with that of an authentic sample.

2-Methyl-3-acetamido-4,5-di(acetoxymethyl)pyridine. A mixture of 1.0 g. of the aminodiol monohydrochloride,[7,8] 0.80 g. of fused sodium acetate, and 20 ml. of acetic anhydride was boiled under reflux for 20 min., and the solvent then removed by vacuum-distillation. The residue was extracted with 15 ml. of chloroform, and the extract treated with decolorizing carbon. The chloroform was removed by vacuum-distillation. The residual brown oil was stirred with 2.0 ml. of ether, giving a solid product. This was collected, again washed with a little ether, and dried, giving 0.40 g. (28%) of colorless product, m.p. 131–133°.

A sample was recrystallized for analysis from benzene (12 ml./g.), giving colorless platelets, m.p. 130–131°.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.12; H, 6.16; N, 9.52. Found: C, 57.30; H, 6.12; N, 9.59.

The infrared spectrum showed N-H stretching absorption at 3300 cm.$^{-1}$, and ester and amide carbonyl absorption at 1740 and 1650 cm.$^{-1}$, respectively.

2-Methyl-3-acetamido-4,5-di(hydroxymethyl)pyridine. The water-soluble triacetyl derivative (0.42 g.) was dissolved in 12.0 ml. of 0.5*M* sodium hydroxide, and the solution kept at about 20° for 2 hr. The clear solution was adjusted to *p*H 6–7 by addition of acetic acid, and the solvent then removed by vacuum-distillation. The colorless solid residue was extracted with acetone for 24 hr., using a Soxhlet extractor. On cooling the extract in the refrigerator colorless crystals separated. These were collected and dried, giving 0.10 g. of product, m.p. 185–186°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.14; H, 6.71; N, 13.32. Found: C, 56.99; H, 6.88; N, 13.32.

The filtrate was evaporated, and the residue recrystallized from ethyl acetate-alcohol (5:1), giving an additional 0.050 g., m.p. 184–186°.

A coupling test[14] for free aromatic primary amino groups was negative. Comparison of the infrared spectrum with that of the triacetyl starting material disclosed that the ester carbonyl peak had disappeared and that an O-H stretching peak was now present at 3520 cm.$^{-1}$

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A New Synthesis of D-Rhamnose (6-Deoxy-D-mannose)[1]

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D-Rhamnose (6-deoxy-D-mannose) (IV), the enantiomorph of the naturally occurring L-rhamnose (6-deoxy-L-mannose) has been synthesized by Haskins, Hann, and Hudson[3] *via* the following sequence: methyl α-D-mannopyranoside → methyl 2,3,4-tri-*O*-benzoyl-6-*O*-*p*-tolylsulfonyl-α-D-mannoside → methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-α-D-mannoside → methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-α-D-mannoside → methyl 6-deoxy-α-D-mannopyranoside → D-rhamnose (IV). Their synthesis was carried out, however, prior to the advent of metal hydrides as reducing agents in organic chemistry. The ability of lithium aluminum hydride to convert primary *O*-*p*-tolylsulfonyl esters to methyl groups provided the key step in the presently described synthesis in which D-mannose was converted to D-rhamnose (IV) in four steps.

Initially, we envisaged a synthesis starting with methyl α-D-mannopyranoside. Attempts to secure a crystalline methyl 6-*O*-arylsulfonyl-α-D-mannopyranoside failed and when methyl α-D-mannopyranoside was treated in pyridine with *p*-toluenesulfonyl, *p*-nitrobenzenesulfonyl, *p*-fluorobenzenesulfonyl, and β-naphthalenesulfonyl chlorides only sirups resulted.[4] We were, however, successful when D-mannose was first converted to D-mannose dimethyl dithioacetal (I)[5] which, when treated under the usual conditions with *p*-toluenesulfonyl chloride, gave crystalline 6-*O*-*p*-tolylsulfonyl-D-man-

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(2) This paper is taken from a dissertation submitted by C. O. Tio to the Graduate School of Georgetown University in partial fulfillment of the degree of Master of Science in Chemistry.

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(4) The authors are indebted to Mr. G. D. Valiaveedan for carrying out these exploratory sulfonations.

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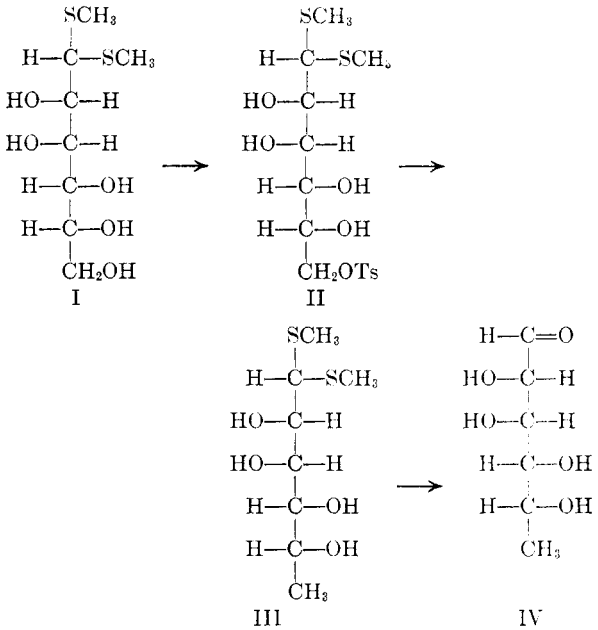

Ts = *p*-tolylsulfonyl

nose dimethyl dithioacetal (II). When II was reduced with lithium aluminum hydride, 6-deoxy-D-mannose dimethyl dithioacetal(III) resulted. Demercaptalation of III[6] gave the expected D-rhamnose (IV).

EXPERIMENTAL

All melting points were determined using a Kofler hot-stage.

D-*Mannose dimethyl dithioacetal* (I). Twenty five grams of D-mannose was treated with methanethiol by a procedure similar to that described by Zinner.[5] In accordance with a suggestion of Levene and Meyer,[7] the reaction time was shortened to 5 min.; this did indeed improve our yields. Also, crystallization of the product was facilitated when hot 95% ethanol was substituted for water. In this manner there was obtained a total of 18.6 g. (52%) of pure D-mannose dimethyl dithioacetal (I), m.p. 144.5–145°, $[\alpha]_D^{25°}$ + 4.0 ± 0.4° (*c* 1.03, methanol).

*6-O-p-Tolylsulfonyl-*D*-mannose dimethyl dithioacetal* (II). A solution of 4.18 g. (0.022 mole) of *p*-toluenesulfonyl chloride in 15 ml. of dry pyridine was added dropwise over a period of 0.5 hr. to a stirring solution of 5.16 g. (0.02 mole) of D-mannose dimethyl dithioacetal (I) in 15 ml. of dry pyridine at −10°. Without allowing the temperature to rise, stirring was continued for 0.5 hr. and the mixture was allowed to stand for an additional 3 hr. The solution was then transferred to a refrigerator and allowed to stand for 20 hr. After this time the material was added dropwise with stirring over a period of 90 min. to 500 ml. of water maintained at 0°. The separated product was filtered by suction and washed well with cold water. After drying in a desiccator over concentrated sulfuric acid for 2 days, a white semi-crystalline mass was obtained. Crystallization from aqueous methanol gave 5.48 g. (66%) of 6-*O*-*p*-tolylsulfonyl-D-mannose dimethyl dithioacetal (II),[8] m.p. 93–94.5° dec., $[\alpha]_D^{25°}$ − 7.3 ± 0.9° (*c* 1.06, pyridine).

*6-Deoxy-*D*-mannose dimethyl dithioacetal* (III). A mixture of 890 mg. (2.14 mmoles) of II and 1 g. of lithium aluminum hydride in 200 ml. of anhydrous ether was refluxed for 40 hr. after which time the excess lithium aluminum hydride was destroyed by the careful addition of water, followed by neutralization to *p*H 7.0 with 5*N* hydrochloric acid. The mixture was filtered by suction and the residue in the funnel was washed four times with 50-ml. portions of hot ethyl acetate. The filtrate was evaporated *in vacuo* at 40° and the resulting residue was dissolved in methanol and treated with Amberlite MB-1 ion exchange resin. After filtering and washing the resin, the filtrate was evaporated again *in vacuo* at 40° giving a residue which, after two recrystallizations from hot 95% ethanol, yielded 118 mg. (22.7%) of pure 6-deoxy-D-mannose dimethyl dithioacetal (III), m.p. 161.5–162.5°, $[\alpha]_D^{25°}$ − 8.0 ± 0.7° (*c* 1.00, methanol) (Zinner reported[5] a m.p. 156.5–157.5 and $[\alpha]_D^{18°}$ + 4.4° for 6-deoxy-L-mannose dimethyl dithioacetal). Employing the directions of Zinner, a quantity of 6-deoxy-L-mannose dimethyl dithioacetal was prepared for paper chromatographic comparisons with our III. Both materials were spotted on Whatman No. 1 paper and developed by an ascending technique employing 1-butanol-ethanol-water (4:1:5). After drying, the paper was exposed to iodine vapor to locate the spots, both of which were exactly coincident in position (R_f = 0.89).

Anal. Calcd. for $C_8H_{18}O_4S_2$: C, 39.62; H, 7.48; S, 26.46. Found: C, 39.21; H, 7.42; S, 26.28.

D-*Rhamnose* (IV). To a solution of 100 mg. (0.41 mmole) of 6-deoxy-D-mannose dimethyl dithioacetal (III) in 90% (v./v.) aqueous acetone was added 393 mg. of yellow mercuric oxide. To the stirring suspension was added a solution of 449 mg. of mercuric chloride in acetone. After stirring for 21 hr. at room temperature, the mixture was filtered with the aid of Celite 545 and the filtrate was evaporated to dryness *in vacuo* at 30° in the presence of a small quantity of added yellow mercuric oxide. The residue was extracted with 50 ml. of methanol and filtered. The filtrate was treated with gaseous hydrogen sulfide until precipitation of mercuric ion was complete. After boiling to remove most of the hydrogen sulfide, the mixture was treated with a small amount of lead carbonate and was then filtered with the aid of Darco G-60. The filtrate thus obtained was purified further by treatment with Amberlite MB-1 ion exchange resin. After filtering, the clear solution was concentrated *in vacuo* at 50° to a thick sirup which was redissolved in 20 ml. of 95% ethanol. The latter solution was concentrated to a thin sirup and carefully seeded with a crystal of synthetic D-rhamnose (m.p. 75–93°). After two days, the bulk of the sirup had crystallized giving 45 mg. (60%) of D-rhamnose monohydrate (IV), m.p. 75–93°, $[\alpha]_D^{25°}$ (equilibrium) −6.13 ± 0.9° (*c* 1.40, water). Samples of L-rhamnose monohydrate and IV were chromatographed simultaneously on Whatman No. 1 paper in two solvent systems employing an ascending technique. In each case, after drying, the spots were detected by spraying the papers with *p*-aminophenol.[9] Employing 1-butanol–ethanol–water (4:1:5) both samples had R_f = 0.43. With 1-butanol–acetic acid–water (4:1:5) spots of both enantiomorphs were exactly coincident in position (R_f = 0.55).

Anal. Calcd. for $C_6H_{12}O_5 \cdot H_2O$: C, 39.56; H, 7.75. Found: C, 38.54; H, 7.87.

2,4-Dinitrophenylhydrazone of IV. A mixture of 46 mg. (0.25 mmole) of D-rhamnose (IV), 50 mg. (0.25 mmole) of 2,4-dinitrophenylhydrazine, and 0.20 ml. of glacial acetic acid in 7 ml. of 95% ethanol was refluxed for 1 hr. The solution was concentrated on a water bath to a volume of 2 ml. and was set aside at room temperature until crystalline material appeared. After standing overnight in a refrigerator, the separated material was filtered by suction and was washed

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with cold 95% ethanol. Two crystallizations from ethyl acetate gave pure D-rhamnose 2,4-dinitrophenylhydrazone, m.p. 165–166°. (The 2,4-dinitrophenylhydrazone of L-rhamnose is reported[10] to be 164–165°.)

Anal. Calcd. for $C_{12}H_{16}O_8N_4$: N, 16.27. Found: N, 16.01.

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The Synthesis of 1-(2-Aminonaphthyl)-β-D-glucopyranosiduronic Acid

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Bladder cancer in man and dogs exposed to 2-naphthylamine[1,2] probably occurs through the action of urinary metabolites of this compound. Accordingly, identification of urinary metabolites in the species which develop this disease is of particular interest. 1-(2-Aminonaphthyl)-β-D-glucopyranosiduronic acid has been recently identified as an important urinary metabolite of 2-naphthylamine in our laboratory in dog urine,[3] and by Levitz *et al.*[4] in human urine.

The present paper describes a convenient chemical synthesis of this material which until now has been prepared biosynthetically.[5]

The essential starting material methyl (tri-*O*-acetyl-α-D-glucopyranosyl bromide)uronate was prepared from glucuronolactone according to the procedure of Bollenback *et al.*[6]

Methyl [1-(2-nitronaphthyl) tri-*O*-acetyl-β-D-glucopyranosid]uronate was prepared by a modification of the procedure of Bollenback *et al.*[6] for the preparation of the corresponding *o*-nitrophenyl derivative. *N,N*-Dimethylformamide was used instead of acetone because of the insolubility of the potassium salt of *o*-nitronaphthol in this solvent. Although the presence of water and room temperature resulted in low yields of about 5%, consistently good yields of about 40% were obtained when the reaction was carried out with dry reagents in the cold.

Attempts at deacetylation of the nitronaphthyl derivative with methanolic sodium or barium methoxide resulted in turbid solutions which became increasingly yellow with time even in the refrigerator. This suggests that the nitro group is activating basic hydrolysis of the glycosidic linkage. The successful synthesis of the desired product was achieved by carrying out the reduction prior to deacetylation.

EXPERIMENTAL

Methyl [1-(2-nitronaphthyl)tri-O-acetyl-β-D-glucopyranosid]uronate. Methyl (tri-*O*-acetyl-α-D-glucopyranosyl bromide)uronate,[6] 2 g. (0.0051 mole) and the potassium salt of *o*-nitronaphthol,[7] 5 g. (0.0216 mole) (prepared from an acetone solution of *o*-nitronaphthol to which an equivalent amount of 5*N* potassium hydroxide was added) were dissolved in 200 ml. of *N,N*-dimethylformamide and allowed to react at 4° for 3 weeks. The dark yellow solution was diluted with an equal volume of chloroform. The unchanged potassium salt precipitated and was collected by centrifugation. The solution was then extracted with water, 2*N* sodium hydroxide, and finally with water until the extracts were nearly colorless. The chloroform layer was dried over anhydrous sodium sulfate and evaporated to dryness at 50° on the water pump. The oily yellow residue was dissolved in acetone and precipitated by addition of water. The oily precipitate was dissolved in a minimum volume of methanol and crystallized on cooling. The crystals were washed with ligroin (b.p. 90–120°) and dried to give faintly yellow crystals (1 g., 39% yield) melting at 150° (uncorrected, Fischer-Johns block).

The infrared spectrum of a 5% chloroform solution was compared with the spectrum of the corresponding *o*-nitrophenyl derivative.[6] The spectra were almost identical and exhibited the characteristic bands for methyl (2,3,4-tri-*O*-acetyl-β-D-glucosid)uronates.[8]

Methyl[1-(2-aminonaphthyl) tri-O-acetyl-β-D-glucopyranosid]uronate. Methyl [1-(2-nitronaphthyl) tri-*O*-acetyl-β-D-glucopyranosid]uronate, 1 g. (0.002 mole) in 180 ml. methanol, was catalytically hydrogenated with 100 mg. of 10% palladium-on-charcoal. The slightly yellow solution became colorless and highly fluorescent. The uptake of hydrogen was quantitative; calcd. 144 ml., found 148 ml. The solution was filtered and evaporated at 40° on the water pump. The residue consisted of light pink crystals melting at 160° (corr.). It was unnecessary to isolate the reduced compound prior to deacetylation.

1-(2-Aminonaphthyl) β-D-glucopyranosiduronic acid. Methyl [1-(2-nitronaphthyl) tri-*O*-acetyl-β-D-glucopyranosid]uronate, 1.5 g. (0.003 mole), was reduced as above. A tenfold excess of sodium methoxide was added to the filtered methanolic solution and allowed to react at 4° for 2 days. The solution was evaporated on the water pump and the residue dissolved in a minimal amount of water. The *p*H was adjusted to 4.0 and cooled. The pink crystals recrystallized from water[5] weighed 910 mg. (86% yield). The melting point was 178–180° (corr.); (reported[5]

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