metaperiodate, followed by bromine water kept neutral with strontium carbonate, the riboside is converted to the same strontium L′-methoxydiglycolate which had been obtained previously from β-methyl-D-arabinopyranoside and β-methyl-D-xylopyranoside. This riboside is thus proved to be β-methyl-D-ribopyranoside.

WASHINGTON, D. C. RECEIVED FEBRUARY 20, 1941

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

2-Methyl-1,4-naphthohydroquinone Di-β-D-glucoside

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The search for water-soluble compounds with antihemorrhagic activity suitable for parenteral administration in small volumes suggested the preparation of a glucoside. Contemporary with this work on water-soluble substances has been that of several other research groups. This has been described in the review on vitamins K.[3]

The octaacetate of the diglucoside was first prepared, and this on deacetylation gave the desired compound. Helferich[4] had prepared aryl glucosides by fusing glucose pentaacetate with various phenols in the presence of suitable catalysts. When zinc chloride was used as the catalyst, α-glucosides were obtained, but *p*-toluenesulfonic acid caused the formation of β-glucosides. On fusing the latter catalyst with 2-methyl-1,4-naphthohydroquinone and glucose pentaacetate, a rather unsatisfactory yield of 2-methyl-1,4-naphthohydroquinone bis-(tetraacetyl-β-D-glucopyranoside) was obtained. Michael's method,[5] which has been widely employed for the preparation of glucosides, proved to be much more satisfactory. The dipotassium salt of 2-methyl-1,4-naphthohydroquinone was condensed with 2,3,4,6-tetraacetyl-α-D-glucosyl bromide in a dilute acetone solution. Deacetylation of the octaacetate was first accomplished by a saturated aqueous solution of barium hydroxide, but subsequent experiments showed that aqueous methanolic ammonia gave almost quantitative yields. The 2-methyl-1,4-naphthohydroquinone di-β-D-glucoside monohydrate melted with decomposition at 275° and gave a specific rotation of −61°.

The solubility of the diglucoside, which could also be named 2-methyl-1,4-di-β-D-glucosidonaphthalene, was eventually shown to be 0.1–0.2 mg. per ml. This very low solubility obviously rendered the compound unsuitable for its intended use. However, this fact was overlooked in our earlier work, due to the ready formation of rather stable supersaturated solutions, and it was not until larger quantities of material had been prepared and checked both for rotation and bioassay that this unfortunate property was discovered.

Preliminary bioassay by Mrs. Flemintine Peirce Dann of the Abbott Laboratories on supersaturated solutions of the diglucoside indicated an activity of about one-third that of 2-methyl-1,4-naphthoquinone. This was the expected value because the diglucoside has a molecular weight about three times that of the naphthoquinone.

Attempts were made to prepare other glycosides. Pacsu's method[6] for converting β-alkyl glucosides to their α-isomers, which consists of treating the acetylated glucoside with titanium tetrachloride in chloroform, proved unsuccessful when applied to our aryl derivative. Since there are some indications in the literature that mannosides may be more soluble than glucosides, an attempt was made to prepare the dimannoside. Apparently, the 2,3,4,6-tetraacetyl-α-D-mannosyl bromide hydrolyzed so rapidly that it failed to condense to give the desired product.

The authors wish to thank the Abbott Laboratories for generously aiding this research and Professor Charles D. Hurd for his helpful suggestions on nomenclature.

Experimental[7]

2-Methyl-1,4-naphthohydroquionone Bis-(tetraacetyl-β-D-glucopyranoside).—(a) A melt of 3 g. (0.0172 mole) of 2-methyl-1,4-naphthohydroquinone, 13.4 g. (0.0344 mole) of β-D-glucose pentaacetate and 0.15 g. of *p*-toluenesulfonic acid was heated with stirring at 130° for thirty minutes, acetic acid being evolved. The products, which

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(3) Riegel, *Ergeb. Physiol. biol. Chem. exptl. Pharmakol.*, **43**, 133 (1940).

(4) Helferich and Schmitz-Hillebrecht, *Ber.*, **66**, 378 (1933).

(5) Michael, *ibid.*, **12**, 2260 (1879).

(6) Pacsu, THIS JOURNAL, **52**, 2563 (1930).

(7) All analyses by Mr. E. Shelberg, microanalyst for the Abbott Laboratories.

were soluble in benzene, were washed and dried and the solvent removed under reduced pressure. The residue was crystallized from 95% ethanol. Recrystallization from methanol raised the melting point from 208° to 212–213°; $[\alpha]^{25}D$ −32 ± 2° (0.415 g. in 9.94 ml. chloroform α_D −1.35°, l 1 dm.). The yield varied between 2.8 and 5%.

Anal. Calcd. for $C_{39}H_{46}O_{20}$: C, 56.11; H, 5.55. Found: C, 55.75, 55.86; H, 5.63, 5.71.

(b) From ten separate experiments the following procedure represents the optimum conditions. In a 200-ml. round-bottom flask were placed 25 ml. of acetone, 20 ml. of water, 1.29 g. (0.0230 mole) of potassium hydroxide, 1 g. of sodium hydrosulfite ($Na_2S_2O_4$), 9.43 g. (0.0230 mole) of 2,3,4,6-tetraacetyl-α-D-glucosyl bromide and 2 g. (0.0115 mole) of 2-methyl-1,4-naphthohydroquinone. The air in the flask was displaced with nitrogen and the flask stoppered. The mixture was mechanically shaken for three to four hours. At the conclusion of the period the shaking was interrupted and to the pale yellow, unstable emulsion were added the same amounts of all the components as were used above except the hydroquinone and the hydrosulfite. No further hydroquinone was added but about 0.5 g. of sodium hydrosulfite was necessary to keep the hydroquinone reduced. Shaking was continued for four hours when the mixture was no longer alkaline. At this point a third 1.29-g. portion of base was added together with a small amount of the reducing agent. After shaking the mixture for an additional two hours, all of the 2,3,4,6-tetraacetyl-α-D-glucosyl bromide had either reacted or hydrolyzed. In a separatory funnel, the reaction products, in a mixture of 80 ml. of ether and 30 ml. of chloroform, were extracted with 2% potassium hydroxide solution containing small amounts of sodium hydrosulfite until the unchanged naphthohydroquinone was removed. 1.1 g. was recovered. The ether–chloroform solution was washed well with water, dried and the solvent removed. The resulting sirup was reacetylated by allowing it to stand overnight in a mixture of 20 ml. of dry pyridine and 10 ml. of acetic anhydride. The mixture was then taken up in ether–chloroform, extracted with dilute hydrochloric acid, washed, dried, and the solvents removed. The remaining sirup was crystallized from 50 ml. of 95% ethanol. Beautiful small white needles were obtained which melted at 212–213° and gave no depression when mixed with those obtained by procedure (a). The yield was 0.93 g. or 21.5% based on the hydroquinone, allowing for that recovered.

Some of the variations tried which failed to increase the yield will be mentioned briefly. The corresponding glucosyl chloride gave no product. The addition of potassium iodide to the bromide or chloride did not help. Continuous and separate addition of the glucosyl bromide and the alkali did not increase the yield. Anhydrous pyridine could not be used in place of the solvent and alkali. Too much alkali caused partial deacetylation of the product thereby rendering it difficult to purify.

2-Methyl-1,4-naphthohydroquinone Di-β-D-glucoside.—(a) The hydrolysis of the acetylated glucoside was first accomplished by suspending 250 mg. in 175 ml. of a clear, saturated solution of barium hydroxide. The suspension was shaken for eight hours and then allowed to stand overnight. Excess barium hydroxide was removed as the carbonate. The residue obtained by vacuum concentration of the filtrate was extracted with alcohol. After removal of the alcohol, the residue was crystallized from water. A yield of 50 mg. (32%), melting at 275° with decomposition was obtained. It proved to be the monohydrate.

Anal. Calcd. for $C_{25}H_{30}O_{12}\cdot H_2O$: C, 53.48; H, 6.24; H_2O, 3.49. Found: C, 53.35, 53.60; H, 6.16, 6.26; H_2O, 3.43, 3.41.

(b) An improved method for the hydrolysis was as follows: in 750 ml. of hot methanol was dissolved 10 g. of 2-methyl-1,4-naphthohydroquinone bis-(tetraacetyl-β-D-glucopyranoside). The solution was cooled in an ice-bath, which caused the precipitation of a small amount of the acetate, and ammonia gas was bubbled into the mixture until 70 g. had been added. After standing at room temperature for two days, a considerable amount of the partially deacetylated material precipitated, as indicated by m. p. and carbon–hydrogen analysis, and this was redissolved by the addition of 750 ml. of water. The solution was again cooled in an ice-bath while 78 g. of ammonia was passed into it. After standing two more days the mixture was concentrated *in vacuo* almost to dryness. The resulting crystalline mass was dissolved in 600 ml. of hot water, filtered through a hot funnel, and allowed to cool and crystallize slowly. Beautiful fine white needles were obtained which melted with decomposition at 273–275°; $[\alpha]^{25}D$ −61 ± 1° (25.1 mg. in 25 ml. of 50% acetone solution α_D −0.124°, l 1 dm.). This material was identical with that prepared in part (a). The yield of the monohydrate was 5.74 g. (93%).

Summary

The preparation of 2-methyl-1,4-naphthohydroquinone di-β-D-glucoside is reported. It is not sufficiently water-soluble to warrant parenteral administration as an antihemorrhagic agent, but does show the expected activity.

EVANSTON, ILLINOIS RECEIVED JANUARY 18, 1941