A NEW SYNTHESIS OF METHYL β-D-GULOPYRANOSIDE[1]

N. J. Antia and M. B. Perry

ABSTRACT

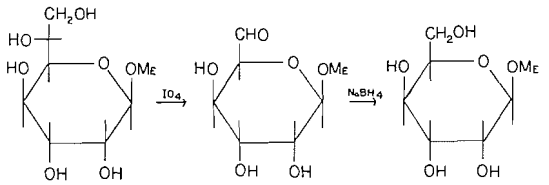
The oxidation of 1 mole of β-D-glycero-D-gulo-heptopyranoside with 1 mole of sodium metaperiodate, followed by reduction with sodium borohydride, gave rise to crystalline methyl β-D-gulopyranoside. The method provides a new synthetic route to the D-guloside and, thence, to D-gulose. The possibility of utilizing this reaction scheme as a general convenient method for preparing the relatively rare aldohexoses as well as for "labelling" carbon atom 1 of these compounds is discussed.

It was shown recently by Perry and Pietak (1) that the periodate oxidation of aldoheptoses proceeds in nearly discrete stages, with the sugars being oxidized in their cyclic forms. Consumption of the first mole of oxidant per mole was correlated with the almost exclusive scission of the C_6–C_7 (exocyclic) bond of the heptose. This observation appeared to be of great potential value for the facile synthesis of hexoses not readily available. The controlled oxidation of 1 mole of the heptose with 1 mole of periodate would be expected to yield the corresponding hexodialdose, which would require a selective reduction of the —CHO group at C_6 to give the corresponding hexose. The reduction step was considered to present insuperable difficulties and, accordingly, we turned our attention to the application of the reaction sequence to the heptosides, where such selective reduction would not be required. An analogous series of reactions was used by Foster, Davies, and Crumpton (2) in their conversion of heptose units in polysaccharides to hexose units.

Methyl β-D-glycero-D-gulo-heptopyranoside had been prepared by Fisher (3) and a proof of its pyranoside structure had been offered by Haworth, Hirst, and Stacey (4). We have prepared the heptoside by the method of the latter authors, but have found difficulty in separating it from contaminating heptose. One mole of the methyl β-D-glycero-D-gulo-heptopyranoside (I) was oxidized with 1 mole of sodium metaperiodate in unbuffered medium, and the product (II) was directly reduced with an excess of sodium borohydride. After deionization with ion-exchange resins, crystalline methyl β-D-gulopyranoside (III) was isolated in 30% yield. Attempts to isolate the guloside from the borohydride reduction reaction without recourse to resin deionization, by acetylation with acetic anhydride/pyridine or by *p*-nitrobenzoylation, failed to yield crystalline material. The D-guloside was shown (*a*) to be homogeneous, by paper chromatography in three solvent systems, and (*b*) to be identical with a sample obtained from Dr. Isbell (5, 6). The identity was established by comparison of infrared spectra and by mixed melting point determination. The pyranoside structure of the D-guloside was confirmed by periodate oxidation studies (2 moles of periodate consumed, 1 mole of formic acid liberated). Mineral acid hydrolysis of the D-guloside gave predominantly a reducing sugar identified as gulose from paper chromatographic evidence.

The synthesis reported above suggests that other heptosides may similarly be converted to the corresponding hexosides, and the method appears to offer a convenient, general, synthetic route for the conversion of heptoses to hexoses. The particular value of this synthetic method lies in (*a*) the simplicity and ease of preparation, in quantity, of the relatively rare hexoses, and (*b*) the possibility of selectively "labelling" a hexose

[1]*Manuscript received May 16, 1960.*
Contribution from the Chemistry Department, Queen's University, Kingston, Ontario.



I II III

at carbon atom 1 by starting with a *1*-C^{14}-heptose. Obviously the preparative value of the method will be governed by the ease of availability of aldoheptoses. Both classical Kiliani/Fischer cyanohydrin synthetic method (7) and the more recent nitromethane/Nef reaction scheme of synthesis (8) provide convenient preparative routes to aldoheptoses from aldohexoses. Both of these methods effect the addition of a one-carbon fragment to the carbon atom 1 of the hexose. The incoming carbon atom may be "labelled" by the use of $HC^{14}N$ or $C^{14}H_3NO_2$. In this way, a readily available hexose (e.g., D-glucose) may be converted to a *1*-C^{14}-aldoheptose (e.g., D-glycero-D-gulo-heptose) which, by the application of the synthetic scheme described above, may be further converted to the desired *1*-C^{14}-hexose (e.g., D-gulose).

EXPERIMENTAL

All melting points reported are uncorrected.

Paper chromatography was performed by the descending method on Whatman No. 1 paper, using the following solvent systems:

solvent I: 1-butanol/ethanol/water (3:1:1 v/v);
solvent II: 1-butanol/pyridine/water (10:3:3 v/v);
solvent III: ethyl acetate/acetic acid/water (9:2:2 v/v).

The following sprays were used to detect the sugars on the chromatograms: (A) 2% solution of *p*-anisidine hydrochloride in 1-butanol, (B) 1% solution of silver nitrate in acetone, followed by 2% ethanolic sodium hydroxide, and (C) saturated aqueous solution of potassium periodate followed, 6 minutes later, by benzidine reagent (9). The rate of movement of the sugars on the chromatograms is given relative to that of 2,3,4,6-tetra-*O*-methyl-D-glucose (R_{TMG}) or of rhamnose (R_{Rha}).

Methyl β-D-Glycero-D-gulo-heptopyranoside

The glycoside was prepared by refluxing D-glycero-D-gulo-heptose (m.p. 190–192°) with 3–5% methanolic hydrogen chloride for 24–48 hours. Yields of the crude crystalline product were of the order obtained by Haworth, Hirst, and Stacey (4). After two recrystallizations from alcohol, the glycoside had a melting point of 166–168°, $[\alpha]_D^{20}$ −72°±2° (*c*, 1.1 in water). Paper chromatography in solvents I and II showed the presence of a heptose. Treatment of the glycoside in aqueous solution with Dowex 1-X2(OH) (by agitation with the resin at room temperature for 20 hours, followed by passage of the solution down a column of the resin) effected removal of most of the contaminating heptose, but traces were still detectable. The treated glycoside crystallized from alcohol as colorless prisms with the same melting point and optical rotation as given above. The following R_{TMG} values were observed for the heptoside: solvent I, 0.33; solvent II, 0.35; solvent III, 0.41.

Methyl β-D-Gulopyranoside

The calculated quantity of an aqueous solution of sodium metaperiodate (49.18 ml, 0.045 *M* $NaIO_4$) was added slowly to a stirred solution of methyl β-D-glycero-D-gulo-heptopyranoside (0.4935 g) in water (25 ml) cooled to 0°. After addition was complete, the solution was agitated for 2 hours at room temperature and allowed to stand overnight. The solution was next cooled to 0°, and a solution of sodium borohydride (0.8 g) in water (25 ml) was added slowly, with mechanical agitation. The solution was agitated for 2 hours at room temperature and allowed to stand overnight. The pH of the solution was adjusted to 5 by the addition of 50% aqueous acetic acid with mechanical agitation and cooling. After 1 hour at room temperature, a test sample showed no reduction of Fehling's solution (absence of reducing sugar as well as of borohydride). The solution (160 ml) was divided into halves at this stage. One half was used for the attempted isolation of the D-guloside by (*a*) acetylation and (*b*) *p*-nitrobenzoylation. The other half was passed successively through columns of Amberlite IR-120(H) and Duolite A-4(OH) ion-exchange resins. The pH of the eluent from the latter column was ca. 3–4 and it was found necessary to deionize the solution further by passing it through Dowex 1-X2(OH) resin. This solution (pH7) was evaporated to dryness *in vacuo* and the residual boric acid was removed as methyl borate by repeated evaporation *in vacuo* with methanol. The residue was next extracted with ethanol, the ethanol-insoluble material being rejected (negative reaction to Molisch reagent). The ethanol extract (0.22 g) was taken up in boiling ethanol, allowed to cool, and ethyl acetate was added to incipient turbidity. The solution was allowed to crystallize at 0–5° for 4 days. Methyl β-D-gulopyranoside crystallized as prisms (0.065 g), m.p. 178–180°, $[\alpha]_D^{20}$ −87.9° (*c*, 1.03 in water). The mother liquors failed to yield any further crystalline product. The over-all yield of the D-guloside was ca. 30% of the theoretical. Isbell (6) has given the following constants for the D-guloside, m.p. 176°, $[\alpha]_D^{20}$ −83°. A mixed melting point determination of the D-guloside with Isbell's sample showed no depression. The infrared spectra (KBr disk) of the D-guloside samples were identical.

The attempted acetylation of the D-guloside with acetic anhydride and pyridine failed to give a crystalline product, although Isbell (5) has described a crystalline tetraacetate.

Paper chromatography of the D-guloside showed (*a*) complete absence of reducing sugars, and (*b*) a homogeneous product having the following R_{TMG} values: solvent I, 0.44; solvent II, 0.51; solvent III, 0.51.

Periodate oxidation studies: The D-guloside (19.4 mg) was oxidized at 0–4° with an aqueous solution of sodium metaperiodate (5 ml, 0.1 *M* $NaIO_4$), the total volume of the reaction mixture being adjusted to 100 ml with distilled water. Aliquots (5 ml) of the reaction mixture were taken at the time intervals stated in Table I, in order to determine the periodate consumed and the formic acid liberated. These determinations were carried out by standard methods.

TABLE I

Periodate oxidation of methyl β-D-gulopyranoside

Oxidation period, hours	Periodate uptake, moles per mole	Formic acid release, moles per mole
1	1.92	0.94
2	2.02	0.94
4	2.02	0.96
21	1.98	0.96

D-Gulose

The D-guloside (10 mg) was hydrolyzed with *N* HCl (10 ml) (refluxed for 2 hours), the mineral acid was neutralized with silver carbonate, and the product was worked up in the usual manner. No attempt was made to crystallize the D-gulose or to prepare a derivative.

Paper chromatography of the product showed the presence of a reducing sugar as the major component, along with traces of what may be 1,6-anhydro-D-gulose, oligosaccharides, and polymeric material formed by the acid treatment. The reducing sugar was identified as D-gulose by comparison of R_{Rha} values with those of D-mannose (see Table II). Thomas (10) has shown that these two sugars are virtually inseparable on paper chromatograms in the solvent systems used.

TABLE II

R_{Rha} values of some reducing sugars

Sugar	Solvent system		
	I	II	III
D-Gulose	0.54	0.52	0.74
D-Mannose	0.62	0.55	0.80
D-Glycero-D-gulo-heptose	0.41	0.31	0.69

ACKNOWLEDGMENTS

The authors wish to express their thanks to the National Research Council for financial assistance (Grant No. 706); to Dr. H. S. Isbell, National Bureau of Standards, Washington, D.C., for kindly supplying an authentic specimen of methyl β-D-gulopyranoside; and to Professor J. K. N. Jones, for his interest and advice.

REFERENCES

1. M. B. Perry and T. Pietak. The periodate oxidation of aldoheptoses. Paper presented to the Royal Society of Canada, June Meeting, Kingston, Ontario. 1960.
2. A. B. Foster, D. A. L. Davies, and M. J. Crumpton. Nature, **181**, 412 (1958).
3. E. Fischer. Ber. **28**, 1156 (1895).
4. W. N. Haworth, E. L. Hirst, and M. Stacey. J. Chem. Soc. 2864 (1931).
5. H. S. Isbell. J. Research Natl. Bur. Standards, **8**, 1 (1932).
6. H. S. Isbell. Proc. Natl. Acad. Sci. U.S. **16**, 699 (1930).
7. C. S. Hudson. Advances in Carbohydrate Chem. **1**, 1 (1945).
8. J. C. Sowden. Advances in Carbohydrate Chem. **6**, 291 (1951).
9. J. A. Cifonelli and F. Smith. Anal. Chem. **26**, 1132 (1954).
10. G. H. S. Thomas. Studies on Polyuronides. M.A. Thesis, Queen's University, Kingston, Ontario. 1956.