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The Reaction of Tribenzoyl-α-D-lyxopyranosyl Bromide with Methanol

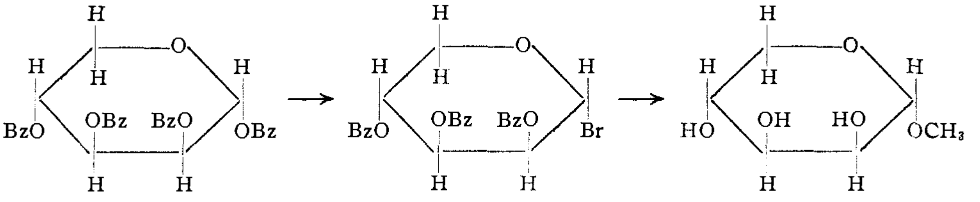
BY HEWITT G. FLETCHER, JR., ROBERT K. NESS[1] AND C. S. HUDSON

Benzoylation of D-lyxose has yielded α-D-lyxopyranose tetrabenzoate in crystalline form. Tribenzoyl-α-D-lyxopyranosyl bromide has been prepared in an amorphous state and shown to react with methanol in the absence of an acid acceptor to give, after debenzoylation of the initial product, methyl α-D-lyxopyranoside in high yield. These facts are in accord with the behavior of other benzoylated glycopyranosyl halides with methanol as previously reported.

In the course of an investigation of the reaction of benzoylated glycopyranosyl halides with methanol in the absence of an acid acceptor, results have been reported in the D-ribose,[2,3] D-glucose,[4] D-mannose,[4] D-arabinose,[5] D-xylose[5] and L-rhamnose[6] series. The present paper describes work carried out in the D-lyxose series.

The benzoylation of pure α-D-lyxopyranose at 0–4° with pyridine and benzoyl chloride furnished in 75% yield a crystalline D-lyxose tetrabenzoate showing $[\alpha]^{20}\text{D}$ $-49.0°$ in chloroform. The same substance could be prepared, in slightly lower yield, through the benzoylation of D-lyxose which had been equilibrated in pyridine solution at room temperature. Chromatography of the mother liquors from both these preparations yielded only amorphous fractions showing stronger levorotations than the crystalline product; for this reason the latter is tentatively assigned to the α-D-series.

Treatment of the crystalline α-D-lyxose tetrabenzoate (I) with hydrogen bromide in glacial acetic acid solution, followed by the usual removal of acidic materials, gave a sirup which showed in chloroform $[\alpha]^{20}\text{D}$ $-58.1°$ and resisted all attempts at crystallization. The tentative conclusion that this material represents predominantly an α-D-halide is based on a comparison of the difference between its rotation and that of α-D-lyxopyranose tetrabenzoate with corresponding differences in the D-arabinose and D-xylose series. Examination of Table I shows that the replacement of the benzoyloxy group attached to carbon one in an α-D-pentopyranose tetrabenzoate by bromine, without changing the configuration at carbon one, produces a relatively small negative change in the molecular rotation (−22,300 in the D-xylose series). Such a replacement, with inversion of configuration, on the other hand, produces a large negative change in molecular rotation (−120,800 in the D-arabinose series). The small difference between the molecular rotations of α-D-lyxopyranose tetrabenzoate and tribenzoyl-α-D-lyxopyranosyl bromide indicates that the latter is most probably an α-D-halide.



I II III

TABLE I

BENZOYLATED PENTOSE DERIVATIVES

	$[\alpha]^{20}\text{D}$ ($CHCl_3$)	$[M]^{20}\text{D}$	Difference
α-D-Xylopyranose tetrabenzoate	+149.5[a]	+84,700	
Tribenzoyl-α-D-xylopyranosyl bromide	+118.7[a]	+62,400	−22,300
α-D-Arabinopyranose tetrabenzoate	−114.4[b]	−64.800	
Tribenzoyl-β-D-arabinopyranosyl bromide	−353.3[c]	−185.600	−120,800
α-D-Lyxopyranose tetrabenzoate	−49.0	−27.800	
Tribenzoyl-α-D-lyxopyranosyl bromide	−58.1	−30,500	−2,700

[a] H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **69**, 921 (1947). [b] H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **69**, 1145 (1947). [c] H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **72**, 4173 (1950).

Reaction of the amorphous bromide (II) with methanol yielded a sirupy benzoate which, upon debenzoylation, furnished crystalline methyl α-D-lyxopyranoside (III) in a yield of 80% based on the original crystalline α-D-lyxopyranose tetrabenzoate. Since the structure and configuration of methyl α-D-lyxopyranoside are known with certainty,[7,8] the ring structures of the crystalline D-lyxose tetrabenzoate and of the amorphous tribenzoyl-D-lyxosyl bromide from which it was derived are evident.

As pointed out in a previous paper,[3] the present theory of the role of neighboring groups in replacement reactions predicts that the halogen in a *trans* halide such as II will be replaced without inversion of the configuration of carbon one; this prediction has again been verified in the present case.

Various attempts to obtain methyl α-D-lyxopyranoside tribenzoate in crystalline form have been unsuccessful.

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[1] Senior Research Fellow, National Institutes of Health, 1948–1950.

[2] R. Jeanloz, H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **70**, 4055 (1948).

[3] R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **73**, 959 (1951).

[4] R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **72**, 2200 (1950).

[5] H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **72**, 4173 (1950).

[6] R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **73**, 296 (1951).

[7] E. L. Hirst and J. A. B. Smith, *J. Chem. Soc.*, 3147 (1928).

[8] W. D. Maclay and C. S. Hudson, THIS JOURNAL, **60**, 2059 (1938).

Experimental[9]

α-D-Lyxopyranose Tetrabenzoate (I).—Ten grams of pure α-D-lyxose[10] ($[\alpha]^{20}\text{D}$ −13.9° at equilibrium in water) was suspended in 60 ml. of anhydrous pyridine previously cooled to 2° and, with efficient stirring, treated with 48 ml. of benzoyl chloride at such a rate that the temperature of the reaction mixture remained at 0–4°. The slurry was held at 0° for three hours, at 5° overnight and then at 60° for 0.75 hour; after decomposition of the excess benzoyl chloride with crushed ice, the mixture was diluted with methylene dichloride and washed successively with ice-water, cold 3 N sulfuric acid and aqueous sodium bicarbonate. After desiccation over sodium sulfate and filtration through a layer of decolorizing carbon, the solution was concentrated *in vacuo* to a stiff sirup. Solution of this latter in 320 ml. of warm absolute ethanol led to the spontaneous separation of stubby prisms (28.3 g., 75%) melting at 137° and rotating −49.4° in chloroform. After two recrystallizations from approximately 12 parts of absolute ethanol the α-D-lyxopyranose tetrabenzoate melted at 138–139°[11] and showed in chloroform a rotation of −49.0° (*c*, 2.16). Further recrystallization failed to change these values.

Anal. Calcd. for $C_{33}H_{26}O_9$: C, 69.96; H, 4.63. Found: C, 69.78; H, 4.70.

Ten grams of α-D-lyxose was dissolved in 80 ml. of anhydrous pyridine (by warming to about 40°), the mixture left at room temperature for 24 hours, treated with 48 ml. of benzoyl chloride and finally worked up as described above, to give crude α-D-lyxopyranose tetrabenzoate in a yield of 62%. Chromatography of the material remaining in the mother liquor gave fractions with levorotations as great as −90.6° but none of these could be induced to crystallize.

Tribenzoyl-α-D-lyxopyranosyl Bromide (II).—Five grams of crystalline α-D-lyxopyranose tetrabenzoate, prepared as described above, was dissolved in 8 ml. of methylene dichloride and treated with 16 ml. of a solution of hydrogen bromide in glacial acetic acid (*ca.* 32% HBr). Polarimetric observations at 20° showed that the reaction was essentially complete in one-half hour; the reaction mixture was then diluted with methylene dichloride and washed with cold water and cold aqueous sodium bicarbonate. The methylene dichloride solution was dried with sodium sulfate and, after filtration through decolorizing carbon, the solution was concentrated *in vacuo* to a clear, colorless sirup. A sample of this material, dried *in vacuo* at 40°, showed in dry, alcohol-free chloroform a rotation of −58.1° (*c*, 4.84). All attempts to obtain the compound in crystalline form failed.

Reaction of Tribenzoyl-α-D-lyxopyranosyl Bromide with Methanol in the Absence of an Acid Acceptor.—Tribenzoyl-α-D-lyxopyranosyl bromide prepared from 10 g. of α-D-lyxopyranose tetrabenzoate as described above was dissolved in 20 ml. of methylene dichloride and the solution diluted to 200 ml. with absolute methanol. Polarimetric observations at 20° showed that the reaction was essentially complete after one hour. Fourteen milliliters of 1.5 N barium methylate was then added and the mixture left at 5° for two days. The pale yellow solution was then deionized by successive passage through columns of Amberlite IR-120[12] and Duolite A-3[13] and, together with the aqueous washings from the columns, concentrated *in vacuo* to a sirup. Solution of this latter in a mixture of methanol and ethyl acetate led to the isolation of 2.32 g. (80%, based on the α-D-lyxopyranose tetrabenzoate used) of crude crystalline material melting at 95–108°. Three recrystallizations from methanol–ethyl acetate gave material rotating in water +58.9° (*c*, 1.91) and melting at 108–109° either alone or in admixture with authentic methyl α-D-lyxopyranoside. Methyl α-D-lyxopyranoside has been reported to have a rotation of +59.4° in water and a melting point of 108–109°.[14]

Acknowledgment.—The authors wish to thank Mrs. Margaret M. Ledyard and Mr. William C. Alford of this Laboratory for combustion analyses.

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[9] Melting points were measured with a calibrated Anschütz-type thermometer completely immersed in the bath liquid. Rotations are specific rotations for the D line of sodium at 20°; concentration is expressed in g. of substance per 100 ml. of solution.

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

[11] In the earlier part of this investigation, a crystalline α-D-lyxopyranose tetrabenzoate was obtained which, after repeated crystallization, melted at 111–117°, showed a rotation of −48.9° in chloroform and gave satisfactory analytical values for carbon and hydrogen. Upon solution in warm alcohol and seeding with the higher-melting form obtained later, this low-melting material was converted to the form of m.p. 138–139°; it is therefore probably a dimorphous form of the higher-melting material.

[12] Product of the Resinous Products and Chemical Co., Washington Square, Philadelphia 5, Pa.

[13] Product of the Chemical Process Co., 901 Spring Street, Redwood City, Calif.

[14] F. P. Phelps and C. S. Hudson, THIS JOURNAL, **48**, 503 (1926).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Periodate Oxidations of Phenyl β-D-Thioglycopyranosides, Phenyl β-D-Glucopyranosyl Sulfones and Related Compounds

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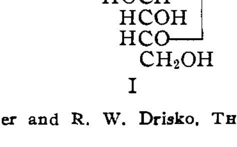
When phenyl β-D-thioglucopyranoside or its tetraacetate are treated with periodate or iodate solutions, elemental iodine is formed. That this is due to oxidation of the sulfur atom to the sulfone or sulfoxide state has been shown by the fact that the action of periodic acid on ethyl sulfide produces iodine and ethyl sulfone. Periodate ring size determinations on phenyl β-D-glucopyranosyl sulfone and several related compounds were hampered by an ambiguous, fading end-point in the back titrations with iodine. This proved due to the susceptibility of the dialdehyde oxidation products to further oxidation by iodine. When the dialdehydes were removed by extraction prior to analysis for excess periodate, the quantities of periodate consumed and formic acid produced indicated the presence of a pyranose ring in each case.

Methods for the synthesis of alkyl and aryl β-D-glycopyranosyl sulfones, such as I, have recently been reported.[1] In attempts to establish experimentally the ring size in I, it was found that the standard periodate procedures[2] led to haphazard results. Similarly, when phenyl β-D-thioglucopyranoside or its acetate, or phenyl β-D-selenoglucopyranoside reacted with periodate, the reaction again proved anomalous in that elemental iodine was produced.[3] The present paper describes more detailed observations along these lines.



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When phenyl β-D-thioglucopyranoside was dissolved in *ca.* 0.7 N periodic acid and allowed to

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[1] W. A. Bonner and R. W. Drisko, THIS JOURNAL, **70**, 2435 (1948).

[2] E. L. Jackson in Chap. 8, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944.

[3] W. A. Bonner and Ann Robinson, THIS JOURNAL, **72**, 354 (1950).