

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Some Reactions of 2,3,4-Tribenzoyl- β -D-ribofuranosyl BromideBY R. JEANLOZ,¹ HEWITT G. FLETCHER, JR., AND C. S. HUDSON

In a preceding paper² the preparation of a crystalline and comparatively stable 2,3,4-tribenzoyl- β -D-ribofuranosyl bromide was reported. Because of the potential usefulness of this compound for synthesizing derivatives of ribose it was felt desirable to investigate some of its chemical properties. The present communication describes in particular the reaction of this bromide with methanol, with ethanol and with water.

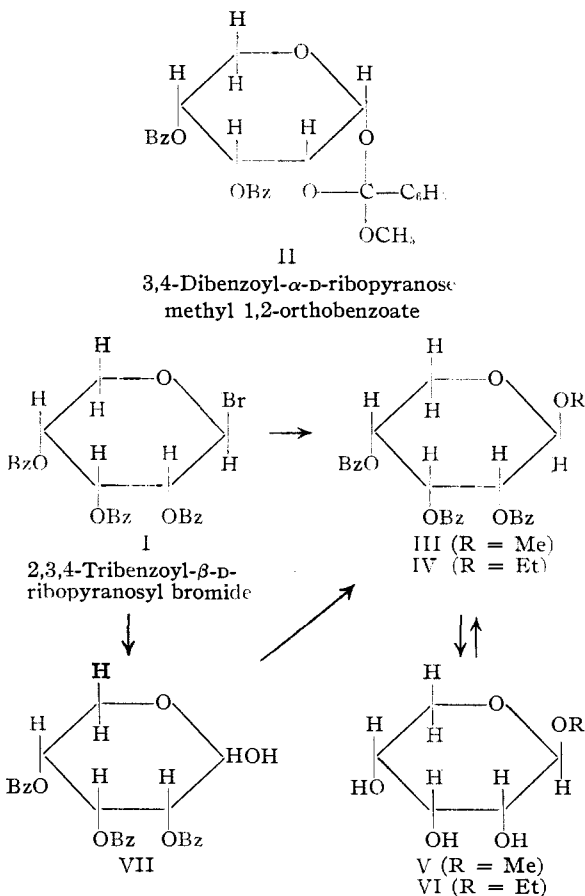
Reaction of 2,3,4-tribenzoyl- β -D-ribofuranosyl bromide (I) with methanol in the presence of silver carbonate was found to give an amorphous mixture from which no crystalline material was obtained. In view of the current ideas of the mechanism of orthoester formation³ and of the known behavior of 2,3,4-triacetyl- β -D-ribofuranosyl bromide⁴ under similar circumstances, it seems probable that the mixture contained *inter alia* methyl 2,3,4-tribenzoyl- β -D-ribofuranoside (III), its α -anomer and 3,4-dibenzoyl- α -D-ribofuranose methyl 1,2-orthoacetate (II).

In one of their early classical experiments Koenigs and Knorr⁵ found that 2,3,4,6-tetraacetyl- α -D-glucopyranosyl bromide, on standing in methanol solution for several days, is converted to methyl β -D-glucopyranoside. Some twenty-three years later Dale⁶ demonstrated that the substance which is now known to be 3,4,6-triacetyl- β -D-mannopyranose methyl 1,2-orthoacetate was converted by methanolic hydrogen chloride into methyl 2,3,4,6-tetraacetyl- β -D-mannopyranoside, though the yield was small and the other products were not identified. These facts strongly suggest that 2,3,4-tribenzoyl- β -D-ribofuranosyl bromide might be expected to furnish a methyl riboside tribenzoate under acid conditions. Such, indeed, actually proved to be the case and pure anhydrous methanol was found to convert 2,3,4-tribenzoyl- β -D-ribofuranosyl bromide into a methyl D-ribofuranoside tribenzoate (III) in 88% yield. It seems likely that this high yield is due in great measure to the marked stability of the benzoyl groups under the conditions of the experiment.

The structure and configuration of this methyl D-ribofuranoside tribenzoate was established as follows: methyl β -D-ribofuranoside (V),⁷ of proven struc-

ture and configuration,^{7b} was benzoylated to give methyl 2,3,4-tribenzoyl- β -D-ribofuranoside, which proved to be identical with the above compound.

Since, as stated in the preceding paper, the overall yield of 2,3,4-tribenzoyl- β -D-ribofuranosyl bromide from D-ribose is 68% and since the debenzoylation of methyl 2,3,4-tribenzoyl- β -D-ribofuranoside is nearly quantitative, this path compares favorably with the direct reaction of D-ribose with acidic methanol⁷ as a means of preparing methyl β -D-ribofuranoside. In fact the somewhat low yields and the difficulty of initiating crystallization in the absence of seeds in the latter process serve to make the path through the 2,3,4-tribenzoyl- β -D-ribofuranosyl bromide more attractive. By way of illustrating this, the hitherto unreported ethyl β -D-ribofuranoside was synthesized by each of the two processes. 2,3,4-Tribenzoyl- β -D-ribofuranosyl bromide (I) was converted by absolute ethanol into ethyl 2,3,4-tribenzoyl- β -D-ribofuranoside (IV) in 80% yield. Catalytic debenzoylation readily gave crystalline ethyl β -D-ribofuranoside



(1) Senior Research Fellow, National Institutes of Health, 1947-1948; present address: Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts.

(2) R. Jeanloz, H. G. Fletcher, Jr., and C. S. Hudson, *THIS JOURNAL*, **70**, 4052 (1948).

(3) See the review by E. Pacsu, "Advances in Carbohydrate Chem.," **1**, 77 (1945).

(4) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **92**, 109 (1931).

(5) W. Koenigs and E. Knorr, *Ber.*, **34**, 957 (1901).

(6) J. K. Dale, *THIS JOURNAL*, **46**, 1046 (1924).

(7) (a) J. Minsas, *Ann.*, **512**, 286 (1934); (b) E. L. Jackson and C. S. Hudson, *THIS JOURNAL*, **63**, 1229 (1941).

(VI). Reaction of D-ribose with ethanolic hydrogen chloride gave ethyl β -D-ribosepyranoside identical with the specimen obtained through the bromide. That this ethyl riboside is a pyranoside is shown by its behavior with sodium metaperiodate; on a molar basis the compound was found to consume 1.93 moles of periodate while 0.95 mole of formic acid was liberated. The assignment of the substance to the β -series is based on the close similarity of its molecular rotation to that of methyl β -D-ribosepyranoside (Table I) the β -D-anomeric configuration of which has been adequately proven elsewhere.^{7b}

The reaction of 2,3,4-tribenzoyl- β -D-ribosepyranosyl bromide with aqueous acetone and silver carbonate was found to give an amorphous product which was essentially 2,3,4-tribenzoyl-D-ribose (VII) since methylation with methyl iodide and silver oxide gave methyl 2,3,4-tribenzoyl- β -D-ribosepyranoside (III) in good yield.

Acknowledgments.—We are indebted to Mr. C. A. Kinser, Mrs. Margaret M. Ledyard and Mrs. Evelyn G. Peake for microanalyses.

TABLE I

COMPARISON OF SOME MOLECULAR ROTATIONS IN THE D-RIBOSE SERIES

	Mol. wt.	$[\alpha]_D^{20}$	$[M]_D^{20}$	Solvent
Methyl β -D-ribosepyranoside	164	-105°	-17,200	H ₂ O
Ethyl β -D-ribosepyranoside	178	-104°	-18,500	H ₂ O
Methyl 2,3,4-tribenzoyl- β -D-ribosepyranoside	476	-69.5°	-33,100	CHCl ₃
Ethyl 2,3,4-tribenzoyl- β -D-ribosepyranoside	490	-83.9°	-41,100	CHCl ₃

Experimental⁸

Methyl 2,3,4-Tribenzoyl- β -D-ribosepyranoside from 2,3,4-Tribenzoyl- β -D-ribosepyranosyl Bromide.—Five grams of finely pulverized 2,3,4-tribenzoyl- β -D-ribosepyranosyl bromide, prepared as described in the previous paper,² was dissolved in 50 ml. of absolute methanol by heating under a reflux condenser with frequent shaking for one minute. On standing overnight at 5° the solution deposited 3.7 g. of material as tetrahedral prisms melting at 108–109°. Concentration of the mother liquor afforded a second crop, raising the total yield to 4.0 g. (88%). Recrystallization from a mixture of ether and pentane did not change the melting point of the substance (109–110°); in chloroform solution it showed -69.5° (*c*, 0.820). Methyl 2,3,4-tribenzoyl- β -D-ribosepyranoside is soluble in the usual chlorinated solvents, acetone, hot methanol and hot ethanol; sparingly soluble in ether and insoluble in alkanes and water.

Anal. Calcd. for C₂₇H₂₄O₈: C, 68.06; H, 5.08; CH₃O, 6.51. Found: C, 68.17; H, 4.95; CH₃O, 6.66.

Methyl 2,3,4-Tribenzoyl- β -D-ribosepyranoside from Methyl β -D-Ribopyranoside.⁹—Methyl β -D-ribosepyranoside (450 mg.), prepared according to the method of Minsas^{7a}

(8) Unless otherwise specified, melting points were taken with a calibrated Anschütz-type thermometer completely immersed in the bath liquid. Rotations are specific rotations for sodium light at 20°; concentration is expressed in g. of substance per 100 ml. of solution.

(9) This preparation was carried out by Mrs. D. Jeanloz.

as modified by Jackson and Hudson,^{7b} was added to a chilled mixture of 1.5 ml. of pyridine, 3.0 ml. of ethylene dichloride and 1.4 ml. of benzoyl chloride. The mixture was shaken until the glycoside dissolved and then left at 5° overnight. The reaction was completed by heating at 40° for one hour, the cooled mixture thereafter being poured on chipped ice. After augmentation of the non-aqueous layer with 50 ml. of chloroform it was washed successively, twice with ice-cold 3 *N* sulfuric acid, twice with saturated aqueous sodium bicarbonate solution and finally thrice with water. The solution was dried with sodium sulfate and concentrated *in vacuo*. The residual sirup, dissolved in 5 ml. of ether and treated with pentane to incipient turbidity, was seeded; after some hours 980 mg. of product in the form of tetrahedral prisms was obtained. Either alone or in admixture with the product obtained from 2,3,4-tribenzoyl- β -D-ribosepyranosyl bromide as described above, the crystals melted at 106–108°. Concentration of the mother liquor afforded 290 mg. of less pure material; total yield 1.18 g. (90%).

Ethyl 2,3,4-Tribenzoyl- β -D-ribosepyranoside from 2,3,4-Tribenzoyl- β -D-ribosepyranosyl Bromide.—This conversion was carried out in the same manner as for the methyl analog described above. Three grams of 2,3,4-tribenzoyl- β -D-ribosepyranosyl bromide thus gave 2.15 g. (80%) of needle-like crystals melting at 130–131°. After recrystallization from absolute alcohol and then from a mixture of ether and pentane the ethyl 2,3,4-tribenzoyl- β -D-ribosepyranoside melted at 132–133° and showed a rotation of -83.9° in chloroform (*c*, 0.900). Its solubility characteristics closely resembled those of its methyl analog.

Anal. Calcd. for C₂₈H₂₆O₈: C, 68.56; H, 5.34. Found: C, 68.86; H, 5.35.

Ethyl β -D-Ribopyranoside from Ethyl 2,3,4-Tribenzoyl- β -D-ribosepyranoside.—One gram of ethyl 2,3,4-tribenzoyl- β -D-ribosepyranoside was debenzoylated with barium methylate in the usual manner. The resulting barium-free sirup was dissolved in 1 ml. of hot ethyl acetate, seeded¹⁰ and left at 5° overnight. A small second crop of crystals was obtained through concentration of the mother liquor; total yield 0.23 g. (63%). Two recrystallizations from 2 ml. of a 1:10 mixture of methanol and ether gave hexagonal plates melting at 92–93° and rotating in water -104° (*c*, 1.34). Ethyl β -D-ribosepyranoside crystallizes from water as large needles devoid of water of crystallization.

Anal. Calcd. for C₇H₁₄O₅: C, 47.18; H, 7.92; C₂H₅O, 25.29. Found: C, 47.20; H, 7.68; C₂H₅O, 25.10.

Ethyl β -D-Ribopyranoside from D-Ribose.—A solution of 5.0 g. of D-ribose in 50 ml. of a 1% absolute ethanolic solution of hydrogen bromide was boiled under reflux for six hours and then freed of acid by treatment with an excess of silver carbonate. After passage through a filter pre-coated with activated carbon the solution was concentrated *in vacuo* to a yellow sirup, diluted with 5 ml. of ethyl acetate and seeded. After one-half hour, 5 ml. of ether was added and the solution left overnight at 5°. The crystals (1.87 g.) were removed by filtration, washed with a cold mixture of methanol and ether and then with ether. Removal of solvent from the mother liquor and solution of the residual sirup in 2 ml. of ethyl acetate gave 0.41 g. of less pure material; total yield 2.28 g. (38%). After recrystallization from 10 parts of a 1:10 mixture of methanol and ether the product melted at 91–92° either alone or in admixture with the ethyl β -D-ribosepyranoside prepared from ethyl 2,3,4-tribenzoyl- β -D-ribosepyranoside above.

Sodium Metaperiodate Oxidation of Ethyl β -D-Ribopyranoside.—The technique of Jackson and Hudson¹¹ was employed. Ethyl β -D-ribosepyranoside (0.1017 g.) was dissolved in a few ml. of water, treated with 3.0 ml. of 0.4352 *M* sodium metaperiodate (2.29 molecular equivalents) and the solution diluted to 10.0 ml. with water. After

(10) The original seeds of ethyl β -D-ribosepyranoside were obtained by sublimation from the sirupy material at a pressure of 0.01 mm. and a bath temperature of 70°.

(11) E. L. Jackson and C. S. Hudson, *THIS JOURNAL*, **59**, 994 (1937).

twenty-four hours at room temperature a 3.0-ml. sample was titrated for formic acid and residual oxidant. On a molar basis 1.93 moles of oxidant was consumed while 0.95 mole of formic acid was formed.

2,3,4-Tribenzoyl-D-ribose.—To a solution of 1.0 g. of 2,3,4-tribenzoyl- β -D-ribofuranosyl bromide in 10 ml. of acetone was added 1 ml. of water and 1 g. of silver carbonate. The suspension was shaken at room temperature for two hours, filtered, treated with carbon and refiltered. Concentration *in vacuo* gave a sirup which rotated -27.9° in chloroform (*c*, 1.130).

Methyl 2,3,4-Tribenzoyl- β -D-ribofuranoside from 2,3,4-Tribenzoyl-D-ribose.—A solution of 0.73 g. of sirupy 2,3,4-tribenzoyl-D-ribose in 10 ml. of methyl iodide was shaken at 2° with 1 g. of silver oxide for six days. After filtration, the methyl iodide was removed *in vacuo*, leaving a residue of 0.765 g. of sirup which rotated -54.8° in chloroform (*c*, 1.114). After solution of the sirup in 2 ml. of methanol and seeding with authentic methyl 2,3,4-tribenzoyl- β -D-ribofuranoside it gave 0.605 g. (80%) of crystalline material whose melting point, either alone or when mixed with authentic methyl 2,3,4-tribenzoyl- β -D-ribofuranoside, was $108-109^\circ$.

Summary

Reaction of 2,3,4-tribenzoyl- β -D-ribofuranosyl

bromide with methanol alone gives satisfactory yields of methyl 2,3,4-tribenzoyl- β -D-ribose, identical with the tribenzoate from the previously known methyl β -D-ribofuranoside.

Ethanol similarly converts 2,3,4-tribenzoyl- β -D-ribofuranosyl bromide into ethyl 2,3,4-tribenzoyl- β -D-ribofuranoside which on catalytic debenzoylation yielded ethyl β -D-ribofuranoside, identical with the product made directly by the interaction of D-ribose with ethanolic hydrogen chloride.

Reaction of 2,3,4-tribenzoyl- β -D-ribofuranosyl bromide with aqueous acetone has given amorphous 2,3,4-tribenzoyl-D-ribose whose structure was confirmed through methylation to methyl 2,3,4-tribenzoyl- β -D-ribofuranoside.

The advantage in the use of 2,3,4-tribenzoyl- β -D-ribofuranosyl bromide for the preparation of ribofuranosides has been pointed out.

BETHESDA, MARYLAND

RECEIVED AUGUST 11, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Unsymmetrical Analogs of DDT¹

BY GEORGE H. SCHNELLER² AND G. B. L. SMITH³

A considerable number of ring-substituted derivatives of 1-trichloro-2-diphenylethane—so-called analogs of DDT—have been described. However, in the special case of analogs in which each of the two phenyl groups bears a different substituent, the compounds to be found in the literature are fewer in number.⁴

The unsymmetrical analogs have been prepared in which the substituent on one phenyl group is a chlorine atom and that on the other phenyl group is a bromine or an iodine atom. In addition, the first two members of a series of analogs have been prepared in which the substituent on one phenyl group is a methoxy group and that on the other phenyl group is a hydroxy or higher alkoxy group. Attempts to prepare the unsymmetrical analog having a para chlorine atom on one benzene ring and a para methoxy group on the other were unsuccessful.

(1) This work was supported in part by a grant from Niagara Sprayer and Chemical Division of Food Machinery Corporation.

(2) Research Fellow, Polytechnic Institute of Brooklyn. Taken in part from a dissertation presented in partial fulfillment for the degree of Doctor of Philosophy, Polytechnic Institute of Brooklyn, June, 1947. Present address: Calco Chemical Division, American Cyanamid Company, Bound Brook, New Jersey.

(3) Professor of Analytical Chemistry, Polytechnic Institute of Brooklyn. Present address: Naval Ordnance Testing Station, Inyokern, California.

(4) Fleck and Haller, *THIS JOURNAL*, **66**, 2095 (1944); Cristol, *ibid.*, **67**, 1494 (1945); Anonymous, *Chem. Eng. News*, **23**, 1520 (1945); Prill, *et al.*, *Contribs. Boyce Thompson Inst.*, **14**, 341 (1946); Haller, *et al.*, *THIS JOURNAL*, **67**, 1591 (1945); Lauger, *et al.*, "Mechanism of Intoxication of DDT Insecticides in Insects and Warm-blooded Animals," Geigy Co., New York, 1946; Chattaway and Muir, *J. Chem. Soc.*, 701 (1934).

In the preparation of these analogs, the 1-trichloro-2-(substituted phenyl)-ethanols were employed as intermediates.

Dinesmann⁵ in 1905 prepared 1-trichloro-2-phenylethanol and its *p*-methoxy derivative in 80% yield by the condensation of benzene or anisole with chloral in the presence of anhydrous aluminum chloride. von Leuthold⁶ applied this method to the preparation of the *p*-chlorophenyl compound. On the other hand, Frankforter and Kritchevsky^{7,8} working with aluminum chloride as the condensing agent for alkyl and alkoxy derivatives of benzene obtained not the respective carbinols, but instead 1-trichlorodiphenylethanes in good yields. These workers were unable to reconcile their results with those of Dinesmann. They postulated two distinct reaction mechanisms, namely, that of the Grignard and the Friedel-Crafts (Dinesmann) reactions, in which simple condensation takes place and no water is eliminated, and secondly that obtaining in the Baeyer sulfuric acid condensation and their own reaction using aluminum chloride, where a molecule of water is eliminated with the formation of a 1-trichloro-2-diphenylethane.

Chattaway and Muir⁴ showed that the carbinols were intermediates in the Baeyer condensation of

(5) Dinesmann, *Compt. rend.*, **141**, 201 (1905).

(6) von Leuthold, French Patent 791,172 (Dec. 5, 1935); *Chem. Abstr.*, **30**, 3137 (1936).

(7) Frankforter and Kritchevsky, original communication to the 8th Int. Congr. of Applied Chem., (Appendix), **25**, 361 (1912).

(8) Frankforter and Kritchevsky, *THIS JOURNAL*, **36**, 1511 (1914); **37**, 385 (1915).