Reduction of the Products of Periodate Oxidation of Carbohydrates. XIV. Reaction of Methyl Pentofuranosides with Periodate and the Correlation of Their Structures[1a-c]

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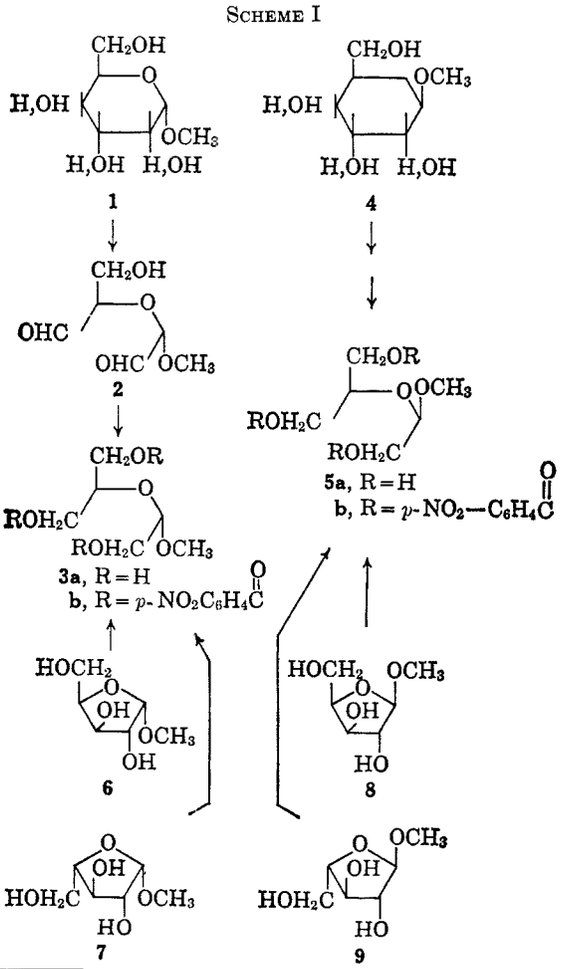
Periodate oxidation of vicinal diols[2,3] provides the basis for a convenient chemical method[4] of correlating the anomeric configuration of glycosides. In this method glycosides such as methyl D-hexopyranosides (**1** and **4**) are degraded to triols (**3a** and **5a**) possessing an asymmetric center only at the carbon atom formerly at the anomeric position of the parent glycoside. Thus, methyl α-D-hexopyranosides (**1**) upon oxidation by periodate gave the dialdehyde **2** which in turn was reduced to the triol **3a**. In a similar manner methyl β-D-hexopyranosides **4** gave the triol **5a** which was enantiomorphic with triol **3a**.[4] (See Scheme I.)

SCHEME I



Methyl pentofuranosides are amenable to similar correlation of anomeric configuration. Thus methyl α-D-xylofuranoside (**6**) and methyl β-L-arabinofuranoside (**7**) should both furnish triol **3a**, and methyl β-D-xylofuranoside (**8**) and methyl α-L-arabinofuranoside (**9**) should both furnish triol **5a**. This paper reports the correlation of anomeric configuration of these four methyl pentofuranosides to each other and to the methyl hexopyranosides.

The furanosides **6–9** were smoothly oxidized by **1** mole equiv of periodate. The resulting dialdehydes, without isolation, were each reduced by borohydride to the triols, which were converted to their characteristic crystalline tris-*p*-nitrobenzoates **3b** and **5b**. The pertinent physical properties of these derivatives are recorded in Table I.

TABLE I

SOME PROPERTIES OF THE TRIS-*p*-NITROBENZOATES OF THE ALCOHOLS DERIVED FROM METHYL PENTOFURANOSIDES AND GLUCOPYRANOSIDES BY PERIODATE OXIDATION AND BOROHYDRIDE REDUCTION

Parent methyl glycosides	Derived tris-*p*-nitrobenzoates— Mp, °C	[α]D ($CHCl_3$), deg
α-L-Arabinofuranoside (**9**)	113–114	+25
β-L-Arabinofuranoside (**7**)	113–114	−28
α-D-Xylofuranoside (**6**)	113–115	−23
β-D-Xylofuranoside (**8**)	107–110	+25
α-D-Glucopyranoside[4]	110	−24
β-D-Glucopyranoside[4]	110	+24

The data show that the tris-*p*-nitrobenzoates (**3b**) of the triols derived from **6** and **7** are, as expected, identical with the tris-*p*-nitrobenzoate derived from methyl α-D-glucopyranoside. Consequently, these three glycosides must possess the same absolute configuration (*S*) at the anomeric carbon atom. Likewise, since the tris-*p*-nitrobenzoates (**5b**) of the triols derived from **8**, **9**, and methyl β-D-glucopyranoside are identical, these three glycosides possess an identical absolute configuration (*R*) at the anomeric carbon atom. Thus, by means of characteristic crystalline compounds, the anomeric configurations of the methyl pentofuranosides of L-arabinose and D-xylose have been correlated with each other and with the methyl D-glucopyranosides.

The structure of methyl α-D-arabinofuranoside was correlated[5] with the structures of the methyl hexopyranosides by periodate oxidation followed by oxidation of the dialdehyde groups to give the characteristic strontium salt of the dicarboxylic acid. This salt was identical with that obtained from methyl α-D-glucopyranoside.[5] A later study[6] examined the periodate oxidation of the methyl furanosides of D- and L-arabinose, D-ribose, and D-xylose. The syrupy triols (corresponding to **3a** and **5b**) obtained upon reduction of the dialdehydes were characterized by optical rotation. It was shown that those methyl glycosides of the α-L- or β-D-anomeric configuration yielded glycols of similar rotation, whereas those glycosides of β-L- or α-D-anomeric configuration afforded glycols of similar

(1) (a) This paper, No. 5768, Scientific Journal Series, Minnesota Agricultural Experiment Station, formed a part of the thesis submitted by T. L. Hullar to the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D., 1963. (b) For the previous paper in this series, see O. P. Bahl, T. L. Hullar, and F. Smith, *J. Org. Chem.*, **29**, 1076 (1964). (c) Supported in part by a grant (G-13046) from the National Science Foundation. (d) Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, N. Y. 14214. (e) Deceased, Feb 1, 1965.

(2) L. Malaprade, *Compt. Rend.*, **186**, 382 (1928); *Bull. Soc. Chim. France*, **43**, 683 (1928).

(3) P. J. Fleury and J. Lange, *Compt. Rend.*, **195**, 1395 (1932).

(4) F. Smith and J. W. Van Cleve, *J. Am. Chem. Soc.*, **77**, 3091 (1955).

(5) E. L. Jackson and C. S. Hudson, *ibid.*, **59**, 994 (1937).

(6) E. Berner and O. Kjolberg, *Acta Chem. Scand.*, **14**, 909 (1960).

rotation but opposite in sign. The results of the present study extend these observations.

Experimental Section

Melting points were taken on a Fisher–Johns melting block and are corrected.

Preparation of the Methyl Pentofuranosides.—Methyl α- and β-L-arabinofuranoside were prepared by the method of Augestad and Berner[7] as syrups: $[\alpha]^{23}D$ −124° (*c* 2.0, water) and +97° (*c* 2.0, water), respectively; lit.[7] $[\alpha]D$ −128° and +118°, respectively. Methyl α-L-arabinofuranoside was also prepared as a syrup, $[\alpha]^{25}D$ −129° (*c* 1.3, methanol), by Zemplen[8] deacetylation of methyl 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranoside.[9] Crystalline methyl α-D-xylofuranoside, mp 82–84°, $[\alpha]^{26}D$ +170° (*c* 2.35, water) (lit.[7] mp 84°, $[\alpha]D$ +182°), and syrupy methyl β-D-xylofuranoside, $[\alpha]^{30}D$ −80° (*c* 3.6, water) (lit.[7] $[\alpha]D$ −90°), were prepared by the method of Augestad and Berner.[7]

General Procedure for Periodate Oxidations, Borohydride Reductions, and *p*-Nitrobenzoylations.—Periodate oxidation of the four methyl pentafuranosides, borohydride reduction of the resulting dialdehydes, and esterification of the enantiomorphic triols were carried out using the methods described by Smith and Van Cleve.[4] The melting points and specific rotations of the tris-*p*-nitrobenzoates thus obtained are recorded in Table I. The mixture melting point of each of the derived tris-*p*-nitrobenzoates was undepressed upon admixture with the corresponding tris-*p*-nitrobenzoate derived from methyl α- or β-D-glucopyranoside.

(7) I. Augestad and E. Berner, *Acta. Chem. Scand.*, **8**, 251 (1954).
(8) G. Zemplen and E. Pacsu, *Ber.*, **62**, 1613 (1929).
(9) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4605 (1961).

Use of the 3,5-Dimethoxybenzyloxycarbonyl Group as a Photosensitive N-Protecting Group

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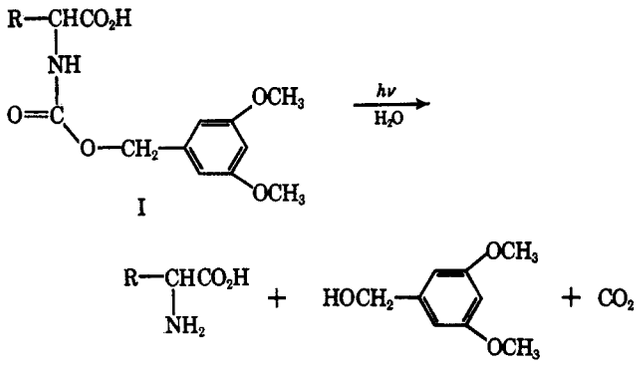
There are now a number of selectively removable groups which can be used for protection of the amino functions during peptide synthesis.[1] Removal of the protecting groups involves, in general, either treatment with acid or base, catalytic or chemical reduction, or a combination of these methods. More recently, Barltrop and Schofield[2] have reported on another method of potential usefulness in this field, *i.e.*, the removal of a protecting group by means of ultraviolet irradiation. Zimmerman and Sandel[3] studied the photochemical solvolysis of certain substituted benzyl acetates and found that *m*-methoxyl substitution enhanced reactivity. In this paper we wish to report on the photolytic cleavage of carbamates of general structure I.

To evaluate the use of this group in peptide synthesis, the 3,5-dimethoxybenzyloxycarbonyl derivatives of several amino acids and a dipeptide were prepared and irradiated in aqueous solution.

(1) (a) R. A. Boissonas, *Advan. Org. Chem.* **3**, 159 (1963); (b) J. Rudinger, *Pure Appl. Chem.*, **7**, 335 (1963).
(2) (a) J. A. Barltrop and P. Schofield, *Tetrahedron Letters*, 697 (1962); (b) *J. Chem. Soc.*, 4758 (1965).
(3) H. E. Zimmerman and V. R. Sandel, *J. Am. Chem. Soc.*, **85**, 915 (1963).



Preparation of the 3,5-dimethoxybenzyloxycarbonyl derivative was accomplished by treating the amino acid with 3,5-dimethoxybenzyl *p*-nitrophenylcarbonate in aqueous tetrahydrofuran in the presence of sodium hydroxide.[4] Properties of the derivatives are listed in Table I.

Irradiations were carried out in aqueous dioxane solution using a high-pressure mercury lamp (Hanovia 654A-36, Vycor glass filter). Initial experiments with 3,5-dimethoxybenzyloxycarbonyl-D-phenylglycine indicated that the maximum concentration of free amino acid was obtained after an irradiation time of approximately 1.5 hr (paper chromatographic assay). The results obtained in preparative experiments are summarized in Table II. Irradiation of benzyloxycarbonylglycine under these conditions resulted in a considerably lower yield (10%) of the free acid in comparison with that obtained from 3,5-dimethoxybenzyloxycarbonylglycine (85%). In the case of the L-lysine derivative (Table I), it was found possible to remove the 3,5-dimethoxybenzyloxycarbonyl group while leaving the ε-benzyloxycarbonyl group intact.

The dipeptide derivative, 3,5-dimethoxybenzyloxycarbonyl-D-phenylglycylglycine, was prepared in 72% yield by a mixed anhydride coupling procedure. Irradiation under the same conditions employed for the amino acid derivatives furnished D-phenylglycylglycine[5] in 65% yield.

No attempt was made to isolate other products of the irradiations except in the case of the glycine derivative where 3,5-dimethoxybenzyl alcohol was isolated in 38% yield.[6]

These results suggest that the 3,5-dimethoxybenzyloxycarbonyl group could be a practical protecting group for use in peptide synthesis and other areas of synthesis. Its removal does not involve the use of acid or base or reductive cleavage.

Experimental Section[7]

3,5-Dimethoxybenzyl *p*-Nitrophenylcarbonate.—Reduction of 3,5-dimethoxybenzoic acid (Aldrich Chemical Co.) with lithium aluminum hydride in tetrahydrofuran afforded 3,5-dimethoxy-

(4) The procedure was essentially that which has been described for the preparation of *t*-butyloxycarbonyl derivatives of amino acids: G. W. Anderson and A. C. McGregor, *ibid.*, **79**, 6180 (1957).
(5) The DL compound has been prepared previously: E. Fischer and J. Schmidlin, *Ann.*, **340**, 190 (1905).
(6) For a detailed analysis of the products from the photolysis of benzyloxycarbonylglycine and a discussion of the mechanism of this reaction, see ref 2b.
(7) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The ultraviolet spectra were obtained in ethanol solution on a Cary Model 14 recording spectropolarimeter. Optical rotations were obtained on a Rudolph Model 200 photoelectric polarimeter. Titrations were carried out in 2:1 dimethylformamide–water solution.