[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 173]

Cleavage of the Carbon Chain of Glycosides by Oxidation with Lead Tetraacetate[1]

BY W. S. MCCLENAHAN[2] WITH R. C. HOCKETT

The glycol-splitting power of lead tetraacetate has been used in several instances to prepare carbohydrate derivatives.[3] In these cases it has been the practice to mask certain hydroxyl groups of a polyhydric alcohol so that no pair of free hydroxyl groups would remain on adjacent carbon atoms except at the position where the carbon chain is to be broken and aldehyde groups produced. Difficulties in preparing such derivatives have seriously limited the extension of this type of synthesis.

Since *cis* glycols are reported to be oxidized much more rapidly than *trans*[4,5] it was thought that a compound containing both types of diol structure might, when treated with an equimolar quantity of lead tetraacetate, be split preferentially at the *cis* position to such an extent that the masking of groups would be unessential. In this respect α-methyl-*d*-mannopyranoside (I)[6] seemed of particular interest since its oxidation with lead tetraacetate might be expected to produce a mixture of (II) and (III) containing a high percentage of the former; hydrolysis of the product would then give a considerable quantity of the difficultly accessible tetrose, *d*-erythrose.

However, Criegee[7] has found that lead tetraacetate produces *two* moles of formaldehyde from glycerol, which can occur only by the further oxidation of the glycolaldehyde first formed; since both (II) and (III) contain an alpha-hydroxyaldehyde grouping, they would probably be capable of further oxidation to a common product (IV). No information exists regarding the rates of such reactions. Karrer and Pfaehler[8] have oxidized α-methyl-*d*-glucoside (V) with lead tetraacetate, but although this would also be expected to produce (II) and (III), the glycoside contains no *cis* glycol structure and its oxidation therefore provides no evidence regarding possible preferential attack at such a position. The products isolated by these workers fail, moreover, to show unequivocally the ultimate fate of the dialdehydes.

Our experiments with the oxidation of α-methyl-*d*-mannoside by somewhat less than an equimolar quantity of lead tetraacetate have provided strong evidence, however, that the product formed is largely (IV), since nearly half the mannoside was recovered unchanged after all the tetraacetate had been consumed, and hydrolyzed portions of the product yielded large quantities of glyceraldehyde osazone. These observations indicate that wherever the initial fission may have occurred, the secondary oxidation of hydroxyaldehyde (II) or (III) is even more rapid and consumes additional oxidizing agent faster than does the unattacked methylmannoside remaining in the mixture. Finally, oxidation of the product with bromine water in the presence of strontium carbonate gave a strontium salt (VI) which was identical in all measured properties with that obtained by Jackson and Hudson[9] when they oxidized α-methyl-*d*-mannopyranoside with periodic acid followed by strontium hypobromite.

The investigation was extended to other glycosides, and in each case the final product corresponded to that obtained by Jackson and Hudson[9] or Maclay and Hudson[10] from the same compound (Table I).

The results show that the method for determining ring structures and alpha and beta configurations of glycosides as developed by Jackson and Hudson may be carried out with lead tetraacetate as well as with periodic acid. The former may be preferable for compounds more soluble in water; the latter, for derivatives more soluble in organic solvents.

---

[1] This paper represents part of a thesis submitted by William S. McClenahan to the Graduate School of the Massachusetts Institute of Technology in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Louis Francisco Verges Fellow in Chemistry in 1936–1937 and 1937–1938.

[3] Von Vargha, *Ber.*, **68**, 18 (1935); Appel, *J. Chem. Soc.*, 425 (1935); Steiger and Reichstein, *Helv. Chim. Acta*, **19**, 1016 (1936).

[4] Criegee, *Ber.*, **64**, 260 (1931).

[5] Criegee, *ibid.*, **65**, 1770 (1932); Criegee, Kraft and Rank, *Ann.*, **507**, 159 (1933).

[6] The configuration of the groups about an asymmetric carbon atom is not conceived, in itself, to restrict the possibility of free rotation about the carbon–carbon bonds; *e. g.*, it is not appropriate to look upon the hydroxyls of active tartaric acids as fixed either in *cis* or *trans* position despite the fact that conventional projectional formulas make them appear so. On the other hand, where a ring structure exists as in a glycoside or in cyclohexanediol, conventional considerations indicate that the rotation around carbon–carbon bonds is prevented and hydroxyl groups bear a fixed relation to one another in space which moreover is determined by the configurations of the asymmetric carbons.

[7] Criegee, *Ann.*, **495**, 211 (1932).

[8] Karrer and Pfaehler, *Helv. Chim. Acta*, **17**, 363 (1934).

[9] Jackson and Hudson, THIS JOURNAL, **59**, 994 (1937).

[10] Maclay and Hudson, *ibid.*, **60**, 2059 (1938).

TABLE I[11]

	Dialdehyde by		Dibasic acid by		Strontium salt by	
	HIO$_4^{(9)}$	Pb(OAc)$_4$	HIO$_4^{(9)}$	Pb(OAc)$_4$	HIO$_4^{(9)}$	Pb(OAc)$_4$
Glycoside	$[\alpha]^{20}\text{D}$	$[\alpha]^{20}\text{D}$	$[\alpha]^{20}\text{D}$	$[\alpha]^{20}\text{D}$	$[\alpha]^{20}\text{D}$	$[\alpha]^{20}\text{D}$
α-Methyl-*d*-mannoside	+119.5	+132^a	+26.3	+25.2^b	−53.0	−52.2
α-Methyl-*d*-glucoside	+121.1	+170^a	+26.0	+24.7^b	−52.9	−50.7
β-Methyl-*d*-arabinoside	−123.7	. .	+12.5	+11.9	+55.7	+55.0
α-Methyl-*d*-lyxoside	. .	. .	. .	−11.5	. .	−56.6^c

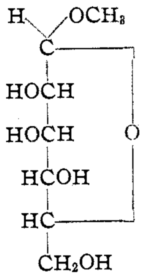
^{a} Calcd. from rotation of aqueous solution after oxidation, on the basis of 100% yield of dialdehyde (IV).

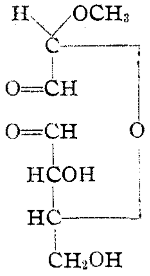
^{b} Determined by liberating the acid (c = *ca.* 1%) from its anhydrous salt with an equivalent quantity of hydrochloric acid.

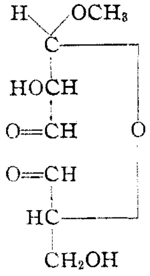
^{c} Recrystallized to constant rotation (c = 1.2108). The values for other salts were determined after one or two recrystallizations.

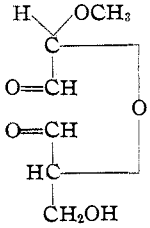
The reaction of lead tetraacetate with glycosides is slow in acetic acid and by-products resembling acetates frequently formed. This could be prevented by substituting chloroform for acetic acid as the solvent, which greatly accelerates the reaction.

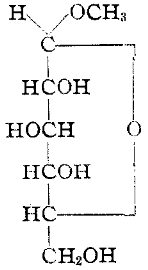
Preliminary studies have also been made concerning the rates of oxidation of the various glycosides. These have proved very useful in determining the quantities of lead tetraacetate to be used and the time required for the different reactions. These experiments will be reported in a separate communication.

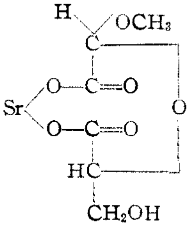

(I)
α-Methyl-*d*-mannopyranoside


(II)


(III)


(IV)
D′-methoxy-D-hydroxymethyl-diglycolic aldehyde


(V)
α-Methyl-*d*-glucopyranoside


(VI)
Strontium D′-methoxy-D-hydroxymethyl diglycolate

We are indebted to Doctors C. S. Hudson and E. L. Jackson of the National Institute of Health for a sample of strontium D′-methoxy-D-hydroxymethyl diglycolate for purposes of comparison.

Experimental

Lead Tetraacetate.—A mixture of 530 cc. of glacial acetic acid and 115 cc. of acetic anhydride was heated to 75° in a 1-liter, 3-necked Pyrex flask provided with an electric stirrer and a thermometer. To this was added 150 g. of dry red lead in six portions. The solution was allowed to become colorless between successive additions, and the temperature was kept below 90°. When the reaction was complete the slightly turbid solution was decanted from a small amount of undissolved red lead and allowed to cool in a closed vessel. The white, crystalline lead tetraacetate was filtered off on a Büchner funnel, washed with a little glacial acetic acid, and was stored in a desiccator over phosphorus pentoxide. These operations could be carried out in the open air if performed rapidly. The product weighed about 60–70 g. and was not recrystallized for use in these experiments.

Oxidation of α-Methyl-*d*-lyxopyranoside.—Three grams (0.0183 mole) of dry lyxoside (of rotation +59.4°) was added to 150 cc. of dried chloroform ($CaCl_2$) in a 500-cc. 3-necked flask, and during the course of an hour 17.5 g. (0.0395 mole) of dry lead tetraacetate was added in small portions with continuous mechanical stirring. The temperature remained below 35° at all times. Stirring was continued for two hours after the last addition. The chloroform solution was then decanted from the nearly insoluble lead diacetate and the chloroform was removed under reduced pressure. The residue was taken up in water, which formed a precipitate of brown lead dioxide, and an excess of hydrogen sulfide was passed into the mixture. The lead diacetate was also dissolved in water and treated with hydrogen sulfide separately. After filtration and aeration the first solution gave a strong Fehling's test, the second only a slight one. The two were combined, concentrated under reduced pressure to a sirup, and reconcentrated several times after addition of sulfur-free toluene to remove all acetic acid. The resulting sirup was diluted to 500 cc., and 20 g. of strontium carbonate and 3 cc. of bromine were added. The flask was shaken until the bromine dissolved, then placed in the dark at room temperature and occasionally shaken during the first hour. After eighteen hours nearly all reducing power had disappeared. The bromine was removed by aeration, and

---

[11] All rotations reported in this paper represent specific rotations of the D line of sodium by aqueous solutions at 20°; c is concentration in grams per 100 cc. of solution, and l is the tube length in decimeters.

the excess strontium carbonate was filtered off and washed with cold water. The filtrate and washings were shaken with silver carbonate until free from bromide ion; the solids were then filtered off and washed. Silver was removed from the filtrate as the sulfide. After filtration and aeration, a slight acidity was neutralized to phenolphthalein with strontium hydroxide solution. The solution was then filtered through carbon and concentrated under reduced pressure to 50 cc., filtered, and the concentration continued to 10 cc. The addition of a few drops of alcohol caused a turbidity which increased slightly after a few hours at room temperature. After filtering, the addition of a little more alcohol caused crystallization to begin. Several crops of fine needles were obtained by alternately adding alcohol and chilling; yield of trihydrate of the salt, 3 g. or 54%. After four recrystallizations of the salt[12] from 8 parts of water the rotation of the anhydrous substance became constant at −56.6° (*c*, 1.2108; *l*, 2).[11] The corresponding free acid rotated −11.5° (*c*, 0.9648; *l*, 4).[11]

Anal. Calcd. for $C_5H_6O_6Sr{\cdot}3H_2O$: H_2O, 17.8. Found (loss in wt. at 105° *in vacuo*); 17.6. Calcd. for $C_5H_6O_6Sr$: Sr, 35.01. Found: Sr, 34.94.

Oxidation of *β*-Methyl-*d*-arabinopyranoside.—The procedure was the same as reported for *α*-methyl-*d*-lyxoside. The yield of strontium salt was 65%. The anhydrous substance rotated +55.0° (*c*, 1.0080; *l*, 2).[11] The corresponding free acid rotated +11.9° (*c*, 0.8390; *l*, 1).[11]

Anal. Calcd. for $C_5H_6O_6Sr{\cdot}3H_2O$: H_2O, 17.8. Found (loss in wt. at 105° *in vacuo*): 17.6. Calcd. for $C_5H_6O_6Sr$: Sr, 35.01. Found: Sr, 34.32.

Oxidation of *α*-Methyl-*d*-mannopyranoside.—This oxidation proceeds more rapidly than in the previous cases so the total reaction time was reduced to one and a half hours. The yield of strontium salt (IV) was 55% after correcting for a small amount of mannoside which was recovered unchanged. The anhydrous form rotated −52.2° (*c*, 0.6280; *l*, 4).[11] The corresponding free acid rotated +25.2° (*c*, 1.044; *l*, 1).[11]

Anal. Calcd. for $C_6H_8O_7Sr{\cdot}2H_2O$: H_2O, 11.41. Found: (loss in wt. at 105° *in vacuo*), 12.18. Calcd. for $C_6H_8O_7Sr$: Sr, 31.25. Found: Sr, 31.08.

Oxidation of *α*-Methyl-*d*-glucopyranoside.—The total reaction time was three and a half hours, and the yield of strontium salt (VI) was 59% after correcting for a small amount of unchanged glucoside. The anhydrous salt rotated −50.7° (*c*, 0.6492; *l*, 2).[11] The corresponding free acid rotated +24.7° (*c*, 1.1440; *l*, 4).[11]

Anal. Calcd. for $C_6H_8O_7Sr{\cdot}2H_2O$: H_2O, 11.41. Found: (loss in wt. at 105° *in vacuo*), 11.8. Calcd. for $C_6H_8O_7Sr$: Sr, 31.25. Found: Sr, 31.13.

Summary

1. Several methyl-pyranosides have been oxidized with lead tetraacetate in glacial acetic acid and in chloroform solutions.

2. There has been observed in each case cleavage of the carbon chain with elimination of one carbon and formation of a dialdehyde through the consumption of two moles of oxidizing agent per mole of glycoside.

3. Further oxidation of these dialdehydes with strontium hypobromite has led to isolation of strontium salts of dibasic acids identical with those produced by Jackson and Hudson and Maclay and Hudson through the action of periodic acid and strontium hypobromite on the same methyl-glycosides.

4. In the case of *α*-methyl-*d*-mannoside it has been shown that in acetic acid at room temperature the removal of carbon three from the first fission product proceeds at a more rapid rate than does the initial cleavage.

CAMBRIDGE, MASS.

RECEIVED JUNE 24, 1938

---

[12] Mother liquors from this salt developed growths of mold during several weeks' exposure to the laboratory air. A small quantity of a water-insoluble organic compound containing strontium was found as a product.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Coupling Action of the Grignard Reagent. VI. A New Synthesis of Hexaalkylbenzils

BY REYNOLD C. FUSON AND JOSEPH CORSE

The coupling action of the Grignard reagent on halogen compounds has been shown to take place according to the general equation $2RMgX + 2R'X \longrightarrow R{-}R + R'{-}R' + 2MgX_2$.[1] The reaction seems to be conditioned largely by the activity of the halogen atom in the R'X molecule. In fact, similar results are obtained when the alkyl halide is replaced by other types of halogen compounds, notably certain metal halides such as cupric chloride[2] and silver bromide.[3] The metals suffer reduction—a change which is analogous to coupling. It would appear that any halogen compound in which the halogen atom is loosely bound might serve to bring about such effects.

It occurred to us that the halogen atoms of

---

[1] Fuson, THIS JOURNAL, **48**, 2681 (1926).

[2] Krizewsky and Turner, *J. Chem. Soc.*, **115**, 559 (1919).

[3] Gardner and Borgstrom, THIS JOURNAL, **51**, 3375 (1929); Gardner, Joseph and Gollub, *ibid.*, **59**, 2583 (1937).