treated with 50 ml. of water. The organic layer was separated and the gaseous phase was washed with ether. The combined organic layers were dried over sodium sulfate, filtered and evaporated to leave an oil which crystallized when triturated under pentane. The solid, m.p. 178–182°, weighed 2.0 g. and melted at 185–186° after crystallization from aqueous alcohol.

Anal. Calcd. for $C_{21}H_{25}NO$: N, 4.56. Found: N, 4.53.

RENSSELAER, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

Reduction of the Products of Periodate Oxidation of Carbohydrates. VI. Methylation Studies on the Monoaldehyde Formed by Catalytic Reduction of D'-Methoxy-D-hydroxymethyldiglycolic Aldehyde[1]

BY I. J. GOLDSTEIN AND F. SMITH

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The monoaldehyde III or IV obtained upon mild catalytic reduction of D'-methoxy-D-hydroxymethyldiglycolic aldehyde (I), reacting as II, has been subjected to methylation studies. Structures are proposed for the cyclic methylated derivatives (V and VI) as a result of the finding that hydrolysis of V and VI gives racemic 1-*C*-methylglyceritol and glyoxal.

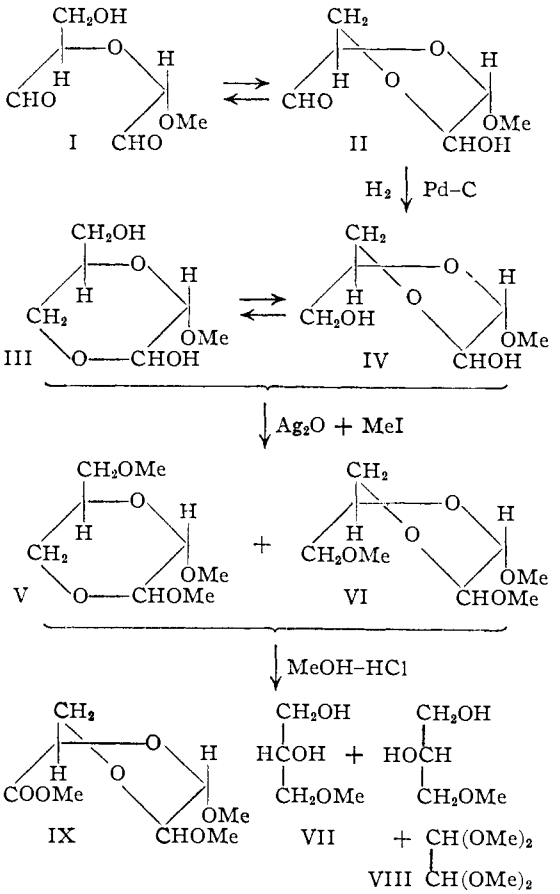
In a previous communication[2] it was shown that hydrogenation in the presence of a palladium–charcoal catalyst of the so-called dialdehyde I, obtained by periodate oxidation[3,4] of methyl α-D-glucopyranoside, effects preferential reduction of the aldehydic group at C_4 of the parent glycoside. The half-aldehyde so formed is shown herein by methylation studies to consist of the two tautomeric forms III and IV.

Treatment of the monoaldehydes III and IV with silver oxide and methyl iodide afforded a sirupy product containing a mixture, A, of the diastereoisomers V and VI. The structures V and VI assigned to the isomers in the methylated product (A) are supported by the following evidence.

The methylated product A derived from II showed $[\alpha]^{25}D$ +132° (ethanol), a value comparable with that, $[\alpha]^{28}D$ +125° (ethanol), of the parent monoaldehyde II which suggests a structural similarity and indicates[5] that the two isomers V and VI in A possess a cyclic structure. The methoxyl content of A revealed that two methoxyl groups had been introduced into III and IV during the methylation. Although showing a formal resemblance to the glycosides, the methylated mixture A proved to be much more stable than the average methyl glycopyranoside, five days treatment with boiling *N* sulfuric acid being required for complete hydrolysis.

Methanolysis of the mixture A containing V and VI gave racemic 1-*O*-methylglyceritol and glyoxal tetramethylacetal. Since L-1-*O*-methylglyceritol does not suffer racemization under the conditions used to methanolize V and VI, the formation of racemic 1-*O*-methylglyceritol (VII) reveals the presence of the two diastereoisomers V and VI. Support for the structure of V and VI also is provided by the characterization of glyoxal tetramethylacetal (VIII).

The methanolyzate of A also was found to contain a small amount of methyl glycerate which is most probably derived from the crystalline methyl ester IX, formed by the simultaneous oxidation and methylation of the dialdehyde I reacting as II. The aldehyde II is present as an impurity in the mixture of III and IV unless the monoaldehyde is purified by distillation.



These results indicate that the monoaldehyde consists of a mixture of diastereoisomeric dioxane compounds, one (IV) in which the ring engages the hydroxyl group at C_6 of the original glucoside and the aldehydic group at C_2 and the second (III) in

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(2) J. E. Cadotte, G. G. S. Dutton, I. J. Goldstein, Bertha A. Lewis, F. Smith and J. W. Van Cleve, THIS JOURNAL, **79**, 691 (1957).

(3) H. Hérissey, P. Fleury and M. Joly, *J. pharm. chim.*, **20**, 199 (1934).

(4) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 944 (1937).

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which cyclic hemiacetal formation occurs between the hydroxyl group at C_4 and the aldehydic group at C_2. The disposition of the hydrogen and methoxyl groups at C_2 in V and VI is not known.

Experimental[6]

Methylation of the Monoaldehydes III and IV with Silver Oxide and Methyl Iodide.—To a cooled (5°) suspension of the undistilled monoaldehyde (4.0 g.), prepared as described previously,[2] in methyl iodide (25 ml.) was added silver oxide (10 g.). The mixture was allowed to reach room temperature and shaken for 10 hr. It was then refluxed for 6 hr. with stirring. The methyl iodide was distilled and the residue extracted first with ether and then with methanol. Concentration of the combined extracts gave a yellow sirup which was methylated three more times as described above. Purification by extraction with ether gave a mobile yellow liquid (3.6 g.) which was distilled giving: fraction 1, a colorless, mobile liquid (0.05 g. approx.), b.p. (bath temp.) 95° (3 mm.), $n^{25}D$ 1.4285. Fraction 2, a colorless, mobile liquid (1.25 g.), b.p. (bath temp.) 98–103° (3 mm.), $n^{25}D$ 1.4338, $[\alpha]^{25}D$ +132° in ethanol (*c* 0.8). *Anal.* Calcd. for $C_8H_{16}O_5$: C, 50.0; H, 8.4; OCH_3, 48.4. Found: C, 50.0; H, 8.4; OCH_3,[7] 47.1. The method of Gran[7] for methoxyl determination was used since the usual Zeisel procedure[8] gives high values[2,9] which result from "extra" alkyl iodide generated from the polyhydric alcohols such as glyceritol produced by hydrolysis. Fraction 3, a colorless, mobile liquid (0.693 g.), b.p. (bath temp.) 106–116° (3 mm.), $n^{25}D$ 1.4358, $[\alpha]^{25}D$ +88.5° in ethanol (*c* 1.1).

Identification of the Mixture of 2(D′),3(DL)-Di-*O*-methyl-6-D-methoxymethyl-1,4-dioxane (V) and 2(D′),3(DL)-Di-*O*-methyl-6-(L)-methoxymethyl-1,4-dioxane (VI).[10]—When fraction 2 (300 mg.) was boiled with *N* sulfuric acid in 50% ethanol (25 ml.), 5 days was required for the solution to reach a constant rotation (αD +0.05°, 1 dm. tube). Neutralization ($BaCO_3$), filtration and concentration afforded a yellow sirup (120 mg.) having $[\alpha]^{25}D$ +8° in ethanol (*c* 4). Paper chromatographic analysis of the hydrolyzate using butanone–water azeotrope as the irrigating solvent and Tollens spray as the detecting reagent, revealed the presence of three components: glyceritol (R_f 0.16), 1-*O*-methylglyceritol (R_f 0.52) the major component, and methyl glycerate (R_f 0.60) in small amount.

A solution of fraction 2 (1.2 g.) in 10% methanolic hydrogen chloride (20 ml.) was heated (sealed tube) for 16 hr. at 125°. After cooling, the mildly acidic solution was neutralized (Ag_2CO_3), filtered and concentrated to a pale yellow sirup (880 mg.) which showed $[\alpha]^{24}D$ +4.3° in ethanol (*c* 8.8).

A portion (15 ml.) of the methanolic distillate obtained in the previous paragraph was treated with an acidified (HCl) solution of 2,4-dinitrophenylhydrazine in the usual way and heated to boiling, whereupon a red precipitate rapidly separated. After filtration and washing with ethanol the bis-2,4-dinitrophenylhydrazone of glyoxal (6 mg.) had m.p. and mixed m.p. of 326°.

Fractional distillation of the sirupy, methanolized product gave: fraction a, 0.0690 g., a colorless liquid, b.p. (bath temp.) 90° (3 mm.), $n^{25}D$ 1.4342; fraction b, 0.1410 g., a colorless, mobile liquid, b.p. (bath temp.) 90–95° (3 mm.), $n^{25}D$ 1.4361; fraction c, 0.2122 g., a colorless liquid, b.p. (bath temp.) 100–108° (3 mm.), $n^{25}D$ 1.4361–1.4410; fraction d, 0.1190 g., a yellow liquid, b.p. (bath temp.), 115–125° (3 mm.), $n^{25}D$ 1.4475.

All four fractions contained 1-*O*-methylglyceritol (R_f 0.50), methyl glycerate (R_f 0.59) and traces of glyceritol. Fraction c appeared to contain the highest concentration of 1-*O*-methylglyceritol.

Separation and Identification of Methanolized Fragments by Column Chromatography.—Fractions b and c were combined, dissolved in a few drops of butanone–water azeotrope and placed on a cellulose–hydrocellulose column.[11] The automatic fraction collector was adjusted to collect at 10-min. intervals (approx. 4 ml. per tube) for tubes 1–98 and at 30-min. intervals for tubes 99–170. Spotting the contents of the tubes on filter paper and spraying with Tollens reagent revealed the presence of three components: glyoxal tetramethylacetal (tubes 5–27), methyl glycerate (tubes 48–58), and 1-*O*-methylglyceritol (tubes 67–94).

The contents of tubes 5–27 were combined and concentrated to yield a pale-yellow, optically inactive liquid which was non-reducing toward Fehling solution (Found: OMe, 53.0). The substance gave a weak spot when sprayed with Tollens solution after paper chromatographic analysis (R_f 0.85) using butanone–water azeotrope as the irrigating solvent. No derivative was obtained upon treatment of the substance with *p*-nitrobenzoyl chloride in dry pyridine, but treatment with an acidic solution of 2,4-dinitrophenylhydrazine gave a reddish powder, m.p. 325°, which proved to be the bis-2,4-dinitrophenylhydrazone of glyoxal. The original substance was most probably glyoxal tetramethylacetal.

Concentration of the combined contents of tubes 48–58 gave methyl glycerate (3 mg.), identical chromatographically (R_f 0.55, using butanone–water azeotrope as the irrigating solvent) with an authentic specimen prepared by boiling a suspension of the barium salt of D′-methoxy-D-hydroxymethyldiglycolic acid in methanol with a cation exchange resin (IR 120).[12]

Concentration of the contents of tubes 67–94 gave a chromatographically pure specimen of 1-*O*-methylglyceritol (101.3 mg.). Distillation yielded a colorless, mobile liquid (64.1 mg.) which showed $n^{25}D$ 1.4385 and no optical activity in ethanol (*c* 2). The di-*p*-nitrobenzoate of the DL-1-*O*-methylglyceritol, prepared in the usual manner, was obtained as fine yellow needles, m.p. 106–107° undepressed in admixture with an authentic specimen of racemic 1-*O*-methylglyceritol di-*p*-nitrobenzoate[13]; the crystalline material showed no rotation in chloroform (*c* 1.5), thus confirming the presence of the racemic modification of 1-*O*-methylglyceritol. It also was observed that the crude di-*p*-nitrobenzoate was optically inactive.

The low recoveries of 1-*O*-methylglyceritol obtained from the methylated monoaldehyde and from the previous synthetic procedures[13] prompted an investigation of its volatility. When a solution of 1-*O*-methylglyceritol (49.9 mg.) in butanone–water azeotrope (10 ml.) was concentrated at the water-pump (bath temp. 35–40°) the recovery was 38.0 mg. or about 76%. Furthermore, the distillate was shown to contain 1-*O*-methylglyceritol by paper partition chromatography. This simple experiment proves that the material is volatile and special precautions should be observed in isolating the substance and interpreting quantitative data relating to yield of 1-*O*-methylglyceritol.

Treatment of L-1-*O*-Methylglyceritol with Methanolic Hydrogen Chloride.—Since conclusions regarding configuration of V and VI were based on the characterization of the racemic modification of 1-*O*-methylglyceritol it was found necessary to ascertain that the reagent employed in the cleavage of V and VI did not effect racemization of optically active 1-*O*-methylglyceritol. Accordingly, a solution of L-1-*O*-methylglyceritol[13] was heated (sealed tube) under the same conditions as those used above for the methanolysis of V and VI. The product was recovered unchanged, $[\alpha]^{25}D$ −4.8° in ethanol (*c* 1.5), and it gave the characteristic crystalline di-*p*-nitrobenzoate of L-1-*O*-methylglyceritol, m.p. and mixed m.p. 82–84° and $[\alpha]^{27}D$ +45° in chloroform (*c* 1). This experiment ruled out the possibility that the DL-1-*O*-methylglyceritol had arisen by racemization.

Identification of 2(D),3(D,L)-Dimethoxy-6(D)-carboxymethyl-1,4-dioxane (IX).—Fraction 4 crystallized spontaneously. Trituration with cold ethanol and filtration gave IX (45 mg.), m.p. and mixed m.p. 127° (after recrystallization from ethanol). $[\alpha]^{25}D$ +185° in chloroform (*c* 1). *Anal.* Calcd. for $C_8H_{14}O_6$: C, 46.6; H, 6.8; OCH_3, 45.1; equiv. wt., 206. Found: C, 46.9; H, 7.0; OCH_3, 45.3; equiv. wt., 212. Further details of this compound will be dealt with in a later communication.

When the monoaldehyde was purified by distillation to remove any unreduced dialdehyde, methylation of it as described above did not yield any of the ester IX.

ST. PAUL, MINN.

(6) Unless otherwise stated all evaporations were conducted *in vacuo* at a bath temperature of 30 to 40°.

(7) G. Gran, *Svensk Papperstidning*, **56**, 179 (1953).

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(9) F. Smith and J. W. Van Cleve, *ibid.*, **77**, 3091 (1955).

(10) For explanation of nomenclature see ref. 5.

(11) J. D. Geerdes, Bertha A. Lewis, R. Montgomery and F. Smith, *Anal. Chem.*, **26**, 264 (1954).

(12) A product of the Rohm and Haas, Co., Philadelphia, Pa.

(13) I. J. Goldstein, J. K. Hamilton and F. Smith, THIS JOURNAL, **79**, 1190 (1957).