(50 ml.) with Dowex 50[21] cation-exchange resin (1 g.) on a boiling water-bath for 4 hours. Removal of the resin and concentration of the solution gave crystalline 3-*O*-methyl-D-xylose which had m.p. 102–103° and $[\alpha]^{22}D$ +15.5° in water (*c* 2.0), after recrystallization from ethyl acetate (yield 0.9 g.).[8b]

D. 2-*O*-Methyl-D-threose.—When 3-*O*-methyl-D-xylose (0.213 g.) was oxidized with 0.1 *N* periodic acid (50 ml.) at 5°, the periodate consumption reached 1.05 moles periodate per mole of sugar in 6 hours and remained constant at this value for 3 hours. The reaction mixture was neutralized ($Ba(OH)_2$) and worked up in the usual way yielding chromatographically pure 2-*O*-methyl-D-threose (yield 65%), R_f, 0.58 (methyl ethyl ketone–water azeotrope), $[\alpha]^{23}D$ −28° in water (*c* 2.0).

Characterization of 2-*O*-Methyl-D-threose. (a) Conversion to D-Threosazone (D-**Erythrosazone**).—A solution of 2-*O*-methyl-D-threose (0.014 g.) in water (1.5 ml.) and acetic acid (0.2 ml.) was treated with phenylhydrazine (0.15 g.) at 80° for 1.5 hours. On cooling the yellow crystalline threose (erythrose) phenylosazone separated, m.p. and mixed m.p. 165–170°[22] after recrystallization from benzene.

(b) Formation of 2-*O*-Methyl-D-threonamide.—A solution of 2-*O*-methyl-D-threose (0.050 g.) in water (1 ml.) was oxidized with bromine (0.1 ml.) at room temperature for 48 hours at which time a chromatogram (methyl ethyl ketone–water) revealed that no 2-*O*-methyl-D-threose remained unoxidized. The 2-*O*-methyl-D-threono-γ-lactone isolated in the manner described above for 3,5-di-*O*-methyl-D-gluconoγ-lactone was distilled, b.p. 85–90° (bath temp.), 0.005 mm., $[\alpha]^{23}D$ −79.2° in methanol (*c* 0.5). Treatment of the lactone with methanolic ammonia for 2 days at 5° followed by removal of solvent furnished 2-*O*-methyl-D-threonamide, m.p. 105–106°, $[\alpha]^{22}D$ −94° in methanol (*c* 1) (after recrystallization from ethanol–petroleum ether). Values of m.p. 105–107°, $[\alpha]^{21}D$ +97.8° in methanol have been reported for 2-*O*-methyl-L-threonamide and for 2-*O*-methyl-L-threono-γ-lactone a rotation of $[\alpha]D$ +78.8° in methanol is recorded.[23] *Anal.* Calcd. for $C_5H_{11}O_4N$: N, 9.4. Found: N, 9.5.

E. 2,5-Di-*O*-methyl-D-arabinose.—Crystalline 3,6-di-*O*-methyl-D-glucose, m.p. 122°, $[\alpha]^{20}D$ +62.7° in water (*c* 1), (0.5 g.), prepared according to the method of Bell[24] was oxidized with 0.1 *N* periodic acid (100 ml.) at 20°. In 3 hours the consumption of periodate reached 1 mole per mole of di-*O*-methylglucose and it remained constant for 2 hours. The sirupy 2,5-di-*O*-methyl-D-arabinose (yield 87%), isolated as described above, showed $[\alpha]^{21}D$ +21°[25] in water (*c* 2.0). *Anal.* Calcd. for $C_7H_{14}O_5$: $-OCH_3$, 34.8. Found: $-OCH_3$, 34.6.

2,5-Di-*O*-methyl-D-arabono-γ-lactone.—Oxidation of 2,5-di-*O*-methyl-D-arabinose (0.03 g.) with bromine (0.1 ml.) in water (1 ml.) for 60 hours in the usual way gave 2,5-di-*O*-methyl-D-arabono-γ-lactone, b.p. (bath temp.) 105° (0.001 mm.), m.p. 58–59° and $[\alpha]^{20}D$ +59.6° in water (*c* 1.0) after recrystallization from ether–petroleum ether. These constants agree with those (m.p. 60°, $[\alpha]D$ −60° in water) reported for the L-isomer.[26]

F. 2-*O*-Methyl-D-arabinose.[12]—Crystalline 3-*O*-methyl-D-glucose (0.500 g.) obtained by hydrolysis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-D-glucofuranose[14] was oxidized with 0.1 *N* periodic acid (100 ml.) at 5°. In 5 hours the periodate consumption reached 1.05 moles periodate per mole of sugar and it remained constant for 2 hours. Isolation in the usual manner yielded 2-*O*-methyl-D-arabinose (yield 85%) $[\alpha]^{23}D$ −87° in water (*c* 2.5), which was shown by chromatography to contain a trace of 3-*O*-methyl-D-glucose.

3,4-*O*-Isopropylidene-2-*O*-methyl-D-arabinose.—To a solution of 2-*O*-methyl-D-arabinose (0.90 g.) in acetone (60 ml.) was added sulfuric acid (0.25 ml.). After 12 hours, the solution was neutralized with gaseous ammonia, filtered and concentrated *in vacuo* to a sirup which upon distillation in high vacuum gave crystalline 3,4-*O*-isopropylidene-2-*O*-methyl-D-arabinose (0.76 g.), m.p. 121° and $[\alpha]^{23}D$ −121° in methanol (*c* 3.0) after recrystallization from acetone–ether–petroleum ether. The values reported for 3,4-*O*-isopropylidene-2-*O*-methyl-L-arabinose[27] are m.p. 116–118° and $[\alpha]^{18}D$ +124.5° in methanol. *Anal.* Calcd. for $C_9H_{16}O_5$: C, 52.9; H, 7.9. Found: C, 53.0; H, 8.1.

Treatment of the 3,4-*O*-isopropylidene-2-*O*-methyl-D-arabinose with ethanolic aniline in the usual way yielded the corresponding anilide m.p. 135° (after recrystallization from ethanol).

(21) A product of Dow Chemical Co., Midland, Michigan.

(22) R. C. Hockett, This Journal, **57**, 2260 (1935).

(23) R. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **20**, 1298 (1937).

(24) D. J. Bell, *J. Chem. Soc.*, 1553 (1936).

(25) A rotation of $[\alpha]D$ +60° (water) has erroneously been quoted for 2,5-di-*O*-methyl-L-arabinose (R. A. Laidlaw and E. G. V. Percival, *Advances in Carbohydrate Chem.*, **7**, 31 (1952)).

(26) F. Smith, *J. Chem. Soc.*, 1035 (1940).

(27) Mary Ann Oldham and J. Honeyman, *ibid.*, 986 (1946).

St. Paul, Minnesota

[Contribution from the Department of Biochemistry, University of California, Berkeley]

The Degradation of Ketoses by the Disulfone Method[1]

By D. L. MacDonald and Hermann O. L. Fischer

Received March 7, 1955

The method of degrading aldoses utilizing the disulfones derived from the mercaptals has been applied to two ketoses, namely, D-fructose and *myo*inosose-2. The degradation proceeds in the anticipated manner, with the splitting of the carbon chain on both sides of the carbon atom bearing the two sulfone groups.

Up to the present, there have been described several methods for the opening of the cyclohexane ring of the inositols. The methods used lead to the production of either dialdehydes or dicarboxylic acids and they have been used frequently for the determination of the configuration of various inositols. For instance, in the determination of the configuration of *myo*inositol, Dangschat[2] cleaved a tetraacetyl *myo*inositol with lead tetraacetate to produce a dialdehyde which was oxidized subsequently to a dicarboxylic acid. More recently, Ballou and Fischer[3] have prepared derivatives of D-*manno*-hexodialdose by oxidation of diisopropylidene-D-inositol with lead tetraacetate. Another method of opening the ring was utilized by Posternak in his studies on cyclitols; for instance,[4] by oxidation of *myo*-inosose-2 with alkaline permanganate, he obtained hexaric acids, a knowledge of the structure of which enabled him to deduce the configuration of *myo*inositol.

Recently, we have described a method of degrading aldose sugars and in the present communication it is shown that it can be utilized as another means

(1) This work was supported by a grant from the Eli Lilly Company, and a preliminary report of the work appeared in Abstracts Papers, *Am. Chem. Soc.*, **126**, 9D (1954).

(2) G. Dangschat, *Naturwissenschaften*, **30**, 146 (1942).

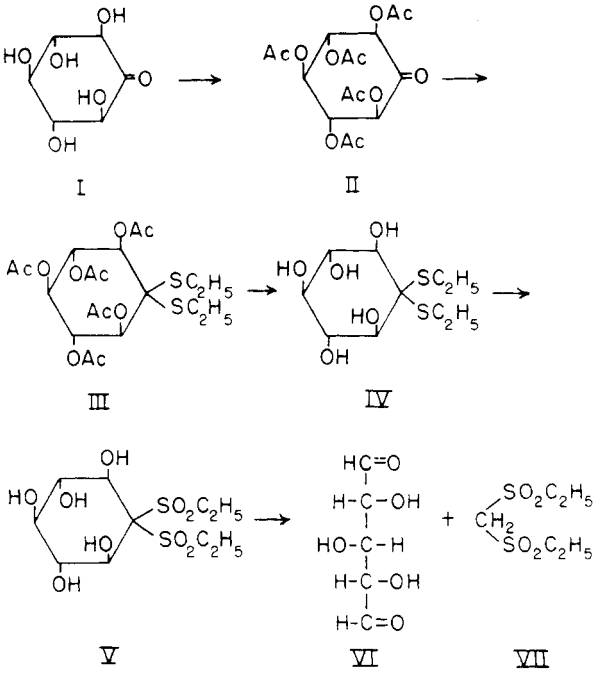
(3) C. E. Ballou and H. O. L. Fischer, This Journal, **75**, 3673 (1953).

(4) T. Posternak, *Helv. Chim. Acta*, **25**, 746 (1942).

of opening the cyclohexane ring of *myo*inositol after conversion to the ketose *myo*inosose-2. The analogous splitting of another ketose, D-fructose, is also reported. In the method, as first described,[5] the acetylated mercaptal of the sugar was oxidized to produce an acetylated olefinic disulfone which on treatment with hydrazine, was degraded smoothly to bis-(ethanesulfonyl)-methane and the next lower aldose. Subsequently, this method of degradation was extended[6] to the unacetylated mercaptals of the sugars and excellent yields of D-arabinose could be obtained from D-mannose diethyl mercaptal. This method of degradation is complicated by the fact that more than one product arises from the oxidation; in the case of D-mannose, however, this does not materially affect the yield of pentose arising from the degradation.

The sulfones arising from the oxidation of unacetylated mercaptals have been investigated recently[7] and as was shown with the acetylated mercaptals,[5] olefins frequently are formed; anhydro sugar disulfones are also among the products formed with the unacetylated mercaptals. The formation of these other products can occur, however, only in the case of the mercaptal of an aldose sugar. In a ketose which has been converted to the mercaptal and to the corresponding disulfone, there exists no possibility for double bond formation between the carbon atom bearing the two sulfone groups and an adjacent carbon atom. As reported in the present paper, no difficulty was experienced in obtaining excellent yields of sulfones derived from the two ketoses investigated, *myo*inosose-2 and D-fructose. While this manuscript was being prepared, Bourne and Stephens[8] reported on the degradation of D-fructose *via* its disulfone. A brief description of the degradation of this sugar is included, however, since the method used is somewhat different from theirs.

*Myo*inosose-2 (I) which is readily prepared from *myo*inositol by bacterial oxidation[9] did not give a diethyl mercaptal under the normal conditions, an observation recalling experiences with D-fructose.[10a] However, the mercaptal of D-fructose has been obtained by an indirect method,[11] and by using this procedure, the mercaptal of the inosose could be obtained readily. The *myo*inosose-2 was converted into the known pentaacetate[9] (II) and this was converted into the acetylated mercaptal (III), using zinc chloride as catalyst. Deacetylation produced the desired mercaptal (IV) which was readily oxidized, using perpropionic acid, to the corresponding disulfone (V). Treatment of the disulfone with dilute aqueous ammonium hydroxide resulted in rapid degradation; from the reaction mixture, the bis-(ethanesulfonyl)-methane (VII) could be isolated by extraction with chloroform, and the *xylo*-pentodialdose (VI), the other fragment from the reaction, was isolated as its bis-(ethylene mercaptal). The yield of mercaptal was low, probably because of the lability of the dialdehyde in alkaline solution.



The dialdehyde formed from *myo*inosose-2 should have the *xylo* configuration and this was confirmed by the preparation of the same bis-(ethylene mercaptal) from 1,2-isopropylidene-D-*xylo*-pentodialdose, a material readily obtainable from 1,2-isopropylidene-D-glucofuranose by lead tetraacetate or periodate oxidation.[12]

In connection with this study, it was found that *myo*inosose-2, unlike D-fructose,[10b] reacted readily with 1,2-ethanedithiol in the presence of concentrated hydrochloric acid to produce, in good yield, the ethylene mercaptal.

In the case of D-fructose, the sugar was converted into the known diethyl mercaptal pentaacetate,[11] and this was oxidized to the corresponding disulfone. This disulfone was then treated with hydrazine in methanol, which should effect a splitting of the molecule in two places, to produce formaldehyde, bis-(ethanesulfonyl)-methane and a derivative of D-erythrose. The bis-(ethanesulfonyl)-methane was extracted with chloroform, while the tetrose derivative was converted to erythritol, which was isolated as its crystalline tetraacetate. The yield of each product was low, but the isolation of these two compounds proves that the reaction proceeded in the anticipated manner. Bourne and Stephens[8] used prolonged treatment with methanolic ammonia for the degradation of the same compound and obtained D-erythrose bisacetamide in good yield. Under the conditions used by them, however, the bis-(ethanesulfonyl)-methane condensed with the formaldehyde to produce the known 1,1,3,3-tetraethanesulfonylpropane.

(5) D. L. MacDonald and H. O. L. Fischer, THIS JOURNAL, **74**, 2087 (1952). See also E. Rothstein, *J. Chem. Soc.*, 684 (1934); 1560 (1940), for an analogous reaction.

(6) D. L. MacDonald and H. O. L. Fischer, *Biochem. Biophys. Acta*, **12**, 203 (1953).

(7) L. Hough and T. J. Taylor, *Chemistry and Industry*, 575, 1018 (1954).

(8) E. J. Bourne and R. Stephens, *J. Chem. Soc.*, 4009 (1954).

(9) T. Posternak, *Biochem. Preps.*, [II] 57 (1952).

(10) (a) E. Fischer, *Ber.*, **27**, 673 (1894); (b) W. T. Lawrence, *ibid.*, **29**, 547 (1896).

(11) M. L. Wolfrom and A. Thompson, THIS JOURNAL, **56**, 880 (1934).

(12) K. Iwadare, *Bull. Chem. Soc., Japan*, **16**, 40 (1941); J. C. Sowden, THIS JOURNAL, **74**, 4377 (1952).

Experimental[13]

*Myo*inosose-2 Diethyl Mercaptal Pentaacetate (III).—Twenty grams of *myo*inosose-2 pentaacetate (m.p. 212–214°) was added to a mixture of 60 ml. of ethanethiol, previously dried over anhydrous calcium sulfate, 10 g. of freshly fused zinc chloride and 10 g. of anhydrous sodium sulfate, and the mixture was allowed to stand in a stoppered flask for five days with occasional swirling. The contents of the flask were poured into 200 ml. of saturated aqueous sodium bicarbonate with stirring, and the resulting mixture was filtered through a layer of Celite, with suction. The solid was extracted seven times with 100-ml. portions of hot chloroform, the last two extracts being subsequently used for extraction of the aqueous layer. The combined chloroform extracts were dried with sodium sulfate and concentrated *in vacuo* to give 25 g. of material, m.p. 155–175°. Recrystallization from absolute alcohol gave 20.4 g. (80%) of material, m.p. 179–181°. For analysis, a sample was recrystallized again from absolute ethanol and after drying *in vacuo* over sodium hydroxide, it melted at 180.5–182°.

Anal. Calcd. for $C_{20}H_{30}O_{10}S_2$ (494.6): C, 48.57; H, 6.11; S, 12.96. Found: C, 48.55; H, 6.12; S, 12.74.

*Myo*inosose-2 Diethyl Mercaptal (IV).—*Myo*inosose-2 diethyl mercaptal pentaacetate (20.35 g.) was added to methanol (500 ml.) and the mixture cooled in ice and saturated with ammonia gas. The mixture was then stirred magnetically at room temperature for one hour, to dissolve the acetate, and left at room temperature overnight. A small amount of insoluble material was removed by filtration, and the solvent removed at reduced pressure. Two recrystallizations from methanol gave 7.60 g. (65%) of material, m.p. 185.5–186.5°. A further 2.92 g. of material of the same melting point was obtained from the mother liquors, making the total yield 90%.

Anal. Calcd. for $C_{10}H_{20}O_5S_2$ (284.4): C, 42.23; H, 7.09; S, 22.55. Found: C, 41.99; H, 7.03; S, 22.42.

Oxidation of *Myo*inosose-2 Diethyl Mercaptal to the Disulfone (V).—*Myo*inosose-2 diethyl mercaptal (1.0 g.) was dissolved by heating in methanol (20 ml.). While cooling the solution in water, a 10% excess of perpropionic acid[14] was added rapidly but dropwise, and the solution left at room temperature overnight. The precipitated crystalline product was filtered and washed carefully with ice-cold methanol and dried *in vacuo* over sodium hydroxide. The material, which weighed 1.16 g. (94%), decomposed at 196–198° when placed in the bath at 190° with the temperature rising at 10° per minute. Paper chromatography on Whatman #1 paper in butanol–acetic acid–water (4:1:5) revealed but one component with R_f 0.47, while the starting mercaptal had R_f 0.66.

Anal. Calcd. for $C_{10}H_{20}O_9S_2$ (348.4): C, 34.46; H, 5.79; S, 18.41. Found: C, 34.68; H, 5.87; S, 18.49.

Degradation of 2-Deoxy-2,2-bis-(ethanesulfonyl)-*myo*-inositol.—The disulfone (0.50 g.) was dissolved in 10 ml. of water and one drop of concentrated ammonium hydroxide was added. After 20 hours at room temperature, the solution was extracted five times with five-ml. portions of chloroform to remove the bis-(ethanesulfonyl)-methane. The aqueous layer was concentrated to a sirup *in vacuo* and 0.45 ml. of 1,2-ethanedithiol and 0.8 ml. of concentrated hydrochloric acid were added. After one hour at room temperature with occasional swirling, ice-water (10 ml.) was added and the precipitate filtered and washed with water and a little ice-cold alcohol. The product (81 mg., 19%) was recrystallized from water with hot filtration to give 34 mg. of *xylo*-pentodialdose bis-(ethylene mercaptal), m.p. 148.5–150°, undepressed on admixture with authentic material.

The chloroform layer was dried (sodium sulfate) and the solvent removed *in vacuo*. The crude material (0.23 g.) was crystallized from water to give 0.15 g. (51%) of bis-(ethanesulfonyl)-methane, m.p. and mixed m.p. 100.5–102°.

Xylo-pentodialdose Bis-(ethylene Mercaptal).—To 2.30 g. of 1,2-monoacetone-D-*xylo*-pentodialdose[12] there was added 4.5 ml. of 1,2-ethanedithiol and 9 ml. of concentrated hydrochloric acid. The mixture was cooled in ice for one minute, then set aside at room temperature, with occasional swirling for one-half hour. The solidified mass was triturated with 100 ml. of ice-water, filtered and washed with water. After drying *in vacuo* over P_2O_5, it weighed 3.21 g. Recrystallization from water (175 ml.) with filtration from considerable insoluble material gave 2.15 g. (62%) of material, m.p. 148–149° (sinters 147°).

Anal. Calcd. for $C_9H_{16}O_5S_4$ (300.5): C, 35.97; H, 5.37; S, 42.68. Found: C, 35.91; H, 5.24; S, 42.80.

Myo-inosose-2 Ethylene Mercaptal.—One gram of *myo*-inosose-2, 1.5 ml. of concentrated hydrochloric acid and 2 ml. of 1,2-ethanedithiol were stirred magnetically for 24 hours at room temperature. The semi-solid mixture was poured into 60 ml. of ethanol, filtered and washed with 95% ethanol and air dried to give 1.24 g. of almost odorless material, m.p. 258–263° (dec.) (hot stage). The material was recrystallized from water by addition of an equal volume of ethanol to give 1.11 g. (78%), m.p. 263–265° (decomposition, on the hot stage).

Anal. Calcd. for $C_8H_{14}O_5S_2$ (254.3): C, 37.78; H, 5.55; S, 25.21. Found: C, 38.10; H, 5.69; S, 24.95.

D-*Arabo*-1,3,4,5,6-pentaacetoxy-2,2-bis-(ethanesulfonyl)-hexane.—To 7.0 g. of pentaacetyl-D-fructose diethyl mercaptal in 70 ml. of dry ether, there was added monoperphthalic acid[15] in ether (20% excess). After standing overnight, the mixture was concentrated *in vacuo* and extracted 5 times with 25-ml. portions of chloroform. The chloroform was washed twice with saturated sodium bicarbonate and with water and the filtered solution concentrated *in vacuo* to give 7.78 g. of crystalline material. Recrystallization from isopropyl alcohol and then from *n*-butyl ether gave 7.00 g. (89%) of material, m.p. 140.5–141.5°, $[\alpha]^{23}D$ +9.6° (*c* 3, chloroform). Bourne and Stephens[8] record m.p. 144–145° and $[\alpha]D$ +7.2° (chloroform).

Anal. Calcd. for $C_{10}H_{17}O_9S_2(CH_3CO)_5$ (560.58): C, 42.85; H, 5.75; S, 11.44; CH_3CO, 38.39. Found: C, 42.98; H, 5.62; S, 11.25; CH_3CO, 38.79.

Degradation of D-*Arabo*-1,3,4,5,6-pentaacetoxy-2,2-bis-(ethanesulfonyl)-hexane.—The sulfone (500 mg.) was mixed with methanol (10 ml.) and 0.5 ml. of hydrazine hydrate (85%) was added. The material soon dissolved and after 1.5 hours at room temperature, the solution was concentrated *in vacuo*. Water (10 ml.) was added and the mixture was extracted several times with an equal volume of chloroform. To the aqueous solution there was added ethanol (20 ml.), benzaldehyde (3 ml.) and a little benzoic acid and the solution refluxed for one hour, then cooled and extracted several times with chloroform. The aqueous solution was treated with sodium borohydride (100 mg.) and after one hour at room temperature, acetic acid was added to destroy the excess reducing agent and the solution was concentrated at reduced pressure. The product was dried by distilling absolute alcohol from it several times at reduced pressure; then it was refluxed for one hour with 50 ml. of methanol containing 6% hydrogen chloride to remove the boric acid as methyl borate.[16] The solution was then concentrated to dryness at reduced pressure and the residue acetylated on the steam-bath for one-half hour with 2 ml. of acetic anhydride containing one drop of concentrated sulfuric acid. The cooled mixture was poured into ice, extracted with chloroform and the chloroform washed with 1 *N* potassium carbonate and water. The solution was then dried (sodium sulfate) and the solvent removed *in vacuo*. The residue was decolorized with charcoal in hot methanol and after removal of the solvent it was crystallized from methanol to give 55 mg. (21%) of erythritol tetraacetate, m.p. 81–84°. Recrystallization from the same solvent gave 43 mg. m.p. 85–86°, undepressed on admixture with authentic material of m.p. 85–86°.

The first chloroform extract after being dried with Na_2SO_4 was concentrated at reduced pressure. The residue was extracted with one ml. of hot water and from this there crystallized 48 mg. (27%) of material, m.p. 97–100°. Recrystallization from ethanol gave material of m.p. 99–101°, undepressed on admixture with authentic bis-(ethanesulfonyl)-methane.

Berkeley, Cal.

(13) Analyses by the Microchemical Laboratory, University of California, and by Dr. A. Elek, Los Angeles.

(14) J. d'Ans and W. Frey, *Ber.*, **45**, 1845 (1912).

(15) H. Böhme, *Org. Syntheses*, **20**, 70 (1940).

(16) M. Abdel-Akher, J. K. Hamilton and F. Smith, This Journal, **73**, 4691 (1951).