residue remaining after removal of the chloroform was dissolved in about 5 ml. of ethanol and carefully acidified with 5 *N* aqueous nitric acid. 3-Iso-reserpine (XVIII) soon separated as the crystalline nitrate. This was filtered, washed with ethanol and converted to the base by shaking with chloroform in the presence of excess 1 *N* aqueous sodium hydroxide. The chloroform solution was washed with water, dried over sodium sulfate and the solvent evaporated. The light yellow sirupy residue crystallized on scratching in the presence of a few ml. of ethanol. The solid was filtered and recrystallized from ethanol–water to yield 1 g. of XVIII, m.p. 150–155° with frothing, $[\alpha]^{24}D$ −164° (chloroform). It is readily distinguishable from reserpine by its low melting point and high solubility in acetone. Similarly, refluxing 1 g. of reserpine in acetic acid for 3 days gave 0.6 g. of XVIII.

Anal. Calcd. for $C_{33}H_{40}N_2O_9 \cdot {}^1/_3H_2O$: C, 64.73; H, 6.69; N, 4.56. Found: C, 64.65; H, 6.35; N, 4.81.

(b) A solution of 0.5 g. of methyl 3-iso-reserpate (XV) and 1.5 g. of 3,4,5-trimethoxybenzoyl chloride in 15 ml. of pyridine was allowed to stand 5 days in the ice-box. Three-quarters of the pyridine was distilled off *in vacuo*, water was added and the mixture was made alkaline with dilute sodium hydroxide and extracted with ethyl acetate. The ethyl acetate was washed with dilute hydrochloric acid, dilute sodium hydroxide and water. The solvent was removed *in vacuo* and the residue dissolved in a small volume of ethanol. It was made acid with 8 *N* ethanolic hydrogen chloride, a large volume of ether was added to precipitate the alkaloid salts which were suspended in chloroform and converted to the base by shaking with dilute ammonia. The residue remaining after removal of the chloroform was taken up in a small volume of ethanol and acidified with 5 *N* nitric acid. The crystalline XVIII nitrate was collected, converted to the base and recrystallized from ethanol–water as described above, yielding 90 mg., m.p. 152–156°. The m.p. of the mixture with a sample prepared by the direct isomerization of reserpine was unchanged.

3-Iso-reserpinediol (XVI) Diacetate from 3-Iso-reserpine (XVIII).—A solution of 200 mg. of XVIII in 20 ml. of tetrahydrofuran was added dropwise to 500 mg. of lithium aluminum hydride in 20 ml. of ether. After refluxing for 1 hour, the excess reagent was destroyed with ethyl acetate and the mixture made acid by the addition of hydrochloric acid. The solvents were distilled almost to dryness and 25 ml. of 0.5 *N* hydrochloric acid added. The solution was extracted with benzene and the residue remaining after removal of the solvent was esterified with 3,5-dinitrobenzoyl chloride in pyridine to yield 3,4,5-trimethoxybenzyl 3,5-dinitrobenzoate, m.p. 144–145°, after recrystallization from acetone–ethanol.

Anal. Calcd. for $C_{17}H_{16}N_2O_9$: N, 7.14. Found: N, 7.55.

The acid extract left after benzene extraction was made basic with a sodium carbonate solution and extracted with chloroform. The crude XVI remaining after removal of the chloroform was acetylated with acetic anhydride–pyridine. The XVI diacetate obtained melted 213–214° and the m.p. of a mixture with a sample prepared by the direct isomerization of reserpinediol showed no depression.

Anal. Calcd. for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.42; H, 7.04; N, 6.06.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF SYDNEY]

Cyclitols. III. Some Tosyl Esters of Inositols. Synthesis of a New Inositol[1,2]

BY S. J. ANGYAL[3] AND N. K. MATHESON[4]

RECEIVED DECEMBER 27, 1954

Two anhydro-inositols (III and IX) have been prepared from partially tosylated inositol derivatives. Acid hydrolysis gave, in one case, a new methyl ether of (−)-inositol, in the other case the new 1,2,3/4,5,6-inositol for which the name *neo*-inositol is proposed.

Tosyl esters have been of manifold use in carbohydrate chemistry.[5] In particular, their reaction with alkalies to give epoxides, and the subsequent opening of the epoxide ring with Walden inversion, has been useful in the interconversion of sugars. Similar reactions have not been applied so far in cyclitol chemistry as the required partially tosylated derivatives were not known. The easy preparation of isopropylidene cyclitols[6] placed in our hand intermediates from which various mono- and ditosyl inositols could be synthesized and their reactions investigated. This paper reports on two cases of epoxide formation; other reactions, *e.g.*, one with sodium iodide, will be described in a subsequent communication.

The readily available diisopropylidenepinitol[6,7] (I) served as the first starting material. Tosylation gave the monotosyl compound from which, by removal of the isopropylidene groups, 3-*O*-methyl-4-*O*-tosyl-(+)-inositol (II) was produced. When this compound, or preferably its tetraacetate, was treated with sodium methoxide at room temperature, it lost the tosyl group and gave the 1-*O*-methyl ether of 2,3-anhydro-*allo*-inositol which was isolated as its triacetate III. This epoxide III was hydrolyzed by hot dilute sulfuric acid giving approximately equal amounts of the two possible products, pinitol (IV) and 1-methyl-(−)-inositol (V), isolated as their pentaacetates. The properties of these two methyl ethers are so similar that separation could only be achieved by handpicking of their well-developed crystals. All these reactions proceeded in good yield.

Demethylation of V confirmed that it was a derivative of (−)-inositol. The whole series of reactions therefore constitutes an inversion of (+)- into (−)-inositol. Since the structure of pinitol has been proved rigidly[8] the structure of V is also established. (+)- and (−)-inositols have a twofold simple axis of symmetry: each therefore can give rise to only three different monomethyl ethers. The fact that V is neither identical nor enantiomorphous with quebrachitol serves as additional proof

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(2) Presented at the American Chemical Society Meeting in Los Angeles, Calif., March, 1953 (Abstracts, 123rd Meeting, 12D).

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(5) R. S. Tipson, *Adv. Carbohydrate Chem.*, **8**, 108 (1953).

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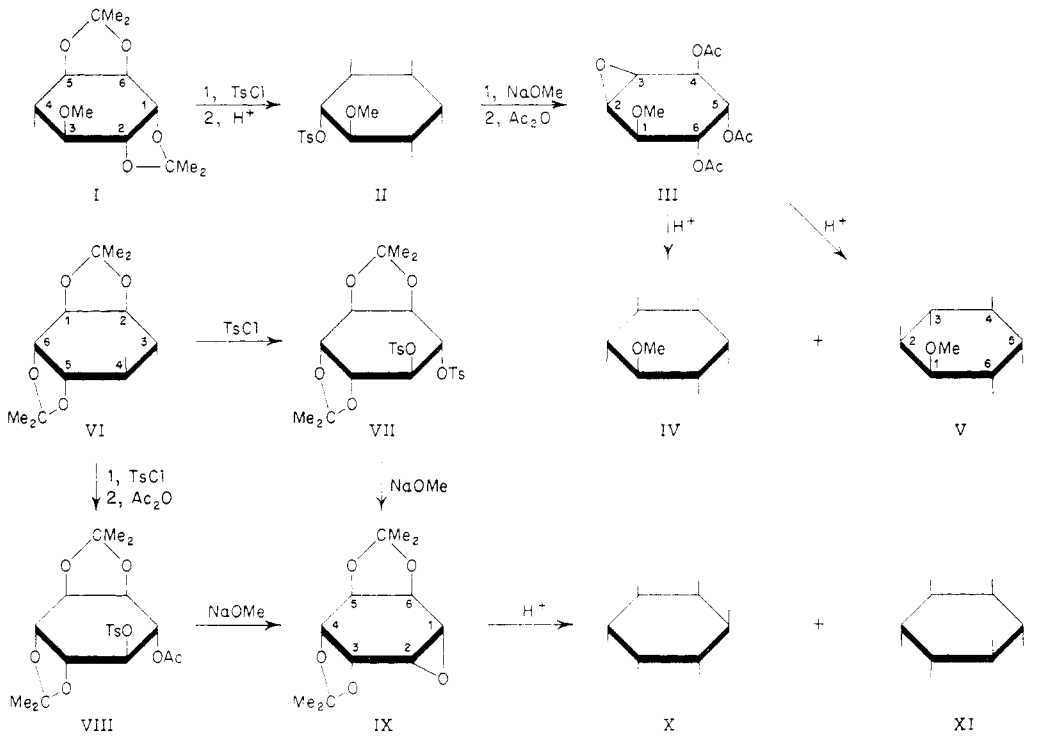

that the latter is the third possible monomethyl compound, *i.e.*, 2-methyl-(−)-inositol.[6,9]

Opening of an epoxide was used for the synthesis of one of the two yet unknown inositol isomers. The starting material, 1,2;5,6-di-*O*-isopropylidene-(−)-inositol (VI),[6,10] readily gave a ditosyl derivative VII, but the required monotosyl compound was obtained only in low yield by reaction with one mole of *p*-toluenesulfonyl chloride in pyridine, being isolated as its acetate VIII. It should be noted that the two hydroxyl groups in VI are equivalent and therefore only one monotosyl monoacetyl compound VIII can be formed. VIII is deacetylated and detosylated smoothly by sodium methoxide at room temperature yielding the epoxide, 3,4;5,6-di-*O*-isopropylidene-1,2-anhydro-*allo*-inositol (IX).

It later was observed by P. T. Gilham[11] that the ditosyl compound VII also gave the epoxide IX on treatment with sodium methoxide, albeit only on boiling; this provides an easier method for the preparation of IX. The formation of epoxides from ditosyl compounds has been described several times,[12] although neither the mechanism of the reaction, nor the direction of the ring formation have been discussed. In the present case, however, only one epoxide can form.

When the epoxide IX was heated with dilute sulfuric acid, stout needles of the new inositol (X) crystallized out: from the mother liquors an approximately equal amount of (−)-inositol (XI) was isolated. The direction of the ring-opening has been discussed elsewhere.[13] The new inositol, for which the name *neo*-inositol is suggested, is distinguished by its high melting point (315°; m.p. of hexaacetate, 253°) and by its very low solubility (*ca.* 0.1 g. in 100 ml. of cold water). No proof of its structure is offered, besides the route of its synthesis; but it is not identical with any of the known six inositol diastereomers[14] and its method of formation precludes it being the only other unknown isomer in which all the hydroxyl groups would be *cis*-oriented to each other.[15]

Lately there has been considerable discussion on the stereospecificity of the dehydrogenation of cyclitols by *Acetobacter suboxydans*[16a,b]: rules have been formulated to describe the minimum steric requirements for cyclitol oxidation. It appeared of interest therefore to submit *neo*-inositol to this reaction. Dr. B. Magasanik, of the Harvard Medical School, whom we supplied with a sample, has kindly reported that no oxygen was taken up when *neo*-inositol was shaken with resting cells of *A. suboxydans*.

It is well established that only axial hydroxyl groups are dehydrogenated by the enzymes present in *A. suboxydans;* as a second requirement the presence of an equatorial hydroxyl group in a *m*-posi-

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(13) S. J. Angyal, *Chemistry & Industry*, 1230 (1954).

(14) See, *e.g.*, H. G. Fletcher, *Adv. Carbohydrate Chem.*, **3**, 45 (1948).

(15) Note added July 2, 1955: This last diastereomer has now been prepared (Angyal and McHugh, *Chemistry & Industry*, in press). The stereochemistry of inositols and the existence of other alleged diastereomers will be discussed in a forthcoming publication.

(16) (a) B. Magasanik and E. Chargaff, *J. Biol. Chem.*, **174**, 173 (1948); T. Posternak and D. Reymond, *Helv. Chim. Acta*, **36**, 260 (1953); R. E. Franzl and E. Chargaff, *Nature*, **168**, 955 (1951); L. Anderson, K. Tomita, P. Kussi and S. Kirkwood, *J. Biol. Chem.*, **204**, 769 (1953). (b) B. Magasanik, R. E. Franzl and E. Chargaff, THIS JOURNAL, **74**, 2618 (1952).

tion has been postulated.[16] *neo*-Inositol conforms with both requirements; the negative result indicates that—as suggested by Chargaff, *et al.*[16b]—an equatorial hydroxyl group in the *p*-position also may be required. *neo*-Inositol has two axial hydroxyl groups but these are *p*-located to each other.

Experimental[17]

1,2;5,6-Di-*O*-isopropylidene-4-*O*-tosylpinitol.—Diisopropylidenepinitol[6] (I) (2.5 g.) was dissolved in anhydrous pyridine (10 ml.), and tosyl chloride (4.9 g.) added. After 48 hours standing the solution was heated on the steam-bath for 30 minutes and then poured into water. The precipitated oil solidified and was crystallized from aqueous methanol to give 3.15 g. (72%) of the product, m.p. 87–89°. For analysis it was recrystallized three times and then had m.p. 90°, $[\alpha]^{24}D$ +53.4° (*c* 4, ethanol).

Anal. Calcd. for $C_{20}H_{28}O_8S$: C, 56.1; H, 6.6; S, 7.5. Found: C, 56.2, 55.8; H, 6.5, 6.5; S, 7.6, 7.8.

3-*O*-Methyl-4-*O*-tosyl-(+)-inositol (II).—The above tosyl compound (3 g.) was heated on the steam-bath for 4 hours with water (10 ml.) and acetic acid (10 ml.). The solution was evaporated to dryness *in vacuo* and the crystalline residue purified by dissolving it in a large volume of ethyl acetate and concentrating to 300 ml. On cooling, the solution deposited 1.6 g. (67%) of the product, m.p. 191° dec. Recrystallization raised the m.p. to 193° dec., $[\alpha]^{25}D$ −1° (*c* 3.7, pyridine).

Anal. Calcd. for $C_{14}H_{20}O_8S$: C, 48.25; H, 5.8; S, 9.2. Found: C, 48.5, 48.8; H, 5.8, 6.0; S, 8.9, 9.1.

1,2,5,6-Tetra-*O*-acetyl-3-*O*-methyl-4-*O*-tosyl-(+)-inositol.—Acetylation of II by acetic anhydride with the addition of pyridine, sodium acetate or sulfuric acid gave the tetraacetate which was, at various occasions, obtained with m.p. 95, 121 or 152°. All the polymorphous forms had the same rotation and gave the same analysis and were converted into the highest melting form by seeding of their saturated solutions with crystals of m.p. 152°. After repeated crystallization from methanol or light petroleum the compound had m.p. 153° and $[\alpha]^{19}D$ −18.2° (*c* 4.3, chloroform),

Anal. Calcd. for $C_{22}H_{28}O_{12}S$: C, 51.15; H, 5.45; S, 6.2. Found: C, 51.0, 51.6; H, 5.5, 5.6; S, 6.2, 6.3.

When diisopropylidenepinitol (9.2 g.) was tosylated, the product hydrolyzed and acetylated without the isolation of intermediate products, 13.6 g. (78%) of the tetraacetate, m.p. 150°, was obtained.

(−)-4,5,6-Tri-*O*-acetyl-1-*O*-methyl-2,3-anhydro-*allo*-inositol (III).—The above tetraacetylmethyltosylinositol (5.0 g.) was dissolved in anhydrous methanol (28 ml.) containing sodium (0.28 g.) and allowed to stand for 12 hours at room temperature. After neutralization with carbon dioxide the solution was evaporated to dryness and the residue heated on the steam-bath for one hour with pyridine (20 ml.) and acetic anhydride (15 ml.). The solution was poured into water (200 ml.) and extracted with chloroform; the organic layer was washed with dilute sulfuric acid, sodium carbonate solution, and water, dried over sodium sulfate and evaporated. The residue was crystallized from light petroleum to give 2.0 g. (67%) of the epoxide, m.p. 74°. After another crystallization it had a constant m.p. of 76° and $[\alpha]^{16}D$ −63.8° (*c* 4.2, chloroform).

Anal. Calcd. for $C_{13}H_{18}O_8$: C, 51.65; H, 6.0. Found: C, 51.5; H, 6.1.

Hydrolysis of III.—The epoxide III (0.5 g.) was heated for two hours on the steam-bath with *N* sulfuric acid (5 ml.). After neutralization with sodium carbonate the solution was evaporated to dryness and the residue heated on the steam-bath for two hours with anhydrous sodium acetate (0.5 g.) and acetic anhydride (4 ml.). The solution was poured into water and extracted with chloroform; the organic layer was washed with sodium carbonate solution, then with water, dried and evaporated to a sirupy residue. This was dissolved in hot light petroleum, filtered and allowed to stand for several weeks. Crystals formed which consisted of a mixture of semi-transparent needles (A) and clusters of clear prisms (B). The crystals were filtered—care being taken not to crush them—and separated by hand picking. Each type of crystal was recrystallized separately from light petroleum; the mother liquors were combined and the slow crystallization repeated. In this way 210 mg. (31%) of A, m.p. 98°, and 254 mg. (38%) of B, m.p. 111°, were collected.

A. Pentaacetylpinitol.—The mixed melting point of crystals A with authentic pinitol acetate (98°) showed no depression. Crystals A had $[\alpha]^{15}D$ +4° and pinitol acetate $[\alpha]^{14}D$ +5° (*c* 2, ethanol). X-Ray powder photographs, kindly taken by Mr. N. C. Stevenson, were identical.

B. Penta-*O*-acetyl-1-*O*-methyl-(−)-inositol.—Crystals B had m.p. 111° and $[\alpha]^{15}D$ −31° (*c* 3.8, ethanol).

Anal. Calcd. for $C_{17}H_{24}O_{11}$: C, 50.5; H, 6.0. Found: C, 50.6; H, 6.0.

1-*O*-Methyl-(−)-inositol (V).—Compound B (150 mg.) was heated under reflux for 2 hours with ethanol (10 ml.) and 15% hydrochloric acid (3 ml.). The solution was evaporated to dryness *in vacuo* and the residue crystallized from ethanol to give 49 mg. of V, m.p. 207°, $[\alpha]^{18}D$ −58° (*c* 1.5, water).

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.3; H, 7.25. Found: C, 43.15; H, 7.2.

Twenty mg. of V was demethylated by refluxing with 47% hydriodic acid (1 ml.) for 2 hours. Crystallization from ethanol gave 13 mg. of (−)-inositol, m.p. 240–243°, $[\alpha]^{18}D$ −71 ± 5° (*c* 0.7, water). Reported for (−)-inositol is the m.p. 246° and $[\alpha]D$ −65° (water).

1,2;5,6-Di-*O*-isopropylidene-3,4-di-*O*-tosyl-(−)-inositol (VII).—1,2;5,6-Diisopropylidene-(−)-inositol[6] (8.0 g.) and tosyl chloride (24 g.) were dissolved in pyridine (80 ml.) and allowed to stand for seven days. The solution then was poured into water from which 15.1 g. (85%) of VII crystallized. On heating it melted at 145–146° but resolidified and melted again at 161–162°. The compound exists in two forms: from hot solution fine needles, m.p. 161–162°, separate, whereas cooler solutions deposit prisms, m.p. 146–147°. Both forms have $[\alpha]^{14}D$ −79.5° (*c* 2.6, chloroform).

Anal. Calcd. for $C_{26}H_{32}O_{10}S_2$: C, 54.95; H, 5.65; S, 11.3. Found: C, 54.9, 55.0; H, 5.4, 5.1; S, 11.6, 11.6.

The isopropylidene groups were removed by heating VII (1.0 g.) with 50% acetic acid (20 ml.) on the steam-bath for 3 hours. On cooling, needles (0.6 g.) of 3,4-di-*O*-tosyl-(−)-inositol separated; they had m.p. 185–186°, $[\alpha]^{27}D$ −28° (*c* 4.3, pyridine). Concentration of the mother liquor gave another 0.14 g. of the ditosyl compound.

Anal. Calcd. for $C_{20}H_{24}O_{10}S_2$: C, 49.2; H, 4.95; S, 13.1. Found: C, 49.4; H, 4.9; S, 12.7.

1,2;5,6-Di-*O*-isopropylidene-3-*O*-acetyl-4-*O*-tosyl-(−)-inositol (VIII).—To a solution of 1,2;5,6-diisopropylidene-(−)-inositol (5.0 g.) in pyridine (20 ml.) a solution of tosyl chloride (4.0 g.) in pyridine (20 ml.) was added dropwise with stirring over a period of 30 minutes. After standing for 4 days, acetic anhydride (3 ml.) was added and the solution concentrated to a small volume *in vacuo*. The residue was poured into water and the resulting sirup, after washing with water, was dissolved in hot methanol (35 ml.) and allowed to crystallize. After two recrystallizations the product weighed 1.8 g. (25%), melted at 144° and had $[\alpha]^{19}D$ −114° (*c* 2.3, chloroform).

Anal. Calcd. for $C_{21}H_{28}O_9S$: C, 55.25; H, 6.2; S, 7.0. Found: C, 55.1; H, 6.15; S, 6.8, 6.9.

(+)-3,4;5,6-Di-*O*-isopropylidene-1,2-anhydro-*allo*-inositol (IX) A.—From the ditosyl compound (VII) (P. T. Gilham): VII (2.0 g.) was boiled under reflux for 5 hours with a solution of sodium (0.5 g.) in anhydrous methanol (20 ml.). The compound dissolved in about 30 minutes and the solution turned very dark. After being cooled, chloroform (40 ml.) was added to the solution and the resulting dark precipitate (1.21 g.) was filtered off. The filtrate was washed twice with 40 ml. of water, dried over sodium sulfate and evaporated to give 0.71 g. (85%) of colorless, crystalline IX. Recrystallization from light petroleum (20 ml.) gave 0.60 g. (72%) of the anhydroinositol, m.p. 108–109°, $[\alpha]^{15}D$ +13.5° (*c* 1.6, methanol).

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.5; H, 7.5. Found: C, 60.2, 59.75; H, 7.5, 7.65.

B. From the Monotosyl Compound VIII.—To a solution of VIII (2.9 g.) in anhydrous methanol (20 ml.) a solution

(17) All melting points are corrected. Microanalyses by the late Mrs. E. Bielski, University of Sydney.

of sodium (0.3 g.) in methanol (20 ml.) was added and the mixture allowed to stand overnight. After neutralization with carbon dioxide, the solution was evaporated to dryness and repeatedly extracted with light petroleum. The solvent was evaporated and the residue sublimed *in vacuo* yielding 1.1 g. (70%) of IX, m.p. 109°.

neo-**Inositol (X).**—The anhydroinositol IX (415 mg.) was heated on the steam-bath with 0.1 *N* sulfuric acid[18] (5 ml.) for three hours. The substance dissolved in a few minutes (with loss of acetone) and after about 30 minutes crystals began to separate. They were filtered and washed with water giving 160 mg. (52%) of *neo*-inositol. For analysis it was recrystallized from water. It decomposes and sublimes on slow heating but when dropped on a heated block it melts at 315°. It has no optical activity.

Anal. Calcd. for $C_6H_{12}O_6$: C, 40.0; H, 6.7. Found: C, 40.3; H, 7.2.

The hexaacetate, prepared by acetylation with sodium acetate and acetic anhydride, was crystallized from ethanol and melted at 253°.

(18) Heating with hydrochloric acid gives chlorodeoxyinositols as by-products; their presence can be shown by paper chromatography in acetone–water (8:2 v./v.).

Anal. Calcd. for $C_{18}H_{24}O_{12}$: C, 50.0; H, 5.6. Found: C, 50.3; H, 5.65.

The acid mother liquor of *neo*-inositol was mixed with an equal amount of ethanol resulting in a precipitate (6 mg.) which was shown by paper chromatography to consist of a mixture of *neo*- and (−)-inositols. The clear liquor was decanted and neutralized with barium carbonate and filtered; the filtrate was evaporated to dryness and the residue crystallized from aqueous ethanol to give 103 mg. (34%) of (−)-inositol which, after another crystallization, had m.p. 242–243°, $[\alpha]^{25}D$ −64.5 ± 2° (*c* 1.0, water); reported for (−)-inositol is the m.p. 246° and $[\alpha]D$ −65° (water).

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SYDNEY, AUSTRALIA

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

Periodate Oxidation in the Synthesis of Some Partially Methylated Sugars[1]

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RECEIVED FEBRUARY 19, 1955

Cleavage of the carbon chain between positions C_1 and C_2 by periodate oxidation, under acid conditions to preserve the intermediate formyl group produced from C_1, has provided a means of synthesizing 2-*O*-methyl-D-arabinose, 2-*O*-methyl-D-threose and 2,5-di-*O*-methyl-D-arabinose from 3-*O*-methyl-D-glucose, 3-*O*-methyl-D-xylose and 3,6-di-*O*-methyl-D-glucose, respectively. Scission of C_1 from the hitherto unknown 3,5-di-*O*-methyl-D-glucose by periodate oxidation has yielded 2,4-di-*O*-methyl-D-arabinose. A similar oxidation of 1,2-*O*-isopropylidene-3-*O*-methyl-D-glucose followed by reduction and hydrolysis provides an additional route to 3-*O*-methyl-D-xylose.

Methylation studies applied to polysaccharides require partially methylated sugar derivatives as reference compounds. Many of these partially methylated sugars are incompletely characterized, some are known only in an impure state while others have never been synthesized. It is shown herein that oxidation of well-characterized partially methylated sugars or their derivatives with periodic acid provides a simple and convenient route for the synthesis of certain methylated sugars.

Cleavage of 1,2-glycols by periodic acid,[2] a reaction which proceeds rapidly to completion unless the glycol is of the fixed *trans* type,[3,4] has been utilized previously both for structural studies of simple and complex carbohydrates[5–7] and for synthetic purposes.[8]

Certain partially methylated sugars, when subjected to oxidation with periodic acid, do not consume the expected quantity of periodate.[9–11] This incomplete oxidation has been attributed to an intermediate stable formyl ester formed by preferential cleavage of the carbon chain between C_1 and C_2 without rupture of the acetal linkage. Support for this theory was forthcoming from the observation that oxidation of 3-*O*-methyl-D-glucose with periodic acid gave the well-defined 4-*O*-formyl 2-*O*-methyl-D-arabinose.[12]

By utilizing the stability of the intermediate formyl ester produced by periodate cleavage of the glycol grouping at C_1 and C_2, the following methylated sugars have been prepared: 2-*O*-methyl-D-arabinose, 2-*O*-methyl-D-threose and 2,5-di-*O*-methyl-D-arabinose from 3-*O*-methyl-D-glucose, 3-*O*-methyl-D-xylose and 3,6-di-*O*-methyl-D-glucose, respectively.

Whereas the formyl esters of some sugars were stable at room temperature, that formed from 3-*O*-methyl-D-glucose underwent hydrolysis and further cleavage of the carbon chain occurred unless the periodate oxidation was carried out in the cold. The intermediate formyl esters are sensitive to alkaline reagents for treatment of them momentarily

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