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THE SYNTHESIS OF HEXOSE DERIVATIVES FROM CYCLITOLS

PART I. THE SYNTHESIS OF (±)-ALLOSE DERIVATIVES FROM *myo*-INOSITOL

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In the course of studies on oxidation of inositols into inososes, we found that (±)-1:2,3:4-di-*O*-isopropylidene-6-*O*-methyl-*epi*-inositol (I) underwent an oxygen insertion reaction[1] on the treatment with active manganese dioxide[2] to give a hemi-acetal lactone (IIa), which may be considered as a key substance for the synthesis of hexoses from cyclitols. In the present paper we wish to report the synthesis of (±)-allose and (±)-ribose derivative from *myo*-inositol *via* the hemi-acetal lactone with a purpose for exploring a general synthetic route to monosaccharides from cyclitols having a desirable configuration.

(±)-1:2,3:4-Di-*O*-isopropylidene-5,6-di-*O*-toluene-*p*-sulphonyl-*epi*-inositol[3] was easily derived from commercially available *myo*-inositol. The treatment of the ditosylate (20g.) with excess of sodium methoxide (metallic sodium 3.6g. in methanol 200ml.) in tetrahydrofuran (200ml.) under reflux for 40 hrs. gave the *O*-methyl derivative I, m.p. 105°, (6.3g.) accompanied with a small amount of the 5:6-anhydro-*allo*-inositol derivative III, m.p. 97°, (0.4g.).

In an attempt to obtain the *epi*-inosose derivative IV, the *O*-methyl derivative I (600mg.) was subjected to the oxidation with active manganese dioxide (15g. of the oxide was added portionswise) in acetonitrile (60ml.) for three weeks. As mentioned above, however, the oxidation reaction proceeded unexpectedly to give the hemi-acetal lactone IIa*, m.p. 153-154°, (170mg.). Its IR spectrum** showed, besides other absorption bands, a

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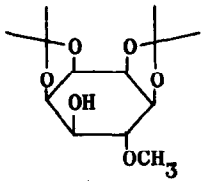
* All new compounds reported here have given satisfactory elemental microanalysis.

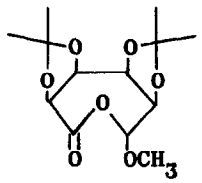
** Unless otherwise mentioned, IR spectra were measured in nujol mull, nmr spectra in deuteriochloroform solution with a Varian A-60. Grateful acknowledgement is hereby made to Prof. T. Mitsui, Kyoto University, for microanalyses and to Dr. T. Shingu, Kyoto University, for nmr measurements.

strong band at 1778 cm^{-1} and its nmr spectrum showed four three-proton singlets for isopropylidene groups at τ 8.61, 8.57, 8.48, 8.40, a sharp singlet for an *O*-methyl at 6.44 and five ring protons (one-proton, quartet, 5.80; one-proton, quartet, 5.30; three-protons, multiplet, centered at 5.08). Although these physical data support not only the structure IIa but also the structure IIb, the latter structure is excluded by the following experimental result; the reduction of the hemi-acetal lactone with lithium aluminum hydride gave 2:3,4:5-di-*O*-isopropylidene-allitol (V), m.p. 102-105°, which was identical with a compound derived from (±)-1:2,3:4-di-*O*-isopropylidene-*epi*-inositol by oxidative cleavage with periodate followed by reduction with lithium aluminum hydride.

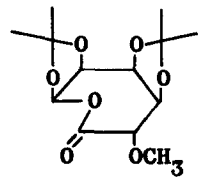
The following method was adopted as a more convenient procedure for the preparation of IIa. The *O*-methyl derivative I (2g.) was oxidized with dicyclohexyl carbodiimide (5g.) and pyridinium trifluoroacetate (500mg.) in dimethyl sulfoxide (20ml.), the Pfitzner-Moffatt reagent[4], for 48 hrs. to give *epi*-inosose derivative IV, m.p. 118-119°, (1.7g.) which was, in turn, subjected to the Baeyer-Villiger reaction with perbenzoic acid in moist chloroform to afford IIa in 80% yield.



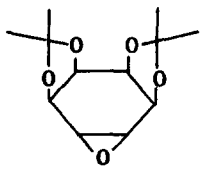
I



IIa



IIb



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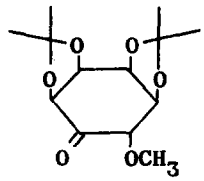
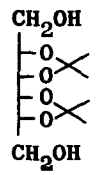


IV



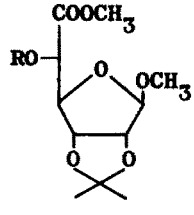
V

The hemi-acetal lactone IIa (200mg.) was heated in methanol (20ml.) in the presence of a catalytic amount of sulfuric acid for 2 hrs. and the oily product was immediately acetylated with acetic anhydride (5ml.) in pyridine (5ml.). The acetylated product was proved to be a mixture of at least two components by tlc on slilica gel plate. By column chromatography on silicic acid (20g.) with ethyl acetate:benzene (3:5), the mixture could

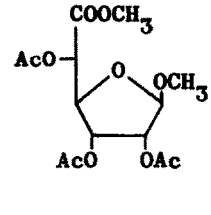
be separated into the mono-acetate VIa, m.p. 80-81°, (90mg.) and the tri-acetate VII, m.p. 102-103°, (40mg.). These structures were established by the following facts : The reduction of the mono-acetate with lithium aluminum hydride gave methyl 2:3-*O*-isopropylidene-β-(±)-allofuranoside (VIIIa), m.p. 66-67°, which was acetylated to the di-acetate VIIIb, m.p. 88-89°. The di-acetate VIIIb was hydrolyzed with 50% acetic acid and subsequently acetylated to give the tetra-acetate IX, m.p. 87-88°, which was identical with the compound derived from the tri-acetate VII by reduction with lithium aluminum hydride followed by acetylation.

The nmr spectrum of the mono-acetate VIa indicates the presence of an isopropylidene group (τ 8.60, 8.50), an *O*-acetyl (7.83), an *O*-methyl (6.64), a methyl ester (6.19), C-1 proton (4.99, singlet), C-5 proton (4.87, doublet $J_{4,5}$=6.0 c.p.s), and not well defined three ring protons (between 5.08 and 5.47). The nmr spectrum of the tri-acetate VII is shown in Fig.1. The signals of the ring protons of VIa and VII, however, do not give us any more reliable informations on these structures.

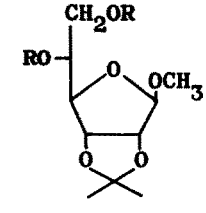
Ultimately the structures VIa and VII, especially concerning the furanose structure and the β-configuration of the methoxyl group at C-1, are elucidated on the basis of the following experimental results: Hydrolysis of VIIIa with 1N-sulfuric acid gave (±)-allose, m.p. 183-185°, (lit.[5] m.p. 180°), which showed identical nmr spectrum in deuterium



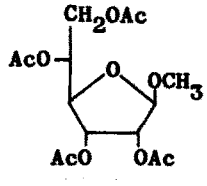
VIa:R=Ac
VIb:R=H



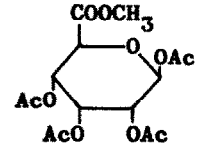
VII



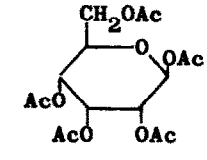
VIIIa:R=H
VIIIb:R=Ac



IX



X



XI

oxide with that of D-allose. The compound VIIIa was subjected to the oxidative cleavage with periodate and subsequent reduction with lithium aluminum hydride. The reduced product was immediately acetylated and hydrolyzed with 50% acetic acid. When the oily product was acetylated, there was obtained methyl 2,3,5-tri-*O*-acetyl-β-(±)-ribofuranoside, which showed identical infrared (in chloroform) and nmr spectra with methyl 2,3,5-tri-*O*-acetyl-β-D-ribofuranoside, $[\alpha]_D^{29}$=-19.6° (in MeOH)* prepared from D-ribose in the manner described by T.Sato et al.[6)]

During the course of these structure elucidations, there was observed an interesting ring conversion between furanose- and pyranose-structure, which is similar to the conversion observed by T.Kinoshita et al,[8)] who reported that 3-keto-D-glucopyranuronic acid gave methyl (methyl 3-keto-D-glucofuranosed)uronate on treatment with cation resin in methanol. After heating the mono-ol VIb (143mg.) in 50% acetic acid (15ml.) on a boiling water bath for 1.5 hrs., an oily product was acetylated with acetic anhydride and pyridine to give the compound X, m.p. 137-139°, (55mg.). The compound X (130mg.) was heated in methanol (15ml.) in the presence of a catalytic amount of sulfuric acid for 2 hrs., and the oily product was acetylated with acetic anhydride in pyridine. The acetylated product was chromatographed on silicic acid (11g.) with ethyl acetate: benzene (1:1) and gave the tri-acetate VII, (39mg.). Assignments of ring protons, in the nmr spectrum of the compound X, are made in Fig.2. R.U.Lemieux et al.[7a)] has already reported the nmr spectrum of β-D-allopyranose pentaacetate (XI), which corresponds structurally to the compound X. The chemical shifts and the coupling constants of individual ring protons of X and XI are summarized in Table 1. The confirmation of the pyranose structure of X is based upon the following facts:

Table 1. The nmr data for ring protons of X and XI

X (in $CDCl_3$)			XI (in $CHCl_3$)		
H-1	τ 3.95	Doublet	H-1	τ 4.00	Doublet
		($J_{1,2}$=8.0c.p.s)			($J_{1,2}$=8.0c.p.s)[7b)]
H-2	τ 4.96	Quartet	H-2	τ ca.5.0	
		($J_{2,3}$=3.0c.p.s)			($J_{2,3}$=2.8c.p.s)
H-3	τ 4.27	Triplet	H-3	τ 4.31	Triplet
		($J_{3,4}$=3.0c.p.s)			($J_{3,4}$=2.8c.p.s)
H-4	τ 4.72	Quartet	H-4	τ ca.5.0	
		($J_{4,5}$=9.4c.p.s)			
H-5	τ 5.46	Doublet	H-5	τ 5.80	

* The claim that this compound is dextrorotatory[6)] is incompatible with our present result.

$J_{1,2}$=1.0c.p.s $J_{3,4}$=6.9c.p.s

$J_{2,3}$=5.0c.p.s $J_{4,5}$=3.7c.p.s

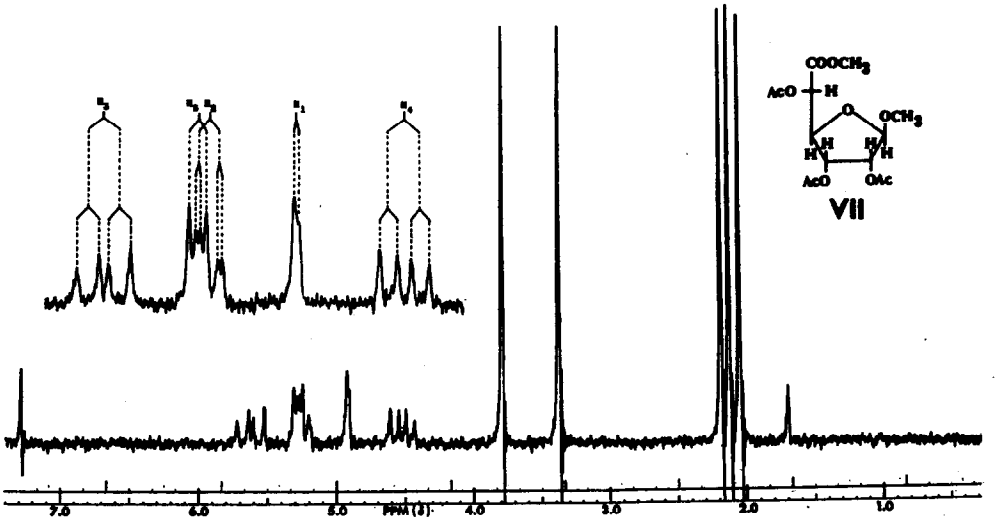


Fig. 1. The nmr spectrum of methyl (methyl 2,3,5-tri-*O*-acetyl-β-(±)-allofuranosid)uronate (VII)

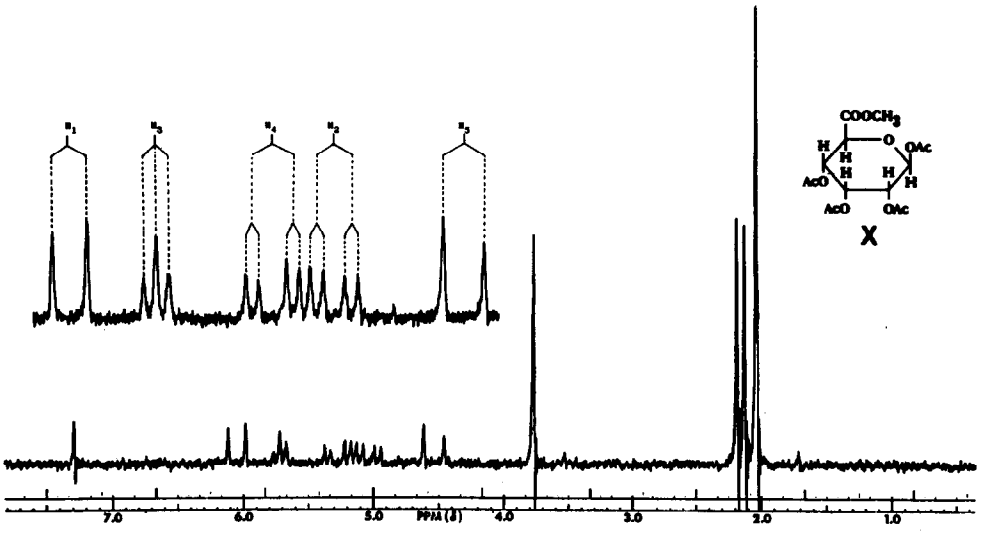


Fig. 2. The nmr spectrum of methyl tetra-*O*-acetyl-β-(±)-allopyranuronate (X)

The C-1 proton and C-3 proton of X are equivalent with those of XI. The variation of chemical shift of C-5 proton (from 5.80 to 5.46) reflects well the effect of carbomethoxyl group of X. The chemical shifts and the coupling constants of C-2 to C-5 protons of X do not correspond with those of the tri-acetate VII. Consequently the compound X is assigned as methyl tetra-*O*-acetyl-β-(±)-allopyranuronate.

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