Tetrahedron Letters, Vol.22, No.45, pp 4529 - 4532, 1981
Printed in Great Britain

0040-4039/81/454529-04$02.00/0

ACETALATION STUDIES-III[1]: SYNTHESIS OF 1,2:3,4:5,6-Tri-O-ISOPROPYLIDENE-GALACTITOL

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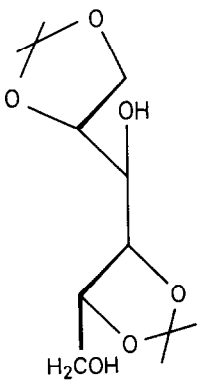
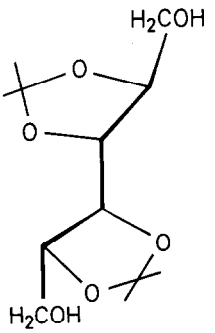
Summary: Treatment of galactitol with 2,2-dimethoxypropane in dimethylsulphoxide unexpectedly yields the title triketal, containing a cis*-dioxolane ring; the structure of the product has been confirmed by spectral measurements.*

Cyclic isopropylidene ketals of sugars and alditols are important for structural, synthetic and conformational studies[2-4]. They are usually formed by the acid-catalysed condensation of acetone with an appropriate substrate. The nature of the product is then thermodynamically-controlled. More recently acetal exchange using 2,2-dimethoxypropane and toluene-p-sulphonic acid in an appropriate solvent has been employed[3,5]. These reactions are considered to be under kinetic control and have led to products not always available by direct methods. The formation of isopropylidene acetals under neutral conditions was described recently[1]. The equilibrium of the reaction and the structure of the products was not influenced by acidic conditions. As part of further studies on these reactions the treatment of galactitol under similar conditions has now been investigated. Galactitol which has an *erythro* arrangement of hydroxyl groups at C_3-C_4 has not so far been shown to yield a triketal. It forms a mixture of the 1,2:4,5 - and 2,3:4,5-di-O-isopropylidene derivatives (1) and (2) respectively[6,7], the relative proportions of which depend on the reaction conditions. It was shown that 1 rearranged readily to 2 indicating that 1 is the kinetic product and that 2 is the thermodynamic product. The synthesis and proof of structure of a new tri-O-isopropylidene ketal is described here.



1



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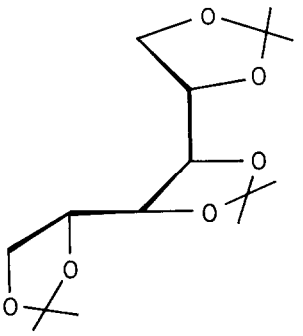

3

Galactitol (30 mmole) suspended in dimethylsulphoxide (25ml) and 2,2-dimethoxypropane (300 mmole) was heated under reflux with stirring for 65-70h. Removal of excess reagent and solvent *in vacuo*, followed by addition of ice-water (100 ml) gave a white precipitate (6.1g). Silica gel chromatography (cyclohexane-ethyl acetate, 9:2) on this product gave a triketal (1.77g, 19.5%) $C_{18}H_{26}O_6$, m.p. 118-119° (Me_2CO-H_2O). The i.r. spectrum of the product was almost identical with that determined for an authentic sample of 1,2:3,4:5,6-tri-O-isopropylidene-D-mannitol[1].

In the mass spectrum a definite molecular ion (M+ 302) was observed. The abundant ion m/e 287 (M-15) was also present, as were m/e 101 (base peak) and m/e (M-101) indicating a triketal containing a terminal 1,3-dioxolane ring. Furthermore the presence of m/e 143 was consistent with the presence of two contiguous O-isopropylidene groups, and the spectrum bore a close resemblance to that noted[8] for the triketal of D-mannitol, excepting for the presence of the molecular ion.

These observations suggested structure 3 for the product. This was in accordance with the ^{13}C n.m.r. spectrum in which there were only three carbon resonances in the region 65-80 p.p.m., at 66.3, 74,75, and 77.24 p.p.m. respectively, indicating a symmetrically substituted compound. The acetal carbons at 109.8 p.p.m. (terminal rings, two carbons giving overlapped lines) and 109.6 p.p.m. (middle ring) suggested they were 1,3-dioxolane rings. This was further substantiated by the separations of the methyl resonances of 1.64 p.p.m. (terminal rings) and 1.03 p.p.m. (middle ring)[9].

In the ^1H n.m.r. spectrum (200 MHz, $CDCl_3$) of 3 the $-C(Me)_2$ groups of the two terminal O-isopropylidene rings occurred as two equal strength singlets (12H intensity) at 1.38 and 1.46 p.p.m. respectively, which could be ascribed to the protons of the two Me^{α} and Me^{β} groups of the two α (terminal) 1,3-dioxolane rings. These values were in close agreement with those noted[10] previously for similarly situated groups. The protons of the two methyl groups of the middle 3,4-O-isopropylidene ring occurred also as two equal strength singlets (6H intensity) at 1.39 and 1.55 p.p.m. respectively. These value

reflected the *erythro* nature of this ring having Me^{α} and Me^{γ} groups. The slight upfield shift of the value of the Me^{α} protons could be accounted for by its closer proximity to the terminal 5,6-group. The remainder of the spectrum was consistent with the assigned structure 3, *inter alia*; 3.77 p.p.m. (dd; H1, 6b), 4.08 p.p.m. (dd; H1, 6a) and 4.16 p.p.m. (Complex, H-3,4).

Acid hydrolysis of 3 gave only galactitol (g.l.c.), indicating the absence of epimerisation of the galactitol configuration during the reaction.

There are very few references to the formation of compounds with an *αC-(erythro)* ring resulting from the condendation of diols with ketones. If no other type of ring is possible, formation of αC-rings may occur, even in the particularly unfavourable case of *erythro*-1,2-diphenyl-1,2-ethanediol[11]. D-Ribose diethyldiothioacetal has been shown to yield a di-O-isopropylidene derivative with αC-ring[12].

The result described here is not predicted by the Barker-Bourne rules[2]. There are some difficulties in interpreting them for ketones due to insufficient data and conflicting observations. The same order should follow from the rotations required[2,13,14] to form rings from a zigzag chain, and this order of stability for αT- and αC-rings should be valid for any carbonyl component. With αC-rings derived from ketones there is the extra destabilizing factor of the 1,3 interaction between an alkyl group and the inherent cis substituents of the ring. The application of these rules is intended to cover situations involving acid catalysis, where the possibility of acetal migration prevails, to give to most stable products. It is obvious that under non-catalysed, equilibrium conditions it is possible to obtain unexpected products that will not re-arrange.

The precise role of dimethylsulphoxide in the reaction is not clear. It has been shown[15] previously that it can affect the structure of products in acetalisation reactions through its solubilizing effect. It apparently assists solubility in the present example, since complete solubility was not obtained after 21 days when the reaction was performed under equilibrium conditions described previously[1], when no dimethylsulphoxide was used. Galactitol is a *meso* hexitol and exists[16,17] preponderantly as the extended chain conformer which has a centre of symmetry. In solution the constraints of the crystal field are released and the molecules undergo thermal movements about a mean structure that is centrosymmetrical[16]. In the reaction described here the extended chain conformation must have undergone rotation about the C_3-C_4 carbon bond to produce a bent chain conformer capable of accomodating the three rings in structure 3, in which C_2 and C_5 lie in a plane, and the two terminal carbon atoms are exoplanar.

Further studies on the system are in progress.

Grateful acknowledgement is made to Dr. A.C. Richardson (Queen Elizabeth College, University of London) for the ^{13}C *and* ^{1}H *n.m.r. spectra.*

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(Received in UK 1 September 1981)