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Preliminary communication

The formation of a 2,1′-anhydro linkage in sucrose

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Interest in the 2,1′-anhydride derived from sucrose arose from the observation[1] that a crude tritosylate of sucrose, thought to be mainly the 6,1′,6′-triester, gave the 2,1′:3,6:3′,6′-trianhydride 2 in low yield after treatment with sodium ethoxide. The structure of 2 was established by degradative means. However, later studies by Isaacs *et al.*[2] and by Khan[3] revealed that 6,1′,6′-tri-*O*-tosylsucrose and its pentabenzoate, which had both been prepared by unequivocal routes, each afforded a high yield of the 3,6:1′,4′:3′,6′-trianhydride **1**, the structure of which was established beyond doubt by X-ray crystallography[2]. Several other anhydro derivatives of sucrose have since been prepared[4–7], but in no case has the 2,1′-anhydro linkage been formed. Thus, 1′,6′-di-*O*-mesylsucrose afforded the 1′,4′:3′,6′-dianhydride in high yield with no trace of the 2,1′:3′,6′-dianhydride[4]. Since the 1′-tosyloxy group has a greatly diminished reactivity in nucleophilic displacement reactions[8], the formation of the 3′,6′-anhydro ring would be expected to precede formation of the 1′,4′-anhydro ring. Molecular models of sucrose reveal that C-1′ and HO-4′ are brought into close proximity by the formation of a 3′,6′-anhydro ring, thereby greatly facilitating subsequent formation of a 1′,4′-anhydro ring in preference to the 2,1′-anhydro ring. Thus, the formation of a 2,1′-anhydro ring might be favoured in the absence of a 3′,6′-anhydro ring. For this reason, we have studied the action of base on a 1′-*O*-tosyl derivative of sucrose.

Selective tosylation of 6,6′-di-*O*-tritylsucrose[10] (**3**) with 3 molar equivalents of tosyl chloride** afforded the 1′-tosylate **4** in 24% yield {m.p. 117–119°, $[\alpha]_D$ +17° (chloroform)} together with 21% of the 2,1′-ditosylate **5**. Treatment of the penta-acetate (**6**) of **4** with sodium methoxide afforded a single, crystalline anhydride (**7**) in 77% yield {m.p. 128°, $[\alpha]_D$ +24° (chloroform)}, which was subjected, in sequence, to acetylation, detritylation (HBr/HOAc), and acetylation, to give the hexa-*O*-acetyl-anhydride **9** {m.p. 141°, $[\alpha]_D$ +79° (chloroform)}. The absence of fragments at *m/e* 331 (Ac_4Glcp^+) and 221 (Ac_2anhydro-Fruf^+) in the mass spectrum of **9** indicated that the anhydro ring spanned the two monosaccharide moieties. The 220-MHz, ^{1}H-n.m.r. spectrum of **9** and the tetra-acetate of the ditrityl derivative **8** were amenable to first-order analysis (Table I) and clearly indicated the presence of a 2,1′-anhydro linkage. For example, in

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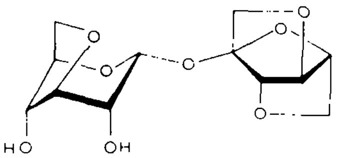
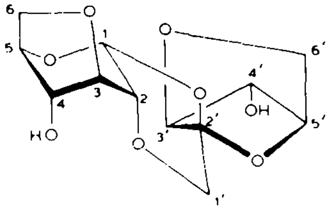
Tosylation of **3 was extremely slow, and in order to achieve a reasonable yield of the monotosylate it was necessary to use substantially more than one molar equivalent.



1



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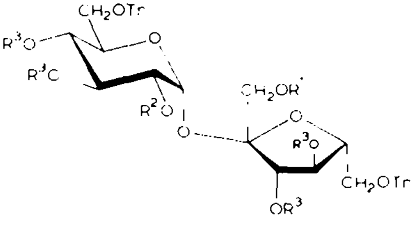
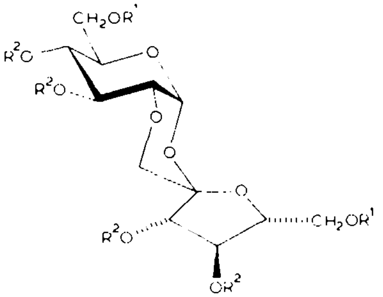


$3\ R^1 = R^2 = R^3 = H$

$4\ R^1 = Ts, R^2 = R^3 = H$

$5\ R^1 = R^2 = Ts, R^3 = H$

$6\ R^1 = Ts, R^2 = R^3 = Ac$



$7\ R^1 = Tr, R^2 = H$

$8\ R^1 = Tr, R^2 = Ac$

$9\ R^1 = R^2 = Ac$

the spectra of both 9 and 8, the resonances due to H-1, H-3, H-4, H-3′, and H-4′ were observed to low field of δ 5.0, indicating the presence of acetyl groups at O-3, O-4, O-3′, and O-4′. The resonance for H-2 was located at higher field (δ 3.84 and 3.60 in 8 and 9, respectively) revealing that O-2 was involved in the anhydro ring. In addition, the resonances for H-1′a and H-1′b were widely separated (0.5 and 0.7 p.p.m. in 8 and 9, respectively), suggesting that C-1′ was part of a ring and that H-1′a, being at lower field, was equatorial. Furthermore, the observed coupling constants (Table I) indicated that there had been no conformational perturbation of the pyranosyl ring, in agreement with a strainless, *cis*-decalin-type, fused-ring system, as in 9.

Our results show that, in the absence of a 3′,6′-anhydro ring, the 2,1′-anhydro ring is formed in preference to a 1′,4′-anhydride. It therefore seems reasonable to suggest that the trianhydride 2 described by Lemieux and Barrette may have originated from a minor tritosylate component in the crude reaction product. The 2,6,6′-tritosylate has been isolated from the crude mixture of tritosylates[9], and could theoretically account for the formation of the 2,1′:3,6:3′,6′-trianhydride 2 (either 2,6,6′-tritosylate → 2,3-epoxide → 2,1′-anhydride → 2, or tritosylate → 2-*O*-tosyl-3,6:3′,6′-dianhydride → 2). However, Ball *et al.*[9] concluded that the 2,6,6′-tritosylate could not be the precursor of 2, because it gave a complex mixture of products on treatment with base. The same authors also established that the 3,6;1′,4′;3′,6′-trianhydride 1 could exist in two crystalline forms, the lower melting of which (m.p. 158–162°) corresponded to that of the anhydride of Lemieux and Barrette (m.p. 163–164.5°), which led to the suggestion that the two

TABLE I

^{1}H-N.M.R. PARAMETERS (δ, Hz) AT 220 MHz

	6^a	8^b	9^a		6^a	8^b	9^a
H-1	5.82d	5.42d	5.63d	$J_{1,2}$	3.5	3.5	3.5
H-2	5.10dd	3.84dd	3.60dd	$J_{2,3}$	10.0	9.5	10.0
H-3	5.5–5.6 m	5.54t	5.97t	$J_{3,4}$	–	9.5	9.5
H-4		5.27t	5.26t	$J_{4,5}$	–	10.0	10.0
H-5	4.31m	3.92m	4.08m	$J_{5,6a}$	1.5	1.5	–
H-6a	3.59dd	3.32dd	4.45–4.24m	$J_{5,6b}$	5.0	3.5	–
H-6b	3.45dd	3.00dd		$J_{6a,6b}$	10.0	11.0	–
H-1'a	4.47d	3.98d	4.24d	$J_{1'a,1'b}$	11.5	12.5	12.5
H-1'b	4.38d	3.48d	3.47d	$J_{3',4'}$	5.0	5.5	7.0
H-3'	5.78d	5.03d	5.23d	$J_{4',5'}$	5.0	4.5	6.0
H-4'	5.65t	5.50t	5.69t	$J_{5',6'a}$	5.0	6.0	–
H-5'	4.27dt	4.10q	4.08m	$J_{5',6'b}$	5.0	6.0	–
H-6'a	3.51dd	3.46dd	4.45–4.24m	$J_{6'a,6'b}$	11.0	12.0	–
H-6'b	3.15dd	3.36dd					

^{a}In C_6D_6. ^{b}In $CDCl_3$.

were identical. However, this postulate has not been tested by a direct comparison and also ignores the substantial chemical studies carried out[1] on 2, which would not be explicable in terms of 1. Our present studies show that formation of the 2,1'-anhydro linkage is feasible, provided its formation precedes 3',6'-anhydride formation. An unambiguous synthesis of the 2,1':3,6:3',6'-trianhydride 2 is planned.

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