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A REAPPRAISAL OF THE SELECTIVITY OF THE MESYL CHLORIDE - N,N-DIMETHYLFORMAMIDE REAGENT. CHLORINATION AT SECONDARY POSITIONS

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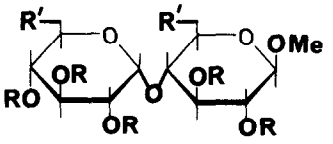
A mixture of mesyl chloride and N,N-dimethylformamide is used for the selective replacement of primary hydroxyl groups of hexopyranosides by chlorine.[1] Studies on methyl β-maltoside (1) led us to investigate this reaction for the synthesis of the 6,6'-dichloro-analogue* (2). Reaction of (1) with mesyl chloride (30 moles) in N,N-dimethylformamide



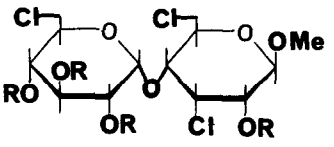
(1) R = H, R' = OH
(2) R = H, R' = Cl
(3) R = Ac, R' = Cl

proceeded further than anticipated and after 8 days at 70° afforded a mixture of methyl 3,6-dichloro-4-O-(6-chloro-6-deoxy-α-D-glucopyranosyl)-3,6-dideoxy-β-D-allopyranoside (4), isolated as its tetra-acetate (5) [m.p. 202-204°, $[\alpha]_D$ +88.5° (c 0.8, $CHCl_3$)] in 46% yield, and methyl 3,6-dichloro-4-O-(4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl)-3,6-dideoxy-β-D-allopyranoside (6), isolated as its triacetate (7) [m.p. 158-160°, $[\alpha]_D$ +114° (c 1.4, $CHCl_3$), Lit.[2] m.p. 161-162°, $[\alpha]_D$ +119°] in 8% yield. The structure of (5) was established by n.m.r. and m.s. analysis, whilst the tetrachloro-triacetate (7) was identical with that from the action of sulphuryl chloride on methyl β-maltoside.[2] At 100°, (5) and (7) were obtained in 37% and 20% yields respectively. Milder conditions produced mixtures of methyl 6,6'-dichloro-β-maltoside (2) and the trichloro derivative (4), isolated as their acetates (3) and (5) respectively, but at no time was (2) present without (4), indicative of the abnormal reactivity of the 3-hydroxyl group. The slow appearance of the tetrachloro-derivative (6) suggested that the reactivity of the 4'-hydroxyl group was considerably less than that at C-3.

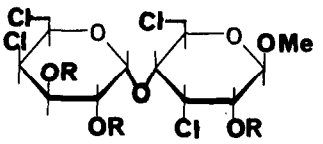
Re-examination of the reaction of methyl glucopyranosides with the reagent has revealed replacements at secondary positions, albeit at a slower rate. The β-anomer gave, in addition to the expected 6-chloro-6-deoxy-glucoside,[1] a 10% yield of methyl 3,6-dichloro-3,6-dideoxy-β-D-

*The primed numbers denote positions in the non-reducing ring

allopyranoside [m.p. 163-164°, $[\alpha]_D$ -54° ($CHCl_3$). Lit.[3] m.p. 162-163°, $[\alpha]_D$ -43°]. Similarly, the α-anomer afforded methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside isolated in 8% yield as its diacetate [m.p. 103.5-105°, $[\alpha]_D$ +190° ($CHCl_3$)].



(4) R = H
(5) R = Ac



(6) R = H
(7) R = Ac

The reaction of benzyl β-cellobioside with the reagent also resulted in chlorination at secondary positions giving the 6,6'-dichloro-, the 3',6,6'-,4',6,6'- and 3,6,6'-trichloro- and 3,3',6,6'- and 3,4',6,6'- tetrachloro-derivatives. In all compounds inversion of configuration accompanied reaction at chiral centers.

The introduction of chloro substituents by this reagent is rationalised by the slow initial, and probably rate limiting, formation of the iminium ion $[Me_2\overset{+}{N} = CHOMs]Cl^-$ which undergoes nucleophilic displacement of the mesyloxy group by the alcohol to give $[Me_2\overset{+}{N} = CHOR]Cl^-$. Bimolecular nucleophilic attack by chloride at "R" would afford the chloro derivative, with inversion of configuration.[1] The reaction rate was insensitive towards added chloride anions,[1] suggesting that the actual S_N2 displacement was not rate limiting. Our results show conclusively that the displacement occurs with inversion of configuration and that reaction at secondary positions occurs only where the steric and electronic factors[4] are favourable for an S_N2 reaction.

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