A New Synthesis of Chlorodeoxy-sugars

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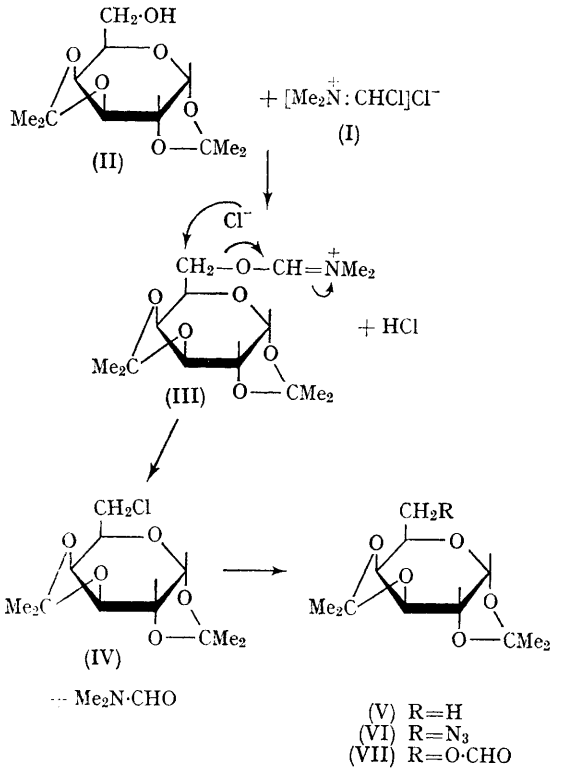
WE report the preliminary results on the uses of the reagent, *NN*-dimethylchloroformiminium chloride (I),[1] in the synthesis of chlorodeoxy-sugars. Reaction of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (II) with a slight molar excess of the chloride (I) in tetrachloroethane or 1,1,2-trichloroethane at room temperature for 1—2 hr. afforded an intermediate complex, presumably (III). The yellow solution was heated under reflux for 3–4 hr., and then treated with aqueous sodium hydrogen carbonate; processing of the organic phase afforded 6-chloro-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (IV), as a pale yellow liquid in 86—90% yield. The product was essentially chromatographically homogeneous, and a portion distilled at 95—100° (bath temp.)/0·1 mm. had $[\alpha]_D$ −66° (*c* 0·78, chloroform);† > 98% by v.p.c. analysis. Compound (IV) was transformed into the 6-deoxy-derivative[2] (V), b.p. 68—70°/0·5 mm., $[\alpha]_D$ −47·5 (*c* 2·67, chloroform), by reduction with

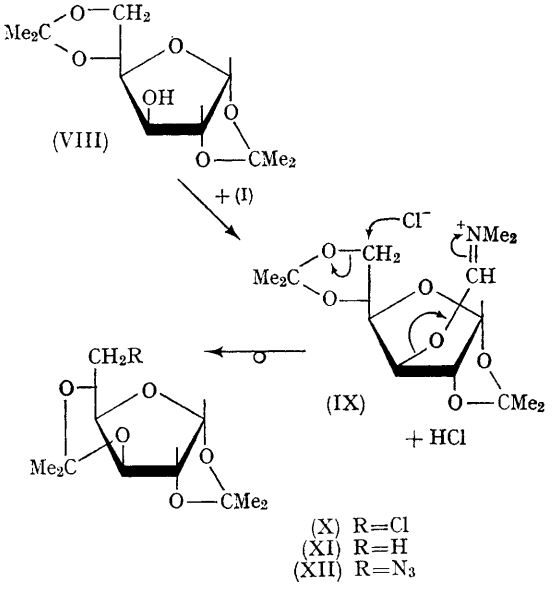
† Melting points are uncorrected. All compounds gave correct elemental analyses and had spectral properties (i.r., n.m.r., mass) consistent with their structures. Thin-layer chromatography was carried out on glass plates coated with silica gel–HF in the solvent system chloroform–2,2,4-trimethylpentane–methanol, 100 : 30 : 0·5 [compounds (IV), (X), (XIII), (XX)].

lithium aluminum hydride in tetrahydrofuran under reflux in the usual way. Reaction of (IV)



with sodium azide in refluxing *NN*-dimethylformamide for 36 hr. gave the corresponding 6-azido-6-deoxy-derivative[3] (VI) as the sole product. Treatment of (III) with aqueous sodium hydrogen carbonate afforded the corresponding 6-formate ester (VII) as a syrup. The latter could also be obtained from the reaction of (II) with *NN*-dimethylmethoxyformiminium methylsulphate[4] at room temperature, followed by treatment with aqueous hydrogen carbonate.

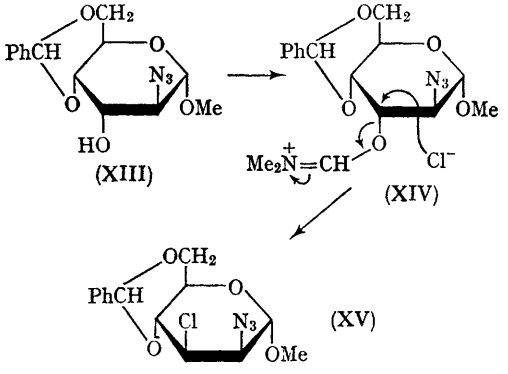
Treatment of 1,2: 5,6-di-*O*-isopropylidene-D-glucofuranose (VIII) with a slight molar excess of (I) gave a clear solution which on heating under reflux for 3—4 hr. afforded a pale yellow syrup in 69—71% yield, consisting of one major component (t.l.c.); b.p. 84—85°/0·05 mm.; $[\alpha]_D$ 36° (*c* 2·64, chloroform); > 98% by v.p.c. analysis. The product proved to be 6-chloro-6-deoxy-1,2: 3,5-di-*O*-isopropylidene-D-glucofuranose[5] (X) and its formation can be explained by attack of chloride ion at C-6 in the intermediate (IX), with concomitant migration[5,6] of the ketal function to the 3,5-position.‡ It should be noted that compound (X) was prepared at best in only 14% yield from the reaction of (VIII) with phosphorus pentachloride.[5,8] The new procedure thus provides a convenient route to 6-substituted D-glucose derivatives from the readily accessible (VIII). The product was converted into 6-chloro-6-deoxy-α-D-glucopyranose,[5] m.p. 135—136°, $[\alpha]_D$ 95·8° → 51·1° (18 hr., water) by acid hydrolysis. Compound (X) was also converted by reduction into the syrupy 6-deoxy-derivative (XI), and into (XII) by reaction with sodium azide in refluxing *NN*-dimethylformamide for 18 hr.



Treatment of methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside[9] (XIII) with (I) gave a chloro-derivative as a colourless syrup in 70% yield. Reduction of this with an excess of Raney nickel in methanol containing acetic anhydride afforded a crystalline product, m.p. 179°, $[\alpha]_D$ 72° (*c*. 0·45, chloroform). This melting point is markedly different from that reported (m.p. 143—144°) for methyl 2-acetamido-4,6-*O*-benzylidene-3-chloro-2,3-dideoxy-α-D-altropyranoside,[10] which would have been the product had the chlorination

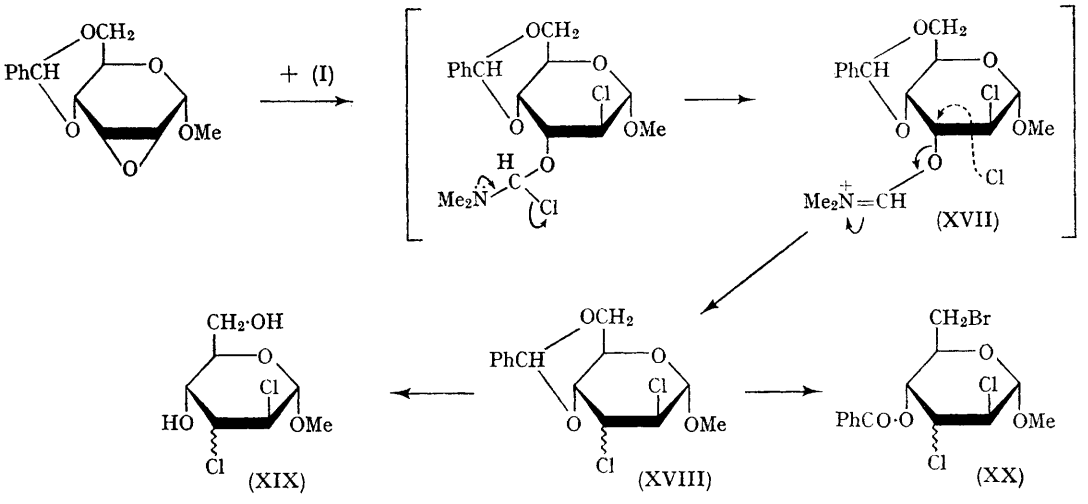
‡ Since rotation about the C-5–O bond is required for the migration of the acetal, the reaction cannot involve a concerted process. It is also interesting to note that while it is possible for the liberated oxygen anion attack to C-3 from the "endo" side, the less hindered topside attack prevails.

proceeded with retention of configuration. The actual product therefore is most likely methyl 2-azido-4,6-*O*-benzylidene-3-chloro-2,3-dideoxy-α-D-mannopyranoside (XV), resulting from attack of chloride ion at C-3 in the intermediate (XIV) with inversion of configuration.



When the reagent (I) was allowed to react with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside[11] (XVI) in tetrachlorethane at room temperature overnight, and the resulting solution was subsequently heated at 110° for 2 hr., a 2,3-dichloro-derivative (XVIII) was formed in 97·3% yield, b.p. 157—160°/0·25 mm., $[\alpha]_D$ 41·5° (*c* 1·47, chloroform). Mild acid hydrolysis or hydrogenolysis over palladium-on-carbon afforded a crystalline methyl 2,3-dichloro-2,3-dideoxy-α-D-hexopyranoside (XIX), m.p. 70—72°, $[\alpha]_D$ 118° (*c* 1, methanol) which was homogeneous; > 99% v.p.c. analysis. The initial reaction can be visualized as being the attack of chloride ion on the epoxide function to give presumably an intermediate having the *altro*- or *gluco*-configurations. The liberated C-3 or C-2 oxygen function, respectively, would then attack the highly electrophilic reagent giving an intermediate (XVII) (shown in the more likely *altro* configuration) which on heating decomposes to give ultimately the product. Such a sequence has been postulated in the reaction of several aliphatic cyclic ethers with (I).[12] The stereochemistry of attack of chloride ion during both stages of the reaction with (XVI) is being investigated. Reaction of (XVIII) with *N*-bromosuccinimide in carbon tetrachloride[13] under reflux afforded the corresponding 6-bromo-4-benzoate derivative (XX) as a syrup.

It is reasonable to expect that the decomposition of the *NN*-dimethylimino-ester chlorides proceeds *via* a bimolecular mechanism already established for the thermal decomposition of simple imino-ester salts.[14] In the carbohydrate series, where a secondary hydroxyl group is involved, such a process would result in chlorodeoxy-derivatives with overall inversion of configuration, provided that the



approach of chloride ion is not sterically hindered. Additional substrates are being investigated in order to establish the scope and the stereochemical course of the chlorination reaction.

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