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SYNTHESES OF "ANOMERIC" GEM DIHALOGENATED GLUCOPYRANOSYL DERIVATIVES

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Summary: Free-radical bromination of peracetylated β -D-glucopyranosyl chloride constitutes an efficient route to new C-1 gem dihalogenated sugars.

The reactivity of the anomeric carbon of carbohydrates mainly shows an electrophilic character (e.g. glycosylation reactions) or sometimes a nucleophilic character by "umpolung" of this carbon (e.g. anomeric sulfones (1), phosphonium salts (2)). The radical character of this anomeric centre has also been studied recently in our laboratory for the creation, by inter or intramolecular processes, of new bonds such as: C-D (3), C-O (4), C-C (5).

For the creation of carbon-halogen bonds, free-radical halogenation of cyclic sugar derivatives has been shown by other groups to proceed mainly on carbon atoms linked to the endocyclic oxygen (6,7,8,9,10) with a remarkable α -stereoselectivity, except for conformationnally labile systems (10, 11). Depending on the relative stabilization of the two proradical centres by electron withdrawing functionalities (e.g. nitrile, carbonyl, hydroxyimine, carboalkoxy), high yields of either C-1 or C-4 (12, 13) and C-5 brominated products can be observed. As a consequence of these highly controlled stereo and regioselectivities, the synthetic potential of such halogenations (14,15) as well as the structural features of the intermediate free-radicals (16) are receiving much attention.

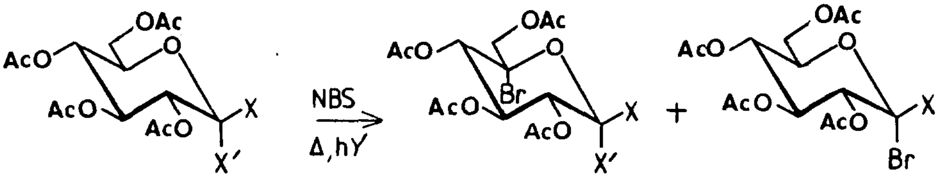
In connection with our interest in free-radical chemistry (3) and in the synthesis of anomeric spiro compounds (4,5), sugar halides appeared well designed for the preparation of new derivatives such as the anomeric gem dibromosugar first obtained in low yield by Ferrier and al. (6). The treatment of five glucopyranosyl halides by N-bromosuccinimide (NBS) in refluxing carbon tetrachloride leads to dihalogenated derivatives 2 and 3 as indicated in Table I.

This free-radical bromination study leads to the following conclusions:

- the β -halides **1a**, **1c** are much more reactive than their α -analogs **1b**, **1d** as a result of the easier abstraction of the axial anomeric proton, as observed in previous studies involving homolytic processes (17). Upon prolonged treatment, α-halides **1b** and **1e** give complex mixtures from which a vicinal dibromide 4 (Scheme 1) is isolated in limited yields. This product probably results from successive dehydrobromination and bromine addition reactions in agreement with its possible preparation from 1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-arabino-hex-1-enitol (peracetylated 2-hydroxy-D-glucal).

- The regioselectivity of these free-radical brominations appears to depend on stereoelectronic factors and on the capto-dative stabilization of the proradical centres by the neighbouring substituents. As indicated by the behavior of β -anomers, the decreasing influence of these substituents on the stability of the intermediate radicals seems to follow the sequence: Cl > CH_2OAc > F.

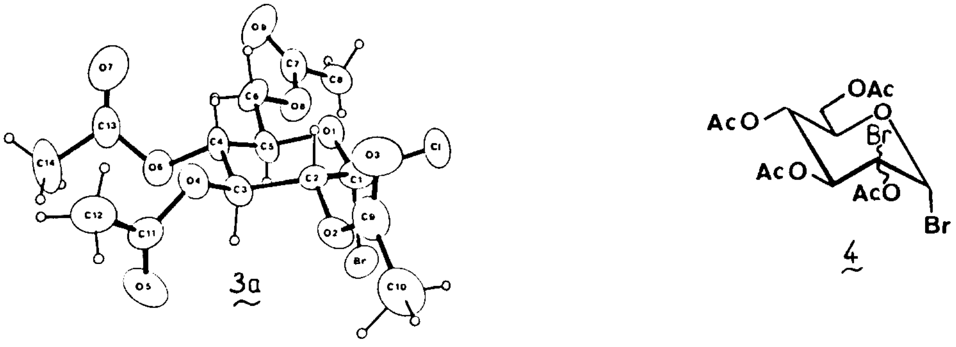
- The stereoselectivity of these substitutions is again shown to be very high with the exclusive formation of α -bromo derivatives. The axial orientation of bromine in **3a** was demonstrated by X-rays analysis [Scheme 1]. For fluoro derivative **3c**, the observed $J_{F\text{-}H_2}$ coupling constant (8Hz) which corresponds to a gauche relationship (18) indicates that the fluorine atom has retained its β-orientation. Axial bromine at C-5 is known to induce a 0.4 ppm deshielding effect for 1,3-syn diaxial protons H-1 and H-3 (6) as observed in the ^1H n.m.r. spectra of **2a**, **2c** and **2d**. The stability and ^1H n.m.r. data (δH-1 = 7.39 ppm in $CDCl_3$) of compound **4** indicate an α-anomeric configuration and by analogy with benzoylated analogs (19, 20),the bromine at C-2 should display an axial orientation.



1 2 3

Substrate			Reaction Time (h.)	Purification[a]	Recovered Material (%)	Products Yield (%)		
1	X	X'				**2**	**3**	**4**[b]
a	Cl	H	0.75	A	0	16[c]	62[d]	-
b	H	Cl	25	B	25	-	-	20
c	F	H	2.5	A	0	56[e]	4[f]	-
d	H	F	23	B	15	57[g]	-	-
e	H	Br	24	B	10	-	-	20
f[h]	OAc	H	2.0	-	0	82	-	
g[i]	F	F	-					

Table 1: a:The substrate (200 mg) and N-bromosuccinimide (400 mg) are irradiated in refluxing carbon tetrachloride using a 275 w heating lamp (6). After completion of the reaction (tlc) and concentration, the residue is partitioned between water and diethylether. The organic materials from the ether phase are then separated by column chromatography on silica gel using the following mixtures: A: diethylether-petroleum ether 1-1 v/v; B: chloroform-acetone 100-5 v/v. b: Colorless crystals, F = 135° (diethyl ether), $[\alpha]^{23}$ + 20.6° c 0.8, acetone; c: Syrup, $[\alpha]^{23}$ -120° c 2.3, chloroform. d: Colorless prisms, F: 109° (diethylether-petroleum ether), $[\alpha]^{20}$ + 136° c 1.4, acetone. e: Syrup, $[\alpha]^{23}$ -109° c 0.75, acetone.f: Needles, F= 38° (diethyl ether), $[\alpha]^{23}$ + 129° c 0.8, acetone. g: Syrup, $[\alpha]^{23}$ -36.8° c 0.65, acetone. h: From reference 6. i: Colorless prisms, F: 97° (diethyl ether petroleum ether), $[\alpha]^{23}$ + 42° c 0.5, acetone.



Scheme 1

The accessibility to 3a is confirmed by the following multigram scale experiment: the crude β-chloride 1a, obtained after treatment of β-D-glucopyranosyl pentaacetate (6.0g) with aluminium chloride in chloroform (21) is photobrominated, after concentration, as indicated in Table I. Two crystallizations from diethyl ether gives 3a (3.42g, 50 %). An additional amount of this material (0.74g, 12 %) and 2a (0.79 g, 12 %) can be recovered from the mother liquors by column chromatography (solvent A).

Finally, submitting 3a to halogen exchange with 3.3 molar equivalents of silver fluoride in acetonitrile (3 days, 35°C) yields 1g (X = X' = F) as a crystalline compound (70 % yield) whose ^{13}C and ^{19}F n.m.r. spectra are unambiguous (δ C-1 = 120.3 ppm, quartet, $J_{C,F}$= 256 and 271.7 Hz).

Therefore, the reactivity of 3a together with its stability and its availability clearly indicate the high potentiality of such anomeric dihalogenosugars for nucleophilic substitution. Such investigations are now in progress in our laboratory.

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