Pure & Appl. Chem., Vol. 50, pp. 1385-1400. 0033-4545/78/1201-1385 $02.00/0
Pergamon Press Ltd. 1978. Printed in Great Britain.

SYNTHESIS OF BROMODEOXY SUGARS FROM HEXOSES, ALDITOLS, AND ALDONIC ACIDS

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Abstract - Reaction of hexoses, anhydroalditols, and aldonic acids with hydrogen bromide in acetic acid leads to the formation of acetylated bromodeoxy compounds. The reaction proceeds by partial acetylation and formation of acetoxonium ions followed by substitution with bromide. Hexoses react only in the furanose form to give 6-bromo compounds. Most 1,4- and 1,5-anhydrides of hexitols give mono- or dibromides. Aldonic acids, or their lactones, yield mono- or dibromolactones with bromine at C-2 and at the primary carbon atom. Some aspects of the chemistry of the bromolactones are discussed.

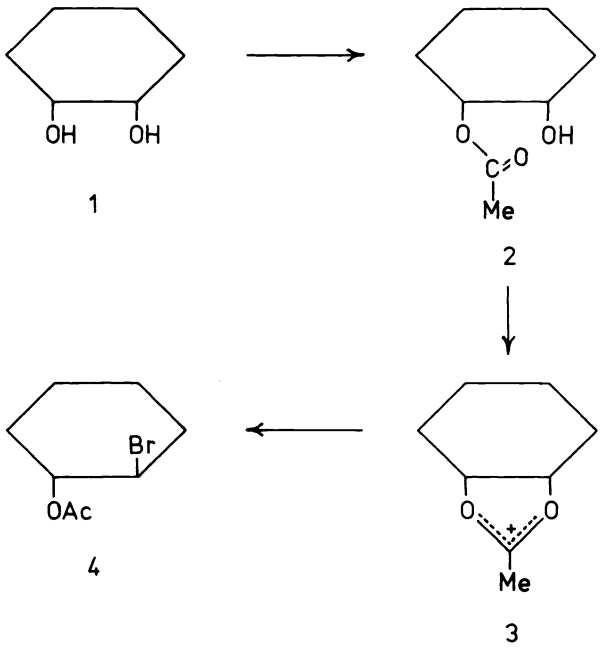
INTRODUCTION

Halogenated carbohydrates are valuable synthetic intermediates which may be used for the preparation of, for example, deoxy sugars, amino sugars, or unsaturated sugars. Numerous methods for the preparation of halogenated carbohydrates have therefore been developed and several reviews have been published (Refs. 1-3).

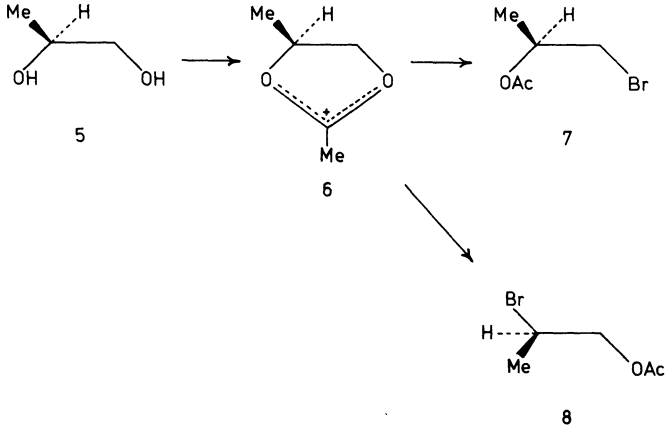
I now describe a new method for the preparation of bromodeoxy compounds which consists simply of treating an aldose, anhydro-alditol, or aldonic acid with a saturated solution of hydrogen bromide in glacial acetic acid at room temperature. This reagent (henceforward called HBA) is a well known reagent in carbohydrate chemistry, used since the turn of the century for the preparation of glycosyl bromides (Ref. 4). In this procedure an acylated (usually acetylated) sugar is treated with HBA at room temperature and the glycosyl bromide is usually formed in high yield as the only product.

However, it has been found in a few cases that reaction of carbohydrate derivatives with hydrogen bromide may lead to substitution of an O-acyl group with bromine at positions other than the glycosidic centre. Thus Fischer (Ref. 5) and, later, Freudenberg *et al.* (Ref. 6) found that penta-O-acetyl-D-glucopyranose gives tri-O-acetyl-6-bromo-6-deoxy-α-D-glucopyranosyl bromide on treatment with anhydrous hydrogen bromide. Penta-O-acetyl-D-galactopyranose behaves in a similar way (Ref. 7). Ohle *et al.* found that treatment of tri-O-acetyl-1,2-O-isopropylidene-α-D-glucofuranose with HBA gave bromodeoxy compounds which were not identified (Ref. 8). Later work has shown that 6-bromo-6-deoxy- and 2-bromo-2-deoxyfuranosyl bromides are formed in low yield in this reaction (Ref. 9).

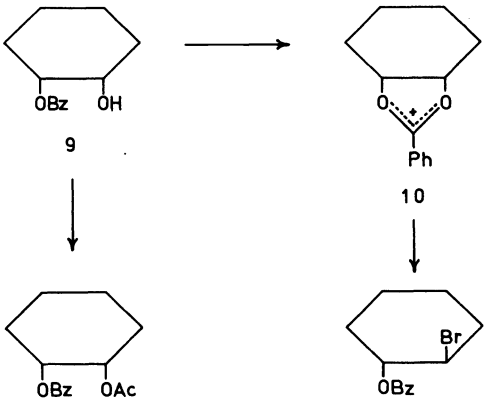
Recently, Golding and coworkers showed that vicinal diols react rapidly at room temperature with HBA to give vicinal acetoxybromides (Ref. 10). Thus *cis* cyclohexane-1,2-diol (1) gave the *trans* bromoacetate (4) in almost quantitative yield. Based on earlier work by Boschan and Winstein (Ref. 11) they showed that the reaction takes place *via* the monoacetate (2) which forms an acetoxonium ion (3) that subsequently reacts with bromide ions to give 4. Cyclohexane-*trans*-1,2-diol did not give a bromocompound when treated with HBA.



Golding et al. found this reaction to be general. Thus, (+)-(S)-propane-1,2--diol (5), when treated with HBA, gave 94% of the primary bromide (7) and 6% of the secondary bromide (8) with the R-configuration. Both products are undoubtedly formed via the acetoxonium ion (6), 8 with inversion of configuration.



We observed that the monobenzoate (9) with HBA gave the trans bromobenzoate (12) in good yield probably via a benzoxonium ion (10) (Ref. 12). In addition, smaller amounts of the cis acetylated product (11) were obtained, formed by acetylation of 9 in a competing reaction.



REACTION OF HBA WITH ALDOSES

The foregoing results indicated that suitably protected carbohydrates might yield bromodeoxy sugars on reaction with HBA provided that they contain a cis-diol moiety capable of forming an acyloxonium ion.

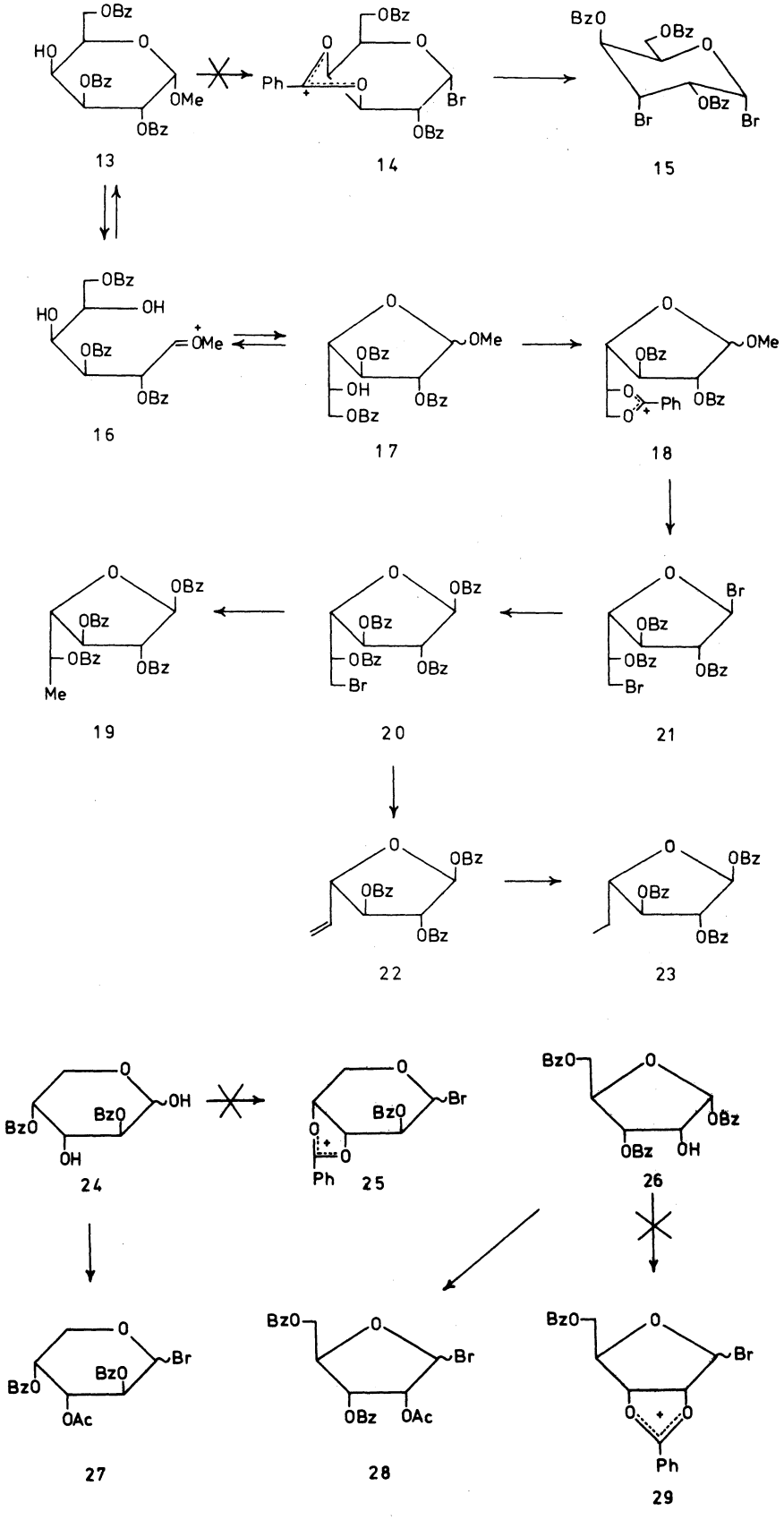
Thus, the readily available methyl tri-O-benzoyl-α-D-galactopyranoside (13) might be expected to form a benzoxonium ion (14) in HBA which would probably react with bromide ions to give the trans-diaxal bromocompound (15) (Ref. 13). However, treatment of 13 with HBA did not give 15, but a good yield of the 6-bromofuranosyl bromide (21) was obtained and isolated as the crystalline β-benzoate (20) after reaction with silver benzoate (Ref. 12). A ring contraction had taken place, probably via the intermediate 16 (Ref. 14). The furanoside (17) may then form an exocyclic benzoxonium ion (18) which, on reaction with bromide ions and replacement of the OMe group, yields 21.

The tetrabenzoate (20) was readily reduced to D-fucofuranose tetrabenzoate (19). With zinc and acetic acid 20 gave the unsaturated product (22) which, in turn, was reduced to 23.

It might be expected that treatment of 2,4-di-O-benzoyl-D-arabinopyranose (24) with HBA would give bromocompounds via the benzoxonium ion (25). However, the only product isolated was the acetylated bromide (27). Similarly, tri-O-benzoyl-α-D-ribofuranose (26) gave only the acetate (28). No bromocompounds derived from the benzoxonium ion (29) were found (Ref. 12).

Therefore, it seems as if dioxolanylium ions which are fused to pyranoses (14 and 25) or to furanoses (29) are not formed by treatment with HBA. Apparently, the exocyclic ion (18) was formed more readily and it was therefore of interest to study the behaviour of other hexofuranoses towards HBA.

Reaction of 2,3:5,6-di-O-isopropylidene-D-mannofuranose (30), or of 32, with HBA for 2 h at room temperature gave an almost quantitative yield of the syrupy dibromo product (31) (Ref. 15). Undoubtedly, the reaction proceeds by loss of the 5,6-isopropylidene group, monoacetylation, formation of a 5,6-acetoxonium ion, and finally attack of bromide upon C-6. The 2,3-isopropylidene group was not affected by HBA. The dibromocompound (31) is a useful synthesis intermediate.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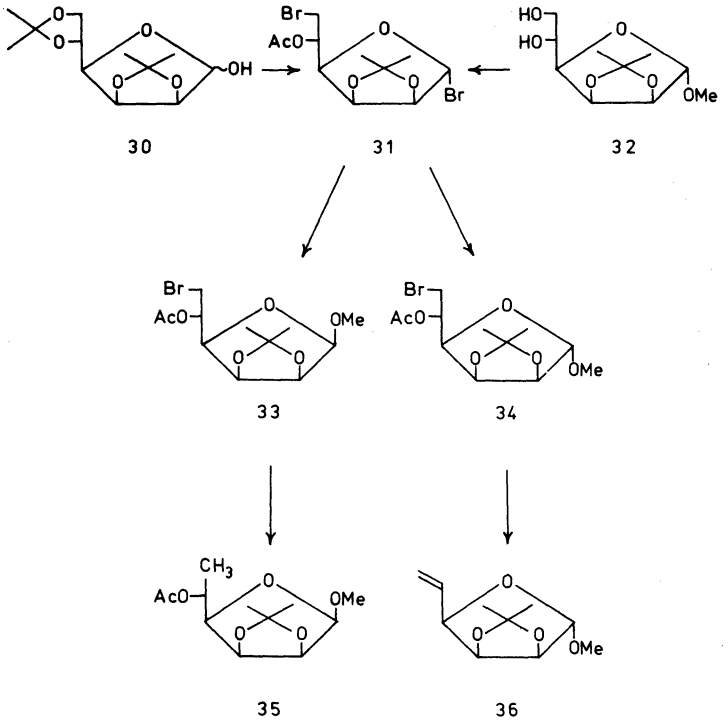
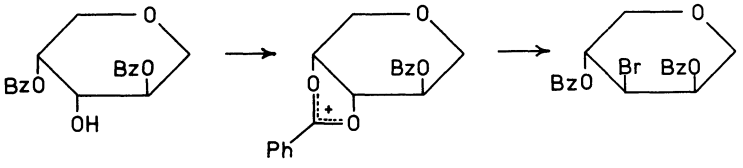


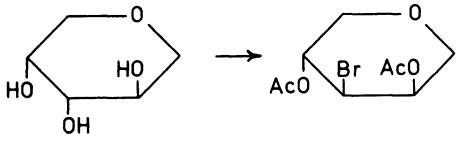
With methanol and silver oxide it was converted into the β-glycoside (33); the thermodynamically stable α-glycoside (34) was the sole product when no acid acceptor was present. Subsequent hydrogenolysis removed the bromine to give the D-rhamnoside (35). Treatment with zinc and acetic acid yielded an unsaturated product (36).

REACTION OF HBA WITH ANHYDROALDITOLS

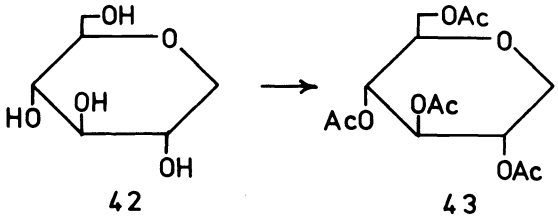
The fact that HBA does not form dioxolanylium ions attached to pyranose or furanose rings limits its use as a reagent for reducing sugars since it can only yield 6-bromo-6-deoxyhexofuranoses. In order to see whether dioxolanylium ions could be formed from other six- or five-membered rings, not containing an anomeric carbon, the reaction of some anhydroalditols with HBA has been studied.

The dibenzoylated anhydro-D-arabinitol (37) with HBA gave a good yield of the bromocompound (39), supposedly via the ion (38). Unprotected anhydroarabinitol (40) also reacted with HBA giving the bromo-acetate (41). The latter reaction must proceed through a partially acetylated compound and an acetoxonium ion. Thus, a dioxanylium ion apparently can be formed in a tetrahydropyran ring as opposed to a pyranose (cf., for example, 24 and 37), and it may therefore be expected that other anhydroalditols will react analogously.

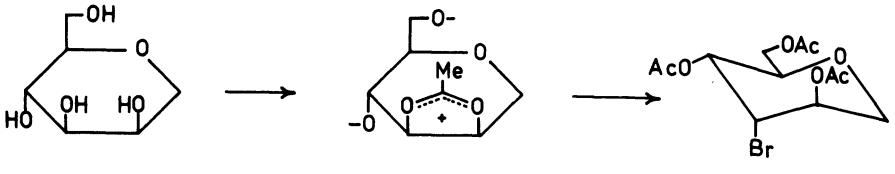




1,5-Anhydrosorbitol (42) has all the hydroxy groups trans oriented and should not be able to form an acetoxonium ion. In agreement with this view the only product isolated after treatment with HBA for 24 h was the tetra-acetate (43).

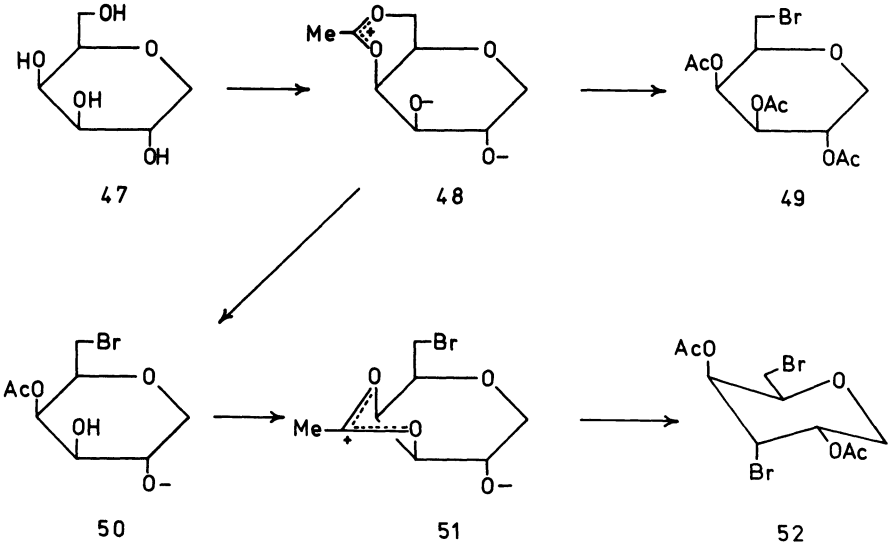


1,5-Anhydro-D-mannitol (44) has HO-2 and HO-3 cis and it may therefore form a 2,3-acetoxonium ion (45) after partial acetylation.



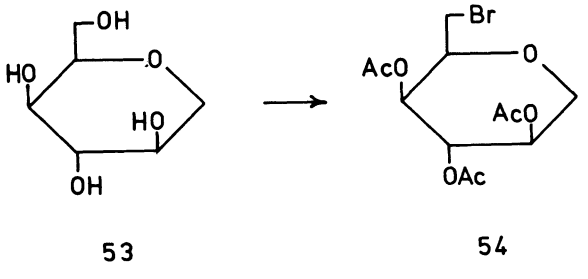
Treatment of 44 with HBA gave 56% of the 3-bromo compound (46), resulting from trans diaxial opening of 45. The only other product isolated was the tetra-acetate of 44.

1,5-Anhydro-D-galactitol (47) gave a mixture of the 6-bromo compound (49, 26%) and the 3,6-dibromo compound (52, 50%) on treatment with HBA. This result indicates that the first intermediate formed (after monoacetylation)

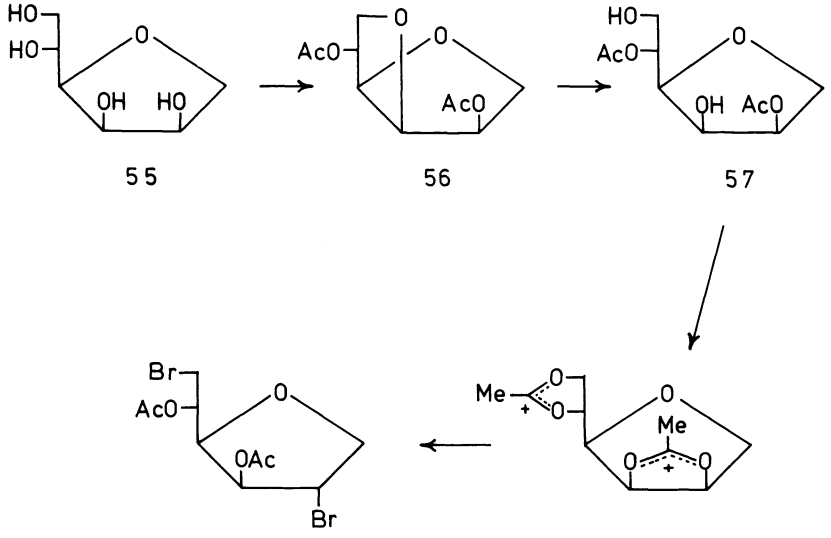


is the 4,6-acetoxonium ion (48). If this is acetylated at O-3 before it reacts with bromide ions it will give 49. On the other hand, if bromide attacks rapidly at C-6, 48 will yield 50, which can subsequently form the 3,4-acetoxonium ion 51. Reaction of 51 with bromide ions will then give the trans-diaxial product 52. In these reactions O-2 is acetylated at some stage of the reaction before or after introduction of the bromine.

Anhydro-D-iditol (53) gave the 6-bromo compound (54) as the only detectable product, presumably via the 4,6-acetoxonium ion.

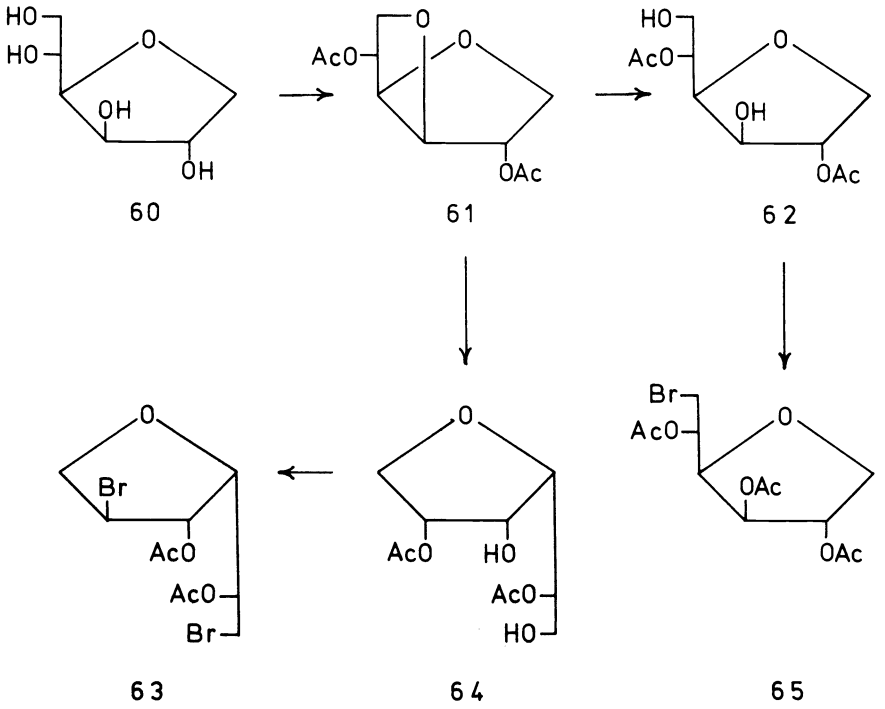


The 1,4-anhydrohexitols were found to react in an analogous, but somewhat more complicated manner. 1,4-Anhydro-D-mannitol (55), when treated with HBA for 24 h at room temperature, gave the 2,6-dibromo compound (58, 60%). This result can be explained by formation of a diacetate (57), a diacetoxonium ion (59), and, finally, attack of bromide ions at C-2 and C-6 to give 58. However, when 55 was treated with HBA for only 1 h, 60% of the acetylated dianhydro-D-mannitol (56) was obtained. Reaction of 56 with HBA for

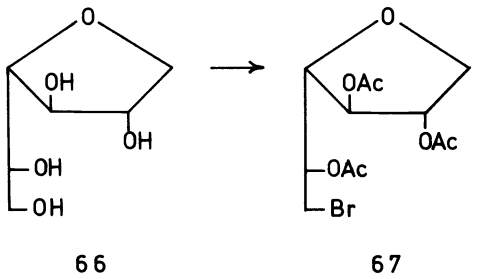


24 h gave the dibromo compound (58). Hence, 56 must be an intermediate in the conversion of 55 into 58.

Analogously, 1,4-anhydroglucitol (60) gave a high yield of the dianhydride (61) on brief treatment with HBA. Ring opening of 61 can take place in two ways to give either 62 or 64. Prolonged reaction of 60, or of 61, with HBA gave a mixture of the bromide (65) and the dibromide (63), i.e. the products that would be expected to arise from 62 and 64, respectively.



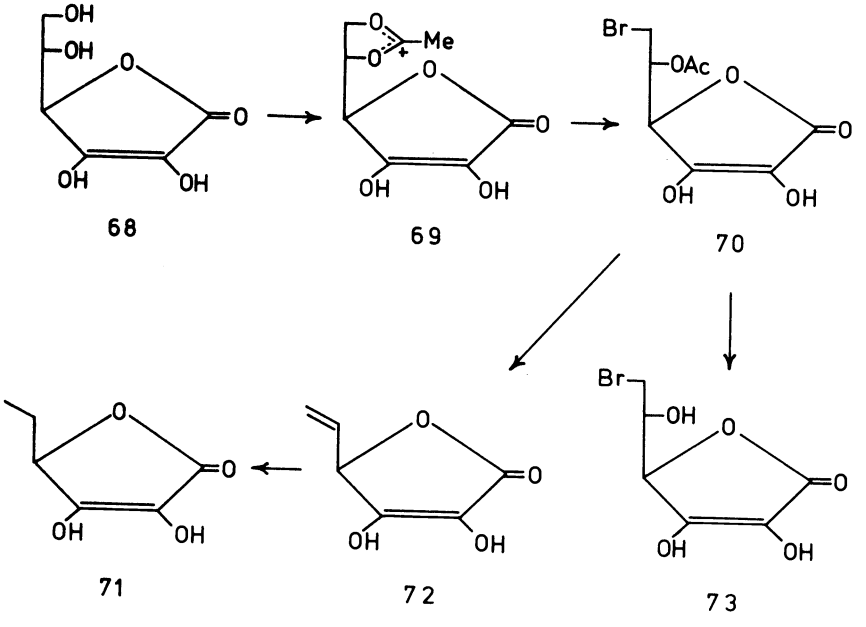
1,4-Anhydro-D-galactitol (66) cannot form a dianhydride, and on treatment with HBA it gave a high yield of the 6-bromo derivative (67).



REACTION OF HBA WITH ALDONIC ACIDS

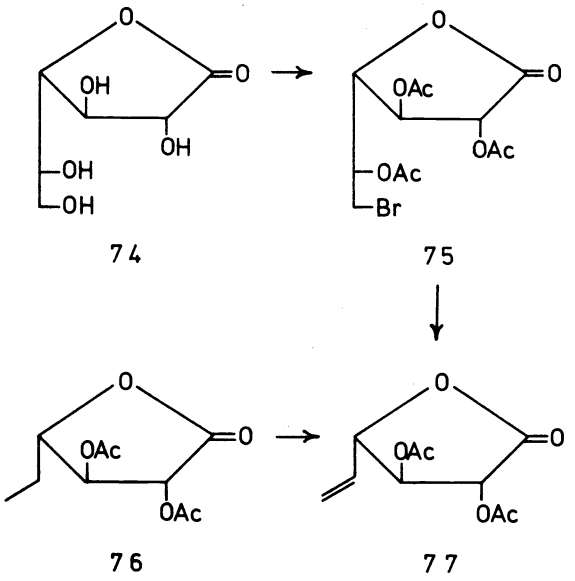
The formation of 6-bromo derivatives from the mannofuranose derivative (30) and from the 1,4-anhydrohexitols suggested that 1,4-lactones of hexonic acids might also yield 6-bromo derivatives on treatment with HBA since they have an exocyclic pair of hydroxyl groups. Also, it was of interest to see whether acetoxonium ions could be formed within a lactone ring.

The first lactone that we investigated was ascorbic acid (68) which reacted rapidly with HBA to give the bromo-acetate (70), presumably via the acetoxonium ion (69). The primary product (70) was a syrup, but treatment of the crude reaction mixture with water gave the crystalline, deacetylated



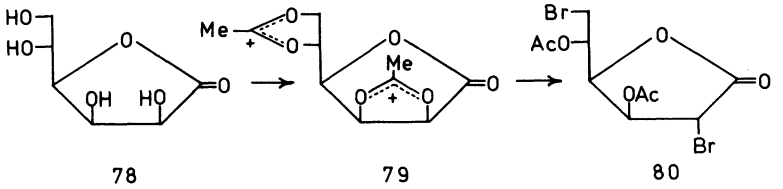
product (73) in 85% overall yield from ascorbic acid. Treatment of crude 70 with zinc in acetic acid gave the 5,6-unsaturated product (72) which was reduced catalytically to (R)-2-hydroxy-4-ethyltetronic acid (71).

This result prompted a study of other lactones. D-Galactono-1,4-lactone (74) was smoothly converted into the acetylated 6-bromo derivative (75). From 75



the unsaturated lactone (77) and the dideoxylactone (76) could be obtained. Treatment of calcium galactonate with HBA also gave 75 in the same yield as that obtained from 74.

D-Mannono-1,4-lactone (78) has HO-2 and HO-3 cis and, in addition to a 5,6-acetoxonium ion it might therefore form a 2,3-ion. Treatment of 78 with HBA

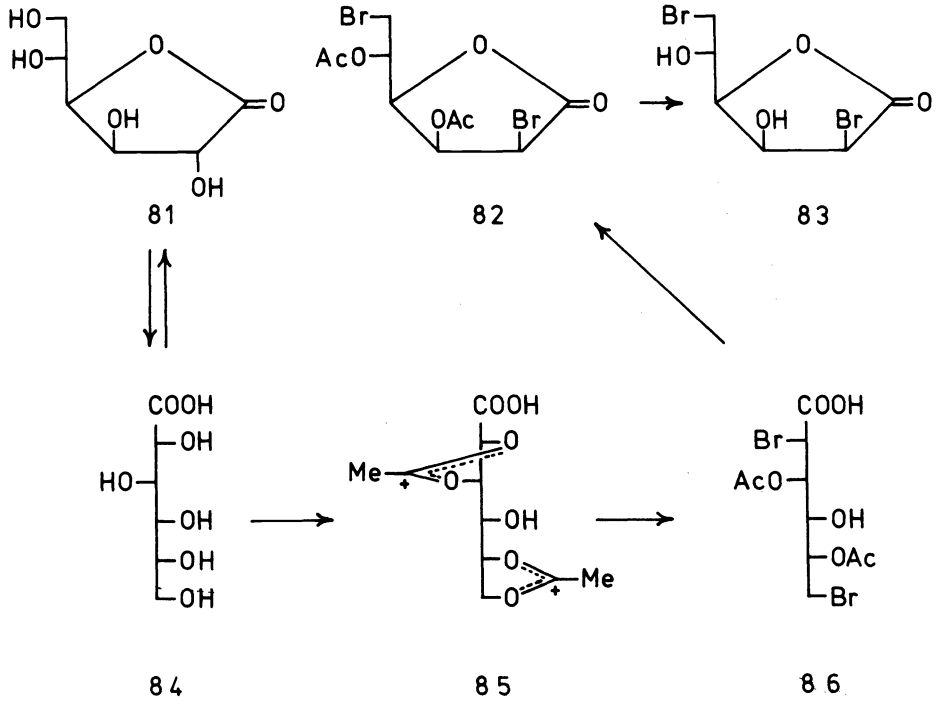


78 79 80

for 2-3 h gave a ~80% of the crystalline dibromolactone (80). The inversion at C-2 indicates strongly that a 2,3-acetoxonium ion has been involved as an intermediate. The two bromine atoms are probably introduced stepwise and not, as shown for convenience, through a diacetoxonium ion (79).

Glucono-1,4-lactone (81) has HO-2 and HO-3 trans and therefore was expected to react in a matter analogous to that of galactonolactone to give a 6-bromo derivative. Surprisingly, treatment of 81, or of calcium gluconate, with HBA for 16 h gave the acetylated dibromolactone (82) in ~75% yield as seen from NMR spectra. It was difficult to crystallize 82 from the reaction mixture, but after deacetylation the crystalline lactone (83) could be isolated in a 40-50% yield from calcium gluconate.

The formation of a dibromolactone from gluconic acid with inversion at C-2 indicates that a 2,3-acetoxonium ion is an intermediate. Since HO-2 and HO-3 are trans such an ion cannot arise from the lactone (81), but must be formed



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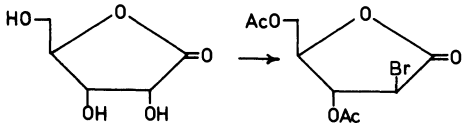
84 85 86

from the acid (84). The conversion of 84 into 82 can be depicted as taking place via 85 and 86, but the 2,3- and the 5,6-acetoxonium ions are probably formed stepwise. Monobromolactones could not be observed after briefer treatment of calcium gluconate with HBA.

The reaction of each of the four D-pentonic acids with HBA was also studied. Similar results were obtained whether the 1,4-lactones or calcium or potassium salts of the acids were used.



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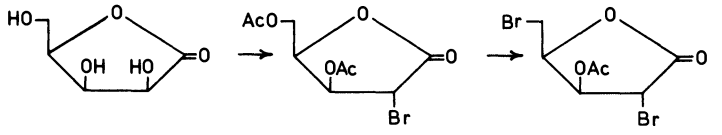

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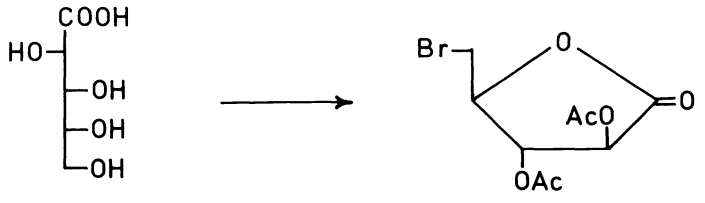
D-Ribonic and D-lyxonic acid have HO-2 and HO-3 cis and on brief treatment of the lactones (87) and (89), or of the corresponding potassium salts, with HBA they gave the 2-bromo-1,4-lactones (88) and (90), respectively. This result may indicate that they react as the lactones via 2,3-acetoxonium ions as described for mannono-1,4-lactone (78 → 79). When ribonolactone (87) was treated with HBA for 3 days the initially formed bromolactone (88) was converted into a mixture of isomeric dibromolactones which have not yet been characterized. Lyxonolactone (89) yielded 91 on reaction with HBA for 3 days. The Br-5 substituent of the latter product may be introduced through an acetoxonium ion which would require that the lactone ring opens, forms a 4,5--acetoxonium ion, and closes again after introduction of Br-5. Alternatively, a direct, acid-catalyzed substitution of the primary O-acetyl group with bromide might take place. Both mechanisms would probably explain the slow substitution at C-5.

Treatment of D-arabonic acid (92, or the 1,4 lactone) with HBA for 24 h gave the 5-bromolactone (93). On longer reaction, more bromine was introduced and, after 1 week, 93 was converted into a mixture of isomeric dibromolactones.



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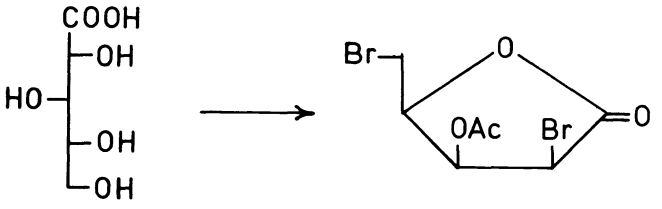

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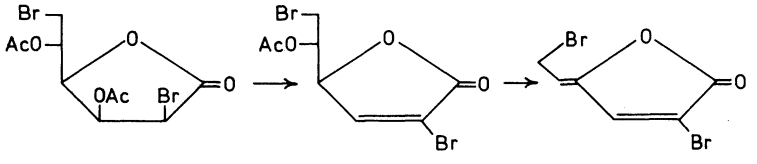
D-Xylonic acid (94) gave the 2,5-dibromolactone (95) in good yield when treated with HBA for 24 h. Apparently, the bromine atoms were introduced at approximately the same rate since it was not possible to isolate monobromolactones after shorter reaction times.

SOME REACTIONS OF THE BROMOLACTONES

The foregoing data shows that a number of bromodeoxy lactones can be prepared by a simple method using readily available starting materials. These bromolactones are therefore potentially useful synthesis intermediates, and some of the more obvious reactions that they may be expected to undergo are as follows: hydrogenolysis of the bromine to give deoxylactones, substitution of bromine with, for example, amino or azido groups, reduction of the lactone group to a hemiacetal, reductive elimination to unsaturated compounds.

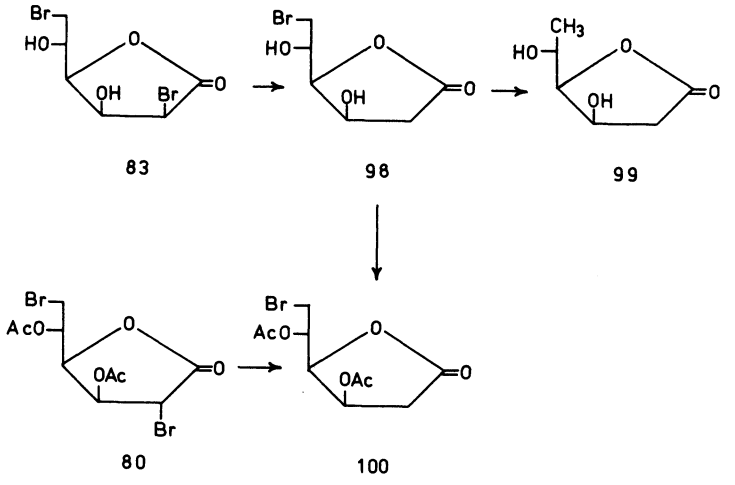
I now present preliminary results on the chemistry of these compounds.

The bromolactones may be obtained as the acetates or as the hydroxy compounds. Those acetylated lactones which have bromine at C-2 eliminate acetic acid readily even with very weak bases. Therefore, it is usually not possible to carry out nucleophilic substitution or hydrogenolysis on the acetylated lactones. Thus, the dibromolactone (82) is quantitatively converted into the 2,3-unsaturated lactone (96) by treatment with $NaHSO_3$ in methanol at room temperature. With $NaHCO_3$ it loses an additional equivalent of acetic acid to give 97.



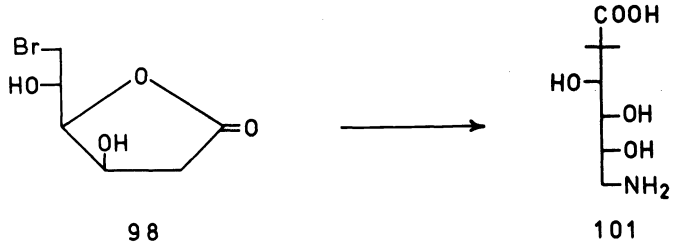
82 96 97

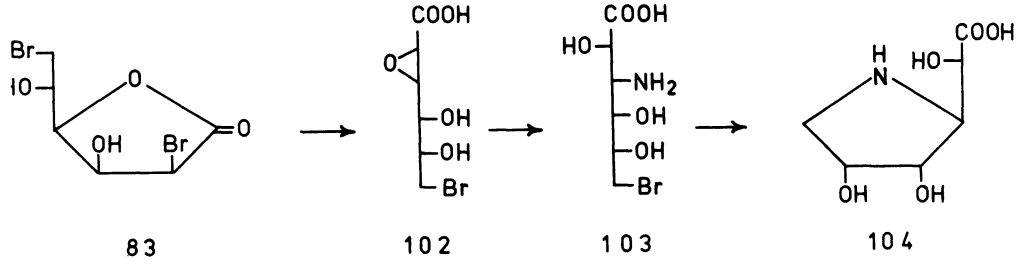
The deacetylated lactones show little tendency to elimination and substitution or hydrogenolysis can be performed easily. On hydrogenation of 83 over Pd-C in the presence of triethylamine, Br-2 was removed rapidly and selectively to produce 98, isolated as the crystalline acetate (100) in 70% yield.



Longer treatment with hydrogen gave the dideoxylactone (99). The 2-deoxylactone (100) was also prepared from 82, or from 80, by treatment with excess sodium iodide in acetone in the presence of trifluoroacetic acid (Ref. 16). The primary bromine atom was completely unaffected by this treatment.

Apparently, substitution of bromine with aqueous or anhydrous ammonia takes place easily. Thus, the 6-bromolactone (98) gave the aminoacid (101) in almost quantitative yield. With the dibromolactones more complicated reactions took place. The dibromo compound (83), when treated with aqueous ammonia, gave a product to which the structure 104 was tentatively assigned from spectroscopic evidence. Monitoring the reaction by ^{13}C-n.m.r. spectroscopy

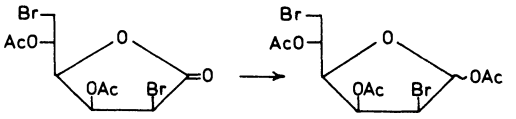




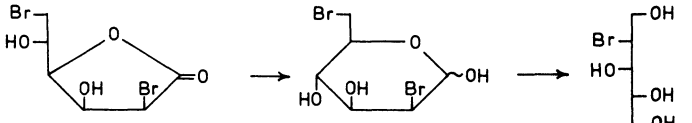
showed that an epoxide, probably 102, was an intermediate. This epoxide reacts with ammonia to give the 3-amino compound (103), which subsequently undergoes ring closure to 104.

Reduction of lactones to hemiacetals may be performed with reagents such as sodium amalgam, sodium borohydride, di-isoamylborane or di-isobutyl aluminium hydride (DIBAH). Some of the lactones described above were reduced in this way to give bromodeoxy or deoxy sugars. However, the yields were not satisfactory (25-50%).

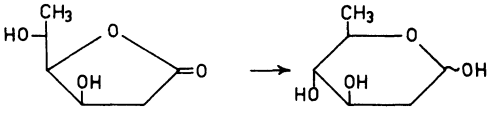
The acetylated 2-bromolactones cannot be reduced conveniently with amalgam or borohydride because of their tendency to undergo elimination. However, with di-isoamylborane or with DIBAH it was possible to reduce 82, and after acetylation the 2,6-dibromo-D-mannofuranose (105) was obtained (30-40%), mainly as the α-anomer. The deacetylated lactone (83) could be reduced with sodium borohydride to give the free sugar (106, ~50%) and some of the polyol (107). With more borohydride, 107 was obtained as the only product. Reduction of the dideoxylactone (99) with borohydride or sodium amalgam proved unsuccessful, but with di-isoamylborane, 2,6-dideoxy-D-hexose (108) was obtained in moderate yield.



82 105



83 106 107



99 108

Thus, by the reaction of HBA with rather readily available compounds it is possible to prepare a number of bromo derivatives which may be useful intermediates, especially for the synthesis of deoxy and aminodeoxy sugars.

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