

Reaction of Esters with Dibromomethyl Methyl Ether

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Acetylated monoalcohols react with dibromomethyl methyl ether (DBE) and zinc bromide to give the corresponding alkyl bromides, secondary acetates with inversion of configuration. Both *cis*- and *trans*-1,2-diacetoxycyclohexane react with DBE-ZnBr₂, probably *via* an acetoxonium ion, to give *trans*-2-bromocyclohexyl acetate. The latter on further reaction yields *trans* 1,2-dibromocyclohexane. 2-Bromo-3-acetoxytetrahydropyrane was readily converted into 2,3-dibromotetrahydropyrane whereas 3-acetoxytetrahydropyrane did not react. The mechanism of the reaction of acylated carbohydrates with DBE-ZnBr₂ is discussed.

Reaction of acylated pentopyranoses or pentofuranoses with dibromomethyl methyl ether (DBE) and zinc bromide leads to formation of 2-bromo-2-deoxy-glycosyl bromides in moderate yield, but with a high degree of stereo- and regio-selectivity.^{1,2} Partial mechanisms have been proposed;^{1,2} but in order to get a more complete picture of these reactions the behaviour of a number of simple esters towards DBE has now been studied, and the results are described in the present paper.

All reactions of esters with DBE and zinc bromide were carried out in chloroform or deuteriochloroform solutions, the conditions which were also used for the reactions with sugar esters. In the previous work the reaction mixtures were often inhomogeneous, either because the zinc bromide was not completely soluble, or because of formation of complexes between the zinc bromide and the sugar esters. In the present work suitable concentrations were chosen to ensure homogeneous reaction mixtures.

Treatment of the acetylated alcohols shown in Table 1 with DBE and zinc bromide gave the corresponding bromides, methyl formate,

and acetyl bromide. The reactions were monitored by NMR spectroscopy and the products were further analysed by GLC. The high rates of reaction of *tert*-butyl and benzyl acetate indicate that these esters react by an S_N1 type of reaction, involving carbonium ion intermediates. The secondary and primary esters do probably not react *via* free carbonium ions since this would lead to rearrangement, and only one product was found in each case. Treatment of 3- β -cholestanyl acetate with DBE and zinc bromide gave a high yield of the thermodynamically unstable 3- α -cholestanyl bromide, the 3- β -bromide not being detectable. Thus secondary esters appear to react with inversion.

The mechanism, as proposed by Szabó *et al.*,³ probably involves reaction of the ester with the oxocarbonium ion **1** to give an unstable intermediate **2**, which decomposes to the alkyl bromide, acetyl bromide, and methyl formate (Scheme 1).

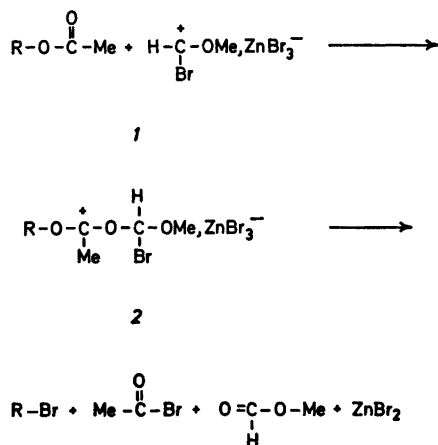


Table 1. Conversion of monoacetates to bromides with DBE and zinc bromide in deuteriochloroform.

Acetate	Bromide	Time to complete the reaction
Isobutyl	Isobutyl	10–20 days
<i>sec</i> -Butyl	<i>sec</i> -Butyl	1 h
Cyclohexyl	Cyclohexyl	10 h
<i>tert</i> -Butyl	<i>tert</i> -Butyl	<2 min
Benzyl	Benzyl	<2 min

Reaction of *trans*- or *cis*-1,2-diacetoxycyclohexanes, **3** and **5**, with DBE and zinc bromide gave a mixture of the *trans*-monobromide (**6**) and *trans*-dibromocyclohexane (**7**). Competitive experiments, in which the rate of reaction of cyclohexyl acetate (**8**) was compared with those of **3**, **5** and **6**, gave the results shown in Table 2. It is seen that **3**, **5** and **6** all react slower than cyclohexyl acetate, probably because of the inductive effect of a neighbouring acetoxy or bromo group.⁴ The reactions of **3** and **6** must involve a *trans* neighbouring group participation by an acetoxy

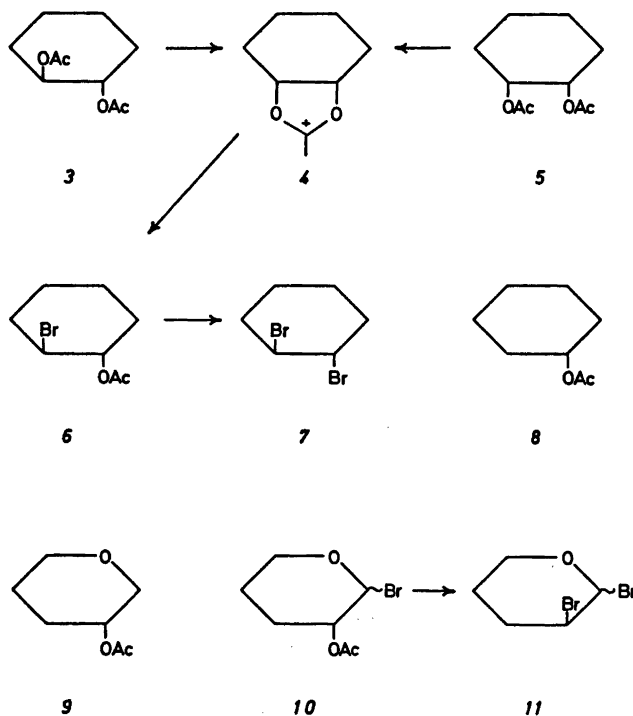
Table 2. Competitive experiments in which a mixture of two esters were treated with DBE-ZnBr₂ in deuteriochloroform.

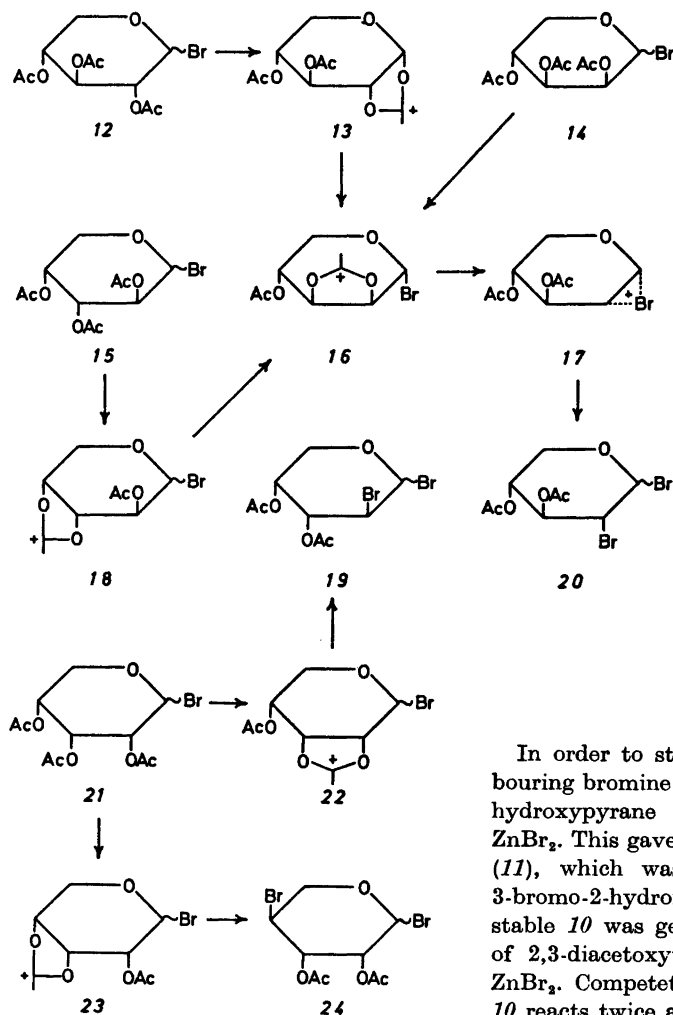
Esters	Reaction time h	% reacted of each ester
3 – 8	4	3 –46
5 – 8	4	10–57
3 – 5	48	26–50
6 – 8	2.5	9–62
9 – 10	1 (in CH ₃ NO ₂)	0–100
8 – 10	1	30–55
8 – <i>a</i>	1.5	40–53

^a Cyclohexyl benzoate.

group or a bromine atom since retention of the configuration is observed. The conversion of **5** to **6**, on the other hand, takes place with inversion which might suggest a direct replacement.

In order to get more information about the influence of neighbouring oxygen on the reaction of 3-acetoxytetrahydropyran (**9**) was treated with DBE-ZnBr₂. It was found not to react at all. Thus a β -oxygen has a strongly retarding effect on the reaction of an acetoxy





group, and the fact that 3 and 5 react with a rate not much lower than 8 strongly suggests that neighbouring group assistance is taking place and that the acetoxonium ion 4 is an intermediate in the conversion of both 3 and 5 into 6.

Thus the reaction of 3 with DBE-ZnBr₂ is probably analogous to its reaction with anti-mony pentachloride to give 4.⁵ The *cis*-neighbouring group assistance in 5 is analogous to its reaction with hydrogen fluoride.⁶ The ability of DBE-ZnBr₂ to form an acetoxonium ion with both *cis*- and *trans*-diacetates is similar to the effect of trifluoromethane sulfonic acid.⁷

In order to study the influence of a neighbouring bromine atom 3-acetoxy-2-bromotetrahydropyran (10) was treated with DBE-ZnBr₂. This gave 2,3-dibromotetrahydropyran (11), which was identified by hydrolysis to 3-bromo-2-hydroxy-tetrahydropyran. The unstable 10 was generated *in situ* by treatment of 2,3-diacetyltetrahydropyran with DBE-ZnBr₂. Competitive experiments showed that 10 reacts twice as fast as 8 (Table 2). This, in connection with the fact that 9 does not react at a detectable rate, shows that the bromine atom at C1 of 10 must participate in the displacement of the acetoxy group to give 11. This probably involves the formation of a 2,3-bromonium ion and results in migration of bromine from C1 to C2. Similarly, the conversion of 6 to 7 must proceed *via* a bromonium ion.

From the experiments described above a mechanism for the reaction of sugar esters with DBE and zinc bromide may be proposed. Sugar esters in which the substituent at C2 and C3 are *trans* oriented, such as tri-*O*-acetyl-D-xylopyranosyl bromide (12), can react *via* a 1,2-acetoxonium ion (13) which rearranges

to a 2,3-ion (16) with simultaneous introduction of bromine at C1. Attack of the bromine atom of C1 upon C2 may then yield the 2-bromo-2-deoxy-derivative 20 via the bromonium ion 17, as proposed previously.¹ This explains the stereoselectivity of the reaction and the fact that bromine is only introduced at C2. An analogous mechanism can explain the reaction of the corresponding furanoses in which the substituents at C2 and C3 are *trans*-oriented.² The compound 20 has *trans*-acetoxy groups at C3 and C4 and it might therefore undergo further substitution similar to that of 3. This was, however, not observed in 20 or in other sugar derivatives.

Sugar derivatives in which C2 and C3 are *cis*-oriented must react by a different mechanism. The lyxosyl bromide 14 can form the 2,3-ion 16 directly by a mechanism analogous to that by which 5 is converted into 4. The ion 16 then yields 20 as described above. The ribo- and arabinofuranosyl bromides may react in the same way.² Tri-*O*-acetylribose bromide (21) has C2 and C3 *cis*-oriented and can therefore give a 2,3-acetoxonium ion 22. On further reaction, analogous to the conversion of 16 to 20, this would give the 2-bromo-2-deoxyarabinose derivative 19 which was found previously.¹ Alone of all pentose-derivatives investigated 21 gave a 4-bromo-4-deoxy compound (24).¹ This probably takes place via the 3,4-acetoxonium ion 23.

Tri-*O*-acetylribose bromide (15) has C2 and C3 *trans*-oriented and could therefore react analogous to 12. In this case the acetoxonium ion 22 would be formed, and the final product would be the 2-bromo-2-deoxyarabinose derivative 19. However, 20 and not 19 was the product actually found,¹ and this must mean that the *cis*-3,4-acetoxy groups of 15 react to give an acetoxonium ion (18) which rearranges to 16 and subsequently yields 20.

A number of benzoylated pentosyl bromides have been studied, and it was found that, of the pyranoses, only tri-*O*-benzoylxylopyranosyl bromide gave a 2-bromo-2-deoxy compound with DBE-ZnBr₂.¹ Benzoylated ribo- and lyxofuranosyl bromide did not react whereas the corresponding arabino- and xylofuranosyl bromides gave 2-bromo-2-deoxy compounds.² This indicates that the benzoylated pentoses

in which the reaction would be expected to start from a pair of *cis*-oriented benzoyloxy-groups do not react.

In agreement herewith it was found that *cis*-1,2-dibenzoyloxycyclohexane did not react with DBE-ZnBr₂. Cyclohexyl benzoate reacted slightly faster than the acetate 8 to give cyclohexyl bromide and 3-*O*-benzoyl-2-bromotetrahydropyran readily gave 2,3-dibromo-tetrahydropyran (11).

EXPERIMENTAL

¹H NMR spectra were measured on Varian A60, Varian HA-100, or Bruker HX-90E instruments. For gas chromatography (GLC) was used a Perkin-Elmer F 11 instrument equipped with a column of silicone E 301. Preparative thin layer chromatography (TLC) was done on 1 mm layers of silica gel (Merck PF₂₅₄).

Dibromomethyl methyl ether (DBE) was prepared according to Gross and Karsch.⁸

Reaction of monoacetates with DBE-ZnBr₂ (Table 1)

The ester (0.5 mmol) was dissolved in a mixture of DBE (0.5 ml) and deuteriochloroform (0.5 ml) at room temperature and zinc bromide (50 mg) was added. The mixture was stirred until a homogeneous solution was obtained and NMR spectra were then measured at intervals.

When the reactions were completed methylene chloride was added and the solution was washed with 4 N hydrochloric acid and with aqueous sodium hydrogen carbonate and dried. The methylene chloride solution was then subjected to GLC to identify the products. The identifications were confirmed by addition of authentic compounds.

Isobutyl acetate reacted very slowly and the reaction was interrupted after 48 h. GLC showed that isobutyl acetate and isobutyl bromide were present in a ratio of 83:17 at this stage.

The other reactions shown in Table 1 were allowed to continue until no ester could be detected from the NMR spectra. *tert*-Butyl acetate was completely converted into *tert*-butyl bromide within 2 min after the addition of ZnBr₂. The NMR spectrum showed that one equivalent of methyl formate and acetyl bromide were formed at the same time. *tert*-Butyl acetate reacted with DBE in the absence of ZnBr₂, the reaction being completed within 1.5 h. Benzyl acetate also reacted rapidly with DBE and ZnBr₂, but no reaction took place in the absence of ZnBr₂.

3- α -Cholestanyl bromide. 3- β -Cholestanyl acetate (990 mg) in chloroform (5 ml) was treated with DBE (2.0 ml) and ZnBr₂ (260 mg) for 5 days at room temperature. Work up as described above gave a product which was purified by preparative TLC with pentane as eluent to give 781 mg (73 %) of 3- α -cholestanyl bromide after recrystallization from acetone, m.p. 96–97 °C, $[\alpha]_D^{20} + 28.4^\circ$ (c 2, CHCl₃). An additional recrystallization gave a product with m.p. 101–102 °C, $[\alpha]_D^{30} + 27.9^\circ$ (c 2.5, CHCl₃) (reported * m.p. 101–102 °C, $[\alpha]_D + 26^\circ$). No β -bromide was found.

Reaction of diacetoxycyclohexanes with DBE-ZnBr₂

cis-1,2-Diacetoxycyclohexane (512 mg) in chloroform (5 ml) was treated with DBE (2 ml) and ZnBr₂ (146 mg) for 48 h at room temperature. Work up as described above gave a product which was separated into 3 fractions by preparative TLC using ether-pentane (1:3) as eluent. The first fraction contained 140 mg (28 %) of *trans*-1,2-dibromocyclohexane (7), the second fraction gave 124 mg (27 %) of *trans*-1-acetoxy-2-bromocyclohexane (6), and the third fraction 126 mg (25 %) unreacted 5. The products were identified by comparing their NMR and IR spectra with those of authentic samples.

When the reaction was allowed to proceed for 5 days 61 % of 7, 5.5 % of 6, and 4.5 % of unreacted 5 was obtained.

trans-1,2-Diacetoxycyclohexane (3) when mixed with DBE and ZnBr₂ in chloroform gave a precipitate and therefore reacted slowly. After 15 days the mixture was worked up and analysed as described above. It gave 6 % of 7, 9.7 % of 6, and 26 % of 3.

Competitive experiments (Table 2). 1.0 mmol of each of the two acetates were dissolved in deuteriochloroform (1.0 ml) and DBE (1.0 ml) and ZnBr₂ (100 mg) were added. The mixtures all became homogeneous when stirred for 30 min. The reactions were followed by NMR spectroscopy and when a suitable amount had reacted the mixtures were worked up as described above. The resulting methylene chloride solutions were analysed by GLC using co-injection of authentic compounds for identifications.

3-Acetoxy-2-bromotetrahydropyrene (10) was prepared *in situ*. To a solution of 2,3-diacetoxytetrahydropyrene¹⁰ (515 mg) in chloroform (2 ml) was added DBE (1 ml) and ZnBr₂ (165 mg). An NMR spectrum measured after 5 min showed that only 10 was present as a 1:2 *cis*–*trans* mixture.

After 4 h at room temperature an NMR spectrum showed that 10 was completely converted in 2,3-dibromotetrahydropyrene (11). The spectrum was identical with that of a sample prepared by addition of bromine to

3,4-dihydro-2*H*-pyrane.¹¹

The reaction mixture was evaporated. The residue in acetone (20 ml) was stirred for 2 h with water (2 ml) and silver carbonate (1 g). Filtration and evaporation gave a residue which was dissolved in dichloromethane and dried. Evaporation gave a product (360 mg) which was purified by preparative TLC (ether-pentane 1:1) to give 215 mg (47 %) of 3-bromo-2-hydroxytetrahydropyrene, which was recrystallized from ether-pentane, m.p. 77–80 °C (reported¹¹ m.p. 79–80 °C). An NMR spectrum was identical with that of an authentic sample.¹¹

Reaction of a mixture of 9 and 10 with DBE-ZnBr₂. 2,3-Diacetoxytetrahydropyrene (201 mg, 1.0 mmol) and 9 (142 mg, 1.0 mmol) were dissolved in deuteriochloroform (1 ml); DBE (1 ml) and ZnBr₂ (106 mg) were then added. After 1 h at room temperature an NMR spectrum showed that all the diacetoxy compound was converted into 10. Since the mixture was inhomogeneous nitromethane (1 ml) was added. After 1 h an NMR spectrum showed that 10 was completely converted in 11, whereas 9 was unaffected. The mixture was worked up as described above and the products were further identified through GLC.

Reaction of a mixture of 8 and 10 with DBE and ZnBr₂. Cyclohexyl acetate (8) (138 mg, 1.0 mmol) and diacetoxytetrahydropyrene (203 mg, 1.0 mmol) in deuteriochloroform (1 ml) were mixed with DBE (1 ml) and ZnBr₂ (98 mg). After 1 h the mixture was diluted with dichloromethane and washed. GLC and NMR spectra showed that 30 % of 8 was converted into cyclohexyl bromide and 55 % of the diacetoxy compound was converted into 11.

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