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SUGAR ESTERS—I

OXIDE FORMATION IN THE SYNTHESIS AND HYDROLYSIS OF SOME FLUORIDES AND PHOSPHATE ESTERS

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Abstract—Investigation of several routes to fluoro-carbohydrates and sugar phosphates has shown that appreciable formation of internal ethers may occur in certain cases.

RECENTLY the formation of anhydro sugars in the attempted synthesis of some sugar phosphates has been reported.[1] We have been interested in the synthesis both of sugar phosphates and fluoro-carbohydrates, and in both cases we have found that oxide formation may interfere with these syntheses. Furthermore we have encountered oxide formation in the hydrolysis of certain diaryl 2-hydroxyalkylphosphates: this type of compound usually hydrolyses with formation of cyclic esters.[2]

The following synthetic methods were amongst those examined in this work. *One*, the action of potassium fluoride upon sulphonyloxy derivatives.[3] *Two*, the action of potassium fluoride,[4] silver phosphate,[5] and silver diarylphosphates[6] upon halohydrins. *Three*, the action of acid fluorides, hydrogen fluoride[7a] and diaryl phosphoric acids[7b] upon epoxides.

6-Fluoro-6-deoxy hexoses have been prepared previously by direct replacement of

* Some of this work has been presented in part fulfilment of the requirements for the degree of M.Sc. Dublin University (1960).

[1] W. G. Overend and S. Brooks, *Chem. & Ind.* 471 (1960). We thank Professor Overend for the communication of some of his results to us prior to publication.

[2] E.g. *vide* P. E. Verkade, J. C. Stoppelenberg and W. D. Cohen, *Rec. Trav. Chim.* **59**, 886 (1940); D. M. Brown and A. R. Todd, *J. Chem. Soc.* 52 (1952); W. E. Cohn, *J. Amer. Chem. Soc.* **72**, 2811 (1950). H. S. Loring, L. W. Levy L. K. Moss and J. M. C. T. Ploesser, *Ibid.* **78**, 3724 (1956); D. M. Brown and H. F. Higson, *J. Chem. Soc.* 2034 (1957); D. M. Brown, R. Hall and H. F. Higson, *Ibid.* 1360 (1958).

[3] cf. eg. F. L. M. Pattinson and J. E. Millington, *Canad. J. Chem.* **34**, 757 (1956); E. D. Bergmann and I. Shahak, *Chem. & Ind.* 157 (1958).

[4] *Vide inter alia*, F. W. Hoffmann, *J. Org. Chem.* **75**, 425 (1950); *J. Amer. Chem. Soc.* **70**, 2596 (1948); G. Olah, *Acta. Chim. Acad. Sci. Hung.* 3, 191 (1953); B. C. Saunders, *J. Chem. Soc.* 1773 (1948); E. D. Bergmann, *Ibid.* 3786 (1953); 3286 (1959).

[5] Eg. G. T. Cori, S. P. Colowick and C. F. Cori, *J. Biol. Chem.* **121**, 465 (1937); M. E. Krahl and C. F. Cori, *Biochemical Preparations* Vol. I, p. 33. John Wiley, New York (1949), S. P. Colowick, *J. Biol. Chem.* **124**, 557 (1938); W. R. Meagher and W. Z. Hassid, *J. Amer. Chem. Soc.* **68**, 2135 (1946); O. Reithel, *J. Amer. Chem. Soc.* **67**, 1056 (1945); M. Touster and A. R. Reynolds, *J. Biol. Chem.* **153**, 571 (1944); F. Lipmann and L. C. Tuttle, *Ibid.* **153**, 571 (1944).

[6] T. Posternak, *J. Amer. Chem. Soc.* **72**, 4824 (1950); *J. Biol. Chem.* **180**, 1269 (1949); O. Zervas, *Naturwiss.* **27**, 317 (1939); O. Reithel, *J. Amer. Chem. Soc.* **67**, 1056 (1945); G. M. Tener, R. S. Wright and H. G. Khorana, *J. Amer. Chem. Soc.* **78**, 506 (1956); R S. Wright and H. G. Khorana, *Ibid.* **77**, 3423 (1955); **78**, 811 (1956).

[7a] T. Knunyants, *Dokl. Akad. Nauk SSSR* **55**, 223 (1947); *Zh. Obshch. Khim.* **19**, 95 (1949). [7b] W. E. Harvey, A. M. Michalski and A. R. Todd, *J. Chem. Soc.* 2271 (1951). cf. G. P. Lampson and H. A. Lardy, *J. Biol. Chem.* **181**, 693 (1949).

terminal mesyloxy* residues[8] and since this work began Taylor *et al.*[9] have reported some similar experiments. The few recorded attempts to introduce secondary fluorine atoms by method *one* were unsuccessful.[10] As far as the authors are aware the action of potassium fluoride upon sugar halohydrins has not been examined, although silver fluoride has been used with varying success.[11] Silver diaryl phosphates have been reacted with sugar halides successfully on several occasions.[6] The action of diaryl phosphoric acids upon epoxides has also been described,[7b] but no investigation of the action of acid fluorides upon sugar epoxides has been reported.

Whilst we successfully synthesized several primary fluoro-sugars, including some previously known 6-deoxy-6-fluoro glucose[8] and galactose[9] derivatives, by method *one*, when we treated methyl-6-O-tosyl-α-D-glucoside with excess potassium fluoride in methanol we obtained material free from sulphur and fluorine; this was shown by its properties and by comparison with authentic material to be methyl-3,6-anhydro-α-D-glucoside (I). Likewise when methyl-2,3-di-O-mesyl-4,6-O-benzylidene-α-D-glucoside (II) was treated at 200° with potassium fluoride in ethylene glycol, some methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III) was obtained from the reaction mixture, together with unchanged starting material. In addition some loss of protecting groups occurred, as was indicated by the production of benzaldehyde and a little material which analysed correctly for a monofluoro methyl-α-D-hexoside. When potassium fluoride acted upon methyl-2,3-di-O-tosyl-4,6-O-benzylidene-α-D-glucoside (IV) and methyl-3-O-mesyl-4,6-O-benzylidene-α-D-glucoside (V) under similar conditions the epoxide (III) was in each case identified amongst the products. In contrast, the treatment of 1,2;5,6-di-O-isopropylidene-3-O-tosyl-D-glucofuranose with potassium fluoride, and of 1,2,3,6-tetra-O-acetyl-4-O-mesyl-β-D-glucose[13] with either potassium fluoride or sodium iodide under such severe conditions gave unsaturated materials, the structure of which will form the subject of a separate communication.

The replacement of other halogens by fluorine and by the diaryl phosphate group has been readily accomplished using the potassium[4] and silver[5,6] salts respectively. We have investigated the action of these reagents upon some sugar halohydrins. Whilst silver fluoride reacted anomalously with several primary halo-sugars,[14] we obtained a low yield of 1,2;3,4-di-O-isopropylidene-6-deoxy-6-fluoro-D-galactose (VI),[9] from the 6-deoxy-6-iodo derivative (VII),[15] by treatment with potassium fluoride. No action was observed when sodium fluoride was used. The solubility of the reagents in the solvent used may be a factor here.[16]

When, however, the following compounds were treated with potassium fluoride,

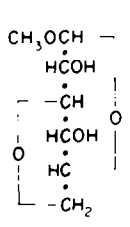
* Mesyl and tosyl are used here as abbreviations for methanesulphonyl and *p*-toluenesulphonyl respectively.

[8] B. Helferich and A. Gnütchel, *Ber. Dtsch. Chem. Ges.* **74**, 1035 (1941); B. Helferich and N. Vock, *Ibid.* **74**, 1807 (1941).
[9] N. F. Taylor and P. W. Kent, *J. Chem. Soc.* 872 (1958).
[10] B. Helferich and M. Vock *Ber. Dtsch. Chem. Ges.* **74**, 1807 (1941); F. H. Newth and L. F. Wiggins, *J. Chem. Soc.* 1734 (1950); P. W. Kent, O. Farmer and N. F. Taylor, *Proc. Chem. Soc.* 187 (1959).
[11] K. Brauns, *J. Amer. Chem. Soc.* **45**, 833 (1923); B. Helferich and E. Himmen, *Ber. Dtsch. Chem. Ges.* **61**, 1825 (1928); K. Hess, O. Littmann and R. Pfleger *Liebigs Ann.* **507**, 55 (1933); B. Helferich and R. Gootz, *Ber. Dtsch. Chem. Ges.* **62**, 2505 (1929);
[12] K. Freudenberg and B. Iver, *Ber. Dtsch. Chem. Ges.* **55**, 929 (1922).
[13] B. Helferich and A. Gnütchel, *Ber. Dtsch. Chem. Ges.* **74**, 1035 (1941).
[14] cf. B. Helferich and E. Himmen, *Ber. Dtsch. Chem. Ges.* **61**, 1825 (1928); K. Hess, O. Littmann and R. Pfleger, *Liebigs Ann.* **507**, 55 (1933).
[15] A. L. Raymond, *J. Amer. Chem. Soc.* **70**, 2785 (1948); K. Freudenberg, *Ber. Dtsch. Chem. Ges.* **59**, 100 (1926).
[16] cf. E. D. Bergmann and T. Blank, *J. Chem. Soc.* 3786 (1953).

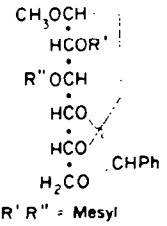
oxides were obtained in every case. *trans*-2-Iodocyclohexanol (VIII), ethylene chlorhydrin (IX), 4-bromobutan-1-ol (X), methyl-6-deoxy-6-iodo-α-D-glucoside (XI), methyl-2-bromo-2-deoxy-4,6-O-benzylidene-α-D-altroside (XII), and methyl-3-bromo-3-deoxy-4,6-O-benzylidene-α-D-altroside (XIII), were treated in this manner, respectively giving, in varying yield, cyclohexeneoxide (XIV), ethylene oxide (XV), tetramethyleneoxide (XVI), methyl-3,6-anhydro-α-D-glucoside (I), methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III), and methyl-2,3-anhydro-4,6-O-benzylidene-α-D-mannoside (XVII).

Similarly silver diphenylphosphate rapidly reacted with the compounds (VIII), (X), and (XI). The corresponding oxides (XIV), (XVI) and (I) were identified amongst the products. Silver phosphate and silver dibenzyl phosphate both gave some methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III) when heated with compound (XII), whilst silver phosphate in boiling acetonitrile converted compound (XI) into the oxide (I).

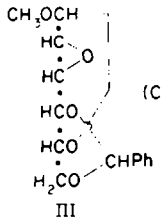
Overend *et al.*[1] have shown recently that 3,6-anhydro sugars are produced by the action of silver diphenylphosphate upon some methyl-6-deoxy-6-iodo-glycosides. They further noted that acetylation of the free hydroxyl groups was sufficient to prevent reaction. We have confirmed these observations when attempting to prepare some phosphate esters by similar reactions. Thus silver iodide is rapidly set free in the reaction of methyl-6-deoxy-6-iodo-α-D-glucoside with silver phosphate, silver diphenyl



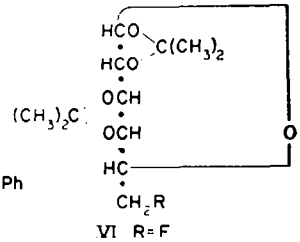
I



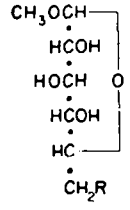
II R' R" = Mesyl
IV R' R" = Tosyl
V R' = H; R" = Mesyl



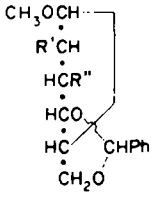
III



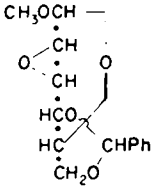
VI R = F
VII R = I



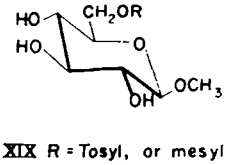
XI R = I



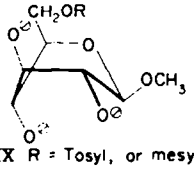
XII R' = Br; R" = OH
XIII R' = OH; R" = Br



XVII



XIX R = Tosyl, or mesyl or I



XX R = Tosyl, or mesyl or I

phosphate, or silver dibenzyl phosphate, but the only sugar derivative isolated was methyl-3,6-anhydro-α-D-glucoside (I).

The strong tendency for hydrogen-bond formation shown by fluoride ions[17a] (leading to the alkaline reaction of solutions of alkali metal fluorides) and the low nucleophilic character of these ions[17b] are probably important factors influencing the course of those reactions above which involve potassium fluoride. Both factors will favour competition by suitable ions when these are present in the media. Thus competition is considerable in alcoholic solvents, alkoxy ions giving ethers[18] and in the cases cited above the alkaline nature of the medium coupled with the suitable situation sterically of the hydroxyl group involved, favours ionization of and competition by this internal alkoxy group to the more or less complete exclusion of attack by the fluoride ion. Although initial formation of a fluoro compound followed by elimination of the elements of hydrogen fluoride is not excluded, and the literature reports concerning the stability of mono-fluoro compounds are conflicting,[19] we consider this unlikely, since a preliminary examination of some fluoro-sugars (e.g. methyl-6-deoxy-6-fluoro-D-galactosides) indicates that these require more severe conditions for conversion to anhydro sugars than the other halo sugars. The fluoro sugars are comparatively stable in the conditions of our experiments.

Further it is likely that formation of such a fluoro-compound would proceed with inversion. The *cis* fluorohydrins thus produced from the secondary halides would form epoxides only with difficulty. (cf. ref.[21])

The 1,2-*trans* arrangement of hydroxy and halo (or sulphonyloxy) groups is always favorable to epoxide formation,[20] and the *trans* diaxial arrangement found e.g. in compounds (XII) and (XIII) is particularly so.[21] Thus attempts to block the hydroxyl groups in these compounds by methylation resulted in dehydrobromination.[22]

We have attempted to prepare the *trans* fluorohydrins corresponding to compounds (XII) and (XIII) for a further investigation of this point, by the action of metal hydrogen fluorides, amine hydrogen fluorides, and hydrogen fluoride upon the epoxides (III) and (XVII). In one particular experiment hydrogen fluoride was reacted with methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III). Three fluorine containing fractions, and methyl-2,3-anhydro-α-D-alloside (XVIII) were among the products of this reaction but so far we have not proved conclusively the structure of any of our fluoro compounds.

The alkaline nature of the reagent is probably important in the action of potassium fluoride upon the 6-substituted methyl-glycosides. In neutral solution the stable conformation of these compounds will be as shown, (XIX),[23] and normal replacements

[17a] cf. P. H Groggins, *Unit Processes in Org. Synthesis* p. 182. McGraw-Hill, New York (1952); [b] cf. C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.* **73**, 141 (1953).

[18] cf. P. W. Kent, O. Farmer and N. F Taylor, *Proc. Chem. Soc.* 187 (1959).

[19] E.g. W. Hickinbottom, *Reactions of Organic Compounds* p. 525. Longmans, Green, London (1957); P. H. Groggins *Unit Processes in Organic Synthesis* p. 180. McGraw-Hill, New York (1952); A. L. Henne and J. B. Hinkamp, *J. Amer. Chem. Soc.* **67**, 1195 (1945); A. L. Henne, *Organic Reactions* **2**, 49 (1948); J. C. Bacon, C. W. Bradley, E. I. Hoegberg, P. Tarrant and J. T. Cassaday, *J. Amer. Chem. Soc.* **70**, 2653 (1948); F. W. Hoffmann, *J. Amer. Chem. Soc.* **70**, 2596 (1948); I. Knunyants, *Dokl. Akad. Nauk SSSR* **55**, 223 (1947).

[20] See for example, C. K. Ingold, *Structure and Mechanism in Organic Chemistry*. Cornell Univ. Press, New York (1953).

[21] E.g. D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 67 (1956).

[22] cf. The ready methylation of methyl-3-bromo-3-deoxy-4-,6-O-benzylidene-α-D-glucoside, F. H. Newth, W. G. Overend and L. F. Wiggins, *J. Chem. Soc.* 10 (1947).

[23] C. Reeves, *J. Amer. Chem. Soc.* **72**, 1499 (1950); *Adv. in Carbohydrate Chem.* **6**, 108 (1951); J. T. Edwards *Chem. & Ind.* 1102 (1955).

occur[24] in neutral solution but in alkaline medium ionization of the hydroxyl groups is favoured, and this will tend to stabilize the form showing widest charge separation (*viz.* XX).[25]* Attack by fluoride ion is strongly hindered in this form; oxide formation is strongly favoured.

The results obtained with silver diphenyl phosphate again probably reflect the low nucleophilic character of the anion. Furthermore hydrolysis of phosphate triesters having a *vicinal* hydroxyl group in their structure usually involves cyclic esters rather than oxide formation,[2] which suggests that initial formation of a diphenyl phosphate, followed by oxide production, is unlikely, particularly since such a replacement would almost certainly give partial inversion; the resultant *cis* diol would be highly favourable to cyclic ester formation. Against this, formation of a cyclic ester from a diol having a fixed *trans* diaxial arrangement would be difficult. Some evidence for this was obtained in a preliminary examination of the dibenzyl phosphates produced by the action of dibenzyl phosphoric acid upon the epoxide (III),[26] when we noted the regeneration of some parent oxide upon alkaline treatment. Difficulties in purification of these dibenzyl phosphates have hindered a closer examination of the reaction, but support for the observation was given when a re-examination of the hydrolysis of dibenzyl *trans*-2-hydroxy-cyclohexyl phosphate[27] indicated that some cyclohexene oxide is formed. In this case the ring system is less rigid and cyclic ester formation consequently more facile.

In the case of the 6-iodo-6-deoxy glycosides there is little doubt that the C3 hydroxyl group plays an important part in directing the *initial* replacement reaction, since blocking this group by acetylation drastically lowers the rate. We consider it unlikely therefore that a phosphate ester forms initially in any of these reactions. The possibility remains that small amounts of silver oxide in the silver phosphate used may cause oxide formation, since it is known to do this; the amounts present, if any, would be insufficient to account for the observed yield however.

It is clear from these experiments that for replacements of this type, involving anions of low nucleophilic character, choice of solvents and reagents is critical if side reactions are to be avoided.

EXPERIMENTAL†

The experimental details given here concern the isolation of the oxide only in most cases. The identity of other products, isolated generally in modified conditions, will be dealt with elsewhere.‡ Yields of oxide are minimal in some cases owing to difficulties in isolation.

The Action of Potassium Fluoride upon Sulphonyloxy Derivatives

(1) *Methyl-6-O-tosyl-α-D-glucoside*[28]

(a) Methyl-6-O-tosyl-α-D-glucoside (0·05 g) and anhydrous potassium fluoride (3·0 g) in methanol (40 ml) were heated at 60° for 10 hr. The mixture was cooled and filtered and the filtrate evaporated

* N.B. Although XX is represented as fully ionized this is unlikely in the mild conditions used. With one of the three hydroxyls ionized, repulsions between this ion and the *p*-electrons of the remaining oxygens will partially stabilize the boat form here represented.

† M.p's. uncorrected.

‡ In preparation

[24] E.g. G. R. Barker and R. W. Goodrich, *J. Chem. Soc.* S 233 (1949); A. L. Raymond, and E. F. Schroeder, U.S. Pat, 2,365,776 (Dec. 26, 1944.); *Chem. Abstr.* **39**, 4434 (1944); *J. Amer. Chem. Soc.* **70**, 2785 (1948); A. B. Foster, W. G. Overend, M. Stacey and L. F. Wiggins, *J. Chem. Soc.*, 2542 (1949).

[25] cf. J. Speakman, *J. Chem. Soc.* 490 (1941), and refs. cited there; D. H. R. Barton, *Ibid.* 1197 (1945); D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 62, 80 (1956).*

[26] A. R. Todd and D. M. Hayes, *J. Chem. Soc.* 2271 (1951).

[27] D. M. Brown, R. Hall and H. F. Higson, *J. Chem. Soc.* 1360 (1958).

[28] J. Compton, *J. Amer. Chem. Soc.* **60**, 395 (1938).

under reduced press to dryness. The white residue was extracted with boiling acetone and the extracts were cooled and filtered. The solvent was removed at the pump and the syrupy residue was examined by chromatography upon paper (Whatman No. 1) eluted with n-butanol–ethanol–water (4:1:5, v/v) and developed with aniline hydrogen chloride in methanol at 100° for 3 min. It gave two spots with R_F 0·51 and 0·56; Authentic methyl-3,6-anhydro-α-D-glucoside[29] (I) gave a spot R_F 0·56 in these conditions. Crystallization from hot anhydrous ethyl acetate gave material which did not reduce Fehling's solution but which readily did so after brief treatment with hot aqueous acid. Recrystallization from ethyl acetate gave material free from fluorine and sulphur as needles, m.p. 100–104°, raised on admixture with methyl-3,6-anhydro-α-D-glucoside.[29]

(b) The above reaction was repeated using ethylene glycol as solvent. The product, isolated in the usual manner, was a syrup, $[\alpha]_D^{17}$ +50° (*c*, 0·37 in H_2O), containing neither sulphur or fluorine. The syrup reduced Fehling's solution after acid treatment, and gave a single spot R_F 0·57, developing at room temp, when chromatographed on Whatman No. 1 paper (eluted with n-butanol–ethanol–water, 4:1:5, v/v) followed by spraying with alcoholic *p*-nitro-aniline hydrochloride.

(2) *Methyl*-2,3-*di*-O-*mesyl*-4,6-O-*benzylidene*-α-D-*glucoside*[30] (II)

Methyl-2,3-di-O-mesyl-4,6-O-benzylidene-α-D-glucoside (5 g) and anhydrous potassium fluoride (5 g) in ethylene glycol (50 ml) were heated under reflux at 140–150° for 1 hr, then at 195–200° for a further 15 min. The mixture was cooled and filtered. The filtrate ("A"), was poured into water (500 ml) and the aqueous mixture was extracted with chloroform. The combined chloroformic extracts were dried over sodium sulphate and evaporated to dryness at the pump. Fractional crystallization of the residue gave a solid (0·19 g) m.p. 190–195°, raised on recrystallization from chloroform–petroleum ether (60–80°) to 197–198°, depressed on admixture with compound (II), undepressed on admixture with authentic methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III),[31] $[\alpha]_D^{16}$ +130° (*c*, 0·1 in $CHCl_3$). [Found: C, 61·3; H, 5·92. Calc. for $2C_{14}H_{16}O_5 \cdot H_2O$: C, 61·5; H, 6·27%]. The filtrate "A" was continuously extracted with ether for 36 hr, and the ether extract was evaporated to dryness and the residue recrystallized from ethanol to m.p. 179–180° (0·23 g). This compound contained fluorine,[32] was non-reducing, and had no aromatic peak in the ultra-violet absorption spectrum, and did not release benzaldehyde with hot aqueous acid; it did not contain sulphur, (Found: C, 36·4; H, 7·3; F, positive. $C_7H_{13}O_5F \cdot 2H_2O$ requires: C, 36·2; H, 7·3%).

The residue separated from filtrate "A" was recrystallized from ethanol, giving prisms m.p. 188–189°, undepressed on admixture with authentic starting material, (2·96 g).

(3) *Methyl*-2,3-*di*-O-*tosyl*-4,6-O-*benzylidene*-α-D-*glucoside* (IV)

Methyl-2,3-di-O-tosyl-4,6-O-benzylidene-α-D-glucoside (0·97 g) was treated as above. The chloroform extract gave methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside, (III),[31] m.p. 187–189°, undepressed on admixture with authentic material, depressed on admixture with compound (IV) (0·008 g).

(4) *Methyl*-3-O-*mesyl*-4,6-O-*benzylidene*-α-D-*glucoside* (V)[30]

Methyl-3-O-mesyl-4,6-O-benzylidene-α-D-glucoside (0·7 g) was treated as above. Recrystallization of the chloroformic extract gave methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside, m.p. and m.p. mixed with an authentic sample, 197–198°, (0·09 g). This material showed absorption peaks in the infra-red at 745, 880, 895, 970, 978, 1012, 1046, 1073, 1150, and 1230 cm^{-1}.

The Action of Potassium Fluoride upon Halogen Compounds

(1) 1,2;3,4-*Di*-O-*isopropylidene*-6-*deoxy*-6-*iodo*-D-*galactose* (VI)

1,2;3,4-di-O-isopropylidene-6-deoxy-6-iodo-D-galactose (0·631 g) m.p. 67–69°, $[\alpha]_D^{18}$ −54·6° (*c*, 0·6239 in $CHCl_3$), in acetamide (5 ml) containing potassium fluoride (1·8 g) was heated under reflux for 96 hr. The cooled solution was poured into water (100 ml) and the aqueous mixture was extracted with chloroform (5 × 50 ml). The iodide present was determined, and corresponded to approximately 95% replacement. The chloroformic extract was dried and reduced to a syrup at the

[29] W. N. Haworth, L. N. Owen and F. Smith, *J. Chem. Soc.* 88 (1941).
[30] J. Honeyman, *J. Chem. Soc.* 3660 (1955).
[31] C. S. Richtmeyer and N. K. Hudson, *J. Amer. Chem. Soc.*, **63**, 1727 (1941).
[32] R. Belcher and T. S. West, *J. Chem. Soc.* 3577 (1959).

pump. Passage through a silica column gave an oil (0·1 g) which contained fluorine but not iodine, and which showed a strong peak in its infra-red absorption spectrum at 1050 cm^{-1} (C—F stretching?) with subsidiary peaks at 1010, 1027, 1110, and 1155 cm^{-1}, $n_{daylight}^{16}$ 1·4467, $[\alpha]_D^{18}$ −56° (*c*, 0·973 in $CHCl_3$). [Taylor *et al.*[9] record n_D^{20} 1·4475, $[\alpha]_D^{20}$ −51·4° (*c*, 1·284 in $CHCl_3$) for 1,2;3,4-di-O-isopropylidene-6-deoxy-6-fluoro-D-galactose].

(2) *trans-2-Iodocyclohexanol* (VIII)[35]

(a) This compound, (4·8 g, m.p. 38–40°), and potassium fluoride (8 g) in methanol (50 ml) were heated at 80° for 30 min. The mixture was cooled and filtered and methanol was removed from the filtrate at the pump. Petroleum ether was added (20 ml) and the mixture cooled at 5–10° for 3 hr. A small amount of *trans*-2-iodocyclohexanol (VIII) separated. The solution was filtered and petrol ether was removed from the filtrate at the pump leaving an oil which contained traces of iodine but no fluorine; A portion of this oil (1·5 g) was steam distilled and the oily distillate was refluxed with aqueous methanol (15 ml) containing three drops of conc hydrochloric acid for 15 min. Periodate titration of the resulting material[36a] indicated an approximate yield of cyclohexandiol of 15%. Thiosulphate titration[36b] of the oil indicated a slightly lower value for cyclohexene oxide (ca. 13%).

(3) *Ethylene chlorhydrin*

Commercial ethylene chlorhydrin (20 ml) and potassium fluoride (20 g) were warmed gently together under a current of nitrogen with vigorous stirring; A colourless gas was evolved which condensed in a receiver cooled to −15° to a colourless liquid which evaporated rapidly at approximately 10°. A solution of this gas in water containing a trace of hydrochloric acid was set aside for 48 hr. The solution was then treated with sodium periodate and the formaldehyde produced was removed in a stream of carbon dioxide and isolated as its dimedone derivative, m.p. 188–190°, (lit. m.p. 188–190°) and as its 2,4-dinitrophenylhydrazone m.p. 163–165° (lit. m.p. 168°).

(4) *4-Bromobutanol*

4-Bromobutanol (15 ml) and potassium fluoride (18 g) in ethylene glycol (30 ml) was heated to reflux, and a fraction boiling at 65–72°, which condensed as a colourless liquid with a characteristic odour, was distilled slowly from the mixture. This redistilled at 66–69°. This liquid showed peaks in the infra-red absorption spectrum at 915, 1030, 1070, 1175, and 1360 cm^{-1} identical with authentic tetrahydrofuran.

(5) *Methyl-2-bromo-2-deoxy-4,6-O-benzylidene-α-D-altroside*[37] (XII)

Methyl-2-bromo-2-deoxy-4,6-O-benzylidene-α-D-altroside,[37] (0·35 g) m.p. 116–118°, $[\alpha]_D^{16}$ + 49° (*c*, 0·250 in $CHCl_3$) and anhydrous potassium fluoride (2 g) in dry methanol (70 ml) were heated under reflux for 10·5 hr. The cooled mixture was evaporated to dryness at the pump, and water (15 ml) was added to the residue. The aqueous mixture was extracted with chloroform (4 × 10 ml) and the extracts dried over sodium sulphate. The dried extracts were evaporated at the pump, and the white residue was recrystallized from chloroform–petroleum ether giving white feathery needles, m.p. 200°, $[\alpha]_D^{17}$ +127° (*c*, 0·2 in $CHCl_3$). This showed peaks in its infra-red absorption spectrum at 695, 705, 720, 745, 880, 899, 970, 978, 1012, 1046, 1073, and 1150 cm^{-1} (Found: C, 63·8; H, 6·27. Calc. for $C_{14}H_{16}O_5$; C, 63·6; H, 6·06%).

(6) *Methyl-3-bromo-3-deoxy-4,6-O-benzylidene-α-D-altroside* (XIII)[37]

Methyl-3-bromo-3-deoxy-4,6-O-benzylidene-α-D-altroside,[37] (0·083 g) m.p. 120–123°, $[\alpha]_D^{17}$ +127° (*c*, 0·49 in $CHCl_3$) in dry methanol (20 ml) containing potassium fluoride (1 g) was heated under reflux for 12 hr. The solvent was removed at the pump and the residue shaken with chloroform (8 ml) and

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[34] A. L. Raymond, *J. Amer. Chem. Soc.* **70**, 2785 (1948).
[35] W. J. Hickinbottom, *Reactions of Organic Compounds* p. 27. Longmans, Green, London (1948); L. Brunel, *Ann. Chim.* 1905, (vii), **6**, 219. (1905).
[36] [a] D. Gottlieb, C. G. Caldwell, and R. H. Hixon, *J. Amer. Chem. Soc.* **62**, 3342 (1940); N. F. Taylor, *Ibid.* **75**, 3912 (1953); R. L. Whistler and J. L. Hickson, *Ibid.* **76**, 1671 (1954).
[b] W. C. J. Ross, *J. Chem. Soc.* 2257 (1950).
[37] G. O. Richards and L. F. Wiggins, *J. Chem. Soc.* 2442 (1953).

water (20 ml). The chloroform layer was separated and the aqueous layer was re-extracted with chloroform (4 × 8 ml). The combined chloroformic extracts were dried over sodium sulphate and evaporated at the pump. The solid residue was recrystallized from chloroform–pet ether giving long colourless needles, m.p. 140–141°, raised on admixture with authentic methyl-2,3-anhydro-4,6-O-benzylidene-α-D-mannoside,[38] $[\alpha]_D$ +110° (*c*, 0·95 in $CHCl_3$). (Found: C, 62·3; H, 5·93. Calc. for $2C_{14}H_{16}O_5 \cdot H_2O$: C, 61·5; H, 6·27. Calc. for $C_{14}H_{16}O_5$: C, 63·6; H, 6·06%].

(7) *Methyl-6-deoxy-6-iodo-α-D-glucoside* (XI)[39]

Methyl-6-deoxy-6-iodo-α-D-glucoside,[39] m.p. 137–139°, (0·5 g) was heated under reflux in dry methanol containing anhydrous potassium fluoride (2 g) for 10 hr. The mixture was cooled and the solvent removed at the pump. The solid residue was extracted with several lots of boiling anhydrous acetone (5 × 10 ml). Examination of the combined extracts by paper chromatography upon Whatman No. 1 paper eluted with butan-1-ol–ethanol–water (4:1:5) indicated the presence of three compounds; (a) Starting material, R_F 0·14 (developed with methanolic aniline hydrogen chloride), (b) methyl-3,6-anhydro-α-D-glucoside (I), R_F 0·56 developed as (a) and (c), not identified, R_F 0·85, (fluoresced in ultra-violet light). The extracts were evaporated at the pump to a syrup from which methyl-3,6-anhydro-α-D-glucoside (I) was obtained with difficulty as cubes, m.p. 105–106°, undepressed on admixture with authentic material (0·016 g).

The Action of Silver Diphenyl Phosphate upon Halohydrins

(1) trans-2- *Iodocyclohexanol*

trans-2-Iodocyclohexanol (3·5 g) and silver diphenyl phosphate (4 g)[40] in methanol (40 ml) were refluxed for 1·5 hr. The cooled mixture was filtered and the filtrate was steam distilled rapidly. The first 50 ml of distillate was acidified with conc hydrochloric acid (4 drops) and refluxed for 1 hr. Titration with periodate[36a] indicated approx 20% conversion to the epoxide.

(2) 4-*Bromobutan*-1-ol

This compound (15 ml) was heated under reflux with silver diphenyl phosphate (4 g) in ethane diol and a fraction boiling at 60–70° was collected. This fraction was dried over sodium sulphate. Comparison of the infra-red absorption spectra of this compound and tetrahydrofuran confirmed its identity.

(3) *Methyl-6-deoxy-6-iodo-α-D-glucoside*

This compound (1·07 g) in toluene (15 ml) containing silver diphenyl phosphate (0·9 g) was heated under reflux in darkness for 24 hr. The solution was filtered and the filtrate was quickly washed with aqueous sodium hydrogen carbonate (10 ml) and water (15 ml), dried over sodium-sulphate and the solvent removed at the pump. The syrupy residue was examined by chromatography on Whatman No. 1 paper, eluted with butan-1-ol–ethanol–water (4:1:5), developed by spraying with methanolic aniline hydrogen chloride. Methyl-3,6-anhydro-α-D-glucoside (R_F 0·57) was present. The syrup gave a small amount of solid, m.p. 97–100°, on treatment with ethanol and ethyl acetate, recrystallized from ethyl acetate, m.p. 101–103°, raised on admixture with authentic methyl-3,6-anhydro-α-D-glucoside (I).

The Action of Silver Phosphate upon Halohydrins

(1) *Methyl-6-deoxy-6-iodo-α-D-glucoside* (XI)

This compound (0·3 g) and silver phosphate (0·25 g) in acetonitrile (5 ml) were heated under reflux for 6 hr. The cooled mixture was filtered and the filtrate was evaporated to dryness at the pump. The syrupy residue was dissolved in chloroform (10 ml) washed with water (5 ml), and dried over sodium sulphate and filtered through charcoal. The presence of methyl-3,6-anhydro-α-D-glucoside (I) was confirmed chromatographically as in the previous experiment. Attempts to crystallize the syrupy residue were unsuccessful, $[\alpha]_D^{16\cdot5}$ +45° (*c*, 0·66 in H_2O).

[38] G. J. Robertson and C. F. Griffith, *J. Chem. Soc.* 1193 (1935).
[39] M. Zief and R. C. Hockett, *J. Amer. Chem. Soc.* **67**, 1267 (1945); A. L. Raymond, U.S. Pat. 2,365,776 (Dec. 26, 1944). *Chem. Abstr.* **39**, 14434[5]
[40] T. Posternak, *J. Biol. Chem.* **180**, 1269 (1949).

(2) *Methyl-2-bromo-2-deoxy-4,6-O-benzylidene-α-D-altroside* (XII)

This compound (0·4 g) and silver phosphate (0·38 g) in acetonitrile (10 ml) were heated under reflux for 15 hr. The cooled solution was filtered and the solvent removed at the pump. The syrupy residue was dissolved in chloroform (25 ml) and the chloroform solution was washed with water (20 ml). The chloroform solution was dried and reduced to small volume (10 ml) at the pump. Petroleum ether (15 ml) was added and the mixture set aside at room temp for 24 hr. As no crystals separated the solution was allowed to evaporate slowly at room temp for several days. Methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside separated as long needles m.p. 190–192°, raised an admixture with authentic material, $[\alpha]_D$ +100° (*c*, 0·7 in $CHCl_3$), showing peaks in its infra-red absorption spectrum at 745, 880, 899, 970, 978, 1012, 1045, 1070, 1150, and 1230 $cm.^{-1}$

The action of silver dibenzyl phosphate upon methyl-2-bromo-2-deoxy-4,6-O-benzylidene-α-D-altroside (XII)

Methyl-2-bromo-2-deoxy-4,6-O-benzylidene-α-D-altroside (XII) (0·15 g) and silver diphenyl phosphate[41] (0·15 g) in benzene (5 ml) and toluene (5 ml) were heated under reflux for 6·3 hr. The solution was cooled and filtered, and the filtrate was washed with aqueous sodium hydrogen carbonate (10 ml) and water (5 ml), and the solvent was removed under reduced press. The syrupy residue was passed through a short charcoal column and a syrup was obtained which was induced to crystallize only with difficulty. Methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (10 mg) was obtained as needles, m.p. 188–190°, undepressed on admixture with authentic material, $[\alpha]_D^{16}$ +125° (*c*, 0·04 in $CHCl_3$), infra-red spectrum identical.

The Alkaline Hydrolysis of Some Diaryl Hydroxyalkyl-Phosphates

(1) *Dibenzyl methyl-4,6-O-benzylidene-α-D-hexoside phosphate*[26]

Attempts to purify the dibenzyl phosphate produced by the method of Todd *et al.*[26] led always to partial decomposition of the ester. The following experiment was carried out using the crude syrupy ester, $[\alpha]_D^{16}$ +54° (Todd *et al.* report no constants.)[26]

The crude ester (1·3 g) in t-butanol (25 ml) containing sodium (0·8 g) was heated under reflux for 50 min. Carbon dioxide was passed through the cooled solution, and the solvent was removed at the pump. The semi solid residue was extracted with several lots of hot chloroform and the combined extracts were washed with water and dried over sodium sulphate. The solvent was removed at the pump and the syrupy residue was triturated with pet ether. The semi solid mass was crystallized from chloroform–pet ether, and after several recrystallizations crude methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III) was obtained (38 mg) m.p. 175–180°. Recrystallization from chloroform–benzene–petroleum ether gave needles, m.p. 185–187°, raised on admixture with authentic material, $[\alpha]_D^{17}$ +108° (*c*, 0·08 in $CHCl_3$).

(2) *Dibenzyl* trans-2-*hydroxycyclohexyl phosphate*[27]

This compound (m.p. 77–78°; 1·8 g) in t-butanol (20 ml) containing sodium (0·6 g) was heated under reflux for 0·5 hr. The solution was steam distilled and the first fraction of the distillate (50 ml) was collected. Ethanol was added to bring the volume up to 75 ml and aliquots of the solution were treated with dil sulphuric acid under reflux and then titrated with periodate.[26a] Separate aliquots were titrated with sodium thiosulphate.[26b] Cyclohexene oxide (4% ± 2%) was produced.

Attempted synthesis of some trans-*fluorohydrins from epoxides*

In a series of experiments potassium hydrogen fluoride, tributylamine di(hydrogen fluoride), and diisopropylamine hydrogen fluoride were heated under reflux with the oxides (III) and (XVII) in inert solvents. In most cases starting material was recovered unchanged.

Action of hydrogen fluoride upon methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside

In a further series of experiments hydrogen fluoride was reacted with (III). No appreciable reaction occurred below 40–50°.

[41] W. C. Lossen and A. Kohler, *Liebigs Ann.* **262**, 212 (1891).

Methyl-2,3-anhydro-4,6-O-benzylidene-α-D-alloside (III) (1·2 g) in anhydrous acetylacetone (120 ml) containing 20 N hydrofluoric acid (3 ml) was kept at 40–50° for 5 days. Excess acid was then removed with calcium carbonate and the mixture was filtered. The residue was washed with acetone and the combined filtrate and washings were evaporated to dryness under reduced press. The syrupy residue was triturated with pet ether and the syrup which remained was passed through a column of silica gel. Successive elution with chloroform–pet ether (80–100°) (1:5, 2:5, 3:5) followed by chloroform–ethanol mixtures gave four main fractions.

Fraction one, colourless syrup, contained fluorine, showed peaks in the ultra-violet spectrum with λ_{max}^{EtOH} 2600 Å, and absorption peaks in the infra-red at 1050 (s), 835, 900, 1033, 1075, 1105, 1135, and 1190 cm^{-1} $[\alpha]_D^{17}$ +51° in ($CHCl_3$).

Fraction two, syrup, contained fluorine, showed absorption peaks at 2600 Å (ultra-violet) and 1055 (s), 895, 965, 1025, 1045, 1070, 1100, and 1133 cm^{-1} (infra-red), released benzaldehyde on treatment with dil aqueous acid, $[\alpha]_D^{17}$ +40° (in $CHCl_3$).

Fraction three, did not contain fluorine or release benzaldehyde on treatment with aqueous acid, showed no peak in the ultra-violet above 2200 Å, but showed peaks in the infra-red at 745, 835, 892, 905, 960, 980, 1075, and 1100 cm^{-1} with associated minor peaks at 715, 790, 1025, 1035, 1045, and 1055 cm^{-1}: m.p. 107–109°, $[\alpha]_D^{16}$ +151° in methanol. (Robertson[42] reports m.p. 105–107°, $[\alpha]_D^{18}$ +153° in methanol for methyl-2,3-anhydro-α-D-alloside.)

The identity of these fractions, and of some similar materials from the anhydro-mannoside, (XVII), are under investigation.

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[42] G. J. Robertson, *J. Chem. Soc. Chem.* 472 (1938).