

580. *The Reactivity of the O-Acylglycosyl Halides. Part II.\**  
*The Effect of the Lactol Ring Oxygen Atom.*

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The reactivity of the halogen in the *O*-acylglycosyl 1-halides is due to its being part of an  $\alpha$ -halogeno-ether system. A comparison with 2 : 3-dichloro-tetrahydropyran has been made, and further comparison with 2 : 3-dichloro-thiacyclohexane establishes that the hetero-atom is responsible for the ease of unimolecular solvolysis of the C<sub>(1)</sub>-Hal bond. When the halogen is elsewhere in the molecule (C<sub>(2)</sub> or C<sub>(3)</sub>), solvolysis cannot be detected. The first-order solvolysis of *cyclohexyl* bromide has been examined.

It has been pointed out that the high reactivity of the halogen atom in the *O*-acylglycosyl 1-halides is typical of that displayed by  $\alpha$ -halogeno-ethers (Pigman and Goepf, "Chemistry of the Carbohydrates," Academic Press Inc., N.Y., 1948, p. 160; Hurd and Holysz, *J. Amer. Chem. Soc.*, 1950, **72**, 2005). The exceptional reactivity of the chloromethyl ethers was discussed by Cocker, Lapworth, and Walton (*J.*, 1930, 440), and Hughes and Ingold (*J.*, 1935, 244) predicted that the reactions of such compounds would belong to the S<sub>N</sub>1 class. The inductive polarization of the C-Cl bond will be increased by an electromeric release of electrons from the oxygen atom, and the effect of electron accession to the centre of reaction in a nucleophilic substitution is to promote a unimolecular rather than a bimolecular mechanism. In Part I\* it was shown that solvolysis of tetra-*O*-acetyl- $\alpha$ -D-glucosyl 1-bromide is unimolecular. The present work is concerned with an assessment, by a quantitative examination of analogous compounds, of the extent to which the lactol ring oxygen atom promotes C-Hal bond fission.

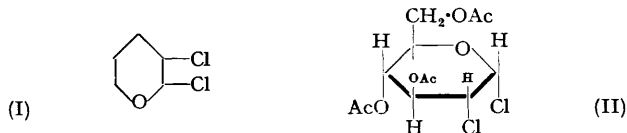
An unsuccessful attempt was made by Clarke (*J.*, 1910, 417) to follow the reaction of chloromethyl methyl ether with alcoholic pyridine, but Conant, Kirner, and Hussey (*J. Amer. Chem. Soc.*, 1925, **47**, 497) were able to measure the rate of reaction with sodium iodide in acetone. Acid catalysis was found (Böhme, *Ber.*, 1941, **74**, 248), and Leimu and Salomaa (*Acta Chem. Scand.*, 1947, **1**, 353), who examined the solvolysis of the 1-chloromethyl ethers, noticed acid catalysis in the apparently unimolecular reaction.

Although it is considered that the same electron transfers operate in the *O*-acylglycosyl

\* Part I, preceding paper.

1-halides as in the 1-chloroalkyl ethers, comparison between cyclic and acyclic structures is not entirely satisfactory. For this reason, a 2-halogenotetrahydropyran was examined. The reactions of 2 : 3-dihydro-4*H*-pyran with halogens and hydrogen halides have been well studied (Jones and Taylor, *Quart. Reviews*, 1950, **4**, 195) : the dihalides undergo alcoholysis and dehydrohalogenation very readily, to give the 2-alkoxy-3-halogenotetrahydropyran and 5 : 6-dihydro-3-halogeno-4*H*-pyran respectively. The 2-halides, although too unstable to be isolated (Paul, *Compt. rend.*, 1944, **218**, 122), give the 2-alkoxy-derivatives.

2 : 3-Dichlorotetrahydropyran (I), obtained by chlorination of dihydropyran, decomposed when kept, and even when freshly prepared contained hydrogen chloride. The methanolysis of a freshly prepared sample followed the first-order rate law and was not catalysed by the liberated acid. The rate-constant is compared in Table I with that for the methanolysis of 3 : 4 : 6-tri-*O*-acetyl-2-chloro-2-deoxy- $\alpha$ -D-glucosyl 1-chloride \* (II) and has a value more than 800—1000 times as great as that for the glucose derivative (II) and tetra-*O*-acetyl- $\alpha$ -glucosyl 1-bromide. The product from methanolysis of 2 : 3-dichlorotetrahydropyran contained, in addition to 3-chlorotetrahydro-2-methoxyppyran, 3-chloro-5 : 6-dihydro-4*H*-pyran (11.4%), showing that elimination and substitution were occurring simultaneously. Hydrolysis of the dichloride in 80% aqueous acetone is also very rapid,  $10^5 k^{21.2}$  being 177 (sec.<sup>-1</sup>) compared with 0.50 (sec.<sup>-1</sup>) for tetra-*O*-acetyl- $\alpha$ -D-glucosyl 1-bromide in the same medium, and the product was 3-chlorotetrahydro-2-hydroxyppyran. The unimolecular character of the solvolytic reactions of tetra-*O*-acetyl- $\alpha$ -D-glucosyl 1-bromide has been established (Part I) and it may be inferred that the corresponding reactions in the tetrahydropyran series are also unimolecular. In *trans*-(I) and *cis*-(II), there may be a small Winstein effect but this would be insufficient to explain such a large



difference in rate between the tetrahydropyran and the sugar derivative where the oxygen atom facilitates reaction at the  $\alpha$ -carbon atom. The much greater reactivity of the former must be attributed to the absence of large substituent groups in the molecule which can impede reaction at the  $\alpha$ -carbon atom in the latter. Such steric effects are discussed more fully in the following paper.

It is well known that the electromeric effect of sulphur is less than that of oxygen and, consequently, the reactivity of a 2-halogenothiacyclohexane would be expected to be less

TABLE I.  
*Comparison of the rate of methanolysis of 2 : 3-dichlorotetrahydropyran with that of several O-acetylglucosyl 1-halides.*

Compound	$10^5 k$ (sec. <sup>-1</sup> )	Temp.
2 : 3-Dichlorotetrahydropyran .....	644	21.2°
Tetra- <i>O</i> -acetyl- $\alpha$ -D-glucosyl 1-bromide .....	2.8	21.2
Tri- <i>O</i> -acetyl-2-chloro-2-deoxy- $\alpha$ -D-glucosyl 1-chloride .....	0.96	35
Tetra- <i>O</i> -acetyl- $\alpha$ -D-glucosyl 1-chloride .....	0.42	35

than that of the analogous tetrahydropyran. In the acyclic series, Böhme (*Ber.*, 1941, **74**, 248) compared the reactivities of alkyl 1-chloromethyl ethers and sulphides and found the first-order solvolysis of the sulphides to be much slower. In the present work, thiacyclohex-2-ene (III), prepared according to Naylor (*J.*, 1949, 2749), gave 2 : 3-dichlorothiacyclohexane (IV) by addition of chlorine. This dichloro-derivative was a distillable liquid which did not decompose with such rapidity as the tetrahydropyran derivative. In its reaction with methanol at 21.2°, the first-order constant decreased during the reaction, in a manner

\* The dichlorotetrahydropyran presumably has *trans*-halogen atoms, by normal double-bond addition, whereas in the 1 : 2-dichloroglucose it can be deduced that they are *cis*. The glucose configuration is present since treatment with ammonia gives *epiglucosamine* (3-amino-3-deoxyaltrose) which could not arise from a 2-chloro-2-deoxymannose derivative. The 1-halogen atom has the  $\alpha$ -configuration since with methanol a  $\beta$ -glycoside is formed (Fischer, Bergmann, and Schotte, *Ber.*, 1920, **53**, 509).

similar to, but more pronounced than, that observed by Böhme with the acyclic compounds (*loc. cit.*). A comparison with 2:3-dichlorotetrahydropyran is shown in Table 2, where it is seen that the reaction of the sulphur compound is much slower. This establishes that, in these compounds, the hetero-atom is largely responsible for the ease of nucleophilic displacement of the halogen by virtue of its ability to release electrons to the seat of substitution. Further support for this is found in the inertness of the halogen atom when it is not part of the  $\alpha$ -halogeno-ether system. Such sugar halides are much more resistant to solvolysis. Methyl 2-chloro-2-deoxy- $\beta$ -D-glucoside (V), its 3:4:6-triacetate, and methyl 3-chloro-3-deoxy- $\alpha$ -D-glucoside (VI) were each heated with methanol at 98° for 500 hr.: in no instance was any reaction detected and the compounds were recovered unchanged. It should be remembered that although this type of compound resists alcoholysis, the formation of an anhydro-ring occurs easily with alkaline reagents.

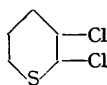
TABLE 2. *Methanolysis of 2:3-Dichlorotetrahydropyran (I) and 2:3-Dichlorothiacyclohexane (IV) at 21.2°. [Halide] = 0.05M.*

<i>t</i> (min.)	1	2	3	4	5	8	15	20	35	45	60
Reaction, %; (I)	37.5	56.6	70.6	79.6	86.9	95.5	—	—	—	—	—
Reaction, %; (IV)	14.9	—	—	25.3	—	30.1	37.5	42.9	52.0	57.4	66.0

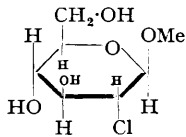
In the foregoing discussion, the influence of the lactol oxygen atom in the *O*-acylglycosyl 1-halides has been examined and it has been suggested that the substituent acyloxy-groups play an important part in the solvolytic reactions of these compounds. At this point it is convenient to make a comparison with *cyclohexyl* bromide. This molecule contains only the six-membered alicyclic ring and the secondary halogen atom, and the absence of the lactol oxygen atom and acyloxy-groups would be expected to have a considerable effect on reactivity. The solvolysis of *cyclohexyl* bromide at 95° in aqueous ethanol gave values of  $10^5k$  of  $3.58 \pm 0.02$  (sec.<sup>-1</sup>) and  $16.6 \pm 0.3$  (sec.<sup>-1</sup>) in 70% and 50% aqueous ethanol respectively [cf.  $10^5k^{21.2} = 22.7$  (sec.<sup>-1</sup>) in 70% aqueous methanol for tetra-*O*-acetyl- $\alpha$ -D-glucosyl 1-bromide]. The ratio  $k^{50\%}/k^{70\%}$  is of the same order as that for *isopropyl* bromide



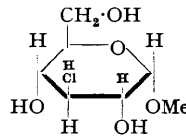
(III)



(IV)



(V)



(VI)

in its unimolecular reaction (Hughes, Ingold, and Shapiro, *J.*, 1936, 225). The solvolysis of *cyclohexyl* bromide was accompanied by almost complete elimination (95%), as would be expected if the bromine were polar in its attachment to the ring (Barton, *J.*, 1953, 1027). In view of this, comparison with the *O*-acylglycosyl 1-halides must be carried no further than to point out that the *cyclohexyl* derivative is much less reactive than molecules containing the lactol ring.

#### EXPERIMENTAL

*Solvents.*—Methanol and acetone were purified as described in the previous paper. Ethanol was purified by Manske's method (*J. Amer. Chem. Soc.*, 1931, 53, 1106). The term *x%* aqueous alcohol or aqueous acetone has the same significance as in Part I.

*2:3-Dichlorotetrahydropyran.*—Dry chlorine was passed into an ice-cold solution of dihydropyran (50 g.; b. p. 84–86°,  $n_D^{20}$  1.4400) in carbon tetrachloride (100 ml.) until 42 g. had been absorbed. The colourless solution had an acid reaction and, after removal of solvent and excess of dihydropyran under reduced pressure, the residual liquid was distilled. The fraction boiling at 80–83°/20 mm.,  $n_D^{20}$  1.4937 (30 g.), was collected (cf. b. p. 74°/11 mm.,  $n_D^{20}$  1.495, given in B.P. 571,265). The 2:3-dichlorotetrahydropyran obtained in this way contained too much acid for kinetic measurements and it was more satisfactory to use the product immediately after passage of slightly less than the theoretical amount of chlorine and removal of the solvent (Found: Cl, 45.4. Calc. for  $C_5H_8OCl_2$ : Cl, 45.8%).

*Thiacyclohex-2-ene.*—This was prepared according to Naylor (*loc. cit.*) by passing dihydropyran and hydrogen sulphide over alumina at 400°. The product had b. p. 142–144°,  $n_D^{20}$  1.5348 (Naylor gives b. p. 142–145°,  $n_D^{20}$  1.5330).

2 : 3-Dichlorothiacyclohexane.—Thiacyclohex-2-ene (5 g.) in carbon tetrachloride (100 ml.) was treated with dry chlorine (3.2 g., 90%) at 0°. The solvent was removed and the 2 : 3-dichlorothiacyclohexane distilled at 100–106°/20 mm.,  $n_D^{25}$  1.5593 (6.5 g.) (Found : C, 35.1; H, 4.7; S, 18.5.  $C_6H_8Cl_2S$  requires C, 35.0; H, 4.7; S, 18.7%).

Tetra-O-acetyl- $\alpha$ -D-glucosyl 1-Chloride.—This was obtained from penta-O-acetyl- $\beta$ -D-glucose by the action of titanium tetrachloride in chloroform (Brauns, *J. Amer. Chem. Soc.*, 1925, **47**, 1280). It had m. p. 75–76°,  $[\alpha]_D^{20} + 166^\circ$  (c, 2.0 in  $CHCl_3$ ).

3 : 4 : 6-Tri-O-acetyl-2-chloro-2-deoxy- $\alpha$ -D-glucosyl 1-Chloride.—This was prepared by adding chlorine to tri-O-acetyl-D-glucal (Fischer, Bergmann, and Schotte, *loc. cit.*). It had m. p. 91–92°,  $[\alpha]_D^{20} + 170^\circ$  (c, 1.5 in  $CHCl_3$ ).

Methyl 3 : 4 : 6-Tri-O-acetyl-2-chloro-2-deoxy- $\beta$ -D-glucoside.—This, m. p. 148°, was formed when the above compound reacted with methanol in the presence of silver carbonate. Deacetylation of the triacetate with methanolic ammonia provided methyl 2-chloro-2-deoxy- $\beta$ -D-glucoside, m. p. 159–160° (Fischer, Bergmann, and Schotte, *loc. cit.*).

Methyl 3-Chloro-3-deoxy- $\alpha$ -D-glucoside.—Separated from the products of the reaction of methyl 2 : 3-anhydro-4 : 6-O-benzylidene- $\alpha$ -D-alloside with hydrochloric acid, this had m. p. 136–138° (Newth, Overend, and Wiggins, *J.*, 1947, 10).

Methanolysis of 2 : 3-Dichlorotetrahydropyran.—The compound (15 g.) was dissolved in dry methanol (100 ml.) and kept at 35° for 48 hr. Acid was neutralised ( $Ag_2CO_3$ ) and, after removal and washing of the inorganic precipitate, the methanol was removed. 3-Chlorotetrahydro-2-methoxypyran (11.3 g.) had b. p. 85°/750 mm.,  $n_D^{25}$  1.4580 (cf. b. p. 38°/2 mm.,  $n_D^{20}$  1.4576, given in B.P. 598,080). 3-Chloro-2 : 3-dihydro-4H-pyran (1.3 g.) was also obtained boiling at 141–142°, with  $n_D^{25}$  1.4808 (cf. b. p. 141–142°,  $n_D^{25}$  1.479, given in B.P. 571,265).

Solvolysis of 2 : 3-Dichlorotetrahydropyran in 80% Aqueous Acetone.—The compound (5 g.) was dissolved in 80% aqueous acetone (100 ml.) and kept at 20° for 56 hr. The solution was extracted with ether, and the extract washed with dilute sodium hydrogen carbonate solution and water. After drying ( $Na_2SO_4$ ), the ether was evaporated. 3-Chlorotetrahydro-2-hydroxypyran, recrystallised from alcohol, had m. p. 62° (Found : Cl, 27.0. Calc. for  $C_5H_9O_2Cl$  : Cl, 25.8%).

Rate Measurements.—The course of a reaction was followed by titrating the acid liberated with standard alkali as described in Part I.  $\log_{10}$  [Halide] was plotted against time,  $t$ , and the first-order rate constant given by  $k = -2.303 \times \text{slope of line (sec.}^{-1})$ . The following run is typical. Concentrations of halide are expressed in equivalent ml. of standard alkali per 5 ml. of solution.

*Methanolysis of tri-O-acetyl-2-chloro-2-deoxy- $\alpha$ -D-glucosyl 1-chloride at 35°.*

$t$ (min.)	0	20	40	60	100	140	180	220	260
[Halide]	9.51	9.39	9.29	9.18	8.97	8.77	8.57	8.37	8.18

[Halide] = 0.019M by wt. Alkali = 0.01N.  
Slope:  $-2.5 \times 10^{-4}$  min. $^{-1}$ .  $k = 0.96 \times 10^{-5}$  sec. $^{-1}$ .

cycloHexyl Bromide.—The thermostat was adjusted to  $95.1^\circ \pm 0.05^\circ$ . cycloHexyl bromide was dissolved in the appropriate medium and 10-ml. aliquots were placed in a series of tubes. These were filled with nitrogen before sealing and immersed in the thermostat for given lengths of time. On removal, a tube was cooled in ice, cleaned, and broken under water (50 ml.). The liberated acid was titrated with standard alkali. The first-order rate constant was calculated from  $k = (2.303/t) \log_{10}$  [Halide]. The details of the solvolysis of cyclohexyl bromide in 50% aqueous acetone are given below. Concentrations of halide are expressed in equivalent ml. of standard alkali per 10 ml. of solution.

$t$ (min.)	0	20	30	40	50	60	70	80	90	100
[Halide]	25.92	21.56	19.51	17.43	15.77	14.27	12.89	11.51	10.64	9.02
$10^{1/2}k$ (sec. $^{-1}$ )	—	1.54	1.58	1.65	1.66	1.66	1.66	1.69	1.73	1.76

Each tube contained 0.0423 g. of  $C_6H_{11}Br$ . Alkali = 0.010N. Mean  $k = 1.66 \pm 0.03 \times 10^{-4}$  sec. $^{-1}$ .

Treatment of Methyl Chlorodeoxy-D-glucosides with Methanol at 98°.—Methanol solutions (0.05M) of methyl 3 : 4 : 6-tri-O-acetyl-2-chloro-2-deoxy- $\beta$ -D-glucoside, methyl 2-chloro-2-deoxy- $\beta$ -D-glucoside, and methyl 3-chloro-3-deoxy- $\alpha$ -D-glucoside were heated at 98° in sealed tubes for 500 hr. No acidity developed and each compound was recovered quantitatively.