213. *The Replacement of the Halogen Group of Acetohalogeno-sugars with Retention of Configuration.*

By G. A. Howard.

Attention is drawn to the reaction, with retention of configuration, of certain acetohalogeno-sugars with nucleophilic reagents. A double inversion involving a cyclic intermediate is the mechanism suggested for the reaction.

The synthesis of cytidine (Howard, Lythgoe, and Todd, *J.*, 1947, 1052) involved the preparation of acetobromoribofuranose, a syrup whose configuration was not established. The two glycosides, cytidine and theophilline-7-D-ribofuranoside prepared from it, were shown, however, to have the β-configuration (Howard, Lythgoe, and Todd, *loc. cit.*; Davoll, Lythgoe, and Todd, *J.*, 1948, 1685), and the acetohalogeno-compound would normally have been designated as an α-compound. At least one case was noted, however, where an isomeric (α-)glycoside appeared to be produced and, although no definite configuration can be assigned to the acetohalogenoribofuranoses without further evidence, this unusual reaction prompted a literature search for the behaviour of acetohalogeno-sugars similar in type.

A number of cases was found (see Table) in which such acetohalogeno-sugars reacted, without inversion, with nucleophilic reagents. This failure to produce glycosides of an opposite configuration has been remarked only by Hickinbottom (*J.*, 1930, 1338) and by Brigl and Keppler (*Ber.*, 1926, **59**, 1588). No satisfactory explanation was given; although the compounds they studied are not identical in type with those dealt with here, their behaviour may have a similar cause.

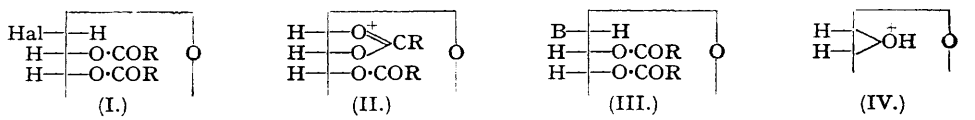
Ingold and his co-workers showed (*J.*, 1937, 1252) that the heterogeneous reaction of an alkyl halide with a silver salt resembled homogeneous S_N1 reactions, the reaction taking place on the surface of the insoluble silver salt. The intermediate reactant is thus a carbonium ion. When acetohalogeno-sugars react with silver salts this carbonium ion will not be free, since the expelled group will shield the ion from attack in that direction, and inversion rather than racemisation will take place. Now there is a configurational similarity between most of the acetohalogeno-sugars listed in the Table: there is a *cis*-arrangement of the acetoxy-groups at $C_{(2)}$ and $C_{(3)}$ and a *trans*-arrangement of the halogen atom at $C_{(1)}$ and the acetoxy-group at $C_{(2)}$, cf. (I). The carbonium ion formed from compounds of this type could be a resonance hybrid in which (II) is one canonical structure (Winstein and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2780). Attack at $C_{(1)}$ by a nucleophilic reagent then gives a compound (III) with the same

configuration as the original acetohalogeno-sugar. This double inversion is the mechanism suggested for the reactions shown in the Table, except that for 1-β-chloro 3 : 4 : 6-triacetyl glucose the intermediate may be of type (IV).

Acetohalogeno-sugar.	Product.	Ref.
α-Acetobromomannose	α-Acetochloromannose	1
,,	α-Penta-acetyl mannose	2
1-α-Bromo 4-β-D-glucosyl-D-mannose	1-α-Methyl-4-β-D-glucosyl-D-mannoside	3
α-Acetobromolyxose	α-Methyl-lyxoside	4
α-Acetobromorhamnose	Theophylline-7-α-rhamnoside	5
,,	Triacetyl 1-menthylrhamnosides	6
β-Acetobromoribopyranose	Theophylline-7-β-riboside	7
1-β-Bromo 2 : 3 : 4-tribenzoyl ribose	Tribenzoyl β-methyl- and β-ethyl-ribosides	8
1-β-Chloro 3 : 4 : 6-triacetyl glucose	α- and β-Glycosides	9
1-β-Chloro 3 : 4 : 6-triacetyl 2-trichloroacetyl glucose	,,	10

[1] Pacsu, *loc. cit.* [2] Micheel and Micheel, *Ber.*, 1930, **63**, 386. [3] Isbell, *J. Amer. Chem. Soc.*, 1930, **52**, 5298. [4] Levene and Wolfrom, *J. Biol. Chem.*, 1928, **78**, 525. [5] Fischer and Fodor, *Ber.*, 1914, **47**, 1058. [6] Fischer, Bergman, and Rabe, *Ber.*, 1920, **53**, 2362. [7] Levene and Sobotka, *J. Biol. Chem.*, 1925, **65**, 463. The configuration of the theophylline riboside was not reported, but its molecular rotation and theoretical considerations (Howard, Kenner, Lythgoe, and Todd, *J.*, 1946, 861) suggest that it, like the acetohalogeno-sugar (Pacsu) is a β-compound. [8] Hudson, *J. Amer. Chem. Soc.*, 1948, **70**, 4055. [9] Brigl and Keppler, *loc. cit.* [10] Hickinbottom, *loc. cit.*

Most acetohalogeno-sugars with a *trans*-1-halogeno-2-acetoxy-grouping react normally with inversion; the presence of a *cis*-2 : 3-diacetoxy-grouping is, apparently, necessary for reaction without inversion to be possible. The function of the 3-acetoxy-group is, presumably, to restrict the movement of the carbonyl group in the $C_{(2)}$-acetoxy-group to the neighbourhood



of $C_{(1)}$. In this connection it is interesting to note that Brauns (*J. Res. Nat. Bur. Stand.*, 1931, **7**, 573) showed by means of models that in the acetyl mannoses the carbonyl oxygen of the $C_{(2)}$-acetoxy-group is in the neighbourhood of $C_{(1)}$. The coplanarity or otherwise of the sugar lactol ring may be another factor of importance in this connection. A mechanism similar to the one advanced here was suggested by Pacsu ("Advances in Carbohydrate Chemistry," 1945, **1**, 113) to explain the formation of ortho-esters from sugars of type (I); the effect of the $C_{(2)}$-acetoxy-group was, however, not considered.

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