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SYNTHESIS OF GLYCOSIDES *via* TERT.-BUTYL ETHERS OF ALCOHOLS

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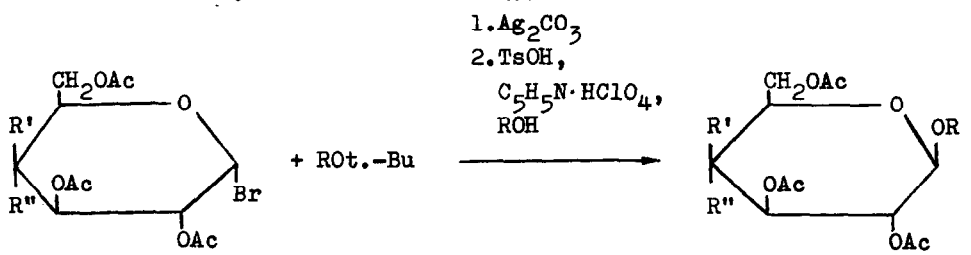
The synthesis of the glycosidic bond, the main intermonomer linkage of polymeric carbohydrates, has been carried out so far only by glycosylating the free hydroxyl group of the aglycone (1-5). No approach through activation of the hydroxyl group in the glycosylation reactions, by converting it into the corresponding derivative, has been known up to now* although this principle is widely used in making up the peptide and phosphodiester linkages.

On studying the synthesis of glycosides of hydroxyamino acides (6,7) we have found that O-tert.-butyl derivatives of C- and N-protected serine and threonine under certain conditions are smoothly glycosylated by acylhalogenoses to form O-glycosides in the yield higher in some cases than that of glycosides obtained by glycosylating the free hydroxy-compounds.

The glycosylation reaction of tert.-butyl ethers proved to be rather general and by this route the glycosides of other alcohols can be obtained in high yield. For instance, 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (3.0 g) in toluene (20 ml) was treated with the methyl ester of N-carbobenzoxy-O-tert.-butyl-L-threonine (0.97 g) in the presence of silver carbonate (2.0 g) for 1 hour under reflux. To the filtered solution 0.05 mole (per 1

*The only example of glycosylating the protected hydroxyl groups is the Bredereck reaction (8-12). But this reaction is not of general character.

mole of the tert.-butyl derivative taken) of methyl ester of N-carbobenzoxy--L-threonine and catalytic amounts of p-toluenesulphonic acid and pyridinium perchlorate were added followed by heating under reflux for 30 min. and the corresponding glycoside (I) was isolated in 45% yield (calculated from the original tert.-butyl derivative) by column chromatography on silica gel (gradient chloroform-acetone elution). The glycoside obtained is identical to tetraacetyl-O-β-D-glucopyranoside of methyl ester of N-carbobenzoxy-L--threonine that was synthesized earlier (7)



	R	R'	R"
I	$CH_3\overset{|}{C}HCH(NHCbz)CO_2Me$	H	OAc
II	$-CH_2CH(NHCbz)CO_2Me$	OAc	H
III	$-CH_2C_6H_5$	H	OAc
IV	$-n-C_7H_{15}$	H	OAc

Under similar conditions from methyl ester of N-carbobenzoxy-O-tert.--butyl-L-serine (0.64 g) and 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide and other reagents in the same proportion tetraacetate of O-β-D--galactopyranoside of methyl ester of N-carbobenzoxy-L-serine (II) was obtained in 51% yield. It was also purified by chromatography on silica gel and found to be identical to the glycoside obtained from corresponding derivative of serine with free hydroxyl.

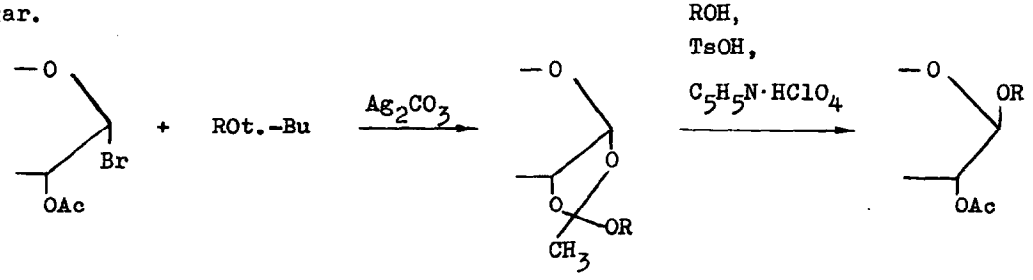
Analogously, from 1.5 g of acetobromglucose and excess of benzyl-tert.-butyl ether (0.82 g) and other components in the same proportion benzyl β-D-glucopyranoside tetraacetate (III) was obtained in 70% yield. It was purified by crystallization from the aqueous alcohol and found to be

identical to the authentic sample obtained by glycosylating the benzyl alcohol by the Koenigs-Knorr method. The excess of the benzyl-tert.-butyl ether was isolated from the reaction mixture unchanged.

Similar results were obtained by glycosylating n-heptyl-tert.-butyl ether with acetobromglucose. The acetate of n-heptyl-β-D-glucopyranoside (IV) was isolated in 63% yield by crystallization from the aqueous ethanol.

A more thorough investigation of this new and important reaction in the case of glycosylation of the threonine derivative has shown the reaction to proceed in two steps. The interaction with O-tert.-butyl derivative of threonine in the presence of silver carbonate gives rise to a compound (in the absence of silver carbonate the first stage of the reaction does not take place and the starting components come out unchanged) which after adding p-toluensulphonic acid, pyridinium perchlorate and small amounts of the corresponding hydroxyl containing compound is converted into threonine glycoside. Although the labile intermediate mentioned above has not been isolated from the reaction mixture, however, its properties, the chromatographic behaviour and the acid lability (it is completely hydrolysed by 0.01 N H_2SO_4 in aqueous acetone at room temperature for 10 min.) clearly show (cf.5) it to be an orthoester of the corresponding monosaccharide. The interaction of this orthoester with a hydroxyl containing compounds in the presence of pyridinium perchlorate and p-toluenesulphonic acid gives rise to the corresponding glycoside as is the case of other orthoesters of sugars (13).

Thus, the above reaction is likely to be a two-step glycosylation of tert.-butyl ethers *via* the formation of an orthoester of the corresponding sugar.



The reaction found extends the orthoester glycosylation method discovered in this laboratory (4). The mechanism of this interesting reaction requires a more careful study. However, the significance of the reaction is quite evident. Tert.-butyl ethers of primary, secondary and tertiary alcohols are readily obtainable by the interaction of the corresponding alcohols with isobutylene in the presence of acid catalysts (14-16). However, a more important point is that the reaction in question is likely to be a general approach for activating the hydroxyl group in the glycosylation reactions. As has been shown by the preliminary data the reaction is applicable to various hydroxyl groups and therefore it is promising for the synthetic in carbohydrate chemistry.

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