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Preliminary communication

A new synthesis of methylene acetals*

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The method commonly used[1] for the preparation of methylene acetals of carbohydrates has remained essentially unchanged since it was first described by Tollens[2] in 1899. Among the noteworthy innovations over the classical, acid-catalyzed condensation of formaldehyde with polyhydric alcohols are the use of methylene halides[3] and dimethoxymethane** as sources of the methylene group in these acetals. Apart from their utility as temporary protecting groups for alcohol functions in polyhydroxy compounds[4], methylene acetals have assumed renewed importance in preparative carbohydrate chemistry because of recent examples of their oxidative-cleavage reactions[5].

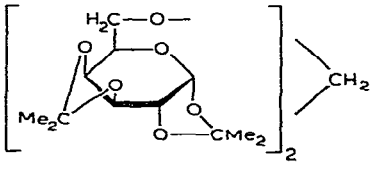
In this Communication, we report a novel method for the preparation of acetals of the dialkoxymethane and 1,3-dioxolane types that consists in allowing alcohols and vicinal diols, respectively, to react with *N*-bromosuccinimide (NBS) in methyl sulfoxide.

$$ROH + Me_2SO + NBS \longrightarrow RO{-}CH_2{-}OR$$

In a typical example, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (1 mmole) was added to a solution of NBS (2 mmoles) in Me_2SO (10 ml), and the solution was stirred overnight at 50°. After aqueous sodium hydrogen carbonate had been added, the excess of methyl sulfoxide was removed by extraction of the solution with isopropyl ether, and the organic layer was processed to give, after column chromatography on silica gel, the symmetrical acetal **1** as an oil in 53% yield***; τ ($CDCl_3$) 5.40, s, $-O-CH_2-O-$; *m/e* 532 (M–15). With methyl sulfoxide-d_6 and the same alcohol, the

*Part of a series on preparative and exploratory carbohydrate chemistry.
**Unpublished observations from this laboratory. The method consists of an acid-catalyzed (*p*-toluenesulfonic acid) exchange with the polyhydric alcohol.
***Oily products were adequately characterized by spectral data; their homogeneity was ascertained by t.l.c. in appropriate systems. In most cases, they were prepared independently by using dimethoxymethane plus *p*-toluenesulfonic acid. New crystalline derivatives gave correct microanalytical values. Mass spectra were recorded with an MS-902, high-resolution, mass spectrometer, and n.m.r. spectra were recorded at 60 and 100 MHz. Melting points are uncorrected.

corresponding dideuteriomethylene acetal ($RO-CD_2-OR$) was obtained [*m/e* 534 (M−15)], thus establishing the source of both methylene hydrogen atoms in the product. The acetal derivative 2 was prepared in a similar way, and obtained as an oil, in 59% yield; $[\alpha]_D^{25}$ −77.8° (*c* 5.41, chloroform); τ ($CDCl_3$) 4.80, s, $-O-CH_2-O-$.



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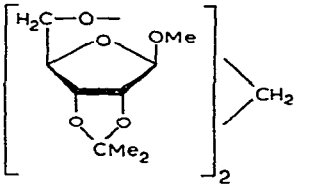

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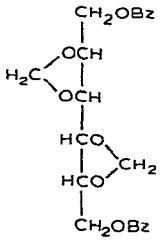
The method is particularly suited for the facile formation of cyclic methylene acetals from vicinal *cis*-diols. Thus, 1,6-di-*O*-benzoyl-D-mannitol[6] (1 mmole) was added to a solution of NBS (2 mmoles) in Me_2SO (5 ml) and carbon tetrachloride (10 ml), and the solution was stirred for 36 h at 50°. Processing of the reaction mixture as just described, followed by chromatographic purification on silica gel, gave 1,6-di-*O*-benzoyl-2,3:4,5-di-*O*-methylene-D-mannitol (3) in 76% yield; m.p. 119–121°; $[\alpha]_D^{25}$ +43.5° (*c* 1.0, chloroform); lit.[7] m.p. 120–122°; $[\alpha]_D^{25}$ +47.5° (*c* 0.80, chloroform). A further application of the reaction is exemplified by the preparation of methyl 5-*O*-benzoyl-2,3-*O*-methylene-β-D-ribofuranoside (4) in 72% yield; m.p. 83.5–84.5°; $[\alpha]_D^{25}$ −55.6° (*c* 1.77, chloroform); τ ($CDCl_3$) 4.90, 4.95, $-O-CH_2-O-$; *m/e* 249 (M−31).



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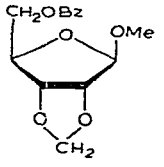

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Such commonly used groups as esters (benzoate, acetate), acetals, and aglycons seem to be compatible with the mild reaction conditions. Based on mechanistic considerations in connection with this new reaction, other synthetic possibilities, such as the preparation of mixed acetals, are under investigation[8].

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