NOTES

A CONVENIENT METHYLATION PROCEDURE

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The use of the more powerful solvents dimethylformamide and (or) dimethyl sulfoxide has permitted one-step complete methylation in good yield, with either silver oxide – methyl iodide or methyl sulfate – barium oxide (hydroxide), of a number of polyhydroxy compounds (1). This is a distinct improvement over the silver oxide – methyl iodide (2) or methyl sulfate – sodium hydroxide (3) procedures, which often required tedious, repeated methylations to produce the fully alkylated products. A recent report (4) illustrates rapid permethylation of a glycolipid and a polysaccharide by methyl iodide in the presence of the methylsulfinyl carbanion (5) obtained from the reaction of sodium hydride with dimethyl sulfoxide.

We wish to draw attention to a methylating procedure which we have employed for some time, and which is rapid and quite broadly applicable, resulting in a clean reaction providing consistently excellent yields of readily isolable, fully methylated material. It involves the addition of sodium hydride to a solution of the hydroxy compound in 1,2-dimethoxyethane, or in dimethylformamide if the solubility of the compound is low in 1,2-dimethoxyethane, or in a mixture of the two solvents. Methyl iodide is added shortly after, or it may be present advantageously in the solution before, the addition of the sodium hydride to the reaction mixture. Yields are above 80%.

A similar procedure has been reported by Eades *et al.* (6) for the preparation of 1,5-anhydro-2,3,4,6-tetra-*O*-methyl-D-mannitol with tetrahydrofuran as solvent, and by Tate and Bishop (7) for the preparation of benzyl ethers with excess benzyl chloride as solvent.

The convenience and utility of this method prompted us to point out the work noted in the last two papers as well as our own experience. Details of our procedure are illustrated by the following two examples.

6-Methoxymethyl-5,6-dihydropyran

To a solution of 6-hydroxymethyl-5,6-dihydropyran[1] (68.4 g, 0.6 mole) and methyl iodide (99.5 g, 0.7 mole) in 350 ml of dried ($LiAlH_4$), distilled 1,2-dimethoxyethane, all contained in a 1 l, three-necked flask equipped with a condenser, dropping funnel, drying tube, and magnetic stirrer, was added 15.6 g (0.65 mole) of sodium hydride[2] over a period of 30 min. Vigorous hydrogen evolution took place after addition of each of the small portions of the hydride. Heat was evolved and sodium iodide precipitated. Ten minutes after the last of the hydride had been added, a further quantity (10 ml) of methyl iodide was added and the solution stirred at room temperature for 1 to 2 h. The 1,2-dimethoxyethane and excess methyl iodide were removed by distillation at atmospheric pressure until the volume was reduced to one-third. Anhydrous ether (60 ml) was added, whereupon more sodium iodide precipitated. The mixture was filtered, the sodium iodide was washed

[1]*Kindly donated by J. A. Craig, Shell of Canada Limited, Winnipeg, Manitoba.*

[2]*The sodium hydride (Metal Hydrides Corporation) was a 56% suspension in mineral oil. The oil was washed out with ether and the hydride obtained by filtration. Satisfactory results were obtained if this was kept covered during the interval of addition to the solution.*

with 20 ml of ether, and the combined washings and filtrate were distilled at atmospheric pressure to remove the bulk of the solvent. Residual 1,2-dimethoxyethane was removed at 100 mm pressure with a spinning-band fractionating column. Further distillation gave the product boiling at 83–84° and 65 mm, yield 70 g (91%), η_D^{27} 1.4400.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.41; H, 9.30.

Methyl 2,3,4,6-Tetra-O-methyl-α-D-glucopyranoside

Into a three-necked flask equipped with an efficient condenser and a mechanical stirrer was placed anhydrous methyl α-D-glucopyranoside (9.7 g, 0.05 mole) dissolved in a mixture of 130 ml of dry dimethylformamide and 70 ml of 1,2-dimethoxyethane (previously dried and distilled from $LiAlH_4$). Methyl iodide (32.5 g, 0.23 mole) was added and the solution cooled to −10° by immersion of the flask for a time in a dry ice – acetone bath. About half of the sodium hydride[2] (total amount: 4.8 g, 0.02 mole) was added in small portions over a period of 7–8 min to the stirred solution. A gentle evolution of gas occurred and the reaction temperature rose slowly. Then the rest of the hydride was added all at once. When the temperature reached 30°, the reaction became vigorous, whereupon the flask was immersed in the dry ice – acetone bath. A maximum temperature of 60° was reached and maintained for about 5 min, and then dropped rapidly. The cooling bath was removed, and then the mixture was stirred for a time (total reaction time ~1 h) and finally poured cautiously into 600 ml of water containing 100 g of dissolved sodium chloride. The resulting mixture was extracted with chloroform (5 × 100 ml). The combined extracts were dried (Na_2SO_4) and freed of solvents by rotary evaporation and finally by distillation under vacuum at 2 mm with a bath temperature of 70 °C. The crude residue (11.5 g, 92%), when analyzed by gas–liquid chromatography on a 6 ft column of 20% butanediol succinate on Gas Chrom P (60–80 mesh) at 200° with a helium flow rate of 70 ml/min, consisted of only two substances: dimethylformamide (~4% on a molar basis) and the fully methylated glucoside. Removal of the residual dimethylformamide was accomplished by passage of the crude product through a column of Woelm neutral alumina (150 g), using successively the eluants (200 ml of each) benzene–pentane (7:4), benzene–chloroform (1:1), and benzene–chloroform (1:3). The sequence of increasing polarity of eluants was used to avoid the possibility of elution of the contaminating dimethylformamide. The higher polarity was required to remove the last portion of the pentamethyl glucoside from the strongly adsorbing column. When British Drug Houses alumina was used, the eluant benzene–pentane (7:4) was sufficient to remove selectively all of the glucoside. The resulting pure methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucoside (10.5 g, 84%) was identical in all respects with an authentic sample (3, 8). The infrared spectrum (neat) showed no absorption in the 3 600 – 3 300 cm^{-1} region (OH).

ACKNOWLEDGMENT

This work was supported by a grant from the National Research Council of Canada.

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RECEIVED MARCH 8, 1966.
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