Carbohydrate Research, 64 (1978) 309–314

Note

Acetalation of some sugar derivatives by enol acetates with catalysis by boron trifluoride-red mercuric oxide*

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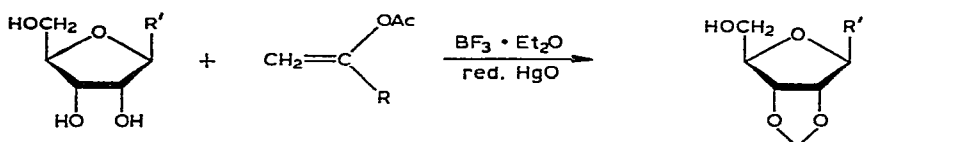
(Received February 21st, 1977; accepted for publication in revised form, September 15th, 1977)

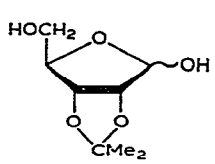
Such enol esters as isopropenyl acetate (**1**) and vinyl acetate (**2**) have been shown to react effectively with alcohols on catalysis with boron trifluoride diethyl etherate and red mercuric oxide, giving the corresponding acetals in good yield[2], and they have been found less susceptible to acid-catalyzed polymerization than the corresponding enol ethers[3]. This aspect of enol acetate chemistry prompted this extension to acetalation of sugar derivatives; although a number of procedures for preparation of cyclic acetals have already been established for sugar, sterol, and glycerol derivatives[4], the traditional cyclic acetalation is generally effected by treatment of the substrates with an excess of such carbonyl reagents as acetone, acetal-



3 R′ = theophylline
5 R′ = OMe
7 R′ = adenine

1 R = Me
2 R = H

4 R′ = theophylline, R = Me
6 R′ = OMe, R = Me
8 R′ = adenine, R = Me
13 R′ = theophylline, R = H
14 R′ = OMe, R = H



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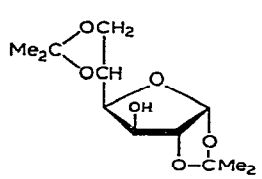

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*Part II of a series: Partial Protection of Carbohydrate Derivatives. For Part I: see ref. 1.

TABLE I

ACETALATION OF SOME SUGAR DERIVATIVES WITH ENOL ACETATES[a]

Sugar derivatives	*Enol acetates*	*(molar eq.)*	*Reaction conditions*		*Yield of products (%)*	
			Temp.	*Time, h*		
3	Isopropenyl	(1.1)	Room temp.	5	**4**	77
5	Isopropenyl	(1.05)	Room temp.	5	**6**	88
7	Isopropenyl	(1.3)	B.p. (reflux)	6	**8**	77
9	Isopropenyl	(2.2)	B.p. (reflux)	1	**10**	30[b]
11	Isopropenyl	(4.4)	B.p. (reflux)	1	**12**	54
3	Vinyl	(1.15)	B.p. (reflux)	8	**13**	47
5	Vinyl	(1.2)	Room temp.	4	**14**	64

[a]Acetone and ethyl acetate were used as solvent for the reactions with isopropenyl acetate (**1**) and with vinyl acetate (**2**), respectively. [b]In this instance, 1,5-anhydro-2,3-*O*-isopropylidene-β-D-ribofuranose was also isolated, in ~12% yield.

dehyde, benzaldehyde, and the like, or by an acid-catalyzed acetal-exchange reaction of these with such acetals as 2,2-dimethoxypropane.

At first, a search was performed for an appropriate solvent for the reaction by use of 7-β-D-ribofuranosyltheophylline (**3**) as a model compound for the acetalation, and **1** as the enol acetate*. The reaction in benzene (reflux), nitrobenzene (100°), acetonitrile (reflux), chloroform (room temperature), and 1,4-dioxane (room temperature) gave only a trace of 7-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)theophylline (**4**). The reaction in acetonitrile afforded an unidentified product assumed to be a partially acetylated derivative of **3**, based on its strong i.r. absorption at 1720 cm^{-1}. The reaction took place in ethyl acetate (reflux), *N*,*N*-dimethylformamide (room temperature), and dimethyl sulfoxide (room temperature), but these solvents gave **4** in only 7, 20, and 20% yields, respectively. The reaction in **1** gave a resinous mass that might have resulted from polymerization of **1**, and no **4** was formed at all. In the light of the reported facile isopropylidenation with 2,2-dimethoxypropane in acetone[5], we thus performed the reaction in benzene containing acetone. The ratio of acetone to benzene was gradually increased from 1:3 to 1:1 to give **4** in yields of 23–34%, comparable with those obtained in *N*,*N*-dimethylformamide and dimethyl sulfoxide. The reaction in acetone was found to be induced very effectively, even at room temperature, to give **4** in 77% yield. Acetone was thus concluded to be appropriate for the isopropylidenation, and **1** was assumed to behave not only as isopropylidenating agent, but also as dehydrating agent in this instance. Confronted with this result, the reaction without **1** was performed to elucidate the actual extent of the effect of **1** on this reaction; the yield of **4** was significantly decreased, down to 17%, and 66% of **3** was recovered.

*All of these reactions were performed by use of **3** (3.1 g, 10 mmol), **1** (1.1 g, 11 mmol), $BF_3 \cdot Et_2O$ (0.2 ml), and red HgO (0.2 g) in the specified solvent (100 ml) for 5 h.

Ethylidenation by **2** was performed in ethyl acetate, as subsequent manipulation was much easier than with reactions performed in *N*,*N*-dimethylformamide or dimethyl sulfoxide.

Isopropylidenation. — As with the isopropylidenation of **3**, methyl β-D-ribofuranoside (**5**), adenosine (**7**), D-ribose (**9**), and D-glucose (**11**), respectively, were treated with **1** in the presence of a catalytic amount of boron trifluoride diethyl etherate and red mercuric oxide (See Table I). The reaction of **5** also proceeded effectively, even at room temperature, as with **3**, to give methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**6**) in 88% yield. The reactions of **9** and **11**, however, required treatment in boiling acetone, and gave 2,3-*O*-isopropylidene-D-ribofuranose (**10**, 30% yield) together with 1,5-anhydro-2,3-*O*-isopropylidene-β-D-ribofuranose (12% yield), and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**12**, 54% yield), respectively. The reaction of **7** was performed in the presence of an amount of boron trifluoride diethyl etherate slightly exceeding the stoichiometric amount of **7**, as the reaction was not induced under the normal conditions, because of quenching of the catalyst by **7**; 2',3'-*O*-isopropylideneadenosine (**8**) was thus obtained in 77% yield. All of the products obtained herein were identified by comparison with the corresponding authentic samples.

Ethylidenation. — As with the foregoing reactions, ethylidenation of **3** and **5** was performed by use of **2**, instead of **1**, in the presence of the combination of catalysts in ethyl acetate (see Table I). These reactions gave 7-(2,3-*O*-ethylidene-β-D-ribofuranosyl)theophylline (**13**, 47% yield) and methyl 2,3-*O*-ethylidene-β-D-ribofuranoside (**14**, 64% yield), respectively. The structures of these products were confirmed by use of Oldham and Rutherford's rule[6]; **13** and **14** were converted into the corresponding 5'-deoxy-5'-iodo- and 5-deoxy-5-iodo derivatives, respectively, via their 5'- and 5-*O*-tosyl derivatives.

The procedure of Croxall *et al.*[2] was thus found to constitute another synthetic method for sugar acetal derivatives.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Isopropenyl acetate (**1**) and vinyl acetate (**2**) were commercial products and were purified by distillation, after drying over anhydrous sodium sulfate, prior to use. Evaporations were performed *in vacuo*. Paper chromatography was effected on Toyo Filter Paper No. 50 (Toyo Roshi Co., Ltd.) and developed with 86:14 butyl alcohol–water; spots were detected by using a u.v. lamp (253 nm, Tokyo Machinery Co., Ltd.). I.r. spectra were recorded with a Hitachi EPI-2S spectrometer.

Isopropylidenation of 7-β-D-ribofuranosyltheophylline (**3**) *with* **1**. — A mixture of compound[7] **3** (3.2 g, 10 mmol), **1** (1.1 g, 11 mmol), and red mercuric oxide (0.2 g) in dried acetone (100 ml) was stirred vigorously, boron trifluoride diethyl etherate (0.2 ml) was added, and the resulting mixture was stirred for 5 h at room temperature. The resultant mixture was poured into sufficient ice-cold, aqueous sodium hydrogen-

carbonate to neutralize the acid catalyst and acetic acid concomitantly formed and to make the mixture alkaline. The mixture was evaporated and the residue was extracted with hot acetone (3 × 30 ml). Evaporation of the combined extracts to a pale-yellow syrup, followed by trituration of the syrup with a small amount of ethanol, gave white crystals, recrystallization of which gave 2.5 g (77%) of **4**; m.p. 161–162° (ethanol), undepressed on admixture with an authentic specimen[8] (lit.[8] m.p. 161°), $[\alpha]_D^{28}$ −23.6° (*c* 0.99, chloroform); λ_{max}^{EtOH} 274 nm (ε 8800).

*Methyl 2,3-*O*-isopropylidene-β-*D*-ribofuranoside* (**6**). — A mixture of methyl β-D-ribofuranoside[9] (**5**) (16 g, 100 mmol), **1** (10.5 g, 105 mmol), and red mercuric oxide (0.3 g) in dried acetone (100 ml) was treated with boron trifluoride diethyl etherate (0.3 ml) as in the foregoing example. Similar processing of the resulting mixture gave 14.5 g (88%) of **6**; b.p. 92–94°/0.07 mmHg, $[\alpha]_D^{28}$ −67.2° (*c* 4.6, chloroform) (lit.[10] b.p. 83–86°/0.05 mmHg).

*2',3'-*O*-Isopropylideneadenosine* (**8**). — A mixture of commercial adenosine (**7**, 1 g, 3.7 mmol), **1** (0.5 g, 5 mmol), and red mercuric oxide (0.1 g) in dried acetone (80 ml) was boiled for 6 h with boron trifluoride diethyl etherate (0.7 ml) under reflux. Subsequent processing gave 0.87 g (77%) of **8**, m.p. 217–219° (ethanol), $[\alpha]_D^{18}$ −55.7° (*c* 0.13, water); $\lambda_{max}^{H_2O}$ 259 nm (ε 15300) {lit.[11] m.p. 220°; lit.[12] m.p. 200–204° (ethanol), $[\alpha]_D^{25}$ −63.9° (*c* 1.04, water)}.

*2,3-*O*-Isopropylidene-*D*-ribofuranose* (**10**). — A mixture of commercial D-ribose (**9**, 5.1 g, 33.3 mmol), **1** (7.3 g, 73 mmol), and red mercuric oxide (0.2 g) in dried acetone (200 ml) was boiled for 1 h with boron trifluoride diethyl etherate (0.2 ml) under reflux. Processing as before gave 1,5-anhydro-2,3-*O*-isopropylidene-β-D-ribofuranose (0.7 g, contaminated by a little **10**), b.p. 60–90°/0.07 mmHg (lit.[13] b.p. 55–60°/0.05 mmHg), and 1.9 g (30%) of **10**, b.p. 127–134°/0.07 mmHg, $[\alpha]_D^{24}$ −76° (*c* 1.56, chloroform) (lit.[13] b.p. 110–117°/0.05 mmHg).

*1,2:5,6-Di-*O*-isopropylidene-α-*D*-glucofuranose* (**12**). — A mixture of commercial D-glucose (**11**, 6 g, 33.3 mmol), **1** (14.6 g, 146 mmol), and red mercuric oxide (0.2 g) in dried acetone (200 ml) was boiled for 1 h with boron trifluoride diethyl etherate (0.2 ml) under reflux. Processing as before gave 4.7 g (54%) of **12**, m.p. 107–109° (petroleum ether) (no depression on admixture with an authentic specimen[15]), $[\alpha]_D^{24}$ −6.7° (*c* 1.2, chloroform) {lit.[13] m.p. 107°, $[\alpha]_D^{20}$ −18.5° (*c* 4.9, water); lit.[15] m.p. 110–111°, $[\alpha]_D^{20}$ −13.5° (chloroform)}.

*7-(2,3-*O*-Ethylidene-β-*D*-ribofuranosyl)theophylline* (**13**). — A mixture of compound[7] **3** (3.2 g, 10 mmol), **2** (1.0 g, 11.5 mmol), and red mercuric oxide (0.4 g) in dried ethyl acetate (450 ml) was boiled under reflux with stirring, and boron trifluoride diethyl etherate (0.4 ml) was then added. After 8 h under reflux, the mixture was poured into ice-cold, aqueous sodium hydrogencarbonate to render it slightly alkaline. The organic layer was separated, and the aqueous layer was evaporated and the residue extracted with chloroform (3 × 30 ml). The organic layers were combined, dried (sodium sulfate), and was evaporated to give 2.4 g of crude crystals, recrystallization of which gave 1.5 g (47%) of **13**, m.p. 167–169° (ethanol), $[\alpha]_D^{18}$ −33.5° (*c* 2.1, chloroform); λ_{max}^{EtOH} 274.5 nm (ε 10400).

Anal. Calc. for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.52; H, 5.78; N, 16.84.

Methyl 2,3-O-ethylidene-β-D-ribofuranoside (**14**). — To a mixture of methyl β-D-ribofuranoside[9] (**5**, 6.5 g, 40 mmol), **2** (4.1 g, 48 mmol), and red mercuric oxide (0.2 g) in dried ethyl acetate (100 ml) was added boron trifluoride diethyl etherate (0.2 ml) with stirring, and the resulting mixture was stirred for 4 h at room temperature. Processing as in the preceding example gave 4.8 g (64%) of **14**; b.p. 70–86°/0.05 mmHg, $[\alpha]_D^{20}$ −80° (*c* 0.42, ethanol).

Anal. Calc. for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.41; H, 7.41.

Tosylation of **13**. — To a solution of **13** (1.02 g) in pyridine (60 ml), was added *p*-toluenesulfonyl chloride (0.7 g) with cooling in an ice–water bath, and the mixture was refrigerated for one day. The resulting solution was then evaporated to a syrup below 50°. Cold water was added to the resulting syrup to precipitate out crude crystals (1.34 g). Recrystallization gave 1.2 g (81%) of 7-(2,3-*O*-ethylidene-5-*O*-tosyl-β-D-ribofuranosyl)theophylline, m.p. 170–172° (ethanol), $[\alpha]_D^{12}$ +27.7° (*c* 1.0, chloroform).

Anal. Calc. for $C_{21}H_{24}N_4O_8S$: C, 51.21; H, 4.91; N, 11.38. Found: C, 51.07; H, 4.96; N, 11.63.

Iodination of 7-(2,3-O-ethylidene-5-O-tosyl-β-D-ribofuranosyl)theophylline. — A solution of the title compound (0.6 g) and sodium iodide (0.6 g) in acetonitrile (15 ml) was heated for 3.5 h at 100° in a sealed glass tube. The tube was cooled, and the precipitated sodium *p*-toluenesulfonate was filtered off, and the filtrate evaporated. The residue was extracted with hot chloroform (50 ml). The extract was washed with 10% aqueous sodium thiosulfate and then with water. The organic layer was dried (anhydrous potassium carbonate) and evaporated to give crude crystals, recrystallization of which gave 0.36 g (65%) of 7-(5-deoxy-2,3-*O*-ethylidene-5-iodo-β-D-ribofuranosyl)theophylline, m.p. 178–180° (ethanol), $[\alpha]_D^{23}$ −8° (*c* 1.0, chloroform).

Anal. Calc. for $C_{14}H_{17}IN_4O_5$: C, 37.51; H, 3.82; N, 12.50. Found: C, 37.63; H, 3.87; N, 12.53.

Tosylation and iodination of **14**. — Tosylation of **14** (5.2 g) with *p*-toluenesulfonyl chloride (6.2 g) in pyridine (13 ml) in the foregoing manner afforded 6.2 g (66%) of methyl 2,3-*O*-ethylidene-5-*O*-tosyl-β-D-ribofuranoside, m.p. 70–71° (ethanol), $[\alpha]_D^{13}$ −21° (*c* 1.0, chloroform).

Anal. Calc. for $C_{15}H_{20}O_7S$: C, 52.32; H, 5.86. Found: C, 52.63; H, 5.95.

Subsequent iodination of the foregoing sulfonate (1.7 g) with sodium iodide (2.3 g) in acetonitrile (40 ml) as already described gave 1.2 g (78%) of methyl 5-deoxy-2,3-*O*-ethylidene-5-iodo-β-D-ribofuranoside, m.p. 71–72° (ethanol), $[\alpha]_D^{13}$ −50° (*c* 1.0, chloroform).

Anal. Calc. for $C_8H_{13}IO_4$: C, 32.01; H, 4.36. Found: C, 31.85; H, 4.49.

ACKNOWLEDGMENT

The authors thank the members of the Laboratory of Organic Analysis, Tokyo Institute of Technology, for the elementary analyses.

REFERENCES

1 Y. ISHIDO, N. NAKAZAKI, AND N. SAKAIRI, *J. Chem. Soc., Perkin Trans. 1*, (1977) 657–660.
2 W. J. CROXALL, F. J. GLAVIS, AND H. T. NEHER, *J. Am. Chem. Soc.*, 70 (1948) 2805–2807.
3 M. F. SHOSTAKOVSKII, *Zh. Obshch. Khim.*, 20 (1950) 608–619; *Chem. Abstr.*, 44 (1950) 7754c.
4 A. N. DE BELDER, *Adv. Carbohydr. Chem.*, 20 (1965) 219–302; C. B. REESE, in J. F. W. MCOMIE (Ed.), *Protective Groups in Organic Chemistry*, Plenum Press, London and New York, 1973, pp. 121–130.
5 A. HAMPTON, *J. Am. Chem. Soc.*, 83 (1961) 3640–3645.
6 J. W. H. OLDHAM AND J. K. RUTHERFORD, *J. Am. Chem. Soc.*, 54 (1932) 366–378.
7 M. SEKIYA, T. YOSHINO, H. TANAKA, AND Y. ISHIDO, *Bull. Chem. Soc. Jpn.*, 46 (1973) 556–561.
8 T. KANAZAWA, H. TAMURA, AND T. SATO, *Nippon Kagaku Zasshi (J. Chem. Soc. Jpn., Pure Chem. Sect.)*, 79 (1958) 393–395; *Chem. Abstr.*, 54 (1960) 4595f.
9 R. BARKER AND H. G. FLETCHER, JR., *J. Org. Chem.*, 26 (1961) 4605–4609.
10 P. A. LEVENE AND E. T. STILLER, *J. Biol. Chem.*, 104 (1934) 299–306.
11 J. BADDILEY, *J. Chem. Soc.*, (1951) 1348–1351.
12 P. A. LEVENE AND R. S. TIPSON, *J. Biol. Chem.*, 121 (1937) 131–153.
13 P. A. LEVENE AND E. T. STILLER, *J. Biol. Chem.*, 102 (1933) 187–201.
14 E. FISCHER, *Ber.*, 28 (1895) 1145–1167.
15 O. T. SCHMIDT, *Methods Carbohydr. Chem.*, 2 (1963) 320–322.