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REACTIONS OF D-MANNITOL CARBONATE DERIVATIVES CATALYZED BY TETRAETHYLAMMONIUM BROMIDE*

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ABSTRACT

Fusion of 1,2;3,4-di-*O*-isopropylidene-D-mannitol 5,6-carbonate (**1**) with nitrogen heterocycles in the presence of catalytic amounts of tetraethylammonium bromide (**9**) and with *p*-toluenesulfonamide present gave the corresponding 1-deoxy-D-mannitol-1-yl derivatives in good yields. Under the same reaction conditions, 1,2,3,4-tetra-*O*-acetyl-D-mannitol 5,6-carbonate (**26**) gave a good yield of 2,3,5,6-tetra-*O*-acetyl-1,4-anhydro-D-mannitol (**27**). Treatment of **1** with benzoyl chloride and **9** afforded 2-*O*-benzoyl-1-chloro-1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol (**36**) and with acid anhydrides the 1,2-di-*O*-acyl derivatives of di-*O*-isopropylidene-D-mannitol. The use of 3,4-*O*-isopropylidene-D-mannitol 1,2;5,6-dicarbonate (**37**) with benzoyl chloride and acid anhydrides in the presence of **9** gave corresponding products through reaction of both carbonate groups. The reaction mechanisms are discussed.

INTRODUCTION

A new method for synthesis of 1-deoxy-alditol-1-yl derivatives of heterocyclic compounds has been reported from our laboratory[1]. Condensation of alditol carbonates with various heterocyclic imines, catalyzed by tetraethylammonium halides, constitutes an extention of similar reactions of ethylene carbonate with a variety of nucleophiles[2]. We now report detailed results of the reactions of D-mannitol carbonate derivatives with several heterocyclic compounds under catalysis by tetraethylammonium bromide. Also reported are different reactions of D-mannitol carbonates with some active, acyl compounds.

RESULTS AND DISCUSSION

Reactions of 1,2;3,4-di-*O*-isopropylidene-D-mannitol 5,6-carbonate[1] (**1**) with theophylline (**2**), 6-benzylaminopurine (**3**), benzimidazole (**4**), 5,6-dimethylbenzi-

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midazole (**5**), 5-nitrouracil (**6**), phthalimide (**7**), and succinimide (**8**) were conducted in the presence of tetraethylammonium bromide (**9**) as the catalyst. The conditions used and the results obtained are summarized in Table I. Thus, 7-*N*-(1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)theophylline (**10**), 6-benzylamino-3-*N*-(1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)purine (**11**), 1-*N*-(1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)benzimidazole (**12**), 1-*N*-(1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)-5,6-dimethylbenzimidazole (**13**), 1-*N*-(1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)-5-nitrouracil (**14**), and *N*-(1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)-phthalimide (**15**) and -succinimide (**16**) were obtained in good yields. Readily fused heterocycles such as **4**, **7**, and **8** reacted in the molten state to give **12**, **15**, and **16** in good yields. The reactions of heterocycles that were less readily fusible were conducted in *N*,*N*-dimethylformamide to give **10**, **11**, and **13** in rather poor yields. Confronted with these lower yields (except for **10**), fusion of each heterocycle with **1** was conducted with 1.5–3.0 molar equivalents of *p*-toluenesulfonamide[3] (**17**) to effect noteworthy improvements: **11** (79%), **13** (65%), and **10** (80%). In addition, the use of **17** permitted use of decreased reaction-times (Table I).

TABLE I

REACTIONS OF **1** WITH VARIOUS HETEROCYCLIC COMPOUNDS (**2–8**) IN THE PRESENCE OF **9**

Heterocyclic compound	*Reaction conditions*[a]			*Product*	*Yield* (%)
	Reaction in	*Temp. (degrees)*	*Period (h)*		
2	$HCONMe_2$	150–160	8	**10**	75
2	**17**	150–160	2.5	**10**	80
3	$HCONMe_2$	170	6	**11**	45
3	**17**	160–170	3.5	**11**	79
4	fusion	160–170	2	**12**	55[b]
5	$HCONMe_2$	160	11.5	**13**	49
5	**17**	155	8.5	**13**	65
6	**17**	160–170	4.5	**14**	53
7	fusion	160	6	**15**	84
8	fusion	150–160	2.5	**16**	82

[a]Reactions other than those performed in *N*,*N*-dimethylformamide were done *in vacuo*. [b]A considerable proportion of **12** was lost on recrystallization from aqueous methanol.

The reaction of **6** was conducted under fusion with **17** because of **6** was infusible in admixture with **1** and had only low solubility in *N*,*N*-dimethylformamide.

The substitution position was determined by comparing the u.v. spectra of the products isolated with those of the corresponding alkylated heterocycles. Deprotected products were, if necessary, used for structural determination; thus the deprotected compound **11** was assigned as substituted at N-3 of **3** by use of the empirical rule proposed by Leonard *et al.*[4]; compound **11** had earlier been erroneously assigned as the corresponding N-7-substituted isomer because of its ambiguous u.v.-spectral behavior[1]. Proof that the mannitol backbone of **1** underwent substitution at C-1 was

obtained by the successful transformation of **10** into 7-*N*-(2-acetoxyethyl)theophylline by methanolysis of the isopropylidene groups with methanolic hydrogen chloride (73%), followed successively by oxidation with sodium metaperiodate, reduction with sodium borohydride, and acetylation with acetic anhydride–pyridine (48% yield over the three steps). Deacetonation of **10–16** was conducted with methanolic hydrogen chloride, as summarized in Table II, to give 7-*N*-(1-deoxy-D-mannitol-1-yl)theophylline (**18**), 6-benzylamino-3-*N*-(1-deoxy-D-mannitol-1-yl)purine hydrochloride monohydrate (**19**), 1-*N*-(1-deoxy-D-mannitol-1-yl)benzimidazole hydrochloride (**20**), 1-*N*-(1-deoxy-D-mannitol-1-yl)-5,6-dimethylbenzimidazole hydrochloride (**21**), 1-*N*-(1-deoxy-D-mannitol-1-yl)-5-nitrouracil monohydrate (**22**), *N*-(1-deoxy-D-mannitol-1-yl)phthalimide (**23**), and 1-amino-1-deoxy-D-mannitol hydrochloride (**24**), respectively. Methanolysis of **16** at room temperature afforded *N*-(1-deoxy-D-mannitol-1-yl)-succinimide (**25**) in 36% yield, together with a 32% recovery of **16**, as shown in Table II. The effective preparation of compounds **23** and **24** may constitute a useful new route for introducing the amino group into the alditol-1-yl backbone.

TABLE II

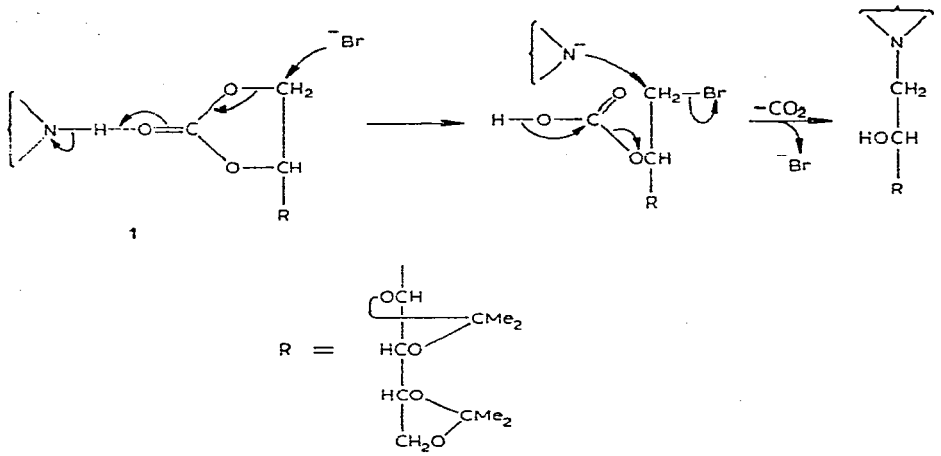
DEACETONATION OF *N*-(1-DEOXY-3,4;5,6-DI-*O*-ISOPROPYLIDENE-D-MANNITOL-1-YL)HETEROCYCLIC COMPOUNDS WITH METHANOLIC HYDROGEN CHLORIDE

Starting material	*Reaction conditions*		*Product*	*Yield* (%)
		Period (*h*)		
10	reflux	20	**18**	73
11	reflux	17	**19**	72[a]
12	reflux	10	**20**	96[b]
13	reflux	17	**21**	72[b]
14	reflux	11	**22**	88[c]
15	reflux	9	**23**	96
16	room temp.	4	**25**	36[d]
16	reflux	15	**24**	60

[a]Obtained as the hydrochloride monohydrate. [b]Obtained as the hydrochloride. [c]Obtained as the monohydrate. [d]The starting material **16** was recovered in 32% yield.

We interpret the probable reaction mechanism as follows. The fact that **1** is not decomposed by ammonium bromide in the absence of heterocyclic compounds under the conditions shown (Table I) suggests that the first step of the reaction is induced by nucleophilic attack of bromide ion on C-1 of the carbonate **1**, with concomitant hydrogen bonding between the heterocyclic imino group and the carbonyl oxygen atom of the carbonate, as depicted in Scheme 1. The second step involves nucleophilic substitution at the terminal bromomethylene carbon atom by the resulting heterocyclic anion, to give the final products with accompanying evolution of carbon dioxide.

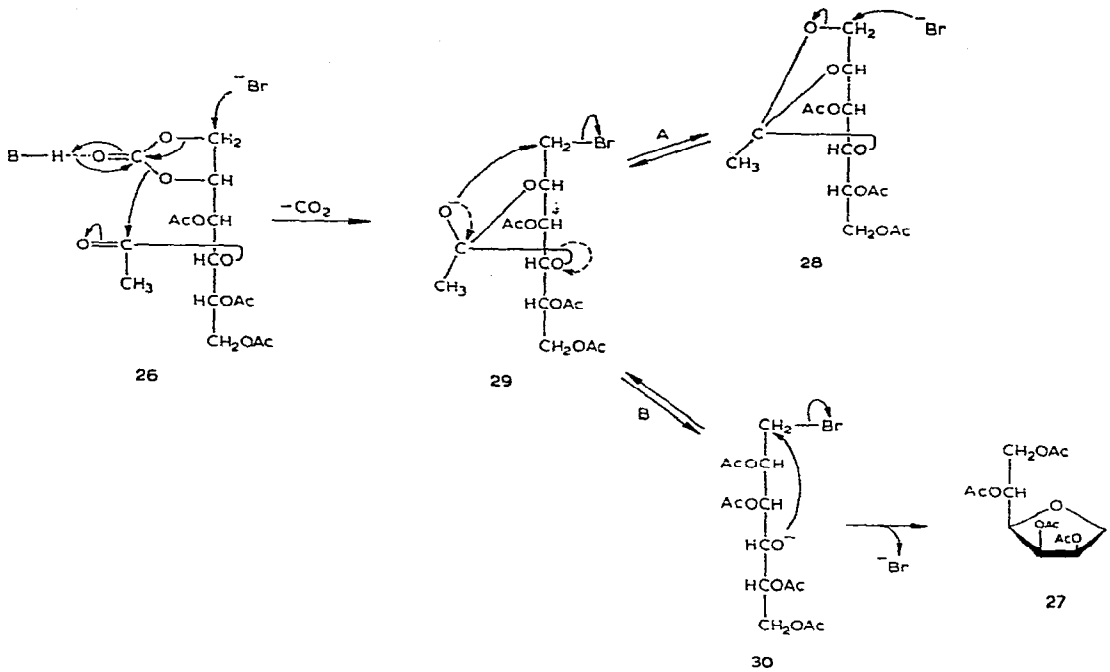
To examine the anchimeric effect of acetyl groups on the reaction, 1,2,3,4-tetra-*O*-acetyl-D-mannitol 5,6-carbonate (**26**) was subsequently used in the reaction instead



Scheme 1.

of the carbonate **1**. Fusion of **26** with **2** in **17**, however, gave no product corresponding to **10**; instead 2,3,5,6-tetra-*O*-acetyl-1,4-anhydro-D-mannitol (**27**) was isolated in 76% yield. Examination of the time-course of this reaction by g.l.c. indicated that the reaction afforded an initial intermediate **28**, which was gradually transformed into **27**. The product **28** was confirmed to be by n.m.r. spectroscopy 3,5,6-tri-*O*-acetyl-D-mannitol 1,2,4-orthoacetate, and was successfully obtained in 42% yield when the reaction was performed under milder conditions for a shorter period of time. Conversion of **27** into 1,4-anhydro-D-mannitol[5] in 75% yield by deacetylation with methanolic ammonia supported the foregoing n.m.r.-spectroscopic assignment. The acid-catalyzed transformation of sugar orthoester derivatives into the corresponding anhydro derivatives has been reported by Bochkov *et al.*[6] and Köll *et al.*[7]. The mechanism for formation of **27** by the reaction catalyzed by tetraethylammonium bromide may be explained in terms of a sequence of electron-transfers, as depicted in Scheme 2; the carbonate **26** may undergo nucleophilic attack by the bromide ion with simultaneous hydrogen-bonding between the carbonyl oxygen atom of the carbonate group of **26** and **2** or **17**, to give the anion **29**, accompanied by release of carbon dioxide. The preponderant formation of **28** in the initial stage of the reaction, and the gradual transformation of **28** into **27**, may be rationalized by assuming that the anion **29** equilibrates with **28** and the anion **30** by way of pathways A and B, and that **28** is formed more rapidly than **27** is formed via **30**.

The proposed mechanism for the reaction of **1** with heterocycles suggested that active acyl compounds such as acid anhydrides or acyl halides might replace the heterocycles and lead to the corresponding 1,2-di-*O*-acyl or 2-*O*-acyl-1-deoxy-1-halo derivatives. Such active acyl compounds as benzoic anhydride (**31**), acetic anhydride (**32**), and benzoyl chloride (**33**) were chosen for the reaction with **1**. The conditions used and the results thus obtained are summarized in Table III; runs 1–5.



Scheme 2.

TABLE III

REACTIONS OF **1** OR **37** WITH SOME ACTIVE ACYL COMPOUNDS IN THE PRESENCE OF **9**

Run No.	*Carbonate precursor*	*Active acyl compound*	*Reaction conditions*		*Product*	*Yield (%)*
			Temp. (degrees)	*Period (h)*		
1	**1**	**31**	155–160	3	**34**	56
2	**1**	**31**	155–160[a]	3	**34**	100
3	**1**	**32**	155–160	3.5	**35**	87
4	**1**	**32**	160[b]	1	**35**	100
5	**1**	**33**	160	2.5	**36**	99
6	**37**	**31**	155	1.5	**41**	63
7	**37**	**31**	155[a]	1.5	**41**	94
8	**37**	**33**	150–160	5	**38**	59

[a]Performed in the presence of a catalytic amount of sodium benzoate. [b]Performed in the presence of a catalytic amount of sodium acetate.

The reaction of **1** with **31** (run 1), **32** (run 3), and **33** (run 5) afforded 1,2-di-*O*-benzoyl-3,4;5,6-di-*O*-isopropylidene-D-mannitol (**34**), 1,2-di-*O*-acetyl-3,4;5,6-di-*O*-isopropylidene-D-mannitol (**35**), and 2-*O*-benzoyl-1-chloro-1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol (**36**), respectively. The lower yields observed for **34** and **35**

led to the reactions being performed in the presence of the corresponding sodium acylates, which may assist the nucleophilic substitution of the resulting bromomethylene group; these conditions afforded both **34** and **35** in quantitative yields (runs 2 and 4). These reactions did not proceed at all without the ammonium bromide **9**, even in the presence of the acylate ions; this may reflect the magnitude of the nucleophilic constants reported by Pearson *et al.*[8]. The structures of **34** and **35** were confirmed by comparing their properties with those of the corresponding acylation products from 1,2;3,4-di-*O*-isopropylidene-D-mannitol. However, the structure of **36** could not be confirmed by n.m.r. spectroscopy because of signal overlap (δ 3.6–4.5, 7 H, including H-1 and H-1'). The reaction of 3,4-*O*-isopropylidene-D-mannitol 1,2;5,6-dicarbonate (**37**) with **33** was thus undertaken (run 8) to give 2,5-di-*O*-benzoyl-1,6-dichloro-1,6-dideoxy-3,4-*O*-isopropylidene-D-mannitol (**38**), whose n.m.r. spectrum was successfully analyzed because of its simplicity. The site of chlorination was subsequently confirmed by comparing the n.m.r.-spectral data with those of 1-chloropropane (**39**), 2-chloropropane (**40**), and 1,2,5,6-tetra-*O*-benzoyl-3,4-*O*-isopropylidene D-mannitol (**41**, also prepared from **37** and **31** in the same manner; runs 6 and 7). The data are summarized in Table IV. The chemical shifts of the terminal methylene signals of **38** are closer to those of **39** than those of **41**. On the other hand, the chemical shifts of its methine signals appear closer to those of **41** rather than those of **40**. It was thus concluded that chlorination had occurred at the terminal bromomethylene group by the chloride ion resulting during the course of the reaction, according to the mechanism depicted in Scheme 1. By analogy, the chlorination of **36** was likewise deduced.

TABLE IV

N.M.R.-SPECTRAL DATA FOR **38**, **41**, AND CHLOROPROPANES **39** AND **40**

Compound	*Chemical shift* (δ)	
	Terminal methylene protons	*Penultimate methine proton*
38	3.88	5.39
1-Chloropropane (**39**)[a]	3.47[b]	—
2-Chloropropane (**40**)[a]	—	4.12[b]
41	~4.7	5.67

[a]See ref. 9. [b]Data obtained in carbon tetrachloride.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Specific rotations were measured with a Hitachi polarimeter Model PO-B. Solutions were evaporated *in vacuo*. I.r. spectra were recorded with a Hitachi 285 model, and n.m.r. spectra were recorded by using Varian NV-14 or NV-21 spectrometers on samples in chloroform-*d* with tetramethylsilane as the internal standard. Chemical shifts are given on the

δ scale, and the J values recorded are first-order spacings. U.v. spectra were recorded with a Hitachi EPS-3T spectrophotometer. Column chromatography was conducted with Wako-gel C-300. G.l.c. was performed on a Hitachi K-53 instrument with a column of 10% of SE-30 on Chromosorb W and nitrogen as the carrier gas.

*General procedure for reaction of 1,2;3,4-di-*O*-isopropylidene-*D*-mannitol 5,6-carbonate* (**1**) *with heterocyclic compounds in the presence of tetraethylammonium bromide* (**9**). — *Procedure A.* A mixture of **1** (ref. 10, 2.9 g, 10 mmol), the heterocyclic compound (**2**, **3**, or **5**, 11–15 mmol), and tetraethylammonium bromide (**9**, 0.5 g, 2.5 mmol) was heated in *N*,*N*-dimethylformamide (10 ml) until no further evolution of carbon dioxide was observed (compare Table I). The solution was then evaporated to dryness, the residue was dissolved in chloroform (50 ml), and the solution was washed successively with M aqueous sodium hydroxide and twice with water. The dried (anhydrous calcium chloride) organic layer was evaporated to give the corresponding products (**10**, **11**, or **13**). The crude products were purified by column chromatography on silica gel and/or by recrystallization.

Procedure B. A mixture of **1** (2.9 g, 10 mmol), the heterocyclic compound (**2**, **3**, or **5**, 11–15 mmol), and compound **9** (0.5 g, 2.5 mmol) was heated with *p*-toluenesulfonamide (**17**, 14–30 mmol) until no further evolution of carbon dioxide was observed. Chloroform (50 ml) was then added to the hot resulting mixture. The chloroform solution was washed successively with M aqueous sodium hydroxide (twice) and twice with water. After drying over anhydrous calcium chloride, the solution was evaporated to give the corresponding products (**10**, **11**, or **13**). The crude products were purified as described in Procedure A.

Procedure C. A mixture of **1** (2.9 g, 10 mmol), the heterocyclic compound (**4**, **7**, or **8**, 10–15 mmol), and **9** (0.5 g, 2.5 mmol) was fused *in vacuo* until no further evolution of carbon dioxide was observed. Chloroform (50 ml) was then added to the hot mixture and the solution thus obtained was washed, dried, evaporated, and the product purified as previously described.

General deacetonation procedure for products **10**–**16**. — Compounds **10**–**16** (2 mmol) were each treated with methanolic hydrogen chloride (from 10 ml saturated at 0°, plus an additional 50 ml of methanol) under reflux. After a suitable interval of time (see Table II), the solvent was evaporated off, and the resulting, crude crystals were washed with hot chloroform to remove contaminants, giving products pure enough for elementary analysis, except for compounds **14** and **15**. Pure **14** was obtained simply by filtering off the crystals that precipitated out on cooling. The purification procedure used for **15** was the same as that for **14**, except that the product precipitated out while the solution was being heated under reflux.

General procedure for reaction of **1** *or 3,4-*O*-isopropylidene-*D*-mannitol 1,2;5,6-dicarbonate* (**37**) *with active acyl compounds* (**31**, **32**, *or* **33**) *catalyzed by* **9**. — A mixture of **1** (0.59 g, 2 mmol) or **37** (ref. 10, 0.55 g, 2 mmol), the active acyl compound (**31**, **32**, or **33**, 13–25 mmol), and **9** (12.5 mmol) was heated until no further evolution of carbon dioxide was observed. Chloroform (50 ml) and water (50 ml, saturated with sodium hydrogencarbonate) was then added, and the resulting mixture was shaken to

decompose the excess of active acyl compound. The dried organic layer was then evaporated to give the corresponding products (**34**, **35**, **36**, **38**, or **41**). The crude products were purified by recrystallization or by chromatography on a silica gel column.

Reaction of **1** *with theophylline* (**2**). — Procedure A or B were used to afford 7-*N*-(1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)theophylline (**10**); recrystallized from benzene–cyclohexane it had m.p. 160–161°, $[\alpha]_D^{22}$ +47° (*c* 1.0, chloroform); λ_{max}^{EtOH} 273 nm (ε 9,400).

Anal. Calc. for $C_{19}H_{28}N_4O_7$: C, 53.76; H, 6.65; N, 13.20. Found: C, 54.06; H, 6.72; N, 13.06.

Deacetonation of **10** gave 7-*N*-(1-deoxy-D-mannitol-1-yl)theophylline (**18**); m.p. 210° (dec), $[\alpha]_D^{22}$ +74° (*c* 1.0, water); $\lambda_{max}^{H_2O}$ 273 nm (ε 6,300).

Anal. Calc. for $C_{13}H_{20}N_4O_7$: C, 45.34; H, 5.85; N, 16.27. Found: C, 45.40; H, 5.74; N, 16.37.

Conversion of **18** *into* 7-N-(*2-acetoxyethyl*)*theophylline.* — A solution of compound **18** (0.34 g, 1 mmol) in water (20 ml) was oxidized with sodium metaperiodate (0.94 g, 4.4 mmol) for 1 h at room temperature, keeping its pH between 4 and 5 by addition of crystalline sodium hydrogencarbonate. The solvent was then evaporated to a volume of 10 ml. The solution was further treated with sodium borohydride (2.0 g, 53 mmol), keeping the pH at ~6 by addition of dilute aqueous sulfuric acid. After reduction, the solvent was evaporated off and the residue was treated conventionally with acetic anhydride (1 ml) and pyridine (2 ml) to give 0.13 g (48%) of 7-*N*-(2-acetoxyethyl)theophylline; after recrystallization from ethanol it had m.p. 103–104°, λ_{max}^{EtOH} 273 nm (ε 9,900); n.m.r.: δ 2.03 (3-proton singlet, OAc), 3.04 and 3.59 (two 3-proton singlets, NMe), 4.4–4.7 (4-proton multiplet, A_2B_2 spin system), and 7.62 (1-proton singlet, H-8).

Anal. Calc. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.64; H, 5.25; N, 21.05.

Reaction of **1** *with 6-benzylaminopurine* (**3**). — Procedure A or B was used to give 6-benzylamino-3-*N*-(1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)purine (**11**), which was triturated with hot ethanol; m.p. 220–221°, $[\alpha]_D^{22}$ +55° (*c* 1.1, *N*,*N*-dimethylformamide); $\lambda_{max}^{CHCl_3}$ 296 nm (ε 18,900).

Anal. Calc. for $C_{24}H_{31}N_5O_5$: C, 61.63; H, 6.66; N, 14.92. Found: C, 61.30; H, 6.58; N, 15.05.

Deacetonation of **11** gave 6-benzylamino-3-*N*-(1-deoxy-D-mannitol-1-yl)purine hydrochloride monohydrate (**19**), m.p. 119–120°, $[\alpha]_D^{22}$ +9° (*c* 1.0, water); $\lambda_{max}^{H_2O\,(acidic)}$ 286 nm (ε 23,500), $\lambda_{min}^{H_2O\,(acidic)}$ 242 nm (ε 4,200), $\lambda_{max}^{H_2O}$ 288 nm (ε 20,600), $\lambda_{min}^{H_2O}$ 248 nm (ε 4,000), $\lambda_{max}^{H_2O\,(basic)}$ 289 nm (ε 19,800), and $\lambda_{min}^{H_2O\,(basic)}$ 249 nm (ε 4,400).

Anal. Calc. for $C_{18}H_{23}N_5O_5 \cdot HCl \cdot H_2O$: C, 48.70; H, 5.90; N, 15.77. Found: C, 48.99; H, 5.94; N, 16.02.

Reaction of **1** *with benzimidazole* (**4**). — Procedure C was used to give 1-*N*-(1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)benzimidazole (**12**); recrystallized from aqueous methanol it had m.p. 128–129°, $[\alpha]_D^{22}$ +47° (*c* 1.0, acetone); λ_{max}^{EtOH} 248

(ε 7,100), 253 (7,100), 265 (4,400), 274 (4,800), and 281 nm (5,000), λ_{min}^{EtOH} 222 (ε 2,000), 250 (6,900), 263 (4,300), 270 (3,900), and 278 nm (2,500).

Anal. Calc. for $C_{19}H_{26}N_2O_5$: C, 62.96; H, 7.23; N, 7.73. Found: C, 62.93; H, 7.20; N, 7.68.

Deacetonation of **12** gave *N*-(1-deoxy-D-mannitol-1-yl)benzimidazole hydrochloride (**20**); m.p. 175–175.5°, $[\alpha]_D^{22}$ +29° (*c* 1.0, water); $\lambda_{max}^{H_2O}$ 248 (ε 5,700), 254 (5,800), 263 (5,200), 269 (6,000), and 276 nm (5,500), $\lambda_{min}^{H_2O}$ 252 (ε 5,700), 259 (5,100), 265 (5,100), and 273 nm (4,100), $\lambda_{max}^{H_2O\,(basic)}$ 247 (ε 6,500), 253 (6,500), 265 (4,600), 273 (4,600), and 280 nm (3,700), $\lambda_{min}^{H_2O\,(basic)}$ 250 (ε 6,500), 262 (4,500), 270 (4,300), and 277 nm (2,800).

Anal. Calc. for $C_{13}H_{18}N_2O_5 \cdot HCl$: C, 48.98; H, 6.00; N, 8.78. Found: C, 48.75; H, 6.01; N, 8.66.

Reaction of **1** *with 5,6-dimethylbenzimidazole* (**5**). — Procedure A or B was used to give 1-*N*-(1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)-5,6-dimethylbenzimidazole (**13**). Recrystallized from cyclohexane–benzene it had m.p. 212–213°, $[\alpha]_D^{22}$ −4° (*c* 1.0, chloroform); λ_{max}^{EtOH} 251 (ε 8,300), 280 (6,850), and 289 nm (6,850), λ_{min}^{EtOH} 267 (ε 4,700), and 286 nm (5,760), $\lambda_{shoulder}^{EtOH}$ 255 nm (ε 8,200).

Anal. Calc. for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found: C, 64.76; H, 7.71; N, 7.02.

Deacetonation of **13** gave 1-*N*-(1-deoxy-D-mannitol-1-yl)-5,6-dimethylbenzimidazole hydrochloride (**21**); m.p. 206–207° (dec.), $[\alpha]_D^{22}$ +32° (*c* 1.1, water); $\lambda_{max}^{H_2O}$ 277 (ε 9,000) and 286 nm (8,600), $\lambda_{min}^{H_2O}$ 283 nm (ε 7,600), and $\lambda_{shoulder}^{H_2O}$ 257 (ε 5,800), and 271 nm (7,300).

Anal. Calc. for $C_{15}H_{22}N_2O_5 \cdot HCl$: C, 51.94; H, 6.68; N, 8.07. Found: C, 51.96; H, 6.62; N, 8.22.

Reaction of **1** *with 5-nitrouracil* (**6**). — Procedure B was used. The 1-*N*-(1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)-5-nitrouracil (**14**) obtained was triturated with hot 19:1 benzene–acetone; m.p. 195–196°, $[\alpha]_D^{22}$ +23° (*c* 1.0, *N*,*N*-dimethylformamide), $\lambda_{max}^{10\%\,aq.\,EtOH}$ 238 (ε 7,200) and 308 nm (10,100), $\lambda_{min}^{10\%\,aq.\,EtOH}$ 216 (ε 6,000) and 263 nm (2,600), $\lambda_{max}^{10\%\,aq.\,EtOH\,(basic)}$ 324 nm (ε 9,800), $\lambda_{min}^{10\%\,aq.\,EtOH\,(basic)}$ 269 nm (ε 2,800), and $\lambda_{shoulder}^{10\%\,aq.\,EtOH\,(basic)}$ 244 nm (ε 6,400).

Anal. Calc. for $C_{16}H_{23}N_3O_9$: C, 47.88; H, 5.78; N, 10.47. Found: C, 47.58; H, 5.73; N, 10.59.

Deacetonation of **14** gave 1-*N*-(1-deoxy-D-mannitol-1-yl)-5-nitrouracil monohydrate (**22**), which was triturated with methanol; m.p. 214–215°, $[\alpha]_D^{24}$ +33° (*c* 0.9, water); $\lambda_{max}^{H_2O\,(basic)}$ 220 (ε 9,000) and 322 nm (17,600), $\lambda_{min}^{H_2O\,(basic)}$ 266 nm (ε 2,200), $\lambda_{max}^{H_2O}$ 241 (ε 8,100) and 312 nm (12,600), $\lambda_{min}^{H_2O}$ 264 nm (ε 2,800), $\lambda_{max}^{H_2O\,(acidic)}$ 242 (ε 8,800) and 309 nm (12,400), and $\lambda_{min}^{H_2O\,(acidic)}$ 264 nm (ε 3,100).

Anal. Calc. for $C_{10}H_{15}N_3O_9 \cdot H_2O$: C, 35.40; H, 5.05; N, 12.39. Found: C, 35.78; H, 5.05; N, 12.45.

Reaction of **1** *with phthalimide* (**7**). — Procedure C was used. *N*-(1-Deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)phthalimide (**15**) crystallized from aqueous methanol; m.p. 76–77.5°, $[\alpha]_D^{22}$ +44° (*c* 1.0, acetone); λ_{max}^{EtOH} 222 (ε 12,400)

and 292 nm (2,000), λ_{min}^{EtOH} 257 nm (ε 600), and $\lambda_{shoulder}^{EtOH}$ 240 (ε 4,000) and 299 nm (1,900).

Anal. Calc. for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.28; H, 6.30; N, 3.54.

Deacetonation of **15** gave *N*-(1-deoxy-D-mannitol-1-yl)phthalimide (**23**); after trituration with methanol it had m.p. 231–233°, $[\alpha]_D^{22}$ +32° (*c* 1.0, *N*,*N*-dimethylformamide); $\lambda_{max}^{H_2O}$ 298 nm (ε 2,700).

Anal. Calc. for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.51; N, 4.50. Found: C, 54.04; H, 5.55; N, 4.57.

Reaction of **1** *with succinimide* (**8**). — Use of procedure C gave *N*-(1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol-1-yl)succinimide (**16**); from benzene it had m.p. 146–147°, $[\alpha]_D^{22}$ +11° (*c* 1.1, chloroform).

Anal. Calc. for $C_{16}H_{25}NO_7$: C, 55.96; H, 7.34; N, 4.08. Found: C, 55.87; H, 7.11; N, 3.92.

Deacetonation of **16**. — Compound **16** (0.69 g, 2 mmol) was stirred in a mixture of methanolic hydrogen chloride (0.5 ml) and methanol (20 ml) for 4 h at room temperature, and the resulting solution was evaporated until colorless crystals began to precipitate. Filtration of the crystals and washing with methanol afforded *N*-(1-(deoxy-D-mannitol-1-yl)succinimide (**25**, 0.19 g 36% yield); m.p. 174–176°, $[\alpha]_D^{22}$ +25° *c* 1.0, water).

Anal. Calc. for $C_{10}H_{17}NO_7$: C, 45.62; H, 6.51; N, 5.32. Found: C, 45.90; H, 6.50; N, 5.21.

From the filtrate, 0.22 g (32%) of the **16** was recovered.

The general deprotection procedure was used to give 1-amino-1-deoxy-D-mannitol hydrochloride (**24**), which was triturated with hot ethanol; m.p. 161.5–162.5°, $[\alpha]_D^{22}$ +3° (*c* 1.0, water) (lit.[11] m.p. 163–165°, $[\alpha]_D$ +5° in water).

Anal. Calc. for $C_6H_{15}NO_5 \cdot HCl$: C, 33.11; H, 7.40; N, 6.44. Found: C, 33.21; H, 7.26; N, 6.46.

*Preparation of 1,2,3,4-tetra-*O*-acetyl-*D*-mannitol 5,6-carbonate* (**26**). — Compound **1** (2.9 g, 10 mmol) was treated in a mixture of anhydrous methanol (100 ml) and methanolic hydrogen chloride (10 ml, saturated at 0°) for 3.5 h at room temperature. The resulting solution was then evaporated to dryness below 25°, and the residue was dissolved in a mixture of chloroform (100 ml) and pyridine (10 ml). The solution was treated with acetic anhydride (6 ml), and conventional processing afforded 3.1 g (82%) of pure 1,2,3,4-tetra-*O*-acetyl-D-mannitol 5,6-carbonate (**26**). Without further purification it had m.p. 130–130.5°, $[\alpha]_D^{22}$ +29° (*c* 1.0, acetone); $\nu_{C=O}^{KBr}$ 1745, 1750 (OAc), and 1805 cm^{-1} (five-membered, cyclic carbonate).

Anal. Calc. for $C_{15}H_{20}O_{11}$: C, 47.87; H, 5.36. Found: C, 48.04; H, 5.39.

Attempted reaction of **26** *with* **2** *in* **17**. — The carbonate **26** (0.75 g, 2 mmol), **2** (0.6 g, 3 mmol), and **9** (0.1 g, 0.5 mmol) were fused together with **17** (0.5 g, 2.9 mmol) at 150–155° *in vacuo* for 5 h, whereupon chloroform (30 ml) was added. The organic solution was treated similarly in the reaction of **1** with **2** in **17** to give a crude syrup that was then purified by chromatography on a column of silica gel with

chloroform as eluant, to give 0.50 g (76%) of 2,3,5,6-tetra-*O*-acetyl-1,4-anhydro-D-mannitol (**27**); $[\alpha]_D^{22}$ +20° (*c* 1.4, chloroform) {lit.[12] [α] +23° (acetic acid)}; $\nu_{C=O}^{KBr}$ 1740 cm^{-1} (OAc); n.m.r.: δ 3.82 (1-proton doublet of doublets, H-1, $J_{1,1'}$ 9.5 Hz and $J_{1,2}$ 6.7 Hz), 4.10 (1-proton doublet of doublets, H-1′, $J_{1',2}$ 6.7 Hz), 5.36 (1-proton multiplet, H-2, $J_{2,3}$ 4.8 Hz), 5.54 (1-proton doublet of doublets, H-3, $J_{3,4}$ 4.0 Hz), 4.17 (1-proton doublet of doublets, H-4, $J_{4,5}$ 9.5 Hz), 5.28 (1-proton multiplet, H-5, $J_{5,6}$ 2.5 Hz and $J_{5,6'}$ 5.5 Hz), 4.57 (1-proton doublet of doublets, H-6, $J_{6,6'}$ 12.2 Hz), 4.09 (1-proton doublet of doublets, H-6′), 1.79, 1.83, and 1.84 (three 3-proton singlets, OAc).

Anal. Calc. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.21; H, 6.09.

Decomposition of **26** *in the presence of* **9** *in* **17**. — The carbonate **26** (0.75 g, 2 mmol) and **9** (0.5 g, 2.5 mmol) were heated in **17** (1.0 g, 5.8 mmol) at 150–160° for 4.5 h *in vacuo*, followed by the same treatment as before, to give 0.65 g (98%) of **27**.

*Isolation of the intermediate, 3,5,6-tri-*O*-acetyl-*D*-mannitol 1,2,4-orthoacetate* (**28**). — The carbonate **26** (0.75 g, 2 mmol) and **9** (0.5 g, 2.5 mmol) were heated in **17** (0.5 g, 2.9 mmol) for 2 h at 140–150° *in vacuo*, followed by the same treatment as before, to give a syrup, purification of which by chromatography on a column of silica gel with chloroform as eluant afforded the starting material **26** (0.17 g, 22% recovery), **27** (0.21 g, 33% yield), and the orthoacetate **28** (0.29 g, 42%). The product **28** had m.p. 136–137°; $\nu_{C=O}^{KBr}$ 1740 cm^{-1} (OAc); n.m.r.: δ 4.06 (1-proton doublet of doublets, H-1, $J_{1,1'}$ 8.2 Hz and $J_{1,2}$ 1.0 Hz), 3.92 (1-proton doublet of doublets, H-1′, $J_{1',2}$ 8.1 Hz), 4.67 (1-proton multiplet, H-2, $J_{2,3}$ 2.2 Hz), 4.74 (1-proton doublet of doublets, H-3, $J_{3,4}$ 3.0 Hz), 4.27 (1-proton doublet of doublets, H-4, $J_{4,5}$ 9.5 Hz), 5.24 (1-proton multiplet, H-5, $J_{5,6}$ 5.2 Hz and $J_{5,6'}$ 2.6 Hz), 4.08 (1-proton doublet of doublets, H-6, $J_{6,6'}$ 12.5 Hz), 4.48 (1-proton doublet of doublets, H-6′), 1.99, 2.06, and 2.13 (three 3-proton singlets, OAc), and 1.64 (3-proton singlet, orthoacetyl methyl protons).

Anal. Calc. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.60; H, 6.08.

Deacetylation of **27**. — Compound **27** (0.44 g, 1.3 mmol) was treated with methanolic ammonia saturated at 0° (30 ml) in a tightly stoppered, round-bottomed flask for 2 days at room temperature whereupon the solution was evaporated and the residue was triturated with a small amount of chloroform to remove acetamide. The insoluble mass was filtered off and recrystallized from aqueous ethanol to give 0.16 g (75%) of 1,4-anhydro-D-mannitol; m.p. 139–140°, $[\alpha]_D^{22}$ −26° (*c* 0.7, water) (lit.[5] 145–148°, $[\alpha]_D$ −24° in water).

Anal. Calc. for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.70; H, 7.26.

Reaction of **1** *with benzoic anhydride* (**31**). — The carbonate **1** (0.59 g, 2 mmol), **31** (0.6 g, 2.6 mmol), and **9** (0.5 g, 2.5 mmol) were heated together for 3 h at 155–160°, and the resulting syrup was then purified by column chromatography on silica gel with benzene as eluant to give 0.53 g (56%) of 1,2-di-*O*-benzoyl-3,4;5,6-di-*O*-isopropylidene-D-mannitol (**34**); m.p. 86.5–87.5°, $[\alpha]_D^{22}$ +28° (*c* 1.0, acetone); $\nu_{C=O}^{KBr}$ 1725 cm^{-1} (OBz).

Anal. Calc. for $C_{26}H_{30}O_8$: C, 66.37; H, 6.48. Found: C, 66.25; H, 6.50.

Reaction of **1** *with* **31** *in the presence of sodium benzoate.* — The carbonate **1** (0.59 g, 2 mmol), **31** (0.6 g, 2.7 mmol), **9** (0.5 g, 2.4 mmol), and sodium benzoate (1 mg) were heated together for 3 h at 155–160°, and subsequent treatment as before afforded 0.98 g (100%) of 1,2-di-*O*-benzoyl-3,4;5,6-di-*O*-isopropylidene-D-mannitol (**34**).

Reaction of **1** *with acetic anhydride* (**32**). — The carbonate **1** (0.59 g, 2 mmol), **32** (0.2 g, 20 mmol), and **9** (0.5 g, 2.5 mmol) were heated together for 3.5 h at 155–160°, and subsequently processed by the general procedure already described to afford 0.6 g (87%) of syrupy 1,2-di-*O*-acetyl-3,4;5,6-di-*O*-isopropylidene-D-mannitol (**35**); $[\alpha]_D^{22}$ +27° (*c* 0.93, chloroform); $\nu_{C=O}^{KBr}$ 1740 cm^{-1} (OAc); n.m.r.: δ 1.36 (3-proton singlet, Me-C), 1.38 (6-proton singlet, Me-C), 1.43 (3-proton singlet, Me-C), 2.05 (3-proton singlet, OAc), 2.10 (3-proton singlet, OAc), 4.52 (1-proton doublet of doublets, H-1, $J_{1,1'}$ 12.0 Hz and $J_{1,2}$ 3.8 Hz), and 5.33 (1-proton multiplet, H-2). These n.m.r.-spectral data were in good accord with those of an authentic sample prepared in quantitative yield by conventional acetylation of 1,2;3,4-di-*O*-isopropylidene-D-mannitol with **32**–pyridine.

Reaction of **1** *with* **32** *in the presence of sodium acetate.* — The carbonate **1** (0.59 g, 2 mmol), **9** (0.5 g, 2.5 mmol), **32** (1 g, 10 mmol), and sodium acetate (1 mg) were heated together for 1 h at 160°, and subsequently processed as before to afford 0.69 g (100%) of **35**. After recrystallization from aqueous methanol it had m.p. 55–56°, $[\alpha]_D^{22}$ +31° (*c* 1.0, acetone); $\nu_{C=O}^{KBr}$ 1740 cm^{-1} (OAc). The n.m.r. spectrum of this product was superposable on that of the foregoing product.

Anal. Calc. for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57. Found: C, 55.62; H, 7.55.

Reaction of **1** *with benzoyl chloride* (**33**). — The carbonate **1** (0.59 g, 2 mmol), **9** (0.5 g, 2.5 mmol), and **33** (1.4 g, 10 mmol) were heated together for 2.5 h at 160° and the resulting mixture was processed by the general procedure to give 0.76 g (99%) of 2-*O*-benzoyl-1-chloro-1-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol (**36**); m.p. 59.5–60.5°, $[\alpha]_D^{22}$ +4° (*c* 1.0, acetone); $\nu_{C=O}^{KBr}$ 1720 cm^{-1} (OBz).

Anal. Calc. for $C_{19}H_{25}ClO_6$: C, 59.29; H, 6.54. Found: C, 59.17; H, 6.52.

Reaction of **37** *with* **33**. — The dicarbonate **37** (1.1 g, 4 mmol), **9** (2.2 g, 10 mmol), and **33** (1.4 g, 10 mmol) were heated together for 5 h at 150–160°, and crystallization and recrystallization (cyclohexane) of the crystals obtained by the general isolation procedure gave 1.1 g (59%)* of 2,5-di-*O*-benzoyl-1,6-dichloro-1,6-dideoxy-3,4-*O*-isopropylidene-D-mannitol (**38**); m.p. 115–116°, $[\alpha]_D^{22}$ −10.4° (*c* 1.1, chloroform); $\nu_{C=O}^{KBr}$ 1715 cm^{-1} (OBz); n.m.r.: δ 1.47 (6-proton singlet, Me-C), 3.88 (4-proton, multiplet having ABX spacings, H-1, H-1′, H-6, and H-6′, $J_{1,2} = J_{5,6} = 4.0$ Hz, $J_{1',2} = J_{5,6'} = 5.0$ Hz, and $J_{1,1'} = J_{6,6'} = 12.0$ Hz), 5.39 (2-proton multiplet, H-2 and H-5), and 4.51 (2-proton multiplet having ABX spacings, H-3 and H-4).

Anal. Calc. for $C_{23}H_{24}Cl_2O_6$: C, 59.10; H, 5.17. Found: C, 59.08; H, 5.11.

Reaction of **37** *with* **31**. — The dicarbonate **37** (0.55 g, 2 mmol), **9** (0.5 g, 2.5 mmol), and **31** (1.0 g, 4.4 mmol) were heated together for 1.5 h at 155°, and

*A considerable amount of **38** was lost on purification on account of its high solubility.

crystallization and recrystallization (cyclohexane) of the crystals obtained by the general procedure described gave 0.80 g (63%) of 1,2,5,6-tetra-*O*-benzoyl-3,4-*O*-isopropylidene-D-mannitol (**41**); m.p. 112–113°, $[\alpha]_D^{22}$ +24° (*c* 1.0, acetone) (lit.[13] m.p. 122–123°, $[\alpha]_D$ +15.5°); $\nu_{C=O}^{KBr}$ 1720 cm^{-1} (OBz); n.m.r.: δ 1.52 (6-proton singlet, Me-C) and 5.67 (2-proton multiplet, H-2 and H-5).

Anal. Calc. for $C_{37}H_{34}O_{10}$: C, 69.58; H, 5.37. Found: C, 69.55; H, 5.66.

Preparation of **41** *from 3,4-O-isopropylidene-D-mannitol.* — In the conventional way, 3,4-*O*-isopropylidene-D-mannitol[14] (0.45 g, 2 mmol) was treated with **33** (2 ml) in a mixture of pyridine (5 ml) and chloroform (20 ml). The resulting mixture was washed with water, M aqueous hydrochloric acid, and water, dried over anhydrous calcium chloride, and evaporated to give a crude syrup that crystallized after storage for about a week at room temperature. Recrystallization of the crystals from benzene–cyclohexane gave 0.92 g (70%) of **41**.

Reaction of **37** *with* **31** *in the presence of sodium benzoate.* — The dicarbonate **37** (0.28 g, 1 mmol), **9** (0.25 g, 1.2 mmol), **31** (0.6 g, 2.7 mmol), and sodium benzoate (1 mg) were heated together for 1.5 h at 155°, and after treatment as already described, 0.60 g (94%) of **41** was obtained.

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