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REGIOSELECTIVE (PHENYLCARBAMOYL)ATION OF POLYHYDROXY COMPOUNDS BY PHENYL ISOCYANATE–ZINC NAPHTHENATE*

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ABSTRACT

In the presence of zinc naphthenate as the catalyst, the reaction of phenyl isocyanate with 1,2-propanediol and 3,4-*O*-isopropylidene-D-mannitol gave the primary phenylcarbamates in high yield. 1,2,6-Hexanetriol was selectively phenylcarbamoylated at O-1, and N^6-benzyladenosine at O-2′. The common methyl aldohexo- and aldopento-pyranosides gave the 3-mono(phenylcarbamate)s in fair to excellent yields, along with substantial proportions of the 2-esters in some cases. When the zinc salt was not used, O-6 was the most reactive of the oxygen atoms in the hexopyranosides.

INTRODUCTION

We have reported regioselective (phenylcarbamoyl)ation reactions with the systems phenyl isocyanate–bis(tributyltin) oxide[2] and phenyl isocyanate–dibutyltin oxide and –tertiary amines[3] with respect to a series of ribonucleosides; the reaction with phenyl isocyanate, after preparation of the tin alkoxide, gave the corresponding 5′-(phenylcarbamate)s specifically, if an equimolar amount of phenyl isocyanate was used; on the other hand, brief treatment with phenyl isocyanate (2 mol. equiv.) and bis(tributyltin) oxide at room temperature gave the corresponding 3′-(phenylcarbamate)s preponderantly, if 11:1 toluene–DMF was the solvent system. Incidentally, the latter reaction using thymidine as an example of a 2′-deoxyribonucleoside was of interest, as it gave[2] the corresponding 5′-(phenylcarbamate) specifically; it was deduced that the equimolar adduct of bis(tributyltin) oxide and phenyl isocyanate is the entity which catalyzes the reaction so effectively. Such excellent regioselectivity prompted us to conduct further investigation of the reaction, in an attempt to find a more effective additive; we now report the results obtained by the use of zinc naphthenate.

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RESULTS AND DISCUSSION

Reactions of polyols. — A kinetic study on (phenylcarbamoyl)ation of monools demonstrated that the reaction velocity of primary is higher than that of secondary alcohols[4], and addition of amines or metallic ions, or both, as the catalyst was found to increase the velocity considerably[5–7]. Therefore, we were interested in potential regioselectivity on applying the reaction to polyhydroxy compounds. First, the reaction of 1,2-propanediol (**1**) as a model compound was examined, and DMF, 11:1 toluene–DMF, toluene, and 1:1 toluene–chloroform were each used as the solvent. As the additives, pyridine (a weak base[6,7]), triethylamine (a stronger catalyst), and zinc ion, which interacts with the nitrogen atom of phenyl isocyanate more strongly than with its oxygen atom[5], were used for comparison with dibutyltin oxide[3]. All of the reactions were performed by adding phenyl isocyanate (1.5 mmol) to the solution of **1** (1 mmol) in the presence of each of the additives; the conditions used and the results obtained are summarized in Table I. The proportions of 1- (**2**) and 2-(phenylcarbamate) (**3**) were determined by ^{1}H-n.m.r. spectroscopy [60 MHz, $(CD_3)_2SO$–D_2O] with respect to each of the resulting mixtures in terms of the area-ratio of the methylene proton signal of **3** (doublet at δ 3.57) and the methyl proton signals of **2** and **3** (two doublets at δ ~1.2, overlapped).

As may be seen from Entry 1, DMF was found to be the best solvent for the reaction without additives, compared with chloroform and 11:1 toluene–DMF. The regioselectivity obtained in chloroform (**2**:**3** = 3.7:1) was the highest, although the total yield (12%) was the lowest. Entries 2, 3, and 4 proved that the reaction catalyzed by triethylamine gives the best regioselectivity when solvents with lower polarity, such as toluene and 1:1 toluene–chloroform, are used. Dibutyltin oxide (Entry 5) and its combination with triethylamine (Entries 6 and 7) were found to be less effective than expected. In the case of zinc salts (Entries 8 and 9), the regioselectivity varied conspicuously, depending on the structure of the counteranions, and the latter reaction gave a higher regioselectivity in DMF (7.6:1) than in 11:1 toluene–DMF (6.1:1). The reactions (Entries 10 and 11) performed with zinc naphthenate in combination with triethylamine improved the regioselectivity up to 12:1. The combination of zinc chloride with triethylamine, as well as with pyridine, was not so fruitful as expected, although their total yields were improved. (Phenylcarbamoyl)ation of the 1,2-diol was thus proved to be sufficiently regioselective to give the corresponding primary phenylcarbamate with high regioselectivity. Elevation of the temperature to 60° resulted in lowering of the regioselectivity, although the total yield of **2** plus **3** was improved. The effect of concentration of triethylamine [0.1 mol. equiv. in a solution of **1** in DMF (0.5 and 3 mL)] was examined; the reaction gave a 67 (**2**/**3** = 11:1) and 40% yield (**2**/**3** = 4.6:1), respectively. These results clearly show that the "catalytic" effect of triethylamine depends on its concentration.

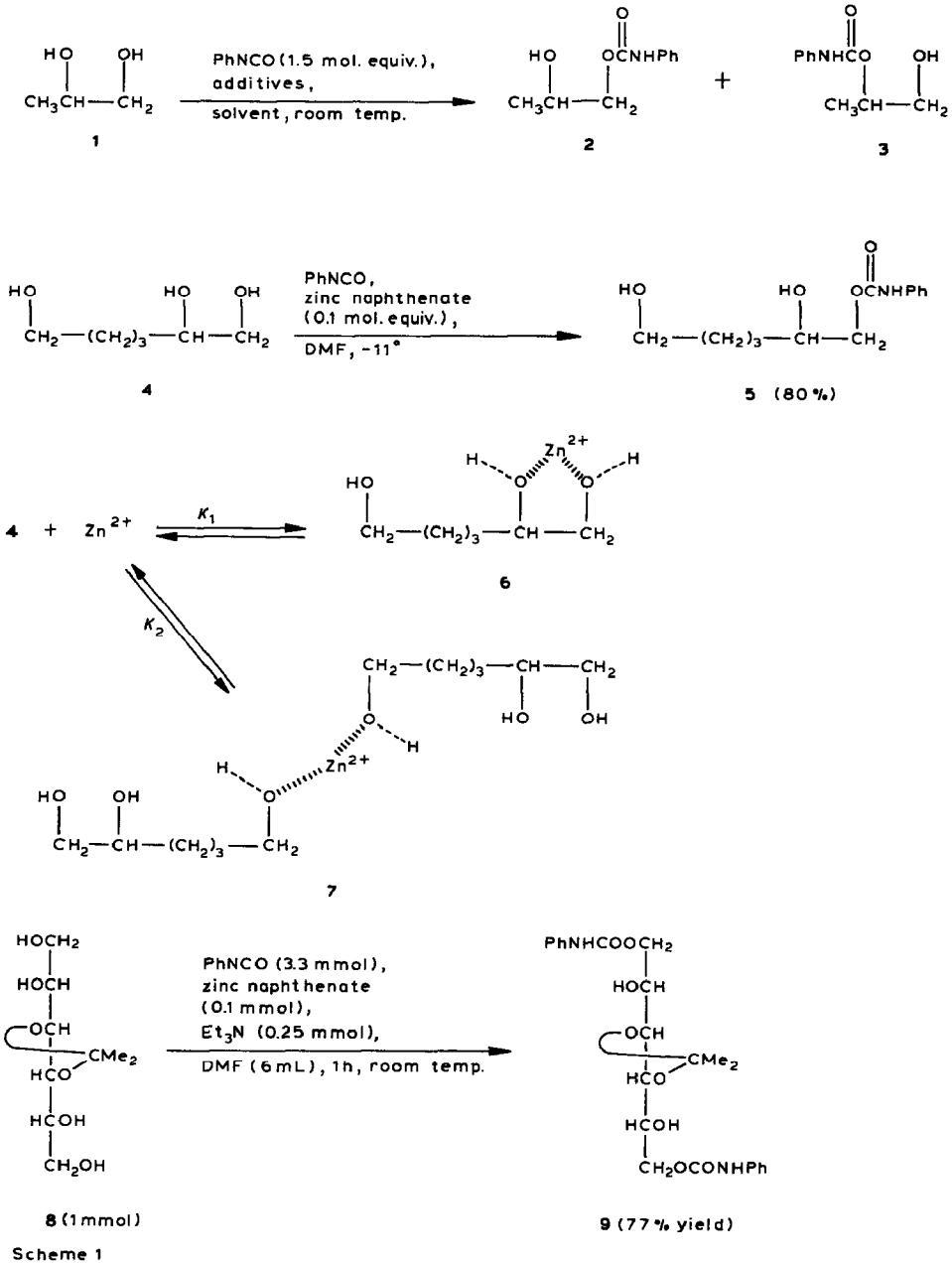
Based on the foregoing results, the reaction of 1,2,6-hexanetriol (**4**) was per-

TABLE I

REGIOSELECTIVE (PHENYLCARBAMOYL)ATION OF 1,2-PROPANEDIOL (**1**) WITH PHENYL ISOCYANATE IN THE PRESENCE OF VARIOUS ADDITIVES[a]

Entry	*Additive (mol. equiv.)*	*Reaction time (h)*	*Yield (%) of* **2** *+* **3** *[Regioselectivity,* **2/3***] obtained in a reaction in*				
			DMF	*11:1 Toluene–DMF*	*Toluene*	*1:1 Toluene–chloroform*	*Chloroform*
1	—	1.0	43 [2.3]	30 [2.3]			12 [3.7]
2	Et_3N (0.1)	0.5	66 [3.6]	53 [6.7]	64 [14]	64 [14]	
3	Et_3N (1.0)	0.5	89 [14]				
4	Et_3N (1.0)	1.0		86 [14]			
5	$(Bu_2SnO)_n$[b] (0.05)	0.5	77 [3.9]	82 [2.2]	63 [3.3]	60 [2.9]	
6	$(Bu_2SnO)_n$–Et_3N (0.05 & 0.1)	0.5	57 [2.8]	51 [1.7]			
7	$(Bu_2SnO)_n$–Et_3N (0.05 & 1.0)	0.5	72 [4.0]	42 [2.5]			
8	$ZnCl_2$ (0.2)	1.0	48 [2.2]	74 [3.1]			
9	Zn naphthenate (0.2)	1.0	52 [7.6]	86 [6.1]	98 [6.4]	98 [6.6]	
10	Zn naphthenate–Et_3N (0.2 & 1.0)	1.0	88 [12]	98 [7.4]			
11	Zn Naphthenate–Et_3N (0.2 & 1.0)	1.25	81 [12]	92 [8.7]			

[a]All of the reactions were performed by the use of **1** (1 mmol) and PhNCO (1.5 mol. equiv.) in a solvent system (3 mL) at room temperature. [b]This additive seemed to be almost insoluble in the solvent systems used.



Scheme 1

formed by addition of a solution of phenyl isocyanate (1.8 mol. equiv.) in DMF (12 mL) to **4** (1.23 mmol) in DMF (6 mL) in the presence of zinc naphthenate (0.1 mol. equiv.) at −11°, giving the corresponding 1-(phenylcarbamate) (**5**) in 80% yield (crystalline). The corresponding 6-(phenylcarbamate) was not isolated, although a spot which might correspond to a bis(phenylcarbamate) was observed in t.l.c. of

the mother liquor (in addition to that of **4**). Incidentally, benzoylation of a stannylene derivative of **4** with benzoyl chloride was reported[8] to give the corresponding 1-benzoate in 47% yield. The strcuture of **5** was confirmed by comparing its ^{1}H-n.m.r. spectrum with that of the corresponding 6-(phenylcarbamate), prepared from **4** by isopropylidenation, followed by (phenylcarbamoyl)ation, and then acid hydrolysis. Interestingly, the 6-(phenylcarbamate) was formed neither on addition of the phenyl isocyanate in one portion nor on performing the reaction in a far less-polar solvent system, 11:1 toluene–DMF; the latter gave **5** in 86 and the corresponding bis(phenylcarbamate), probably a mixture of the 1,2 and 1,6 derivatives, in 13% yield.

These results make possible a discussion of the difference in stability between the potential intermediates **6** and **7** (see Scheme 1), which resulted in the preponderant formation of **5**; K_1 should be much larger than K_2 judging from their structure coordinated to a Zn^{2+} ion bearing the bulky ligand of two naphthenate ions, which may also be important in giving a higher regioselectivity than the chloride ions involved in zinc chloride (see Table I). The predominant catalytic activity of metallic ions over that of amine species[6,7] may induce greater reaction at O-1 over O-6, although DMF was reported to be a useful catalyst for polymerization of isocyanates for the synthesis of urethane resins[9], and the (phenylcarbamoyl)ation of **1** was also induced in neat DMF, as already described.

Subsequently, the reaction of 3,4-*O*-isopropylidene-D-mannitol (**8**) was performed in DMF, with zinc naphthenate–triethylamine catalysis, which gave the 1-(phenylcarbamate) with high regioselectivity and in high yield, in the case of **1**; it gave, as expected, 3,4-*O*-isopropylidene-1,6-di-*O*-(phenylcarbamoyl)-D-mannitol (**9**) in 77% yield.

The excellent regioselectivity obtained in the reactions of **1**, **4**, and **8** further prompted us to perform the reactions with methyl glycosides, which involve many hydroxyl groups variously oriented and the ring-oxygen atom, and were thus expected to bring peculiar steric effects to the reaction, depending on the structure of each.

Reaction conditions with respect to the effects of additives, solvents, and reaction temperature were examined by the use of methyl β-D-glucopyranoside; the results are summarized in Table II. The reaction in DMF introduced a phenylcarbamoyl group at O-6 with high regioselectivity (Entry 4), but addition of zinc naphthenate to the system resulted in highly regioselective (phenylcarbamoyl)ation at O-3 (Entries 1 and 2). The addition of lithium chloride, instead of zinc naphthenate, on the other hand, did not affect the reaction to give the corresponding 6-(phenylcarbamate) to an extent similar to that observed in Entry 4. On changing the solvent to pyridine, reaction was also induced at O-6 of the glucoside (Entry 5), and, unexpectedly, the addition of zinc naphthenate did not affect the reaction to give the corresponding 6-(phenylcarbamate) with high regioselectivity (Entry 3). These results suggested the further possibility of (phenylcarbamoyl)ation showing

TABLE II

REGIOSELECTIVE (PHENYLCARBAMOYL)ATION OF METHYL β-D-GLUCOPYRANOSIDE[a]

Entry	*Zinc naphthenate (mol. equiv.)*	*PhNCO (mol. equiv.)*	*Solvent*	*Temp.*	*Yield[b] (%) of phenylcarbamate*			*Recovery yield of the glycoside (%)*
					2-	*3-*	*6-*	
1	0.2	1.2	DMF	room temp.	12	60	7	9
2	0.17 with pyridine (2.5)	1.2	DMF	room temp.	11	58	—	12
3	0.48	1.5	pyridine	room temp.	3	4	32	13
4	—	1.7	DMF	room temp.	—	3	51	22
5	—	1.2	pyridine	room temp.	1	1	58	33
6	0.2	1.2	DMF	−10°	7	65	—	17
7	—	1.2	pyridine	−10°	—	1	41	35

[a]All of the reactions were performed by the use of the glucoside (1 mmol) and PhNCO (1.5 mmol) in a solvent (6 mL) for 1–1.5 h. [b]These are the yields of the products isolated.

different, but high, regioselectivity toward a specific hydroxyl group (depending on the conditions applied) as a unique protecting procedure.

The effect of temperature was next investigated on the reactions performed with zinc naphthenate in DMF, which gave the 3-(phenylcarbamate) with high regioselectivity, and in pyridine alone, which gave the 6-(phenylcarbamate) similarly; also the results obtained at −10° were compared with those at room temperature. Comparison of Entries 1 and 6 showed that lowering of the temperature to −10° improved both the yield and regioselectivity of the 3-(phenylcarbamate) compared to those of the 6-(phenylcarbamate). Comparison of Entries 5 and 7, on the other hand, demonstrated that the lowering of temperature unexpectedly brought about a diminution of the yields of the 6-(phenylcarbamate); the reaction in pyridine is thus assumed to be better performed at room temperature.

Next, the effect of dilution, by use of a drop-by-drop addition procedure, was examined. Incidentally, the result shown in Entry 4 (Table II) showed that it is possible to perform 6-*O*-(phenylcarbamoyl)ation even in neat DMF, and the 3-*O*-(phenylcarbamoyl)ation catalyzed by zinc naphthenate was likely to be somewhat faster than the 6-*O*-(phenylcarbamoyl)ation. These aspects led us to presume that it should be possible to improve the regioselectivity in the 3-*O*-(phenylcarbamoyl)-ation through catalysis by zinc naphthenate, by which the possibility of 6-*O*-(phenylcarbamoyl)ation might be minimized. A dilute solution of phenyl isocyanate in DMF was slowly added dropwise to the reaction mixture during >1 h; the results are summarized in Table III. The effect expected was not observed in the reaction at room temperature (Entry 1), but was clearly demonstrated on performing it at a lower temperature (Entries 2 and 3). By increase of the proportion of catalyst, the reaction was somewhat accelerated, to give, undesirably, a mixture of the corresponding bis(phenylcarbamate)s in 35% yield. The effect was also found in the 6-*O*-(phenylcarbamoyl)ation in pyridine (Entry 4).

TABLE III

REGIOSELECTIVE (PHENYLCARBAMOYL)ATION OF METHYL β-D-GLUCOPYRANOSIDE THROUGH DILUTION BY THE DROP-BY-DROP ADDITION PROCEDURE[a]

Entry	*Solvent (mL)*	*PhNCO (mol. equiv.)*	*Additive (mol. equiv.)*	*Reaction temp.*	*Yield (%) of phenylcarbamate*			
					2-	*3-*	*6-*	*bis-*
1[b]	DMF (10)	1.5	zinc naphthenate (0.92)	room temp.	13	58	6	11
2	DMF (10)	2.2	zinc naphthenate (0.26)	−12°	4	72	1	23
3	DMF (10)	1.5	zinc naphthenate (1.68)	−14°	5	61	—	34
4[b]	pyridine (3)	2.2	—	room temp.	1		73	14

[a]All of the reactions were performed for 1–1.5 h under the conditions described, by use of the glucoside (0.5 mmol) in a solvent to which was added a solution of phenyl isocyanate in DMF (8 mL). [b]In these cases, the starting material was recovered in 12% yield.

TABLE IV

ATTEMPTED REGIOSELECTIVE (PHENYLCARBAMOYL)ATION OF METHYL α-D-GLUCOPYRANOSIDE[a]

Entry	*Solvent*	*PhNCO (mol. equiv.)*	*Additive (mol. equiv.)*	*Yield (%) of phenylcarbamate*			
				2-	*3-*	*6-*	*bis-*
1	DMF	1.2	zinc naphthenate (0.22)	29	53	2	—
2	DMF	1.7	LiCl (1.0)	11	6	33	5
3	pyridine	1.2		12	1	43	16
4	pyridine	1.6	LiCl (1.0)	3	1	45	6

[a]All of the reactions were performed by the use of the glucoside (1 mmol), under the conditions shown, in a solvent (6 mL), for 1–1.5 h at room temperature. The starting material was recovered in 4, 45, 23, and 45% yield, respectively, for Entries 1–4.

Consequently, the reaction of methyl α-D-glucopyranoside was performed, in order to compare the effect of difference in anomeric configuration on regioselectivity in the reaction; the results are summarized in Table IV, together with the conditions used. The reaction mediated by zinc naphthenate (Entry 1) was still regioselective, but gave the 2-(phenylcarbamate) in 29 and the 3-(phenylcarbamate) in 53% yield. Lithium chloride (Entry 2) showed almost no catalytic effect on the 3-*O*-(phenylcarbamoyl)ation. The reaction in neat pyridine (Entry 3) was also not so regioselective as that of the β anomer, as it gave the 2-(phenylcarbamate), in 12, the 6-(phenylcarbamate) in 43, and the bis(phenylcarbamate) in 16% yield. Addition of lithium chloride suppressed the formation of the 2-(phenylcarbamate) in the reaction in pyridine (Entry 4).

Based on the foregoing results, the reaction using the zinc naphthenate–DMF

TABLE V

REGIOSELECTIVE (PHENYLCARBAMOYL)ATION OF SOME GLYCOSIDES BY DROP-BY-DROP ADDITION USING THE PhNCO–ZINC NAPHTHENATE SYSTEM

Entry	*Glycoside*	*Yield (%) of phenylcarbamate*[a]					*Recovery (%) of the starting glycoside*
		2-	*3-*	*4-*	*6-*	*bis-*	
1	Methyl α-D-glucopyranoside	29	53		2		4
2	β anomer	4	72		1	23	
3	Methyl α-D-mannopyranoside		83	2	1	10	4
4	Methyl α-D-galactopyranoside	26	58			5	8
5	β anomer		84			14	
6	Benzyl β-D-arabinopyranoside	4	93	2			
7	Methyl α-D-xylopyranoside	18	64	8			8
8	β anomer	11	61	9			8
9	Phenyl β-D-xylopyranoside	10	53	9			11
10	Methyl β-D-ribofuranoside	9	63				

[a]All of these are the isolated yields of the corresponding phenylcarbamates.

system was extended to other glycosides, in order to compare the effect of difference in anomeric configuration on regioselectivity in the reaction; to a solution of a glycoside in DMF containing zinc naphthenate was slowly added a solution of phenyl isocyanate in DMF during >1 h at −15°. The results thus obtained are summarized in Table V. The difference in the reactions of methyl α- and β-D-galactopyranoside (*cf.* Entries 4 and 5) was similar to that in the reactions shown in Entries 1 and 2; the latter is quite practical, giving the 3-(phenylcarbamate) in 84% yield. The reactions of methyl α-D-mannopyranoside (Entry 3) and of benzyl β-D-arabinopyranoside (Entry 6) were induced with high regioselectivity, to give the corresponding 3-(phenylcarbamate)s in high yields. The difference in the regioselectivity between the reactions of methyl α- and β-D-xylopyranoside was not so conspicuous, but the reaction was still regioselective, and both reactions gave the 3-carbamates preponderantly. Furthermore, the reaction of methyl β-D-ribofuranoside showed similar regioselectivity, to afford the 3-(phenylcarbamate) in 63 and the 2-(phenylcarbamate) in 9% yield.

Because of the result shown in Entry 10, our interest was directed toward the behavior of ribonucleosides under the conditions used, and we examined that of N^6-benzyladenosine as a model compound. Slow addition of phenyl isocyanate in DMF to a solution of the nucleoside in DMF containing zinc naphthenate at −17° gave the corresponding 2'-(phenylcarbamate) in 60% yield, which is in remarkable contrast to the reaction of methyl β-D-ribofuranoside.

EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto micro melting-point apparatus, and are uncorrected. Specific rotations were determined, for solutions in methanol, with a JASCO DIP-4 polarimeter. T.l.c. was conducted on Merck Silica Gel 60 F_{254} by developing with 9:1 chloroform–methanol or 3:2 benzene–ethyl acetate. Column chromatography was performed on silica gel (Wakogel C-300) by use of chloroform–methanol as the eluant. Elemental analyses were achieved with a Perkin–Elmer 240-002 apparatus. ^{1}H-N.m.r. spectra were recorded with Varian T-60, EM-360, XL-200, and Bruker WM 250 instruments, for solutions in a solvent chosen from chloroform-*d*, methanol-d_4, and dimethyl sulfoxide-d_6, depending on the solubility of the sample, with tetramethylsilane as the internal standard.

1,2-Propanediol and 1,2,6-hexanetriol were purchased from Aldrich Chemical Co., and the glycosides were from Sigma Chemical Co., except for benzyl β-D-arabinopyranoside[10], methyl β-D-ribofuranoside[11], and N^6-benzyladenosine[12]. Zinc naphthenate was purchased from Nippon Chemical Industry Co., Ltd. [Naphthex "Zn"; metal content, 10%].

Synthesis of 1,2-propanediol mono(phenylcarbamate)s (**2** *and* **3**) *and bis(phenylcarbamate) (see Table I).* — To a solution of 1,2-propanediol (**1**; 76 mg, 1 mmol) in an organic solvent was added an additive and then phenyl isocyanate

(0.16 mL, 1.5 mmol), and the mixture was treated under the conditions described in Table I, the reaction quenched with methanol, the solution evaporated. The residue was subjected to column chromatography on silica gel, to give, in turn, a mixture of bis(phenylcarbamate) and phenyl isocyanate polymeric by-product, and a mixture of mono(phenylcarbamate)s (**2** and **3**), by the use of commercial chloroform (containing 0.5% of ethanol). The former mixture was separated by further chromatography on silica gel by the use of 2:2:1 benzene–cyclohexane–ethyl acetate.

Compound **2**: ^{1}H-n.m.r. [60 MHz, $(CD_3)_2SO$–D_2O]: δ 4.15–3.82 (m, 3 H, H-1,2,1′); ($CDCl_3$–CD_3OD): δ 1.20 (d, 3 H, *J* 6 Hz, CH_3), 3.98 (d, 1 H, H-2), 4.04 (s, 1 H, H-1), and 4.02 (d, 1 H, *J* 1 Hz, H-1′).

Compound **3**: ^{1}H-n.m.r. [60 MHz, $(CD_3)_2SO$–D_2O]: δ 4.92 (m, 1 H, H-2) and 3.57 (d, 2 H, H-1,1′); (60 MHz, $CDCl_3$–CD_3OD): δ 1.25 (d, 3 H, *J* 7 Hz, CH_3), 3.63 (d, 2 H, H-1,1′), and 4.88 (d, 1 H, H-2).

1,2-Di-O-(phenylcarbamoyl)propanediol had m.p. 146° (from chloroform–methanol); ^{1}H-n.m.r. (60 MHz, $CDCl_3$–CD_3OD): δ 7.42–6.78 (m, 10 H, 2 C_6H_5), 5.12 (q, 1 H, $J_{1,2}$ 5, $J_{2,3}$ 6 Hz, H-2), 4.17 (d, 2 H, H-1,1′), and 1.26 (d, 3 H, CH_3).

Anal. Calc. for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 65.05; H, 5.53; N, 8.82.

1-O-(Phenylcarbamoyl)-1,2,6-hexanetriol (**5**). — To a solution of 1,2,6-hexanetriol (**4**; 165 mg, 1.23 mmol) in DMF (12 mL) containing zinc naphthenate (76 mg, 0.12 mmol) was very slowly added a solution of phenyl isocyanate (241 μL, 2.2 mmol) in DMF (12 mL) during >1 h at −11°; the mixture was then stirred for 1 h, silica gel (~2 mL) was added and the mixture was kept at room temperature for a while, the volatile portion evaporated, the powdery residue put on the top of a silica gel column, and the column eluted with chloroform, to give **5**, recrystallization of which from diisopropyl ether–ethyl acetate afforded a pure sample (249 mg, 80% yield); m.p. 98.5–99.5°; ^{1}H-n.m.r. (60 MHz, $CDCl_3$–CD_3OD): δ 4.13 (d, 1 H, $J_{1,2}$ 3 Hz, H-1′), 3.98 (s, 1 H, H-1′), 3.85 (m, 1 H, H-2), 3.57 (br. t, 2 H, H-6,6′), and 1.52 (br. s, 6 H, 3 CH_2).

Anal. Calc. for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.60; H, 7.52; N, 5.51.

6-O-(Phenylcarbamoyl)-1,2,6-hexanetriol. — Compound **4** (2.5 mL, 21 mmol) in DMF (20 mL) containing *p*-toluenesulfonic acid monohydrate (200 mg) and 2,2-dimethoxypropane (8 mL) was stirred overnight at room temperature. The acid was neutralized by portionwise addition of solid sodium hydrogencarbonate, and the mixture evaporated. The residue was distributed between dichloromethane (40 mL) and water (10 mL), and the organic layer was dried (anhydrous sodium sulfate) and evaporaed. The residue was dissolved in DMF (15 mL) and treated with phenyl isocyanate (3.0 mL, 27 mmol) in the presence of triethylamine (0.1 mol. equiv.) overnight at room temperature, with stirring. The mixture was evaporated to dryness, and the residue was subjected to chromatography on silica gel with benzene as the eluant. The fractions containing 1,2-*O*-isopropylidene-6-*O*-

(phenylcarbamoyl)-1,2,6-hexanetriol were combined, evaporated to dryness, and the residue was treated with 20% aqueous methanol to which a few drops of conc. sulfuric acid had been added; the hydrolysis was monitored by t.l.c. The acid was neutralized with solid sodium hydrogencarbonate, and the mixture evaporated to dryness. The residue was extracted with diethyl ether (50 mL), and the extract was dried (anhydrous sodium sulfate), and evaporated to a syrup which was chromatographed by use of benzene as the eluant, to give 6-*O*-(phenylcarbamoyl)-1,2,6-hexanetriol; m.p. 90.5–92.5° (from acetone); ^{1}H-n.m.r. (60 MHz, CD_3OD): δ 4.08 (br. t, 2 H, *J* 6 Hz, H-6,6'), 3.48 (br. s, 2 H, H-1,1'), 3.33 (m, 1 H, H-2), and 1.88–1.34 (br. s, 6 H, 3 CH_2).

Anal. Calc. for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.65; H, 7.57; N, 5.58.

*1,6-Di-*O*-(phenylcarbamoyl)-3,4-*O*-isopropylidene-*D*-mannitol* (**9**). — To a solution of 3,4-*O*-isopropylidene-D-mannitol[13] (**8**; 222 mg, 1 mmol) in DMF (6 mL) containing zinc naphthenate (64 mg, 0.1 mmol) and triethylamine (0.02 mL, 0.25 mmol) was added phenyl isocyanate (0.36 mL, 3.3 mmol) in 3 aliquots at room temperature. After 1 h, silica gel (~2 mL) was added, and the mixture was evaporated to a powder which was put on the top of a column of silica gel and eluted with chloroform–methanol. A mixture of bis(phenylcarbamate)s thus obtained was further chromatographed by the use of benzene–ethyl acetate, to give **9** (353 mg, 77% yield); m.p. 148.5–149.5°, $[\alpha]_D^{25}$ +43° (*c* 0.5); ^{1}H-n.m.r. [200 MHz, $(CD_3)_2SO$]: δ 5.50 (d, 2 H, *J* 5.5 Hz, O*H*-2 and -5), 4.39 (dd, 2 H, $J_{1,1'} = J_{6,6'}$ 11.5 Hz, $J_{1,2} = J_{5,6}$ 2.5 Hz, H-1,6), 4.09 (dd, 2 H, H-1',6'), 4.08 (br. d, 2 H, $J_{2,3} = J_{4,5}$ 2.5 Hz, H-3,4), 3.96–3.82 (m, 2 H, H-2,5), and 1.38 (s, 6 H, 2 CH_3).

Anal. Calc. for $C_{23}H_{28}N_2O_8$: C, 59.99; H, 6.13; N, 6.09. Found: C, 60.26; H, 6.22; N, 6.16.

*General procedure for regioselective 3-*O*-(phenylcarbamoyl)ation of glycosides through use of drop-by-drop addition.* — To a solution of a glycoside (1 mmol) in DMF (6 mL) containing zinc naphthenate (63 mg, 0.1 mmol) was slowly added dropwise a solution of phenyl isocyanate (131 μL, 1.2 mmol) in DMF (8 mL) during >1 h at −15°, and the solution stirred for 1 h. Silica gel was added (~2 mL), and the mixture was evaporated to a powder which was transferred to the top of a column of silica gel, and chromatographed by use of chloroform–methanol. Further chromatography was conducted repeatedly, as required (monitoring of the fractions by t.l.c. and ^{1}H-n.m.r. spectroscopy). The proportions were determined by weighing each of the products isolated. The structure of each compound thus obtained was determined by proton-homodecoupling in ^{1}H-n.m.r. spectroscopy; the methine proton signal of a carbon atom bearing a hydroxyl group showed a downfield shift by ~1.1 p.p.m., and the methylene proton signals by ~0.6 p.p.m., on (phenylcarbamoyl)ation. Moreover, the structure of the 3-(phenylcarbamate)s was confirmed by lack of change in thin-layer chromatograms of their solution, treated under the usual conditions of periodate oxidation. The properties of the corresponding 3-(phenylcarbamate)s thus obtained are listed next.

Methyl 3-O-(phenylcarbamoyl)-β-D-glucopyranoside: m.p. 167.6–168° (from chloroform–methanol), $[\alpha]_D^{25}$ −27° (*c* 1.0); ^{1}H-n.m.r. [250 MHz, $(CD_3)_2SO$]: δ 5.37 (d, 1 H, $J_{2,2\text{-OH}}$ 6 Hz, O*H*-2), 5.19 (d, 1 H, $J_{4,4\text{-OH}}$ 7 Hz, O*H*-4), 4.74 (t, 1 H, $J_{2,3} = J_{3,4}$ 9 Hz, H-3), 4.61 (t, 1 H, $J_{6,6\text{-OH}} = J_{6',6\text{-OH}}$ 6 Hz, O*H*-6), 4.21 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), and 3.39 (s, 3 H, OCH_3); ^{1}H-n.m.r. [$(CD_3)_2SO$ + D_2O]: δ 4.72 (br. t, 1 H, $J_{2,3} = J_{3,4}$ 9 Hz, H-3), 4.18 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 3.42 (s, 3 H, OCH_3), and 3.16 (dd, 1 H, H-2).

Anal. Calc. for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.57; H, 6.06; N, 4.45.

Methyl 3-O-(phenylcarbamoyl)-α-D-galactopyranoside was obtained as a solid on evaporation of its fractions; m.p. 94–95°, $[\alpha]_D^{25}$ +173° (*c* 0.9); ^{1}H-n.m.r. (250 MHz, $CDCl_3$–CD_3OD): δ 4.97 (dd, 1 H, $J_{2,3}$ 11, $J_{3,4}$ 3 Hz, H-3), 4.79 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), and 4.03 (dd, 1 H, H-2).

Anal. Calc. for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.49; H, 6.28; N, 4.65.

Methyl 3-O-(phenylcarbamoyl)-β-D-galactopyranoside had m.p. 170–171.5° (from diisopropyl ether–chloroform–methanol), $[\alpha]_D^{25}$ +55° (*c* 0.5); ^{1}H-n.m.r. (250 MHz, $CDCl_3$–CD_3OD): δ 4.66 (dd, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 3 Hz, H-3), 4.23 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), and 4.08 (br. d, 1 H, H-4).

Anal. Calc. for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.52; H, 6.10; N, 4.48.

Methyl 3-O-(phenylcarbamoyl)-α-D-mannopyranoside was a glass; $[\alpha]_D^{25}$ +34° (*c* 1.3); ^{1}H-n.m.r. [250 MHz, $(CD_3)_2SO$]: δ 5.25 (d, 1 H, $J_{2,2\text{-OH}}$ 5 Hz, O*H*-2), 5.03 (d, 1 H, $J_{4,4\text{-OH}}$ 7 Hz, O*H*-4), 4.85 (dd, 1 H, $J_{2,3}$ 3, $J_{3,4}$ 10 Hz, H-3), 4.63 (t, 1 H, $J_{6 \text{ or } 6',6\text{-OH}}$ 6 Hz, O*H*-6), 4.59 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), and 3.92 (m, 1 H, H-2).

Anal. Calc. for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.81; H, 6.09; N, 4.32.

Benzyl 3-O-(phenylcarbamoyl)-β-D-arabinopyranoside had m.p. 169.5–171° (from benzene–methanol), $[\alpha]_D^{25}$ −200° (*c* 0.5); ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 5.05 (dd, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 6 Hz, H-3), 4.99 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.68 (d, 1 H, *J* 12 Hz, CH_2Ph), 4.43 (d, 1 H, *J* 12 Hz, CH_2Ph), 4.17 (dd, 1 H, H-2), 4.08 (d, 1 H, $J_{4,5a}$ 2, $J_{4,5e}$ 0 Hz, H-4), 3.82 (br. d, 1 H, $J_{5a,5e}$ 12 Hz, H-5*e*), and 2.64 (dd, 1 H, H-5*a*).

Anal. Calc. for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.54; H, 5.85; N, 3.86.

Methyl 3-O-(phenylcarbamoyl)-α-D-xylopyranoside was obtained as a solid on evaporation of its fractions; m.p. 157–158°, $[\alpha]_D^{25}$ +127° (*c* 1.0); ^{1}H-n.m.r. (250 MHz, $CDCl_3$–CD_3OD): δ 4.87 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9 Hz, H-3), and 4.63 (d, 1 H, $J_{1,2}$ 4 Hz, H-1).

Anal. Calc. for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05; N, 4.95. Found: C, 55.22; H, 6.10; N, 5.51.

Methyl 3-O-(phenylcarbamoyl)-β-D-xylopyranoside was obtained as a solid on evaporation of its fractions; m.p. 143–144°, $[\alpha]_D^{25}$ −42° (*c* 1.0); ^{1}H-n.m.r. (250

MHz, $CDCl_3$): δ 4.75 (dd, 1 H, $J_{3,4}$ 9, $J_{2,3}$ 8.5 Hz, H-3), 4.26 (d, 1 H, $J_{1,2}$ 7 Hz, H-1), 3.98 (dd, 1 H, $J_{5a,5e}$ 11.5 Hz, H-5*e*), 3.74 (m, 1 H, $J_{4,5a}$ 9.5 Hz, H-4), 3.47 (dd, 1 H, H-2), and 3.33 (d, 1 H, H-5*a*).

Anal. Calc. for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05; N, 4.95. Found: C, 54.71; H, 6.08; N, 5.24.

*Phenyl 3-*O*-(phenylcarbamoyl)-β-*D*-xylopyranoside* was obtained as a solid on evaporation of its fractions; m.p. 179.5–180°, $[\alpha]_D^{25}$ −21° (*c* 0.5); ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ 5.02 (d, 1 H, $J_{1,2}$ 7 Hz, H-1), and 4.98 (dd, 1 H, $J_{2,3}$ 8, $J_{3,4}$ 9 Hz, H-3).

Anal. Calc. for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.49; H, 5.43; N, 4.45.

*Methyl 3-*O*-(phenylcarbamoyl)-β-*D*-ribofuranoside* was obtained as a glass; ^{1}H-n.m.r. (250 MHz, $CDCl_3$–D_2O): δ 4.92 (br. t, 1 H, *J* 5 Hz, H-3), 4.70 (d, 1 H, $J_{1,2}$ 1 Hz, H-1), and 4.14 (dd, 1 H, $J_{2,3}$ 1 Hz, H-2).

N^6-*Benzyl-2′-*O*-(phenylcarbamoyl)adenosine* had m.p. 117.6–119° (from diisopropyl ether–chloroform), $[\alpha]_D^{25}$ −72° (*c* 0.8); ^{1}H-n.m.r. (250 MHz, CD_3OD): δ 8.08, 8.04 (2 s, 2 H, H-2,8), 7.3–7.0 (m, 10 H, 2 C_6H_5), 6.17 (d, 1 H, $J_{1',2'}$ 6 Hz, H-1′), 5.57 (t, 1 H, $J_{2',3'}$ 6 Hz, H-2′), 4.17 (br. d, 1 H, H-4′), and 3.79 (br. s, 2 H, H-5′,5″).

Anal. Calc. for $C_{24}H_{24}N_6O_5$: C, 60.49; H, 5.08; N, 17.64. Found: C, 60.48; H, 5.30; N, 17.35.

*Synthesis of methyl 6-*O*-(phenylcarbamoyl)-β-*D*-glucopyranoside by drop-by-drop addition.* — To a solution of methyl β-D-glucopyranoside (97 mg, 0.5 mmol) in pyridine (3 mL) was added dropwise a solution of phenyl isocyanate (0.12 mL, 1.1 mmol) in DMF (8 mL) with stirring, during 1 h at room temperature. After 1 h, silica gel (~2 mL) was added, and the mixture was evaporated to a powder which was put on the top of a column of silica gel and chromatographed with chloroform–methanol, to give the 6-(phenylcarbamate) (114 mg, 73% yield), together with the corresponding bis(phenylcarbamate)s (17% yield), the 2-(phenylcarbamate) (1% yield), and the starting material (12% recovery).

*Methyl 6-*O*-(phenylcarbamoyl)-β-*D*-glucopyranoside* was obtained as a solid on evaporation of its fractions; m.p. 100–100.5°, $[\alpha]_D^{25}$ −21° (*c* 1.0); ^{1}H-n.m.r. [250 MHz, $(CD_3)_2SO$)]: δ 5.17 (br. d, 3 H, *J* 10 Hz, O*H*-2,3,4), 4.36 (dd, $J_{5,6}$ 2, $J_{6,6'}$ 12 Hz, H-6), 4.21 (dd, 1 H, $J_{5,6'}$ 6 Hz, H-6′), 4.12 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 3.41 (t, 1 H, $J_{2,3} = J_{3,4} = 8$ Hz, H-3), 3.40 (s, 3 H, OCH_3), and 3.02 (br. t, 1 H, H-2).

Anal. Calc. for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.48; H, 6.19; N, 4.80.

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