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GLYCOSYL AND GLUCURONIC ESTERS OF AMINO ACIDS. SYNTHETIC METHODS LEADING TO FULLY PROTECTED 1-O-(2-ACYLAMIDOACYL)-α- AND -β-D-GLUCOPYRANOSES AND -GLUCOPYRANURONATES

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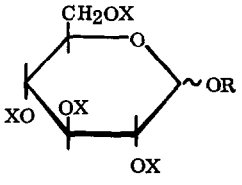
Recent interest in the nature of sugar - amino acid linkages in glycopeptides and glycoproteins has stimulated inter alias intensive research on simple model compounds. In our Laboratory we have been particularly interested in the compounds of the "ester" type of linkage, involving the C-1 hydroxyl group of carbohydrate and the carboxyl group of amino acid, and the syntheses of some fully acetylated 1-O-(N-acetylaminoacyl)-D-glucopyranoses have already been published[1,2]. We report here an extension of the synthetic approaches to fully protected glucosyl and glucuronic C-1 esters of amino acids with special emphasis on their applicability to various kinds of the sugar and amino acid components.

Model experiments were carried out with the C-1 free tetra-O-benzyl- α-D-glucopyranose (1), tetra-O-acetyl-D-glucopyranose (7), methyl tri-O-acetyl-, methyl tri-O-methyl- and benzyl tri-O--benzyl- D-glucopyranuronates (9[3], 12[4] and 17[5], respectively) and with N-acetyl (Ac), -benzyloxycarbonyl (Z) and -phthaloyl (Phth) -DL-amino acid derivatives, if not stated otherwise.

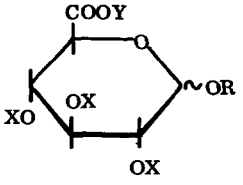


X = $PhCH_2$

1 R = H
2 R = Ac-Ala
3 R = Ac-Met
4 R = Ac-L-Phe
5 R = Z-Gly
6 R = Phth-Gly

X = Ac

7 R = H
8 R = Ac-Ala



X = Ac, Y = Me

9 R = H
10 R = Ac-Ala
11 R = Z-Ala

X = Y = Me

12 R = H
13 R = Z-Gly
14 R = Z-Ala
15 R = Z-L-Phe
16 R = Phth-Gly

X = Y = $PhCH_2$

17 R = H
18 R = Z-Gly
19 R = Z-Ala
20 R = Z-L-Phe

Silver salt method (Ag-salt). Chloride[6] of the benzylated glucose 1 and bromides of the acetylated- and benzylated-[5] glucuronates 9 and 17 (all α-anomers) gave with the Ag-salts of several N-acylamino acids the β-anomers of the esters 2, 3, 4, 10, 18, 19 and 20, respectively in fair yields*. The flexibility of the method with respect to the nature of protecting groups makes it usable for the preparation of anomerically pure esters in all cases where the sugar halide is available.

Acid chloride method. The method proved to be of limited value mainly because of the instability of the starting acid chlorides. Phth-glycyl chloride reacted with benzylated glucose 1 and methylated glucuronate 12 (pyridine-CH_2Cl_2, 0°) giving anomeric mixtures, 6 and 16, respectively; *the high proportion of β-anomers is presumably due to the steric hindrance of the phthaloyl* group which prevents the formation of an axially oriented bond, usually favoured in this type of reaction. Analogous reaction of Z-glycyl chloride and 1 led to the anomeric mixture of 5, highly enriched in the α-form.

Condensation methods. Acetylated glucuronate 9 in the presence of one equivalent of dicyclohexylcarbodi-imide (DCC) in CH_2Cl_2 condensed with Ac-Ala-OH and Z-Ala-OH giving the anomeric mixtures of the corresponding esters 10 and 11, respectively. Under the same conditions the fully methylated glucuronate 12 gave, with Z-Gly-OH, Z-Ala-OH and Z-L-Phe-OH, the anomeric esters 13, 14 and 15, respectively; significantly different yields imply that the reaction depends strongly on the nature of the amino acid residue. All attempts to condense, analogously, the benzylated sugar components 1 or 17 with several N-protected amino acids failed; addition of either pyridine or triethylamine to the reaction mixture had no significant effect. However, the reaction was substantially promoted on the addition of two equivalents of imidazole, and in this way very good yields of 2, 3 and 5 were obtained as anomeric mixtures in different proportions. When imidazole was used without DCC there was no condensation. Esterification of 1 also succeeded, though in considerably lower yields, by using equivalent amounts of either N,N'-carbonyldi-imidazole[7] (NCD) or 1-diethylaminopropin[8] (DAP) *as condensing agents; by this route esters 2, 3 and 4 were* prepared.

Accelerated active ester method (AAE). Attempts to reach the sugar - amino acid esters by applying, directly, the peptide coupling procedures (mixed anhydride and active esters methods) failed; this could be ascribed to a higher requirement for activation of the carboxyl component in ester bond formation. It was observed[9,10] that imidazole increases considerably the rate of peptide coupling with active esters, and Stewart[11] used successfully the AAE method with α-hydroxy acid esters to form depsipeptide ester bonds.

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* Methods of preparation and properties of all compounds obtained are summarized in the Table.

Table PRODUCT DATA[a]

No	Method of preparation (yield %)[b]	β - Anomer			α - Anomer		
		m.p.°	$[\alpha]_D^o$	τ ($J_{1,2}$)	m.p.°	$[\alpha]_D^o$	τ ($J_{1,2}$)
2	Ag-salt (28); NCD (30); DAP (40); DCC+Im. (60); AAE (-,50,60)	124-126	+13	4.32d (7)	oil[c]	+30	3.58d (3)
3	Ag-salt (16); NCD (14); DAP (14); DCC+Im. (58);	80- 82	+18	4.30d (7)	not isolated		
4	Ag-salt (30); NCD (15)	140-141	+14	4.32d (8)	not isolated		
5	Acid chloride (45); DCC+Im. (57); AAE (60,77,77)	85- 86	+ 5	4.33d (7)	oil	+47	3.58d (3)
6	Acid chloride	117-118	+37	4.29d (7)	oil[c]	+51	3.66d (3)
8	Ag-salt (35)[1]; AAE (-,50,-)	reference[1]			oil	+86	3.60d (3)
10	Ag-salt (40); DCC (45)	125-126	+ 3	4.15d (7)	43-45	+85	3.57d (3)
11	Ag-salt (35); DCC (50)	102-103	0[d]	4.16d (7)	not isolated		
13	DCC (8); AAE (73,67,65)	oil	-40	3.90s	oil	+58	3.63d (4)
14	DCC (45); AAE (45,50,65)	oil	-30	3.91s	oil	+50	3.64d (4)
15	DCC (20); AAE (40,40,70)	oil	-12	3.87s	oil	+66	3.65d (4)
16	Acid chloride	99-100	-27	3.86s	oil	+55	3.62d (4)
18	Ag-salt (25); AAE (-,-,75)	114-115	-12	4.25d (8)	oil	+28	3.60d (3)
19	Ag-salt (25)	139-140	-13		-	-	-
20	Ag-salt (50)	129-130	-11		-	-	-

[a] The products were purified by silica gel column chromatography; complete anomeric resolution of 13-16 took place in benzene-EtOAc (1:1). With other products the resolution of anomers was achieved either after repeated crystallization (anhydrous Et_2O- or benzene- petroleumether) or after excessive column chromatography. All compounds gave satisfactory analyses. Optical rotations were measured in $CHCl_3$ ($c \sim 1$). N.m.r. spectra were recorded on a Varian A-60A instrument in $CDCl_3$; chemical shifts refer to internal standard of Me_4Si (τ 10.00) and coupling constants (J) are measured in Hz.

[b] Abbreviations are given in the text; Im.: imidazole. The yields obtained by the AAE method refer to the activated amino acid ester in the following order: PS, NP, PCP.

[c] Not completely resolved from the β-anomer.

[d] $[\alpha]_D$ in benzene: +28°.

When sugar components 1, 7, 12 and 17 were treated with an equimolar amount, or a 50% excess, of phenylsulphenyl- (PS), 4-nitrophenyl- (NP) or pentachlorophenyl- (PCP) esters of N-acylamino acids in the presence of 5 equiv. of imidazole (CH_2Cl_2, room temp.), 2, 5, 8, 13, 14, 15 and 18, respectively, were formed in good to excellent yields as anomeric mixtures in different proportions. With glucuronic components 12 and 17 the reaction was essentially complete within few hours while the esterification of the benzylated glucose 1 proceeded at a slower rate. Among the active esters investigated NP and PCP were more effective; the latter is prefered because pentachlorophenol can be removed from the reaction mixture by filtration.

The results show that the imidazole catalyzed DCC- and AAE- methods are the most satisfactory. The mechanism of both reactions probably involves the participation of the intermediate N-acylimidazole formed by the nucleophilic attack of imidazole on the O-acylurea and the activated amino acid ester, respectively. In the former case this attack most likely preceeds the O $\longrightarrow$ N acyl migration and thus prevents N-acylurea formation. The finding that the rate of formation of ester 5 by the AAE method was faster with imidazole than with more basic, but more hindered 2-methylimidazole, suggests the direct intervention of N-acylimidazole in the transfer of the acyl group to the sugar component.

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