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FORMATION OF 1,5-LACTONES FROM 3-DEOXY-D-manno-2-OCTULOSONIC ACID DERIVATIVES.

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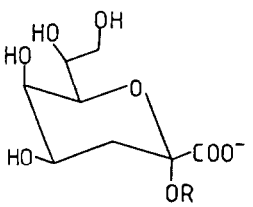
SUMMARY: Acylation of ammonium 3-deoxy-α-D-manno-2-octulopyranosonate (1a) leads to the formation of peracetylated 3-deoxy-α-D-manno-2-octulopyranosono-1,5-lactones (3a,b). The proposed structures were confirmed by independent syntheses. The 1,7-lactone was not formed even when only OH-7 was available for lactonisation.

Treatment of aldonic acids with acetic anhydride/sodium acetate or pyridine often gives rise to acetylated aldonolactones.[1,2] It has been reported that acetylation of methyl-3-deoxy-α-D-manno-2-octulopyranosidonic acid gives methyl-4,5,8-tri-O-acetyl-3-deoxy-α-D-manno-2-octulopyranosidono-1,7-lactone in reasonable yield.[3]

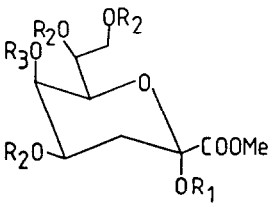
T.l.c. [EtOAc-cyclohexane (6:4)] of the material formed upon acetylation and esterification (CH_2N_2) of ammonium 3-deoxy-α-D-manno-2-octulopyranosonate (1a), consistently revealed the presence of a compound having a lower mobility (Rf .51) than methyl-2,4,5,7,8-penta-O-acetyl-3-deoxy-α-D-manno-2-octulopyranosonate (2a)(Rf .56), the main product.The elementary composition of this material, obtained crystalline [m.p.123-125°C, $[\alpha]_D^{20}$+4.4° (c 1, $CHCl_3$)] in about 5% yield after column chromatography [Silica gel 60,Merck, 60-230 mesh; EtOAc-cyclohexane (1:1)], was compatible with that of a lactone of a 3-deoxy-2-octulosonic acid carrying 4 acetate groups; the presence of the latter was confirmed by the ^1H n.m.r. spectrum (Table), while that of a lactone could be deduced from an absorption band, distinct from the ester bands, observed in the i.r. spectrum at 1775 cm^{-1}. The presence of a pyranose ring was suggested by the fact that H-6 was more shielded than H-5; the chemical shift of H-5 (δ 4.9) was in agreement with the attachement of an acyl-group to O-5. The presence of a furanose-ring could be excluded because in the ^{13}C n.m.r. spectrum no signal was detectable in the region where C-5 of this structure is known to appear.[4] A 1,4-lactone was excluded, the coupling pattern of H-4 and H-5 being incompatible with the dihedral angle present in this type of lactone. Finally, a 1,8-lactone was unlikely to be present as H-8 and H-8' had exactly the same chemical shifts as H-8 and H-8' of methyl (methyl-4,5,7,8-tetra-O-acetyl-3-deoxy-α-D-manno-2-octulopyranosid)onate[5] (2b)(Table). However, no clear-cut decision could be reached regarding the choice between a 1,5-, (3a), or a 1,7-lactone. Accordingly, an unambiguous synthesis of methyl-3-deoxy-α-D-manno-2-octulopyranosidono-1,5-lactone was attempted.

To this end, methyl (methyl-3-deoxy-α-D-manno-2-octulopyranosid)onate[5-8] (2c) was treated with a small excess of 2-methoxypropene under acid catalysis,[9] to yield the 7,8-isopropylidene acetal (4). This,when treated,first, with dibutyltin oxide and then with benzyl bromide using quaternary ammonium halide as catalyst,[10] afforded methyl-4-O-benzyl-3-deoxy-7,8-O-

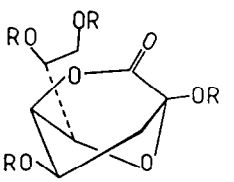
isopropylidene-α-D-manno-2-octulopyranosid)ono-1,5-lactone (5), that was isolated as a solid [yield:73%, $[\alpha]_D^{20}$ -13°(c 1, $CHCl_3$), $\nu_{C=O}$ 1775 cm^{-1}]. The proposed structure is in keeping with preferential substitution of equatorial hydroxyl groups known to take place in galactopyranose derivatives,[10] and was confirmed by the compound's ^1H n.m.r. spectrum: H-5 appeared at 5.0 p.p.m., a value comparable to that found for H-5 of methyl (methyl-4,5,7,8-tetra-O-acetyl-α-D-manno-2-octulopyranosid)onate (2b), (δ 5.33) and quite different from that of H-5 of methyl (methyl-5-O-benzyl-α-D-manno-2-octulopyranosid)onate[7] (2d) (δ 3.94). Reduction of one molar equivalent of periodate with simultaneous production of one molar equivalent of formaldehyde by the diol 6a, obtained from the acetal 5 by removal of the isopropylidene group, definitively proved the proposed structure. Hydrogenolytic removal of the benzyl group in neutral medium from the ether 6a, gave the syrupy lactone 6b, the structure of which was confirmed by its ^1H n.m.r. spectrum (Table). Treatment of the unprotected lactone with acetic anhydride/pyridine and 4-dimethylaminopyridine, transformed it into the 4,7,8-tri-O-acetate (6c), the ^1H n.m.r. data of which (Table) were, within experimental error, the same as those found[3] for the compound obtained by acetylation of (methyl-3-deoxy-α-D-manno-2-octulopyranosid)onic acid (1b).



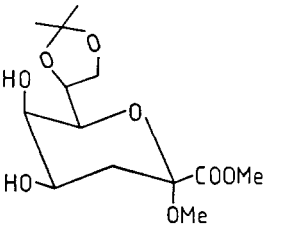
1a R = H
1b R = Me



2a $R_1 = R_2 = R_3 = Ac$
2b $R_1 = Me$, $R_2 = R_3 = Ac$
2c $R_1 = Me$, $R_2 = R_3 = H$
2d $R_1 = Me$, $R_2 = H$, $R_3 = Bn$



3a R = Ac
3b R = Bz



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When methyl (methyl-4,5-O-isopropylidene-α-D-manno-2-octulopyranosid)onate (7a) [m.p. 139-142°C, $[\alpha]_D^{20}$ +56° (c 1, $CHCl_3$)], prepared by selective hydrolysis of the 4,5:7,8-di-O-isopropylidene derivative 8 [m.p. 120-123°C, $[\alpha]_D^{20}$ +43° (c 1, $CHCl_3$)], was treated with dibutyltin oxide and benzyl bromide in the same conditions as described above for the 7,8-O-isopropylidene acetal (4), the oily product, isolated in 80% yield, was methyl (methyl-8-O-benzyl-4,5-isopropylidene-α-D-manno-2-octulopyranosid)onate (7b) ($[\alpha]_D^{20}$ +41° (c 1, $CHCl_3$)), and although a free hydroxyl group was present on C-7 (H-7: δ 3.55) that could be acetylated to give the acetate 7c (H-7: δ 5.27), no 1,7-lactone was detected. Similarly, treatment of methyl (methyl-3-deoxy-α-D-manno-2-octulopyranosid)onate (2c) with dibutyltin oxide and 4 molar equivalents of benzyl bromide, gave a 25% yield (not optimized) of methyl-4,8-di-O-benzyl-3-deoxy-α-D-manno-2-octulopyranosidono-1,5-lactone (6d) [$[\alpha]_D^{20}$ +6° (c 1, $CHCl_3$)], the structure of which was unequivocally defined by its ^1H n.m.r. spectrum (Table); no 1,7-lactone was detected.

TABLE

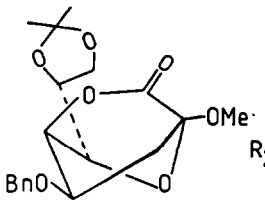
CHEMICAL SHIFTS (p.p.m.)

	[a]2b	[a]2d	[b]3a	[a]3b	[a]4	[a]5	[c]6b	[d]6c	[b]6d	[a]7a	[a]7b	[b]7c	[a]8
H_3	2.1	2.14	2.80	3.33	2.15	2.55	2.67	2.35	2.47	2.63	2.67	2.58	2.79
$H_{3'}$	2.1	1.92	2.1	2.55	1.88	2.02	1.75	1.81	1.93	1.92	1.89	1.92	1.86
H_4	5.30	4.06	5.32	5.61	4.05	3.98	4.29	4.63	3.87	4.53	4.50	4.4	4.52
H_5	5.33	3.95	4.98	5.15	4.02	5.00	4.88	4.70	5.05	4.35	4.40	4.18	4.31
H_6	4.09	3.62	4.45	4.72	3.53	3.69	3.92	3.85	3.64	3.75	3.8	4.09	3.57
H_7	5.22	3.97	5.15	5.73	4.42	4.13	3.60	5.24	3.55	4.03	4.18	5.27	4.42
H_8	4.17	3.77	4.15	4.70	4.00	4.0	3.65	4.00	3.7	3.8	3.8	3.8	4.02
$H_{8'}$	4.58	3.87	4.59	5.00	4.19	4.1	3.80	4.62	3.7	3.8	3.8	3.8	4.17
$COOCH_3$	3.82	3.78	-	-	3.81	-	-	-	-	3.81	3.77	3.78	3.80
OCH_3	3.26	3.20	-	-	3.24	3.55	3.55	3.50	3.47	3.23	3.14	3.15	3.25
OAc	1.9-2.1	-	2.0-2.2	-	-	-	-	1.5-1.7	-	-	-	2.07	-
CH_2Ph	-	4.8	-	-	-	4.6	-	-	4.5	-	4.6	4.5	-

COUPLING CONSTANTS (Hz)

3,3'		12.7	15.0	15.0	13.0	15.0	14.5	15.0	15.0	15.5	15.0	15.0	15.0
3,4		4.9	9.0	10.0	5.0	9.0	9.0	9.5	8.8	4.5	4.5	5.0	4.0
4,3'		11.7	2.5	3.0	11.5	2.0	2.0	2.5	2.3	3.5	3.5	3.7	3.0
4,5	3.0	2.9	2.0	2.0		1.5	2.0	2.3	2.5	7.5	7.0	7.0	7.5
5,6	1.0	1.0	0	0	1.0	0	0	0	0	2.0	2.0	2.0	2.0
6,7	10.0	8.8	9.0	10.0	8.5	7.0	9.5	9.0	10.0	7.5		8.3	8.0
7,8	3.5	4.4	4.0	3.0	4.5		5.0	4.0				3.0	4.5
7,8'	2.5	3.9	2.5	3.0	6.0		2.5	2.5				3.0	6.0
8,8'	12.5	11.2	12.5	13.0	8.5		11.5	12.5					9.0
5,3			1.0				1.0	0.8	1.0				

[a] : $CDCl_3$, 360 MHz ; [b] : $CDCl_3$, 250 MHz ; [c] : CD_3OD, 250 MHz ; [d] : C_6D_6, 360 MHz.



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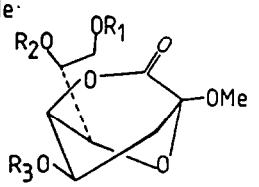
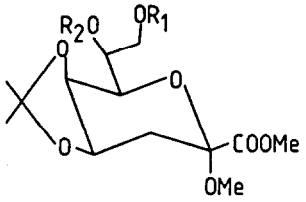
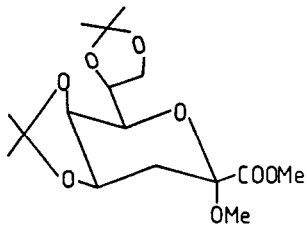


6a $R_1=R_2=H$, $R_3=Bn$
6b $R_1=R_2=R_3=H$
6c $R_1=R_2=R_3=Ac$
6d $R_1=R_3=Bn$, $R_2=H$



7a $R_1=R_2=H$
7b $R_1=Bn$, $R_2=H$
7c $R_1=Bn$, $R_2=Ac$



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In the above-mentioned series of reactions the 1,5-lactone was formed in all cases when OH-5 of the octulosonic acid derivative was free; when only OH-7 was available, detectable lactone-formation did not occur. Accordingly, it was concluded that the by-product formed upon acetylation of ammonium 3-deoxy-α-D-manno-2-octulopyranosonate (1a), was (2,4,7,8-tetra-O-acetyl-3-deoxy-α-D-manno-2-octulopyranos)ono-1,5-lactone (3a). It is likely that the compounds to which the 1,7-lactone structures have been assigned are, in fact, also 1,5-lactones. It has already been suggested[11] that in acidic medium the $^5C_2$ chair conformation of 3-deoxy-D-manno-2-octulopyranosonic acid (1a) is in equilibrium with a monocyclic 1,5-lactone, the keto group of which is hydrated.

Upon benzoylation of the ammonium salt 1a, a 40% yield of a lactone-tetrabenzoate [m.p. 178°C, $[\alpha]_D^{20}$ -58° (c 1, $CHCl_3$)] was isolated, to which the structure 3b can be assigned on the basis of the present data. The formation of large amounts of this lactone is compatible with the hypothesis that a mixed anhydride is formed between the carboxyl group of the octulosonic acid and that of the acylating agent, this mixed anhydride being an intermediate in the lactonization. Indeed, it would be expected that a mixed anhydride formed with an acid stronger than the carboxyl function of the sugar should lead more readily to lactone-formation than an anhydride formed with a weaker acid, that should lead preferentially to O-acylation.

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