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Note

The chemistry of maltose

Part I. The reaction of methyl β-maltoside with sulphuryl chloride

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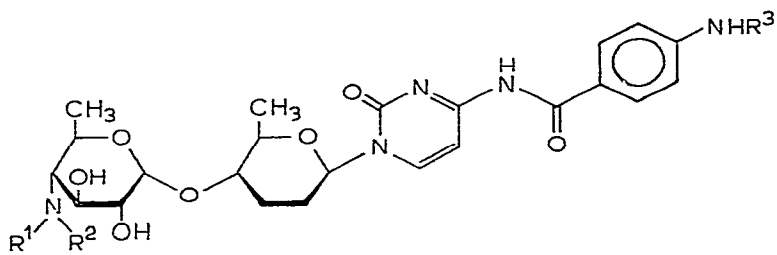
The nucleoside antibiotics amicetin (**1**), bamicetin (**2**), and plicacetin (**3**) contain, as the sugar moiety, a monoamino-pentadeoxy disaccharide that is closely related to maltose (4-*O*-α-D-glucopyranosyl-D-glucose). In view of the reported antibiotic and antitumour activity of these pyrimidine nucleosides[1,2], we have initiated studies of the total synthesis of these disaccharide nucleosides and closely related analogues, directly from the disaccharide maltose, which is readily available. Initially, we have investigated the reaction of methyl β-maltoside (**4**) with sulphuryl chloride with the aim of arriving at disaccharides, containing several chloro substituents, which could be employed as potential precursors of the polydeoxy framework that is found in the antibiotics **1–3**



1 $R^1 = R^2 = CH_3, R^3 = L\text{-}\alpha\text{-methylseryl}$
2 $R^1 = CH_3, R^2 = H, R^3 = L\text{-}\alpha\text{-methylseryl}$
3 $R^1 = R^2 = CH_3, R^3 = H$

Treatment of methyl β-maltoside (**4**) with sulphuryl chloride, followed by dechlorosulphation with sodium iodide in methanol[3] and subsequent acetylation, gave, after chromatography, a highly crystalline, tetrachloro derivative in 48% yield The product was identified, on the basis of elemental analysis, 220-MHz ^1H n m r spectroscopy, and mass spectrometry, as the hemi-ethanolate of methyl 2-*O*-acetyl-

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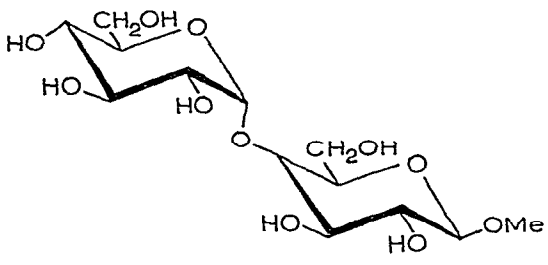
3,6-dichloro-3,6-dideoxy-4-*O*-(2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-α-D-galacto-pyranosyl)-β-D-allopyranoside (**7**) The intermediate trichlorosulphate (**5**) and dechlorosulphated derivative (**6**) were not isolated



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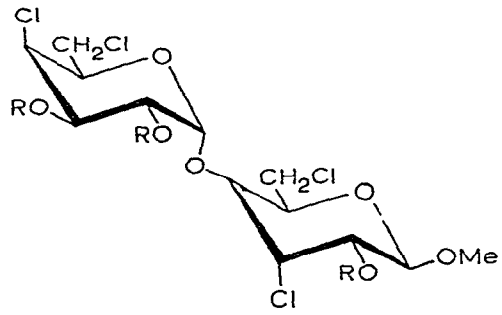


5 R = SO_2Cl
6 R = H
7 R = Ac

The n m r assignments (see Table I) were confirmed by spin-decoupling experiments The *allo* configuration in the $^4C_1$ conformation of the pyranosyl ring at the reducing end of the disaccharide was indicated by the resonances of H-1–4 The H-1 signal appeared as a doublet ($J_{1,2}$ 7 7 Hz), indicating that H-1 and H-2 have an antiperiplanar arrangement The H-2 signal appeared as a quartet through additional, small coupling (3 3 Hz) with H-3, in accord with a *syn*-clinal disposition of H-2 and H-3 The H-3 signal was identified as a narrow triplet as a result of further coupling (2 8 Hz) with the *syn*-clinal H-4 The H-4 signal appeared as a quartet through additional, large coupling (9 1 Hz) with H-5, in accord with an antiperiplanar arrangement of H-4 and H-5 The *galacto* configuration in the C_1^4 conformation of the pyranosyl ring at the non-reducing end of the disaccharide was also clearly indicated by the H-1′–4′ resonances* The H-1′ signal appeared as a doublet ($J_{1',2}$ 3 6 Hz), indicating that H-1′ and H-2′ are gauche-disposed. The H-2′ and H-3′ signals appeared at lowest field, as a pair of strongly coupled quartets[4,5] ($J_{2',3}$ 10 8 Hz; $J_{3',4}$ 3.2 Hz), which indicated that H-2′ and H-3′ are attached to the same carbon atoms as the acetoxy groups[4] The H-4′ signal appeared as a narrow quartet through coupling (1 3 Hz) with H-5′ The rather small coupling $J_{4',5'}$ is indicative of an axial 4-substituent since, in this case, both hydrogens bear an antiperiplanar arrangement with vicinal electronegative substituents[6] (O-5′ and Cl-4′, respectively)

The mass-spectral fragmentation of **7** is shown in Scheme 1 The major pathway was initiated by cleavage of the interglycosidic bond [1′–(C–O)] to give the glycosyl carbonium ion (*m/e* 283) of the non-reducing end of the disaccharide, which then underwent sequential loss of HOAc, CH_2CO, HCl, CO, and HCl The first stage,

*The ring positions of the pyranosyl moiety at the non-reducing end of the disaccharide are designated with primed numbers

TABLE I

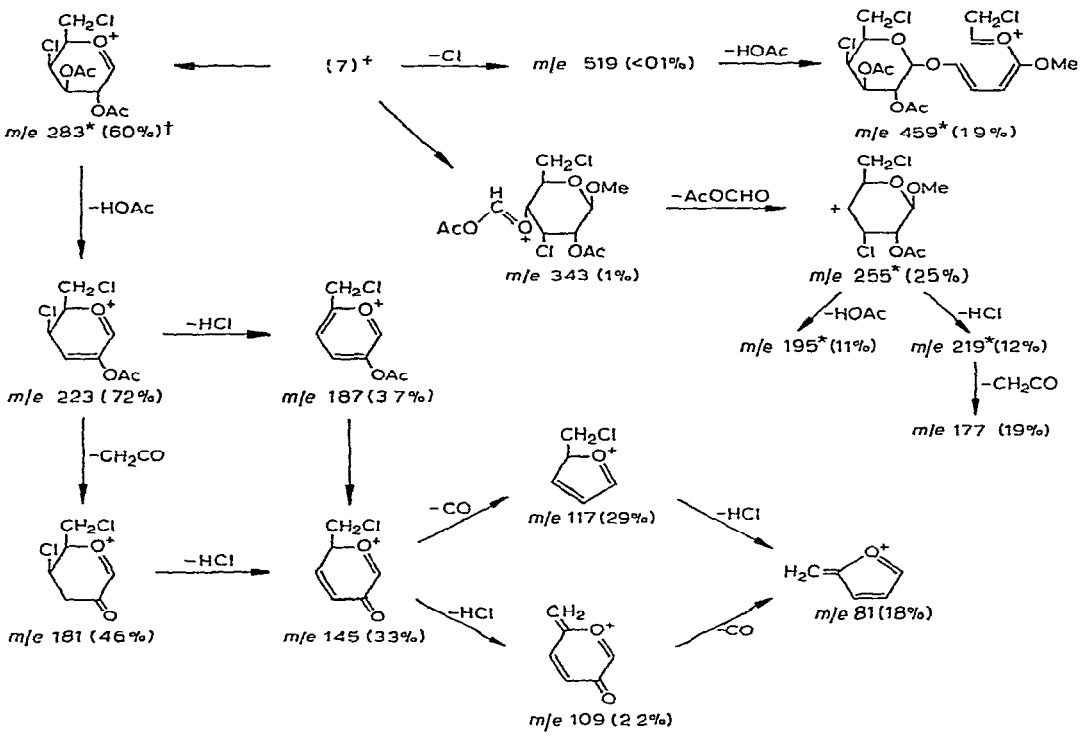
N M R. SPECTRAL DATA FOR 7 IN BENZENE-d_6 AT 220 MHz[a]

	Chemical shifts (τ)								
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*OMe*	*OAc*
Allopyranosyl ring	5 25d	5 03dd	5 25t	6 02dd	6 11dt	6 50–6 68m		6 81	8 18, 8 31, 8 33
Galacto-pyranosyl ring	4 85d	4 57dd	4 49dd	5 32dd	5 81t				

	First-order coupling constants (Hz)						
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6}$	$J_{6,6'}$
Allopyranosyl ring	7 7	3 3	2 8	9 1	2 5	3 9	—
Galactopyranosyl ring	3 6	10 8	3 2	1 3	~6 3		—

[a]Ethanol of crystallization gave rise to a triplet at τ 9 04 and a quartet at τ 6 66.

Scheme 1 Mass-spectral fragmentation of 7



* Verified by accurate mass measurement All stated *m/e* values are based on ^{35}Cl

† Percentage relative to base peak *m/e* 43 (CH_3CO^+)

being the loss of acetic acid, is indicative of a 3′-acetoxy group, and the following loss of ketene suggests the presence of a 2′-acetoxy group[7]. These factors are consistent with a 4,6-dichloropyranosyl structure for the "non-reducing" end of the disaccharide The fragment having *m/e* 255 originated from the reducing end of the disaccharide and was formed either by cleavage of the 4–(C–O) bond, or by cleavage of the C-1′–C-2′ bond followed by rearrangement of the 3′-acetoxy group to C-1′ and cleavage of the C-1′–O-5 bond to give the fragment *m/e* 343 ($AcOCH{=}\overset{+}{O}R$, R = "reducing-end" glycosyl group). The loss of AcOCHO would afford[8] the fragment at *m/e* 255 This structural analysis demonstrates the potential of a combination of high field-strength n m r and mass spectrometry for structural studies of oligosaccharides, which circumvents the more tedious, classical procedures

The structure of the tetrachloro-tetradeoxy derivative **2** may be rationalised in terms of the stereoelectronic forces that have been demonstrated to influence the course of nucleophilic displacement reactions in carbohydrate molecules[9] Thus, the conversion of the α-D-glucopyranosyl ring at the non-reducing end into a 4′,6′-dichloro-galactopyranosyl residue is in agreement with previous results obtained with methyl α-D-glucopyranoside[10] The resistance of the equatorial chlorosulphate group at C-3′ to displacement by chloride ion is attributed to the presence of a vicinal, axial-chloro substituent at C-4 and to the *β-trans*-diaxial effect of the C-1′ substituent[9]. In the β-D-glucopyranosyl ring at the reducing end, the C-1 substituent has the equatorial orientation, and, in addition, reaction at C-4 is blocked by the presence of the sugar residue, therefore, the equatorial C-3 chlorosulphate group can undergo displacement by chloride ion to give a 3,6-dichloro-allopyranosyl residue The lack of reactivity of the chlorosulphate groups at C-2 and C-2′ is primarily due to the high energy of the transition state in the nucleophilic displacement reaction resulting from an unfavourable alignment of dipoles[9] Similar conversion of a β-D-glucopyranosyl ring into a 3-chloro-allopyranosyl system has been observed with methyl 4,6-*O*-benzylidene-β-D-glucopyranoside[10] and methyl 2,2′,3′,4′,6,6′-hexa-*O*-acetyl-β-maltoside[11]

Jennings and Jones[12] have reported that treatment of maltose with sulphuryl chloride, followed by formation of the methyl glycoside and dechlorosulphation, gives a low yield of a trichloro derivative, the structure of which was assigned as methyl 6-chloro-6-deoxy-4-*O*-(4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl)-D-glucopyranoside, the anomeric configuration was not ascertained In this case, the lack of reactivity of the C-3 chlorosulphate group in the glucopyranosyl ring at the reducing end can be attributed to the 1,3-steric hindrance[9] by the axial, anomeric chloro-substituent in its thermodynamically more-stable configuration Hence, depending upon whether the methyl glycoside is formed before or after treatment with sulphuryl chloride, either a trichloro or a tetrachloro derivative may be obtained The relatively good yield of the tetrachloro-tetradeoxy derivative 7 here described makes feasible its further transformation into polydeoxy systems analogous to those found in the naturally occurring, biologically active, "maltose nucleoside" antibiotics

EXPERIMENTAL

Methyl β-maltoside monohydrate (**4**) — This compound was prepared from maltose by slight modification of the procedure of Wolfrom *et al.*[13] In the glycosidation reaction, mercuric cyanide was replaced by mercuric acetate, and the de-esterification step was effected by the Zemplén method Crystallization of the residue from 95% ethanol gave the desired product as the monohydrate, m p 109–111°, lit [14] m p 110–111°

Methyl 2-O-acetyl-3,6-dichloro-3,6-dideoxy-4-O-(2,3-di-O-acetyl-4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl)-β-D-allopyranoside (**7**) — To a slurry of dry methyl β-maltoside (5 0 g, dried over phosphoric oxide under diminished pressure at 100°) in anhydrous chloroform (60 ml) and dry pyridine (30 ml) at ~ −70°, sulphuryl chloride (15 ml) was added dropwise with vigorous stirring The reaction mixture was cooled for an additional 2 h and then stirred at room temperature for 24 h. After dilution with chloroform (100 ml), the mixture was washed with 3M hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated. The syrupy residue was dissolved in methanol (200 ml), and a 10% solution of sodium iodide in 1.1 methanol–water was added dropwise with stirring until iodine was no longer liberated The solution was then neutralized with solid sodium hydrogen carbonate, filtered, and concentrated to a residue that was partitioned between chloroform and water The water layer was extracted several times with chloroform, and the combined organic extracts were dried ($MgSO_4$) and concentrated to a syrup that was acetylated with acetic anhydride and pyridine overnight at room temperature in the usual way. The reaction mixture was then poured into ice–water and extracted with dichloromethane (4 × 40 ml). The combined organic extracts were washed with 10% sulphuric acid, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated The residue was chromatographed on silica gel (7734, Merck), using ether–dichloromethane (1 25) as the eluant. The fractions containing the product were collected and evaporated to a solid, which was recrystallized from ethanol to give **7** as a hemi-ethanolate (3 9 g, 48%), m p 129–135° (loss of ethanol of crystallization), 161–162°; $[\alpha]_D^{27}$ +118 9° (*c* 2 4, chloroform) (Found C, 41.5, H, 5 1, Cl, 24 6 $C_{19}H_{26}Cl_4O_{10}$ 0 5C_2H_6O calc.· C, 41 5, H, 5 1; Cl, 24 5%)

ACKNOWLEDGMENT

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