Synthesis of N-(methyl-6-deoxy-β-D-glucopyranos-6-ide) Saccharin

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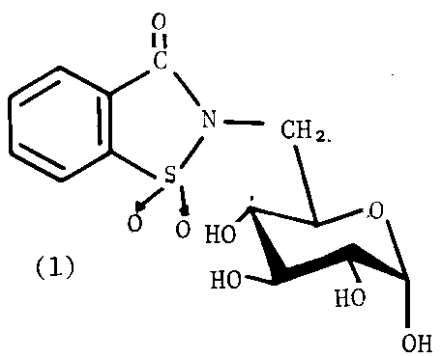
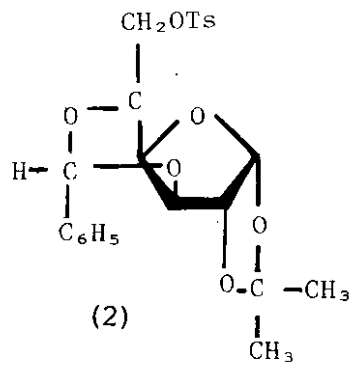
It is now generally recognised that the fundamental unit of sweetness is an AH, B system[1,2] (where A and B are electronegative atoms in suitable geometric proximity) and that the initial mechanism of the sweet taste response is a simultaneous intermolecular hydrogen bond between a compound's saporous unit and the taste receptor site.

The molecular feature responsible for the sweet taste of sacchairn was described by Shallenberger[2] to be the imide and sulphoxide groups, the NH group representing the AH moiety and the sulphoxide oxygen atom the B moiety; the third or (hydrophobic) site[3] was assigned to the C-4 methine group of the aromatic ring. Most N-substituted derivatives of saccharin are either only very slightly water soluble or completely insoluble, leading to loss of sweetness, as is shown in N-methyl saccharin. It is thus not possible to use such derivatives to test Shallenberger's assignment. However, N-sugar saccharin derivatives should retain their water solubility and may even modify the bitter aftertaste of saccharin.

The substitution of the sulphimide hydrogen of saccharin by D-glucose to give N-(6-deoxy-D-glucos-6-yl)-saccharin (1) has been reported[4]. The synthesis involves the treatment of sodium saccharin with 3,5-O-benzylidene-1,2-O-isopropylidene-6-O- tosyl-α-D-glucofuranose (2) in N,N-dimethylformamide at 135°C for 9 hours. More recently, Szarke et al[5] reported the synthesis of the galactose isomer (3) by reacting 1,2: 3,4-di-O-isopropylidene-α-D-galactopyranose with equimolar quantities of saccharin, diethyl azodicarboxylate and tri-



(1)



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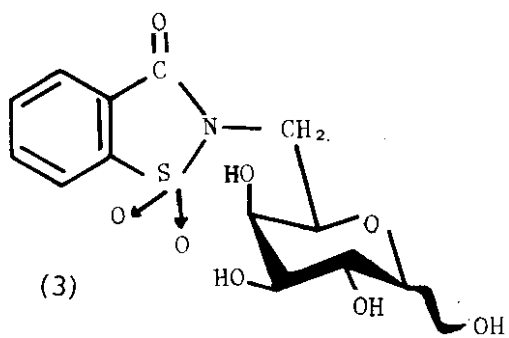

(3)

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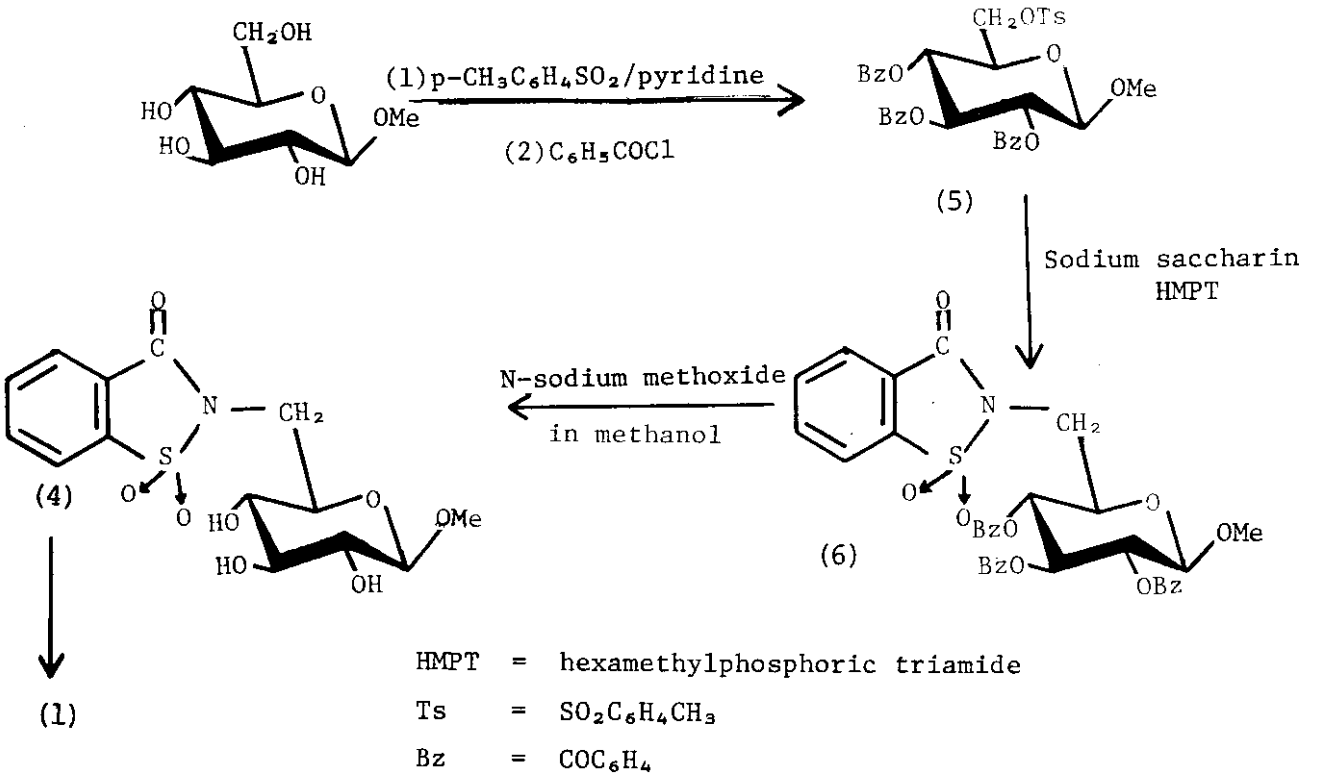


phenylphosphine. In both cases, apart from the low overall yield, the synthesis of the starting intermediate are lengthy, involving several steps. Furthermore, purification of the products required column chromatography. A much easier and more convenient method of synthesis of N-(methyl-6-deoxy-β-D-glucopyranos-6-ide)-saccharin (4) is now described.

Unimolar tosylation of methyl-β-D-glucopyranoside in pyridine[6] followed by benzoylation with benzoyl chloride yielded 55% of crystalline methyl-2,3,4-tri-O-benzoyl-6-O-tosyl-β-D-glucopyranoside (5), m.p. 166-167°, $[\alpha]_D$ + 9.4° (c 0.46, chloroform). A solution of this (3.0g) in hexamethylphosphoric triamide (10 ml) was stirred at 70°C with sodium saccharin (3.0g) for 10 hours when t.l.c. (benzene: ethyl acetate, 15:1) showed only one compound formed. The reaction mixture was poured into ice water, the precipitate filtered and washed well with water, dried and recrystallised (twice) from ethanol to give pure N-(methyl-2,3,4-tri-O-benzoyl-6-deoxy-β-D-glucopyranos-6-ide)-saccharin (6) in 72% (2.2g) yield, m.p. 163-164°, $[\alpha]_D$-22.7° (c 0.46, chloroform) Found; C, 62.18; H 4.51; N, 2.03; S, 5.13 $C_{35}H_{29}NO_{11}S$ calc.: C, 62.59; H, 4.32; N, 2.09; S. 4.77%).

The structure of (6) was characterised by its 220 MHz ^1H n.m.r. spectrum in deuteriochloroform. The spectrum was virtually first order showing the expected chemical shifts (τ) and coupling constants for all the ring protons (Table 1).

Nineteen aromatic protons were detected in their normal positions and the resonance due to the anomeric methoxy methyl proton occurred as singlet at 6.51.

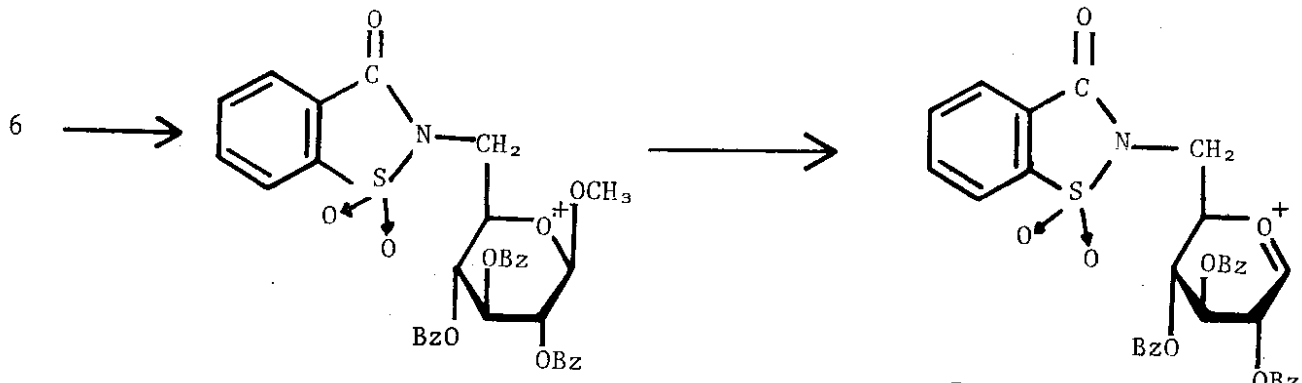
The mass spectral data indicated a fragment at m/e 671.2042 (corresponding to the ion $(C_{35}H_{29}NO_{11}S)^+$) (A) and another at m/e 640 (corresponding to the glycosyloxy carbonium ion $(C_{34}H_{27}NO_{10}S)^+$ (B).

Conventional debenzoylation of (6) using N-sodium methoxide in methanol[7], followed by deionising with

Table 1

H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
5.27(d)*	4.55(dd)*	4.10(t)*	4.48(t)*	5.69(td)*	5.80(dd)*	5.96(dd)*
$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
8.0	9.5	9.5	9.5	8.0	2.0	14.0

* d = doublet; dd = double doublet; td = triple doublet; t = triplet



Amberlite IR-120 (H^+) resin and concentration gave N-(methyl-6-deoxy-β-D-glucopyranos-6-ide)-saccharin (4) as a syrup in 89% yield, $[\alpha]_D$ -55.1° (c0.52, water) (Found; C, 46.55; H, 4.69; N, 4.05; S, 8.90. $C_{14}H_{17}NO_8S$ calc.: C, 46.80; H, 4.74; N, 3.90; S, 8.91%).

Acid catalysed hydrolysis of (4) by treatment with 2N hydrochloric acid at 100° for 2 hours gave, after deionising with Biodeminrolit mixed bed (CO_3^{2-}) resin, a crystalline solid (from ethanol), having the same melting point and specific rotation as those reported by Acton et al[4]. This N-(glucose)-saccharin compound was also conveniently synthesised from 1,2,3,4-tetra-O-tosyl-D-glucopyranose by the same procedure in over 75% overall yield.

Acknowledgements

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