

## Synthesis of Carbohydrate-Saccharin Conjugates

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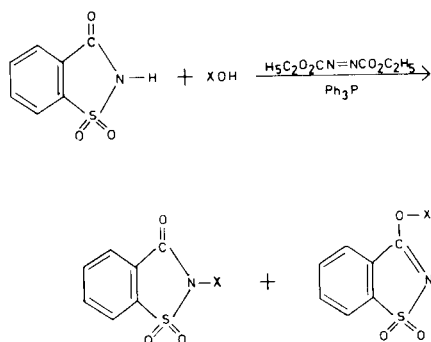
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The synthesis of some carbohydrate-saccharin conjugates has been achieved by treatment of sugar derivatives containing "isolated" hydroxyl groups with equimolar amounts of saccharin, diethyl azodicarboxylate, and triphenylphosphine. Both C-N-linked and C-O-linked compounds can be obtained.

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Mitsunobu and co-workers (1) have recently reported a stereospecific, one-stage formation of *N*-alkylphthalimides from alcohols by treatment with phthalimide, diethyl azodicarboxylate, and triphenylphosphine; the reaction presumably involves the formation initially of a betaine (2), from triphenylphosphine and diethyl azodicarboxylate, and then of an alkoxyphosphonium intermediate. The utility of the reaction for the synthesis of certain amino sugars has been described (3). Here we report the synthesis of some carbohydrate-saccharin conjugates by the substitution of saccharin for phthalimide in the Mitsunobu reaction; both C-N-linked and C-O-linked compounds can be obtained (see Scheme A). Klemmer and



Scheme A

co-workers (4) have prepared compounds of the latter type by the reaction of *D*-glucose derivatives containing "isolated" hydroxyl groups with 3-chloro-1,2-benzisothiazole 1,1-dioxide; *N*-(glucopyranosyl)saccharin derivatives were synthesized by the reaction of substituted  $\alpha$ -*D*-glucopyranosyl halides with the sodium or silver salts of saccharin. In the present work, the carbohydrate

substrates employed were 1,2:3,4-di-*O*-isopropylidene- $\alpha$ -*D*-galactopyranose (5) (1), methyl 5-deoxy-2,3-di-*O*-*p*-tolylsulfonyl- $\alpha$ -*L*-arabinohexofuranoside (6) (5), and 5-deoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl- $\alpha$ -*D*-xylohexofuranose (6) (8).

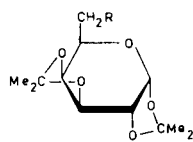
Treatment of compound 1 for 12 hours according to the General Procedure afforded approximately equal amounts of *N*-(6-deoxy-1,2:3,4-di-*O*-isopropylidene- $\alpha$ -*D*-galactopyranos-6-yl)saccharin (2) and 6-*O*-(1,2-benzisothiazol-3-yl 1,1-dioxide)-1,2:3,4-di-*O*-isopropylidene- $\alpha$ -*D*-galactopyranose (3). The two isomers were differentiated on the basis of their ir and carbon-13 magnetic resonance (cmr) spectra. The ir spectrum of 2 showed an absorption at 1730  $\text{cm}^{-1}$  attributable to the carbonyl group of the lactam structure, whereas the spectrum of 3 showed an absorption at 1550  $\text{cm}^{-1}$  attributable to the C=N link of the lactim structure. Carbon-13 chemical shift data for 1,2:3,4-di-*O*-isopropylidene- $\alpha$ -*D*-galactopyranose (1), compounds 2 and 3, and saccharin are documented in Table I. A diagnostic feature of the spectra is the resonance of C-3 of the saccharin moiety; in the case of the C-N-linked compound (2), this signal is shifted slightly upfield (1.8 ppm) relative to the corresponding signal in the spectrum of saccharin, whereas the signal in the spectrum of the C-O-linked compound (3) is shifted downfield by 8.5 ppm. Also, there is a significant difference between the chemical shift of the signal for C-6 of the carbohydrate moiety in the spectrum of 2 and those of the corresponding signals in the spectra of the compounds (1 and 3) bearing oxygen functions at C-6. Attempts to isomerize, by a Chapman-type rearrangement (7,8), compound 3 to the C-N-linked compound (2), by heating in a sealed tube at 170° for 0.5 hour or in "xylene" (b.p. 137-140°) or tetrahydrofuran at reflux temperature for 24 hours, were unsuccessful; in contrast,

Table I

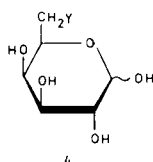
## Carbon-13 Chemical-shift Data (a)

| Compound  | Carbohydrate Carbon |                          |      |                       |                          | C-3 of Saccharin Moiety |
|-----------|---------------------|--------------------------|------|-----------------------|--------------------------|-------------------------|
|           | C-1                 | (C-2, C-3, C-4, C-5)     | C-6  | Me <sub>2</sub> -OCO- | Me's                     |                         |
| 1         | 96.3                | (70.7, 70.7, 68.8, 71.3) | 61.5 | 108.5<br>109.2        | 24.5, 24.9<br>26.0       | --                      |
| 2         | 96.4                | (71.0, 70.5, 65.3, 71.3) | 39.5 | 108.9<br>109.9        | 24.6, 25.0<br>25.8, 26.1 | 158.9                   |
| 3         | 96.4                | (70.9, 70.9, 70.5, 71.0) | 65.6 | 109.1<br>110.0        | 24.5, 25.0<br>26.1       | 169.2                   |
| Saccharin | --                  | --                       | --   | --                    | --                       | 160.7                   |

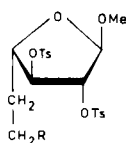
(a) In ppm downfield from internal tetramethylsilane in chloroform-*d*. Cmr spectra were recorded on a Bruker HX-60 spectrometer equipped with a FT60M Fourier transform accessory at 15.1 MHz.



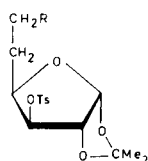
1 R = OH  
2 R = Y  
3 R = Z



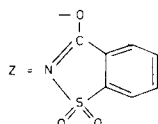
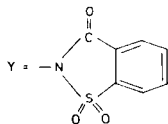
4



5 R = OH  
6 R = Y  
7 R = Z



8 R = OH  
9 R = Z



Klemer and co-workers (4) were able to achieve such a thermal rearrangement when the saccharin moiety was bonded to the carbohydrate at the anomeric center. Hydrolysis of compound **2** with 90% (v/v) aqueous trifluoroacetic acid (9) at room temperature rapidly afforded powdery *N*-(6-deoxy-**D**-galactos-6-yl)saccharin (**4**).

In the case of methyl 5-deoxy-2,3-di-*O*-*p*-tolylsulfonyl- $\alpha$ -**L**-arabinohexofuranoside (**5**), after 4 hours, a syrupy product was obtained, which migrated as a single component in tlc, but whose ir spectrum suggested that it was a mixture of *N*-(methyl 5,6-dideoxy-2,3-di-*O*-*p*-tolylsulfonyl- $\alpha$ -**L**-arabinohexofuranosid-6-yl)saccharin (**6**) and methyl 6-*O*-(1,2-benzisothiazol-3-yl 1,1-dioxide)-5-deoxy-2,3-di-*O*-*p*-tolylsulfonyl- $\alpha$ -**L**-arabinohexofuranoside (**7**). 5-Deoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl- $\alpha$ -**D**-xylohexofuranose (**8**) afforded, after 6 hours, crystalline 6-*O*-

(1,2-benzisothiazol-3-yl 1,1-dioxide)-5-deoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl- $\alpha$ -**D**-xylohexofuranose (**9**) in 86% yield.

## EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 141 automatic polarimeter at  $23 \pm 3^\circ$ . Infrared spectra were recorded with a Perkin-Elmer 180 spectrophotometer. The pmr spectra were recorded at 60 MHz with tetramethylsilane as the internal standard. Tlc and column chromatography were performed on silica gel; the developed plates were air-dried, sprayed with 5% ethanolic sulfuric acid, and heated at about  $150^\circ$ .

Preparation of Carbohydrate-Saccharin Conjugates: General Procedure.

Equimolar quantities of the carbohydrate substrate, saccharin, triphenylphosphine, and diethyl azodicarboxylate were dissolved in dry tetrahydrofuran, and the solution was kept at room temperature. The progress of each reaction was monitored by tlc; usually, reaction times of 4-12 hours were employed. The solvent was evaporated, and the product was isolated by column chromatography, with the same solvent as used for tlc as eluent.

*N*-(6-Deoxy-1,2:3,4-di-*O*-isopropylidene- $\alpha$ -**D**-galactopyranos-6-yl)saccharin (**2**) and 6-*O*-(1,2-Benzisothiazol-3-yl 1,1-dioxide)-1,2:3,4-di-*O*-isopropylidene- $\alpha$ -**D**-galactopyranose (**3**).

1,2:3,4-Di-*O*-isopropylidene- $\alpha$ -**D**-galactopyranose (**1**) was treated for 12 hours according to the General Procedure to afford a mixture of **2** and **3**, which was resolved by column chromatography.

Compound **2** was obtained in crystalline form (33% yield), m.p.  $155.5$ - $157^\circ$  dec., [from diethyl ether-petroleum ether (b.p.  $60$ - $80^\circ$ )];  $[\alpha]_{\text{D}}^{19} \pm 1^\circ$  (c 1.6, chloroform);  $R_f$  0.72 [ethyl acetate-benzene (1:1)]; ir (potassium bromide):  $1590$  and  $1730$   $\text{cm}^{-1}$  (*N*-substituted saccharin); pmr (chloroform-*d*):  $\delta$  7.9-7.7 (4H, C<sub>6</sub>H<sub>4</sub>), 5.5 (d, 1H,  $J_{1,2} = 5$  Hz, H-1), 4.7-3.9 (6H, H-2, H-3, H-4, H-5, H-6 and H-6'), 1.6-1.2 [12H, 2C(CH<sub>3</sub>)<sub>2</sub>].

Anal. Calcd. for C<sub>19</sub>H<sub>23</sub>NO<sub>8</sub>S: C, 53.6; H, 5.5; N, 3.3. Found: C, 53.8; H, 5.5; N, 3.5.

Compound **3** was obtained in crystalline form (32% yield), m.p. 168.5-170° dec., [from diethyl ether-petroleum ether (b.p. 60-80°)];  $[\alpha]_{\text{D}} -39 \pm 1^\circ$  (*c* 1.4, chloroform);  $R_f$  0.67 [ethyl acetate-benzene (1:1)]; ir (potassium bromide): 1550 (C=N), 1605  $\text{cm}^{-1}$ ; pmr (chloroform-*d*):  $\delta$  7.8-7.7 (4H,  $\text{C}_6\text{H}_4$ ), 5.6 (d, 1H,  $J_{1,2} = 5$  Hz, H-1), 4.8-4.2 (6H, H-2, H-3, H-4, H-5, H-6 and H-6'), 1.6-1.2 [12H,  $2\text{C}(\text{CH}_3)_2$ ].

Anal. Calcd. for  $\text{C}_{19}\text{H}_{23}\text{NO}_8\text{S}$ : C, 53.6; H, 5.5; N, 3.3. Found: C, 53.4; H, 5.7; N, 3.4.

*N*-(6-Deoxy-D-galactos-6-yl)saccharin (**4**).

A solution of compound **2** (200 mg.) in 90% (v/v) aqueous trifluoroacetic acid (5 ml.) was stirred at room temperature for 10 minutes; tlc revealed that all of the starting material had been consumed. The solvent was evaporated, and the residue was triturated with ether to afford compound **4** as a white powder (119 mg., 74%), m.p. 110-112°;  $[\alpha]_{\text{D}} +39 \pm 1^\circ$  (equil., *c* 1.1, water); ir (potassium bromide): 1730 (C=O), 3400 (OH)  $\text{cm}^{-1}$ . The product reduced Fehling's solution.

Anal. Calcd. for  $\text{C}_{13}\text{H}_{15}\text{NO}_8\text{S}$ : C, 45.2; H, 4.4; N, 4.1. Found: C, 44.9; H, 4.4; N, 4.1.

Mixture of *N*-(Methyl 5,6-dideoxy-2,3-di-*O*-*p*-tolylsulfonyl- $\alpha$ -L-arabinohexofuranosid-6-yl)saccharin (**6**) and Methyl 6-*O*-(1,2-Benzisothiazol-3-yl 1,1-dioxide)-5-deoxy-2,3-di-*O*-*p*-tolylsulfonyl- $\alpha$ -L-arabinohexofuranoside (**7**).

Methyl 5-deoxy-2,3-di-*O*-*p*-tolylsulfonyl- $\alpha$ -L-arabinohexofuranoside (**5**) was treated for 4 hours according to the General Procedure to afford a syrupy mixture of **6** and **7**, which migrated as a single component (98% yield), having  $R_f$  0.60, in tlc [ethyl acetate-benzene (1:4)];  $[\alpha]_{\text{D}} -34 \pm 2^\circ$  (*c* 1.4, chloroform); ir (Nujol): 1560 (C=N), 1590, 1610, 1735 (C=O)  $\text{cm}^{-1}$ ; pmr (chloroform-*d*):  $\delta$  7.9-7.3 (12H, aromatic protons), 4.9-3.6 (6H, H-1, H-2, H-3, H-4, H-6 and H-6'), 3.3 (s, 3H,  $\text{OCH}_3$ ), 2.5 (s, 6H,  $2\text{CH}_3\text{-C}_6\text{H}_4$ ),  $\sim$ 2.4-1.9 (m, 2H, H-5 and H-5'). The mixture could not be resolved by chromatography in several solvent systems.

Anal. Calcd. for  $\text{C}_{28}\text{H}_{29}\text{NO}_{11}\text{S}_3$ : C, 51.6; H, 4.5; N, 2.2. Found: C, 51.5; H, 4.6; N, 2.1.

6-*O*-(1,2-Benzisothiazol-3-yl 1,1-dioxide)-5-deoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl- $\alpha$ -D-xylohexofuranose (**9**).

This compound was obtained in crystalline form (86% yield) after 6 hours; m.p. 174-176° dec., (from chloroform-diethyl ether);  $[\alpha]_{\text{D}} -12.8 \pm 1^\circ$  (*c* 2.0, chloroform);  $R_f$  0.39 [ethyl acetate-benzene (1:1)]; ir (potassium bromide): 1550 (C=N), 1595, 1610  $\text{cm}^{-1}$ ; pmr (chloroform-*d*):  $\delta$  7.8-7.2 (8H, aromatic protons), 5.85 (d, 1H,  $J_{1,2} = 4$  Hz, H-1), 4.8-4.2 (5H, H-2, H-3, H-4, H-6 and H-6'), 2.5 (s, 3H,  $\text{CH}_3\text{-C}_6\text{H}_4$ ),  $\sim$ 2.2-1.9 (m, 2H, H-5 and H-5'), 1.5 and 1.3 [2s, 3H each,  $\text{C}(\text{CH}_3)_2$ ].

Anal. Calcd. for  $\text{C}_{23}\text{H}_{25}\text{NO}_9\text{S}_2$ : C, 52.8; H, 4.8; N, 2.6. Found: 52.8; H, 4.8; N, 2.6.

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