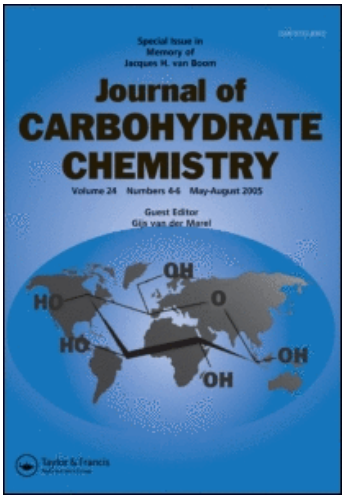

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Aldonamides as Potential Bulking Agents

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ALDONAMIDES AS POTENTIAL BULKING AGENTS

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ABSTRACT

Nine aldonamides with molecular weights and chemical structures similar to that of sucrose were synthesized. Aldonamides were synthesized by reacting 1-amino-1-deoxy-**D**-glucitol or 2-amino-2-hydroxymethyl-1,3-propanediol with monosaccharide lactones in methanol or ethanol. Eight of the aldonamides were crystalline. All were tasteless. The solubility, hygroscopicity, and solution enthalpy of four of the compounds were determined and found to vary greatly. Most of the aldonamides tested possess physiochemical characteristics similar to that of sucrose and, therefore, could potentially be used as reduced-calorie bulking agents.

INTRODUCTION

Sucrose imparts many of the functional and structural characteristics associated with foods, in addition to sweetness. Properties of sucrose important to its usage in food include high solubility, crystallizability, and a small negative heat of solution. Sucrose also has the ability to increase osmotic pressure, depress the freezing point, increase viscosity, impart body, form glasses, and bind water.[1,2] Replacement of sucrose with a reduced-calorie bulking agent (RCBA) requires that the bulking agent have many of these properties, which ones depending on the product to be made.

Because some of the desirable properties are colligative properties, it seems important that RCBAs have a molecular weight, number of carbon atoms, number of hydroxyl groups, and ratio of carbon atoms-to-hydroxyl groups similar to that of sucrose. In the present work, potential RCBAs with sizes and polarities similar to that of sucrose were synthesized and some important physiochemical properties determined.[3] Compounds with amide bonds were chosen because they are generally rather stable to heat and acids, so that breakdown should not occur during processing or cooking. Additionally, humans do not have as digestive enzymes amidases other than specific proteases and peptidases, so digestion would be unlikely and the compounds should have little or no caloric value by direct metabolism.

$$R\text{-}CH_2NH\text{-}CO\text{-}R'$$

Cmpd.	Configuration of RCH_2NH-	Configuration of R'-CO
1	Glc	Glc
2	Glc	Gal
3	Glc	Man
4	Glc	Xyl
5	Glc	Rib
6	Glc	Ara
7	Glc	**D**-*glycero*-**D**-*gulo*-hepto
8	$(CH_2OH)_3C$-NH-	Glc
9	$(CH_2OH)_3C$-NH-	Gal

RESULTS AND DISCUSSION

Nine aldonamides were synthesized by reaction of various aldonolactones with a linear primary amine derivative of glucose, 1-amino-1-deoxy-**D**-glucitol (**D**-glucamine), or a branched primary amine, 2-amino-2-hydroxymethyl-1,3-propanediol [tris-(hydroxymethyl)aminomethane, THAM], by modification of reported methods.[4,5] Reactions were completed using a minimum of reactants, in one step, and with good yields (67-81% for **D**-glucamine aldonamides and 51-59% for THAM aldonamides). All were shown to be amides by IR spectroscopy. Of the aldonamides synthesized, only *N*-[tris(hydroxymethyl)methyl]-**D**-gluconamide has been reported previously.[3,5] None had any significant taste, especially sweetness.

TABLE 1. Structural Characteristics of Synthesized Aldonamides

Compound	No. of C atoms	No. of OH groups	C/OH	Molecular Weight
1	12	10	1.20	359
2	12	10	1.20	359
3	12	10	1.20	359
4	11	9	1.22	329
5	11	9	1.22	329
6	11	9	1.22	329
7	13	11	1.18	389
8	10	8	1.25	299
9	10	8	1.25	299
Sucrose	12	8	1.50	342

All aldonamides were isolated in a crystalline form except for **7**, which formed a "gelatinous" precipitate under conditions used to isolate the other compounds. Although this compound was isolated by exchanging the solvent with ether followed by drying in a vacuum oven, the "gelatinous" material could be isolated by filtration and washed with 100% ethanol. The synthesized compounds have carbon atoms and hydroxyl group numbers, carbon/hydroxyl group ratios, and molecular weights similar to that of sucrose (Table 1).

Aldonamides **1**, **2**, **4** and **8** were selected on the basis of structural diversity and commercial viability as RCBAs to be tested with sucrose for solubility, hygroscopicity under various conditions, and solution enthalpy. All compounds showed greater solubility at 50 °C than at 25 °C (Table 2). Compounds **1** and **8**, both of which are gluconamides, were found to have solubilities at both temperatures only slightly less than that of sucrose. Compound **4** was less soluble at both temperatures, and **2** was much less soluble.

The hygroscopicity of **1**, **2**, **4**, **8** and sucrose at 37 °C and 100% RH (relative humidity) is presented in Figure 1. Compound **1** adsorbed moisture at a rate slightly greater than that of sucrose and **8** at a rate slightly less than that of sucrose. Compound

TABLE 2. Solubilities at 25 °C and 50 °C of **1**, **2**, **4**, **8**, and Sucrose

Compound	Concentration of saturated solution (g/mL H_2O)[a]	
	25°C	50°C
1	0.8031 ±0.0009	0.9680 ±0.0036
2	0.0248 ±0.0005	0.0784 ±0.0020
4	0.4332 ±0.0034	0.7924 ±0.0014
8	0.7412 ±0.0013	0.9604 ±0.0015
Sucrose	0.8222 ±0.0030	1.0134 ±0.0083

a. Values are means ±S.D. of triplicate determinations.

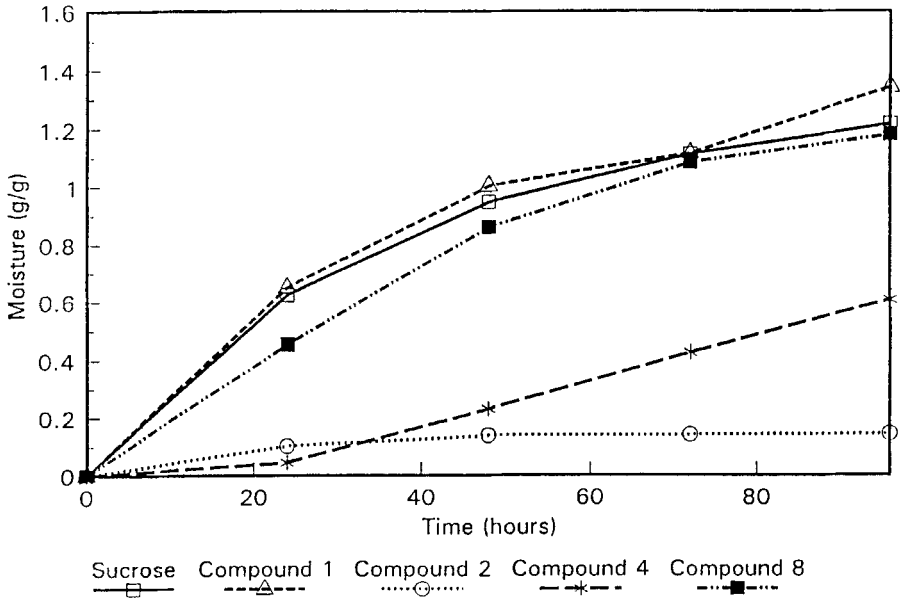

FIG. 1. Hygroscopicity of **1**, **2**, **4**, **8** and sucrose at 100% RH and 37 °C.

TABLE 3. Hygroscopicity of **1**, **2**, **4**, **8** and Sucrose at 25 °C

	Moisture gain (g/g)						
RH	33	57	75	80	88	93	100
Compound							
1	0.000	0.000	0.000	0.000	0.000	0.000	2.011
2	0.011	0.090	0.101	0.101	0.101	0.103	0.116
4	0.001	0.001	0.001	0.001	0.001	0.001	1.751
8	0.001	0.001	0.002	0.001	0.001	0.001	1.734
Sucrose	0.001	0.001	0.000	0.000	0.000	0.001	2.358

4 adsorbed moisture at a slower linear rate compared to the other compounds tested and, after 96 h, had absorbed approximately half as much moisture as did sucrose. As compared to sucrose, **2** equilibrated rapidly and adsorbed little moisture. The two compounds having the least hygroscopicity (**2** and **4**) both remained solid after 96 h at test conditions, while **1**, **8** and sucrose adsorbed sufficient miosture to have dissolved to a solution after 96 h. These results indicate that **1** and **8** are very similar to sucrose in terms of hygroscopicity, and **2** and **4** are much less hygroscopic than sucrose under the conditions of 37 °C and 100% RH.

Table 3 presents the moisture gain of **1**, **2**, **4**, **8** and sucrose at 25 °C and 33, 57, 75, 80, 88, 93, and 100% RH. The isotherm for sucrose showed expected hygroscopic behavior.[6] Compounds **1**, **4**, and **8** have isotherms similar to that of sucrose with little moisture adsorbtion at less than 93% RH, but with a large increase in hygroscopicity at 100% RH. At 100% RH, **8** adsorbed slightly more moisture than sucrose, and **1** and **4** adsorbed slightly less than sucrose. Compound **2** showed little adsorbtion of moisture at 100% RH and remained a solid, while **1**, **4**, **8** and sucrose adsorbed sufficient moisture to become solutions. Under these conditions, therefore, **2** is much less hygroscopic than sucrose, while **1**, **4**, and **8** behave very similarly to sucrose.

The solution enthalpy indicates to what extent a compound will give the sensation of heating or cooling upon dissolving in the mouth. Sucrose has a small negative solution enthalpy and therefore imparts a very mild cooling sensation that is important to the organoleptic properties of some foods containing crystalline sucrose.

TABLE 4. Solution Enthalpy of **1**, **2**, **4**, **8**, and Sucrose

Compound	Enthalpy (J/g)[a]
1	-60.7 ±0.0
2	-52.3 ±0.5
4	-106.0 ±0.5
8	-68.9 ±0.4
Sucrose	-16.7 ±0.2

a. Values are means ±S.D. of triplicate determinations.

Compounds such as sorbitol and xylitol have much greater negative solution enthalpies, 111 and 146 J/g, respectively,[7] and therefore impart a greater cooling effect. The solution enthalpy of **1**, **2**, **4**, **8** and sucrose are presented in Table 4. The enthalpy value determined for sucrose was similar to values determined by other investigators.[6] All compounds were found to have negative solution enthalpies greater than that of sucrose. Compound **4** has the greatest solution enthalpy and would probably exhibit a very noticeable cooling effect when crystals of it dissolve in the mouth. Compounds **1**, **2**, and **8** have solution enthalpies approximately half as great as **4** and greater than that of sucrose, but considerably less than that of sorbitol or xylitol. These compounds would likely produce a mild cooling sensation upon dissolving on the tongue.

EXPERIMENTAL

Materials. The following reagents were obtained from the sources indicated: **D**-galactono-1,4-lactone, **L**-mannono-1,4-lactone, **D**-ribono-1,4-lactone, **D**-xylono-1,4-lactone and **D**-*glycero*-**D**-*gulo*-heptono-1,4-lactone (Pfanstiehl Laboratories); **D**-glucono-1,5-lactone and 2-amino-2-hydroxymethyl-1,3-propanediol (Sigma Chemical Co.); **D**-arabino-1,4-lactone (K & K Laboratories); 1-amino-1-deoxy-**D**-glucitol (Fluka Chemical Co.).

General Procedures. Amides based on 1-amino-1-deoxy-**D**-glucitol were prepared with a 10% excess of amine. Excess amine was then removed from the product mixture using cation-exchange resin. If subsequent crystallization was unsucessful, the product was further purified using an anion-exchange resin to remove unreacted lactone. For crystallization, compounds were dissolved in water, then

methanol was added to incipient turbidity on a steam bath. Mixtures were then allowed to cool.

2-Amino-2-hydroxymethyl-1,3-propanediol based amides were prepared using a modification of the method previously used for the synthesis of *N*-[tris-(hydroxymethyl)methyl]-**D**-gluconamide.[5]

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were recorded as Nujol mulls with a Perkin-Elmer model 1800 infrared spectrophotometer. Fast atom bombardment mass spectra were recorded on a KRATOS MS50 mass spectrometer using a DTT/DTE matrix.

Standard Synthesis Procedure. A mixture of an aldonolactone and an amine in anhydrous methanol was heated at the reflux temperature with exclusion of moisture. The mixture was then concentrated under reduced pressure. Water and Amberlite IR-120(H^+) cation-exchange resin were added, and the mixture was stirred for 15 min, then filtered. The resin was washed with H_2O. The resulting solution was concentrated under reduced pressure to a syrup, then crystallized from aqueous methanol at 5 °C. Crystals were washed with 100% ethanol. The product was recrystallized from aqueous methanol.

***N*-(D-Glucitol-1-yl)-D-gluconamide (1).** The standard synthesis procedure was used with a mixture of **D**-glucono-1,5-lactone (8.907 g, 0.050 mol) and 1-amino-1-deoxy-**D**-glucitol (9.965 g, 0.055 mol) in 225 mL methanol. The mixture was heated 6 h, then concentrated to *ca.* 100 mL; 100 mL H_2O and 10.5 mL cation-exchange resin were added. The resin was washed with 30 mL H_2O after filtration. Yield 14.08 g (78.4%); mp 147-148 °C; IR 1636 cm^{-1} (amide I), 1546 cm^{-1} (amide II); FAB-mass spectrum: m/z 360 [M+1].

Anal. Calcd for $C_{12}H_{25}NO_{11}\cdot 0.25H_2O$: C, 39.62; H, 7.06; N, 3.85. Found: C, 39.26; H, 7.27; N, 3.85.

***N*-(D-Glucitol-1-yl)-D-galactonamide (2).** The standard synthesis procedure was used with **D**-galactono-1,4-lactone (8.907 g, 0.050 mol) and 1-amino-1-deoxy-**D**-glucitol (9.965 g, 0.055 mol) in 150 mL methanol. The mixture was heated 5 h, then concentrated to *ca.* 100 mL; 200 mL H_2O was added with 10.5 mL cation-exchange resin. The resin was washed with 30 mL H_2O after filtration. Yield 13.36 g (74.4%); mp 148-150 °C; IR 1648 cm^{-1} (amide I), 1558 cm^{-1} (amide II); FAB-mass spectrum: m/z 360 [M+1].

Anal. Calcd for $C_{12}H_{25}NO_{11}\cdot 0.5H_2O$: C, 39.13; H, 7.12; N, 3.80. Found: C, 39.19; H, 7.24; N, 3.82.

***N*-(D-Glucitol-1-yl)-L-mannonamide (3).** The standard synthesis procedure was used with **D**-mannono-1,4-lactone (0.3563 g, 0.002 mol) and 1-amino-1-deoxy-**D**-

glucitol (0.3986 g, 0.0022 mol) in 20 mL anhydrous ethanol. The reaction mixture was heated for 4 h, then concentrated to a syrup; 20 mL H_2O and 5 mL cation-exchange resin were added. The resin was washed with 10 mL H_2O after filtration, and the product was crystallized and recrystallized from aqueous ethanol. Yield 0.5826 g (81.1%); mp 202-203 °C; IR 1656 cm^{-1} (amide I), 1562 cm^{-1} (amide II); FAB-mass spectrum: m/z 360 [M+1].

Anal. Calcd for $C_{12}H_{25}NO_{11}\cdot H_2O$: C, 38.20; H, 7.21; N, 3.71. Found: C, 39.14; H, 7.28; N, 3.69.

***N*-(D-Glucitol-1-yl)-D-xylonamide (4).** The standard synthesis procedure was used with **D**-xylono-1,4-lactone (0.2963 g, 0.002 mol) and 1-amino-1-deoxy-**D**-glucitol (0.3986 g, 0.0022 mol) in 25 mL anhydrous ethanol. The reaction mixture was heated 4 h, then concentrated to a syrup; 25 mL H_2O and 5 mL cation-exchange resin were added. The resin was washed with 10 mL H_2O, and the product was crystallized and recrystallized from aqueous ethanol. Yield 0.5215 g (79.2%); mp 110-113 °C; IR 1648 cm^{-1} (amide I), 1550 cm^{-1} (amide II); FAB-mass spectrum: m/z 330 [M+1].

Anal. Calcd for $C_{11}H_{23}NO_{10}\cdot H_2O$: C, 38.04; H, 7.26; N, 4.03. Found: C, 38.12; H, 7.35; N, 3.96.

***N*-(D-Glucitol-1-yl)-D-ribonamide (5).** The standard synthesis procedure was used with **D**-ribono-1,4-lactone (0.2963 g, 0.002 mol) and 1-amino-1-deoxy-**D**-glucitol (0.3986 g, 0.0022 mol) in 15 mL anhydrous ethanol. The reaction mixture was heated 5 h, then concentrated to a syrup; 20 mL H_2O and 5 mL cation-exchange resin were added. The resin was washed with 10 mL H_2O after filtration, and the product was crystallized and recrystallized from aqueous ethanol at -5 °C. Yield 0.5098 g (77.4%); mp 100-103 °C; IR 1628 cm^{-1} (amide I), 1560 cm^{-1} (amide II); FAB-mass spectrum: m/z 330 [M+1].

Anal. Calcd for $C_{11}H_{23}NO_{10}\cdot H_2O$: C, 38.04; H, 7.26; N, 4.03. Found: C, 38.56; H, 7.24; N, 4.02.

***N*-(D-Glucitol-1-yl)-D-arabinonamide (6).** The standard synthesis procedure was used with **D**-arabinono-1,4-lactone (0.2963 g, 0.002 mol) and 1-amino-1-deoxy-**D**-glucitol (0.3986 g, 0.0022 mol) in 20 mL anhydrous ethanol. The reaction mixture was heated 2 h, then concentrated to a syrup; 20 mL H_2O and 5 mL cation-exchange resin were added. The resin was washed with 10 mL H_2O after filtration, and the product was crystallized and recrystallized from aqueous ethanol. Yield 0.4685 g (67.4%); mp 148-150 °C; IR 1636 cm^{-1} (amide I), 1560 cm^{-1} (amide II); FAB-mass spectrum: m/z 330 [M+1].

Anal. Calcd for $C_{11}H_{23}NO_{10}\cdot 0.5H_2O$: C, 39.05; H, 7.15; N, 4.14. Found: C, 39.47; H, 7.32; N, 4.10.

***N*-(D-Glucitol-1-yl)-D-*glycero*-D-*gulo*-heptonamide (7).** The standard synthesis procedure was used with D-*glycero*-D-*gulo*-heptono-1,4-lactone (0.4163 g, 0.002 mol) and 1-amino-1-deoxy-D-glucitol (0.3986 g, 0.0022 mol) in 30 mL anhydrous ethanol, and the mixture was heated 10 h. Product precipitated upon cooling to room temperature. The precipitate was filtered and washed with 100% ethanol, then dissolved in 20 mL warm H_2O. 5 mL Amberlite IR-120(H^+) cation-exchange resin (5 mL) was added, and the mixture was stirred 20 min. The mixture was filtered, and the resin was washed with 10 mL H_2O. The resulting solution was concentrated under reduced pressure to a syrup. The syrup was then dissolved in 15 mL H_2O. Amberlite IRA-400 (OH^-) anion-exchange resin (2.5 mL) was added. The mixture was stirred 1 h at 50 °C, then filtered. The resin was washed with 20 mL H_2O, and the filtrate and washings were concentrated under reduced pressure to a syrup. After attempting crystallization from aqueous methanol at 5 °C, a gelatinous precipitate formed. The solvent was decanted from the flask and replaced with 25 mL ethyl ether. This solvent exchange was repeated. The resulting solid was dried in a vacuum oven at 50 °C. Yield 0.3965 g (50.9%); IR 1648 cm^{-1} (amide I), 1554 cm^{-1} (amide II); FAB-mass spectrum: m/z 390 [M+1].

Anal. Calcd for $C_{13}H_{27}NO_{11}\cdot 0.25H_2O$: C, 39.65; H, 7.04; N, 3.56. Found: C, 39.36; H, 7.10; N, 3.57.

***N*-[Tris(hydroxymethyl)methyl]-D-gluconamide (8).** The standard synthesis procedure was used with D-glucono-1,5-lactone (10.688 g, 0.06 mol) and 2-amino-2-hydroxymethyl-1,3-propanediol (7.996 g, 0.066 mol) in 120 mL anhydrous methanol. The mixture was heated 20 min. Amberlite IR-120 (H^+) cation-exchange resin (12.5 mL in methanol) was added to the mixture. The mixture was filtered, and the resin was washed with 50 mL methanol, and the product was crystallized and recrystallized from methanol at -20 °C. Yield 10.87 g (58.2%); mp 135-137 °C; IR 1654 cm^{-1} (amide I), 1524 cm^{-1} (amide II); FAB-mass spectrum: m/z 300 [M+1].

Anal. Calcd for $C_{10}H_{21}NO_9$: C, 40.13; H 7.07; N, 4.68. Found: C, 39.44; H, 7.36; N, 4.48.

***N*-[Tris(hydroxymethyl)methyl]-D-galactonamide (9).** The standard synthesis procedure was used with D-galactono-1,4-lactone (0.3563 g, 0.002 mol) and 2-amino-2-hydroxymethyl-1,3-propanediol (0.2423 g, 0.002 mol) in 10 mL anhydrous methanol. The mixture was heated 30 minutes; no cation-exchange resin was added. The product crystallized upon cooling the solution to -20 °C; it was recrystallized from methanol and 100% ethanol. Yield 0.3538 g (59.1%); mp 143-145 °C; IR 1654 cm^{-1} (amide I), 1524 cm^{-1} (amide II); FAB-mass spectrum: m/z 300 [M+1].

Anal. Calcd for $C_{10}H_{21}NO_9$: C, 40.13; H 7.07; N, 4.68. Found: C, 39.90; H, 7.17; N, 4.65.

Solubility. Solubility was determined using a modification of the method previously used for sucralose.[1] First, 2 mL of water was placed in flasks immersed in water baths at 25.0±0.1°C and 50.0±0.1°C. Compounds were added to the flasks, and the mixtures were stirred (magnetic stirrers) until equilibria between dissolved and undissolved crystals were achieved. Continuous stirring was maintained for 20 h to ensure solution saturation. Solutions were allowed to settle for 1 h, then triplicate 0.50 mL samples were removed and placed in tared weighing boats. Samples were dried in a forced air oven at 50 °C for 24 h, followed by drying in a vacuum oven at 50 °C to constant weight.

Hygroscopicity. Triplicate 0.1000 g samples of compounds were weighed into tared weighing pans that were then placed in chambers maintained at 33, 57, 75, 80, 88, 93, and 100% relative humidities at 25 °C. Relative humidities of < 100% were maintained using saturated aqueous solutions of $MgCl_2$, NaBr, NaCl, KBr, $ZnSO_4$, and KNO_3, respectively.[8,9] The pans were removed and weighed at various times until constant weight was achieved.

Solution Enthalpy. Triplicate 0.2500 g or 0.5000 g samples were dissolved in 100.0 mL of H_2O and a Parr model 1451 solution calorimeter was used to determine the resulting temperature change. Temperature changes were then used to calculate solution enthalpy.

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3. After this work was completed, the authors became aware of a patent application which names one of the compounds (1), but which gives none of the specific data, reported here. K. Hahn and B. Schneider, Eur. Pat. Appl. EP 408,887 (1991); *Chem. Abstr.*, **115**, 29841d (1991).

   Later, the authors were made aware of the following patent applications by G.E. Dubois, W.H. Owens, G. Roy, S.Y. Stevens, and M. Yalpani of The NutraSweet Co. that describe the synthesis and use of the same class of compounds as bulking agents: WO 92/06601 (1992), FI 92/01352 (1992), NO 92/00934 (1992), AU 91/89143, EP 506952 (1992). A paper presented orally at the American Chemical Society meeting in New York, NY, 25-30 August 1991 (about the same time that the experimental work on the project reported here was completed) by M. Yalpani (Manssur Yalpani, Grant E. DuBois, Shawn Y. Stevens, William H. Owens, Edmund E. Lee and Glenn Roy, "Synthesis and properties of novel, zero calorie sugar macronutrient substitutes", CARB 026) reported the preparation and

properties of at least some of the same compounds and many others. This group's work was also presented at International Workshop II on Carbohydrates as Organic Raw Materials, 2-3 July 1992, Lyon, France [see *Zuckerind.*, **117**, 478 (1992)]. A detailed report of compounds made as RCBAs by The NutraSweet Company is being prepared for publication.

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