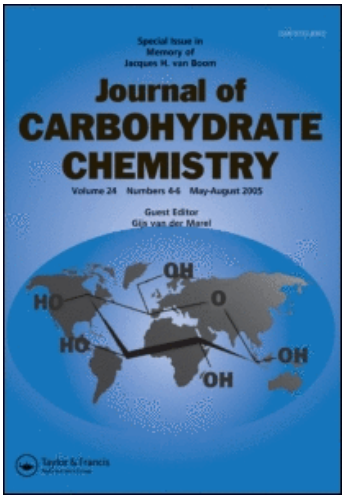
This article was downloaded by:
On: *23 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

The Synthesis of Some Amides of 1-Amino-l-deoxyglucitol and Correlation of Their Structures with the Tinti-Nofre Sweetness Model

Jerry W. Ellis[a]; Steven H. Malehorn[a]; Lorinda M. Browning[a]; Thomas A. Heischmidt[a]; James N. BeMiller[b]; James R. Daniel[c]

[a] Department of Chemistry, Eastern Illinois University, Charleston, IL [b] Director, Whistler Center for Carbohydrate Research, [c] Department of Foods and Nutrition, Purdue University West, Lafayette, IN

To cite this Article Ellis, Jerry W. , Malehorn, Steven H. , Browning, Lorinda M. , Heischmidt, Thomas A. , BeMiller, James N. and Daniel, James R.(1992) 'The Synthesis of Some Amides of 1-Amino-l-deoxyglucitol and Correlation of Their Structures with the Tinti-Nofre Sweetness Model', Journal of Carbohydrate Chemistry, 11: 6, 761 — 778

To link to this Article: DOI: 10.1080/07328309208020091

URL: http://dx.doi.org/10.1080/07328309208020091

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

J. CARBOHYDRATE CHEMISTRY, 11(6), 761-778 (1992)

THE SYNTHESIS OF SOME AMIDES OF 1-AMINO-1-DEOXYGLUCITOL AND CORRELATION OF THEIR STRUCTURES WITH THE TINTI-NOFRE SWEETNESS MODEL

Jerry W. Ellis,[1] Steven H. Malehorn, Lorinda M. Browning and (in part) Thomas A. Heischmidt

Department of Chemistry, Eastern Illinois University, Charleston, IL 61920

James N. BeMiller*# and James R. Daniel^

#Director, Whistler Center for Carbohydrate Research,
^Department of Foods and Nutrition, Purdue University
West Lafayette, IN 47907

Received February 14, 1992 - Final form May 26, 1992

Downloaded At: 10:15 23 January 2011

ABSTRACT

A series of amides of 1-amino-1-deoxy-D-glucitol and 1-deoxy-1-methylamino-D-glucitol was prepared as possible sweeteners. A crucial feature was direct amidation without blocking and deblocking. Several strategies to induce sweetness were considered and a study of the correlation of these compounds with the Tinti-Nofre model was conducted.

INTRODUCTION

The objectives of this project were to (1) investigate the properties of amides of 1-amino-1-deoxy-D-glucitol **(1)** and its *N*-methyl analog **(2)** as possible candidates for non-nutritive sweeteners and bulking agents and (2) to study the incorporation of this moiety into other systems that exhibit sweetness. The reasons for using these amines were several: (1) **1** and **2** are available commercially; (2) the nucleophilicity of the amino group is so much greater than that of the hydroxyl group that

Copyright © 1992 by Marcel Dekker, Inc.

the usual blocking and deblocking steps could be omitted, therefore greatly simplifying the syntheses; (3) these amines would not undergo side reactions or produce products such as those from the Amadori rearrangement of glycosylamines; (4) the amide products would very probably be white, crystalline solids, perhaps similar in appearance to sucrose, and could be purified easily; and (5) the carbohydrate moiety would confer substantial water solubility to the amide.

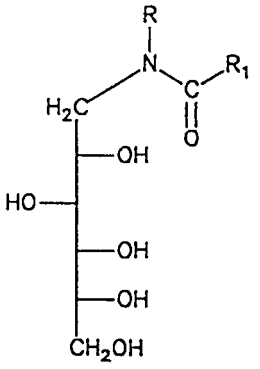
Surprisingly, few reports have appeared concerning the preparation and properties of amides of aminodeoxyglucitols. Most studies have involved preparation of amides of typical monomers, such as acrylic acid, for the purpose of preparing polymers bearing an alditol type side chain,[2] or amides of long chain fatty acids which were of interest because of their surfactant properties.[3]

In this study, a series of amides of 1-amino-1-deoxy-D-glucitol (1) and 1-deoxy-1-methylamino-D-glucitol (2) was prepared from carboxylic acid anhydrides, chlorides, or methyl esters by reported[2] or modified methods.

The AH,B theory of sweetness proposed by Shallenberger and Acree[4] was extended by Kier[5] to include a hydrophobic group, usually referred to as X, and the AH,B and X groups form an isosceles triangle. As this project was coming to a close, Tinti and Nofre[6] extended and refined this model to include eight sites. They redefined the B group of Shallenberger and Acree to be an anionic group such as CO_2^-, SO_3^- or CN_4^- (tetrazole) and relabelled the X group of Kier as G. One of their first observations was that there was a fourth group, which they called D, that was important for very high potency sweeteners.[6] They suggested NO_2, CN or Cl for the D group, which in their examples were bonded to an aromatic ring. Other results[7] suggest that an alternative view might be that the D group is an electron deficient aromatic ring and that π-stacking might be the attractive force. According to Tinti and Nofre,[6] AH, B, D and G are the more important of the eight sites. Not all of the eight groups need to be present for the molecule to exhibit sweetness, but in general, the more of these groups present, the sweeter the compound. The system of molecules designed by Tinti and Nofre clearly demonstrate Kier's observation of the importance of the hydrophobic group in highly potent sweeteners. These observations regarding hydrophobicity have been further discussed by Daniel.[8]

Downloaded At: 10:15 23 January 2011

TABLE I



R_1	Compound # D-glucamine series R = H	*N*-methyl-D-glucamine series R = CH_3
H	3	4
CH_3	5	6
CH_3CH_2	7	8
$CH_3CH_2CH_2$	9	10
phenyl	11	12
2-chlorophenyl	13	14
2-hydroxyphenyl	15	-
CH_2COCH_3	-	16
2-(4-methoxyphenyl)ethenyl	-	17
2-(4-methoxyphenyl)ethyl	-	18
2-(3-hydroxy-4-methoxyphenyl) ethyl	19	-

Downloaded At: 10:15 23 January 2011

RESULTS AND DISCUSSION

Based on the notion that increased hydrophobicity may increase sweetness,[8] a series of amides in which the acyl group varied in polarity would be of interest. The first twelve compounds were prepared to evaluate this concept.

Table I lists the compounds that were synthesized in this study. All were white, crystalline solids, usually with melting points above 100 °C. Their water solubility was high, but as would be expected, decreased, as the R_1 group increased in size. Preliminary screening

suggested that none of the compounds were sweet, and so none were subjected to detailed analysis by a taste panel.

As the hydrophobicity of the R_1 group increased the water solubility decreased and some of these compounds exhibited slight surfactant properties. Also some experimental difficulties were encountered in the syntheses of the larger amides. The acid chlorides, which were chosen in preference to anhydrides because of the ease and efficiency of preparation, were extremely reactive, and this required much greater precaution in excluding water from the reaction media. Another difficulty was the insolubility of the polar aminoglucitols in nonpolar solvents suitable for dissolution of the acid chlorides. A convenient solution to this problem was direct amidation of the corresponding methyl ester with the aminoglucitol in refluxing methanol. The esters are stable and readily available or easily prepared. Again, the high nucleophilicity of the amines allowed the amidation reaction to proceed without hydroxyl group blocking. It was thought that, if any hydroxyl acylation occurred by transesterification of the ester with aminoglucitol hydroxyl groups, it could easily be reversed by including sodium methoxide in the reaction mixture to deacylate the glucitol and regenerate the starting ester. It was later learned that the methoxide was unnecessary and good yields could be obtained in its absence.[9]

^{1}H NMR spectra of the *N*-methyl amides exhibited two signals for the nitrogen bonded methyl groups. This is in direct analogy to the ^{1}H NMR spectrum of *N,N*-dimethylformamide which shows two signals due to hindered rotation about the acyl carbon-nitrogen bond. In the case of the compounds reported here, the rotomers were not present in equal amounts as demonstrated by the unequal peak heights of the methyl signals. Changing the temperature altered the relative signal heights, suggesting that the position of equilibrium was temperature dependent.

Comparison with the Tinti-Nofre Model.

In light of the recently reported Tinti-Nofre model,[6] it was deemed desirable to reevaluate the results of this study. A physical replica of the Tinti-Nofre model was constructed with a scale identical to that of Fieser models.[10] The base was made of 1.5 inch thick plywood and quarter inch dowels were used to provide the third dimension y where the tops of

Downloaded At: 10:15 23 January 2011

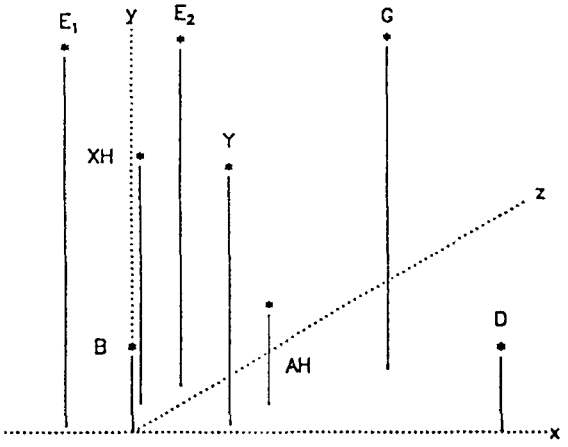


Figure 1

Downloaded At: 10:15 23 January 2011

the dowels defined the actual locations of the eight sites. The cartesian coordinates reported[6] were used except that the values in the y direction were increased by a common quantity to raise the model above the x-z plane. (This was to allow for the use of Fieser models in which some atom might need to extend slightly below the x-z plane.) Figure 1 shows a drawing of the physical replica, which is somewhat different than that presented by Tinti and Nofre.[6]

Careful scrutiny of Figure 1 reveals that in the report by Tinti and Nofre[6] the location of site Y is incorrect in either their Tables II and III or in their Figure 1. Tables II and III in that report, giving distances between each of the eight points and the cartesian coordinates respectively, are self-consistent. However, the data in those two tables are inconsistent with the presentation of the model given on the previous page and the cover of the monograph. The inconsistency can be resolved by interchanging the x and z coordinates and changing the sign of the reported x coordinate for site Y. This would place site Y behind and to the left of site AH as Tinte and Nofre show and as appears in Figure 2. It is not clear which is correct. This is not a critical point here since site Y is not used in our discussion but does partially detract from their discussion of Table II involving the distances between site Y and sites AH or XH.

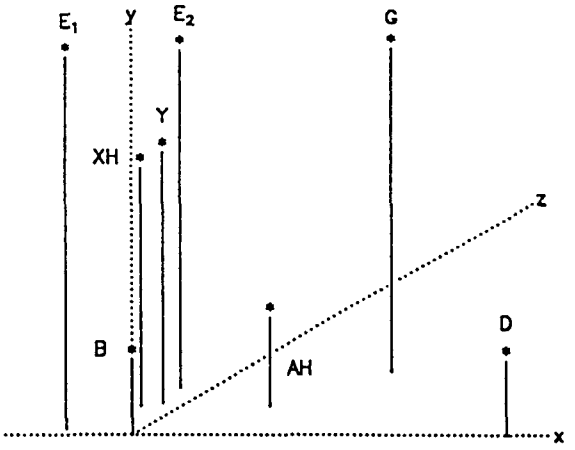


Figure 2

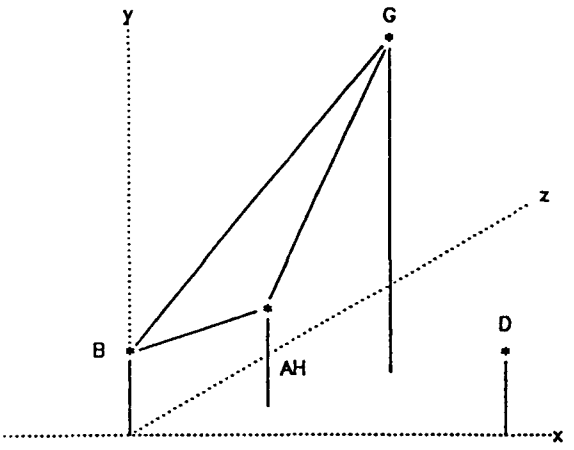


Figure 3

Downloaded At: 10:15 23 January 2011

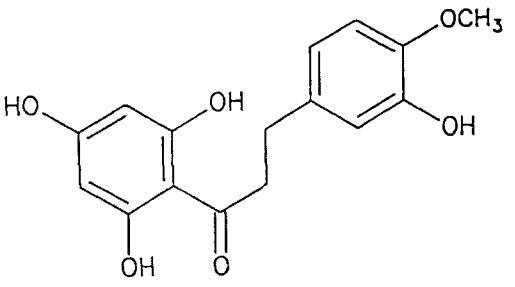
Figure 3 shows the drawing with only those most important four groups appearing with the original Kier triangle outlined.

For ethylene glycol, Tinti and Nofre[6] assigned the two hydroxyl groups as AH and XH. This includes only the AH of the four most important groups and then the minor group XH, thus accounting for its low potency. All the molecules 3-19 include five adjacent hydroxyl groups which correspond to four glycol groupings and a G group of increasing hydrophobic character. Fieser models of these compounds were fitted to

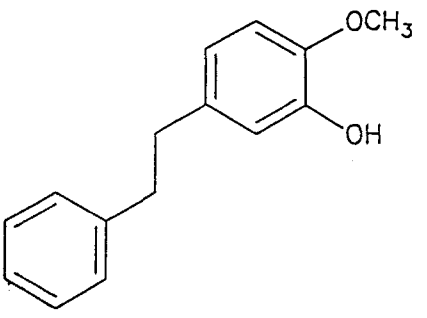
the physical replica previously described. Since the flexibility of the glucitol chain allows for a great variety of conformations, all four of these glycol groupings and the G group could be fit onto the physical model using the AH and XH groups as Tinti and Nofre described for ethylene glycol. So with this system, increasing the hydrophobicity by increasing the size of the G group does not induce sweetness. Just why these results do not correlate with the Tinti-Nofre model is not clear. For evaluation of structure-activity relationships it is clearly better to start with a sweet substance rather than to start with one that is tasteless and attempt to induce sweetness.

In another attempt to induce sweetness, the structural features of the dihydrochalcones and related molecules were considered. The dihydrochalcones, such as 20, generally exhibit sweetness. The dihydrochalcone mimic 21 has been reported to be about 300 times sweeter than sucrose.[11]

The Shallenberger-Acree[4] hypothesis requires that there be an AH,B unit present in the molecule. There is little doubt as to what the AH and B groups are in compound 21, and it was suggested that the unsubstituted aromatic ring was the Kier X site. A Fieser model of this mimic could be



20
Dihydrochalcone



21

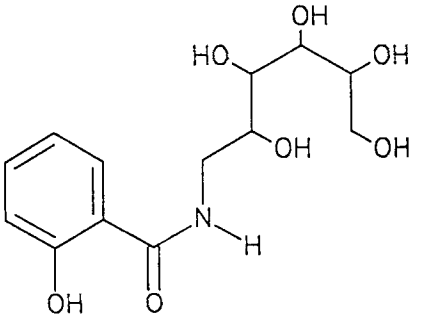
fit to the Tinti-Nofre replica with a slight steric interaction between the phenyl ring hydrogen atoms and those of the other ring when OH and OCH_3 were aligned with AH and XH, respectively. A much better fit of the

Downloaded At: 10:15 23 January 2011

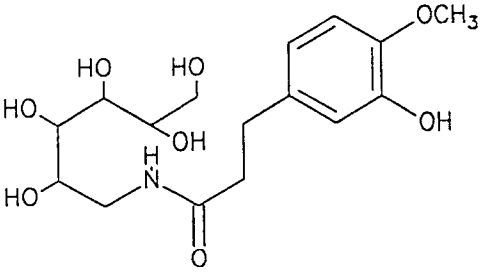
phenyl ring with the G site was obtained by fitting the methoxyl group with the B site. It should be borne in mind that the sites of the model are those of the substrate and that, in the receptor, the group at that point would be one that would complement the group on the substrate. So the B group on the substrate could be an anionic group as Tinti and Nofre require or a proton acceptor as required by Shallenberger and Acree. Since little is known about the structure of the receptor site, one could imagine that a $-NH_3^+$ group for example could satisfy both cases since it would attract the anionic group and also hydrogen bond to a lone pair of an oxygen or nitrogen atom of a B group of the substrate. In that light, the more attractive fit of the mimic **21** with the methoxyl group acting as a B group is not unrealistic and would perhaps help account for the relatively high sweetness of the compound, since now two of the four important sites would be occupied.

Downloaded At: 10:15 23 January 2011

Another approach used was what might be called a "look-a-like" strategy analogous to that rationalized for the activity of stilbestrol.[11] Stilbestrol "looks like" estradiol and has a similar estrogenic effect. It was realized that the 1-amino-1-deoxy-D-glucitol amides could assume a conformation that would resemble the shape of the dihydrochalcones such as **20**. This can be seen in compound **15** where the amide is drawn to show that resemblance.



15



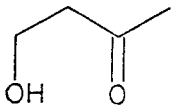
19

Alternatively the aminodeoxyglucitol might be incorporated into an isovanillin system. In this case, the amide **19** would resemble **20**. While the lone A-H,B unit of **21** would appear to be necessary for sweetness, an additional A-H,B unit or Kier type moiety seems to enhance the sweetness.

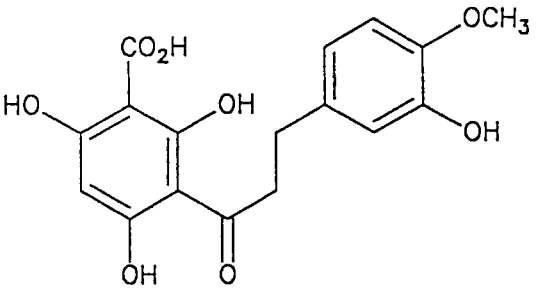
Another hypothesis was based upon the observation that the structural unit **22** is very common in sweet substances. Daniel and Whitelaw[12] found that compound **23** was very sweet and suggested that the carboxyl unit may be responsible for the increased sweetness compared to related compounds. One explanation would be that the A-H,B unit responsible for the sweetness switched from the isovanillin unit to one like **22**, since ring A now has two such units.[13] If that were true, then the incorporation of such a unit into the aminodeoxyglucitol moiety may confer sweetness to the system.

These lines of reasoning partially influenced the selection of the amides **15-19** prepared in this portion of the study. Again, models of these amides could be fit onto the Tinti-Nofre replica. The concept of incorporating a "sweet unit" into a molecule to confer sweetness was suggested earlier by DuBois.[13] While it was unsuccessful here, it still seems to have some merit. For example, the naturally occurring sweet proteins such as monellin[14] are polymers that must have a "sweet unit" since it is highly unlikely that the entire polymer would fit into the receptor site.

Downloaded At: 10:15 23 January 2011



22



23

CONCLUSIONS

It was found that sweetness could not be induced by increasing the hydrophobicity of the parent molecule even though the compounds studied here do seem to fit the Tinti-Nofre model. Also, more is required than a

strong conformational and functional group similarity of the "look-a-like" strategy.

EXPERIMENTAL SECTION

General Procedures. ^1H NMR spectra were recorded on a 300 MHz General Electric QE-300 spectrometer in D_2O with 3-(trimethylsilyl)-propionic-2,2,3,3-d_4 acid, sodium salt as the internal standard or in deuterochloroform ($CDCl_3$) or DMSO-d_6 using tetramethylsilane as the internal standard. Infrared spectra were recorded on a Nicolet 20DX-B FTIR spectrometer (KBr pellets); only the frequencies due to the amide carbonyl stretching absorptions are reported (cm^{-1}). Melting point ranges were determined on a Fisher-Johns Melting Point Apparatus and are uncorrected. The anion-exchange resin was Dowex 2-X4 (20-50 Mesh) in bicarbonate form and the cation-exchange resin was AG Rexyn 101 (18-50 Mesh) in hydrogen form. Both resins were used in water unless otherwise indicated and were removed by suction filtration. Solvents were removed under reduced pressure at 40 °C unless otherwise stated and solids were dried for 48 h at 0.01 torr in an Abderhalden apparatus over P_2O_5 unless otherwise stated. Thin layer chromatography was performed using Analtech 250 micron silica gel GF 10 cm glass plates in solvent A, methanol:chloroform (1:1) or in solvent B, methanol:0.33% acetic acid (9:1). Visualization was done with 0.0095M $KMnO_4$ in 0.20M NaOH or with UV light. Elemental analysis were performed by Galbraith Laboratories, Inc., Knoxville, TN or the analytical facilities of Purdue University.

***N*-(1-Deoxy-D-glucitolyl)formamide (3).** A solution containing 2.50 g (13.8 mmol) of 1-amino-1-deoxy-D-glucitol in 35 mL (820 mmol) of 88% formic acid was heated to 50 °C in a water bath and 11.0 mL (120 mmol) of acetic anhydride was added dropwise with stirring over 1 h while maintaining the temperature between 50 and 60 °C. Following the addition of 10 g of ice/water, the solvent was removed. The solid was crystallized from ethanol to give *N*-(1-deoxy-D-glucitolyl)formamide as white crystals: mp 147-148 °C; ^1H NMR δ (D_2O) 3.3-3.9 (m, H-C-O), 8.00 (s, HC=O), 8.11 (s, HC=O); IR 1632.9 (s).

Anal. Calcd: C, 40.19; H, 7.23; N, 6.70. Found: C, 40.15; H, 7.48; N, 6.77.

Downloaded At: 10:15 23 January 2011

***N*-(1-Deoxy-D-glucitolyl)-*N*-methylformamide (4).** A solution containing 2.50 g (12.8 mmol) of *N*-methyl-1-amino-1-deoxy-D-glucitol in 35 mL (820 mmol) of 88% formic acid was heated to 50 °C in a water bath and 11.0 mL (117.0 mmol) of acetic anhydride was added dropwise while maintaining the temperature between 50 and 80 °C. The solution was removed from the bath and stirred for 1 h, then treated with 10 g of ice/water. After solvent removal, 20 mL of anion-exchange resin was added and the mixture was stirred for 30 min. The resin was removed, and 20 mL of cation exchange resin was added and stirred for 30 min. The mixture was filtered and the solvent was removed. The syrup was dissolved in 35 mL of methanol and 0.200 g (0.0037 mol) of sodium methoxide was added. After stirring for 30 min, 50 mL of cation exchange resin was added and stirred for 15 min. The mixture was filtered and the solvent was removed. The solid was crystallized from ethanol to give 1.305 g (45.7%) of *N*-(1-deoxy-D-glucitolyl)-*N*-methylformamide as a white powder: mp 120-123 °C; ^{1}H NMR δ (D_2O) 2.91 (s, N-Me), 3.09 (s, N-Me), 3.4-4.2 (m, H-C-O), 8.00 (s, HC=O), 8.06 (s, HC=O); IR 1664.

Anal. Calcd: C, 43.06 H, 7.88; N, 6.28. Found: C, 43.29; H, 7.81; N, 6.26.

General method for the synthesis of the acetamide, propanamide, and butanamide derivatives. A solution containing 38.4 mmol of the amine in 75 mL of methanol was chilled in an ice-water bath and 82.8 mmol of the appropriate anhydride was added dropwise and stirred for 2 h while maintaining the temperature below 5 °C. After the reaction mixture was warmed to room temperature, 100 mL of anion exchange resin was added. The mixture was stirred for 30 min, then filtered. The solvent was removed, the resulting syrup was dissolved in 100 mL of methanol and 0.600 g (11.1 mmol) of sodium methoxide were added. After stirring for 30 min, 100 mL of cation-exchange resin was added and stirred for 30 min. The mixture was filtered and the solvent was removed.

***N*-(1-Deoxy-D-glucitolyl)acetamide (5).** The product was recrystallized from methanol in 69.3% yield; mp 128.5-129.5 °C; ^{1}H NMR (D_2O) δ 2.01 (s, Me-C=O), 3.2-3.9 (m, H-C-O); IR 1636.

Anal. Calcd: C, 43.05;, H, 7.68; N, 6.27. Found: C, 43.22; H, 7.83; N, 6.21.

***N*-(1-Deoxy-D-glucitolyl)-*N*-methylacetamide (6).** The compound was produced in 64.4% yield, recrystallized twice from ethanol then dried at

Downloaded At: 10:15 23 January 2011

100 °C: mp 119-121 °C; ^{1}H NMR (D_2O) δ 2.14 (s, MeC=O), 2.16 (s, MeC=O), 2.95 (s, N-Me), 3.13 (s, N-Me)3.4-4.2 (m, H-C-O); IR 1629.

Anal. Calcd: C, 45.56; H, 8.07; N, 5.90. Found: C, 45.88; H, 8.25; N, 5.86.

***N*-(1-Deoxy-D-glucitolyl)propanamide (7).** The compound was prepared in 58.0% yield, decolorized with activated carbon, then recrystallized twice from methanol/diethyl ether and dried 100 °C: mp 124-125 °C; ^{1}H NMR (D_2O) δ 1.11 (t, J=6 Hz, Me), 2.28 (q, J=6 Hz, CH_2), 3.2-3.9 (m, H-C-O); IR 1629.

Anal. Calcd: C, 45.56; H, 8.07; N, 5.90. Found: C, 45.48; H, 8.06; N, 5.91.

***N*-(1-Deoxy-D-glucitolyl)-*N*-methylpropanamide (8).** The compound was recrystallized twice from ethanol/diethyl ether in 51.0% yield then dried at 78 °C: mp 94-95 °C; ^{1}H NMR (D_2O) δ 1.09 (t, J=6 Hz, Me), 2.47 (m, CH_2), 2.96 (s, N-Me), 3.13 (s, N-Me), 3.3-4.2 (m, H-C-O); IR 1624.

Anal. Calcd: C, 47.80: H, 8.42; N, 5.57. Found: C, 47.91; H, 8.67; N, 5.47.

***N*-(1-Deoxy-D-glucitolyl)butanamide (9).** The compound was recrystallized twice from methanol/diethyl ether in 61.6% yield and dried for 72 h at 100 °C: mp 128-130 °C; ^{1}H NMR (D_2O) δ 0.91 (t, J=6 Hz, Me), 1.61 (sextet, J=6 Hz, CH_2), 2.23 (t, J=6 Hz, CH_2), 3.2-3.9 (m, H-C-O); IR 1633.

Anal. Calcd: C, 47.80; H, 8.42; N, 5.57. Found: C, 47.70; H, 8.64; N, 5.64.

***N*-(1-Deoxy-D-glucitolyl)-*N*-methylbutanamide (10).** The compound was recrystallized twice from methanol/diethyl ether to give 6.00 g (58.9%) as a white solid, then dried for 72 h at 78 °C: mp 96-98 °C; ^{1}H NMR (D_2O) δ 0.92 (t, J=6 Hz, Me), 0.94 (t, J=6 Hz, Me), 1.62 (sextet, J=6 Hz, CH_2), 2.44 (m, CH_2), 2.96 (s, N-Me), 3.15 (s, N-Me), 3.4-4.2 (m, H-C-O); IR 1625.

Anal. Calcd: C, 49.80; H, 8.74; N, 5.28. Found: C, 49.48; H, 8.95; N, 5.17.

***N*-(1-Deoxy-D-glucitolyl)benzamide (11).** A solution containing 1.00 g (5.52 mmol) of 1-amino-1-deoxy-D-glucitol and 0.78 mL (5.52 mmol) of triethylamine in 10.0 mL of methanol was cooled in an ice/water bath and 0.64 mL (5.56 mmol) of benzoyl chloride was added. The solution was stirred for 2 h while maintaining the temperature below 5 °C. After warming to room temperature, 40 mL of anion-exchange resin was added and

Downloaded At: 10:15 23 January 2011

the mixture was stirred for 15 min. The resin was removed and 40 mL of cation-exchange resin was added and stirred for 15 min. The mixture was filtered, and the solvent was removed. The solid was recrystallized twice from ethanol/water to give 0.317 g (20.1%) of product as a white solid, then dried for 72 h at 100 °C: mp 184-185 °C; ^{1}H NMR (DMSO-d_6) δ 3.31-3.67 (m, H-C-O), 3.79 (m, H-C-O), 4.37 (d, J=5 Hz, OH), 4.38 (d, J=7 Hz, OH), 4.46 (d, J=5 Hz, OH), 4.52 (d, J=5 Hz, OH), 4.92 (d, J=5 Hz, OH), 7.48 (m, Ar-H), 7.85 (m, Ar-H), 8.36 (m, N-H); IR 1631.

Anal. Calcd: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.76; H, 6.68; N, 4.91.

***N*-(1-Deoxy-D-glucitolyl)-*N*-methylbenzamide (12).** A solution containing 0.250 g (1.28 mmol) of 1-amino-1-deoxy-*N*-methyl-D-glucitol and 0.19 mL (1.38 mmol) of triethylamine in 2.5 mL of methanol was cooled in an ice-water bath and 0.16 mL (1.39 mmol) of benzoyl chloride was added and stirred for 2 h while maintaining the temperature below 5 °C. After warming to room temperature, 10 mL of anion-exchange resin was added and the mixture stirred for 15 min. The resin was removed and 10 mL of cation-exchange resin was added and then stirred for 15 min. The mixture was filtered and the solvent removed. The solid was crystallized from ethanol to give 0.279 g (72.8%) of *N*-(1-deoxy-D-glucitolyl)-*N*-methylbenzamide as a white solid: mp 140-142 °C; ^{1}H NMR (D_2O) δ 3.05 (s, N-Me), 3.14 (s, N-Me), 3.40-3.87 (m, H-C-O), 3.98 (m, H-C-O), 4.20 (m, H-C-O), 7.48 (m, Ar-H); IR 1608.

Anal. Calcd: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.20; H, 7.12; N, 4.73.

***N*-(1-Deoxy-D-glucitolyl)-2-chlorobenzamide (13).** A solution containing 0.500 g (2.76 mmol) of 1-amino-1-deoxy-D-glucitol and 0.39 mL (2.76 mmol) of triethylamine in 5.0 mL of methanol was cooled in an ice-water bath and 0.486 g (2.78 mmol) of 2-chlorobenzoyl chloride was added dropwise and stirred for 2 h while maintaining the temperature below 5 °C. After removal from the bath, 40 mL of anion-exchange resin was added and stirred for 15 min. The mixture was filtered and 20 mL of cation exchange resin was added and stirred for 15 min. The mixture was filtered and the solvent was removed. The solid was recrystallized twice from methanol to give 0.261 g (29.6%) of *N*-(1-deoxy-D-glucitolyl)-2-chlorobenzamide as white crystals. It was then dried for 96 h at 100 °C: mp 162-163 °C; ^{1}H NMR (DMSO-d_6) δ 3.23-3.76 (m, H-C-O), 4.36 (m, OH), 4.42 (d, J=5 Hz, OH),

Downloaded At: 10:15 23 January 2011

4.52 (d, J=4 Hz, OH), 4.84 (d, J=4 Hz, OH), 7.43 (m, Ar-H), 8.29 (m, N-H); IR 1632; TLC, solvent A, R_f 0.69.

Anal. Calcd: C, 48.83; H, 5.67; N, 4.38. Found: C, 48.81; H, 5.79; N, 4.32.

***N*-(1-Deoxy-D-glucitolyl)-*N*-methyl-2-chlorobenzamide (14).** A solution containing 1.00 g (5.12 mmol) of 1-amino-1-deoxy-*N*-methyl-D-glucitol and 0.77 mL (5.52 mmol) of triethylamine in 10 mL of methanol was cooled in an ice/water bath, 0.972 g (5.56 mmol) of 2-chlorobenzoyl chloride was added dropwise and then stirred for 2 h below 5 °C. The solution was removed from the bath and stirred for 15 min with 40 mL of anion-exchange resin, filtered and stirred for 15 min with 40 mL of cation-exchange resin. The mixture was filtered, the solvent removed. The product was dissolved in methanol three times followed by solvent removal. The solid was recrystallized twice from ethanol to give 1.039 g (63.5%) of white crystals, then dried at 100 °C: mp 111-112 °C; ^{1}H NMR (D_2O) δ 2.97 (s, N-Me), 3.19 (s, N-Me), 3.32-3.90 (m, H-C-O), 4.04 (m, H-C-O), 4.21 (m, H-C-O), 7.36-7.57 (m, Ar-H); IR 1623; TLC, solvent A, R_f 0.56, solvent B, R_f 0.75.

Anal. Calcd: C, 50.38; H, 6.04; N, 4.20. Found: C, 50.22; H, 6.12; N, 4.17.

***N*-(1-Deoxy-D-glucitolyl)-2-hydroxybenzamide (15).** A mixture of 1.411 g (7.80 mmol) of 1-amino-1-deoxy-D-glucitol, 65 mL methanol, 1.112 g (7.32 mmol) of methyl salicylate and 0.842 g (15.6 mmol) of sodium methoxide was heated to reflux under a drying tube. TLC monitoring indicated that, after 72 h of refluxing, there was little additional change. The solvent was removed from the cooled reaction mixture and the residue dissolved in water, and treated with cation-exchanger as before to remove unreacted amine and sodium ion. Removal of the resin and solvent gave 1.700 g of crude product which upon recrystallization from methanol gave two crops of white product with a combined weight of 1.380 g (62.7%). A second recrystallization from methanol gave 0.840 g of analytical sample which was dried at 100 °C: mp 178.5-180.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.2-3.7 (m, H-C-O), 3.8 (m, H-C-O), 4.5 (m, H-C-O), 4.95 (m, H-C-O), 6.9 (m, Ar-H), 7.4 (m, Ar-H), 7.9 (m, Ar-H), 8.78 (m, N-H), 12.5 (s, Ar-OH); IR 1641; TLC in 5:2 methanol:chloroform, R_f 0.46.

Anal. Calcd: C, 51.82; H, 6.36; N, 4.65. Found: C, 52.00; H, 6.51; N, 4.58.

Downloaded At: 10:15 23 January 2011

***N*-(1-Deoxy-D-glucitolyl)-*N*-methyl-3-oxobutanamide (16).** A stirred suspension of 0.975 g (5.00 mmol) of 1-amino-1-deoxy-*N*-methyl-D-glucitol in 20 mL of dry dimethylformamide (DMF) (stored over 4A molecular sieves) was cooled in an ice/salt bath to -5 °C, 0.35 mL (0.378 g, 4.5 mmol) of diketene was added and treated with two drops of a solution of 10 mg of 4-dimethylaminopyridine (DMAP) in 2 mL of DMF. After standing for 30 min at -4 °C, the ice bath was removed and the mixture was allowed to warm to room temperature overnight. An equal volume of water was added, excess amine removed with cation-exchanger, and the solvent removed. To remove DMF, water was added and the solution concentrated repeatedly to give a viscous yellow oil which gave a positive $FeCl_3$/methanol test for enols. Treatment with decolorizing carbon, removal of the solvent, and standing for several months gave a solid. Most solvents gave a gel upon recrystallization, except acetone which provided, after a second recrystallization, the analytical sample which was dried at 65 °C: mp 77-78 °C; TLC, 10:1, chloroform:methanol, R_f 0.63; ^1H NMR (D_2O) δ 2.29 (s, MeC=O), 2.31 (s, MeC=O), 3.00 (s, N-Me), 3.08 (s, N-Me), 3.5-3.8 (m, H-C-O), 4.1 (m, H-C-O); IR 1624.

Anal. Calcd: C, 47.31; H, 7.58; N, 5.02. Found: C, 47.24; H, 7.93; N, 4.93.

***N*-(1-Deoxy-D-glucitolyl)-*N*-methyl-3-(4-methoxyphenyl)-2-propenamide (17).** A mixture of 0.48 mL of dry triethylamine (3.44 mmol), 0.739 g (3.78 mmol) of oven-dried 1-amino-1-deoxy-*N*-methyl-D-glucitol, and 8.0 mL of dry DMF was cooled to -5 to -10 °C in an oven-dried flask under a nitrogen atmosphere. A solution of 0.674 g (3.44 mmol) of 4-methoxycinnamoyl chloride in 8.0 mL of dry DMF was added dropwise over a period of 20 min. The reaction was allowed to warm to room temperature and the white amine hydrochloride was filtered off. The filtrate was diluted with 20 mL of water and treated with 25 mL of anion-exchange resin followed by 25 mL of cation-exchange resin, each followed by 100 mL water washings of the resin. The DMF was removed by repeated dilutions with water and then evaporative removal to give a white solid. Two recrystallizations from ethanol gave the analytical sample, which was dried at 100 °C; mp 120-121 °C; ^1H NMR (DMSO-d_6 + trace D_2O) δ 3.02 (s, N-Me), 3.26 (s, N-Me), 3.4-3.7 (m, H-C-O), 3.84 (s, O-Me), 7.05 (m, Ar-H), 7.12 (d, J=16 Hz, C=C-H), 7.46 (d, J=16 Hz, C=C-H), 7.50 (d, J=16 Hz, Ar-H), 7.65 (d, J=8 Hz, Ar-H), 7.71 (d, J=8 Hz, Ar-H); IR 1643.

Downloaded At: 10:15 23 January 2011

Anal. Calcd: C, 57.45; H, 7.09; N, 3.94. Found: C, 57.70; H, 7.38; N, 3.80.

***N*-(1-Deoxy-D-glucitolyl)-*N*-methyl-3-(4-methoxyphenyl)propanamide (18).** A suspension of 25 mg of 10% Pd/C in a solution of 0.221 g (0.652 mmol) of **15** in 15 mL of abs. ethanol was subjected to one atmosphere of hydrogen with stirring. After absorbing 21 mL of hydrogen, the reaction was stopped, the Pd/C removed by filtration through a Millipore filter and the solvent removed. Recrystallization from abs ethanol gave the analytical sample which was dried at 65 °C; mp 128-129 °C; ^{1}H NMR (DMSO-d_6) δ 2.50-2.76 (m, -CH_2-CH_2-), 2.82 (s, N-Me), 2.97 (s, N-Me), 3.25-3.61 (m, H-C-O), 3.71 (s, OCH_3), 4.26-4.39 (m, OH), 3.47 (t, J=5 Hz OH), 4.70 (d, J=5 Hz, OH), 4.87 (d, J=5 Hz, OH), 6.82 (m, Ar-H), 7.14 (m, Ar-H); IR 1628.

Anal. Calcd: C, 57.13; H, 7.61; N, 3.92. Found: C, 57.49; H, 7.94; N, 3.78.

Methyl 3-(3-hydroxy-4-methoxyphenyl)propanoate (20). A solution of 1.99 g (10.2 mmol) of 3-hydroxy-4-methoxyhydrocinnamic acid, mp 149-150 °C, (reported[15] 146 °C), and 0.5 mL of conc sulfuric acid in 25 mL of methanol was refluxed for 15 h. Most of the methanol was distilled off and approximately 10 mL of water was added, followed by solid ammonium carbonate until a color change was observed. Cooling produced the product which was recrystallized from methanol to give 1.655 g (79%); mp 96.0-96.2 °C (reported[16] 94 °C); ^{1}H NMR ($CDCl_3$) δ 2.58 (t, J=8 Hz, CH_2), 2.85 (t, J=8 Hz, CH_2), 3.66 (s, O-Me), 3.84 (s, O-Me), 5.69 (s, OH), 6.67(m, Ar-H), 6.75(m, Ar-H); IR 1732.

***N*-(1-Deoxy-D-glucitolyl)-3-(3-hydroxy-4-methoxyphenyl)propanamide (19).** A solution of 1.31 g (6.24 mmol) of **20**, 1.417 g (7.83 mmol) of 1-amino-1-deoxy-D-glucitol and 0.674 g (12.5 mmol) of sodium methoxide in 20.0 mL of methanol was refluxed 40 h after which time TLC showed no additional change. The methanol was removed; 20 mL of water and 10 mL of cation-exchanger was added. After stirring for 20 min, the mixture was filtered and the solvent removed. The crude product was dissolved in methanol, treated with decolorizing carbon, filtered and allowed to crystallize. Two crops totaled 1.645 g (73.6%). Two recrystallizations from abs ethanol and drying at 100 °C gave the analytical sample; mp 161.5-162.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.31 (t, J=8 Hz, CH_2), 2.65 (t, J=8 Hz, CH_2), 3.01-3.57 (m, H-C-O), 3.71 (s, O-Me), 4.28 (d, J=6 Hz, OH), 4.39 (m, OH),

Downloaded At: 10:15 23 January 2011

4.46 (d, J=6 Hz, OH), 4.76 (d, J=4 Hz, OH), 6.57 (m, Ar-H), 6.78 (d, J=8 Hz, Ar-H) 7.78 (t, J=5 Hz, N-H), 8.81 (s, Ar-OH); IR 1629.

Anal. Calcd: C, 53.48; H, 7.01; N, 3.90. Found: C, 53.66; H, 7.01; N, 3.95.

ACKNOWLEDGEMENTS

One of us (JWE) is indebted to Eastern Illinois University for support of the one semester sabbatical leave and to the Council on Faculty Research of Eastern Illinois University for support for part of this work. We also thank Dr. Ellen A. Keiter for performing the temperature dependent NMR experiment.

Downloaded At: 10:15 23 January 2011

REFERENCES AND NOTES

1. Much of this work was done at Eastern Illinois University while this author was on sabbatical leave during the fall semester of 1989.

2. For example see, R. L. Whistler, H. P. Panzer, and H. J. Roberts, *J. Org. Chem.*, **26**, 1583 (1961).

3. For example see, J. E. K. Hildreth, *Biochem. J.*, **207**, 363 (1982).

4. R. S. Shallenberger and T. E. Acree, *Nature*, **216**, 480 (1967).

5. L. B. Kier, *J. Pharm. Sci.*, **61**, 1394 (1972).

6. J.-M. Tinti and C. Nofre in *Sweeteners, Discovery, Molecular Design, and Chemoreception*; D. E. Walters, F. T. Orthoefer and G. DuBois, Eds.; ACS Symposium Series 450; American Chemical Society: Washington, DC, 1991; Chapter 15; p 206.

7. W. H. Owens, M. S. Kellogg, C. A. Klade, D. L. Madigan, R. H. Muzur and G. W. Muller in *Sweeteners, Discovery, Molecular Design, and Chemoreception*; D. E. Walters, F. T. Orthoefer and G. DuBois, Eds.; ACS Symposium Series 450; American Chemical Society: Washington, DC, 1991; Chapter 8.

8. J. R. Daniel in *Frontiers in Carbohydrate Research-1: Food Applications*; R. P. Millane, J. N. BeMiller and R. Chandrasekaran, Eds.; Elsevier: London, 1989; p.34.

9. D. E. Kiely, T-H. Lin and L. Chen, *Abstracts of Papers*, 201st National Meeting of the American Chemical Society, Atlanta, GA, April, 1991; paper CARB 15.

10. L. F. Fieser, *J. Chem. Ed.*, **40**, 457 (1963).

11. C. R. Noller, *Chemistry of Carbon Compounds*, 3rd ed.; Saunders: Philadelphia, 1965, p 976.

12. M. L. Whitelaw, H-J. Chung and J. R. Daniel, *J. Agric. Food Chem.*, **39**, 663 (1991).

13. R. W. Wingard Jr., G. A. Crosby and G. DuBois, *CHEMTECH*, **8**, 616, (1978).

14. J. A. Morris and R. H. Cagan, *Biochim. Biophys. Acta*, **261**, 114 (1972).

15. M. B. Moore, H. B. Wright, M. Vernsten, M. Freifelder and R. K. Richards, *J. Am. Chem. Soc.*, **76**, 3656 (1954).

16. R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 3163 (1931).

Downloaded At: 10:15 23 January 2011