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Preliminary communication

Design and synthesis of potential megacaloric parenteral nutrients

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Providing the necessary complement of parenteral nutritive needs for patients requiring extended intravenous feeding is a critical problem in hospitals today[1]. In a number of post-operative cases and in many other instances where prolonged abstinence from solid food must be observed, alternative means for the intake of sufficient calories becomes the only life-sustaining device. Under normal conditions a daily infusion of three liters of a 5% glucose solution provides 170 Kcal/liter, while the desired daily regimen is 850 Kcal/liter. Fat and protein intake usually account for an additional supplement[2]. Clearly, the maintenance of such a regimen for an extended period is inadequate for the speedy restoration of the patient's health. Indeed, while medical intervention may have been successful, the subsequent insufficient nutritional intake may lead to a gradual decline in the patient's health and the onset of other life-threatening disease states. Several possibilities exist for increasing the intake of calories from carbohydrates, such as the use of higher concentrations, or the administration of polymeric preparations. However problems associated with peripheral damage in the first instance, and ineffective enzymatic hydrolysis in the second, impose serious limitations on these alternatives. Clearly, other avenues must be sought.

We wish to report on a conceptually novel approach which may provide a viable solution to this important clinical problem. We reasoned that a means for the delivery of *several* glucose units might consist in preparing glucosyl "cluster" compounds, anchored to or hinged on a central molecule *via* ester linkages. By virtue of the presence of a variety of esterases in the body, these compounds would undergo enzymatic hydrolysis to release glucose and a dicarboxylic acid, thus providing both carbohydrate and a metabolic intermediate of high caloric value. We describe here two types of cluster compounds (**1** and **2**), based on pentaerythritol and D-glucose, respectively.

Thus, treatment of benzyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **3** (ref. 3) with succinic anhydride (1.1 equiv.) and 4-dimethylaminopyridine (0.1 mmol) in dichloromethane for 5 h at 25° gave the corresponding 6-succinate **4** as a syrup in over 90% yield*. Esterification of pentaerythritol with **4** (4.1 equiv.) in the presence of dicyclo-

*New compounds were characterized by their n.m.r. and i.r. spectra, and high resolution mass spectra. All gave satisfactory microanalytical data.

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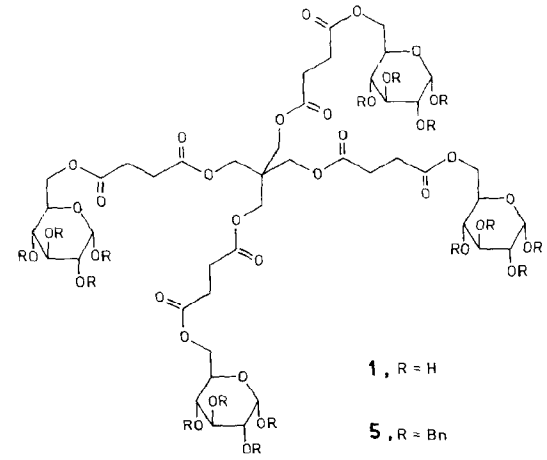
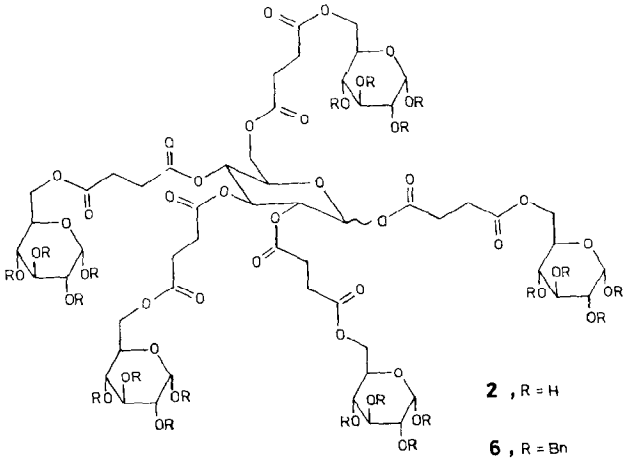


1, R = H

5, R = Bn

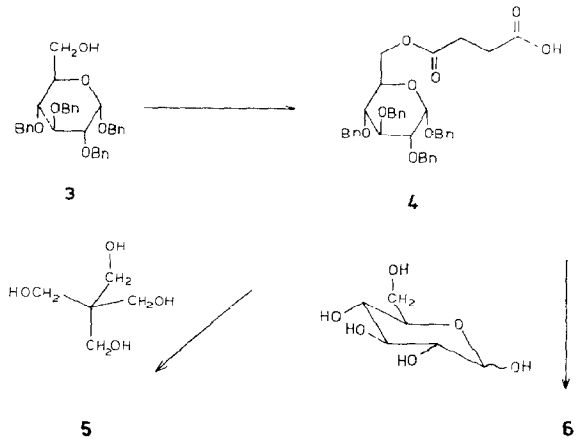


2, R = H

6, R = Bn

hexylcarbodiimide and 4-pyrrolidinopyridine as catalyst[4] in dichloromethane (18 h) gave, after flash chromatography[5] (EtOAc–hexane, 1:2 v/v), the corresponding tetrakis-*O*-(3-carboxypropionyl)pentaerythritol tetrakis(benzyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosid-6-yl) tetraester **5** as a colorless syrup in 70% yield. Removal of the benzyl groups was achieved by hydrogenolysis over 20% palladium hydroxide on charcoal[6] in 1:1 oxolane–ethanol for 48 h then in water for 18 h to give **1** as a colorless fluffy solid (freeze-dried) in 60% yield; $[\alpha]_D$ +40° (*c* 0.5, H_2O); ^{1}H-n.m.r. (90 MHz, D_2O): δ 5.17 (d, $J_{1,2}$ 3 Hz, H-1α) and 4.58 (d, $J_{1,2}$ 8 Hz, H-1β); R_f 0.4 (silica gel, 8:4:3 *n*-BuOH–pyridine–H_2O) (compare D-glucose, R_f 0.5).

The pentasubstituted D-glucopyranose ester **6** was prepared by essentially the same method from **4** and D-glucose, and obtained as a colorless foam (65%). Hydrogenolysis as described above gave **2** (68%) as a fluffy colorless powder, $[\alpha]_D$ +71° (*c* 0.49, H_2O); ^{1}H-n.m.r. (90 MHz, D_2O): δ 6.30 (d, $J_{1,2}$ 3 Hz, H-1α of central D-glucose unit),



5.18 (d, $J_{1,2}$ 3 Hz, H-1α), and 4.60 (d, $J_{1,2}$ 8 Hz, H-1β); R_f 0.25–0.3 (8:4:3 *n*-BuOH–pyridine–H_2O).

The chemical constitution of these cluster compounds was further substantiated by degradative studies. Thus methanolysis of **5** (NaOMe, MeOH) followed by acetylation gave benzyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside and pentaerythritol tetraacetate in a 4:1 molar ratio (by n.m.r. and isolation). Compounds **1** and **2** were easily soluble in water giving clear solutions that could be stored at 0° for prolonged periods without appreciable change. There was no formation of free D-glucose.

Thus, we have demonstrated the feasibility of combining two important nutritive ingredients in a unique molecular form which may prove advantageous in providing added calories. Results pertaining to the biological tests will be reported in due course.

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