Synthesis of Furan Derivatives Condensed with Carbohydrates

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Abstract: Eight new furan derivatives have been prepared and characterized. These compounds were obtained by condensation of aminosugar and aminocyclitol intermediates with furan derivatives.

Keywords: nitrofurans, aminosugar, aminocyclitol

Introduction

Synthetic antibacterial compounds which do not derive from sulfonamide are numerous and chemically varied. An important group is formed by the 5-nitrofurfural derivatives (eg.- nitrofurazone, furazolidone, nitrofurantoin, Figure 1), generically known as nitrofurans [1].

Figure 1: Antibacterial nitrofurans
The antimicrobial activity of nitroaromatic compounds is related to an enzymatic reduction of the nitro group in vivo, yielding toxic species: nitro compounds can be reductively metabolized to form highly potent cytotoxins and can act as radiosensitizers of hypoxic cells [2-5]. Despite its rare occurrence in natural products, the nitro group is present in various synthetic substances used as antibacterials, trypanocides, fungicides, vasodilators, tranquilizers, antivirals and others. The nitro group is also present in compounds with antiparasitic activity [6].

The therapeutic use of nitrofurans is severely limited by their toxic effects: nausea, vomiting, pulmonary and allergic reactions, mutagenicity and carcinogenicity [7-9]. The use of nitrofuran drugs as a prophylactic feed additive in animal husbandry is no longer allowed by the FDA since 1992, these drugs being unsafe for oral or parenteral use: residues of both the parent compound and its toxic metabolites in edible tissues of treated animals represent a health hazard for the consumer [10].

These side effects are mainly due to the weak hydrosolubility of these compounds. Thus, the introduction of hydrophilic groups in the furan ring could compensate the negative effect of the nitro group on water solubility. With this aim, we synthesized intermediates from carbohydrates and cyclitol which were afterwards condensed with furan derivatives. D-Glucosamine, D-galactose, D-fructose and D-quinic acid were chosen as starting materials.

Results and Discussion

During this work, we synthesized eight final compounds by condensing furfural, furoic acid and 5-nitro furoic acid with three different aminosugars obtained by described methods [11-12], and with an aminocyclitol derived from D-quinic acid [13]. The amide 6 was obtained in quantitative yield by treating 2-D-glucosamine 1 with furoyl chloride 4 in dichloromethane, in the presence of pyridine. Compound 7 was synthesized in 92 % yield using the same reaction conditions as for 6, but with 5-nitrofuroyl chloride 5 (Scheme 1). The imine 8 was prepared in 32% yield by condensing 1 with furfural in anhydrous methanol in the presence of sodium bicarbonate (Scheme 1).
Using a similar method, amines 2 and 3 were treated with furoyl chloride 4 or 5-nitrofuroyl chloride 5, in dichloromethane in the presence of pyridine, leading to compounds 9 (yield 87%), 10 (yield 93%), 11 and 12, respectively (both in quantitative yields) (Scheme 2).

To prepare D-quinic acid derivatives, compound 13 [13, 14] was converted to the corresponding monotosylate 14 in 60% yield by treatment with p-toluenesulfonyl chloride in pyridine (Scheme 3).
Following this procedure the ditosylated compound 18 was also isolated in 15% yield. Treatment of 14 with sodium azide in DMF gave compound 15 in 95% yield. The latter was hydrogenated in ethanol in the presence of Pd/C 10% to furnish the amine 16 in 88% yield. Condensation of 16 with 5-nitrofuroyl chloride, as described above, afforded the target compound 17 in 60% yield. Deprotection reactions and biological evaluation of the final compounds are under investigation.

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Experimental

General

Melting points were determined on a MQAPF-301 apparatus and are uncorrected. Infrared spectra were obtained on a Bomem FT IR MB-102 spectrometer in KBr pellets. $^1$H-NMR (400 MHz) and $^{13}$C-NMR (100 MHz) spectra were recorded on Bruker Avance DRX 400 spectrometer at the Federal University of Minas Gerais. The $[\alpha]_D$ were recorded on Perkin-Elmer 241-MC sodium absorption at 20 °C. Column chromatography was performed using silica gel 60 G (0.063-0.200 mm. E. Merck). Elemental analyses were done at the Laboratory of Elemental Analyses of ICSN-CNRS, Gif sur Yvette, France. All chemicals were reagent grade and were used without further purification.

General method for preparation of acid chlorides.

Furoyl chloride 4 and 5-nitrofuroyl chloride 5 were prepared by reacting the corresponding acids with thionyl chloride in dichloromethane. The mixture was heated at reflux for 12 h and the solvent was removed under reduced pressure. The residue was used without further purification.

General method for condensation reactions: preparation of compounds 6, 7 and 9-12.

To a stirred solution of the amine (1 mmol) in anhydrous dichloromethane (10 mL) at 0 °C, were slowly added the acid chloride (1.5 mmol) and pyridine (3 mmol). The resulting mixture was stirred at 0 °C for 4 h and partitioned between water and dichloromethane. The organic phase was evaporated under vacuum to dryness and the residue was purified by column chromatography on silica gel, eluting with AcOEt/hexane.

$2$-Deoxy-$2$-(2-furamido)-$1,3,4,6$-tetra-$O$-acetyl-$\beta$-$D$-glucopyranoside (6): m p 208-210 °C; $[\alpha]_D$ +55(c 1, CH$_2$Cl$_2$); IR (KBr) 1650 (NHC=O); 1750 (OC=O) cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$ 1.99; 2.05; 2.08; 2.11; (4s, 12H, CH$_3$); 3.87 (ddd, 1H, H$_5$, J$_{5-4}$=9.6 Hz; J$_{5-6}$=4.6 Hz; J$_{5-6'}$=2.2 Hz); 4.15 (dd, 1H, H$_6'$, J$_{6'-6}$=4.6 Hz; J$_{5-6'}$=2.2 Hz); 4.15 (dd, 1H, H$_6'$, J$_{6'-6}$=4.6 Hz; J$_{5-6'}$=2.2 Hz); 4.15 (dd, 1H, H$_6'$, J$_{6'-6}$=4.6 Hz; J$_{5-6'}$=2.2 Hz).
2-Deoxy-2-(5-nitro-2-furamido)-1,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (7): m p 109-111 °C; [α]D +48 (c 0.7, DMSO); IR (KBr) 1660 (NHC=O); 1740 (OC=O) cm-1; 1H-NMR (CDCl3) δ 2.03; 2.09; 2.10 (3s, 12H, CH3); 3.98 (ddd, 1H, H5, J5-4=9.6 Hz; J5-6=4.9 Hz; J5-6'=2.3 Hz); 4.17 (dd, 1H, H6', J6'-6=12.5 Hz); 4.32 (dd, 1H, H6); 4.51 (q, 1H, H2); 5.20 (t, 1H, H4, J4-3 = J4-5=9.6 Hz); 5.50 (dd, 1H, H3, J3-2=10.4 Hz); 5.89 (d, 1H, H1, J1-2=8.7 Hz); 7.27 (d, 1H, H3a, J3a-4a=3.9 Hz); 7.30 (d, 1H, H4a); 7.41 (d, 1H, NH, J NH-2=9.6 Hz); 13C-NMR (CDCl3) δ 20.49, 20.59, 20.67, 20.86 (CH3); 52.58 (C2); 61.79 (C6); 68.11; 72.47; 72.81 (C3, C4, C5); 91.97 (C1); 112.31; 116.70 (C3a, C4a); 147.15; 151.19; 156.30 (NHC=O); 169.28; 169.36; 170.64; 171.46 (OC=O); Anal. Calcd. for C19H22N2O13: C, 46.92; H, 4.56; N, 5.76. found: C, 46.98; H, 4.79; N, 5.49.

6-Deoxy-6-(2-furamido)-1,2,3,4-di-O-isopropylidene-α-D-galactopyranoside (9): oil; [α]D -35 (c 1, CH2Cl2); IR (KBr) 1650 (C=O) cm-1; 1H-NMR (CDCl3) δ 1.27; 1.32; 1.48 (3s, 12H, CH3); 3.42 (ddd, 1H, H6, J6-6'=14 Hz; J6-5=4 Hz); 3.89 (ddd, 1H, H6', J6'-5=4 Hz); 4.00 (ddd, 1H, H5, J5-4=1.7 Hz); 4.02 (dd, 1H, H2, J2-1=5.0 Hz, J2-3=2.4 Hz); 4.62 (dd, 1H, H3); 5.54 (d, 1H, H1); 6.48 (dd, 1H, H4a, J4a-3a=3.5 Hz, J4a-5a=1.8 Hz); 6.80 (sl, 1H, NH); 7.10 (d, 1H, H3a); 7.43 (d, 1H, H5a); 13C-NMR (CDCl3) δ 24.33; 24.94; 25.93; 26.01 (CH3); 39.65 (C6); 66.27; 70.53; 70.82; 71.79 (C2, C3, C4, C5); 96.29 (C1); 108.81, 109.48 [C(CH3)2]; 111.95; 114.01 (C3a, C4a); 148.18 (C2a, C5a); 151.19 (C2a, C5a); 156.30 (NH=O); 169.28; 169.36; 170.64; 171.46 (OC=O); Anal. Calcd. for C17H23NO7: C, 57.78; H, 6.56; N, 3.96. found: C, 57.67; H, 6.86; N, 3.78.

6-Deoxy-6-(5-nitro-2-furamido)-1,2,3,4-di-O-isopropylidene-α-D-galactopyranoside (10): oil; IR (KBr) 1650 (C=O) cm-1; 1H-NMR (CDCl3) δ 1.32; 1.38; 1.49; 1.54 (4s, 12H, CH3); 3.46 (ddd, 1H, H6, J6-6'=13.8 Hz; J6-5=4.2 Hz); 3.97 (ddd, 1H, H6', J6'-5=4.2 Hz); 4.02 (ddd, 1H, H5, J5-4=1.7 Hz); 4.32 (dd, 1H, H4, J4-3=8.0 Hz); 4.33 (dd, 1H, H2, J2-1=5.0 Hz, J2-3=2.4 Hz); 4.64 (dd, 1H, H3); 5.54 (d, 1H, H1); 6.48 (dd, 1H, H4a, J4a-3a=3.5 Hz, J4a-5a=1.8 Hz); 6.80 (sl, 1H, NH); 7.10 (d, 1H, H3a); 7.43 (d, 1H, H5a); 13C-NMR (CDCl3) δ 24.33; 24.94; 25.93; 26.01 (CH3); 39.65 (C6); 66.27; 70.53; 70.82; 71.79 (C2, C3, C4, C5); 96.29 (C1); 108.81, 109.48 [C(CH3)2]; 111.95; 114.01 (C3a, C4a); 143.86 (C5a); 147.97 (C2a); 158.58 (C=O); Anal. Calcd. for C17H22N2O9: C, 51.26; H, 5.57; N, 7.03. found: C, 51.53; H, 5.87; N, 6.67.

1-Deoxy-1-(2-furamido)-2,3,4,5-di-O-isopropylidene-β-D-fructopyranoside (11): oil; [α]D -16 (c 1.3, CH2Cl2); IR (KBr) 1640 (C=O) cm-1; 1H-NMR (CDCl3) δ 1.33; 1.41; 1.43; 1.54 (4s, 12H, CH3); 3.72 (dd, 1H, H1, J1-NH=6.0 Hz; J1-1'=14 Hz); 3.76 (d, 1H, H6, J6-6'=13.2 Hz); 3.85 (dd, 1H, H1', J1'-NH=6.0 Hz); 4.30 (dd, 1H, H2, J2-1=6.0 Hz; J2-2=8.7 Hz); 4.67 (d, 1H, H3, J3-2=9.4 Hz); 5.30 (dd, 1H, H3, J3-2=10.4 Hz); 5.81 (d, 1H, H1, J1-2=8.7 Hz); 6.47 (d, 1H, NH, J NH-2=9.4 Hz); 6.49 (dd, 1H, H4a, J4a-3a=3.5 Hz, J4a-5a=1.2 Hz); 7.11 (dd, 1H, H3a); 7.43 (d, 1H, H5a); 13C-NMR (CDCl3) δ 20.56, 20.57, 20.72, 20.85 (CH3); 52.51 (C2); 61.68 (C6); 67.88; 72.43; 72.97 (C3, C4, C5); 92.63 (C1); 112.21; 115.16 (C3a, C4a); 144.56 (C5a); 146.93 (C2a); 158.10 (NH=O); 169.29; 169.49; 170.67; 171.03 (OC=O); Anal. Calcd. for C19H23NO11: C, 51.70; H, 5.25; N, 3.17. found: C, 52.06; H, 4.92; N, 3.12.
Molecules 2001, 6 733

1-Deoxy-1-(5-nitro-2-furamido)-2,3;4,5-di-O-isopropylidene-β-D-fructopyranoside (12): m p 159-162 °C; [α]D -27 (c 0.5, DMSO); IR (KBr) 1650 (C=O) cm⁻¹; ¹H-NMR (CDCl₃) δ 1.37; 1.42; 1.48; 1.55 (4s, 12H, CH₃); 3.72 (dd, 1H, H1, J1-NH=5.4 Hz; J1-1'=14 Hz); 3.77 (d, 1H, H6, J6-6'=13.1Hz); 3.86 (dd, 1H, H3, J3-4= 2.7 Hz); 4.60 (dd, 1H, H4); 7.16 (sl, 1H, NH); 7,28, 7.37 (2d, 2H, H3a, H4a, J 3a-4a=3.7 Hz; 13C-NMR (CDCl₃) δ 24.05, 24.86, 25.75, 26.13 (CH₃); 46.79 (C1); 61.73 (C6); 68.07; 72.64; 73.08; 73.19 (C2, C3, C4, C5); 51.26; H, 5.57; N, 7.03. found: C, 51.46; H, 5.45; N, 6.85.

2-Deoxy-2-(furfural)-imino-1,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (8). To a stirred solution of hydrochloride 1 (1 mmol) in anhydrous methanol (10 mL) at room temperature was added sodium bicarbonate (1.2 mmol) and distilled furfural (2 mmol). The mixture was heated at reflux for 12 h and the solvent was removed. The residue was redissolved in dichloromethane and filtered on celite. The solvent was removed in vacuo and the residue was crystallized from AcOEt/hexane, yielding 32% of 8. Attempts to purify compound 8 by chromatography led to decomposition of the product. m p 114-116 °C; IR (KBr) 1640 (C=N); 1740 (C=O) cm⁻¹; ¹H-NMR (CDCl₃) δ 1.92; 2.03; 2.04; 2.09 (4s, 12H, CH₃); 3.43 (dd, 1H, H2, J2-1=8.4 Hz; J2-3=9.6 Hz); 3.96 (dd, 1H, H5, J5-4=9.6 Hz; J5-6=4.5 Hz; J5-6'=2.2 Hz); 4.12 (dd, 1H, H6', J6'-6=12.5 Hz); 4.37 (dd, 1H, H6); 5.13 (t, 1H, H4, J4-3=9.6 Hz); 5.43 (t, 1H, H3); 5.94 (d, 1H, H1); 6.50 (dd, 1H, H4a, J4a-3a=3.5 Hz; J4a-5a=1.8 Hz); 6.84 (d, 1H, H3a); 7.54 (d, 1H, H5a); 8.04 (s, 1H, HC=N); ¹³C-NMR (CDCl₃) δ 20.48; 20.58; 20.63; 20.77 (CH₃); 61.73 (C6); 68.07; 72.64; 73.08; 73.19 (C2, C3, C4, C5); 93.08 (C1); 111.86, 115.89 (C3a, C4a); 145.67 (C5a); 150.70 (C2a); 153.2 (C=N); 168.50; 169.40; 169.90; 170.61 (C=O);

Preparation of compounds 14 and 18.

To a solution of compound 13 (2.58 g, 10 mmol) in pyridine (20 mL) at 0 °C was added, in small portions, p-toluenesulfonyl chloride (2.28 g, 12 mmol). The mixture was stirred for 24 h at room temperature and extracted with AcOEt. The organic phase was concentrated in vacuo and the residue was chromatographed on silica gel to give the desired compound 14 and the ditosylate 18 in 60% and 15% yield, respectively.
(1R,2S,3R,5R)-1,2-O-cyclohexylidene-5-C-[(O-tosyl)-hydroxymethyl]-cyclohexane-1,2,3,5-tetrol (14): m p 134-136 °C; [α]D -16 (c 0.5, DMSO); IR (KBr) 1350 (ROSO₂R) cm⁻¹; ¹H-NMR (CDCl₃) δ 1.60 (m, 11H, cyclohex., H6); 1.86 (ddd, 1H, H6', J₆₆'=13.5 Hz); 1.90 (dd, 1H, H4, J₄₄'=15.4 Hz); 2.11 (d, 1H, OH); 2.20 (dt, 1H, H4'); 2.45 (s, 3H, CH₃); 3.24 (s, 1H, OH); 3.82 (d, 1H, H7); 3.86 (d, 1H, H7', J₇₇'=9.7 Hz); 3.90 (t, 1H, H2, J₂₂'=J₃₃'=6.0 Hz); 4.09 (m, 1H, H1); 4.42 (m, 1H, H3); 7.35; 7.80 (2d, 4H, Ph); ¹³C-NMR (CDCl₃) δ 25.65 (CH₃); 23.61; 23.97; 24.87; 33.15; 34.81; 38.05; 38.16 (cyclohex., C4, C6); 69.21; 73.71; 79.79; (C1, C2, C3); 71.13 (C5); 75.36 (C7); 110.05 (OCO); 127.98; 129.92; 132.63; 145.02 (Ph). Anal. Calcd. for C₂₀H₂₈O₇S: C, 58.24; H, 6.84. found: C, 58.17; H, 6.82.

(1R,2S,3R,5R)-1,2-O-cyclohexylidene-3-O-tosyl-5-C-[(O-tosyl)-hydroxy-methyl]-cyclohexane-1,2,3,5-tetrol (18): m p 124-126 °C (lit [13] m p 123-125 °C); IR (KBr) 1350 (ROSO₂R) cm⁻¹; ¹H-NMR (CDCl₃) δ 1.50 (m, 10H, cyclohex.); 1.89 (dd, 1H, H4, J₄₄'=15.7 Hz); 1.99 (dt, 1H, H6, J₆₆'=13.6 Hz; J₆₆'=13.6 Hz); 2.07(dd, 1H, H6'); 2.20 (dt, 1H, H4'); 2.46; 2.48 (2s, 6H, CH₃); 3.20 (sl, 1H, OH); 3.77 (d, 1H, H7); 3.83 (d, 1H, H7', J₇₇'=9.7 Hz); 4.06 (t, 1H, H2, J₂₂'=J₃₃'=6.0 Hz); 4.44 (m, 1H, H1); 4.75 (ddd, 1H, H3); 7.34; 7.37; 7.80; 7.82 (4d, 8H, Ph); ¹³C-NMR (CDCl₃) δ 21.64; 21.73 (CH₃); 23.48; 23.83; 24.83; 32.82; 34.53; 36.62; 37.43 (cyclohex., C4, C6); 73.62; 76.00; 79.77 (C1, C2, C3); 70.86; 75.00 (C5, C7); 110.35 (OCO); 128.00; 128.15; 129.77; 130.01; 132.49; 133.60; 144.78; 145.20 (Ph).

(1R,2S,3R,5R)-1,2-O-cyclohexylidene-5-C-azidomethyl-cyclohexane-1,2,3,5-tetrol (15). Sodium azide (0.65 g, 10 mmol) was added to a solution of the tosylate 14 (2.06 g, 5 mmol) in DMF (20 mL). The mixture was stirred overnight at 140 °C and extracted with AcOEt. The organic phase was concentrated in vacuo and the residue was chromatographed on silica gel to afford the azide derivative 15 in 95% yield; m p 100-102 °C; IR (KBr) 2100 (N 3) cm⁻¹; ¹H-NMR (CDCl₃) δ 1.60 (m, 11H, cyclohex., H6); 1.80 (dd, 1H, H4, J₄₄'=15.5 Hz); 2.02 (dd, 1H, H6', J₆₆'=13.4 Hz); 2.30 (dt, 1H, H4'); 2.59 (d, 1H, OH); 3.13 (d,1H, H7, J₇₇'=12.3 Hz); 3.28 (d, 1H, H7); 3.37 (s, 1H, OH); 3.93 (t, 1H, H2, J₂₂'=J₃₃'=6.0 Hz); 4.11 (m, 1H, H1); 4.45 (ddd, 1H, H3); 7.34; 7.37; 7.80; 7.82 (4d, 8H, Ph); ¹³C-NMR (CDCl₃) δ 23.64; 21.73 (CH₃); 23.48; 23.83; 24.83; 32.82; 34.53; 36.62; 37.43 (cyclohex., C4, C6); 73.62; 76.00; 79.77 (C1, C2, C3); 70.86; 75.00 (C5, C7); 110.35 (OCO); 128.00; 128.15; 129.77; 130.01; 132.49; 133.60; 144.78; 145.20 (Ph).

(1R,2S,3R,5R)-1,2-O-cyclohexylidene-5-C-aminomethyl-cyclohexane-1,2,3,5-tetrol (16). The azide 15 (0.85 g, 3 mmol), dissolved in 10 mL of ethanol, was hydrogenated for 4 h in the presence of Pd/C 10% (0.1 g). The catalyst was removed by filtration and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel and the amine 16 was isolated in 88% yield; oil; IR (KBr) 3100-3500 (NH, OH) cm⁻¹; ¹H-NMR (C₅D₅N) δ 1.60 (m, 11H, cyclohex., H6); 1.88 (dd, 1H, H4, J₄₄'=13.6 Hz); 2.13 (dd, 1H, H6', J₆₆'=14.6 Hz); 2.40 (m, 1H, H4'); 2.88 (2d, 2H, H7, H7'; J₇₇'=12.8 Hz); 4.34 (t, 1H, H2, J₂₂'=J₃₃'=6.0 Hz); 4.60 (m, 2H, H1, H3); 4.83 (sl, 4H, NH₂, OH); ¹³C-NMR (C₅D₅N) δ 24.31; 24.58; 25.59; 35.82; 39.20 (cyclohex., C4, C6); 60.55 (C7); 69.50; 74.47; 80.80 (C1, C2, C3); 73.92 (C5); 110.04 (OCO).
(1R,2S,3R,5R)-1,2-O-cyclohexylidene-3-O-(5-nitro-2-furoyl)-5-C-[(5-nitro-2-furamide)methyl]cyclohexane-1,2,3,5-tetrol (17). To a stirred solution of 16 (0.257 g, 1 mmol) in anhydrous CH₂Cl₂ at 0 °C, were slowly added 5-nitrofuroyl chloride 5 (0.53 g, 3 mmol) and pyridine (0.5 mL). The resulting mixture was stirred at room temperature for 4 h and extracted with dichloromethane. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel, to give the desired compound 17 in 60% yield; m p 129-131°C; IR (KBr) 1650 (NHC=O), 1740 (OC=O) cm⁻¹; ¹H-NMR (CDCl₃) δ 1.60 (m, 12H, cyclohex., H₆, H₆'); 1.94 (dd, 1H, H₄, J₄-H₄'=15.4 Hz); 2.35 (dt, 1H, H₄'); 3.50 (dd, 1H, H₇, J₇-H₇'=13.6 Hz; J₇-NH=7.1 Hz); 3.65 (dd, 1H, H₇', J₇'-NH=5.7 Hz); 4.24 (t, 1H, H₂, J₂-1=J₂-3=5.5 Hz); 4.54 (m, 1H, H₁); 5.56 (m, 1H, H₃); 7.15-7.40 (m, 5H, NH, H furanic); ¹³C-NMR (CDCl₃) δ 23.58; 23.92; 24.83; 33.85; 34.77; 36.85; 37.83 (cyclohex., C₄, C₆); 48.89 (C₇); 72.12; 73.82; 73.91; 76.23 (C₁, C₂, C₃, C₅); 110.79 (OC=O); 111.56; 112.36; 116.26; 119.30 (C₃a, C₃b, C₄a, C₄b); 144.61; 147.71 (C₂a, C₂b); 151.40; 153.00 (C₅a, C₅b); 156.15; 156.80 (NHC=O, OC=O).

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Sample Availability: Samples of compounds 1, 2, 3, 6, 7, 8, 9 and 10 are available from MDPI.

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