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A New, Hydrolytically Stable, Sweet Tasting Aspartic Acid Derivative

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ABSTRACT

N-Aspartylethanolamines are a novel class of sweet tasting compounds which offer greater hydrolytic stability than L-*aspartyl-*L-*phenylalanine methyl ester (Aspartame) at neutral pH. Within the class, optimum relative potency (60 X) and sucrose-like taste character were observed for N-(α-*L-*aspartyl)-3S-amino-2S-hydroxy-6-methylheptane. Physical properties and a practical synthesis of this compound are described.*

INTRODUCTION

Since the accidental discovery of their sweet taste, α-amides of L-aspartic acid have been widely investigated as potential low calorie sweeteners for foods (for reviews see Beck, 1978; Pavlova *et al.*, 1981). The excellent sucrose-like sweetness of these amides is evidenced by the wide acceptance of L-aspartyl-L-phenylalanine methyl ester (1) as a new food additive (Homler, 1984).

In spite of its popularity, 1 is known to be accompanied by a lack of stability that can lead to loss of sweetness. In neutral or slightly alkaline solution 1 rapidly cyclizes to form the non-sweet diketopiperazine, 2. Decomposition also takes place under acidic conditions, e.g. pH 4 with probable formation of the non-sweet dipeptide, L-Asp-L-Phe(OH) (Homler, 1984).

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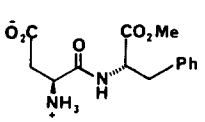
Although 1 is being successfully used to sweeten some foods, a definite need still clearly exists for alternative sweetening agents with wider tolerances to temperature and pH. Toward this end we have been synthesizing and evaluating molecules structurally similar to 1 but lacking the chemically labile ester function (Rizzi, 1985).



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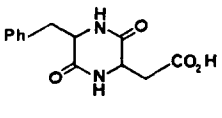

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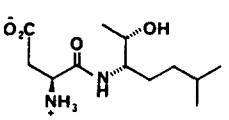

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One compound in particular, *N*-(α-L-aspartyl)-3*S*-amino-2*S*-hydroxy-6-methylheptane, 3, was found to be hydrolytically more stable than 1 while maintaining a potent, sucrose-like sweet taste. In this paper we summarize the pertinent physical and taste properties of 3 and present a practical method for its preparation.

RESULTS

Physical and taste properties of 3

Amide 3 is a water-soluble (2·5% at ambient pH at 22 °C), colorless crystalline solid (melting point, 197·5–200 °C) whose aqueous solution has excellent quality sucrose-like sweetness. A 0·13% solution is equivalent in sweetness to an 8% sucrose solution corresponding to a sweetness potency of 60×.

The hydrolytic stability of 3 is significantly greater than that of 1, especially at neutral pH (Rizzi, 1983). In buffer solutions at pH 6·9 (43 °C) the decomposition half life of 3 was 148 days compared with the 9 h reported for 1 under similar conditions (Homler, 1984). Stability of 3 was enhanced in more acidic solutions; for example, no detectable decomposition took place in 0·1% solution at pH 3·5 and 43 °C after 32 days. Higher temperatures (54 °C and 66 °C) led to more rapid hydrolysis of 3 at both pH 3·5 and 6·9. At these temperatures and at pH 6·9 the half lives for the decomposition of 3 were 64 and 22 days, respectively. An Arrhenius analysis of the kinetic data at pH 6·9 predicts the decomposition half life of 3 at 25 °C to be *ca.* 760 days.

Synthesis of 3

Only one of the four possible diastereoisomers of *N*-(α-L-aspartyl)-3-amino-2-hydroxy-6-methylheptane, e.g. 3, exhibits a useful degree of sweet taste (Rizzi, 1985). Initially, we obtained 3 via activated ester coupling of L-aspartic acid to the optically active amino alcohol, 4 derived from commercially available D-threonine according to Fig. 1 (Rizzi, 1983). For scale-up purposes we desired a simpler, less expensive, route to 3 that avoided using D-threonine.

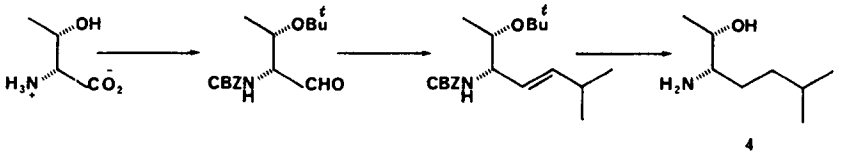

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Fig. 1. Synthesis of D-threonine-derived amino alcohol.

A more practical synthesis of 3 was developed as shown in Fig. 2. The synthesis was designed to yield the prerequisite *threo* amino alcohol in racemic form, 7b, which, in a later stage, would be coupled to L-aspartic acid to affect optical resolution and isolation (by fractional crystallization) of the desired diastereoisomer, 3. The present synthesis offers the advantages of: (a) a small number of high to moderate yield steps; (b) a maximum use of inexpensive starting materials and (c) simple procedures amenable to large-scale operation.

A literature search revealed numerous syntheses of dichiral ethanolamines like 4, and the simplest, most direct, route appeared to be the catalytic hydrogenation of α-ketooximes (Rylander, 1979). Most chiral ethanolamine syntheses (including α-ketooxime reductions) take place stereoselectively to form a preponderance of *erythro* isomers. In view of this known stereochemical preference we decided to optimize production of the *erythro* amide, 6a, and then to convert it to the desired *threo* isomer, 7b, by modification of a published rearrangement/hydrolytic process (for example, compare Johnson & Schubert, 1950; Weijlard *et al.*, 1951; Saino *et al.*, 1978).

The key intermediate, ketooxime, 5, was readily prepared from ethyl isopentylacetoacetate by modification of a pyruvaldehyde aldoxime synthesis (Beech, 1955).

Medium pressure catalytic hydrogenation of 5 in acetic acid/acetic

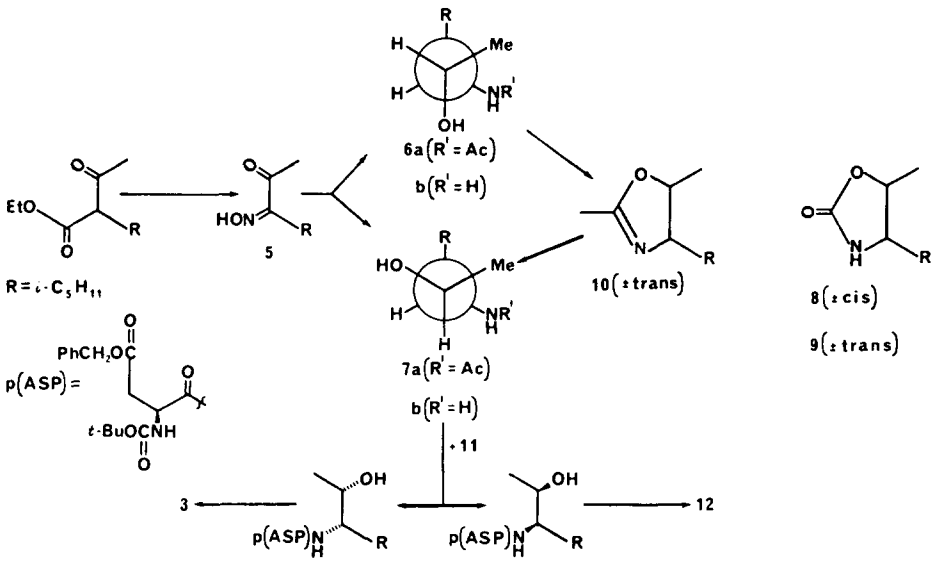

Fig. 2. Total synthesis of diastereomeric aspartic acid amides 3 and 12.

anhydride solvent gave a 66:34 mixture of diastereoisomeric acetamido alcohols 6a and 7a which, on recrystallization, led to the pure (racemic) *erythro* isomer 6a (melting point, 115·5–116·5 °C) in 48 % yield. The *threo* product 7a was isolated with difficulty by repeated preparative scale HPLC on the crystallization mother liquor.

The relative stereochemistry of 6a and 7a was established by proton magnetic resonance (^{1}H NMR) analysis of their respective oxazolidinone derivatives, 8 and 9 (Fig. 2). For derivatization, amides 6a and 7a were hydrolyzed (4N HCl) to amino alcohols 6b and 7b which subsequently were reacted with phosgene. Homonuclear decoupling of oxazolidinone C-5 methine protons by irradiation of the C-5 methyl group produced doublets with $J = 7{\cdot}9$ Hz for 8 and $J = 5{\cdot}9$ Hz for 9. Based on precedent in which *cis* oxazolidinone isomers were reported to have larger coupling constants (Abraham *et al.*, 1971; Futagawa *et al.*, 1973) we assigned 8 and 9 as the *cis* and *trans* isomers, respectively. Consequently, the stereochemistry of *erythro* 6a/6b and *threo* 7a/7b ethanolamine derivatives was also established. Finally, the *threo* amino alcohol 7b was found to be identical (except for lack of optical activity) with 4 derived from D-threonine.

Rearrangement of *erythro* acetamido alcohol 6a was affected by reaction with thionyl chloride in acetonitrile. The crude reaction product

containing the intermediate *trans* oxazoline 10 (HCl salt) was not isolated but hydrolyzed immediately (4N HCl) to afford (racemic) *threo* amino alcohol 7b (melting point, 43–46 °C, 85 % yield) which was spectroscopically identical with the product obtained by hydrolysis (4N HCl) of 7a.

Activated ester coupling of 7b with conventional *N*-carboxy-diprotected L-aspartic acid derivatives gave mixtures of diastereomeric amides from which the less soluble L,*S*,*S* isomer was easily separated. Coupling was most conveniently done with commercially available *β*-benzyl *α*-*p*-nitrophenyl *N*-*t*-butoxycarbonyl-L-aspartate [*N*-*t*-Boc-L-Asp(ONp) *β*-benzyl ester], 11, to afford a quantitative yield of the diprotected amides of 3 and 12. Fractional crystallization of the mixture gave pure diprotected 3 (melting point, 122·5–124 °C in 64 % yield), identical with material obtained by reacting 11 with 4. Removal of protective groups by sequential treatment with: (a) low pressure catalytic hydrogenolysis and (b) 70/30 trifluoroacetic acid-water led to 3 (melting point, 197·5–200 °C dec) in 81 % yield. Similar deblocking of the mother liquor material from crystallization of protected 3 gave the L,*R*,*R* diastereomer, 12 (melting point, 190·5–192 °C) whose aqueous solution was completely tasteless.

MATERIALS AND METHODS

Materials

All common reagents and catalysts were commercial samples unless otherwise specified. Ethyl isopentylacetoacetate was prepared from ethyl acetoacetate and isopentyl bromide (method of Marvel & Hagar, 1944). *β*-Benzyl *α*-*p*-nitrophenyl *N*-*t*-Boc-L-aspartate was purchased from BaChem Corp., Marina Del Ray, California 90291, USA.

Analysis

Products were identified by IR and ^{1}H NMR spectroscopy and by combustion analysis. NMR were generally obtained at 60 MHz in chloroform-d solution with tetramethylsilane (TMS) as internal reference standard. Spectral data are reported in the format: chemical shift (δ) downfield from TMS, multiplicity (s = singlet, d = doublet, etc., m = unresolved multiplet), structural assignment substantiated by

proton integration. Homonuclear decoupling was performed in a high resolution NMR spectrometer at 270 MHz. IR data are expressed in reciprocal centimeters.

Product purity was monitored by TLC with 0·25 mm silica gel plates using 85:15 v/v ethyl acetate/ethanol (Solvent A) or 4:1:1 v/v *n*-butanol/acetic acid/water (Solvent B). Preparative HPLC separations were done on PrePak-500 silica cartridges obtained from Waters Associates, division of Millipore, Inc., Milford, Mass., USA.

Experimental procedures

6-Methyl-3-oximino-2-heptanone (5)

For saponification, 5·36 liters of ice-cold 5% aqueous/sodium hydroxide was added to 1·5 kg (7·5 mol) of previously chilled (2 °C) ethyl isopentylacetoacetate and the mixture was stirred with an efficient mechanical stirrer for 18 h at below 7 °C (ice bath). After recovery of unreacted ester (15%) by ether extraction, the aqueous phase containing the sodium salt was stirred at 2 °C while 437·5 g (6·33 mol) of powdered sodium nitrite was added and allowed to dissolve. The stirred mixture was treated with 40% sulfuric acid (2·7 liters) for 1·5 h while temperature was maintained at 2–10 °C. Following another 2 h in the cold the mixture was neutralized at 22 °C by adding 3·2 liters of saturated aqueous sodium carbonate (caution foaming!). Ether extraction, followed by drying over sodium sulfate and concentration, gave 800 g of crude 5 (80% yield based on saponified ester) as a yellow–green oil. The crude product was suitable for subsequent reactions, but crystallization from cold hexane gave what appeared to be a single geometric isomer as colorless prisms: MP 32·5–34·5 °C; IR (liquid film) 3300 (broad OH), 1690 (C = O), 1675 (C = N); NMR 0·90 [d, $J = 6$ Hz, $(\underline{CH}_3)_2CH$], 1·07–1·80 (unresolved group of peaks, $\underline{CH}_2CH$), 2·37 (s, $CH_3C{=}O$), 2·55 (t, $J = 7$ Hz, $N{=}C{-}\underline{CH}_2$).

Erythro and threo N-acetyl-3-amino-2-hydroxy-6-methylheptane, 6a, and 7a

A two-gallon stainless steel stirred autoclave was charged with 5 (780 g, 4·97 mol), acetic acid (1076 ml), acetic anhydride (1076 ml) and 200 g of 5% Pt-on-activated carbon catalyst. The stirred reactor was pressurized to 750 psig with hydrogen, and evolved heat was removed via external cooling to maintain the reaction at *ca.* 25 °C. After 48 h water was added

(175 ml) to decompose excess anhydride, catalyst was filtered off and the filtrate was concentrated by rotary evaporation to yield an amber colored oil. The oil was dissolved in 80% v/v methanol–water (2·4 liters) and treated with sodium hydroxide at pH 10 for 4 h at 22 °C to saponify a small amount of O-acetylated 6a and 7a. After vacuum removal of methanol, reaction products were extracted with ethyl acetate. Evaporation of the dried (sodium sulfate) solvent gave 797·8 g (86% yield) of 6a/7a mixture as a light brown solid. Recrystallization from toluene gave 443·8 g of 6a (48% yield), MP 115·5–116·5 °C; NMR: 0·87 [d, $J = 6$ Hz, $(\underline{CH_3})_2CH$], 1·12 [d, $J = 6$ Hz above an envelope of unresolved peaks, $\underline{CH_3}CH—O$ and $(CH_3)_2\underline{CHCH_2}CH_2$], 2·00 (s, $\underline{CH_3}CONH$), 2·92 (broad s, OH), 3·50–4·07 (group of unresolved peaks, O—$\underline{CHCH}$—N), 5·75 (broad s, NH). TLC of 6a mother liquor (Solvent A) separated 6a, R_f 0·31 and minor isomer 7a, R_f 0·35. Preparative HPLC on 61 g of 6a mother liquor material using isocratic elution with 85:15 v/v ethyl acetate/ethanol and TLC to monitor fractions yielded 5·57 g of pure 7a as an oil. NMR: 0·97 [d, $J = 7$ Hz, $(\underline{CH_3})_2CH$], 1·17 (d, $J = 6$ Hz above an envelope of unresolved peaks, $\underline{CH_3}CH—O$ and $(CH_3)_2\underline{CHCH_2CH_2}$, 2·05 (s, $\underline{CH_3}CONH$), 2·9–4·2 (group of unresolved peaks, O—CHCH—N), 6·23 (broad q, $J = 9$ Hz, NH).

Erythro 3-amino-2-hydroxy-6-methylheptane (6b)
Amide 6a (5·15 g, 27·5 mmol) was treated with 75 ml 4N HCl and heated at reflux for 3·5 h. Water and excess HCl were evaporated under vacuum and 50% aqueous sodium hydroxide was added to basify the residue (pH > 12). Ether extraction followed by drying (sodium sulfate) and distillation gave 3·54 g (89% yield) of 6b as a colorless oil, BP 116–118 °C (16 mm Hg). IR (liquid film): 3300 (NH, OH), 1590 (C—N), 1465, 1380, 1365, 1110. NMR: 0·88 [d, $J = 6$ Hz, $(\underline{CH_3})_2CH$], 1·08 (d, $J = 7$ Hz, $\underline{CH_3}CHOH$), 2·33 (broad s, OH and NH), 2·63 m, $\underline{CH}NH_2$), 3·70 (partially resolved eight line m, $\underline{CH}$—OH). TLC (Solvent B), R_f 0·30. Similar hydrolysis of 7a gave 7b which was spectroscopically identical with the product from the rearrangement of 6a (see below).

Threo 3-amino-2-hydroxy-6-methylheptane, 7b, via rearrangement of 6a
A slurry of 6a (704 g, 3·76 mol) in anhydrous acetonitrile (5·0 liters) was stirred at 0–5 °C while thionyl chloride (437 ml, 6·07 mol) was added dropwise during 55 min. Following the addition, the mixture was stirred at 0–5 °C for 4 h before warming to 22 °C during 18 h. Vacuum removal of

excess thionyl chloride and solvent gave 819·5 g of crude 2,5-dimethyl-4-isopentyl-2-oxazoline hydrochloride (unique NMR signal at 2·57 ppm due to C-2 methyl group) which was hydrolyzed by adding 4N HCl (6·0 liters) and heating the mixture at reflux for 3 h. After cooling to 0–5 °C, 50 % aqueous sodium hydroxide was added to basify the mixture (pH 11). The product was isolated by ether extraction. Vacuum removal of solvent followed by short path distillation gave 462·2 g (85 % yield) of 7b as a colorless oil, BP 114–116 °C (23 mm Hg) which rapidly solidified to a mass of white needles, MP 43–46 °C. IR (liquid film): 3360 (broad NH/OH), 1585 (C—N), 1465, 1380, 1365, 1110, 1060. NMR: 0·90 [d, $J = 6$ Hz, $(\underline{CH_3})_2CH$], 1·17 (d, $J = 6$ Hz above an envelope of unresolved peaks, $\underline{CH_3}CH$—O and $\underline{CHCH_2CH_2}$), 2·17 (broad s, NH/OH), 2·40 (broad m, $\underline{CH}$—N), 3·40 (five line m, $J = 6$ Hz, $\underline{CH}$—O).

Oxazolidinone derivatives of 6b and 7b

A solution of 6b (606 mg, 4·18 mmol) in toluene (25 ml) was stirred at 0 °C, 2·0 ml of *s*-collidine was added, followed (dropwise) by 4·29 ml (5·0 mmol) of 12·5 % phosgene in toluene solution. After 0·5 h at 0 °C and 0·5 h at 22 °C, water and ether were added, the organic phase was separated, washed with dilute aqueous hydrochloric acid, dried (sodium sulfate) and vacuum concentrated to give 620 mg of crude product. Short path distillation at 100–120 °C (0·8 mm Hg) gave 590 mg (83 % yield) of 8 as a pale yellow oil. IR (liquid film): 1750 (C=O), NMR: 0·93 [d, $J = 6$ Hz, $(\underline{CH_3})_2CH$], 1·37 (d, $J = 6$ Hz above an envelope of unresolved peaks, $\underline{CH_3}CH$), 3·77 (broad q, $J = 6$ Hz, $\underline{CH}$—N), 4·78 (five line m, $J = 7$ Hz, $\underline{CH}$—O), 7·22 (broad s, NH). Similarly, 7b (936 mg) afforded 953 mg (86 % yield of 9 as a nearly colorless oil, BP 100–120 °C (0·45 mm Hg). IR (liquid film): 1750 (C=O). NMR: 0·90 [d, $J = 6$ Hz, $(\underline{CH_3})_2CH$], 1·42 (d, $J = 7$ Hz, above an envelope of unresolved peaks, $\underline{CH_3}CH$), 3·37 (q, $J = 6$ Hz, CH—N), 4·27 (five line m, $J = 6$ Hz, CH—O), 7·10 (broad s, NH).

Preparation of amides 3 and 12

A solution of *threo* amino alcohol 7b (11·92 g, 0·0822 mol) in 135 ml dry tetrahydrofuran (THF) was stirred magnetically and maintained at *ca.* 22 °C with water bath cooling while 36·5 g (0·0822 mol) of *N*-*t*-Boc-L-Asp(ONp) β-benzyl ester, 11, was added during 5 min. After 3 h THF was removed under vacuum, and the residue was redissolved in ethyl acetate (300 ml). The solution was washed with 5 % aqueous sodium carbonate to remove *p*-nitrophenol, dried over anhydrous sodium sulfate and

evaporated to give 40·81 g of crude amide product. Crystallization from ethyl acetate/toluene gave 11·91 g (64% yield) of *N*-*t*-Boc-3 β-benzyl ester, MP 122·5–124 °C, $[\alpha]_D^{22}$-15·95° (c, 0·959, $CHCl_3$). NMR: 0·87 [d, $J = 6$ Hz, $(\underline{CH}_3)_2CH$], 1·12 (d, $J = 6$ Hz) and 1·43 [s, $CH_3\underline{CH}$—O, $(CH_3)_3C$ and $CHCH_2CH_2$ (unresolved)], 2·87 [d, $J = 5$ Hz, $(\underline{CH}_2CH$—NH and OH)], 3·73 [m, $CH_2\underline{CH}$—NH], 5·10 (s, CH_2Ph), 5·72 (d, $J = 9$ Hz, NH) and 7·27 (s, phenyl ring).

A Parr hydrogenation bottle was charged with *N*-*t*-Boc-3 β-benzyl ester (20·03 g, 0·0445 mol), acetic acid (70 ml), 5% Pd-on-C catalyst (0·05 g) and the mixture was hydrogenated under 50 psig H_2 at 22 °C for 2·5 h. Filtration of catalyst and evaporation of solvent under vacuum gave 16·20 g of white solid (97% yield of de-benzylated product) whose structure was verified by NMR.

The de-benzylated product (14·73 g, 0·0392 mol) was treated with 35 ml of 70/30 v/v trifluoroacetic acid (TFA)/water and heated for 30 min in a steam bath (86 °C, reaction temperature). Excess TFA was removed under vacuum, and the residue was dissolved in 100 ml of water to give a clear, colorless solution of 3/TFA salt. The salt solution was passed through an ion-exchange column containing 230 ml of 50–100 mesh BioRad AG50W-X8 resin [H^+-form, *ca.* 0·392 mol-equiv., column dimensions: 21·5 × 4 cm]. The column was successively eluted with (1) 700 ml 5% acetic acid–95% water v/v, (2) 700 ml water and (3) 1600 ml of 1N ammonium hydroxide. Evaporation of (3) under vacuum gave 10·37 g of crude 3 as a white solid. Recrystallization from 9:1 methanol/water v/v gave (in two crops) 8·31 g of 3, MP 197·5–201 °C dec (81% yield). The product was homogeneous by TLC and HPLC analysis. For the first crop material (MP 197·5–200 °C dec) found: $[\alpha]_D^{23}$ + 4·79° (c, 1·043, 0·5N HCl). NMR (D_2O, TMS): 0·67–2·1 [group of partially resolved peaks, 1·07 (d, $J = 6$ Hz), 1·13 (d, $J = 7$ Hz), $(CH_3)_2CH$, CH_3CH and CH_2CH_2], 3·03 (d, $J = 7$ Hz, $\underline{CH}_2CO_2H$) 4·07 (m, $CH_3\underline{CH}$ and $CH_2\underline{CH}$NH) and 4·53 (t, $J = 7$ Hz, $\underline{CH}CH_2CO_2H$).

The deprotection procedure was also applied to 2·75 g of the mother liquor material from crystallization of *N*-*t*-Boc-3 β-benzyl ester. Evaporation of the 1N ammonium hydroxide solution gave 1·1 g of white solid which, on recrystallization from water, afforded colorless needles, MP 190·5–192 °C dec.

The L,*R*,*R*, diastereoisomer 12 was homogeneous by TLC and HPLC and had $[\alpha]_D^{22}$ + 29·2° (c, 0·720, 0·5 N HCl). A 0·12% aqueous solution of the material was completely tasteless.

ACKNOWLEDGEMENTS

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