Water-Soluble Constituents of Fennel. VII.[1] Acyclic Monoterpenoid Glycosides

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From the water-soluble portion of the methanol extract of the herbal medicine fennel, six new acyclic monoterpenoid glycosides, three of which contained an oxide linkage, were obtained. Their structures were clarified by spectral investigations.

Key words fennel; *Foeniculum vulgare* fruit; Umbelliferae; acyclic monoterpenoid glycoside; linalyl oxide glycoside

In previous papers, we reported the isolation and characterization of new 1,8-cineole,[1] fenchane[2] and menthane[3] glycosides from the herbal medicine fennel. In this paper, we discuss the separation and structure elucidation of six new acyclic monoterpenoid glycosides.

The methanolic extract of commercial fennel, prepared from the fruit of *Foeniculum vulgare* MILLER (Umbelliferae), was worked up as described in the Experimental section, and from the aqueous portion, one free form (**1**) and seven glycosyl form (**2**—**8**) acyclic monoterpenoids were obtained. NMR data are listed in Tables 1 and 2, and molecular formulae were suggested from the accurate mass number of $[M+H]^+$ or $[M+Na]^+$ ion peaks in the high-resolution positive FAB-MS. All glycosides were found to be β-D-glucopyranoside, as evidenced from their ^{13}C-NMR data (Table 2).

Monoterpenoid **1** ($C_{10}H_{20}O_4$, a colorless syrup) and glycoside **2** ($C_{16}H_{28}O_7$, an amorphous powder, $[\alpha]_D^{21}$ −18.3°) were identified as 3,7-dimethyloct-3(10)-ene-1,2,6,7-tetrol (as a mixture of stereoisomers)[4] and betulalbuside A,[5] respectively, by comparison of ^{1}H- and ^{13}C-NMR data with published values.

Glycoside **3** ($C_{16}H_{30}O_9$, an amorphous powder) showed a single peak by HPLC [octadecyl silica (ODS)], but was indicated to be a mixture of two stereoisomers [**3a**, **3b** (4 : 3)] by analysis of ^{1}H- and ^{13}C-NMR data. It contained two *tert*-methyls, three methylenes (one of them oxygenated), two oxygenated methines and one vinyl group, along with one oxygenated quaternary carbon. From comparison of its ^{1}H- and ^{13}C-NMR data with those of **1**, **3** was concluded to be a glucoside of **1**. The position of the glucosyl unit was found to be C-7 by the downfield shift of the C-7 (by 8.1 ppm) signal, and the upfield shifts of the C-6 (by 1.6 ppm), C-8 (by 4.4 ppm) and C-9 (by 1.9 ppm) signals, and the chemical shift of the glucosyl C-1 (δ 98.74).[6] Therefore, **3** was concluded to be a mixture of a pair of stereoisomers of 3,7-dimethyloct-3(10)-ene-1,2,6,7-tetrol 7-*O*-β-D-glucopyranoside. Attempts to separate these two isomers were not successful.

Glycoside **4** ($C_{16}H_{30}O_9$, an amorphous powder, $[\alpha]_D^{25}$ −51.4°) was also revealed to be a glucoside of **1** by ^{1}H- and ^{13}C-NMR analysis, and the position of the glucosyl unit was indicated to be C-2 by the downfield shift of C-2 (by 6.4 ppm) and the upfield shift of the C-1 (by 1.5 ppm) and C-3 (by 4.2 ppm) signals.[6] It was also supported by the results of an heteronuclear multiple-bond correlation (HMBC) experiment. The absolute configuration at C-2 was confirmed to be *R* by comparison of the ^{13}C-NMR data with those of **9** (a stereoisomer of **4**).[7] The chemical shifts of C-2 (**4**: δ 82.72, **9**: δ 85.18) and the glucosyl C-1 (**4**: δ 101.69, **9**: δ 104.71) were in good agreement with a 2*R* configuration for **4** and a 2*S* configuration for **9**.[6] The chemical shifts of C-1 [**4**: δ 65.25 (pro-*R*), **9**: δ 64.87 (pro-*S*)] and C-3 [**4**: δ 147.49 (pro-*S*), **9**: δ 148.96 (pro-*R*)] also supported this assignment.[6,8] Therefore, **4** was concluded to be (2*R*,6ζ)-3,7-dimethyloct-3(10)-ene-1,2,6,7-tetrol 2-*O*-β-D-glucopyranoside.

Glycoside **5** ($C_{16}H_{30}O_7$, an amorphous powder) showed a single peak by HPLC (ODS), but was suggested to be a mixture of two stereoisomers [**5a**, **5b** (3 : 1)] by the analysis of ^{1}H- and ^{13}C-NMR spectral data. Acid hydrolysis of **5** gave D-glucose as a sugar component, and its aglycone contained one *tert*-methyl, one *sec*-methyl, four methylenes (one of them oxygenated), one methine, one vinyl group, and one oxygenated quaternary carbon. From analysis of the HMBC spectrum, the planar structure of **5** was suggested. The position of the glucosyl unit was proved to be C-8 by a correlation between C-8 and the glucosyl H-1 signals in the HMBC spectrum. Therefore, **5** was characterized as a pair of stereoisomers of 3,7-dimethyloct-1-ene-3,8-diol 8-*O*-β-D-glucopyranoside. Attempts to separate these two isomers were not successful and the configuration at C-3 and C-7 could not be assigned.

Acid hydrolysis of glycoside **6** ($C_{16}H_{28}O_8$, an amorphous powder, $[\alpha]_D^{21}$ −13.8°) gave D-glucose as a sugar component, and it contained two *tert*-methyls, three methylenes (one of them oxygenated), one oxygenated methine, one vinyl group, and two oxygenated quaternary carbons in the aglycone. From the HMBC experiment, the gross planar structure of **6** was deduced, and the location of the glucosyl unit was confirmed to be C-7 by the cross peak between C-7 and the glucosyl H-1. The molecular formula and a correlation between C-3 and H-6 signals in the HMBC spectrum revealed that the aglycone has a terahydrofuran unit, and suggested it to be a glucoside of 10-hydroxylinalyl oxide.[9] Since a cross peak between H-1b and H_2-6 was observed in the nuclear Overhauser and exchange spectroscopy (NOESY) spectrum (Fig. 1), a *trans* relationship between the vinyl and 2-hydroxy isopropyl groups was suggested. From these results, **6** was characterized as 10-hydroxy-*trans*-linalyl oxide 7-*O*-β-D-glucopyranoside.[9,10]

Glycoside **7** ($C_{16}H_{28}O_8$, an amorphous powder, $[\alpha]_D^{25}$ −3.5°) has the same skeleton and functional groups as **6**, and by comparison of ^{1}H- and ^{13}C-NMR with those of **6**, was indicated to be 10-hydroxylinalyl oxide 7-*O*-β-D-glucopyra-

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Table 1. ^{1}H-NMR Chemical Shifts of **3**—**8** (in Pyridine-d_5, 500 MHz)

	3a	3b	4	5a	5b
H_2-1	4.16 dd (7.5, 11.5)	4.16 dd (7.5, 11.5)	4.09 dd (7.0, 11.5)	5.14 dd (2.0, 11.0)	5.14 dd (2.0, 11.0)
	4.17 dd (4.0, 11.5)	4.17 dd (4.0, 11.5)	4.15 dd (4.5, 11.5)	5.54 dd (2.0, 17.5)	5.54 dd (2.0, 17.5)
H-2	4.73 dd (4.0, 7.5)	4.73 dd (4.0, 7.5)	5.04 dd (4.5, 7.0)	6.14 dd (11.0, 17.5)	6.14 dd (11.0, 17.5)
H_2-4	2.61 ddd (6.5, 9.5, 15.0)	2.47 ddd (6.5, 10.0, 15.0)	2.72 br dd (8.0, 15.0)	1.65 m	1.65 m
	2.84 ddd (4.5, 9.5, 15.0)	2.98 ddd (4.5, 10.0, 15.0)	2.79 m	—	—
H_2-5	1.86 m	1.86 m	1.94 m	1.67 m	1.67 m
	2.04 m	2.04 m	2.23 m	—	—
H-6	3.95 br d (10.0)	3.95 br d (10.0)	3.83 br d (10.5)	1.13 m	1.13 m
	—	—	—	1.55 m	1.55 m
H-7	—	—	—	1.88 m	1.88 m
H_3-8	1.46[a] s	1.47[a] s	1.47[a] s	—	—
H_2-8	—	—	—	3.45 dd (7.0, 9.0)	3.56 dd (7.0, 9.5)
	—	—	—	4.02 dd (7.0, 9.0)	3.91 dd (7.0, 9.5)
H_3-9	1.50[a] s	1.51[a] s	1.50[a] s	0.97 d (7.0)	0.96 s
H_3-10	—	—	—	1.44 s	1.44 s
H_2-10	5.18 br s	5.16 br s	5.29 br s	—	—
	5.57 br s	5.53 br s	5.65 br s	—	—
Glc-1	5.20 d (8.0)	5.21 d (8.0)	5.07 d (7.5)	4.84 d (7.5)	4.84 d (7.5)

	6	7	8
H-1a	5.16 dd (2.0, 11.0)	5.12 dd (2.0, 11.0)	4.20 br d (10.0)
b	5.51 dd (2.0, 17.0)	5.54 dd (2.0, 17.0)	4.31 br d (10.0)
H-2	6.07 dd (11.0, 17.0)	6.17 dd (11.0, 17.0)	4.39 br s
H-4α	1.74 ddd (6.0, 9.0, 12.0)	1.82 ddd (4.0, 9.0, 12.0)	2.22 ddd (2.0, 10.5, 12.0)
β	2.29 ddd (7.0, 9.0, 12.0)	2.29 ddd (7.0, 9.0, 12.0)	2.36 ddd (9.0, 10.5, 12.0)
H-5α	1.95 m	1.91 dddd (4.0, 7.0, 12.0, 17.0)	1.93 m
β	2.19 m	2.03 m	2.05 m
H-6α	4.13 t (7.0)	—	4.30 br d (9.0)
β	—	4.38 dd (6.0, 9.0)	—
H_3-8	1.51 s	1.44 s	1.46[a] s
H_3-9	1.55 s	1.56 s	1.47[a] s
H_2-10	3.76 d (11.0)	3.77 d (11.0)	4.06 br s
	3.87 d (11.0)	3.85 d (11.0)	—
Glc-1	5.14 d (7.5)	5.22 d (8.0)	5.17 d (8.0)

δ in ppm from TMS [coupling constants (J) in Hz are given in parentheses]. *a*) Assignments may be interchanged in each column.

Table 2. ^{13}C-NMR Chemical Shifts of **1**, **3**—**9** (in Pyridine-d_5, 125 MHz)

	1a	1b	3a	3b	4	9	5a	5b	6	7	8
C-1	66.79	66.75	66.84	66.78	65.25	64.87	111.06	111.01	113.24	113.18	63.78
C-2	76.30	76.56	76.22	76.56	82.72	85.18	147.29	147.38	141.94	142.59	75.56
C-3	151.72	151.88	151.65	151.78	147.49	148.96	72.43	72.43	87.31	86.85	88.12
C-4	30.49	30.54	30.57	30.48	29.56	30.19	43.52	43.46	32.41	32.71	30.00
C-5	30.83	30.97	30.61	30.79	30.16	30.19	21.79	21.86	26.77	27.60	27.65
C-6	78.38	78.66	76.85	77.02	78.04	78.42	34.46	34.51	85.54	86.76	86.98
C-7	72.68	72.71	80.85	80.82	72.63	72.66	34.11	34.00	79.03	78.23	78.79
C-8	25.94	25.94	21.49[a]	21.49[a]	25.96[a]	25.51[a]	75.48	75.48	23.81	23.62	24.36[a]
C-9	25.94	25.94	24.08[a]	24.08[a]	26.08[a]	25.85[a]	17.18	17.37	23.29	22.85	22.25[a]
C-10	110.07	109.85	110.14	110.00	113.40	111.22	28.49	28.35	67.67	67.75	66.12
Glc-1			98.75	98.75	101.69	104.71	105.13	104.96	98.86	98.96	98.93
Glc-2			75.40	75.40	75.26	75.54	75.31	75.31	75.40	75.43	75.45
Glc-3			78.77	78.77	78.68	78.24	78.64	78.64	78.78	78.93	78.79
Glc-4			71.72	71.72	71.76	71.33	71.77	71.77	71.66	71.88	71.64
Glc-5			78.28	78.28	78.53	78.24	78.54	78.54	78.16	78.88	78.29
Glc-6			62.76	62.76	62.64	62.33	62.87	62.87	62.86	62.98	62.77

δ in ppm from TMS. *a*) Assignments may be interchanged in each column.

noside, having a stereoisomeric aglycone of **6**. From the observed cross peak between H-1b and H_3-9 in the NOESY spectrum (Fig. 1), the aglycone of **7** was suggested to be a derivative of *cis*-linalyl oxide.[9,10] Therefore, **7** was characterized as 10-hydroxy-*cis*-linalyl oxide 7-*O*-β-D-glucopyranoside.

Glycoside **8** ($C_{16}H_{30}O_{10}$, an amorphous powder, $[\alpha]_D^{23}$ +0.5°) showed the presence of two *tert*-methyls, four methylenes (two of them oxygenated), two oxygenated methine groups and two oxygenated quaternary carbons in the aglycone part. From the HMBC experiment, and comparison of the ^{13}C-NMR data with those of **6** and **7**, **8** was indicated to

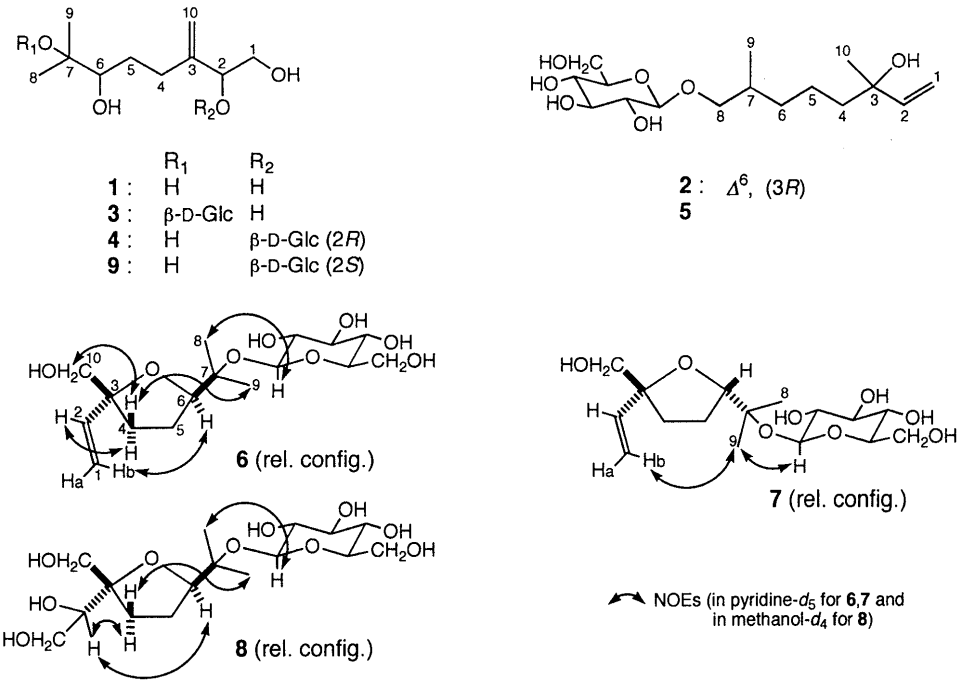

Fig. 1. Structures of **1**—**9** and Nuclear Overhauser Effect (NOE) Interactions Observed in the NOESY Spectra of **6**—**8**

be a 1,2-dihydroxy derivative of **6** or **7**. The cross peak between H-2 and H-6 in the NOESY spectrum (Fig. 1; measured in CD_3OD) suggested that **8** was a derivative of **6**, therefore, it was characterized as 1,2,10-trihydroxydihydro-*trans*-linalyl oxide 7-*O*-*β*-D-glucopyranoside.

Compounds **3**—**8** are new compounds and have not been described. However, the absolute configuration of these aglycones could not be established from the avaiable data.

Experimental

The instruments and experimental conditions for obtaining spectral data and for chromatography were the same as in the preceeding paper.[11]

Extraction and Separation of 1—8 As reported in the previous paper,[11] commercial fennel (2.0 kg) was extracted with methanol. The aqueous portion of this methanol extract was then subjected to Amberlite XAD-II (H_2O→MeOH), and the methanol eluate (29.5 g) was chromatographed over Sephadex LH-20 (MeOH) to give seven fractions (frs. A—G). Fraction C (16.9 g) was chromatographed over silica gel [$CHCl_3$–MeOH–H_2O (4 : 1 : 0.1)→MeOH] to give fifteen fractions (frs. C_1—C_{15}). Fraction C_6 (1.9 g) was subjected to a Lobar RP-8 column [CH_3CN–H_2O (3 : 17)] to give thirteen fractions (frs. C_{6-1}—C_{6-13}), and fr. C_{6-3} was subjected to HPLC [carbohydrate analysis, CH_3CN–H_2O (49 : 1)] to afford **1** (40 mg). Fraction C_{6-6} was subjected to HPLC [ODS, CH_3CN–H_2O (1 : 7)] to afford **6** (18 mg). Fraction C_{6-8} was acetylated with Ac_2O and pyridine, and the acetylated fraction was subjected to HPLC [ODS, CH_3CN–H_2O (3 : 2)] to give five fractions (frs. C_{6-8-1}—C_{6-8-5}). Fraction C_{6-8-3} was deacetylated by heating in a water bath with 15% NH_4OH–MeOH for 4 h, then subjected to silica gel [$CHCl_3$–MeOH (9 : 1)] to afford **7** (8 mg). Fractions C_{6-9} and C_{6-12} were subjected to HPLC [ODS, CH_3CN–H_2O (3 : 17)] to afford **2** (85 mg) and **5** (13 mg), respectively. Fraction C_{10} (0.4 g) was subjected to a Lobar RP-8 column [MeOH–H_2O (1 : 4)] to give seven fractions (frs. C_{10-1}—C_{10-7}). Fraction C_{10-3} was acetylated with Ac_2O and pyridine, and the acetylated fraction was subjected to HPLC [symmetryprep C_{18}, CH_3CN–H_2O (9 : 11)] to give two fractions. Each fraction was deacetylated by heating in a water bath with 15% NH_4OH–MeOH for 4 h and subjected to HPLC [carbohydrate analysis, CH_3CN–H_2O (9 : 1)] to afford **3** (8 mg) and **4** (4 mg), respectively. Fraction C_{12} (1.1 g) was subjected to a Lobar RP-8 column [MeOH–H_2O (1 : 4)] to give eight fractions (frs. C_{12-1}—C_{12-8}), and fr. C_{12-4} was subjected to HPLC [ODS, MeOH–H_2O (7 : 33)] to afford **8** (7 mg).

3,7-Dimethyloct-3(10)-ene-1,2,6,7-tetrol (1) A colorless syrup. ^{1}H-NMR (pyridine-d_5) δ: signals in brackets were allocated to the minor stereoisomeric component; 1.45 [1.47], 1.49 [1.50] (each 3H, s, H_3-8 and H_3-9), 1.95 (2H, m, H_2-5), 2.64 [2.50] (1H, ddd, J=7.0, 10.0, 16.0 Hz, H-4a), 2.87 [3.04] (1H, ddd, J=4.5, 10.0, 15.0 Hz, H-4b), 3.80 (1H, m, H-6), 4.06 (1H, dd, J=8.5, 10.0 Hz, H-1a), 4.16 (1H, br d, J=10.0 Hz, H-1b), 4.74 (1H, m, H-2), 5.19, 5.53 (each 1H, br s, H_2-10).

Betulalbuside A (2) An amorphous powder, $[\alpha]_D^{21}$ −18.3° (c=1.0, MeOH), [lit.,[5b] $[\alpha]_D$ −31.8° (c=0.2, MeOH)].

3,7-Dimethyloct-3(10)-ene-1,2,6,7-tetrol 7-*O*-*β*-D-Glucopyranoside (3) An amorphous powder. Positive FAB-MS *m/z*: 733 $[2M+H]^+$, 367.1990 $[M+H]^+$ (base; Calcd for $C_{16}H_{31}O_9$; 367.1968), 205 $[M-C_6H_{10}O_5+H]^+$.

(2*R*,6*ζ*)-3,7-Dimethyloct-3(10)-ene-1,2,6,7-tetrol 2-*O*-*β*-D-Glucopyranoside (4) An amorphous powder, $[\alpha]_D^{25}$ −51.4° (c=0.3, MeOH). Positive FAB-MS *m/z*: 733 $[2M+H]^+$, 405 $[M+K]^+$, 389 $[M+Na]^+$, 367.1948 $[M+H]^+$ (base; Calcd for $C_{16}H_{31}O_9$; 367.1968), 205 $[M-C_6H_{10}O_5+H]^+$.

3,7-Dimethyloct-1-ene-3,8-diol 8-*O*-*β*-D-Glucopyranoside (5) An amorphous powder. Positive FAB-MS *m/z*: 699 $[2M+H]^+$, 373 $[M+K]^+$, 357 $[M+Na]^+$, 335.2072 $[M+H]^+$ (Calcd for $C_{16}H_{31}O_7$; 335.2070), 317 $[M-H_2O+H]^+$ 155 $[M-C_6H_{12}O_6+H]^+$(base).

10-Hydroxy-*trans*-linalyl Oxide 7-*O*-*β*-D-Glucopyranoside (6) An amorphous powder, $[\alpha]_D^{21}$ −13.8° (c=0.9, MeOH). Positive FAB-MS *m/z*: 387 $[M+K]^+$ (base), 371 $[M+Na]^+$, 349.1888 $[M+H]^+$ (Calcd for $C_{16}H_{29}O_8$; 349.1862), 331 $[M-H_2O+H]^+$, 169 $[M-C_6H_{12}O_6+H]^+$.

10-Hydroxy-*cis*-linalyl Oxide 7-*O*-*β*-D-Glucopyranoside (7) An amorphous powder, $[\alpha]_D^{25}$ −3.5° (c=0.2, MeOH). Positive FAB-MS *m/z*: 697 $[2M+H]^+$, 349.1843 $[M+H]^+$ (Calcd for $C_{16}H_{29}O_8$; 349.1862), 331 $[M-H_2O+H]^+$, 169 $[M-C_6H_{12}O_6+H]^+$ (base).

1,2,10-Trihydroxydihydro-*trans*-linalyl Oxide 7-*O*-*β*-D-Glucopyranoside (8) An amorphous powder, $[\alpha]_D^{23}$ +0.5° (c=0.2, MeOH). Positive FAB-MS *m/z*: 421 $[M+K]^+$, 405.1753 $[M+Na]^+$ (Calcd for $C_{16}H_{30}O_{10}Na$; 405.1736), 383.1891 $[M+H]^+$ (Calcd for $C_{16}H_{31}O_{10}$; 383.1917), 203 $[M-C_6H_{12}O_6+H]^+$ (base). ^{1}H-NMR (CD_3OD) δ: 1.23 (3H, s, H_3-9), 1.27 (3H, s, H_3-8), 1.85 (1H, ddd, J=2.0, 7.0, 15.0 Hz, H-4β), 1.88 (2H, m, H_2-5), 1.99 (1H, ddd, J=2.5, 8.0, 15.0 Hz, H-4α), 3.51, 3.56 (each 1H, d, J=11.5 Hz, H_2-10), 3.60 (1H, dd, J=4.0, 10.0 Hz, H-1a), 3.72 (1H, dd, J=4.0, 4.0 Hz, H-2), 3.74 (1H, dd, J=4.0, 10.0 Hz, H-1b), 3.99 (1H, dd, J=6.0, 9.0 Hz, H-6), 4.59 (1H, d, J=7.5 Hz, glucosyl H-1).

Acid hydrolysis of 2, 5 and 6 Each compound, **2** (12 mg), **5** (4 mg) and **6** (5 mg) was dissolved in aq. 2 N H_2SO_4 and heated on a water bath for 3 h, respectively. The hydrolysate was the neutralized with $NaHCO_3$ and the salt filtered off, and the filtrate was chromatographed over silica gel [$CHCl_3$–MeOH–H_2O (7 : 3 : 0.5)]. The sugar fraction was subjected to HPLC analysis [column; carbohydrate analysis (3.9×300 mm), detector; JASCO RI-930 detector and JASCO OR-990 chiral detector, solv.; CH_3CN–H_2O (17 : 3), 2 ml/min. A peak of t_R 4.53 min (same retention time as that of D-glucose)]

which showed the presence of D-glucose.

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