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REACTION OF PAEONIFLORIN WITH LOWER ALCOHOLS IN THE PRESENCE OF CATION EXCHANGER

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*The reaction of paeoniflorin (PF) with refluxing MeOH in the presence of cation exchanger KU-2-8 (H^+) formed a mixture of the 4-*O*-methyl- and 4-oxo-9-*O*-methyl ethers (1:1, overall yield 90%) that were separated by chromatography over silica gel. The reaction of PF with EtOH and BuOH under analogous conditions also formed mixtures of the ethyl and butyl ethers from which 4-oxo-9-*O*-ethyl(butyl) ethers were isolated as the tetra-*O*-acetates. The structures of the obtained compounds were confirmed using PMR and ^{13}C NMR spectra.*

Keywords: paeoniflorin, ethers, alcohols, cation exchanger.

Roots of various species of peony (*Paeonia*) contain unique plant metabolites, e.g., cage-like monoterpenes with the pinane skeleton that are considered the main constituents of peony roots responsible for their biological activity (antioxidant, anti-allergic, hepatoprotective, antiproliferative, etc.) [1–5].

The glycoside paeoniflorin (PF) (**1**), which was also isolated from roots of *Paeonia anomala* L., Altai), is one of the most well-known monoterpene constituents of peony roots [6]. It exhibited a broad spectrum of pharmacological activity (antioxidant, anti-inflammatory, anti-allergic, hepatoprotective, antitumor, etc.) [7–10]. PF had neuroprotective activity for the CNS, protected the brain from the neurotoxic action of the β-amyloid complex, which is considered to cause the inception and development of Alzheimer's disease, and inhibited the production of tumor necrosis factor TNF-α and interleukins IL-1β and IL-6 [11, 12]. Chemical modification of PF is interesting as a route to new biologically active compounds for medicine.

Previously, 4-*O*-methyl(ethyl)- and 4-oxo-9-*O*-methyl(ethyl)-PF were prepared as mixtures from the reaction of **1** with MeOH or EtOH in the presence of *p*-toluenesulfonic acid and were isolated as the tetra-*O*-acetates [13]. However, ^{13}C NMR spectra of the obtained PF ethers were not reported in that work.

In continuation of our research [14] on chemical modification of **1**, we found that PF reacted at the ketal hydroxyl (4-OH) with lower alcohols (MeOH, EtOH, BuOH) in the presence of strong-acid cation exchanger KU-2-8 (H^+). Compound **1** in refluxing MeOH (2 h) in the presence of the cation exchanger produced in 90% overall yield a mixture of the 4-*O*-methyl- (**2**) and 4-oxo-9-*O*-methyl ethers (**3**) (1:1, Scheme 1) that was separated by column chromatography (CC) over silica gel (SG).

The PMR spectrum of **2** showed the OCH_3 proton resonance at δ 3.31 ppm; of **3**, at 3.34 ppm. The aromatic protons were observed at weak field (8.0–7.5 ppm). The ^{13}C NMR spectrum of **2** contained resonances for C-9 and C-4 with chemical shifts (CS) δ 109.75 and 101.59 ppm, which indicated that the starting pinane structure of the aglycon was retained. The ^{13}C NMR spectrum of **3** exhibited the C-4 carbonyl resonance at δ 207.58 ppm.

Acetylation of ethers **2** and **3** by acetic anhydride in Py produced tetra-*O*-acetates **4** and **5**. The PMR spectrum of **4** contained resonances for protons of four CH_3CO groups. The OCH_3 protons resonated at δ 3.35 ppm; C-9 (singlet), 5.39 ppm. The ^{13}C NMR spectrum of tetra-*O*-acetate **4** exhibited resonances for C-4 (107.66 ppm) and C-9 (101.06 ppm). The ^{13}C NMR spectrum of **5** showed the C-4 resonance at 204.9 ppm.

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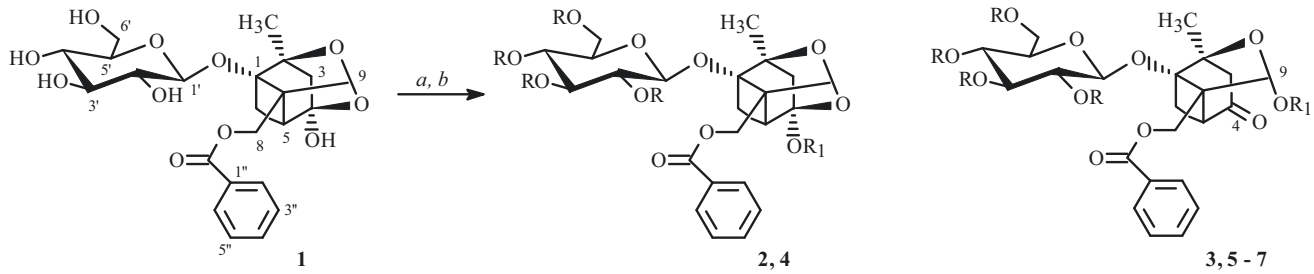

1 **2, 4** **3, 5 - 7**

2: R = H, R_1 = Me; **3:** R = H, R_1 = CH_3; **4:** R = Ac, R_1 = Me; **5:** R = Ac, R_1 = CH_3
6: R = Ac, R_1 = CH_2CH_3; **7:** R = Ac, R_1 = $C^{1'''}H_2(CH_2)_2C^{4'''}H_3$

a. MeOH (EtOH, BuOH), KU-2-8 (H^+), t°, 2 h; *b*. Ac_2O, Py, 20–22°C, 24 h

Scheme 1

The reaction of PF with EtOH in the presence of KU-2-8 (H^+) also formed a mixture of ethers with similar R_f values. Their ^{13}C NMR spectra contained resonances for C-atoms with CS 206.05 ppm (C=O) and 107.56, 105.84, and 100.83 ppm (C-9, C-4) that belonged to the 4-oxo-9-*O*-ethyl and 4-*O*-ethyl ethers of PF that could not be separated. The obtained mixture was acetylated by Ac_2O in Py and chromatographed over a column of SG to isolate 4-oxo-9-*O*-ethyl-PF tetra-*O*-acetate (**6**) in 38% yield. The PMR spectrum of **6** showed proton resonances for four acetyls with CS 2.09, 2.05, 2.03, and 1.99 ppm. Resonances of the ethoxy protons (OCH_2CH_3) were observed at δ 3.35 and 1.35 ppm. The H-9 resonance had CS 4.52 ppm (singlet). The ^{13}C NMR spectrum of **6** exhibited the oxo C-4 resonance at 204.87 ppm and resonances for acetate C=O groups at weak field (170.31, 170.16, 169.36, 169.26 ppm).

Reaction of **1** with BuOH under analogous conditions also formed a mixture of the 4-oxo-9-*O*-butyl and 4-*O*-butyl ethers of PF according to ^{13}C NMR spectral data. The mixture was acetylated and chromatographed over a column of SG to afford pure 4-oxo-9-*O*-butyl ether of PF (**7**) in 35% yield. The PMR spectrum of **7** contained proton resonances for four acetyls (2.05, 2.03, 2.00, 1.99 ppm). The ^{13}C NMR spectrum of **7** was characterized by the resonance for the oxo C-atom at 204.92 ppm (C-4) and butyl C-atoms ($OCH_2CH_2CH_2CH_3$) (31.33, 26.21, 26.21, 13.75 ppm).

Thus, the reaction of **1** with MeOH in the presence of strong-acid cation exchanger KU-2-8 (H^+) formed a 1:1 mixture of the 4-*O*-methyl and 4-oxo-9-*O*-methyl ethers. The reaction of PF with EtOH and BuOH also produced mixtures of 4-*O*-alkyl and 4-oxo-9-*O*-alkyl ethers from which the 4-oxo-9-*O*-ethyl and -butyl ethers were isolated as the tetra-*O*-acetates.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD, Me_2CO-d_6, and Py-d_5 with TMS internal standard on Bruker spectrometers [AM-300, operating frequencies 300 (^1H) and 75.5 MHz (^{13}C); pulsed Avance-III, operating frequencies 500.13 (^1H) and 125.47 MHz (^{13}C)]. Resonances in NMR spectra in the usual regime were assigned using the ACDLABS software, literature data for PF and its derivatives [6, 13, 14], and the standard set of 2D programs embedded in the Avance-III 500 spectrometer.

Molecular ions were determined in EtOH solutions by LC-MS on a Shimadzu LCMS-2010 instrument in chemical ionization at atmospheric pressure mode. Optical activity was measured on a PerkinElmer 341 MC polarimeter in a 1-dm cuvette. Melting points were determined on a Boetius apparatus. TLC used Sorbfil plates (ZAO Sorbpolimer, Russia). Spots were detected by H_2SO_4 (5%) in EtOH followed by heating at 110–120°C for 2–3 min. CC used KSK SG (50–150 μm fraction, Sorbpolimer). Solvents were purified and dried as usual [15]. Elemental analyses agreed with those calculated. The plant raw material was roots of wild *P. anomala* (Altai). Paeoniflorin was isolated from ground peony roots by the literature method [6], $[\alpha]_D^{20}$ –15° (*c* 1.0, MeOH) (lit. [6] $[\alpha]_D^{20}$ –15.6° (*c* 4.5, EtOH).

Synthesis of Paeoniflorin Methyl Ethers. A solution of **1** (320 mg, 0.7 mmol) in MeOH (10 mL) was treated with KU-2-8 (H^+) (0.8 g) and refluxed for 2 h. The resin was filtered off and rinsed with MeOH. The filtrate was evaporated to afford a mixture of **2** and **3** (296 mg, 90%) that was separated by CC over SG with gradient elution by $CHCl_3$–EtOH (200:1→10:1).

4-*O*-Methylpaeoniflorin (2). Yield 132 mg (40%) (amorphous compound). R_f 0.28 (C_6H_6–EtOH, 5:1), $[\alpha]_D^{20}$ –13° (*c* 0.04, EtOH). ^1H NMR spectrum (300 MHz, Me_2CO-d_6, δ, ppm, J/Hz): 8.02 (2H, d, J = 7.0, H-2″, 6″), 7.60 (1H, t, J = 7.0,

H-4″), 7.50 (2H, t, J = 7.0, H-3″, 5″), 5.40 (1H, s, H-9), 5.09 (1H, m, H-4′), 4.75–4.60 (7H, m, H-1′, 2′, 3′, 6″, 8), 3.31 (3H, s, OCH_3), 2.90–2.10 (5H, m, H-5, 6, 3), 1.40 (3H, s, CH_3). ^{13}C NMR spectrum (75.5 MHz, Me_2CO-d_6, δ, ppm): 167.11 (C-7″), 146.12, 134.07, 130.80, 130.29, 129.40, 129.20 (C-1″–6″), 109.75 (C-4), 101.56 (C-9), 99.45 (C-1′), 88.18 (C-1), 86.96 (C-2), 77.81 (C-5′), 77.31 (C-3′), 74.67 (C-2′), 71.41 (C-4′), 55.70 (C-7), 63.65 (C-6′), 62.67 (C-8), 51.93 (OCH_3), 49.27 (C-5), 47.77 (C-3), 23.16 (C-6), 19.58 (C-10), *m/z* $[M + H]^+$ 495. Calcd for $C_{24}H_{30}O_{11}$, 494.5 $[M]^+$.

4-Oxo-9-*O*-methylpaeoniflorin (3). Yield 138 mg (42%) (amorphous compound). R_f 0.25 (C_6H_6–EtOH, 5:1); 0.34 ($CHCl_3$–EtOH, 5:1). $[\alpha]_D^{20}$ –40° (*c* 0.06, MeOH). ^1H NMR spectrum (500 MHz, CD_3OD, δ, ppm, J/Hz): 8.03 (2H, d, J = 7.8, H-2″, 6″), 7.60 (1H, t, J = 7.8, H-4″), 7.47 (2H, t, J = 7.8, H-3″, 5″), 5.46 (1H, m, H-5′), 4.81 (1H, d, J = 11.8, H-1′), 4.75 (2H, m, H-6′), 4.71, 4.55 (2H, both d, J = 8.3, H-8), 3.90 (1H, t, J = 10.5, H-3′), 3.63 (1H, dd, J = 10.5, 5.7, H-4′), 3.40 (2H, m, H-2′, 5′), 3.34 (3H, s, OCH_3), 2.96 (2H, m, H-3), 2.93 (1H, d, J = 8.1, H-5), 2.50 (2H, m, H-6), 1.53 (3H, s, CH_3). ^{13}C NMR spectrum (125 MHz, CD_3OD, δ, ppm): 207.58 (C-4), 165.96 (C-7″), 132.48 (C-4″), 129.00 (C-1″), 128.64 (C-2″, 6″), 127.70 (C-3″, 5″), 105.57 (C-9), 97.93 (C-1′), 86.56 (C-1), 85.54 (C-2), 76.00 (C-5′), 75.89 (C-3′), 73.00 (C-2′), 69.80 (C-4′), 63.05 (C-7), 61.91 (C-6′), 60.85 (C-8), 53.86 (OCH_3), 50.35 (C-3), 49.52 (C-5), 25.50 (C-6), 18.72 (CH_3), *m/z* $[M + H]^+$ 495. Calcd for $C_{24}H_{30}O_{11}$, 494.5 $[M]^+$.

2,3,4,6-Tetra-*O*-acetyl-4-*O*-methylpaeoniflorin (4). Compound **2** (50 mg, 0.1 mmol) was acetylated overnight by an Ac_2O–Py mixture (1:1, 2 mL) at 20–22°C. The mixture was diluted with cold H_2O. The precipitate was filtered off, rinsed with H_2O, dried, and recrystallized from aqueous EtOH. Yield 52 mg (78%), mp 121–123°C. Lit. [13]: 123–125°C (EtOH). ^1H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 7.95 (2H, d, J = 8.1, H-2″, 6″), 7.53 (1H, t, J = 8.1, H-4″), 7.40 (2H, t, J = 8.1, H-3″, 5″), 5.39 (1H, s, H-9), 5.14 (1H, dd, J = 10.5, 5.4, H-4′), 5.06 (1H, t, J = 10.5, H-3′), 5.01 (1H, d, J = 10.5, H-1′), 4.90 (1H, t, J = 10.5, H-2′), 4.50, 4.31 (2H, both dd, J_1 = 9.2, 5.4, H-6′), 4.44 (2H, m, H-8), 3.58 (1H, m, H-5′), 3.35 (3H, s, $OC\underline{H}_3$), 2.98 (1H, d, J = 6.0, H-5), 2.50 (2H, m, H-6), 2.10 (2H, m, H-3), 1.98, 1.96, 1.93, 1.91 (12H, all s, 4OAc), 1.18 (3H, s, CH_3). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 170.37, 170.21, 169.40, 169.31 (each C=O), 166.35 (C-7″), 133.50 (C-4″), 129.67 (C-2″, 6″), 129.35 (C-1″), 128.62 (C-3″, 5″), 107.66 (C-4), 101.06 (C-9), 96.31 (C-1′), 87.61 (C-1), 85.89 (C-2), 72.85 (C-3′), 71.92 (C-5′), 71.73 (C-2′), 71.36 (C-7), 68.26 (C-4′), 62.87 (C-6′), 61.36 (C-8), 51.45 (OCH_3), 48.66 (C-5), 46.73 (C-3), 26.18 (C-6), 20.70, 20.57, 20.56, 20.32, 19.10 (4 $\underline{C}H_3CO$, CH_3). $C_{32}H_{38}O_{15}$, [M] 662.6.

2,3,4,6-Tetra-*O*-acetyl-4-oxo-9-*O*-methylpaeoniflorin (5) was prepared analogously to **4**. Yield 53 mg (79%). ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 8.02 (2H, d, J = 6.5, H-2″, 6″), 7.59 (1H, d, J = 7.0, H-4″), 7.46, 7.34 (2H, s, H-3″, 5″), 5.13–4.96 (3H, m, H-2′, 3′, 4′), 4.76 (1H, d, J = 8.7, H-1′), 4.52 (1H, s, H-9), 4.17, 3.66 (5H, m, H-8, 6′, 5′), 3.35 (3H, s, $OC\underline{H}_3$), 3.05 (1H, d, J = 7.2, H-5), 2.65–2.28 (4H, m, H-3, 6), 2.09, 2.05, 2.03, 1.99 (12H, all s, 4 $COC\underline{H}_3$), 1.25 (3H, s, CH_3). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 204.90 (C-4), 170.32, 170.17, 169.37, 169.28 (4 $CH_3\underline{C}O$), 166.38 (C-7″), 133.42 (C-4″), 129.71, 129.66 (C-2″, 6″), 128.90 (C-1″), 128.61, 128.31 (C-3″, 5″), 105.84 (C-9), 96.19 (C-1′), 87.83 (C-1), 85.44 (C-2), 72.87 (C-3′), 71.96 (C-5′), 71.40 (C-2′), 68.40 (C-4′), 62.15 (C-8), 61.98 (C-6′), 55.67 (C-7), 51.40 ($O\underline{C}H_3$), 48.68 (C-5), 46.76 (C-3), 29.67 (C-6), 20.66, 2×20.54, 20.31 (4$\underline{C}H_3CO$), 19.10 (CH_3). $C_{32}H_{38}O_{15}$, [M] 662.6.

2,3,4,6-Tetra-*O*-acetyl-4-oxo-9-*O*-ethylpaeoniflorin (6). 1) A solution of **1** (160 mg, 0.35 mmol) in EtOH (5 mL) was treated with KU-2-8 (H^+) (0.5 g) and refluxed for 2 h. The resin was filtered off, rinsed with EtOH, and evaporated to afford a mixture of ethyl ethers (145 mg, 85%) that gave two TLC spots with similar R_f values and could not be separated by CC. ^{13}C NMR spectrum (75.5 MHz, Py-d_5, δ, ppm): 206.05 (C-4), 166.75 (C-7″), 133.16, 2×129.38, 129.06, 2×128.26 (C-1″–6″), 107.56, 105.84, 100.83 (C-4, 9), 96.2 (C-1′), 87.95, 87.36 (C-1), 85.70, 85.38 (C-2), 76.07, 75.55, 73.19, 69.61, 69.46, 63.11, 62.64, 61.36, 55.22, 50.86, 48.34, 46.58, 29.37, 26.23, 22.34, 20.10, 18.97.

2) The mixture of PF ethyl ethers was acetylated by an Ac_2O–Py mixture (1:1, 5 mL) as described above for **4**. The resulting acetate was chromatographed over a column of SG with elution by C_6H_6–EtOH mixtures (300:1, 200:1, 100:1, 50:1) to afford **6** (amorphous compound, 94 mg, 38%). ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 8.02 (2H, d, J = 7.0, H-2″, 6″), 7.59 (1H, d, J = 7.0, H-4″), 7.46 (2H, d, J = 7.0, H-3″, 5″), 5.12–4.96 (3H, m, H-2′, 3′, 4′), 4.78 (1H, d, J = 8.0, H-1′), 4.52 (1H, s, H-9), 4.15, 3.66 (5H, m, H-8, 6′, 5′), 3.35 (2H, m, $OC\underline{H}_2CH_3$), 3.05 (1H, d, J = 7.0, H-5), 2.66–2.30 (4H, m, H-3, 6), 2.09, 2.05, 2.03, 1.99 (12H, all s, $C\underline{H}_3CO$), 1.40 (3H, s, CH_3), 1.35 (3H, t, J = 7.0, ($OCH_2C\underline{H}_3$). ^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 204.87 (C-4), 170.31, 170.16, 169.36, 169.26 (4 $CH_3\underline{C}O$), 166.34 (C-7″), 133.46 (C-4″), 129.67 (C-2″, 6″), 128.61 (C-1″, 3″, 5″), 105.85 (C-9), 96.21 (C-1′), 87.84 (C-1), 85.91 (C-2), 72.90 (C-3′), 71.98 (C-5′), 71.43 (C-2′), 68.35 (C-4′), 62.16 (C-8), 61.99 (C-6′), 55.68 (C-7), 51.40 ($O\underline{C}H_2CH_3$), 48.70 (C-5), 46.79 (C-3), 29.67 (C-6), 26.25, 2×20.55, 20.32, 19.95 (CH_3, 4$\underline{C}H_3CO$). $C_{38}H_{40}O_{15}$, [M] 736.7.

2,3,4,6-Tetra-*O*-acetyl-4-*O*-butylpaeoniflorin (7). 1) Compound **1** (160 mg, 0.35 mmol) in BuOH (5 mL) was treated with KU-2-8 (H^+) (0.5 g) and refluxed for 2 h. The resin was filtered off and rinsed with BuOH. The filtrate was

evaporated to afford a mixture of butyl ethers (142 mg, 80%) that gave two spots on TLC. ^{13}C NMR spectrum (75.5 MHz, CD_3OD, δ, ppm): 210.05 (C-4), 169.56 (C-7″), 134.99, 134.58, 131.63, 131.24, 130.17, 130.11, 129.99 (C-1″–6″), 107.09, 104.85, 102.81, 100.48 (C-4, 9), 89.11, 88.08, 87.83, 78.56, 75.57, 74.12, 72.26, 71.15, 69.77, 69.36, 66.05, 65.82, 64.53, 63.42, 62.25, 56.38, 52.86, 48.75, 45.08, 33.23, 33.07, 32.46, 32.24, 31.25, 30.63, 28.07, 21.28, 20.95, 20.79, 20.16, 14.80, 14.63.

2) The obtained mixture of ethers was acetylated as described above for **6**. The acetates were chromatographed over a column of SG with elution by mixtures of C_6H_6–EtOH (300:1, 200:1, 100:1, 50:1, v/v). Fractions that were pure according to TLC were combined and evaporated to afford **7** (89 mg, 35%) (amorphous compound). ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 8.00 (2H, d, J = 7.9, H-2″, 6″), 7.62 (1H, t, J = 7.9, H-4″), 7.45 (2H, t, J = 7.9, H-3″, 5″), 5.16 (1H, t, J = 9.3, H-3′), 5.05–4.90 (3H, m, H-2′, 4′, 9), 4.77 (1H, d, J = 7.8, H-1′), 4.56, 4.48 (2H, both d, J = 8.0, H-8), 4.16 (1H, d, J = 12.3, H-6′$_a$). 4.10 (1H, dd, J = 12.3, 5.6, H-6′$_b$), 3.65 (1H, m, H-5′), 3.02 (1H, d, J = 7.5, H-5), 2.60–2.75 (4H, m, H-3, 6), 2.05, 2.03, 2.00, 1.99 (12H, all s, 4 $COCH_3$), 2.07 (1H, m, H-1‴$_a$), 1.96 (1H, m, H-1‴$_b$), 1.42–1.38 (2H, m, H-2‴), 1.40 (3H, s, CH_3), 1.22–1.28 (2H, m, H-3‴), 0.83 (3H, t, J = 7.3, CH_3). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): 204.92 (C-4), 170.34, 170.18, 169.37, 169.29 (4 $\underline{C}OCH_3$), 166.34 (C-7″), 133.45 (C-4″), 129.67, 129.57 (C-2″, 6″), 129.38 (C-1″), 128.61, 128.52 (C-3″, 5″), 96.18 (C-1′), 87.82 (C-1), 85.90 (C-2), 105.83 (C-9), 72.67 (C-3′), 71.95 (C-5′), 71.39 (C-2′), 68.31 (C-4′), 62.15 (C-8), 61.97 (C-6′), 55.68 (C-7), 48.80 (C-5), 48.67 (C-3), 29.68 (C-6), 31.33 (C-1‴), 26.21 (C-2‴), 20.67 (C-3‴), 20.60, 20.57, 20.54, 20.31 (4 $CO\underline{C}H_3$), 19.16, 13.75 (CH_3, C-4″). $C_{40}H_{42}O_{15}$, [M] 762.7.

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