A Convenient Method for the Preparation of N^2-Ethylguanine Nucleosides and Nucleotides

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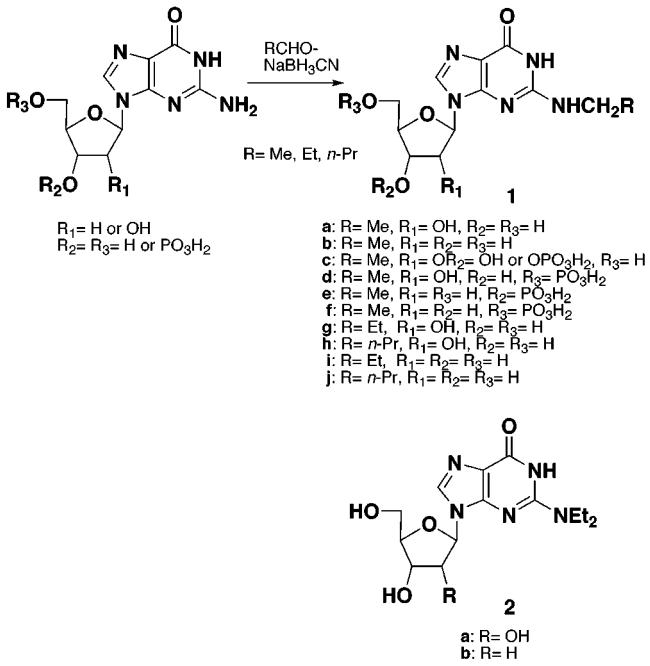
Recently, it has been documented that N^2-ethyl-*d*GTP is efficiently incorporated in place of *d*GTP as a substrate for *Escherichia coli* DNA-polymerase I with a template-primer system to give the corresponding full-length oligodeoxyribonucleotides.[1] And also, an N^2-ethyl-3′-*d*GMP moiety has been reported to be involved in the granulocyte and lymphocyte DNA of alcohol abusers at a high level as the ultimate DNA adduct of acetaldehyde which is formed as a primary product during the metabolic oxidation of ethanol by NAD-dependent alcohol dehydrogenase in the liver.[2] These facts are of interest in relation to the occurrence of cancers of the pharynx, esophagus, and liver in alcohol abusers. To study the molecular mechanisms explaining the carcinogenic effects of the primary metabolite of ethanol, the preparation of a variety of N^2-ethylated guanosine derivatives was required.

The synthetic methods for N^2-ethylguanine nucleosides and nucleotides previously reported involve (1) $NaBH_4$ reduction of N^2-[1-(*p*-tolylthio)-ethyl]guanosine formed in the thermal condensation of guanosine with acetaldehyde in the presence of *p*-thiocresol,[3a] (2) oxidative deprotection of 5-ethyl-4-desmethylwyosine and its 2′-deoxy derivative, prepared by the cyclocondensation of guanosine and 2′-deoxyguanosine with bromoacetone followed by regioselective ethylation,[3b] (3) nucleophilic substitution at the 2-position in 2-bromo-2′-deoxyinosine by ethylamine under thermal conditions,[1] and (4) thermal condensation of 3′-*d*GMP with acetaldehyde followed by $NaBH_4$ reduction.[2d,e] AICA Riboside[3c,d] and the O^6-mesyl-N^2-benzoylguanosine derivative[3e] are also useful as the starting materials for the preparation of N^2-ethylguanosine. These methods, however, required many steps from commercially available starting materials and are inadequate in overall yields for the preparation of the desired N^2-ethylguanosine derivatives.

We now report that the reductive ethylation using an acetaldehyde−$NaBH_3CN$ system in aqueous methanol and subsequent purification with a reversed-phase column at atmospheric pressure is a convenient method for the preparation of a variety of N^2-ethylguanine nucleosides and nucleotides. Characteristics of this synthetic method are the use of commercially available starting materials and the reactions proceeding efficiently even without any protection of the functional groups in the sugar moiety.

Scheme 1



A mixture of guanosine and excess acetaldehyde was heated at 50 °C for 2 days in aqueous methanol containing $NaBH_3CN$. After pH adjustment to pH 4, chromatographic separation of the reaction mixture with the reversed-phase column afforded N^2-ethylguanosine (**1a**) in 71% yield, together with the unchanged guanosine (13%) and N^2,N^2-diethylguanosine (**2a**) (10%). Analogous results were obtained using neutral or alkaline buffered solution in place of the aqueous methanol. On the other hand, the use of acidic buffered solution as the solvent or the use of $NaBH_4$ in place of $NaBH_3CN$ as the reducing agent caused a decrease in the formation of (**1a**) (27−36%) but recovery of most of the starting guanosine even after prolonged reaction times, e.g., 1 week. The structure of (**1a**) was confirmed by comparison with the ^{1}H NMR spectral data previously reported.[2a,3a,b] For example, its ^{1}H NMR spectrum showed a broad triplet signal assignable to the NH group at δ 6.35 (1H, J = 5 Hz) ppm and characteristic signals for the N^2-ethyl group at δ 3.28 (2H, br dq, J = 5, 7, and 14 Hz) and 1.12 (3H, t, J = 7 Hz) ppm. In a similar manner, N^2-ethyl-2′-deoxyguanosine (**1b**),[2c−e,3b] N^2-ethyl-3′(and/or 2′)-GMP (**1c**), N^2-ethyl-5′-GMP (**1d**), N^2-ethyl-3′-*d*GMP (**1e**),[2e] and N^2-ethyl-5′-*d*GMP (**1f**) [1] were obtained in high conversion yields. The present methodology was applicable to the syntheses of other N^2-alkylated guanosines, i.e., N^2-*n*-propylguanosine (**1g**), N^2-*n*-butylguanosine (**1h**),[2b] N^2-*n*-propyl-2′-deoxyguanosine (**1i**), and N^2-*n*-butyl-2′-deoxyguanosine (**1j**). The structural proofs of the N^2-alkylated guanosines (**1b**−**j** and **2a**,**b**) rest upon their spectral data (see Experimental Section).

The direct alkylations of guanosine derivatives using alkyl halides and diazoalkanes have been known to occur

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at the N_1- or N_7-position of the guanine ring.[4] The present method is based on the thermal condensation of the aldehydes with the exocyclic amino group in the guanine ring and subsequent reduction of the resulting imino group by a moderately active reducing agent. It should be noted that no detectable formation of any products were observed in the reactions of adenosine, cytidine, thymidine, and uridine with acetaldehyde in the presence of $NaBH_3CN$ under the conditions employed, suggesting that the present method is, in principle, applicable to the regioselective modification of guanine residues in oligonucleotides.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were obtained at 400 MHz. Column chromatography was performed with Sep-Pak [Waters, Vac 35 cm^3 (10 g), C18 Cartridges]. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

Preparation of N^2-Ethylguanosine Derivatives (1). General Procedure. To a suspension of the appropriate guanosine derivative (Sigma, >98% purity) (0.05 mmol) and $NaBH_3CN$ (Aldrich, 95% purity) (20 mg, 0.30 mmol) in 50% aqueous methanol (3 mL) was added acetaldehyde (Nacalai tesque, >95% purity) (100 μL, 1.7 mmol) in one portion, and the mixture was heated at 50 °C for 2 days in a test tube equipped with an argon balloon. After removal of the solvent under reduced pressure, the residue was dissolved in water (3 mL) and acidified to pH 4 with 1 N HCl. The resulting solution was subjected to the reversed-phase column eluting with 0, 10, 20, 30, 40, and 50% methanol-containing water (each 50 mL). The UV-positive fractions were collected, evaporated to dryness, and triturated with diethyl ether to obtain the desired products (**1**) as a powder in a pure state.

***N*^{2}-Ethylguanosine (1a):** from fractions eluted with 30% methanol-containing water; 11.1 mg (71% yield) [with recovery of the starting guanosine (1.8 mg, 13%), together with N^2,N^2-diethylguanosine (**2a**) (1.7 mg, 10%)]; mp 237−239 °C (dec.) (lit.[3b] mp 229−230 °C); IR (KBr) 1686, 1610 cm^{-1}; UV (ϵ) λ_{max} 275 (sh, 8.6×10^3), 254 (1.5×10^4) nM in H_2O; ^{1}H NMR (DMSO-d_6) δ 1.12 (3H, t, J = 7 Hz), 3.28 (2H, br dq, J = 5, 7, and 14 Hz), 3.49 (1H, br dq, J = 5, 5, and 12 Hz), 3.58 (1H, dq, J = 4, 5, and 12 Hz), 3.86 (1H, br dt, J = 4 and 4 Hz), 4.10 (1H, br dq, J = 3, 4, and 5 Hz), 4.50 (1H, br dq, J = 5, 5, and 6 Hz), 4.90 (1H, br t, J = 5 Hz), 5.13 (1H, br d, J = 5 Hz), 5.35 (1H, br d, J = 6 Hz), 5.69 (1H, d, J = 6 Hz), 6.35 (1H, br t, J = 5 Hz), 7.90 (1H, s), 10.51 (1H, br); HR-FAB MS m/z [M + H]$^+$ 312.1306 (calcd for $C_{12}H_{18}N_5O_5$ [M + H]$^+$ 312.1308).

For N^2,N^2-diethylguanosine (**2a**): from fractions eluted with 40% methanol-containing water; mp 118−120 °C; IR (KBr) 1686, 1588 cm^{-1}; UV (ϵ) λ_{max} 280 (sh, 7.9×10^3), 261 (1.5×10^4) nM in H_2O; ^{1}H NMR (DMSO-d_6) δ 1.10 (6H, t, J = 7 Hz), 3.51 (4H, m), 3.55 (2H, m), 3.84 (1H, dt, J = 4 and 4 Hz), 4.09 (1H, br dt, J = 4, 5, and 5 Hz), 4.50 (1H, br q, J = 5 and 6 Hz), 4.90 (1H, br t, J = 5 Hz), 5.13 (1H, br d, J = 5 Hz), 5.35 (1H, br d, J = 6 Hz), 5.67 (1H, d, J = 6 Hz), 7.90 (1H, s), 10.60 (1H, br); HR-FAB MS m/z [M + H]$^+$ 340.1624 (calcd for $C_{14}H_{22}N_5O_5$ [M + H]$^+$ 340.1621).

***N*^{2}-Ethyl-2′-deoxyguanosine (1b):** from fractions eluted with 30% methanol-containing water; 11.8 mg (80% yield) [with recovery of the starting 2′-deoxyguanosine (1.1 mg, 8%), together with N^2,N^2-diethyl-2′-deoxyguanosine (**2b**) (1.3 mg, 8%)]; mp 240−242 °C (dec.) (lit.[3b] 236−237 °C); IR (KBr) 1692, 1606 cm^{-1}; UV (ϵ) λ_{max} 275 (sh, 8.9×10^3), 254 (1.5×10^4) nM in H_2O; ^{1}H NMR (DMSO-d_6) δ 1.12 (3H, t, J = 7 Hz), 2.18 and 2.61 (each 1H, each m), 3.28 (2H, br q, J = 7 and 14 Hz), 3.46 (1H, br dq, J = 5, 6, and 12 Hz), 3.54 (1H, br dq, J = 4, 5, and 12 Hz), 3.80 (1H, m), 4.34 (1H, m), 4.85 (1H, br t, J = 5 Hz), 5.26 (1H, br d, J = 4 Hz), 6.14 (1H, q, J = 6 and 7 Hz), 6.33 (1H, br t, J = 5 Hz), 7.88 (1H, s), 10.48 (1H, br); HR-FAB MS m/z [M + H]$^+$ 296.1353 (calcd for $C_{12}H_{18}N_5O_4$ [M + H]$^+$ 296.1359).

For N^2,N^2-diethyl-2′-deoxyguanosine (**2b**): from fractions eluted with 40% methanol-containing water; mp 103−105 °C; IR (KBr) 1685, 1585 cm^{-1}; UV (ϵ) λ_{max} 280 (sh, 7.6×10^3), 261 (1.5×10^4) nM in H_2O; ^{1}H NMR (DMSO-d_6) δ 1.10 (6H, t, J = 7 Hz), 2.18 and 2.61 (each 1H, each m), 3.52 (6H, m), 3.79 (1H, m), 4.33 (1H, m), 4.85 (1H, br t, J = 6 Hz), 5.26 (1H, br d, J = 4 Hz), 6.12 (1H, t, J = 7 Hz), 7.88 (1H, s), 10.59 (1H, br); HR-FAB MS m/z [M + H]$^+$ 324.1676 (calcd for $C_{14}H_{22}N_5O_4$ [M + H]$^+$ 324.1672).

***N*^{2}-Ethylguanosine-3′(and/or 2′)-phosphate (1c):** from fractions eluted with 10−20% methanol-containing water; 13.1 mg (66% yield) [with recovery of the starting 3′-GMP (2.4 mg, 13%); the ratios of 2′- and 3′-isomers were not determined]; IR (KBr) 1688, 1612 cm^{-1}; UV (ϵ) λ_{max} 275 (sh, 8.2×10^3), 254 (1.5×10^4) nM in H_2O; ^{1}H NMR (DMSO-d_6) δ 1.12 (3H, t, J = 7 Hz), 3.29 (2H, br dq, J = 5, 7, and 14 Hz), 3.51 and 3.57 (each 1H, each Q, each J = 4 and 12 Hz), 3.95 (1H, m), 4.53 (1H, m), 4.54 (1H, br), 5.69 (1H, br d, J = 6 Hz), 6.41 (1H, br t), 7.90 (1H, s), 10.53 (1H, br); HR-FAB MS m/z [M + H]$^+$ 392.0966 (calcd for $C_{12}H_{19}N_5O_8P$ [M + H]$^+$ 392.0972).

***N*^{2}-Ethylguanosine-5′-phosphate (1d):** from fractions eluted with 10−20% methanol-containing water; 14.4 mg (73% yield) [with recovery of the starting 5′-GMP (2.2 mg, 12%)]; mp 260 °C (dec.); IR (KBr) 1685, 1611 cm^{-1}; UV (ϵ) λ_{max} 275 (sh, 8.9×10^3), 254 (1.5×10^4) nM in H_2O; ^{1}H NMR (DMSO-d_6−D_2O) δ 1.09 (3H, t, J = 7 Hz), 3.26 (2H, q, J = 7 and 14 Hz), 3.76 (2H, m), 4.00 (1H, m), 4.13 (1H, q, J = 3 and 4 Hz), 4.53 (1H, t, J = 5 Hz), 5.70 (1H, d, J = 7 Hz), 7.99 (1H, s); HR-FAB MS m/z [M + H]$^+$ 392.0980 (calcd for $C_{12}H_{19}N_5O_8P$ [M + H]$^+$ 392.0971).

***N*^{2}-Ethyl-2′-deoxyguanosine-3′-phosphate (1e):** from fractions eluted with 10−20% methanol-containing water; 12.2 mg (65% yield) [with recovery of the starting 3′-*d*GMP (3.0 mg, 17%)]; mp 190−192 °C (dec.); IR (KBr) 1688, 1610 cm^{-1}; UV (ϵ) λ_{max} 274 (sh, 1.1×10^4), 250 (1.5×10^4) nM in H_2O; ^{1}H NMR (DMSO-d_6) δ 1.16 (3H, t, J = 7 Hz), 2.48 and 2.65 (each 1H, each m), 3.29 (2H, m), 3.54 (2H, m), 4.01 (1H, m), 4.80 (1H, br), 6.11 (1H, t, J = 7 Hz), 6.42 (1H, br t), 7.88 (1H, s), 10.54 (1H, br); HR-FAB MS m/z [M + H]$^+$ 376.1031 (calcd for $C_{12}H_{19}N_5O_7P$ [M + H]$^+$ 376.1022).

***N*^{2}-Ethyl-2′-deoxyguanosine-5′-phosphate (1f):** from fractions eluted with 10−20% methanol-containing water; 14.2 mg (76% yield) [with recovery of the starting 5′-*d*GMP (3.0 mg, 17%)]; mp 267−270 °C (dec.); IR (KBr) 1689, 1615 cm^{-1}; UV (ϵ) λ_{max} 275 (sh, 7.8×10^3), 255 (1.5×10^4) nM in H_2O; ^{1}H NMR (DMSO-d_6) δ 1.12 (3H, t, J = 7 Hz), 2.17 and 2.61 (each 1H, each m), 3.26 (2H, br q, J = 7 and 14 Hz), 3.76 (2H, m), 3.86 (1H, m), 4.46 (1H, m), 6.13 (1H, t, J = 7 Hz), 6.45 (1H, br), 7.92 (1H, s), 10.52 (1H, br); HR-FAB MS m/z [M + H]$^+$ 376.1022 (calcd for C $C_{12}H_{19}N_5O_7P$ [M + H]$^+$ 376.1022).

***N*^{2}-*n*-Propylguanosine (1g):** from fractions eluted with 40% methanol-containing water; 13.2 mg (81% yield) [with recovery of the starting guanosine (1.8 mg, 13%)]; mp 129−132 °C; IR (KBr) 1686, 1610 cm^{-1}; UV (ϵ) λ_{max} 275 (sh, 8.8×10^3), 255 (1.5×10^4) nM in H_2O; ^{1}H NMR (DMSO-d_6) δ 0.89 (3H, t, J = 7 Hz), 1.53 (2H, q, J = 7 and 14 Hz), 3.22 (2H, br dt, J = 6, 7, and 7 Hz), 3.50 (1H, br dq, J = 5, 5, and 12 Hz), 3.60 (1H, br dq, J = 4, 5, and 12 Hz), 3.86 (1H, dt, J = 4 and 4 Hz), 4.09 (1H, dt, J = 4, 5, and 5 Hz), 4.50 (1H, dt, J = 5, 6, and 6 Hz), 4.90 (1H, br t, J = 5 Hz), 5.13 (1H, br d, J = 5 Hz), 5.37 (1H, br d, J = 6 Hz), 5.69 (1H, d, J = 6 Hz), 6.38 (1H, br t, J = 5 Hz), 7.89 (1H, s), 10.44 (1H, br); HR-FAB MS m/z [M + H]$^+$ 326.1459 (calcd for $C_{13}H_{20}N_5O_5$ [M + H]$^+$ 326.1464).

***N*^{2}-*n*-Butylguanosine (1h):** from fractions eluted with 40% methanol-containing water; 13.6 mg (80% yield) [with recovery of the starting guanosine (1.1 mg, 8%)]; mp 121−122 °C (lit.[2b] mp 188−190 °C); IR (KBr) 1686, 1610 cm^{-1}; UV (ϵ) λ_{max} 275 (sh, 8.9×10^3), 254 (1.5×10^4) nM in H_2O; ^{1}H NMR (DMSO-d_6) δ 0.90 (3H, t, J = 7 Hz), 1.33 (2H, m), 1.50 (2H, m), 3.26 (2H, br dt, J = 5, 7, and 7 Hz), 3.50 and 3.60 (each 1H, each br dq, each J = 4, 5, and 12 Hz), 3.86 (1H, br dt, J = 4 and 4 Hz), 4.09 (1H, br dq, J = 3, 4, and 5 Hz), 4.50 (1H, br dt, J = 5, 6, and 6 Hz), 4.90 (1H, br t, J = 5 Hz), 5.13 (1H, br d, J = 4 Hz), 5.37 (1H, br d, J = 6 Hz), 5.69 (1H, d, J = 6 Hz), 6.37 (1H, br t), 7.89 (1H, s), 10.42 (1H, br); HR-FAB MS m/z [M + H]$^+$ 340.1614 (calcd for $C_{14}H_{22}N_5O_5$ [M + H]$^+$ 340.1621).

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***N*²-*n*-Propyl-2′-deoxyguanosine (1i)**: from fractions eluted with 40% methanol-containing water; 10.5 mg (68% yield) [with recovery of the starting 2′-deoxyguanosine (3.9 mg, 29%)]; mp 252−255 °C (dec.); IR (KBr) 1687, 1610 cm^{-1}; UV (ϵ) λ_{max} 275 (sh, 8.8×10^3), 254 (1.5×10^4) nM in H_2O; ^1H NMR (DMSO-d_6) δ 0.89 (3H, t, J = 7 Hz), 1.53 (2H, m), 2.18 and 2.62 (each 1H, each m), 3.22 (2H, br dt, J = 5, 7, and 7 Hz), 3.47 (1H, br q, J = 5 and 12 Hz), 3.55 (1H, br q, J = 4 and 12 Hz), 3.80 (1H, dq, J = 4, 4, and 5 Hz), 4.34 (1H, m), 4.85 (1H, br), 5.26 (1H, br d, J = 3 Hz), 6.13 (1H, t, J = 7 Hz), 6.38 (1H, br t, J = 5 Hz), 7.88 (1H, s), 10.43 (1H, br); HR-FAB MS m/z $[M + H]^+$ 310.1506 (calcd for $C_{13}H_{20}N_5O_4$ $[M + H]^+$ 310.1515).

***N*²-*n*-Butyl-2′-deoxyguanosine (1j):** from fractions eluted with 40% methanol-containing water; 11.8 mg (73% yield) [with recovery of the starting 2′-deoxyguanosine (2.7 mg, 20%)]; mp 285−287 °C (dec.); IR (KBr) 1687, 1610 cm^{-1}; UV (ϵ) λ_{max} 275 (sh, 8.9×10^3), 254 (1.5×10^4) nM in H_2O; ^1H NMR (DMSO-d_6) δ 0.90 (3H, t, J = 7 Hz), 1.31 (2H, m), 1.50 (2H, m), 2.18 and 2.62 (each 1H, each m), 3.26 (2H, br dt, J = 5, 7, and 7 Hz), 3.48 and 3.55 (each 1H, each br dq, each J = 5, 5, and 12 Hz), 3.80 (1H, br dq, J = 3, 4, and 5 Hz), 4.33 (1H, m), 4.85 (1H, br t, J = 5 Hz), 5.26 (1H, br d, J = 4 Hz), 6.13 (1H, t, J = 7 Hz), 6.35 (1H, br t, J = 5 Hz), 7.88 (1H, s), 10.42 (1H, br); HR-FAB MS m/z $[M + H]^+$ 324.1664 (calcd for $C_{14}H_{22}N_5O_4$ $[M + H]^+$ 324.1672).

pH Dependency during the Reductive *N*²-Ethylation of Guanosine Using the Acetaldehyde−$NaBH_3CN$ System. The reactions of guanosine (0.05 mmol) with acetaldehyde (1.7 mmol) in the pH range of 4.25−9.05 of 0.5-mol phosphate buffers (3 mL) containing $NaBH_3CN$ (0.30 mmol) were carried out under the conditions described in the general procedure. TLC densitometric analyses of the reaction mixtures with the developing solvent chloroform−methanol−acetic acid (16/6/3) showed the presence of guanosine, N^2-ethylguanosine (**1a**), and/or N^2,N^2-diethylguanosine (**2a**) in the following yields: guanosine (60%) and **1a** (36%) in pH 4.25; guanosine (62%) and **1a** (26%) in pH 5.06; guanosine (53%) and **1a** (45%) in pH 6.00; guanosine (10%), **1a** (71%), and **2a** (9%) in pH 7.03; **1a** (73%) and **2a** (19%) in pH 7.96; **1a** (75%) and **2a** (18%) in pH 9.05.

Effect of the $NaBH_3CN$ Quantity on the Reductive *N*²-Ethylation of Guanosine. The reaction of guanosine (0.05 mmol) with acetaldehyde (1.7 mmol) in the presence of $NaBH_3CN$ [10 mg (0.15 mmol), 20 mg (0.30 mmol), 30 mg (0.45 mmol), or 40 mg (0.60 mmol)] was carried out in aqueous methanol (3 mL) under the conditions described in the general procedure. TLC densitometric analyses of the reaction mixtures with the developing solvent chloroform−methanol−acetic acid (16/6/3) showed the presence of guanosine, **1a**, and **2a** in the following yields: guanosine (23%), **1a** (72%), and **2a** (5%) in the case of $NaBH_3CN$ (3 equiv); guanosine (15%), **1a** (71%), and **2a** (10%) in the case of $NaBH_3CN$ (6 equiv); guanosine (9%), **1a** (72%), and **2a** (15%) in the case of $NaBH_3CN$ (9 equiv); guanosine (9%), **1a** (73%), and **2a** (14%) in the case of $NaBH_3CN$ (12 equiv).

Supporting Information Available: Spectral data and spectra for compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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