Synthesis of an Aziridinomitosene Analog

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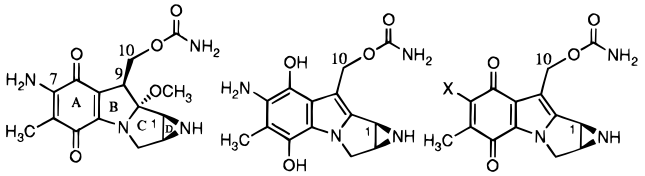
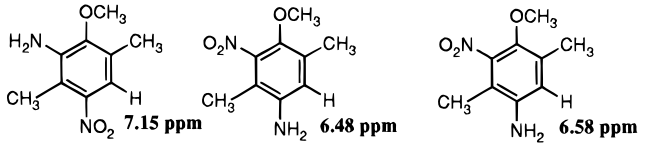
Mitomycin C (**1**) is a potent antitumor agent, which is activated under reductive conditions. Alkylation of the 2-amino group of guanine results in the formation of both monoalkylated adducts and DNA cross-links (alkylation of two adjacent guanine residues).[1] The active intermediate generated by reduction of mitomycin C is believed to be 7-aminoleucoaziridinomitosene (**2**).[2] Several 7-substituted 1,2-aziridinomitosenes **3** have shown activity comparable to mitomycin C against various tumor model systems.[3]



Mitomycin C (1) **2** **3**

As part of an effort toward new approaches to aziridinomitosenes, we developed a short synthesis of 2-(alkoxycarbonyl)-4-aminoindoles. Nitration of 2,5-dimethylanisole with nitronium tetrafluoroborate gives a 75% yield of 3,6-dimethyl-2,4-dinitroanisole (**4**). Our original goal was to selectively reduce the *o*-nitro group of **4** as a first step in the synthesis of a hexasubstituted benzene. The *o*-nitro group of 2,4-dinitroanisole has been selectively reduced with sodium sulfide.[4] Treatment of **4** with sodium sulfide resulted in a nitroaniline whose aromatic hydrogen appeared at 6.58 ppm. The chemical shifts of the aromatic hydrogens of multisubstituted benzenes can be predicted.[5] The predicted value for 2-methoxy-3,6-dimethyl-5-nitroaniline (reduction of the ortho group) is 7.15 ppm, whereas the value for 4-methoxy-2,5-dimethyl-3-nitroaniline (reduction of the para group) is 6.48 ppm.

Predicted Values of Chemical Shifts **Actual Value**



7.15 ppm **6.48 ppm** **6.58 ppm**

Therefore it appeared that the less hindered *p*-nitro group had been reduced to the corresponding amino group. We quickly realized that this result opened up an expedient route to the 4-aminoindole **6**. Reaction of **4** with diethyl oxalate in the presence of potassium *tert*-butoxide results in the precipitation of the potassium salt **5a** (plus a minor amount of **5b**). Filtration of **5**, followed by reduction with zinc in ethanolic HCl[6] produced **6a** contaminated with a minor amount of **6b**. Indole **8**, which is the isomer that would result if the *o*-nitro group is reduced first, was not detected. Indole **6a** has two aromatic singlets at 6.66 and 7.14 ppm. A 2D correlated spectroscopy (COSY) experiment revealed that the peak at 6.66 ppm is adjacent to the 6-methyl group.[7] Irradiation of the NH showed an NOE enhancement of the 6.66 ppm peak, which indicates formation of **6a** rather than **8**. Furthermore, oxidation with potassium nitrosodisulfonate (Fremy's salt)[8] gives a 90% yield of **7** as identified by ^{1}H NMR and mass spectral data (data not shown). Indoloquinone **7** is thus formed in three steps from 2,5-dimethylanisole and has the correct substitutents on what will become the A ring of mitosene **17**.

When **4** is reacted with dimethyl oxalate, followed by zinc reduction, 4-aminoindole **10** is formed in a 47% yield. Oxidation with Fremy's salt gives a 90% yield of indoloquinone **11**. Reduction of **11** with H_2/10% Pd−C, followed by the addition of triethylamine and *tert*-butyldimethylsilyl triflate results in a 95% yield of **12**. The 2-formylindole **13** was obtained in a 64% yield by reduction of **12** to the corresponding alcohol with diisobutylaluminum hydride (DIBAL), followed by immediate oxidation to the aldehyde with manganese(IV) oxide. Reaction of **13** with dimethylvinylsulfonium iodide in the presence of sodium hydride, followed by ring opening of the resultant tetracyclic epoxide with sodium azide, gives a 65% yield of the tricyclic azido alcohol **14**.[9] The corresponding mesylate **15** is obtained in a 90% yield. Treatment of **15** with pyridinium chlorochromate (PCC) in dichloromethane gives a 99% yield of indoloquinone **16**.[10] Reaction with triphenylphosphine results in a 75% yield of **17**.

Experimental Section

General. Elemental analyses were processed by Quantitative Technologies, Inc, Whitehouse, NJ, and National Chemical Consulting, Tenafly, NJ. Mass spectra were processed by the University of California Mass Spectroscopy Facility, Riverside, CA, and the Center for Advanced Food Technology, Rutgers University, New Brunswick, NJ.

Dichloromethane and tetrahydrofuran were distilled from calcium hydride. Anhydrous methanol, toluene, ethyl ether, and 1.0 M hydrogen chloride in ethyl ether were obtained from Aldrich Chemical Co.

3,6-Dimethyl-2,4-dinitroanisole (4). A total of 720 mg (5.29 mmol) of 2,5- dimethylanisole was added to 10 mL of anhydrous CH_2Cl_2 in an ice bath under a N_2 atmosphere. To the solution, 23.3 mL of NO_2BF_4 (0.5 M in sulfolane) was slowly added over a period of 1 h. The mixture was allowed to warm to room temperature and stirred for about 26 h. A total of 150 mL of benzene was added. The mixture was washed with 10% $NaHCO_3$ (3 × 20 mL) and brine (3 × 20 mL). The phases were separated, and the organic layer was dried over $MgSO_4$, evaporated under reduced pressure, and then purified by flash

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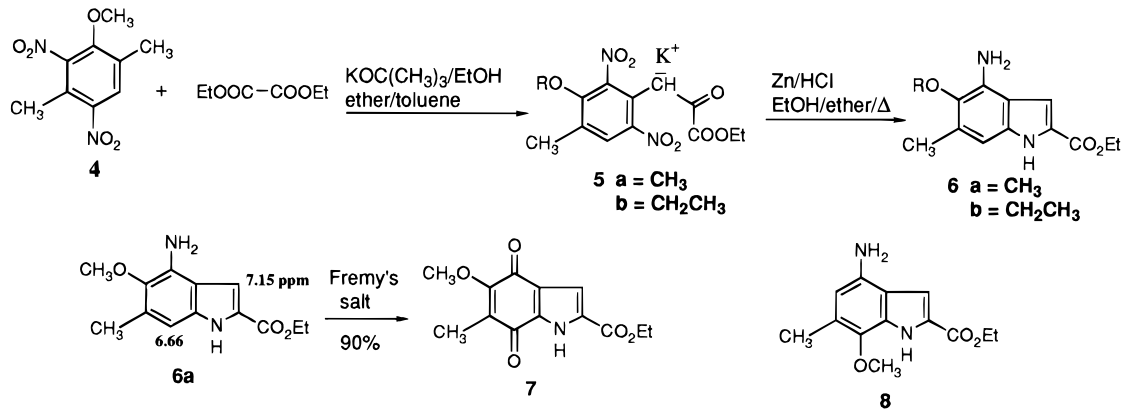
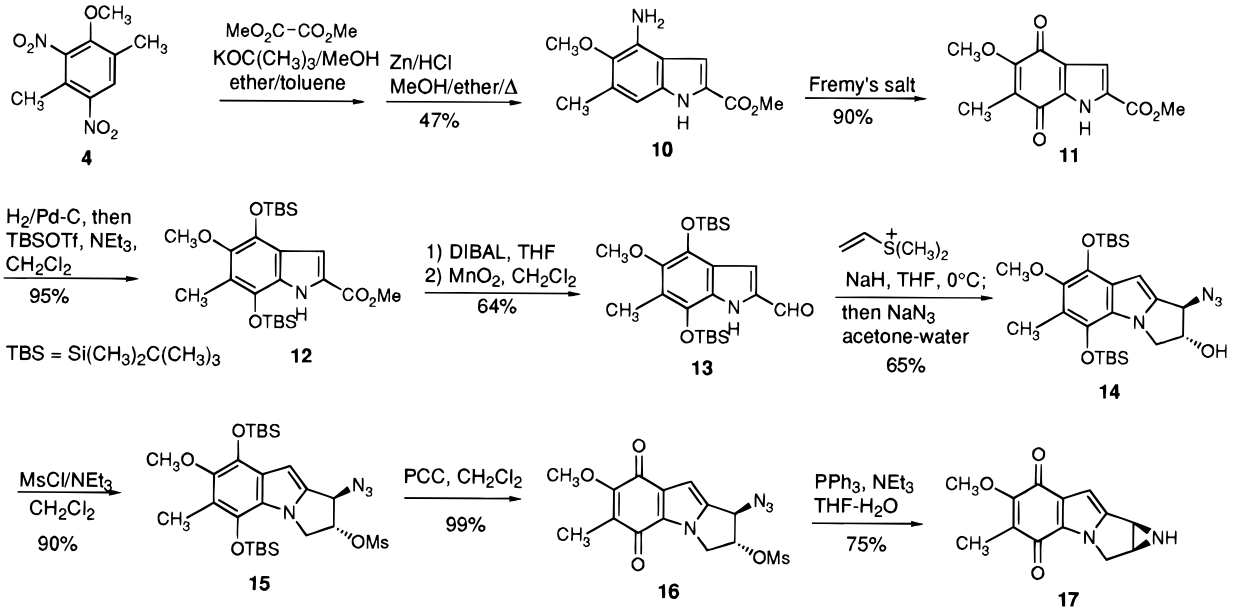
Scheme 1



Scheme 2



chromatography (1:1 CH_2Cl_2:petroleum ether). A total of 896 mg was obtained (75%). Mp 63−64 °C. ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H), 2.44 (s, 3H), 3.91 (s, 3H), 7.95 (s, 1H). MS (EI) m/z 226 (M^+). Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.38. Found: C, 47.75; H, 4.43; N, 12.41.

4-Amino-5-methoxy-2-(methoxycarbonyl)-6-methylindole (10). A solution of 560 mg (5 mmol) potassium *tert*-butoxide in 1 mL of methanol and 20 mL of ether was added to a solution of 565 mg (2.5 mmol) of **4**. A total of 2.36 g (20 mmol) of dimethyl oxalate in 15 mL of toluene was added dropwise over a period of 1 h at 0 °C (ice bath). A reddish precipitate was obtained. The mixture was allowed to warm to room temperature and stirred for 2 days. The reddish salt was collected by suction filtration and washed with ethyl ether (3 × 30 mL) and then petroleum ether (3 × 30 mL). The solid was transferred into a 100-mL round-bottom flask, and then 10 mL of methanol and 1.5 g of zinc powder were added. The suspension was treated with 30 mL of 1.0 M HCl in ether and then refluxed for about 24 h. The reaction mixture was filtered through Celite, the Celite pad washed with CH_2Cl_2, and the solvent removed under reduced pressure. The product was purified by flash chromatography (2:1 petroleum ether:ethyl acetate). A total of 275 mg was obtained (47%). Mp 125.5−126 °C. ^{1}H NMR ($CDCl_3$) δ: 2.36 (s, 3H), 3.75 (s, 3H), 3.90 (s, 3H), 4.12 (br s, 2H), 6.58 (s, 1H), 7.12 (d, 1H, J = 1.2 Hz), 8.80−9.00 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 16.98, 51.84, 59.62, 102.19, 105.80, 116.85, 125.53, 131.09, 132.46, 134.65, 138.23, 162.20. MS (EI) m/z 234 (M^+). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.15; H, 6.02; N, 11.95. Found: C, 61.17; H, 6.12; N, 11.98.

5-Methoxy-2-(methoxycarbonyl)-6-methylindole-4,7-dione (11). A solution of 660 mg (2.4 mmol) of potassium nitrosodisulfonate (Fremy's salt) in 30 mL of pH = 4 phosphate buffer was added to a solution of 150 mg (0.64 mmol) of **10** in 30 mL of ethyl ether. The reaction mixture was stirred for 10 h and then extracted by ether (5 × 30 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (5:2 petroleum ether:ethyl acetate). A total of 144 mg was obtained (90%). Mp 225−226 °C; ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 3H), 3.92 (s, 3H), 4.07 (s, 3H), 7.16 (s, 1H), 9.70−10.20 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 8.66, 52.49, 61.38, 112.39, 123.64. 127.40, 128.79, 132.90, 158.27, 160.55, 178.11, 178.74. MS (EI) m/z 249 (M^+). Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.80; H, 4.42; N, 5.50.

4,7-Bis[(1,1-dimethylethyl)dimethylsilyloxy]-5-methoxy-2-(methoxycarbonyl)-6-methylindole (12). A solution of 130 mg of **11** in 2 mL of THF was stirred with 30 mg of 10% palladium on activated carbon under a hydrogen atmosphere for about 0.5 h, at which point the reaction solution had turned colorless. A total of 400 μL of NEt_3 and 460 μL of *tert*-butyldimethylsilyl trifluoromethanesulfonate was syringed into the reaction flask. The mixture was stirred for 12 h at room temperature and then filtered through a Celite pad. Concentration and purification of the filtrate by column chromatography (6:1 petroleum ether:ether) resulted in a 95% yield of a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 0.16 (s, 6H), 0.17 (s, 6H), 1.06 (s, 9H), 1.09 (s, 9H), 2.22 (s, 3H), 3.68 (s, 3H), 3.90 (s, 3H), 7.14 (d, 1H, J = 2.3 Hz), 8.40−8.60 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: −4.48, −3.77, 10.91, 18.45, 25.90, 51.88, 60.12, 107.05, 120.22, 121.38, 125.47, 128.46, 133.06, 136.26, 142.89, 162.20. MS (EI) m/z 479 (M^+). Anal. Calcd for $C_{24}H_{41}NO_5Si_2$: C, 60.08:H, 8.61; N, 2.92. Found: C, 59.88; H, 8.51; N, 2.85.

4,7-Bis[(1,1-dimethylethyl)dimethylsilyloxy]-5-methoxy-2-formyl-6-methylindole (13). In a 50-mL round-bottom flask, a total of 100 mg (0.21 mmol) of **12** was dissolved in 3 mL of dry THF under a N_2 atmosphere. The solution was cooled to −78 °C (acetone−dry ice bath), and 1.0 mL (1.0 mmol) of 1.0 M DIBAL in THF was added over a period of 1 h. The mixture was stirred for 2 h at −78 °C, quenched with 2 mL of 1 N HCl, and then allowed to warm to room temperature. The reaction mixture was then extracted with CH_2Cl_2 (4 × 10 mL), 1 N HCl (2 × 10 mL), and brine (2 × 10 mL). The organic layer was dried over $MgSO_4$, and filtered, and the solvent volume was reduced to about 10 mL *in vacuo*. A total of 87 mg (1.0 mmol) of MnO_2 was added to the solution, and then the reaction mixture was stirred at room temperature for 10 h. The mixture was filtered through Celite, the filtrate was evaporated under reduced pressure, and the product was purified by flash chromatography (10:1 petroleum ether:ether). A total of 60 mg of a pale yellow oil was obtained (64%). ^{1}H NMR ($CDCl_3$) δ: 0.18 (s, 12H), 1.07 (s, 9H), 1.08 (s, 9H), 2.23 (s, 3H), 3.69 (s, 3H), 7.20 (d, 1H, J = 2.3 Hz), 8.50−8.65 (br s, 1H), 9.73 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: −4.48, −3.72, 11.15, 18.47, 25.92, 60.16, 113.00, 121.62, 122.63, 129.56, 133.29, 134.74, 136.86, 143.11, 181.23. MS (EI) m/z 449 (M^+). Anal. Calcd for $C_{23}H_{39}NO_4Si_2$: C, 61.43; H, 8.74; N, 3.11. Found: C, 61.73; H, 8.63; N, 2.95.

1-Azido-5,8-Bis[(1,1-dimethylethyl)dimethylsilyloxy]-2,3-dihydro-2-hydroxy-7-methoxy-6-methyl-1*H*-pyrrolo-[1,2-*a*]indole (14). In a 100-mL round-botttom flask, a total of 210 mg (0.47 mmol) of **13** and 28 mg (0.93 mmol) of NaH (80% dispersion in mineral oil) was stirred in 150 mL of dry THF under N_2 at 0 °C (ice bath). A total of 122 mg (0.56 mmol) of dimethylvinylsulfonium iodide was added after 20 min, and then the reaction mixture was stirred overnight (about 15 h) at ambient temperature. A total of 260 mg (4 mmol) of NaN_3 in 3 mL of 1:1 acetone:water was added to the reaction mixture, and then the reaction mixture was stirred at room temperature for approximately 12 h. The mixture was evaporated under reduced pressure and then purified by flash chromatography (5:1 CH_2Cl_2:petroleum ether). A total of 158 mg (65%) of a colorless oil was obtained. IR: 2099 (N_3), 3439 (broad, OH) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.16 (s, 6H), 0.17 (s, 6H), 1.02 (s, 9H), 1.05 (s, 9H), 2.19 (s, 3H), 3.68 (s, 3H), 4.17 (dd, 1H, J_1 = 2.0, J_2 = 11.6), 4.46 (dd, 1H, J_1 = 4.8, J_2 = 11.6), 4.65−4.70 (br m, 1H), 4.72 (d, J = 3.0 Hz, 1H), 6.50 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: −4.41, −3.11, 11.00, 18.56, 26.00, 53.13, 60.04, 64.02, 80.30, 95.76, 117.07, 125.24, 125.96, 133.59, 135.68, 136.21, 142.72. Anal. Calcd for $C_{25}H_{42}N_4O_4Si_2$: C, 57.88; H, 8.16. Found: C, 58.14; H, 7.99.

1-Azido-5,8-Bis[(1,1-dimethylethyl)dimethylsilyloxy]-2,3-dihydro-7-methoxy-6-methyl-2-(methanesulfonyloxy)-1*H*-pyrrolo[1,2-*a*]indole (15). A total of 50 mg (0.1 mmol) of **14** was dissolved in 2.0 mL of dry CH_2Cl_2 at 0 °C. Next, 43 μL of triethylamine (0.4 mmol) was added, and then 12 μL (0.2 mmol) of methanesulfonyl chloride. The reaction mixture was stirred about 5 h at room temperature (monitored by TLC), and then 10 mL of ether and 10 mL of water were added. The phases were separated, and the organic layer was washed with 1 N HCl (3 × 10 mL), 5% $NaHCO_3$ (3 × 10 mL), and brine (3 × 10 mL) and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatogrphy (5:2 petroleum ether:CH_2Cl_2). A total of 52 mg of **15** as a colorless oil (90%) was obtained. IR: 2104 (N_3) cm^{-1}. ^{1}H NMR ($CDCl_3$) δSPCLN 0.16 (s, 12H), 1.02 (s, 9H), 1.05 (s, 9H), 2.19 (s, 3H), 3.07 (s, 3H), 3.68 (s, 3H), 4.45 (dd, 1H, J_1 = 2, J_2 = 12), 4.59 (dd, 1H, J_1 = 4.8, J_2 = 12), 5.02 (d, 1H, J = 2), 5.32−5.40 (m, 1H), 6.53 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: −3.92, −2.68, 11.48, 18.56, 25.96, 38.51, 51.20, 60.04, 61.49, 84.71, 95.95, 117.54, 125.11, 126.14, 133.63, 134.82, 135.80, 143.04. HRMS, m/z (M^+, $C_{26}H_{44}N_4O_6SSi_2$) calcd 596.2520, obsd 596.2528. Anal. Calcd for $C_{26}H_{44}N_4O_6SSi_2$: C, 52.32; H, 7.43. Found: C, 52.90; H, 7.39.

1-Azido-2,3-dihydro-7-methoxy-6-methyl-2-(methanesulfonyloxy)-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione (16). A total of 60 mg (0.11 mmol) of **15** was dissolved in 2.0 mL of CH_2Cl_2. A total of 46 mg (0.21mmol) of pyridinium chlorochromate (PCC) was added, and then the mixture was stirred at room temperature for 15 min. The reaction mixture was filtered through Celite and washed with CH_2Cl_2. Concentration and purification of the filtrate by column chromatography (5:1 CH_2Cl_2:ether) gave 36.5 mg (99%) of **16**. IR: 1729 (C=O), 2114 (N_3) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.95 (s, 3H), 3.10 (s, 3H), 4.02 (s, 3H), 4.50 (dd, 1H, J_1 = 1.8, J_2 = 14), 4.63 (dd, 1H, J_1 = 5, J_2 = 14), 5.06 (d, 1H, J = 1.8), 5.40−5.50 (m, 1H), 6.62 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 8.54, 38.72, 51.63, 61.27, 61.63, 84.19, 102.72, 127.85, 128.00, 128.29, 136.46, 157.65, 178.25, 178.73. Anal. Calcd for $C_{14}H_{14}N_4O_6S$: C, 45.90; H, 3.85. Found: C, 45.85; H, 4.02.

1,1a,2,8b-Tetrahydro-6-methoxy-5-methylazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione (17). A total of 40 mg of **16** (0.11 mmol), 32 mg of PPh_3 (0.12 mmol), and 30 μL of NEt_3 (0.22 mmol) was stirred in 2 mL of THF/H_2O (10:1) under N_2 at rt for 10 h. The mixture was evaporated under reduced pressure, and the product was purified by flash chromatography (3:1 ether:acetone) twice to remove all but a trace of triphenylphosphine oxide. The product appeared to be >98% pure by ^{1}H NMR. A total of 20 mg of **17** was obtained as an orange gum (75%). A further purification by flash chromatography (95:5 ethyl acetate:triethylamine) was performed on a 5 mg sample to obtain a ^{13}C NMR spectrum free of triphenylphosphine oxide. The aziridine hydrogen and the hydrogens on carbons 1−3 appear broad in the ^{1}H NMR spectrum of **17**. Carbons 1 and 2 appear to exist in two different isomeric forms in the ^{13}C NMR spectrum. This is presumably because **17** exists as a mixture of invertomers (isomers by inversion at the azirdine center).[2a,11] ^{1}H NMR ($CDCl_3$): δ 1.20−1.25 (m, 1H), 1.94 (s, 3H), 3.20−3.70 (m, 2H), 3.99 (s, 3H), 4.10−4.50 (m, 2H), 6.45 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 8.50, (31.24 and 31.51 for C-2), (38.56 and 40.03 for C-1), 49.82, 61.15, 100.69, 101.09, 127.16, 127.56, 128.13, 157.30, 178.54, 178.63. MS (EI 70 eV) 244 (M^+). MS (DCI): m/z 245 (M + H^+). HRMS (DCI, M + H^+) calcd for $C_{13}H_{13}N_2O_3$: 245.0926; obsd 245.0921.

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