Polycyclic Nitrogen Compounds. Part I. Synthesis of New Heterotricyclic Quinoxalinones with Bridgehead Nitrogen Atoms

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New tricyclic quinoxalinone skeletons with a fully-reduced ring 'C' -1,2,3,3a-tetrahydropyrrolo[1,2-*a*]quinoxalin-4-one (I-II) and 7,8,9,10-tetrahydropyrido[1,2-*a*]quinoxalin-6-one (III-IV) derivatives were obtained by selective hydrogen transfer reductive cyclisation of *N*-(2-nitrophenyl)pyrrolidine-2-carboxylic acid esters and *N*-(2-nitrophenyl)piperidine-2-carboxylic acid esters (VIa,b and VIIIa,b), respectively.

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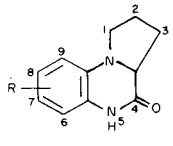
Poly-condensed nitrogen heterocycles have attracted considerable interest because of their importance in chemotherapeutics (1) (2) and their marked activity in many biological systems (3). Heterotricyclic quinoxalines with bridgehead nitrogen atoms having a fully-reduced ring 'C'are relatively few in number. The renewed interest in the use of certain quinoxaline derivatives as drugs (4) and the paucity of literature on such tricyclic quinoxaline systems led us to work out a general and facile method for the synthesis of these ring systems as a continuation of our work on nitrogen tricycles (2).

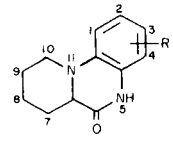
Pyrrolo[1,2-*a*]quinoxaline derivatives were first obtained by Taylor and Hand (5) *via* Diels-Alder reactions of maleic anhydrides with 2-methylquinolines. Cheeseman, *et al.* (6) extended this method for the synthesis of dihydro derivatives using substituted maleic anhydrides like citraconic and phenylmaleic anahydrides and obtained low yields. They highlighted other problems attendant to this synthetic route which included the equilibrium distribution of citraconic anhydride with its itaconic anhydride tautomer resulting in an undesirable side reaction. West, *et al.* (7) recently prepared the benzoquinone derivatives of the pyrroloquinoxalines *via* a modified Cheeseman's method.

Pyrido[1,2-*a*]quinoxalines on the other hand, are not well-known. No definite efforts to obtain them have been reported. Only recently Ames *et al.* (8) obtained pyrido[1,2-*a*]quinoxalin-4-one derivatives by condensation of alkynylquinoxalines with carbanions of diethyl malonate and related compounds.

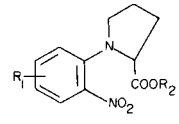
This paper describes the synthesis of derivatives of the new 1,2,3,3a-tetrahydropyrrolo[1,2-*a*]quinoxalin-4-one (I-II) and 7,8,9,10-tetrahydropyrido[1,2-*a*]quinoxalin-6-one (III-IV) *via* a modified hydrogen transfer reductive cyclization of the esters VIa,b and VIIIa,b, respectively. The reductions gave initially the corresponding *N*-(2-aminophenyl) derivatives of the cycloamine carboxylic esters. These were achieved by the use of palladium catalyst and cyclohexene (9) according to Braude's method (10). The reduced compounds, in this case, were generally not isolated but were cyclized *in situ* intramolecularly to give the desired compounds. This non-conventional quinoxalone synthesis provides a relatively facile route to the unknown heterotricyclic compounds and avoids the possible use of refractory dicarbonyl compounds.



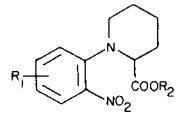
I, R = 7-NO_2
II, R = 9-NO_2



III, R = 3-NO_2
IV, R = 1-NO_2



Va, R_1 = 4-NO_2, R_2 = H
b, R_1 = 6-NO_2, R_2 = H
VIa, R_1 = 4-NO_2, R_2 = CH_3
b, R_1 = 6-NO_2, R_2 = CH_3



VIIa, R_1 = 4-NO_2, R_2 = H
b, R_1 = 6-NO_2, R_2 = H
VIIIa, R_1 = 4-NO_2, R_2 = CH_3
b, R_1 = 6-NO_2, R_2 = CH_3

Table A

Properties of 1,2,3,3a-Tetrahydropyrrolo[1,2-*a*]quinoxalin-4-one

Compound Number	mp	ν max, cm^{-1}	^{1}H-NMR, δ	ms	% RI
I	288° dec	3480 (N-H)	2.2 (m, 4H, pyrrolidine)	232.97	(100)
		1680 (lactam C=O)	3.4 (m, 2H)	205	(32)
		1530 (NO_2)	4.7 (t, 1H)	176.97	(96)
			6.9-7.6 (aromatic 3H)	131	(24)
II	270° dec	3400 (N-H)	2.0 (4m, 4H, pyrrolidine)	232.97	(100)
		1670 (lactam C=O)	3.4 (m, 2H, pyrrolidine)	204.98	(35)
		1520 (-NO_2)	4.5 (m, 1H)	176.98	(85)
			6.0-7.0 (aromatic 3H, m)	131	(24)

Table B

Properties of 7,8,9,10-Tetrahydropyrido[1,2-*a*]quinoxalin-6-one

Compound Number	mp	ν max, cm^{-1}	^{1}H-NMR, δ	ms	%	RI
III	290° dec	3450 (N-H)	1.6 (m, 4H, piperidine)	246.89		(98)
		1680 (lactam C=O)	2.4 (m, 2H)	218.9		(30)
		1530 (-NO_2)	3.6 (m, 2H)	190.92		(100)
			4.2 (m, 1H)	85		(31)
			6.9-7.4 (aromatic 3H)			
IV	286° dec	3450 (N-H)	1.6 (m, 4H, piperidine)	246.98		(100)
		1670 (lactam C=O)	2.4 (m, 2H)	218.19		(28)
		1530 (-NO_2)	3.6 (m, 2H)	190.29		(85)
			4.2 (m, 1H)			
			6.0-7.0 (aromatic 3H)			

Condensation of 1-halogeno-2,4-dinitrobenzene with the cycloamine carboxylic acids (pyrrolidine-2-carboxylic acid and piperidine-2-carboxylic acid) in dilute bicarbonate solutions gave the new 2,4-dinitrophenyl adducts Va and VIIa, respectively, as yellow crystalline solids which were esterified to give the esters VIa and VIIIa. Similar condensation and esterification with 1-chloro-2,6-dinitrobenzene gave initially the acids Vb and VIIb and then the nitroesters VIb and VIIIb, respectively.

Catalytic hydrogen transfer reduction of the nitroesters over 10% palladium charcoal in ethanol and cyclohexene gave, in each case, the corresponding *N*-(2-aminophenyl) compounds. Continued reflux in added ethanol caused the latter to cyclize to the heterotricyclic quinoxalinones I-IV. The structures of the tricycles were assigned on the basis of elemental analysis, mass spectra, ir and nmr data. (Tables A and B).

The shift of the carbonyl absorption from 1740 cm^{-1} to 1680 cm^{-1} due to the lactam formed after cyclization was characteristic. The nmr spectra substantiated this by a corresponding collapse of the -OCH_3 singlet at *ca* δ 3.2 and a change in the positions of the aromatic H multiplets from between δ 7.4 and 8.0 to between δ 6.0 and 7.0. The mass spectra of each of the quinoxalines showed abundant molecular ions consistent with their polycondensed character (2) (11). A simple fission in each of the molecules which resulted in the next abundant M-28 peak due to loss of CO is followed by loss of HCN.

These new heterotricyclic quinoxalinones are considered to arise from intramolecular nucleophilic attack on the carbonyl of the esters by the amino nitrogen leading to a cyclocondensation accompanied by loss of a molecule of methanol. The synthetic method reported provides a new route to these polycyclic systems.

EXPERIMENTAL

Melting points were determined with a Kofler hot plate apparatus and are uncorrected. Infra red absorption spectra were measured on a Perkin Elmer 257 for Nujol mulls and potassium bromide discs. The nmr spectra were recorded in DMSO-d_6 solutions (unless otherwise stated) with a Varian 60 MHz instrument using tetramethylsilane as internal reference. The mass spectra were obtained on a MAT CH 7 mass spectrometer at 70 eV at the Department of Chemistry, University of Guelph, Ontario, Canada. Microanalyses were carried out by Mr. Patrick Mowete, Department of Chemistry, University of Ibadan, Nigeria.

N-(2,4-Dinitrophenyl)pyrrolidine-2-carboxylic Acid (Va).

1-Chloro-2,4-dinitrobenzene (8 g, 0.04 mole) in ethanol (150 ml) was mixed with L-proline (7.0 g, 0.06 mole) in sodium hydrogen carbonate solution. The solution was heated under reflux for 4 hours. The basic solution was allowed to cool and washed by extraction with chloroform. The aqueous solution was acidified (2*M* hydrochloric acid) and the precipitate was taken up in chloroform. The organic layer was washed with water and dried over anhydrous magnesium sulphate. After removal of the chloroform a product which crystallized from petroleum ether (40°-60°) as yellow prisms was obtained; 6.6 g (60%); ir: 3260 (OH), 1720 (C=O), 1505 (s), 1530 (s), (NO_2), 830 (s), 8.05 (s), 7.40 (s), 7.20 (s) cm^{-1}; nmr (deuteriochloroform): δ 2.4 (4H, m, pyrrolidine), 3.4 (2H, m), 4,46 (1H, t), 6.9 (1H, d, ArH), 8.2 (1H, dd, ArH), 8.6 (1H, d, ArH), 10.0 (1H, s, OH).

Anal. Calcd. for $C_{11}H_{11}N_3O_6$: C, 46.97; H, 4.01; N, 14.94. Found: C, 46.54; H, 4.01; N, 15.33.

N-(2,4-dinitrophenyl)piperidine-2-carboxylic Acid (VIIa).

1-Chloro-2,4-dinitrobenzene (4g, 0.02 mole) in ethanol (75 ml) was mixed with pipecolinic acid (3.5 g, 0.03 mole) in sodium hydrogen carbonate. The experiment was carried out and worked up as described for *N*-(2,4-dinitrophenyl)pyrrolidine-2-carboxylic acid above. On recrystallization from petroleum ether (40°-60°), the product 3.8 g, (70%) had mp 130-131°; ir: 1720, (C=O), 1610 (s), 1530 (NO_2), 760, 750, 710 cm^{-1}; nmr (deuteriochloroform): δ 1.8 (4H, piperidine), 2.2 (2H, m), 3.0 to 3.6 (2H, m), (4.2 (1H, t, *H*-C-COOH), 7.0 (m, aromatic 1H), 7.4 (m, aromatic 1H), 7.9 (aromatic 1H, d, J = 8 Hz), 10.0 (1H, s, exchangeable OH).

Anal. Calcd. for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.41; N, 14.24. Found: C, 49.01; H, 4.05; N, 14.25.

N-(2,6-Dinitrophenyl)pyrrolidine-2-carboxylic Acid (Vb).

1-Chloro-2,6-dinitrobenzene (5 g, 0.025 mole) in ethanol (130 ml) was mixed with L-proline (3.8 g, 0.03 mole) in sodium hydrogen carbonate. The experiment was carried out and worked up as for *N*-(2,4-dinitrophenyl)pyrrolidine-2-carboxylic acid. Crystallization from diethyl ether afforded 3.5 g, (51%) of yellow needles mp 130-131°; ir (potassium bromide): 1720 (COOH), 1605, m, 1580 (NO_2), 1520 (s), 830 (s), 740 (s), 700 (s), (1,2,3-trisubstituted benzene) cm^{-1}; nmr: δ 1.9 (4H, m, pyrrolidine), 3.0 (2H, m, -CH_2-N-), 4.0 (1H, m, J = 6H_z), 6.9 (1H, m, aromatic), 7.3 (1H, s, aromatic), 7.14 (1H, s, aromatic), 8.2 (1H, s, exchangeable OH).

Anal. Calcd. for $C_{12}H_{11}N_3O_6$: C, 46.97; H, 4.01; N, 14.94. Found: C, 46.58; H, 4.05; N, 14.84.

N-(2,6-Dinitrophenyl)piperidine-2-carboxylic Acid (VIIb).

1-Chloro-2,6-dinitrobenzene (5 g, 0.025 mole) in ethanol (130 ml) was mixed with pipecolinic acid (4.5 g, 0.03 mole) in sodium hydrogen carbonate. The experimental was carried out and worked up as described for *N*-(2,6-dinitrophenyl)pyrrolidine-2-carboxylic acid. Crystallization from diethyl ether afforded 4.10 g (56.3%) of product as yellow needles mp 136-138°; ir: 1720 (C=O), 1590 (s), 1530 (-NO_2), 1450, 740, 700 cm^{-1}; (1,2,3-trisubsituted benzene); nmr: δ 1.8 (6H, m, piperidine), 3.4 (2H, m, CH_2-N-), 3.9 (1H, m, *H*-C-COOH), 7.0 (1H, s, exchangeable OH), 7.4 (1H, m, aromatic), 7.9 (1H, s, aromatic), 8.0 (1H, s, aromatic).

Anal. Calcd. for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.41; N, 14.24. Found: C, 48.60; H, 4.13; 14.30.

Methyl *N*-(2,4-Dinitrophenyl)-L-pyrrolidine-2-carboxylate (VIa).

Dry hydrogen chloride gas was continuously passed into a solution of *N*-(2,4-dinitrophenyl)-L-pyrrolidine-2-carboxylic acid (2.5 g, 0.009 mole) in anhydrous methanol (100 ml) while the solution was kept under reflux for 6 hours. Excess methanol was distilled off and the mixture was allowed to cool. It was taken up in chloroform, the organic layer washed successively with sodium hydrogen carbonate solution, dilute hydrochloric acid, water and was dried over anhydrous magnesium sulphate. After removal of the chloroform, the resulting residue was recrystallised from a mixture of petroleum ether (40-60°) and diethyl ether giving 1.9 g (72%) of yellow crystals mp 86-89°; ir: 1750 (C=O), 1605 (s), 1530 (s), (NO_2), 1150 (C-O), 830, 820, 805, 730, 710 cm^{-3}; nmr (deuteriochloroform): δ 2.4 (4H, m, pyrrolidine), 3.4 (2H, m), 3.9 (S, OCH_3), 4.6 (1H, m), 6.9 (aromatic, 1H, d, J = 8.5 Hz), 8.2 (1H, dd, aromatic), 8.6 (aromatic, 1H, d, J = 2 Hz); ms: 294.89, (M^+, 5.2%), 236 (M-59, 100%).

Anal. Calcd. for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.41; N, 14.24. Found: C, 49.03; H, 4.81; N, 14.57.

Methyl *N*-(2,4-Dinitrophenyl)piperidine-2-carboxylate (VIIIa).

Carboxylic acid (2 g, 0.007 mole) in anhydrous methanol (100 ml) was treated as described for methyl *N*-(2,4-dinitrophenyl)-L-pyrrolidine-2-carboxylate above. The initial product was an oil (1.3 g, 60%) which later solidified. The yellow solid was recrystallised from petroleum ether (60-80°)-diethyl ether mp 86-87°; ir: 1740 (s), 1600 (s), 1530, 1510, 830, 800 cm^{-1}; nmr: δ 1.8 (piperidine 4H, m), 2.2 (piperidine 2H, m), 3.5 (2H, m, -CH_2-N-), 3.9 (3H, s, OCH_3), 4.3 (1H, m, *H*-C-COOH), 7.0 (aromatic 1H, d, J = 9 OHz), 8.4 (aromatic 1H, dd, J = 12 Hz), 8.8 (aromatic 1H, d, J = 2 Hz); ms: 308.95 (M^+, 5.4%) 250, (M^+ -59, 100%).

Anal. Calcd. for $C_{13}H_{15}N_3O_6$: C, 50.48; H, 4.85; N, 13.59. Found: C, 50.45; H, 5.23; N, 13.64.

Methyl *N*-(2,6-Dinitrophenyl)pyrrolidine-2-carboxylate (VIb).

N-(2,6-Dinitrophenyl)pyrrolidine-2-carboxylic acid (2.5 g, 0.009 mole) was added to anhydrous methanol (100 ml) containing concentrated sulphuric acid (1.5 ml). The mixture was made to reflux for 6 hours. It was allowed to cool. Excess methanol was removed, and the mixture was extracted with chlorofrom (3 × 100 ml). The organic layer was successively washed with sodium hydrogen carbonate, hydrochloric acid and water. After drying over anhydrous magnesium sulphate, the chloroform was removed leaving an oil which later solidified and was recrystallized from diethyl ether to give 2.4 g (90%) of yellow prisms, mp 79-80°; ir: 1750 (s), (C=O) 1600 (m), 1530 (NO_2), 1350 (C-O), 760, broad, 40 cm^{-1}; nmr: δ 1.8 pyrrolidine, 4H, m), 3.0 (2H, m, CH_2-N), 3.2 (3H, s, -OCH_3), 3.4 (1H, t, -*C*H-COO), 6.9 (aromatic, 1H, m) 7.4 (1H, d, J = 7.0 Hz) 7.9 (1H, d, J = 8 Hz) ms: 294.85 (M^+, 13.01%) 235.95 (M^+ -59, 100%).

Anal. Calcd. for $C_{12}H_{13}N_3O_6$: C, 48.82; H, 4.41; N, 14.24. Found: C, 48.47; H, 4.93; N, 14.39.

Methyl *N*-(2,6-Dinitrophenyl)piperidine-2-carboxylate (VIIIb).

N-(2,6-Dinitrophenyl)piperidine-2-carboxylic acid (2.5 g, 0.008 mole) in absolute methanol (100 ml) containing concentrated sulphuric acid (1.5 ml) was kept under reflux for 6 hours and the reaction worked up as described for methyl *N*-(2,6-dinitrophenyl)-L-pyrrolidine-2-carboxylate above. The product afforded 1.4 g, (67%) of orange crystals, mp 80-81°; ir: 2950 (C-H), 1740 (C=O), 1600 (s), 1530 (s), (NO_2), 1350 (C-O), 1220 (C-O), 760, broad; nmr: δ 1.9 (piperidine (6H, m), 7.9 (aromatic 1H, s), 8.0 (1H, s); ms: 308.85 (M^+, 5.7%), 249.85 (M^+ -59, 100%).

*Anal.*Calcd. for $C_{13}H_{15}N_3O_6$: C, 50.48; H, 4.85; N, 13.59. Found: C, 49.99; H, 4.85; N, 13.26.

1,2,3,3a-Tetrahydro-7-nitropyrrolo[1,2-*a*]quinoxalin-4-one (I).

To *N*-(2,4-dinitrophenyl)-L-pyrrolidine-2-carboxylic acid methyl ester (1.5 g, 0.005 mole) was added dried and redistilled cyclohexene (4 ml, 0.05 mole) and 10% palladized charcoal (5 g). Absolute ethanol (50 ml) was added and the mixture was heated under reflux for 2 hours. The dark mixture was filtered through Celite (filter-aid) after which the solvents were completely removed leaving a gum which crystallized from a mixture of diethyl ether and petroleum ether (40-60°) to give a brown microcrystalline product 400 mg, (51%) mp 288° dec; ir: 1680 (s), (lactam C=O), 1610 (s), 1530 (s), (NO_2), 1460, 1320, 880, 800, 740, cm^{-1}; nmr: δ 2.2 (pyrrolidine 4H, m), 3.4 (2H, m, -CH-N-), 4.7 (1H, t, J = 10 Hz and 6 Hz), 6.9 (aromatic, 1H, d, J = 10 Hz), 7.4 (1H, dd, J = 10 Hz and 6 Hz), 7.6 (1H, d, J = 2 Hz) ms: 232.92 (M^+, 100.0%), 205 (M^+ -28 32%), 176.97 (96%), 131 (24%).

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.72; N, 18.02. Found: C, 56.36; H, 5.18; N, 18.07.

1,2,3,3a-Tetrahydro-9-nitropyrrolo[1,2-*a*]quinoxalin-4-one (II).

To methyl *N*-(2,6-dinitrophenyl)-L-pyrrolidine-2-carboxylic (800 mg, 0.003 mole) was added dried and redistilled cyclohexene (4 ml, 0.05 mole) and 10% palladium in charcoal (5 g). Absolute ethanol (50 ml) was added before the mixture was heated under reflux as usual for 2 hours. Within 10 minutes, the mixture changed from a yellowish coloration to a greenish-brown coloration. The dark mixture was filtered through Celite (filter-aid) after which solvents were distilled off leaving a gum which crystallized almost immediately on cooling to give a brown microcrystalline product (370 mg, 59%) mp 270° dec; ir: 3400 (broad, N-H), 1670, (C=O), 1610, 1520 (NO_2), 460 (s), 1320, 1100, 810, 740, 710 cm^{-1}; nmr: δ 2.0 (pyrrolidine 4H, m), 3.4 (2H, m, CH_2-N), 4.5 (1H, m, -*CH*-C=O), 6.0 to 7.0 (aromatic 3H, m), 9.6 (1H, broad, singlet exchangeable N-H); ms: 232.96 (M^+, 100%), 204.98 (M^+ -28.35%), 176.98, (85%), 131 (24%) 85, 71, 57 (64%).

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.72; N, 18.02. Found: C, 57.07; H, 5.02; N, 18.17.

7,8,9,10-Tetrahydro-3-nitropyrido[1,2-*a*]quinoxalin-6-one (III).

To methyl *N*-(2,4-dinitrophenyl)piperidine-2-carboxylate (1.0 g, 0.003 mole) was added, dried and redistilled cyclohexene (4 ml, 0.05 mole) 10% palladium on charcoal (5 g). Absolute ethanol (50 ml) was added before the mixture was heated under reflux for 2 hours. Within 10 minutes the mixture changed from a yellowish coloration to a greenish-brown colouration which later gave way to a brown colour. The dark mixture was filtered through Celite (filter-aid) after which solvents were completely removed leaving a gum which crystallized from diethyl ether to give a brown microcrystalline compound 320 mg, 40%, mp 290° dec; ir: 1680 (lactam) (C=O), 1610, 1530 (s), (-NO_2), 880 (s), 800, 740 cm^{-1}; nmr (DMSO-d_6): δ 1.6 (piperidine 6H, m), 2.4 (2H, m), 3.6 (2H, m, -CH_2-N-), 4.2 (1H, m, -*C*H-C=O), 6.9 (aromatic 1H, d, J = 10 Hz), 7.4 (1H, dd, J = 10 Hz and 2 Hz), 7.6 (1H, d, J = 2 Hz), ms: 246.89 (M^+, 98%), 218.9 (M^+ -28, 30%), 190.92 (100%), 85 (31%), 71 (46%), 57 (64%).

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.30; H, 5.26; N, 17.01. Found: C, 58.33; H, 5.60; N, 17.07.

7,8,9,10-Tetrahydro-1-nitropyrido[1,2-*a*]quinoxalin-6-one (IV).

Methyl *N*-(2,6-dinitrophenyl)piperidine-2-carboxylate (740 mg, 0.003 mole) was dissolved in dried and redistilled cyclohexene (4 ml, 0.05 mole) and 10% palladium on charcoal (5 g) was added. To the mixture was added absolute ethanol (50 ml) before heating under reflux for 2 hours. Within ½ hour, the mixture changed from a yellowish coloration to a greenish-brown coloration. The dark mixture was as usual filtered through Celite after which the solvents were removed to leave a brown solid mass. This was recrystallized from diethyl ether-chloroform to give a brown microcrystalline material (0.35 g, 60%) mp 270° dec; ir: 3450 (broad, N-H) 1670 (C=O), lactam), 1600, 1530 (NO_2), 1460 (s), 1350 (s), 1220, 760, broad, 740, 700 cm^{-1}; nmr: δ 1.6 piperidine 4H, m), 2.4 (2H, m), 3.6 (2H, m, -CH_2-N) 4.2 (1H, m, broad, -CH-CO), 6.0 (aromatic 3H, m) 10.0 (1H, s, exchangeable N-H); ms: 246.98 (M^+, 100.0%), 218.19 (M^+ -28, 28%), 190.29 (85%).

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.30; H, 5.26; N, 17.01. Found: C, 58.31; H, 5.01; N, 16.95.

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