

Synthesis of some novel 4-substituted coumarins having potential biological activity (Part II)

U C Mashelkar * & A A Audi

Organic Research Laboratory, SS & LS Patkar College, Goregaon (West), Mumbai 400 062, India
E-mail: drucm@yahoo.com

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Coumarin 4-methyl acetates are oxidized to coumarin-4-methyl glyoxalate using SeO_2 . Unlike the oxidative decarboxylation observed in the case of coumarin-4-acetic acid, here the oxidation is very selective for the active methylene group, without affecting the COOH group protected with ester function. The product thus obtained is analogous to the phenyl glyoxalic acid methyl ester i.e., coumarin-4-methyl glyoxalate and can be a useful moiety for the various synthetic manipulations of heterocycles substituted at 4-position of the coumarin.

Keywords: Coumarin 4-methyl acetates, coumarin-4-methyl glyoxalate, SeO_2

IPC: Int. Cl. 7 C 07 D

In the previous papers studies have been carried out on the oxidation of trimethyl coumarins with one of the methyl group attached to the 4-position¹. Here the methyl group attached to the 4-position has been selectively oxidized to formyl group by using SeO_2 ²⁻⁴. Similarly the oxidation of coumarin-4-acetic acids with SeO_2 gave 4-formylcoumarins following the mechanism of oxidative decarboxylation⁴.

Efforts have been carried out to synthesize new 4-substituted coumarins by novel approaches using selective bromination of active methylene group of the coumarin-4-methyl acetates and utilized both the active sites, thus formed for the synthesis of the novel heterocycles substituted at 4-position of the coumarins⁵.

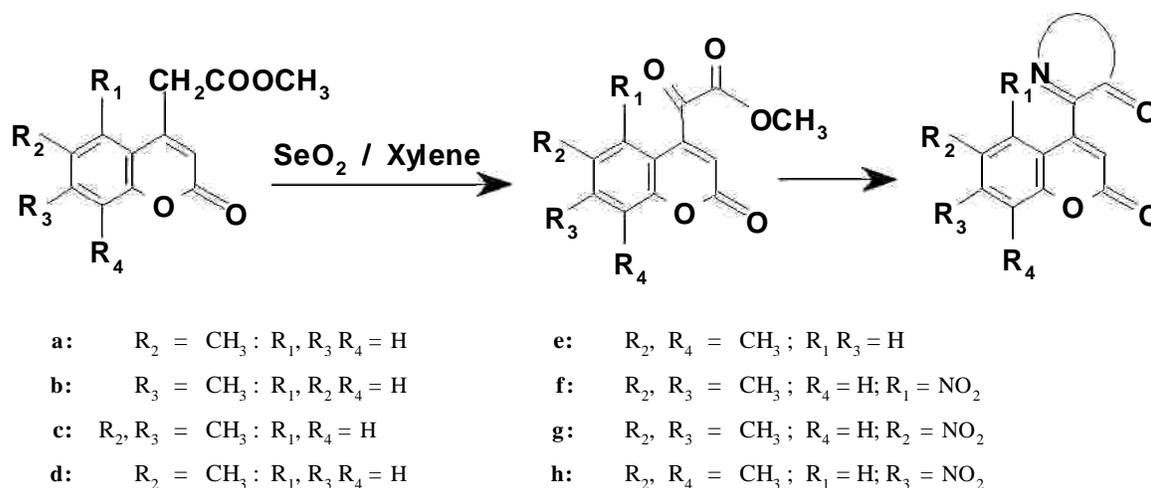
Results and Discussion

In continuation of our efforts on previous work, the present paper describes the selective oxidation of methylene group of various coumarin-4-methyl acetates using selenium dioxide, to result the methyl glyoxalate group at 4-position. The interesting aspect of this oxidation lies in the high selectivity attained towards the oxidation of active methylene group, without affecting the carboxylic acid group protected with ester function.

The product thus formed is a very interesting moiety of $\alpha,2$ -dioxo-2H-1-benzopyran-4-acetic acid methyl ester **3a-h**, analogous to the methyl ester of phenyl glyoxalic acid. The yields of the oxidized products obtained are very high in the non-polar solvents like toluene or xylene and can be isolated in the pure form without much difficulty **Scheme I**. Structures of the compounds **3a-h** were established by their elemental and spectral data **Table I**.

The oxidation looks difficult in presence of any substitution at 3-position of the coumarin. Thus in the oxidation of 2H-1-benzopyran-2-one-3-bromo-4-acetic acid methyl ester, no reaction occurred and starting product was obtained back in pure form.

The compounds $\alpha, 2$ -dioxo-2H-1-benzopyran-4-acetic acid methyl esters **3a-h**, can also be called as coumarin-4-methyl glyoxalates and can be used effectively for the synthetic manipulations of coumarins substituted with novel heterocycles at 4-position. In our earlier study, coumarins substituted with different heterocycles at 4-position have shown promising antibacterial activity⁶. Keeping this in view we have attempted to synthesize different heterocycles substituted at 4-position of the coumarin moiety.



Scheme I

Table I—Analytical data of compounds 3

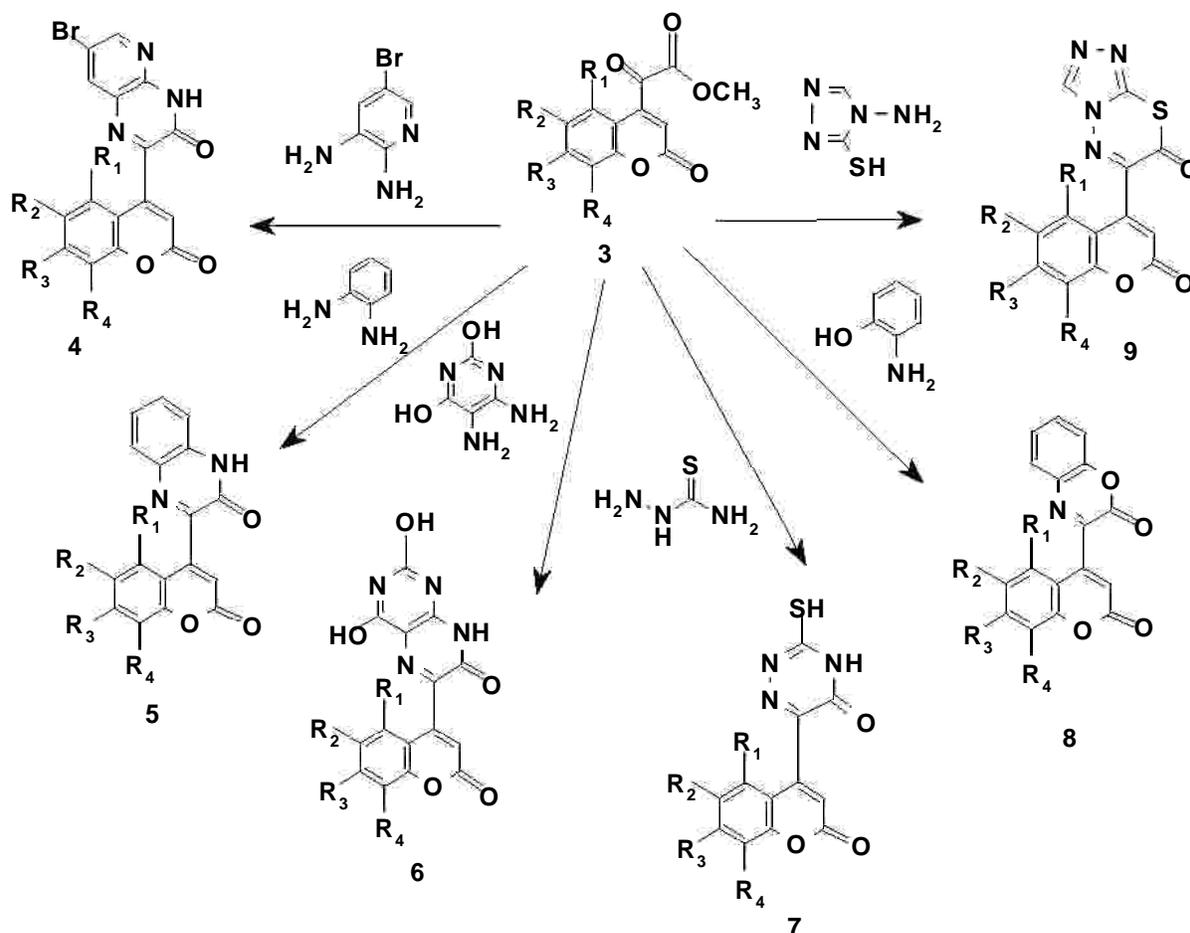
| Compd | Mol. Formula | Found % (Calcd) | | | ¹ H NMR (CDCl ₃ , δ) |
|-----------|-------------------------------------------------|------------------|----------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | | C | H | N | |
| 3b | C ₁₃ H ₁₀ O ₅ | 63.4 (63.41) | 4.09 (4.06) | — | 2.48(s, 3H, CH ₃), 4.01(s, 3H, COCOOCH ₃), 6.79 (s, 1H, C ₃ -H), 7.14-7.18 (d, 1H, C ₆ -H), 7.21 (s, 1H, C ₈ -H), 7.86-7.90(d, 1H, C ₅ -H). |
| 3c | C ₁₄ H ₁₂ O ₅ | 64.56 (64.61) | 4.57 (4.61) | — | 2.32(s, 3H, CH ₃), 2.37(s, 3H, CH ₃), 4.01(s, 3H, COCOOCH ₃), 6.75 (s, 1H, C ₃ -H), 7.18 (s, 1H, C ₈ -H), 7.71(s, 1H, C ₅ -H). |
| 3d | C ₁₄ H ₁₂ O ₅ | 64.65 (64.61) | 4.58 (4.61) | — | 2.24(s, 3H, CH ₃), 2.41(s, 3H, CH ₃), 3.98(s, 3H, COCOOCH ₃), 6.30 (s, 1H, C ₃ -H), 6.93 (s, 1H, C ₈ -H), 7.07(s, 1H, C ₅ -H). |
| 3f | C ₁₄ H ₁₁ NO ₇ | 55.12 (55.08) | 4.01 (3.60) | 4.58 (4.59) | 2.28 (s, 3H, CH ₃), 2.47 (s, 3H, CH ₃), 4.00 (s, 3H, COCOOCH ₃), 6.67 (s, 1H, C ₃ -H), 7.39 (s, 1H, C ₈ -H). |
| 3g | C ₁₄ H ₁₁ NO ₇ | 55.06 (55.08) | 3.97 (3.60) | 4.65 (4.59) | 2.15 (s, 3H, CH ₃), 2.39 (s, 3H, CH ₃), 4.00 (s, 3H, COCOOCH ₃), 6.49 (s, 1H, C ₃ -H), 7.21 (s, 1H, C ₈ -H). |

The new glyoxalate derivatives *viz.*, α , 2-dioxo-2*H*-1-benzopyran-4-acetic acid methyl esters are thus consisting of two carbonyl functions (one ketonic and other of ester) neighbouring each other. This gives special reactivity to the glyoxalate group. Taking advantage of these active functional groups, the synthesis of the various heterocycles substituted at 4-position of coumarins was carried out.

α , 2-Dioxo-2*H*-1-benzopyran-4-acetic acid methyl esters **3a-h**, were reacted with compounds like *o*-phenylene diamine to form 3-(2*H*-1-benzopyran-2-one-4-yl)-1*H*-quinoxalin-2-one derivatives **5a-c**, Reaction with 2,3-diamino uracil gives 2', 4'-dihydroxy-6'-(2*H*-1-benzopyran-2-one-4-yl)-8*H*-pteridin-7'-one

derivatives **6a-c** and with 5-bromo-2,3-diamino pyridine results in 7'-bromo-2-(2*H*-1-benzopyran-2-one-4-yl)-4'*H*-pyrido (2,3-*b*) pyrazin-3'-one derivatives **4a-c** in good yields (Scheme II).

Reaction of α , 2-dioxo-2*H*-1-benzopyran-4-acetic acid methyl esters **3a-h**, with 2-aminophenol resulted in 3'-(2*H*-1-benzopyran-2-one-4-yl)-benzo(1,4)oxazin-2'-one derivatives **8a-c**. On reaction with 4-amino-3-thio-1, 2, 4-triazines, coumarin-4-glyoxalates gave 6'-(2*H*-1-benzopyran-2-one-4-yl)-(1, 2, 4) triazolo (3,4*b*) (1', 3', 4') thiadiazin-7'-one derivatives **9a-c**. Thiosemicarbazide reacted with coumarin-4-glyoxalates to result in formation of biologically active heterocycles like 3'-mercapto-6-(2*H*-1-benzopyran-2-



- a: R₁, R₂, R₄ = H; R₃ = CH₃
 b: R₁, R₄ = H; R₂, R₃ = CH₃
 c: R₁, R₃ = H; R₂, R₄ = CH₃

Scheme II

one-4-yl)-4*H*-(1,2,4)-triazine-5'-one derivatives respectively **7a-c** at 4-position of the coumarins. NH₂ group first reacted with C=O group of methyl glyoxalate function to form amidine (C=N) linkage, which subsequently undergoes cyclization with ester function to liberate methanol, thus forming various heterocycles at 4-position of the coumarin derivatives under study. Structures of the various heterocycles substituted at 4-position of coumarin **4-9a-c** were established by their elemental analysis and spectral data (**Table II**).

Experimental Section

Melting points are uncorrected. ¹H NMR spectra were recorded on a Bruker spectrometer (200 MHz)

with TMS as internal reference. The IR spectra were recorded on a FTIR spectrometer with KBr pellets.

Synthesis of 2*H*-1-Benzopyran-2-one-4-acetic acid 1. Citric acid (96 g, 0.5 mole) was heated with concentrated H₂SO₄ (160 mL) at 60-65°C with constant stirring. Excess foaming was avoided. The solution of acetonedicarboxylic acid in concentrated H₂SO₄ was then cooled to 0°C in ice-bath and cresols or xylenols or naphthols (0.51 mole) were added to the solution under vigorous stirring at 0-5°C over a period of 1-1.5 hr. Stirring was continued at 5°C for 2 hr. Temperature of reaction mixture was then raised slowly to 30°C and allowed to stand for 24 hr. The solution was then poured in ice-cold water. The product precipitated was filtered. The crude product was dissolved in NaHCO₃

Table II—Analytical data of compounds 4-9

| Compd | Mol. Formula | Found % (Calcd) | | | | ¹ H NMR, (DMSO- <i>d</i> ₆ , δ) |
|-----------|-----------------------------------------------------------------|------------------|----------------|------------------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | | C | H | N | Br \S | |
| 4b | C ₁₈ H ₁₂ BrN ₃ O ₃ | 54.32 (54.27) | 3.00 (3.01) | 10.61 (10.55) | 20.20 (20.10) | 2.17 (s, 3H, CH ₃), 2.31 (s, 3H, CH ₃), 6.63 (s, 1H, C ₃ -H), 7.29 (d, 1H, C ₈ -H), 7.42 (d, 1H, C ₅ -H), 7.93 (s, 1H, NH), 8.58-8.73 (m, 2H, pyridine). |
| 5a | C ₁₈ H ₁₂ N ₂ O ₃ | 70.98 (71.05) | 3.93 (3.94) | 9.29 (9.21) | — | 2.41 (s, 3H, CH ₃), 6.68 (s, 1H, C ₃ -H), 7.82 (d, 1H, C ₅ -H), 7.14-7.64(m, 6H, ArH), 12.75 (bs, 1H, NH). |
| 6a | C ₁₆ H ₁₀ N ₄ O ₅ | 56.6 (56.8) | 2.92 (2.95) | 16.49 (16.56) | — | 2.40 (s, 3H, CH ₃), 6.54 (s, 1H, C ₃ -H), 7.01 (bs, 1H, NH), 7.12 (d, 1H, C ₆ -H), 7.39 (s, 1H, C ₈ -H), 7.43 (d, 1H, C ₅ -H), 10.88 (bs, 1H, OH), 11.42 (bs, 1H, OH). |
| 7a | C ₁₃ H ₉ N ₃ O ₃ S | 54.01 (54.3) | 3.18 (3.13) | 14.58 (14.63) | 11.8 (11.1) | 2.40 (s, 3H, CH ₃), 6.59 (s, 1H, C ₃ -H), 7.10-7.26(m, 4H, NH+OH+C ₈ -H+ C ₆ -H), 7.67-7.71 (d, 1H, C ₅ -H) |
| 8a | C ₁₈ H ₁₁ NO ₄ | 70.68 (70.8) | 3.62 (3.61) | 4.65 (4.59) | — | 2.41 (s, 3H, CH ₃), 6.72 (s, 1H, C ₃ -H), 7.16 (d, 1H, C ₆ -H), 7.31 (s, 1H, C ₈ -H), 7.47-7.54(m, 2H, ArH), 7.69 (d, 1H, C ₅ -H), 7.82-7.86(m, 2H, ArH) |
| 9a | C ₁₄ H ₈ N ₄ O ₃ S | 53.7 (53.8) | 2.64 (2.56) | 17.91 (17.95) | 10.19 (10.25) | 2.41 (s, 3H, CH ₃), 6.62 (s, 1H, C ₃ -H), 7.21-7.26 (m, 2H, C ₆ -H+C ₈ -H), 8.26-8.35(d, 1H, C ₅ -H), 8.89(s, 1H, triazine-H). |

solution and the solution was clarified with activated charcoal and filtered. Filtrate was acidified with conc. HCl to give respective coumarin-4-acetic acids **1**.

1a: Yield 55%; **1b**: Yield 60%; **1c**: Yield 57%; **1d**: Yield 70%; **1e**: Yield 63%; **1f**: Yield 59%.

Synthesis of 2H-1-Benzopyran-2-one-4-acetic acid methyl ester 2. Intimate mixture of coumarin-4-acetic acid **1a-f**, (0.1 mole) and alcohol (75 mL) was heated to reflux in presence of catalytic amount of concentrated sulfuric acid. Reflux was maintained for 5-6 hr. Reaction mixture was cooled to 15-20°C when 2H-1-benzopyran-2-one-4-acetates **2** was crystallized out. Product was now filtered and treated with dilute NaHCO₃ solution. The crystals of 2H-1-benzopyran-2-one-4-acetates were then washed thoroughly with water and dried.

2a: Yield 90%; **2b**: Yield 92%; **2c**: Yield 94%; **2e**: Yield 89%; **2d**: Yield 91%; **2f**: Yield 95%.

Synthesis of α,2-dioxo-2H-1-benzopyran-4-acetic acid methyl ester 3a-h (Scheme I). Coumarin-4-methyl acetates **2a-g** (0.1 mole) were dissolved in xylene (50 mL) at 60-70°C. SeO₂ (0.13 mole) was added to a clear warm solution of coumarin-4-methyl acetates. Mixture was refluxed for 6-7 hr with simultaneous removal of water drops formed during the reaction. Reaction mass was filtered hot to remove insoluble selenium.

Filtrate on cooling to 10°C gave fine crystalline product.

3a: Yield 88%, m.p. 92-94°C; **3b**: Yield 89%, m.p. 140-42°C; **3c**: Yield 87%, m.p. 168-69°C; **3d**: Yield 75%, m.p. 163-64°C; **3e**: Yield 86%, m.p. 120-22°C; **3f**: Yield 90%, m.p. 214-15°C; **3g**: Yield 73%, m.p. 194-96°C; **3h**: Yield 74%, m.p. 183-85°C.

7c-bromo-2c-(2H-1-benzopyran-2-one-4-yl)-4cH-pyrido (2, 3-b) pyrazin-3c-one 4a-c. Intimate mixture of α,2-dioxo-2H-1-benzopyran-4-methyl acetate (1 mmole), 5-bromo-2,3-diamino pyridine (1.05 mmole) in *n*-butanol (25 mL), was heated to reflux. Reaction mixture was maintained at reflux for 5-6 hr with simultaneous distillation of water and methanol formed in the reaction. Reaction mass was then cooled to 20°C. Product was isolated by filtration and then washed with methanol. Solid thus obtained was dried in oven.

4a: Yield 76%, m.p. not melting up to 325°C; **4b**: Yield 77%, m.p. not melting up to 325°C; **4c**: Yield 79%, m.p. not melting up to 325°C.

2c-(2H-1-benzopyran-2-one-4-yl)-1H-quinoxalin-2c-one 5a-c. Intimate mixture of α, 2-dioxo-2H-1-benzopyran-4-methylacetate (1 mmole), *o*-phenylene diamine (1.05 mmole) in *n*-butanol (25 mL), was heated to reflux. Reaction mixture was maintained at reflux for 5-6 hr with simultaneous distillation of water

and methanol formed in the reaction. Reaction mass was then cooled to 20°C. Product was isolated by filtration, followed by washing with *n*-butanol and then with acetone. Solid thus obtained was dried in oven.

5a: Yield 98%, m.p. not melting up to 325°C; **5b:** Yield 91%, m.p. not melting up to 325°C; **5c:** Yield 86%, m.p. not melting up to 325°C.

2*ϕ*, 4*ϕ*-dihydroxy-6*ϕ*-(2*H*-1-benzopyran-2-one-4-yl)-8*H*-pteridin-7*ϕ*-one 6a-c. Intimate mixture of α , 2-dioxo-2*H*-1-benzopyran-4-methyl acetate (1 mmole), 5,6-diamino uracil (1.05 mmole) in *n*-butanol (25 mL), was heated to reflux. Reaction mixture was maintained at reflux for 5-6 hr with simultaneous distillation of water and methanol formed in the reaction. Reaction mass was then cooled to 20°C. Product was isolated by filtration, followed by washing with *n*-butanol and then with acetone. Solids thus obtained was dried in oven.

6a: Yield 83%, m.p. not melting up to 325°C; **6b:** Yield 63%, m.p. not melting up to 325°C; **6c:** Yield 58%, m.p. not melting up to 325°C.

3*ϕ*-mercapto-6*ϕ*-(2*H*-1-benzopyran-2-one-4-yl)-4*H*-(1,2,4)-triazin-5*ϕ*-one 7a-c. Intimate mixture of α , 2-dioxo-2*H*-1-benzopyran-4-methyl acetate (1 mmole), thiosemicarbazide (1.05 mmole) in *n*-butanol (25 mL), was heated to reflux. Reaction mixture was maintained at reflux for 5-6 hr with simultaneous distillation of water and methanol formed in the reaction. Reaction mass was then concentrated completely and the residual solids were triturated in mixture of *n*-hexane and ethyl acetate. Precipitated solid was then filtered and dried in oven.

7a: Yield 70%, m.p. 175-77°C (d); **7b:** Yield 47%, m.p. 211-13°C; **7c:** Yield 50%, m.p. 155°C (d).

3*ϕ*-(2*H*-1-benzopyran-2-one-4-yl)-benzo(1,4)oxazin-2*ϕ*-one 8a-c. Intimate mixture of α , 2-dioxo-2*H*-1-benzopyran-4-methylacetate (1 mmole), 2-

aminophenol (1.05 mmole) in *n*-butanol (25 mL), was heated to reflux. Reaction mixture was maintained at reflux for 5-6 hr with simultaneous distillation of water and methanol formed in the reaction. Reaction mass was then cooled to 20°C. Product was isolated by filtration, followed by washing with *n*-butanol and then with methanol. Solid thus obtained was dried in oven.

8a: Yield 82%, m.p. 252-53°C; **8b:** Yield 69%, m.p. 307-08°C; **8c:** Yield 79%, m.p. 288-89°C.

6*ϕ*-(2*H*-1-benzopyran-2-one-4-yl)-(1,2,4)triazolo(3,4*b*)(1*ϕ*, 3*ϕ*, 4*ϕ*)thiadiazin-7*ϕ*-one derivatives 9a-c. Intimate mixture of α , 2-dioxo-2*H*-1-benzopyran-4-methyl acetate (1 mmole), 4-amino-1,2,4-triazin-3-thione (1.05 mmole) in *n*-butanol (25 mL), was heated to reflux. Reaction mixture was maintained at reflux for 5-6 hr with simultaneous distillation of water and methanol formed in the reaction. Reaction mass was then concentrated under reduced pressure and residue was dissolved in 2-3 mL acetone and cooled to 5°C with stirring. Reaction mass was stirred at 5°C for 2 hr, when the product was crystallized out. Product was then isolated by filtration, followed by washing with cold acetone. Solids thus obtained was dried in oven.

9a: Yield 80%, m.p. 268-70°C; **9b:** Yield 74%, m.p. 290-92°C; **9c:** Yield 66%, m.p. 280-82°C.

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