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# Synthesis of a New Pentalongin Derivative and its Saturated Analogue

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The synthesis of a new derivative of pentalongin **8** and its saturated analogue **9** was ascertained. Pyridinium salt **10** was prepared by the reaction of bromoketone **11** and pyridine **12** in an excellent yield. Pyridinium ylide **10a**, formed *in situ*, then underwent Michael addition reaction with menadione **14** to produce acylmethyl substituted naphthoquinone **15** in a high yield. The following bromination and intramolecular cyclization reaction of **15** successfully gave pentalongin derivative **8** in a good yield. The newly obtained 3,4-dehydropyranonaphthoquinone **8** was subsequently reduced to furnish the saturated analogue, pyranonaphthoquinone **9**.

**Key words**: Pyranonaphthoquinone; pyridinium ylide; Michael addition; intramolecular cyclization

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Pyranonaphthoquinone natural products are distributed widely in various bacteria, fungi and higher plants. This family of antibiotics displays significant medicinal properties including antimicrobial, antiviral and antifungal properties [1]. Additionally, many of these antibiotics also possess anticancer activities [1,2,3].

The basic structural framework of pyranonaphthoquinones is the naphtho[2,3-*c*]pyran-5,10-dione ring system, as some examples shown in Figure 1. Pentalongin **1**, psychorubrin **2** and eleutherin **3** are among the structurally simplest members of the pyranonaphthoquinone family with little functionalization. Some pyranonaphthoquinones contain additional γ-lactone ring such as kalafungin **4** and heterocyclic ring such as Griseusin A **5** [1].

Taking a closer look at pentalongin **1**, it is revealed that pentalongin **1** contains a double bond between C3 and C4, making it a 3,4-dehydropyranonaphthoquinone. Other examples of this group of 3,4-dehydropyranonaphthoquinones include dehydroherbarin **6** and anhydrofusarubin **7** (Figure 2). The 3,4-dehydropyranonaphthoquinones were also found to possess interesting antimicrobial, antiparasitic, phytotoxic, and antineoplastic activities. Pentalongin **1**, for example, was isolated from Rubiaceae (*Pentas longiflora* Oliv.) in Rwanda and found to show antifungal and antiparasitic activities [4].

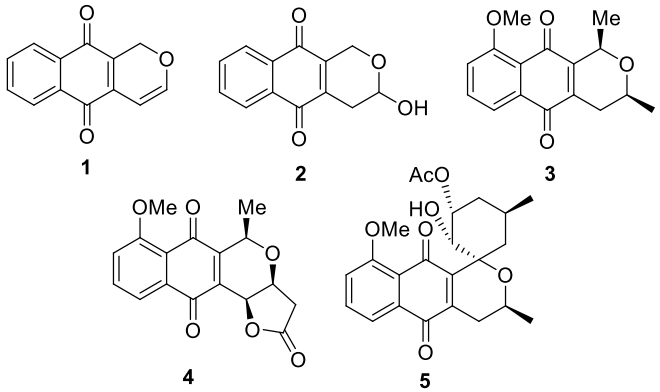


**Figure 1**. Examples of pyranonaphthoquinone compounds

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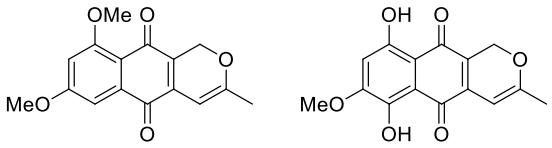



**Figure 2**. Examples of 3,4-dehydropyranonaphthoquinone compounds

The broad range of biological properties and fascinating structures of pyranonaphthoquinones has made them attractive to synthetic chemists. Hence the development of new derivatives and synthetic strategies for pyranonaphthoquinone compounds has become important and popular in organic chemistry [4,5,6].

This work focused on the naphthoquinone ring substitution with pyridinium ylide as the key step, followed by bromination-cyclization to provide naphtho[2,3-c]pyran-5,10-diones. Although the synthesis of alkyl and aryl derivatives of pentalongin **1** has been reported previously using this synthetic strategy, the yield of some products picturing the efficiency of the methodology was however missing [7,8]. Herein, we report a new derivative of pentalongin **8** and its saturated counterpart **9** prepared with a high yielding improved procedure.

## EXPERIMENTAL DETAILS

Commercially available reagents and solvents were used as supplied without further purification. Column chromatography was carried out using Merck 9385 Kieselgel 60-45 (230-400 mesh). Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 $GF_{254}$. For preparative layer chromatography, glass plates with Merck Milipore silica gel 60 were used.

Melting points were determined on Buchi 535 apparatus. $^{1}H$ and $^{13}C$-NMR spectra were recorded using either Bruker Ultra Shield 300 spectrometer (300 MHz for $^{1}H$ nuclei and 75 MHz for $^{13}C$ nuclei) or Bruker DRX 400 spectrometer (400 MHz for $^{1}H$ nuclei and 100 MHz for $^{13}C$ nuclei). IR spectra were measured with Perkin Elmer Spectrometer on a film ATR sampling accessory.

### 1. Synthesis of pyridinium salt, 1-(2-oxobutyl) pyridinium bromide (10)

THF (150 mL), 1- bromo-2-butanone **11** (2.0 ml, 16.8 mmol), and pyridine **12** (2.71 mL, 20.1 mmol) were added into a 250 mL round bottom flask. The reaction mixture was heated under reflux and stirred continuously for 36 hours. The resulting crude salt was filtered under vacuum, washed with cold ethanol, and dried in an oven for 30 minutes. Hot ethanol was added little by little to the crude salt until all the salt dissolved in the solution. The solution was cooled at room temperature overnight. The recrystallized salt was filtered under vacuum, and washed with cold ethanol. Pyridinium salt **10** was obtained in the form of pale yellow semi solid (1.1787 g, 93%). FTIR 3306 $cm^{-1}$ C-H (aro), 2980 $cm^{-1}$ C-H (aliphatic), 1703 $cm^{-1}$ C=O (ketone), 1593 $cm^{-1}$ C=C (aro). δ $^{1}H$-NMR (300 MHz, MeOD), 1.17 (3H, t, $CH_3$), 2.77 (2H, q, $CH_2$), 5.80 (2H, s, $CH_2$), 8.19 (2H, t, CH aro), 8.69 (1H, m, CH aro), 8.84 (2H, m, CH aro). δ $^{13}C$-NMR (300 MHz, $CDCl_3$), 7.83 ($CH_3$), 35.55 ($CH_2$), 64.55 ($CH_2$), 129.04 (CH aro), 147.51 (CH aro), 202.38 (C=O).

### 2. Synthesis of substituted naphthoquinone, 2-methyl-3-(2-oxobutyl)naphtahelen-1.4-dione (15)

In a 100 ml round bottom flask, pyridinium salt **10** (1.1787 g, 5.12 mmol) was dissolved in acetonitrile (40 mL) and menadione **14** (1.058 g, 6.15 mmol) was added. The flask was cooled in an ice bath (0ºC) for 15 minutes then followed by addition of triethylamine (0.9282 mL, 6.66 mmol) via a syringe. The reaction mixture was left stirring for 30 min under nitrogen atmosphere. The reaction mixture turned dark green then reddish brown. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (20 mL × 3) and the layers were separated. The combined organic layers were washed with HCl (1 M, 20 mL) then with saturated sodium hydrogen carbonate (20 mL) and the layers were separated. The organic layer was dried over anhydrous magnesium sulphate and filtered. The solvent was evaporated and the solid crude product was then purified using column chromatography (Hexane: Ethyl acetate, 9:1) to give compound **15** in the form of yellow solid (1.0666 g, 86%, m.p. 123-125ºC). FTIR 3306 $cm^{-1}$ C-H (aro), 2980 $cm^{-1}$ C-H (aliphatic), 1703 $cm^{-1}$ C=O (ketone), 1593 $cm^{-1}$ C=C (aro). δ $^{1}H$-NMR (300 MHz, $CDCl_3$), 1.05 (3H, t, $CH_3$), 2.56 (3H, s, $CH_3$), 2.57 (2H, m, $CH_2$), 3.72 (2H, s, $CH_2$), 7.61(2H, m, CH aro), 7.97 (2H, m, CH aro). δ $^{13}C$-NMR (300 MHz, $CDCl_3$), 7.83 ($CH_3$), 13.25 ($CH_3$), 36.33 ($CH_2$), 40.55 ($CH_2$), 131.8 (quart C), 140.76 (quart C), 145.79 (quart C), 126.38 (CH aro), 133.59 (CH aro), 184.19 (C=O), 184.72 (C=O), 206.13 (C=O).

### 3. Synthesis of pentalongin derivative, 3-ethyl-1*H*-benzo[*g*]iso chromen-5,10-dione (8)

Compound **15** (0.5 g, 2.21 mmol) was dissolved in $CCl_4$ (50 mL) in a 100 mL round bottom flask. Then, bromine in $CCl_4$ (28.93 mL, 2.21 mmol) was added via a syringe into the flask. The mixture was refluxed and stirred for 3 hours under nitrogen atmosphere. Triethylamine (0.77 mL, 5.53 mmol) was added slowly until an intense red colour mixture formed and stirred for 15 minutes. The solution was diluted with DCM (30 mL) and washed with water (30 mL × 3). The organic layers were collected and dried over anhydrous magnesium sulphate and filtered. The solvent was evaporated and the crude mixture was purified via column chromatography (Dichloromethane: Petroleum ether 2:8) to give compound **8** (0.24 g, 66% over 2 steps) as dark red semi-solid. FTIR 2984 $cm^{-1}$ C-H (aro), 2949 $cm^{-1}$ C-H (aliphatic), 1702 $cm^{-1}$ C=O (ketone), 1659 $cm^{-1}$ C=C (alkene), 1592 $cm^{-1}$ C=C (aro), 1167 $cm^{-1}$ C-O (ether). δ $^1$H-NMR (300 MHz, $CDCl_3$), 1.15 (3H, t, $CH_3$), 2.29 (2H, m, $CH_2$), 5.11 (2H, s, $CH_2$), 5.91 (1H, s, CH), 7.65 (2H, m, CH aro), 8.01 (2H, m, CH aro). δ $^{13}$C-NMR (300 MHz, $CDCl_3$), 11.03 ($CH_3$), 27.41 ($CH_2$), 63.17 ($CH_2$), 93.27 (CH), 125.87 (quart C), 131.71 (quart C), 138.09 (quart C), 126.41 (CH aro), 133.10 (CH aro), 181.93 (C=O), 182.42 (C=O).

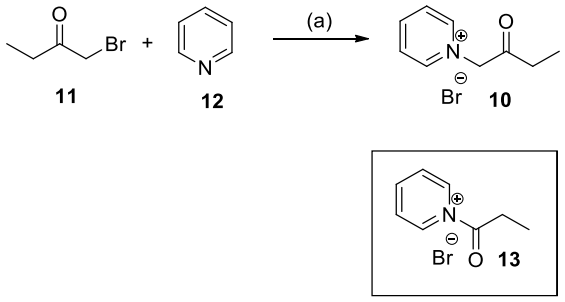
### 4. Synthesis of pyranonaphthoquinone, 3-ethyl-3,4-dihydro-1*H*-benzo[*g*]isochromen-5,10-dione (9)

Compound **8** (0.06 g, 0.29 mmol) was dissolved in dried DCM (30 mL) in a 100 mL round bottom flask and trifluoroacetic acid (0.73 mL, 0.95 mmol) was added via a syringe. From the reaction, a dark purple mixture was formed. The mixture was stirred in an ice bath for 30 minutes under nitrogen gas. Triethylsilane (0.12 mL, 0.72 mmol) was added and the mixture was stirred continuously for 30 minutes forming a brown solution. The solution was diluted with DCM (5 mL) and washed with water (5 mL × 3). The organic layers were collected and dried over anhydrous sodium sulphate and filtered. The solvent was evaporated and the crude mixture was purified using column chromatography (Dichloromethane: Hexane 2:3) to give compound **9** (0.049 g, 70%) in the form of yellow semi-solid. FTIR 2921 $cm^{-1}$ C-H (aliphatic), 1656 $cm^{-1}$ C=O (ketone), 1638 $cm^{-1}$ C=C (alkene), 1590 $cm^{-1}$ C=C (aro), 1175 $cm^{-1}$ C-O (ether). δ $^1$H-NMR (300 MHz, $CDCl_3$), 1.01 (3H, t, $CH_3$), 1.66 (2H, m, $CH_2$), 2.28 (2H, m, $CH_2$), 2.69 (1H, m, CH), 4.49 (2H, t, $CH_2$), 7.69 (2H, m, CH aro), 8.03 (2H, m, CH aro). δ $^{13}$C-NMR (300 MHz, $CDCl_3$), 9.82 ($CH_3$), 28.57 ($CH_2$), 29.78 (CH2), 63.46 ($CH_2$), 74.92 (CH), 131.88 (quart C), 126.39 (CH aro), 133.79 (CH aro), 142.11 (quart C), 142.77 (quart C), 183.47 (C=O).

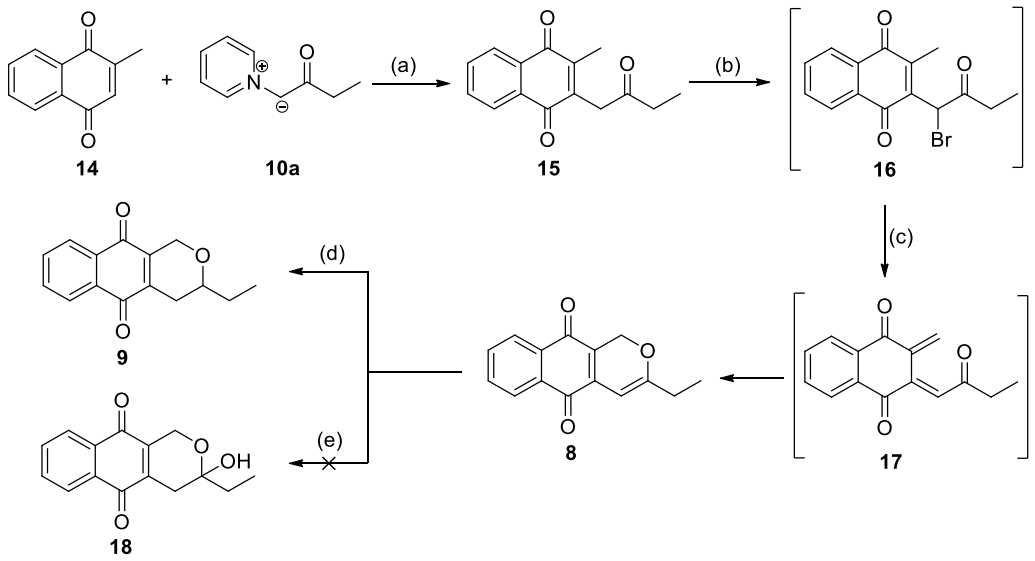
## RESULTS AND DISCUSSION

The synthesis of pentalongin derivatives **8** and **9** started with the preparation of pyridinium salt **10**. Salt **10** was prepared from bromoketone **11** and pyridine **12** via a straightforward SN2 reaction in which pyridine **12** replaced the bromine atom in **11**. The reaction was done very carefully by steadily refluxing compound **11** and **12** in THF for 36 hours. It was found that compound **13** was produced when the reaction was done with rapid heating (Scheme 1). Upon rapid heating, pyridine attacked the carbonyl carbon of bromoketone **11** to release ethylbromide and produced the undesirable salt **13**.

After the formation of **10**, the synthesis of substituted napthoquinone **15** was executed (Scheme 2). Pyridinium ylide **10a** required for this step was formed *in situ* from pyridinium salt by adding trimethylamine. The subsequent addition of ylide **10a** to naphthoquinone **14** in Michael addition fashion delivered acylmethyl substituted napthoquinone **15** in 86% yield. This reaction was done by simply dissolving **14** and **10** in acetonitrile followed by addition of trimethylamine at 0˚C and the reaction completed in 45 min. This reaction did not require long reaction time (12 h -24 h) and the use of preformed ylide as in earlier reports [7,8].




**Scheme 1**: Synthesis of pyridinium salt **10**. Reagents and conditions: (a) $Et_3N$, THF, reflux, 36 h, 93% (**10**).




**Scheme 2**: The synthesis of pentalongin derivative **8** and saturated analogue **9**. Reagents and conditions: (a) $Et_3N$, MeCN, 45 min, 86%; (b) bromine in $CCl_4$, 3 h; (c) $Et_3N$, 15 min, reflux, 66% over 2 steps; (d) TFA, $Et_3SiH$, $CHCl_3$, 0 °C, 30 min, 70%; (e) pTSA, $H_2O$/MeCN, reflux, 48h.

Having compound **15** in hand, the next step in the sequence was the bromination and cyclization. Some alkyl and aryl substituted pentalongin were previously synthesized using 1 equivalent of bromine by slow reaction in the dark [7]. In this work, compound **15** (in $CCl_4$) was refluxed for only 15 minutes to produce bromoketone **16**. Addition of trimethylamine to crude **16** gave an intense red solution indicating the formation of 3,4-dehydropyranonaphthoquinone **8** through cyclization of quinone methide intermediate **17**. This bromination-cyclization step produced the target pentalongin derivative **8** in 66% yield over two steps.

Efforts to expand the synthetic strategy toward the saturated analogue of **8** were also undertaken. Reduction of compound **8** with trifluoroacetic acid and triethylsilane (as hydride source) [6] successfully delivered pyranonaphthoquinone **9** in a good 70% yield. However, treatment of **8** with *p*-toluene sulfonic acid to produce psychorubrin derivative **18** was unsuccessful (Scheme 2).

## CONCLUSION

In conclusion, new pentalongin derivative **8** and its saturated analogue **9** were synthesized in excellent yields using pyridinium ylide-mediated Michael addition followed by bromination-intramolecular cyclization and acid-promoted reduction.

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