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Faculty of Pharmaceutical Sciences,
Kanazawa University, Takara-machi,
Kanazawa, 920, Japan

Chikara Kaneko*
Toshihiko Naito
Nayomi Nakayama

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Synthesis of Renierone, Antimicrobial Metabolite from a Marine Sponge *Reniera* sp.

Renierone, a unique isoquinolinequinone antimicrobial metabolite produced from a marine sponge *Reniera* sp., was synthesized.

Keywords——renierone; antimicrobial metabolite; *Reniera* sp.; marine sponge; isoquinolinequinone; synthesis

Renierone, isolated from the ethanolic extracts of an intense blue sponge *Reniera* sp., has been characterized as 1-(7-methoxy-6-methyl-5,8-dioxoisoquinolyl)carbinyl angelate (**2**) by an X-ray crystallographic study. It shows strong antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Candida albicans*.[1]

Recently we have reported the structure determination and synthesis of mimocin (**1**), a new isoquinolinequinone antibiotic, from the fermentation broth of *Streptomyces lavendulae*.[2]

Their structural feature and antimicrobial activities led us to undertake the synthesis of **2** and its isomer **3**.

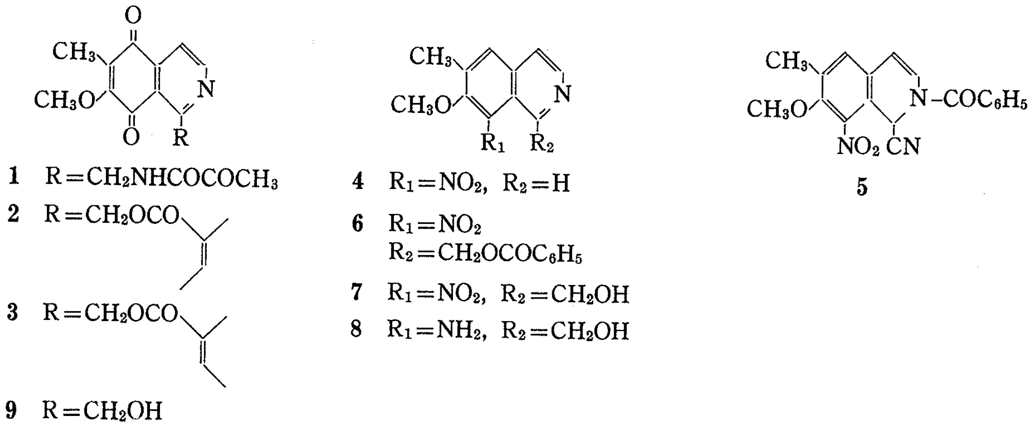
7-Methoxy-6-methyl-8-nitroisoquinoline (**4**) [mp 84—86°][3,4] was converted to the Reissert compound (**5**) [mp 160—161°; MS *m/e*: 349 (M^+), 105; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 2.40 (3H, s, C_6–CH_3), 3.95 (3H, s, C_7–OCH_3), 6.11 (1H, d, J=8 Hz, C_4–H), 6.54 (1H, s, C_1–H), 6.71 (1H, d, J=8 Hz, C_3–H), 7.24 (1H, s, C_5–H), 7.3—7.6 (5H, br s)] in 40% yield by Uff's procedure.[5]

The lithium salt of **5**, prepared by treatment with phenyllithium in dioxane–ether at −20°, was treated with gaseous formaldehyde[6] [−20°—−5°, 30 min; then 10°, 30 min] to yield 1-(7-methoxy-6-methyl-8-nitroisoquinolyl)carbinyl benzoate (**6**) [mp 128—129°; MS *m/e*: 352 (M^+), 247, 105; ^{1}H NMR ($CDCl_3$) δ: 2.54 (3H, s, C_6–CH_3), 3.96 (3H, s, C_7–OCH_3), 5.75 (2H, s, CH_2O), 7.53 (1H, d, J=6 Hz, C_4–H), 7.76 (1H, s, C_5–H), 8.45 (1H, d, J=6 Hz, C_3–H)] in 61% yield.

Upon hydrolysis[2% NaOH–EtOH, 45°, 5 min], **6** gave in 90.3% yield 1-(7-methoxy-6-methyl-8-nitroisoquinolyl)carbinol (**7**) [mp 148—149°; MS *m/e*: 248 (M^+), 231, 201; ^{1}H NMR ($CDCl_3$) δ: 2.56 (3H, s, C_6–CH_3), 3.97 (3H, s, C_7–OCH_3), 4.96 (2H, s, CH_2O), 7.56 (1H, d, J=6 Hz, C_4–H), 7.81 (1H, s, C_5–H), 8.44 (1H, d, J=6 Hz, C_3–H); IR (KBr) 3340 cm^{-1}].

The Fremy's salt oxidation of 1-(8-amino-7-methoxy-6-methylisoquinolyl)carbinol (**8**) [mp 150—151° (dec); MS *m/e*: 218 (M^+); IR (KBr) 3390, 3320 cm^{-1}], obtained in 92.1% yield by catalytic reduction of **7**, provided 1-(7-methoxy-6-methyl-5,8-dioxoisoquinolyl)carbionl (**9**) [mp 131—133°; MS *m/e*: 233 (M^+); ^{1}H NMR ($CDCl_3$) δ: 2.12 (3H, s, C_6–CH_3), 4.24 (3H, s, C_7–OCH_3), 5.24 (2H, s, CH_2O), 7.86 (1H, d, J=5 Hz, C_4–H), 8.84 (1H, d, J=5 Hz, C_3–H); IR (KBr) 3400, 1670 cm^{-1}] in 63.7% yield.

The compound **9** was treated with phenyllithium in dioxane-ether at −20° followed by addition of angeloyl chloride to afford **2** [mp 92.0—92.5°][7] in 37% yield, which was identified with the natural renierone by comparison of IR, ^{1}H and ^{13}C NMR spectra.



1 R=$CH_2NHCOCOCH_3$
2 R=CH_2OCO
3 R=CH_2OCO
9 R=CH_2OH
4 $R_1=NO_2$, $R_2=H$
6 $R_1=NO_2$, $R_2=CH_2OCOC_6H_5$
7 $R_1=NO_2$, $R_2=CH_2OH$
8 $R_1=NH_2$, $R_2=CH_2OH$
5

Chart 1

Reaction of **9** with tigloyl chloride under the same conditions provided the tiglate ester **3** [mp 111—112.5°; MS *m/e*: 315 (M^+); ^1H NMR ($CDCl_3$) δ: 1.82 (3H, dd, $J=7$, 1.5 Hz, $=CH-C\underline{H}_3$), 1.89 (3H, d, $J=1.5$ Hz, $=C-CH_3$), 2.09 (3H, s, C_6-CH_3), 4.20 (3H, s, C_7-OCH_3), 5.82 (2H, s, CH_2O), 7.01 (1H, q, $J=7$ Hz, $=C\underline{H}-CH_3$), 7.87 (1H, d, $J=5$ Hz, C_4-H), 8.90 (1H, d, $J=5$ Hz, C_3-H); IR (KBr) 1715, 1675, 1648 cm^{-1}] in 37.7% yield.

Detailed biological studies are now in progress.

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Meiji College of Pharmacy
1-35-23 Nozawa, Setagaya-ku,
Tokyo, 154, Japan

AKINORI KUBO*
SHINSUKE NAKAHARA

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