Communications to the Editor

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SYNTHESIS OF ISOQUINOLINEQUINONE ANTIBIOTICS FROM A MARINE SPONGE *Reniera* sp.

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Synthesis of two isoquinolinequinone antibiotics, 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione(**3**) and *N*-formyl-1,2-dihydrorenierone(**4**), isolated from a marine sponge *Reniera* sp., are described.

KEYWORDS ——— synthesis; isoquinolinequinone; antibiotic; marine sponge; *Reniera* sp.; ceric ammonium nitrate

In recent years several naturally occurring monomeric and dimeric isoquinolinequinones have been isolated from Actinomycetes and from marine sponges.[1)]

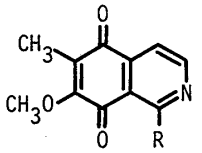
In continuation of our research on isoquinolinequinone antibiotics, we have recently described a general process for the synthesis of heterocyclic quinones using the oxidative demethylation reaction with ceric ammonium nitrate(CAN).

And we have reported the synthesis of mimocin(**1**)[2a)] and renierone(**2**)[2b)], respectively the monomeric isoquinolinequinone antimicrobial metabolites of *Streptomyces lavendulae* and a marine sponge *Reniera* sp..[3)]

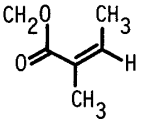
In 1982, Frincke and Faulkner reported the isolation of mimosamycin, 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione(**3**), *O*-demethylrenierone, *N*-formyl-1,2-dihydrorenierone(**4**), 6-methoxy-2,5-dimethyl-4,7-dihydroisoindole-4,7-dione, and four dimeric metabolites, renieramycins A-D from the sponge *Reniera*.[4)]

The potent biological properties of the isoquinolinequinone metabolites and their limited supply from natural sources have prompted us to undertake their synthesis.

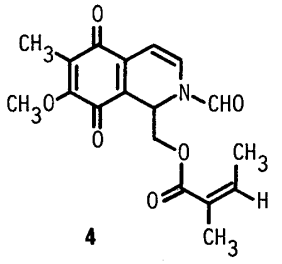
We now report the synthesis of 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione(**3**) and (±)-*N*-formyl-1,2-dihydrorenierone(**4**) by utilizing the oxidative demethylation reaction with CAN.



1: R = $CH_2NHCOCOCH_3$

2: R = CH_2O 

3: R = CH_3



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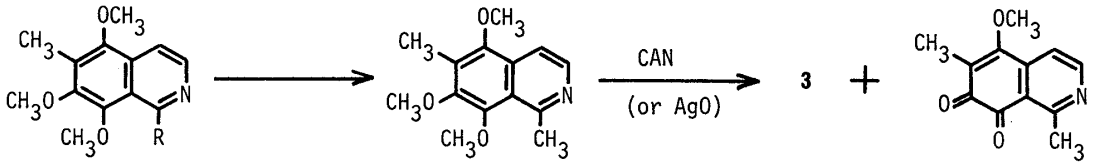
We first studied the synthesis of 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione(**3**). The carbinol **5**[5,6] was treated with phenyl lithium and tosyl chloride in dioxane-ether at 0°C to give the tosylate **6**[7] (mp 107-108°C, 74% yield), which was reduced with lithium triethylborohydride in THF (r.t. for 30 min) to afford 5,7,8-trimethoxy-1,6-dimethylisoquinoline(**7**) in 69% yield. The oxidative demethylation of **7** with CAN in aqueous CH_3CN provided after chromatography on silica gel (10:1-5:1 hexane-ethyl acetate) the desired paraquinone **3** (mp 137-138°C, 30% yield) and the methoxy orthoquinone isomer **8** (mp 149°C(dec.), 42% yield).[8] Our synthetic paraquinone **3** was identical in spectral (^{1}H-NMR, ^{13}C-NMR, MS and UV) properties with the natural product except for the melting point.[9]

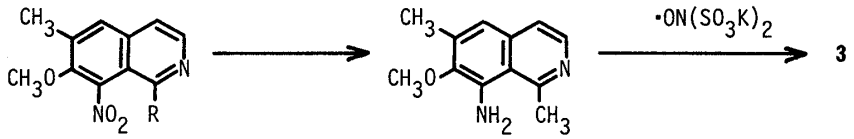


5: R = CH_2OH

6: R = CH_2OTs

7 **8**

So we examined an alternative synthesis of the paraquinone **3**. Treatment of nitrocarbinol **9**[2b] with phenyl lithium and tosyl chloride in dioxane-ether gave the tosylate **10** (mp 148-149°C, 85% yield), which was subsequently reduced with lithium triethylborohydride in THF (r.t. for 30 min) to give 7-methoxy-1,6-dimethyl-8-nitroisoquinoline(**11**) (mp 128-129°C, 57% yield). Catalytic hydrogenation of **11** with Pd-C in MeOH (r.t. for 1 h) yielded the aminoisoquinoline **12** (mp 150-151°C, 78% yield). The Fremy's salt oxidation of **12** gave **3** in 83% yield, which was identical with the synthetic paraquinone **3** in all respects (mixed melting point, TLC, ^{1}H-NMR, ^{13}C-NMR, and MS spectra).



9: R = CH_2OH

10: R = CH_2OTs

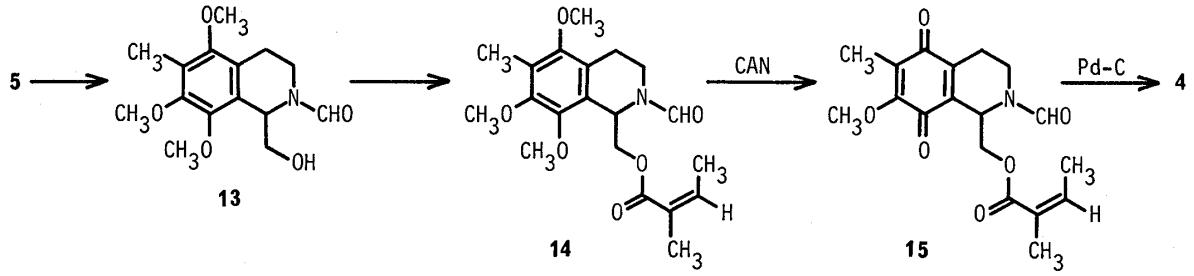
11: R = CH_3

12

Next we examined the synthesis of *N*-formyl-1,2-dihydrorenierone(**4**). The carbinol **5** was reduced with PtO_2 in AcOH to furnish the tetrahydroisoquinoline carbinol (mp 120-121°C) followed by formylation with ethyl formate to afford *N*-formyltetrahydroisoquinoline carbinol **13** (mp 131-133°C, 77% yield from **5**).

Treatment of **13** with phenyl lithium and angeloyl chloride in THF (-40°C for 5 min) afforded the angelate **14** in 66% yield, which was subsequently oxidized with CAN to give the paraquinone **15** in 40% yield.[10] Finally, dehydrogenation of **15** with Pd-C in benzene (reflux for 48 h) furnished the desired (±)-*N*-formyl-1,2-di-

hydrorenierone(**4**) in 59% yield. Its spectral (^{1}H-NMR, ^{13}C-NMR, MS, IR) properties were found to be identical with those of the natural *N*-formyl-1,2-dihydrorenierone. Finally, we confirmed that in solution **4** equilibrated to a 2:1 mixture of *cis* and *trans* rotamers,[11] by ^{13}C-NMR spectroscopy measuring with the gated decoupling non NOE mode.[12]



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3) A. Kubo, Y. Kitahara, S. Nakahara, and R. Numata, Chem. Pharm. Bull., **31**, 341 (1983).
4) J. M. Frincke and D. J. Faulkner, J. Am. Chem. Soc., **104**, 265(1982).
5) S. Danishefsky, E. Berman, R. Cvetovich, and J. Minamikawa, Tetrahedron Lett., **1980**, 4819.
6) The carbinol **5** was prepared alternatively from 5,7,8-trimethoxy-6-methylisoquinoline by the following reaction sequence involving 1) KCN, C_6H_5COCl; 2) C_4H_9Li, HCHO; 3) KOH-CH_3OH.
7) Satisfactory elemental analyses or exact mass molecular weights, and satisfactory spectroscopic (IR, ^{1}H-NMR, ^{13}C-NMR, MS) data were obtained on all new compounds.
8) The oxidative demethylation with AgO[5] gave **3** in 31% yield and the methoxy orthoquinone isomer **8** in 28% yield.
9) The melting point of the natural product was reported as mp 188-190°C(dec.).[4]
10) The paraquinone structure was confirmed by the independent synthesis from the nitrocarbinol **9** by the following 5 steps: 1) 10% Pd-C/H_2, CH_3OH; 2) PtO_2/H_2, AcOH; 3) $HCOOC_2H_5$; 4) Fremy's salt oxidation; 5) C_6H_5Li, angeloyl chloride.
11) C. Szántay, G. Blaskó, M. Barczai-Beke, G. Dörnyei, and L. Radics, Heterocycles, **14**, 1127(1980).
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