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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⁾

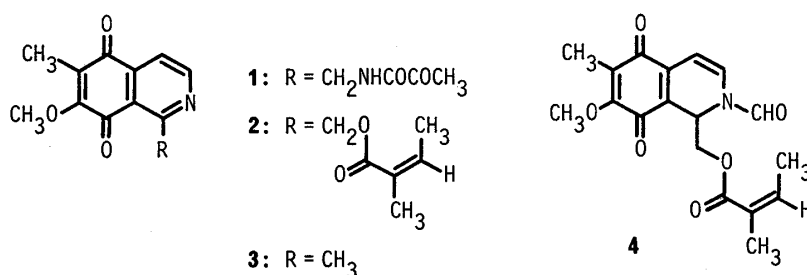
In continuation of our research on isoquinolinequinone antibiotics, we have recently described a general process for the synthesis of heterocyclic quinones using the oxidative demethylation reaction with ceric ammonium nitrate (CAN).

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⁾

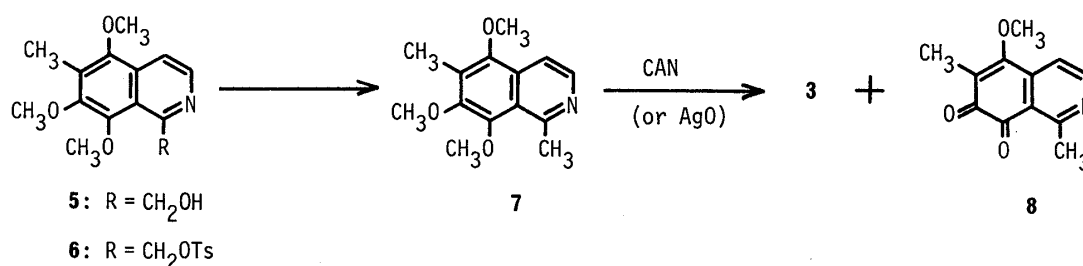
In 1982, Frincke and Faulkner reported the isolation of mimosamycin, 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (**3**), *O*-demethylrenierone, *N*-formyl-1,2-dihydrorenierone (**4**), 6-methoxy-2,5-dimethyl-4,7-dihydroisoindole-4,7-dione, and four dimeric metabolites, renieramycins A-D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

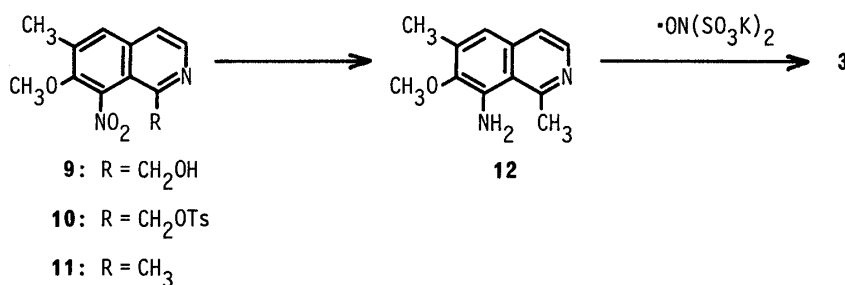
We now report the synthesis of 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (**3**) and (±)-*N*-formyl-1,2-dihydrorenierone (**4**) by utilizing the oxidative demethylation reaction with CAN.



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 6⁷⁾ (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 CH₃CN 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 (¹H-NMR, ¹³C-NMR, MS and UV) properties with the natural product except for the melting point.⁹⁾



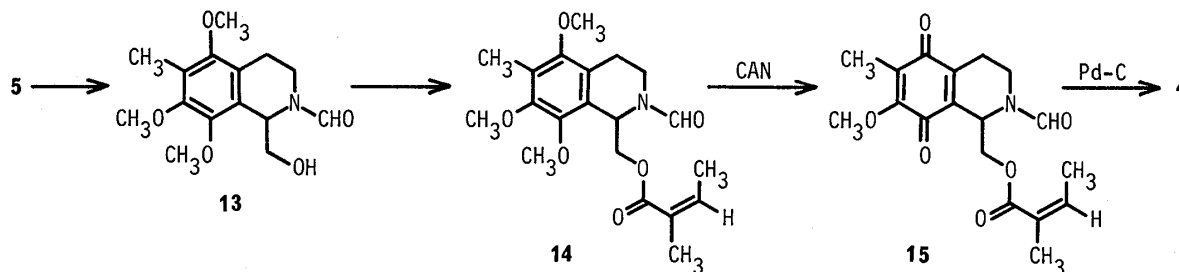
So we examined an alternative synthesis of the paraquinone 3. Treatment of nitrocarbinol 9^{2b)} with phenyl lithium and tosyl chloride in dioxane-ether gave the tosylate 10 (mp 148-149°C, 85% yield), which was subsequently reduced with lithium triethylborohydride in THF (r.t. for 30 min) to give 7-methoxy-1,6-dimethyl-8-nitroisoquinoline(11) (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, ¹H-NMR, ¹³C-NMR, and MS spectra).



Next we examined the synthesis of *N*-formyl-1,2-dihydrorenierone(4). The carbinol 5 was reduced with PtO₂ 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 ($^1\text{H-NMR}$, $^{13}\text{C-NMR}$, 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 $^{13}\text{C-NMR}$ spectroscopy measuring with the gated decoupling non NOE mode.¹²⁾



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- 6) The carbinol 5 was prepared alternatively from 5,7,8-trimethoxy-6-methylisoquinoline by the following reaction sequence involving 1) KCN, $\text{C}_6\text{H}_5\text{COCl}$; 2) $\text{C}_4\text{H}_9\text{Li}$, HCHO; 3) KOH- CH_3OH .
- 7) Satisfactory elemental analyses or exact mass molecular weights, and satisfactory spectroscopic (IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, MS) data were obtained on all new compounds.
- 8) The oxidative demethylation with $\text{AgO}^{5)}$ 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) $\text{C}_6\text{H}_5\text{Li}$, angeloyl chloride.
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