Synthesis of New Isoquinolinequinone Metabolites of a Marine Sponge, *Xestospongia* sp., and the Nudibranch *Jorunna funebris*

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Three isoquinolinequinone metabolites of a marine sponge, *Xestospongia* sp., and the nudibranch *Jorunna funebris*, *i.e.* renierol propionate (3), *N*-formyl-1,2-dihydrorenierol acetate (7) and *N*-formyl-1,2-dihydrorenierol propionate (8), were synthesized.

Keywords synthesis; isoquinolinequinone; antimicrobial metabolite; renierol; renierol propionate; *N*-formyl-1,2-dihydrorenierol acetate; *N*-formyl-1,2-dihydrorenierol propionate; marine sponge; ^{1}H-NMR; ^{13}C-NMR

During the past ten years several naturally occurring isoquinolinequinones have been isolated from marine sponges as well as from Actinomycetes.[1] Faulkner and co-workers reported the isolation and the structural determination of renierone (**1**), 7-methoxy-1,6-dimethyl-5,8-isoquinolinedione (**4**) and *N*-formyl-1,2-dihydrorenierone (equilibrated in solution to a 2 : 1 mixture of two inseparable rotamers, **6a** and **6b**) from a marine sponge, *Reniera* sp.[2,3] In 1987, McKee and Ireland isolated renierol (**5**) from a hard blue sponge, *Xestospongia caycedoi*.[4] Furthermore, very recently four new isoquinolinequinone metabolites, *i.e.* renierol acetate (**2**), renierol propionate (**3**), *N*-formyl-1,2-dihydrorenierol acetate (**7**) and *N*-formyl-1,2-dihydrorenierol propionate (**8**), have been isolated from a marine sponge, *Xestospongia* sp., and its associated nudibranch *Jorunna funebris*[5] (Chart 1). All four isoquinolinequinones, **2**, **3**, **7** and **8** showed activity against *Bacillus subtilis* and *Staphylococcus aureus*. We have already synthesized the isoquinolinequinones, **1**, **2**, and **4**—**6**.[6,7] Now we wish to report the synthesis of three other isoquinolinequinones, **3**, **7** and **8**.

Treatment of 1-hydroxymethyl-7-methoxy-6-methyl-5,8-isoquinolinedione (renierol, **5**)[6] with propionyl chloride in pyridine furnished (7-methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl propionate (renierol propionate, **3**), mp 89—90 °C in 84% yield. The ester **3** thus obtained was identical with the natural product in terms of infrared (IR), ultraviolet (UV), proton and carbon-13

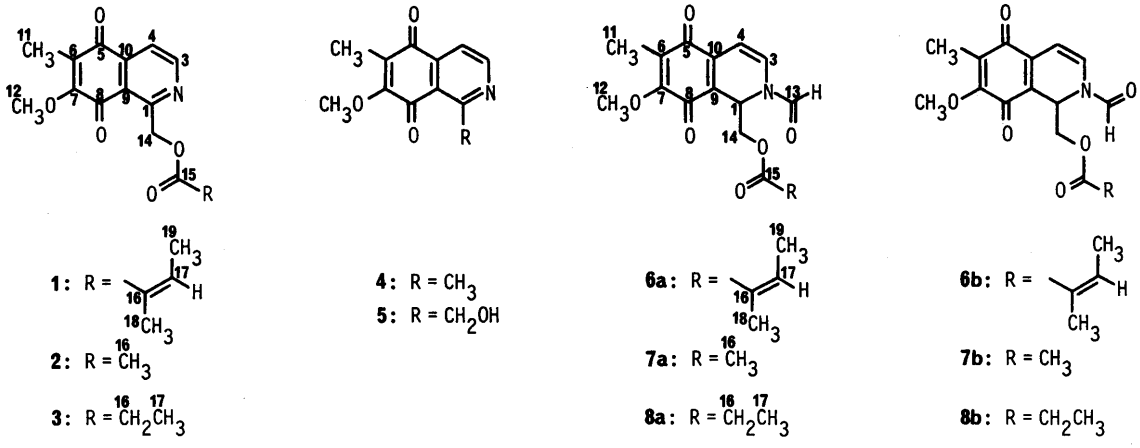

Chart 1

TABLE I. ^{1}H-NMR Data for **6**, **7** and **8**[a]

H at C No.[b]	6a[c]	6b[c]	7a	7b	8a	8b
1	5.99 (dd, 4, 3)	5.37 (dd, 9, 4)	5.94 (dd, 4.9, 3.7)	5.31 (dd, 9.8, 4.0)	5.95 (dd, 4.9, 3.4)	5.32 (dd, 9.5, 3.7)
3	6.92 (d, 8)	7.45 (d, 8)	6.92 (d, 7.6)	7.43 (d, 7.6)	6.92 (d, 7.6)	7.43 (d, 7.6)
4	6.03 (d, 8)	6.25 (d, 8)	6.06 (d, 7.6)	6.23 (dd, 7.6, 1.2)	6.05 (d, 7.6)	6.22 (dd, 7.6, 1.2)
11	1.95 (s)	1.98 (s)	1.96 (s)	1.98 (s)	1.96 (s)	1.98 (s)
12	4.05 (s)	4.07 (s)	4.07 (s)	4.05 (s)	4.07 (s)	4.05 (s)
13	8.43 (s)	8.22 (s)	8.42 (s)	8.23 (brs)	8.42 (s)	8.22 (brs)
14	4.21 (dd, 12, 3)	3.91 (dd, 12, 4)	4.18 (dd, 11.9, 3.7)	3.81 (dd, 11.3, 4.0)	4.18 (dd, 11.9, 3.4)	3.82 (dd, 11.3, 3.7)
14	4.37 (dd, 12, 4)	4.24 (dd, 12, 9)	4.24 (dd, 11.9, 4.9)	4.16 (dd, 11.3, 9.8)	4.27 (dd, 11.9, 4.9)	4.21 (dd, 11.3, 9.5)
16			1.97 (s)	2.08 (s)	2.24 (q, 7.6)	2.35 (q, 7.6)
17	6.06 (q, 7)	6.15 (q, 7)			1.06 (t, 7.6)	1.14 (t, 7.6)
18	1.77 (brs)	1.87 (brs)				
19	1.91 (d, 7)	2.00 (d, 7)				

a) Multiplicities and coupling constants (Hz) in parentheses. *b*) See Chart 1. *c*) Reference 3.

nuclear magnetic resonance (^{1}H- and ^{13}C-NMR), and mass spectra. The ^{13}C-NMR signals of **3** were easily assigned by comparison with the spectrum of **1** (Table II).

The *N*-formylisoquinolinequinones **7** and **8** were synthesized from *N*-formyl-1-hydroxymethyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline (**9**)[6] (Chart 2). The ester (**10**), prepared by treatment of **9** with acetyl chloride in pyridine, was oxidized with ceric ammonium nitrate (CAN) to give the *p*-quinone **12** (52% yield) but no *o*-quinone isomer. The *p*-quinone structure for **12** was confirmed by independent synthesis from the *p*-quinone **15** prepared by Fremy's salt oxidation of the 8-amino-1,2,3,4-tetrahydroisoquinoline **14**.[6] Treatment of **15** with acetyl chloride in pyridine afforded the *p*-quinone **12** (80% yield), which was identical with the quinone obtained from **10** (^{1}H-NMR, IR and mass spectra). Dehydrogenation of **12** with 10% palladium on carbon in refluxing benzene furnished *N*-formyl-1,2-dihydrorenierol acetate (**7**) in 48% yield. Similarly, *N*-formyl-1,2-dihydrorenierol propionate (**8**) was

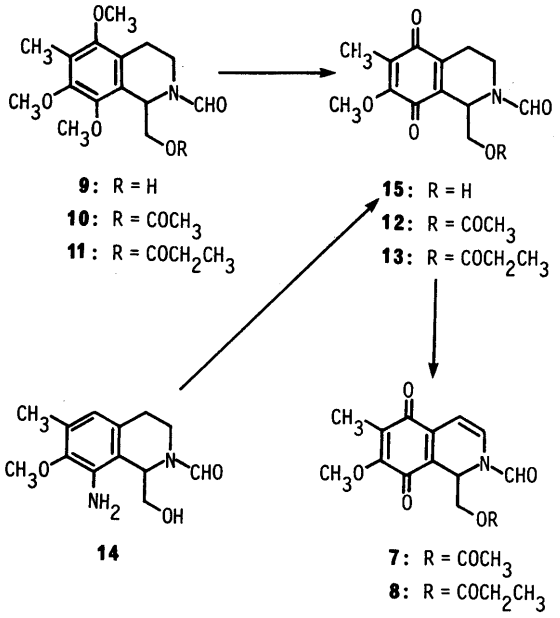

Chart 2

TABLE II. ^{13}C-NMR Data for **1**, **3**, **6**, **7** and **8**

C No.	1[a]	3	6a[a]	6b[a]	7a	7b	8a	8b
1	156.6	156.77	47.3	49.7	47.28	49.61	47.33	49.64
3	153.8	153.95	133.2	129.3	133.35	129.36	133.26	129.32
4	118.2	118.42	100.8	102.8	100.96	102.88	100.91	102.82
5	184.2	184.46	184.7	184.6	184.91	184.70	184.86	184.66
6	130.3	130.54	127.0	127.9	127.31	128.12	127.18	128.05
7	158.2	158.47	156.2	155.9	156.28	156.02	156.24	155.97
8	181.5	181.71	180.1	180.1	180.24	180.27	180.19	180.23
9	122.5	122.70	123.9	123.1	123.81	123.13	123.81	123.11
10	138.7	138.93	135.4	136.1	135.58	136.28	135.50	136.23
11	9.2	9.13[b]	8.5	8.6	8.66	8.76	8.59[b]	8.70[b]
12	61.2	61.23	61.0	61.0	61.16	61.16	61.13	61.13
13			162.1	161.2	162.17	161.28	162.09	161.24
14	65.3	65.37	63.0	60.8	63.09	61.27	63.07	61.11
15	167.6	174.33	167.2	166.6	170.79	170.14	174.15	173.55
16	127.7	27.43	126.9	126.5	20.73	20.64	27.39	27.30
17	137.8	9.04[b]	139.6	140.6			8.91[b]	8.86[b]
18	20.7		20.5	20.4				
19	15.8		15.6	15.8				

a) Reference 7. *b*) Assignments may be interchanged.

synthesized from **9**. Our synthetic *N*-formylisoquinolinequinones, **7** and **8**, were identical with the corresponding natural product in terms of IR, UV, ^{1}H- and ^{13}C-NMR, and mass spectra. Finally we confirmed that **7** and **8** were each equilibrated in solution to an approximately 2:1 mixture of two inseparable rotamers (**7a** and **7b**, and **8a** and **8b**, respectively) by examination of the ^{1}H- and ^{13}C-NMR spectra (Tables I and II). Other *N*-formylisoquinolines **10**—**13** were also equilibrated to a mixture of *cis* and *trans* rotamers[8] as judged from the ^{1}H-NMR spectra, which displayed characteristic chemical shift differences for the two rotamers. The chemical shift values for the pertinent protons are given in the experimental section.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 400 and 100.4 MHz, respectively, with tetramethylsilane as an internal standard.

Esterification of Renierol (5) Propionyl chloride (93 mg, 1 mmol) was added to an ice-cooled solution of renierol **5** (117 mg, 0.5 mmol) in dry pyridine (1 ml) with stirring. The mixture was stirred for an additional 10 min, then diluted with water and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residual solid was recrystallized from methanol to give 122 mg (84%) of renierol propionate (**3**) as yellow needles melting at 89—90 °C. *Anal.* Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.27; H, 5.19; N, 4.81. MS *m/z*: 289 (M^+, 0.4), 233 ($M^+ - COC_2H_5 + H$, 100), 57 (COC_2H_5, 71), IR ν_{max}^{KBr} cm^{-1}: 2950, 1750, 1672, 1652, 1614, 1570, 1306, 1216, 1162, 1112. UV $\lambda_{max}^{methanol}$ nm (log ε): 246 (4.25), 318 (3.70). ^{1}H-NMR δ: 1.21 (3H, t, J=7.6 Hz, CH_3CH_2), 2.09 (3H, s, C_6-CH_3), 2.51 (2H, q, J=7.6 Hz, CH_3CH_2), 4.15 (3H, s, OCH_3), 5.71 (2H, s, CH_2O), 7.88 (1H, d, J=5.2 Hz, C_4-H), 8.92 (1H, d, J=5.2 Hz, C_3-H). ^{13}C-NMR: see Table II.

Esterification of 9 and *N*-Formyl-1-hydroxymethyl-7-methoxy-6-methyl-1,2,3,4-tetrahydro-5,8-isoquinolinedione (15) Acetyl chloride (or propionyl chloride) (1 mmol) was added to an ice-cooled solution of **9** (or **15**) (0.5 mmol) in dry pyridine (1 ml) with stirring. The mixture was stirred for an additional 10 min, then diluted with water and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate as the eluent to give **10** (or **11**, **12**, **13**) as an oil.

(*N*-Formyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydro-1-isoquinolyl)methyl Acetate (**10**): Yield 99%. MS *m/z*: 337 (M^+, 2), 264 ($M^+ - CH_2OCOCH_3$, 100). High-resolution MS Calcd for $C_{17}H_{23}NO_6$: 337.1525. Found: 337.1528. IR ν_{max}^{KBr} cm^{-1}: 1744, 1674 (C=O). ^{1}H-NMR δ: 2.04 and 2.09 (3H, each s, CH_3CO), 2.19 and 2.20 (3H, each s, C_6-CH_3), 3.66 (3H, s, OCH_3), 3.78 and 3.79 (3H, each s, OCH_3), 3.91 and 3.93 (3H, each s, OCH_3), 8.21 and 8.24 (1H, each s, CHO).

(*N*-Formyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydro-1-isoquinolyl)methyl Propionate (**11**): Yield 87%. MS *m/z*: 351 (M^+, 2), 264 ($M^+ - CH_2OCOC_2H_5$, 100). High-resolution MS Calcd for $C_{18}H_{25}NO_6$: 351.1682. Found: 351.1685. IR ν_{max}^{KBr} cm^{-1}: 1740, 1676 (C=O). ^{1}H-NMR δ: 1.11 and 1.15 (3H each t, J=7.6 Hz, CH_3CH_2), 2.19 and 2.20 (3H, each s, C_6-CH_3), 2.38 and 2.46 (2H, each q, J=7.6 Hz, CH_3CH_2), 3.66 and 3.67 (3H, each s, OCH_3), 3.78 and 3.79 (3H, each s, OCH_3), 3.91 and 3.93 (3H, each s, OCH_3), 8.21 and 8.23 (1H, each s, CHO).

(*N*-Formyl-7-methoxy-6-methyl-5,8-dioxo-1,2,3,4,5,8-hexahydro-1-isoquinolyl)methyl Acetate (**12**): Yield 80%. MS *m/z*: 307 (M^+, 11), 234 ($M^+ - CH_2OCOCH_3$, 100). High-resolution MS Calcd for $C_{15}H_{17}NO_6$: 307.1056. Found: 307.1029. IR ν_{max}^{KBr} cm^{-1}: 1742, 1678, 1658 (C=O). ^{1}H-NMR δ: 1.95 and 1.97 (3H, each s, C_6-CH_3), 2.02 and 2.08 (3H, each s, CH_3CO), 4.03 and 4.05 (3H, each s, OCH_3), 8.14 and 8.20 (1H, each s, CHO).

(*N*-Formyl-7-methoxy-6-methyl-5,8-dioxo-1,2,3,4,5,8-hexahydro-1-isoquinolyl)methyl Propionate (**13**): Yield 81%. MS *m/z*: 321 (M^+, 9), 234 ($M^+ - CH_2OCOC_2H_5$, 100). High-resolution MS Calcd for $C_{16}H_{19}NO_6$: 321.1212. Found: 321.1229. IR ν_{max}^{KBr} cm^{-1}: 1740, 1678, 1656 (C=O). ^{1}H-NMR δ: 1.08 and 1.13 (3H, each t, J=7.6 Hz, CH_3CH_2), 1.95 and 1.97 (3H, each s, C_6-CH_3), 2.29 and 2.36 (2H, each q, J=7.6 Hz, CH_3CH_2), 4.03 and 4.05 (3H, each s, OCH_3), 8.13 and 8.19 (1H, each s, CHO).

Oxidative Demethylation of 10 and 11 A solution of CAN (548 mg,

1 mmol) in water (2 ml) was added dropwise to an ice-cooled solution of **10** (or **11**) (0.2 mmol) in acetonitrile (4 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (183 mg, 1 mmol) with stirring. The mixture was stirred at 0—5 °C for 2 h, then diluted with water, adjusted to pH 9 with 5% $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using 40—70% ethyl acetate in hexane as the eluent to give **12** (52% yield) (or **13**, 56% yield) as an oil. The quinones **12** and **13** thus obtained were identical with the corresponding *p*-quinone prepared by the esterification of **15** (MS, IR and ^{1}H-NMR spectra).

Dehydrogenation of 12 and 13 A solution of **12** (or **13**) (30 mg) in benzene (5 ml) containing 10% palladium on carbon (120 mg) as a catalyst was refluxed for 24 h with stirring. The catalyst was filtered off and the solvent was removed. The residue was chromatographed on a silica gel column using 30—40% ethyl acetate in hexane as the eluent to give **7** (or **8**) as a dark red oil.

N-Formyl-7-methoxy-6-methyl-5,8-dioxo-1,2,5,8-tetrahydro-1-isoquinolyl)methyl Acetate (*N*-Formyl-1,2-dihydrorenierol Acetate, **7**): Yield 48%. MS *m/z*: 305 (M^+, 3), 232 ($M^+ - CH_2OCOCH_3$, 100), 204 ($M^+ - CH_2OCOCH_3 - CO$, 98). High-resolution MS Calcd for $C_{15}H_{15}NO_6$: 305.0899. Found: 305.0880. IR ν_{max}^{KBr} cm^{-1}: 2957, 1744, 1702, 1648, 1615, 1552, 1440, 1390, 1324, 1286, 1264, 1224, 1186, 1150, 1047, 947, 747, 718. UV $\lambda_{max}^{methanol}$ nm (log ε): 269 (3.99), 340 (3.54), 500 (3.19). ^{1}H-NMR: see Table I. ^{13}C-NMR: see Table II.

(*N*-Formyl-7-methoxy-6-methyl-5,8-dioxo-1,2,5,8-tetrahydro-1-isoquinolyl)methyl Propionate (*N*-Formyl-1,2-dihydrorenierol Propionate, **8**): Yield 53%. MS *m/z*: 319 (M^+, 3), 232 ($M^+ - CH_2OCOC_2H_5$, 100), 204 ($M^+ - CH_2OCOC_2H_5 - CO$, 93). High-resolution MS Calcd for $C_{16}H_{17}NO_6$: 319.1055. Found: 319.1015. IR ν_{max}^{KBr} cm^{-1}: 2947, 1742, 1702, 1648, 1617, 1554, 1440, 1385, 1324, 1286, 1266, 1204, 1188, 1146, 1090, 947, 747, 720. UV $\lambda_{max}^{methanol}$ nm (log ε): 268 (4.00), 340 (3.57), 500 (3.24). ^{1}H-NMR: see Table I. ^{13}C-NMR: see Table II.

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