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THE TOTAL SYNTHESIS OF RENIERONE

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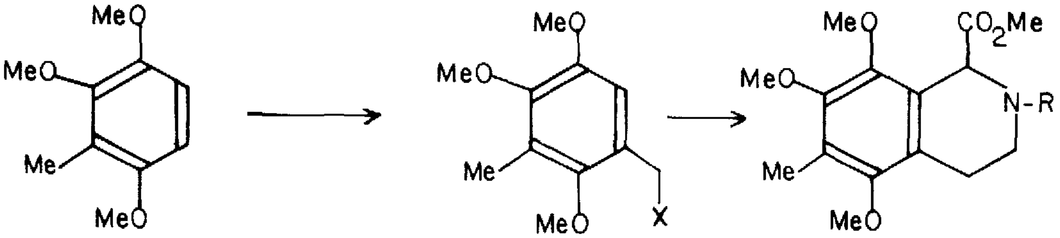
Summary: The use of an intramolecular Ben-Ishai reaction is described.

The antibacterial metabolite, renierone (10) was isolated from the marine sponge, *Reniera*, in the vicinity of Isla Grande Mexico. Its characterization and crystallographic structure determination were reported by Faulkner and Clardy.[1] It is interesting to note that antibiotic activity has been asserted on behalf of several structurally related congeners of renierone. Most notable among these are the microbially derived mimosamycin, saframycin A, B, and C and mimocin.[2] A tetrahydro variation of 10 is also discerned in the AB rings of the antibiotic, naphthyridinomycin.[3,4] Furthermore, it will be recognized that a quinonoid ring containing a substitution pattern similar to that of 10 appears as a substructural unit of mitomycin B[5]. Thus, the biological activity of renierone is not an isolated curiosity, but appears to fit into a larger framework. Indeed, a plausible rationale for the biological activity of 10 and its analogs, is available from the well known bioreductive alkylation model of Moore.[6]

Our interest in a total synthesis of renierone was part of a more general involvement with other members of the series. From a chemical standpoint, we sought to address the feasibility and utility of the intramolecular variation of the Ben-Ishai reaction.[7] Remarkably, prior to the inception of this study, the application of this reaction to the synthesis of complex tetrahydroisoquinolines had not been investigated.[8] Below we describe the synthesis of renierone (10), using as its key step (see 4→5) such a process.

Chloromethylation of 1[9] under standard conditions afforded 2[10,11] which, upon reaction of potassium cyanide in dry dimethylsulfoxide gave 3[10,11], mp 65.0-65.5° (70-75% from 1). Reduction of 3 with borane-THF, followed by acylation of the resultant amine with benzylchloroformate ($K_2CO_3/CHCl_3$) gave rise to 4, mp 63.0-63.5° (50% from 3).

An addition reaction[7] was clearly indicated upon treatment of 4 with glyoxylic acid. The adduct was not characterized, but was treated directly with dichloroacetic acid (rt, 16 hr). Esterification of the crude acid with diazomethane afforded 5.[10,11] Hydrogenolysis of 5 (H_2/ MeOH/Pd-C) afforded 6 (80% from 4).



1

2 X = Cl

3 X = CN

4 X = $CH_2NHCO_2CH_2\phi$

5 R = $CO_2CH_2\phi$

6 R = H

Dehydrogenation of **6** (chloranil/xylene; 150°)[12] afforded **7** (60-65%) which was not rigorously purified. Reduction of **7** with di-isobutyl aluminumhydride (0°; T.H.F.) gave the carbinol **8**,[10,11] mp 90-91°, in (50-70% yield). Treatment of **8** with pure angelic acid under the acylating conditions described by Ziegler[13] (D.C.C.-DMAP/ether) afforded a 55% yield of **9**.[11] In addition, there was isolated 19% of recovered **8** and 17% of the corresponding tiglate ester.

Oxidative demethylation of **9** according to Rapoport[14] ($AgO/6NHNO_3$-dioxane) gave a 90% yield of renierone (**10**) and its methoxyorthoquinone isomer **11**.[11] The isolated yields of **10** and **11** were 52 and 38%, respectively.

Treatment of **11** with aqueous sulfuric acid in dioxane-acetone[15] afforded, quantitatively **12**, which upon reaction with Ag_2O-MeI/$CHCl_3$[16], afforded only renierone (combined yield from starting **9** = 83%). The infrared, nmr (270 MHz) and mass spectra of pure synthetic **10**, (mp 87-88°) as well as its chromatographic properties, were in accord with those obtained from a sample kindly furnished by Professor Faulkner.

Application of these findings to other synthetic targets will be described in due course.

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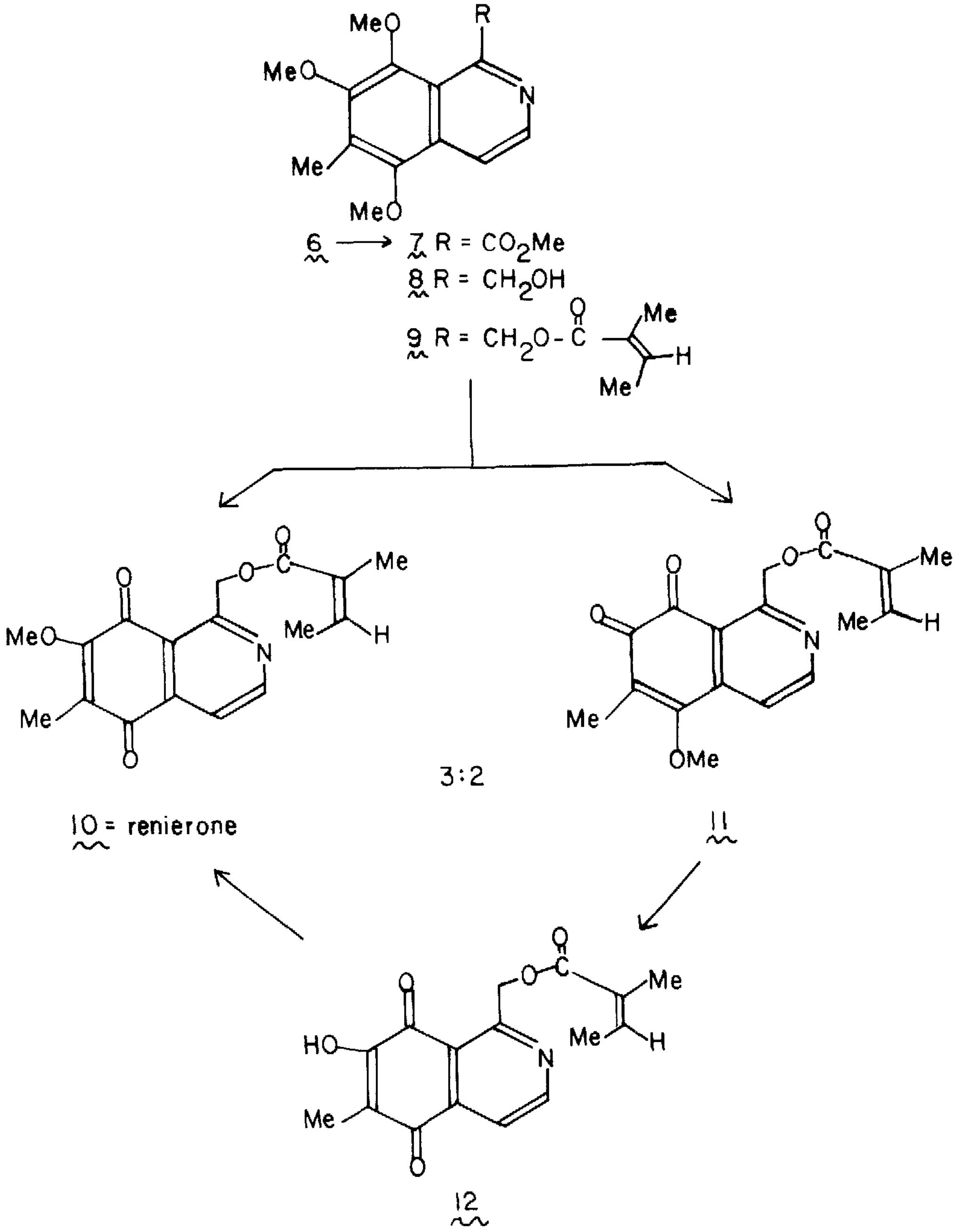
MeO
MeO
Me
MeO
R
N
6 ⟶ 7 R = CO_2Me
8 R = CH_2OH
9 R = $CH_2O-\overset{O}{C}$
Me
H
Me
MeO
Me
O
O
N
Me
Me
H
3:2
10 = renierone
O
O
N
Me
OMe
Me
Me
H
11
HO
Me
O
O
N
Me
Me
H
12

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