The Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 18 [1]. A Short Synthesis of Swietenidin A

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N-Methylisatoic anhydrides react with the lithium enolate of ethyl methoxyacetate at low temperatures to produce intermediates which, when cyclized, afford 4-hydroxy-3-methoxy-2(1*H*)-quinolinones. By this route, 3-methoxy-*N*-methylisatoic anhydride (**8**) can be converted to the alkaloid swietenidin A (**2**) in 71% yield.

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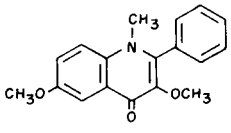
In the family of naturally occurring quinoline alkaloids, oxygenation of the quinoline nucleus (as a hydroxyl or carbonyl function) primarily occurs at either the 2- or 4-position [2]. Oxygen containing substituents are rarely found at the 3-position. Several of these exceptions are shown below. Japonine (**1**) is isolated from the aerial parts of *Orixa japonica* Thunb. [3,4] while swietenidin A (**2**) and B (**3**) are found in the bark of *Chloroxylon swietenia* (East Indian satin wood) [5].



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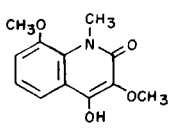

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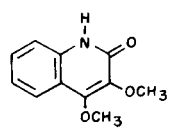
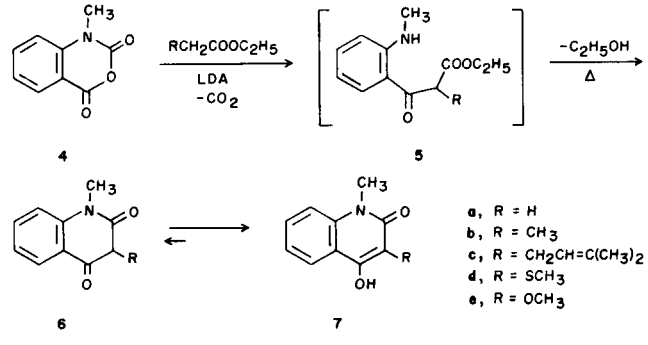


3

In an earlier paper [6], the synthesis of Japonine was easily accomplished by the reaction of 5-methoxy-*N*-methylisatoic anhydride with the lithium enolate of α-methoxyacetophenone. In a continuing investigation into the application of isatoic anhydride chemistry to natural product synthesis, I wish to describe the facile preparation of swietenidin A (**2**).

It has been shown that the introduction of various substitutents into the 3-position of 2-quinolones can be accomplished by the reaction of *N*-methylisatoic anhydride (**4**) with the lithium enolate of an α-substituted acetic acid ester [7]. As can be seen in Scheme 1, the R group on the ester ultimately resides in the 3-position of the product **7**. Previously only hydrogen (**7a**), methyl (**7b**), prenyl (**7c**), and thiomethyl (**7d**) groups were studied.

Scheme I

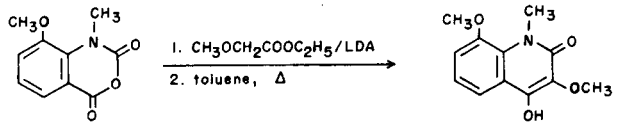


4 5 6 7

In the present investigation, the introduction of a methoxyl group (leading to **7e**) will be explored and, if successful, the methodology will be applied to the synthesis of the natural product **2** which contains an additional methoxy attached to the carbon in position 8.

Ethyl methoxyacetate, the requisite ester for the synthesis of **7e** is commercially available [8] and its lithium enolate is readily generated with lithium diisopropylamide (LDA) at -78°. The addition of *N*-methylisatoic anhydride (**4**) to the solution of the enolate results in an almost instantaneous reaction which affords **5e** after workup. The crude β-ketoester is then refluxed in toluene for 30 min. to effect cyclization. This two-step process affords the product **7e** in 68% yield.

The stage is now set to apply these conditions to the synthesis of swietenidin A. The preparation of the desired starting material, 3-methoxy-*N*-methylisatoic anhydride (**8**), has been described in an earlier report from this laboratory [7].



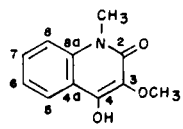
8 2

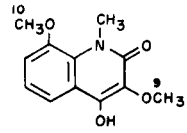
When **8** is allowed to react with the enolate of ethyl methoxyacetate in the same manner as in the previous example, an equally rapid reaction is observed. The reactants are completely consumed immediately upon the addition of **8**. The crude intermediate is then cyclized in refluxing toluene for 45 min. and, after flash chromatography, swietenidin A (**2**) is isolated in 71% yield (overall from **8**). It should be noted that these reactions were only performed once and are by no means optimized.

In summary, 4-hydroxy-3-methoxy-2-quinolones are easily accessible from the reaction of an appropriate isatoic anhydride derivative with the lithium enolate of ethyl methoxyacetate. The synthesis of 4-hydroxy-3,8-dimethoxy-1-methyl-2(1*H*)-quinolinone (swietenidin A) has been accomplished in 71% yield using this methodology.

Table

Carbon-13 NMR Assignments for Compounds **7e** and **2**





Carbon	7e	2
2	159.83	160.50
3	130.42	130.36
4	149.76	148.56 [a]
4a	115.41	117.31
5	123.27	113.35
6	121.91	122.61
7	129.76	115.73
8	113.78	148.94 [a]
8a	136.75	128.63
9	60.04	60.09
10	—	56.68
N-CH_3	29.16	34.91

[a] Assignments are interchangeable.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on either Perkin-Elmer Model 257 and 457, or Analect FX-6200 spectrophotomers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on EM-360 and Jeol FX-90-Q spectrometers using TMS as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Jeol FX-200 spectrometer system. The spectra were obtained at an observing frequency of 50.1 MHz. Sample concentrations were *ca.* 0.1 molar in 5 mm (od) sample tubes. General nmr spectral and instrumental parameters employed were: Internal deuterium lock to the solvent; spectral width of 10000 Hz; a pulse width of 3 *ms* corresponding to a 45° pulse angle, and a pulse repetition time of 1.8 seconds. For all spectra, 16K time-domain points were used. All shifts reported are referenced to internal TMS and are estimated to be accurate to ±0.05 ppm.

Enolate generating reactions were conducted under a nitrogen atmosphere using tetrahydrofuran which was freshly distilled over lithium aluminum hydride. No attempt has been made to optimize the yields of the described reactions.

4-Hydroxy-3-methoxy-1-methyl-2(1*H*)-quinolinone (**7e**).

To a solution of 2.0 g (0.02 mole) of diisopropylamine in 75 ml of tetrahydrofuran (at -30°) was added 1.28 g of *n*-butyllithium (0.02 mole, 1.6*M* in hexane) [9]. After cooling to -78°, a solution of 1.18 g (0.01 mole) of ethyl methoxyacetate in 10 ml of tetrahydrofuran was added dropwise and the mixture was stirred at -78°C for 1 hour. To this was added slowly a solution of 1.77 g (0.01 mole) of *N*-methylisatoic anhydride (**4**) in 40 ml of tetrahydrofuran and the mixture was stirred at -78° for 10 minutes. The mixture was quenched with saturated ammonium chloride solution and the organic phase was separated. The aqueous layer was extracted twice with methylene chloride, the organic solutions were combined and then dried over sodium sulfate. The solvent was removed under reduced pressure and the residual oil was dissolved in 30 ml of toluene. After refluxing for 30 min., the solvent was evaporated. The resulting oil was flash chromatographed on a column of silica gel using 5% methanol/methylene chloride to elute the product, 1.4 g (68%) of **7e**. An analytical sample was crystallized from methylene chloride/methyl *t*-butyl ether, mp 157-158°, Lit [10] mp 153°; ir (chloroform): 3511, 1630, 1601, 1485, 1213, 1118 cm^{-1}; nmr (DMSO-d_6): δ 10.57 (s, broad, 1H, enol OH), 7.88 (m, 1H), 7.65-7.14 (m, 3H), 3.80 (s, 3H), 3.61 (s, 3H).

Swietenidin A (**2**).

To a solution of 620 mg of diisopropylamine in 25 ml of tetrahydrofuran (at -30°) was added 400 mg of *n*-butyllithium (1.6 *M* in hexane). After cooling to -78°, a solution of 375 mg of ethyl methoxyacetate in 3 ml of tetrahydrofuran was added dropwise. The mixture was stirred at -78° for 1 hour, then a solution of 600 mg of **8** [7] in 15 ml of tetrahydrofuran was added slowly. After stirring at -78° for 10 minutes the reaction was quenched with saturated ammonium chloride solution. The mixture was extracted twice with methylene chloride and the organic solution was dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting oil was dissolved in 15 ml of toluene. This solution was refluxed for 45 minutes then the solvent was removed under reduced pressure. The residue was flash chromatographed on a column of silica gel using 5% methanol/methylene chloride to elute the product, 480 mg (71%) of **2**. An analytical sample was crystallized from ethyl acetate, mp 164-166°, Lit [5] mp 158-159°; ir (chloroform): 3505, 1639, 1454, 1253 cm^{-1}; nmr (deuteriochloroform): δ 7.55 (dd, 1H), 7.29-6.93 (m, 2H), 4.00 (s, 3H), 3.95 (s, 3H), 3.89 (s, 3H).

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REFERENCES AND NOTES

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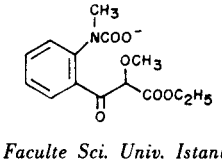
[9] The extra equivalent of LDA is necessary to satisfy the highly acidic proton of the initially produced β-ketoester.



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