The Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 10. Reactions With Ester Enolates. Synthesis of 4-Hydroxy-1-methyl-3-prenyl-2(1*H*)-quinolinones, Crucial Intermediates in the Synthesis of Quinoline Alkaloids

Gary M. Coppola

Chemistry Research Department, Pharmaceutical Division, Sandoz, Inc.,
Route 10, East Hanover, New Jersey 07936

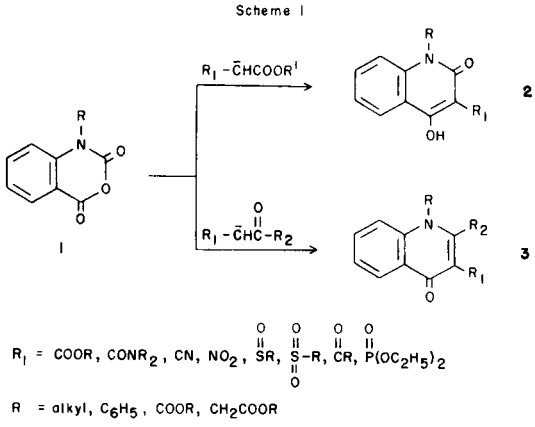
Received January 27, 1983

N-Methylisatoic anhydride reacts with the lithium enolates of esters to produce β-ketoesters **4** in nearly quantitative yield. Thermal cyclization of these relatively unstable intermediates afford the corresponding 3-substituted-4-hydroxy-1-methyl-2(1*H*)-quinolinones (**5**) in good yields. The reaction of the lithium enolate of 5-methyl-4-hexenoic acid ethyl ester (**14**) with various nuclear substituted isatoic anhydrides gives 4-hydroxy-1-methyl-3-prenyl-2(1*H*)-quinolinones **8, 9,** and **18** which are highly desirable intermediates in the synthesis of a variety of quinoline alkaloids. Treatment of **18** with DDQ furnishes oricine in 73% yield.

J. Heterocyclic Chem., **20**, 1217 (1983).

A variety of 3-substituted-2-oxo **2** and 4-oxoquinolines **3** have been synthesized from the reaction of an appropriate isatoic anhydride **1** and a metallated active methylene compound possessing a functionality capable of cyclization with the anilino group which is generated during the reaction [1-3]. The reaction required that R_1 be an electron withdrawing group which facilitated the generation of the anionic species with the chosen base (sodium hydride) at a reasonable temperature (ambient). These conditions, however, somewhat restricted the selection of the functionality represented by R_1 in Scheme 1.

Scheme 1

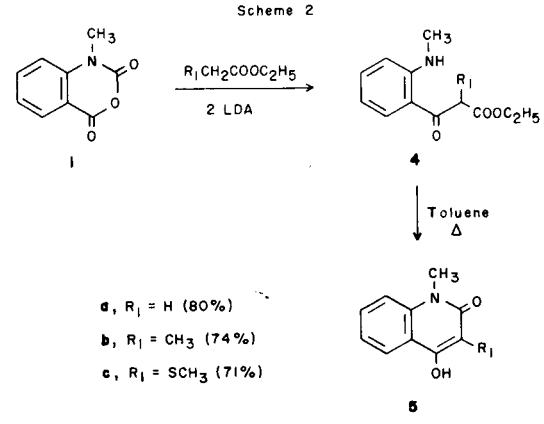


It was of interest to be able to reduce the limitations described above and further expand the scope of the reaction to include substituents such as H, alkyl, *etc.* In order to generate these compounds it is required that an α-metallated carboxy function ($-CHR_1COOR$) be employed.

Stable tetrahydrofuran solutions of ester enolates can be easily prepared at low temperatures by the treatment of an ester with such bases as lithium diisopropylamide (LDA) [4,5], lithium *N*-isopropylcyclohexylamide [6], and lithium bis(trimethylsilyl)amide [7].

With this in mind, the enolate of ethyl acetate was generated with LDA at $-70°$ and was allowed to react with *N*-methylisatoic anhydride (**1**, R = CH_3) (Scheme 2). Analysis of the reaction mixture indicated the presence of a new product plus an approximately equal amount of unreacted **1**. The experiment was repeated using two equivalents of LDA and subsequent analysis indicated complete consumption of the reactants. The reaction is extremely rapid and is essentially complete after the addition of **1**. Analogous reaction times are observed for ethyl propionate and ethyl methylthioacetate.

Scheme 2



These new products, **4**, which are isolated in nearly quantitative yield, are intensely yellow in color and are virtually pure. These intermediates are relatively unstable and spontaneously cyclize, even at room temperature, over varying periods of time. In fact, **4c** is completely converted to **5c** in less than 12 hours.

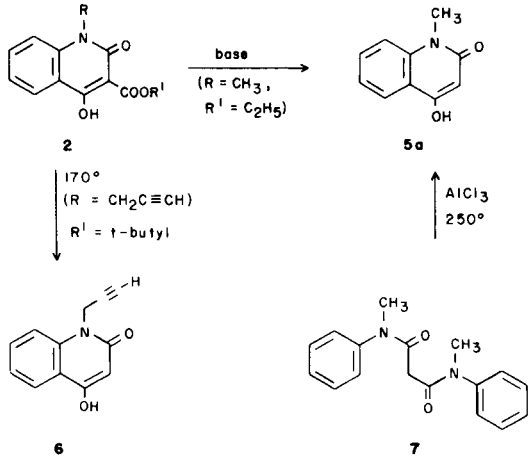
Cyclization, however, can be effected in less than one hour by refluxing **4**, in toluene. The products, **5**, crystallize directly from the reaction mixture and can be isolated pure simply by filtration.

To insure the integrity of **4**, a representative example, **4c**, was spectrally characterized prior to cyclization. The ir spectrum exhibited an N-H band at 3460 cm^{-1} and carbon-

yl absorptions at 1735 cm^{-1}. The nmr spectrum showed typical ethyl ester signals (δ 4.28, quartet, 2 protons; and δ 1.24, triplet, 3 protons). The SCH_3 signal was observed as a singlet at δ 2.26 while the NCH_3 peak fell as a doublet (J = 4 Hz) at δ 2.95. The signal representing the proton α to the ester was seen as a singlet at δ 5.08. After cyclization, the ir spectrum of **5c** showed absorptions at 3450 (OH) and 1625 cm^{-1}, typical for a 2-quinolone system. In the nmr spectrum, both SCH_3 and NCH_3 groups appeared as singlets at δ 2.35 and 3.67 respectively.

This method provides an exceedingly mild route to *N*-substituted-4-hydroxycarbostyrils (*e.g.*, **5a**). Previous preparations of such compounds (Scheme 3) required fairly vigorous conditions such as heating the malonic acid dianilide **7** with aluminum chloride at 250° [8]. Compound **5a** has also been synthesized from *N*-methylisatoic anhydride (**1**) by reaction with sodio diethylmalonate (to give **2** R = CH_3, R' = $COOC_2H_5$) followed by base hydrolysis where decarboxylation occurs during the work-up phase [1,2]. If the molecule contained certain base sensitive functional groups (*e.g.*, $CH_2C{\equiv}CH$), the product **6** could be obtained by the thermal decarboxylation of the corresponding *t*-butyl ester of **2** [2].

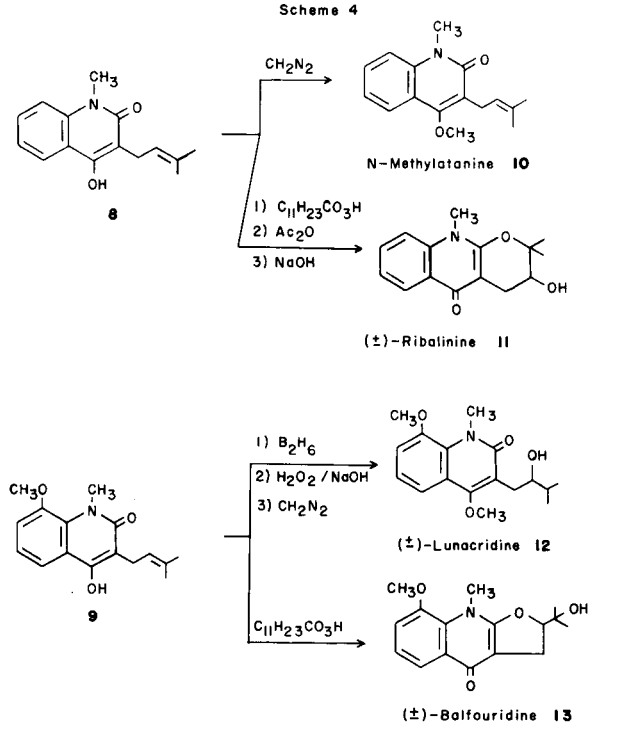
Scheme 3



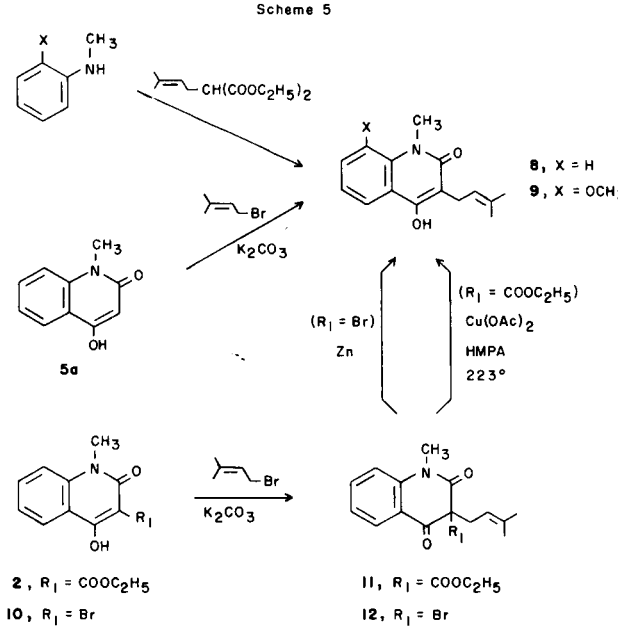
It is interesting to note that **5a** is also accessible in 71% yield by the new methodology described herein (Scheme 2) by the reaction of **1** with ethyl trimethylsilylacetate [R_1 = $Si(CH_3)_3$] followed by cyclization in toluene. It is not clear at what point protodesilation occurs because the intermediate **4** was cyclized directly without characterization, but it is speculated that it happens during the work-up phase in the preparation of **4**, due to the highly unstable nature of the silyl function in relation to the β-ketoester moiety.

A variety of quinoline alkaloids can be readily prepared from 4-hydroxy-3-prenyl-2-quinolones. Scheme 4 contains only a few representative examples of such transformations with many more being the subject of a recent review [9]. Such an appetizing array of natural products available through these intermediates resulted in a variety of routes aimed at the synthesis of the 4-hydroxy-3-prenyl-2-quinolones (Scheme 5).

Scheme 4



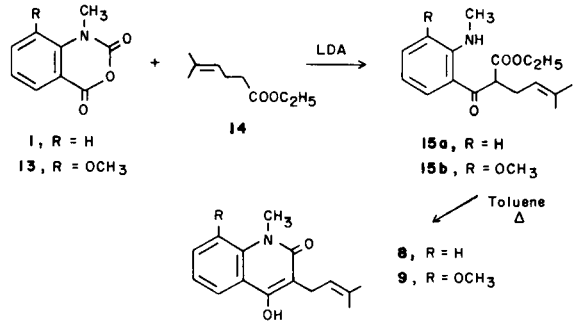
Scheme 5



The most popular method to date has been the reaction of an aniline with 2-prenylmalonic ester in refluxing diphenylether. The reaction is fairly capricious and, although isolated examples are acceptable, generally the yields are less than 30% [10,12]. In addition, the reaction is not amenable to meta substituted anilines (where product mixtures of isomers are likely to occur) or anilines possessing deactivating groups in the ring. Direct alkyla-

tion of **5a** with 4-bromo-2-methyl-2-butene in the presence of potassium carbonate furnished **8** in only 3% yield, the major products being **O**-alkylation of the 4-hydroxyl group and 3,3-dialkylation [14]. The suppression of dialkylation was achieved by the corresponding alkylation of the 3-substituted quinolones **2** (derived from **1**) or **10** [1]. Either decarbethoxylation of **11** with copper(II) acetate in hot hexamethylphosphoramide, or dehalogenation of **12** with zinc dust afforded **8** (28% overall yield from **1**).

It appears that a more convergent synthesis of these 4-hydroxy-3-prenylated quinolones is possible by the new methodology described in this report. An analogous reaction (similar to the preparation of **5**) using 5-methyl-4-hexenoic acid ethyl ester (**14**) should give the desired products. The carbon α to the ester ultimately becomes the 3-carbon of the quinoline and any substituents attached to this carbon will consequently reside in the correct position.



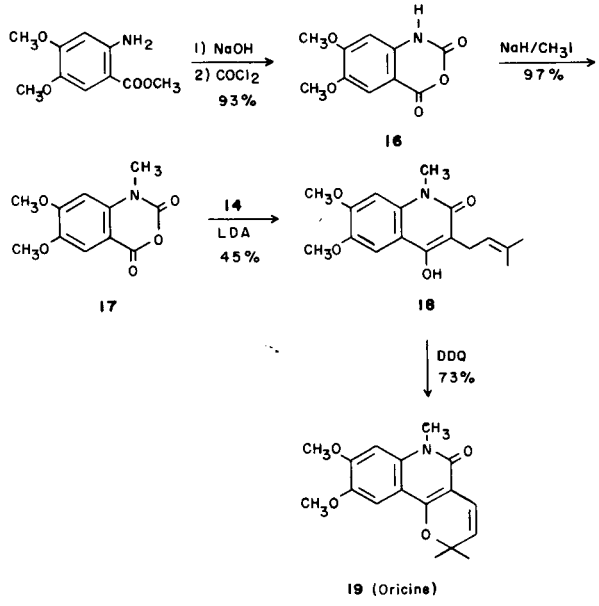
Ester **14** is readily available by the alkylation of lithio ethyl acetate (prepared at $-70°$ from ethyl acetate and LDA) with 4-bromo-2-methyl-2-butene. The reaction of the lithium enolate of **14** with **1** is extremely rapid and produces essentially pure **15a** in less than five minutes. Subsequent cyclization in refluxing toluene affords the desired product **8** in 52% overall yield from **1**. An analogous reaction sequence starting from **13** furnishes **15b** which completely cyclizes to the 8-methoxy derivative **9** (50% yield) when allowed to stand at room temperature for 24 hours.

It should be emphasized that the majority of the reactions described herein were only performed once and the yields are by no means optimized. As in the case of intermediates **4**, compounds **15a** and **15b** were isolated in nearly quantitative yield. The reduction in overall yield of the two step sequence occurs during the cyclization phase and no other products are formed in appreciable yield, only polar degradation materials are seen. Since carbon-nitrogen bond forming reactions are relatively straightforward, minor modifications in the cyclization step should lead to an increasing yield. At present other conditions are being explored.

Another group of alkaloids, 2,2-dimethylpyranoquinolines, are also readily accessible from 4-hydroxy-3-prenyl-2-quinolones. One in particular which would be readily adaptable to the presently described chemistry is oricine (**19**), isolated from the heart-wood or *Oricia suaveolens* [15,16]. A previous synthesis of oricine utilized the *N*-unsubstituted analog of **18** (derived from the reaction of aminoveratrole with diethyl (γ,γ-dimethylallyl)malonate) to produce demethyl-oricine which was then methylated to give the natural product **19** [15,16].

In applying the synthetic route shown (Scheme 6) to the synthesis of **19**, the requisite 4,5-dimethoxy-*N*-methylisatoic anhydride (**17**), which is readily prepared from 2-amino-4,5-dimethoxybenzoic acid methyl ester, reacts with the lithium enolate of **14** at $-50°$ to give the 4,5-dimethoxy analog of **15** in 98% yield, unlike the previously described examples where reaction times were virtually instantaneous, this reaction requires 24 hours for complete consumption of the reactants (probably due to the highly insoluble nature of **17** in the reaction medium). The intermediate is then cyclized to the desired quinolone **18** by stirring in toluene at room temperature for 12 hours. Subsequent treatment of **18** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) furnishes oricine (73% yield) whose spectral properties are identical with those reported in the literature.

Scheme 6



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are noted in reciprocal centimeters. The proton nmr spectra were recorded on Varian T-60 and EM-360 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on LKB 9000 spectrometer.

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions. all reactions were performed under a nitrogen atmosphere.

General Procedure for the Synthesis of 3-Substituted-4-hydroxy-1-methyl-2(1*H*)-quinolinones **5**.

Lithium diisopropylamide (LDA) was prepared under a nitrogen atmosphere in the following manner: to a solution of 2.02 g (0.02 mole) of diisopropylamine in 30 ml of dry tetrahydrofuran at −30° was added 0.02 mole of *n*-butyllithium (1.6 *M* in hexane).

The LDA solution was cooled further to −70° then a solution of 0.01 mole of the appropriate ester in 10 ml of tetrahydrofuran was added dropwise. The mixture was stirred at −70° for 1 hour then a solution [17] of 1.77 g (0.01 mole) of **1** in 35 ml of tetrahydrofuran was added slowly. The mixture was stirred at −70° for 10 minutes, then the reaction was quenched with saturated aqueous ammonium chloride. The organic phase was separated and the aqueous layer was extracted twice with methylene chloride. The organic solutions were combined and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished essentially pure **4**.

4-Hydroxy-1-methyl-2(1*H*)-quinolinone (**5a**).

A solution of **4a** in 30 ml of toluene was refluxed for 45 minutes. The mixture was allowed to cool to room temperature and the precipitate was filtered, washed once with toluene and once with ether to give **5a** (80% yield from **1**), mp 270-273° (lit [2] mp 266-270°).

1,3-Dimethyl-4-hydroxy-2(1*H*)-quinolinone (**5b**).

A solution of **4b** in 35 ml of toluene was refluxed for 45 minutes. The solvent was removed under reduced pressure and ethyl acetate was added. The precipitate was filtered and washed with ethyl acetate and ether to give **5b** (74% from **1**). An analytical sample was crystallized from methylene chloride/ethyl acetate, mp 218-220° (lit [18] mp 217-218°).

4-Hydroxy-1-methyl-3-methylthio-2(1*H*)-quinolinone (**5c**).

A solution of **4c** in 25 ml of toluene was refluxed for 1 hour. The solvent was removed under reduced pressure and the residue chromatographed on a column of silica gel using 5% isopropyl alcohol/methylene chloride to elute the product, **5c** (71% yield from **1**). An analytical sample was crystallized from methylene chloride/ether, mp 158-161°. It should be noted that **4c** also completely cyclizes to **5c** on standing at room temperature for 12 hours; ir (chloroform): 3450, 1625 cm^{-1}; nmr (deuteriochloroform): δ 7.95 (m, 1), 7.75-7.0 (m, 4), 3.67 (s, 3), 2.35 (s, 3); ms: (70 eV) m/e 221 (M^+).

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.7; H, 5.0; N, 6.3; S, 14.5. Found: C, 60.2; H, 5.0; N, 6.2; S, 14.8.

Reanalysis of carbon did not improve the value.

3-Methoxy-*N*-methylisatoic Anhydride (**13**).

To a suspension of 5.0 g of 3-methoxyisatoic anhydride [19] in 80 ml of dimethylacetamide was added 1.25 g of sodium hydride (50% in mineral oil, pentane washed) in portions. The mixture was stirred at room temperature for 1 hour, 4.0 g of methyl iodide was then added, and stirring was continued for 24 hours. The solvent was removed under reduced pressure and water was added to the residue. The organic material was extracted into methylene chloride and the solution was dried over sodium sulfate. The solvent was removed under reduced pressure and the product was crystallized from methylene chloride/ether to give 4.8 g (90%) of **13**, mp 162-164°; ir (chloroform): 1780, 1720, 1610 cm^{-1}; nmr (deuteriochloroform): δ 7.75 (m, 1), 7.35 (s, 1), 7.3 (m, 1), 4.0 (s, 3), 3.8 (s, 3).

Anal. Calcd. for $C_{10}H_9NO_4$: C, 58.0; H, 4.4; N, 6.8. Found: C, 58.3; H, 4.2; N, 6.7.

5-Methyl-4-hexenoic Acid Ethyl Ester (**14**).

A solution of LDA In tetrahydrofuran (200 ml) was prepared from 11.0 g of diisopropylamine and 7.04 g of *n*-butyllithium (1.6 *M* in hexane) as described in the general procedure for the preparation of **5**. After cooling to −70°, a solution of 9.68 g of ethyl acetate in 15 ml of tetrahydrofuran was added dropwise and the mixture was stirred at −70° for 1 hour. A solution of 14.9 g of 4-bromo-2-methyl-2-butene [20] in 30 ml of tetrahydrofuran was added dropwise. The mixture was stirred at −70° for 5 hours then at −50° for 24 hours. After quenching with 2*N* hydrochloric acid, the organic material was extracted into methylene chloride and was dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting liquid was distilled at 70 mm to give 10.0 g (64%) of **14**, bp 113-115° (lit [21] bp 105°/11 mm); ir (chloroform): 1725, 1450, 1380 cm^{-1}; nmr (deuteriochloroform): δ 5.1 (m, 1), 4.15 (q, 2), 2.35 (m, 4), 1.72 (s, 3), 1.65 (s, 3), 1.3 (t, 3).

4-Hydroxy-1-methyl-3-prenyl-2(1*H*)-quinolinone (**8**).

A solution of LDA in 60 ml of tetrahydrofuran was prepared from 4.1 g of diisopropylamine and 2.6 g of *n*-butyllithium (1.6 *M* in hexane) as described in the general procedure for the preparation of **5**. After cooling to −70°, a solution of 3.1 g of **14** in 30 ml of tetrahydrofuran was added dropwise and the mixture was stirred at −70° for 1 hour then a solution [17] of 3.6 g of *N*-methylisatoic anhydride (**1**) in 60 ml of tetrahydrofuran was added slowly and the mixture was stirred at −70° for 20 minutes. The reaction was quenched with saturated aqueous ammonium chloride and the organic phase was separated. The aqueous layer was extracted twice with methylene chloride. The organic solutions were combined and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished 6.2 g (100%) of **15a**. The yellow oil was dissolved in 40 ml of toluene and was refluxed for 45 minutes. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using chloroform to elute the product, 2.5 g (52%) of **8**. An analytical sample was crystallized from methylene chloride/ethyl acetate, mp 162-165° (lit [11] mp 162-163°); ir (chloroform): 3360, 1635, 1610, 1590 cm^{-1}; nmr (deuteriochloroform): δ 8.0 (m, 1), 7.8 (s, broad, 1, OH), 7.7-7.0 (m, 3), 5.35 (m, 1), 3.7 (s, 3), 3.52 (d, J = 7.5 Hz, 2), 1.8 (s, 3), 1.75 (s, 3).

4-Hydroxy-8-methoxy-1-methyl-3-prenyl-2(1*H*)-quinolinone (**9**).

The reaction, using 2.0 g of diisopropylamine, 1.28 g of *n*-butyllithium, 2.07 g of **13**, and 1.56 g of **14**, was performed similar to that of **8** to give 3.2 g (100%) of **15b**. The yellow oil was dissolved in 30 ml of toluene and was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure and the residue was crystallized from ether/pentane to give 1.4 g (50%) of **9**, mp 147-150° (lit [12] mp 145-148°); nmr (deuteriochloroform): δ 7.55 (m, 1), 7.3-6.95 (m, 3), 5.35 (m, 1), 3.9 (s, 3), 3.83 (s, 3), 3.45 (d, J = 7.5 Hz, 2), 1.78 (s, 3), 1.72 (s, 3).

4,5-Dimethoxy-*N*-methylisatoic Anhydride (**17**).

To a suspension of 35.0 g of **16** [22] in 400 ml of dimethylacetamide was added 7.6 g of sodium hydride (50% in mineral oil, pentane washed) in portions and the mixture was stirred at room temperature for 3 hours. Then 30.0 g of methyl iodide was added and stirring was continued for 24 hours. Approximately one half of the solvent was removed under reduced pressure then the remainder was poured into cold water, the resulting precipitate was filtered, washed with water, ethanol, then ether to give 35.8 g (97%) of **17**, mp 224-227° (lit [23] mp 213-217°); ir (chloroform): 1770, 1720, 1620, 1610 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 7.4 (s, 1), 6.77 (s, 1), 4.03 (s, 3), 3.9 (s, 3), 3.56 (s, 3).

Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.7; H, 4.7; N, 5.9. Found: C, 55.6; H, 4.6; N, 6.0.

6,7-Dimethoxy-4-hydroxy-1-methyl-3-prenyl-2(1*H*)-quinolinone (**18**).

A solution of LDA in 75 ml of tetrahydrofuran was prepared from 2.0 g of diisopropylamine and 1.28 g of *n*-butyllithium (1.6 *M* in hexane) as described in the general procedure for the preparation of **5**. After cooling to −70°, a solution of 1.56 g of **14** in 15 ml of tetrahydrofuran was added dropwise. After stirring at −70° for 1 hour a suspension of 2.37 g of **17** in 100 ml of tetrahydrofuran was added slowly then the mixture was

stirred at −50° for 24 hours. The reaction was quenched with saturated aqueous ammonium chloride and the organic phase was separated. The aqueous layer was extracted twice with methylene chloride. The organic solutions were combined and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished 3.4 g (98%) of the uncyclized intermediate. The yellow oil was dissolved in toluene (35 ml) and was stirred at room temperature for 12 hours. The resulting precipitate was filtered and washed with toluene then ether to give 1.35 g (45%) of **18**, mp 228-230°; ir (potassium bromide): 1610 cm^{-1}; nmr (DMSO-d_6): δ 7.55 (s, 1), 6.95 (s, 1), 5.2 (m, 1), 3.96 (s, 3), 3.9 (s, 3), 3.63 (s, 3), 3.32 (d, J = 7.5 Hz, 2), 1.78 (s, 3), 1.65 (s, 3).

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.3; H, 7.0; N, 4.6. Found: C, 67.3; H, 6.8; N, 4.3.

Oricine (**19**).

A mixture of 0.9 g of **18** and 0.9 g of 2,3-dichloro-5,6-dicyanobenzoquinone in 400 ml of toluene was stirred at 80° for 3 hours. Any insoluble material was filtered and the filtrate was washed with dilute sodium bicarbonate then with saturated sodium chloride solutions. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to give 0.65 g (73%) of **19**. An analytical sample was crystallized from ether, mp 155-158° (lit [16] mp 150-152°); ir (potassium bromide): 1625 cm^{-1}; nmr (deuteriochloroform): δ 7.32 (s, 1), 6.76 (d, J = 10 Hz, 1), 6.73 (s, 1), 5.5 (d, J = 10 Hz, 1), 4.0 (s, 3), 3.96 (s, 3), 3.69 (s, 3), 1.53 (s, 6).

Acknowledgement.

The authors wish to thank Dr. Sandor Barcza and associates for running the ir and nmr spectra, Mr. William Bonkoski and associates for performing the microanalyses, and Mr. Robert Clark for running the mass spectra.

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