2*H*-3,1-Benzoxazine-2,4-(1*H*)-dione (Isatoic Anhydride). **15** [1]. Reactions With Lactone Enolates.

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The reaction of *N*-methylisatoic anhydride, **1**, with the lithium enolates derived from various butyrolactones or δ-valerolactone produces stable anthranoyl lactone derivatives **4**. Heating these products in toluene results in a cyclization to afford 4-hydroxy-3-(2-hydroxyalkyl)-1-methyl-2(1*H*)-quinolinones, **8** and **14**, in good yields.

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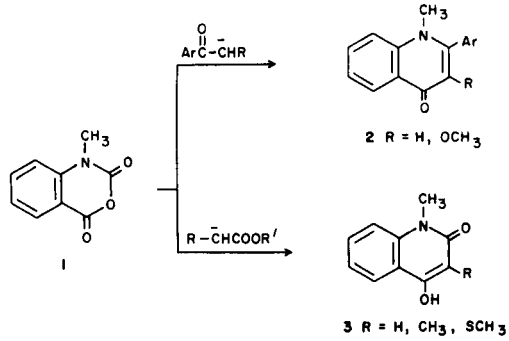
In recent publications from this laboratory, it has been shown that *N*-methylisatoic anhydride, **1**, reacts at low temperatures with lithium enolates derived from aromatic ketones [2] or non-activated esters [3] to produce 2-aryl-4-quinolones, **2**, or 4-hydroxy-2-quinolones, **3**, respectively.



In an effort to expand the scope of these condensations, the reaction of **1** with the lithium enolate of various lactones was investigated. The experimental techniques employed were essentially the same as those described in earlier reports [2,3].

The reaction of **1** with the enolate of butyrolactone (generated with two equivalents of lithium diisopropylamide [4]) proceeds very rapidly at −65° and is complete within one minute. The conversion proceeds in quantitative yield to afford a yellow crystalline product whose spectral properties (see experimental section) indicate it to be the β-ketolactone **4a**. This intermediate can be recrystallized and is relatively stable. It can be stored at room temperature for several weeks with no appreciable decomposition. This is in sharp contrast to the acyclic intermediates produced in similar reactions of **1** with ketone or ester enolates, which spontaneously cyclize upon work-up or within several days at room temperature [2,3].

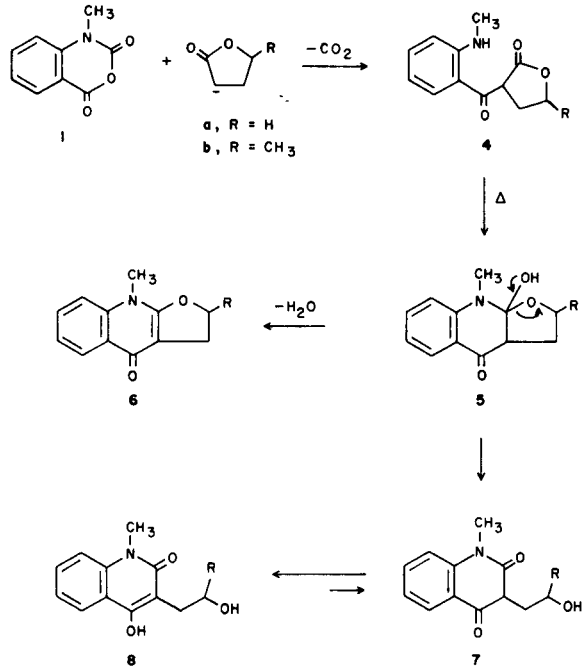
The potential cyclization of **4** presents some interesting possibilities. The transient intermediate **5**, which would be formed in such a process, can undergo two modes of elimination. Dehydration would form a dihydrofuroquinolone, **6**, a highly desirable ring skeleton found in a host of naturally-occurring alkaloids [5]. Alternately, ring fission (depicted by the curved arrows) which is in essence an elimination of an alcohol, would produce 3-(2-hydroxyethyl)-2-quinolone derivatives **8** (see Scheme 1).

When a solution of **4a** is refluxed in toluene for two hours, a new product forms. Upon cooling, the product crystallizes directly from the reaction mixture and is isolated analytically pure in 98% yield. Analysis of the spectral data indicates that the product possesses structure **8a**. Evidently, the dehydration process leading to **6a** does not occur even to a minor extent (at least to the limits of visual detection).

The cyclization of **4a** was also attempted under acidic conditions at ambient temperature. Upon addition of 1.0*N* hydrochloric acid to a solution of **4a** in methanol, the yellow color of the starting material immediately disappears and a single product is formed. Again, analogous to the thermal conditions, only **8a** is produced.

A parallel sequence of reactions using 5-methylbutyrolactone (γ-valerolactone) was performed under the same

SCHEME I

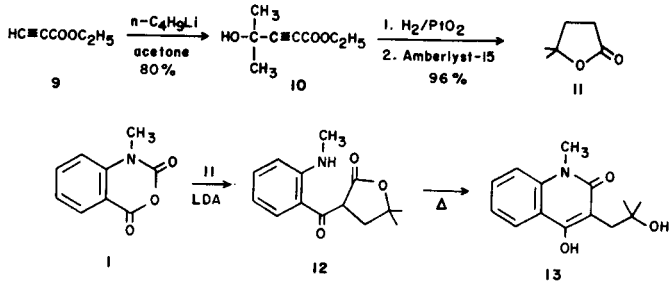


conditions as described above. Compound **4b** was produced in 99% isolated yield. Thermal cyclization produced **8b** as the only isolable material.

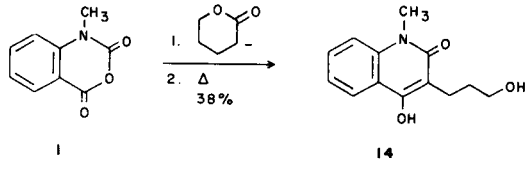
In an effort to reduce the susceptibility of the molecule to the ring fission pathway, it was felt that using a 5-disubstituted butyrolactone would suppress the formation of **8** and the dehydrative route (leading to **6**) would become competitive since now elimination of a tertiary alcohol is required to produce **8**.

The preparation of the required disubstituted butyrolactone, **11**, is easily accomplished according to the method outlined in Scheme 2. When *N*-methylisatoic anhydride, **1**, is allowed to react at −65° with the lithium enolate derived from **11**, a rapid reaction ensues and **12** is isolated as a yellow oil in nearly quantitative yield. Heating **12** in toluene produces a single product, **13**, which again results from the ring fission pathway. It is interesting to note that in contrast to derivatives **4**, compound **12** exhibits reduced stability and even undergoes appreciable conversion to **13** within one hour at room temperature.

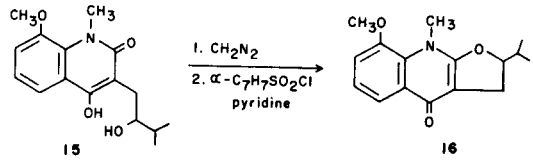
SCHEME 2



Extending the method to include reaction with δ-valerolactone produces the corresponding 3-hydroxypropyl quinolone, **14**, although in lower overall yield.



The presently described methodology has potential utility in the synthesis of the alkaloid lunacrine, **16**. The conversion of **15** → **16** has been described by Goodwin and Horning [6]. It can be envisioned that **15** can easily be prepared by the reaction of 3-methoxy-*N*-methylisatoic anhydride with the enolate of 5-isopropylbutyrolactone. This possibility is currently being explored.



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 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 mass spectra were determined on an LKB 9000 spectrometer.

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.

Dihydro-3-(2-methylaminobenzoyl)-2(3*H*)-furanone (**4a**).

To a solution of 4.1 g (0.04 mole) of diisopropylamine in 150 ml of tetrahydrofuran (at −30°) was added 2.6 g (0.045 mole) of *n*-butyllithium (1.6*M* in hexane). The LDA solution was cooled to −65° then a solution of 1.75 g (0.021 mole) of butyrolactone in 10 ml of tetrahydrofuran was added dropwise. After stirring at −65° for one hour, a solution of 3.6 g (0.021 mole) of **1** in 75 ml of tetrahydrofuran was added slowly. The resulting yellow suspension was stirred at −65° for an additional 15 minutes. The mixture was quenched with saturated ammonium chloride solution and the organic phase was separated. The aqueous phase was extracted 2 × with methylene chloride. The organic solutions were combined and dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting yellow solid was crystallized from methylene chloride/ether to give 4.3 g (98%) of **4a**, mp 128-130°; ir (chloroform): 3360, 1770, 1631 cm^{-1}; nmr (deuteriochloroform): δ 8.6 (m, broad, 1H, NH), 8.05-7.3 (m, 2H), 6.85-6.5 (m, 2H), 4.75-4.25 (m, 3H), 2.95 (d, 3H), 2.85-2.4 (m, 2H).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.7; H, 6.0; N, 6.4. Found: C, 66.1; H, 6.0; N, 6.4.

Dihydro-5-methyl-3-(2-methylaminobenzoyl)-2(3*H*)-furanone (**4b**).

The reaction using 5-methylbutyrolactone was performed on the same scale, in the same manner as described for the preparation of **4a**. The product was crystallized from ether to give 4.6 g (99%) of **4b**, mp 97-100°; ir (chloroform): 3360, 1770, 1630 cm^{-1}; nmr (deuteriochloroform): δ 8.5 (m, broad, 1H, NH), 8.0-7.3 (m, 2H), 6.85-6.5 (m, 2H), 5.05-4.45 (m, 2H), 2.9 (d, 3H), 2.8-1.95 (m, 2H), 1.45 (dd, 3H).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5; N, 6.0. Found: C, 67.2; H, 6.5; N, 5.9.

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

A solution of 0.6 g of **4a** in 10 ml of toluene was refluxed for 2 hours. The mixture was allowed to cool to room temperature and the resulting precipitate was filtered, washed 1 × with toluene, then 2 × with ether to give 0.59 g (98%) of **8a**, mp 182-183°; ir (potassium bromide): 3230, 1626, 1605, 1580, 1235 cm^{-1}; nmr (deuteriochloroform): δ 8.6 (broadening of the base line, 2H, exchangeable), 8.07 (dd, 1H), 7.8-7.1 (m, 3H), 3.8 (m, 2H), 3.65 (s, 3H), 3.0 (s, 2H).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.7; H, 6.0; N, 6.4. Found: C, 66.1; H, 6.2; N, 6.4.

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

A solution of 2.0 g of **4b** in 30 ml of toluene was refluxed for 2 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a Waters Prep-500 apparatus using 7% 2-propanol/chloroform to elute the product, 1.4 g (70%) of **8b**. An analytical sample was crystallized from methylene chloride/ether, mp 152-154°; ir (potassium bromide): 3170, 1627, 1595, 1555 cm^{-1}; nmr (deuteriochloroform): δ 10.6 (s, broad, 1H), 8.6 (s, broad, 1H, OH), 8.0 (dd, 1H), 7.7-6.95 (m, 3H), 4.3-3.9 (m, 1H), 3.62 (s, 3H), 3.0-2.8 (m, 2H), 1.25 (d, J = 6 Hz, 3H); ms (70 eV): m/e 233 (M^+).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5; N, 6.0. Found: C, 66.8; H, 6.3; N, 5.8.

4-Hydroxy-4-methyl-2-pentynoic Acid Ether Ester (**10**).

To a solution of 5.9 g of ethyl propiolate (**9**) in 125 ml of tetrahydrofuran at −65° was added dropwise 3.8 g of *n*-butyllithium (1.6*M* in hexane). After the addition, the solution was stirred at −70° for one hour then a solution of 3.5 g of acetone in 10 ml of tetrahydrofuran was added dropwise. The mixture was then stirred at −70° for 24 hours. The reaction was quenched with saturated ammonium chloride solution and the organic phase was separated. The aqueous layer was extracted 2 × with methylene chloride. The organic solutions were combined and dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting liquid was distilled to give 7.5 g (80%) of **10**, bp 46-49° (0.2 mm); ir (chloroform): 3605, 3450, 3320, 2240, 1690 cm^{-1}; nmr (deuteriochloroform): δ 4.23 (q, 2H), 2.72 (s, 1H), 1.55 (s, 6H), 1.31 (t, 3H).

Dihydro-5,5-dimethyl-2(3*H*)-furanone (**11**).

A solution of 4.0 g of **10** in 50 ml of ethyl acetate was hydrogenated at one atmosphere over platinum oxide until the theoretical amount of hydrogen was absorbed (15 minutes). The catalyst was filtered and the filtrate was evaporated. The residual oil was dissolved in 25 ml of methylene chloride and then 0.5 g of Amberlyst-15 resin was added. After stirring at room temperature for 4 hours, the resin was filtered and the solvent was removed under reduced pressure. The resulting liquid was distilled at 15 mm to give 2.8 g (96%) of **11**, bp 88-90° (lit [7] bp 40-42°, 0.01 mm); ir (chloroform): 1755 cm^{-1}; nmr (deuteriochloroform): δ 2.75-2.4 (m, 1H), 2.2-1.83 (m, 1H), 1.4 (s, 6H), 1.45-0.7 (m, 2H).

4-Hydroxy-3-(2-hydroxy-2-methylpropyl)-1-methyl-2(1*H*)-quinolinone (**13**).

Lithium diisopropylamide was prepared in 50 ml of tetrahydrofuran from 2.0 g of diisopropylamine and 1.28 g of *n*-butyllithium according to the procedure described for the preparation of **4a**. After cooling to −65°, a solution of 1.15 g of **11** in 5 ml of tetrahydrofuran was added dropwise. The mixture was stirred at −65° for one hour then a solution of 1.8 g of **1** in 50 ml of tetrahydrofuran was added slowly. After the addition, the mixture was stirred at −65° for 20 minutes. The reaction was quenched with saturated ammonium chloride solution and the organic phase was separated. The aqueous layer was extracted 2 × with methylene chloride. The organic solutions were combined and dried over sodium sulfate. The solvent was removed under reduced pressure to give 2.8 g of **12** as a yellow oil. This was dissolved in 25 ml of toluene and was refluxed for 4 hours. The mixture was concentrated to one-half volume at which point the product crystallized. The solid was washed with toluene then ether to give 1.6 g (65%) of **13**, mp 193-196°; ir (chloroform): 3620, 3200, 1630, 1610, 1580 cm^{-1}; nmr (deuteriochloroform): δ 12.4 (s, broad, 1H), 8.6 (s, broad, 1H), 8.05 (dd, 1H), 7.75-7.05 (m, 3H), 3.73 (s, 3H), 3.0 (s, 2H), 1.22 (s, 6H).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9; N, 5.7. Found: C, 67.8; H, 6.9; N, 5.5.

4-Hydroxy-3-(3-hydroxypropyl)-1-methyl-2(1*H*)-quinolinone (**14**).

The reaction of **1** with 2.0 g of δ-valerolactone was performed on the same scale, in the same manner as the preparation of **4a**. The crude acyclic intermediate was dissolved in 50 ml of toluene and was refluxed for 2 hours. The solvent was removed under reduced pressure and the residue was chromatographed on a Waters Prep-500 apparatus using 10% 2-propanol/methylene chloride to elute the product, 1.65 g (38%) of **14**. An analytical sample was crystallized from methylene chloride, mp 161-163°; ir (potassium bromide): 3220, 1635, 1605, 1575 cm^{-1}; nmr (deuteriochloroform): δ 8.0 (dd, 1H), 7.75-7.05 (m, 3H), 3.56 (s, 3H), 3.43 (t, 2H), 2.68 (t, 2H), 1.67 (m, 2H), hydroxyls are seen as a broadening of the base line; ms (70 eV): m/e 233 (M^+).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5; N, 6.0. Found: C, 66.5; H, 6.4; N, 5.8.

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[2] G. M. Coppola, *ibid.*, **19**, 727 (1982).

[3] G. M. Coppola, *ibid.*, **20**, 1217 (1983).

[4] If one equivalent of LDA is used, only 50% reaction occurs due to partial quenching of the enolate with the highly acidic proton of the developing β-ketolactone **4**.

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