Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 16 [1]. Facile Construction of the Furacridone Ring System

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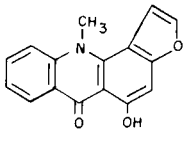
March 2, 1984

The synthesis of the furacridone ring skeleton was accomplished in one step by the reaction of *N*-methylisatoic anhydride (**7**) with the lithium enolate derived from 6,7-dihydro-4(5*H*)-benzofuranone (**10**). Aromatization of the C ring with DDQ furnished 5-dehydroxyfuracridone (**6**).

J. Heterocyclic Chem., **21**, 1569 (1984).

Furacridone (**1**) is one of a series of acridone alkaloids which can be found in the root portion of the plant *Ruta graveolens* [2].



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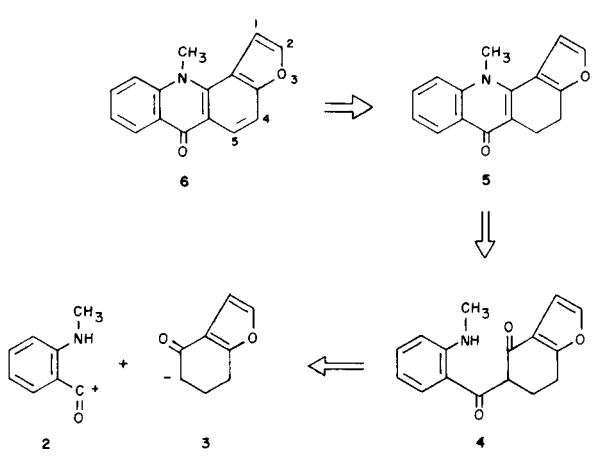
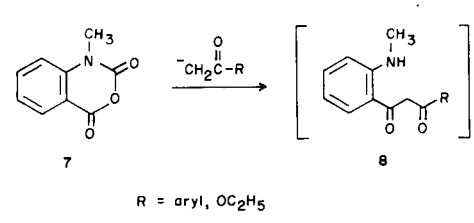
The synthetic strategy (Scheme I) for the convergent assembly of the ring system hinges on the ability to prepare the β-diketone **4**. A subsequent dehydrative cyclization would furnish the basic skeleton **5** which, upon aromatization, would then afford 5-dehydroxyfuracridone (**6**). Intermediate **4**, in turn, should be accessible from the two charged species **2** and **3**.

In previous reports from this laboratory [3,4] it has been shown that *N*-methylisatoic anhydride (**7**) reacts readily with ketone or ester enolates to initially produce unstable intermediates **8** which, upon cyclization, furnish either 4- or 2-quinolones. These findings clearly demonstrate the viability of *N*-methylisatoic anhydride as an effective synthetic equivalent for **2**.

6,7-Dihydro-4(5*H*)-benzofuranone (**10**), the precursor to the charged species **3**, was conveniently prepared in one step from 1,3-cyclohexanedione (**9**) using a procedure simi-

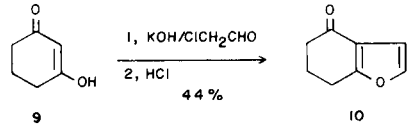
Scheme I





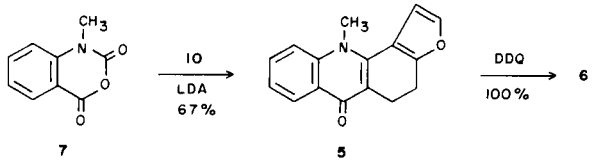
R = aryl, OC_2H_5

lar to that described by Stetter and Lauterbach [5]. Alkylation of **9** with chloroacetaldehyde in the presence of potassium hydroxide directly furnished **10** in moderate yield upon acidic work-up.



The generation of **3** is readily accomplished by the deprotonation of **10** with lithium diisopropylamide at −65°. The reaction of *N*-methylisatoic anhydride (**7**) with two equivalents of **3** proceeds smoothly at −40° with **7** being completely consumed within two hours. When a stoichiometric ratio of **7** and **3** are used, a significant quantitity of unreacted **7** is observed in the reaction mixture. This may be attributed to partial quenching of the enolate **3** with the highly acidic proton of the developing β-diketone **11** [6].

Intermediate **4** is not isolable and spontaneously cyclizes upon work-up therefore allowing **5** to be isolated directly from the reaction. Aromatization of the C ring is easily accomplished with DDQ in toluene at 70° to give **6** in quantitative yield. The reaction is extremely rapid and is complete within 30 seconds.



This facile construction of the basic furacridone skeleton presents the possibility of synthesizing a variety of interesting derivatives, including the natural product **1**, pro-

vided that the appropriate functionalized starting materials can be prepared, or through potential manipulations of the described intermediates.

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 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton 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 (od) sample tubes. General nmr spectra and instrumental parameters employed were: Internal deuterium lock to the solvent; spectral width of 1000 Hz; a pulse width of 3μs 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.

6,7-Dihydro-4(5*H*)-benzofuranone (**10**).

To a solution of 1,3-cyclohexanedione (22.4 g, 0.2 mole) in methanol (80 ml) was added a solution of potassium hydroxide (11.2 g, 0.2 mole) in water (16 ml). After the initial exothermic reaction subsided the mixture was allowed to cool to room temperature (30 minutes) then, under ice cooling, chloroacetaldehyde (33 g of a 50% aqueous solution, 0.021 mole) was added. After stirring at room temperature for 24 hours, 2*N* hydrochloric acid (200 ml) was added. After 10 minutes the mixture was extracted with methyl *t*-butyl ether (2 × 300 ml). The organic phase was dried (sodium sulfate) and evaporated. The residual oil was distilled on a Kugelrohr apparatus at 20 mm to give **10**, 12.0 g (44%), (lit [7] bp 118-122°); ir (chloroform): 1681, 1451, 1242.5, 1121.5 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.28 (1H, d, J = 2.25 Hz), 6.64 (1H, d, J = 2.25 Hz), 2.89 (2H, t), 2.50 (2H, m), 2.20 (2H, m).

4,5-Dihydro-11-methylfuro[2,3-*c*]acridin-6(11*H*)-one (**5**).

To a solution of diisopropylamine (6.7 g, 0.066 mole) in THF (150 ml) at −30° was added *n*-butyllithium (4.4 g, 0.068 mole, 1.7 *M* in hexane). After cooling to −65°, a solution of **10** (9.3 g, 0.068 mole) in THF (30 ml) was added dropwise. The mixture was stirred at −65° for 45 minutes then a solution of **7** (6.0 g, 0.034 mole) in THF [8] (120 ml) was added slowly. The mixture was placed in a cold bath at −40° and stirring was continued for 2 hours. Cold, saturated ammonium chloride was added to the reaction then the mixture was extracted twice with methylene chloride. The organic phase was dried (sodium sulfate) and evaporated. The residual solid was recrystallized from methylene chloride-ethyl acetate to give **5**, 5.7 g (67%), mp 212-215°; ir (chloroform): 1604, 1570, 1519 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.47 (1H, dd), 7.65-7.25 (4H, m), 6.72 (1H, d, J = 2 Hz), 3.97 (3H, s), 3.16 (2H, t), 2.88 (2H, t); ^{13}C nmr (deuteriochloroform): δ 175.4, 160.3, 144.9, 141.5, 141.4, 131.4, 126.6, 125.7, 123.1, 115.4, 114.8, 113.3, 189.7, 37.9, 21.9, 21.4.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.5; H, 5.2; N, 5.6. Found: C, 76.2; H, 5.1; N, 5.3.

11-Methylfuro[2,3-*c*]acridin-6(11*H*)-one (**6**).

To a stirred solution of **5** (251 mg, 1 mmole) in toluene (80 ml) at 70° was added DDQ (460 mg, 2 mmoles). After stirring at 70° for 15 minutes, the solvent was removed under reduced pressure. Chloroform was added to the residue and any insoluble material was filtered off. The filtrate was chromatographed on a column of silica gel using 2% methanol-chloroform to elute the product **6**, 250 mg (100%). An analytical sample was recrystallized from methylene chloride-ethyl acetate, mp 218-220°; ir (chloroform): 1628, 1598, 1496, 1219 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.5 (1H, dd), 8.46 (1H, d, J = 10 Hz), 7.67 (2H, m), 7.48-7.20 (4H, m), 4.1 (3H, s); ^{13}C nmr (deuteriochloroform): δ 177.6, 158.9, 143.5, 143.1, 139.5, 133.2, 127.4, 124.8, 122.9, 121.7, 118.8, 115.2, 115.0, 108.4, 107.5, 38.5.

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.1; H, 4.4; N, 5.6. Found: C, 77.2; H, 4.4; N, 5.6.

Acknowledgement.

The author wishes to thank Frances McCrink for running the infrared spectra, Lucille Lowe for running the ^1H nmr spectra, Mike Shapiro and Mike Kolpak for the ^{13}C nmr spectra, and Jacki Misuro for performing the microanalyses. Also special thanks to Ellen Brennan for typing the manuscript.

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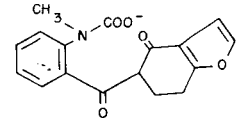
[5] H. Stetter and R. Lauterbach, *Ann. Chem.* **652**, 40 (1962).

[6] The reaction of **7** with **3** initially produces the non decarboxylated species **11**.



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[7] W. A. Remers and G. S. Jones, Jr., *J. Heterocyclic Chem.*, **12**, 421 (1975).

[8] Some warming is required to keep the *N*-methylisatoic anhydride in solution.