Synthesis of 2,3-Quinolinedicarboxylic Acid

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A new procedure for making 2,3-quinolinedicarboxylic acid (**6**), starting with aniline and maleic anhydride has been developed. Evidence for the formation of 2-anilino-3-formyl-*N*-phenylmaleimide (**7**) in the cyclization of 3-phenylimino-4-dimethylaminomethylene-*N*-phenylsuccinimide (**4a**) to *N*-phenylacridinimide (**5a**) is presented.

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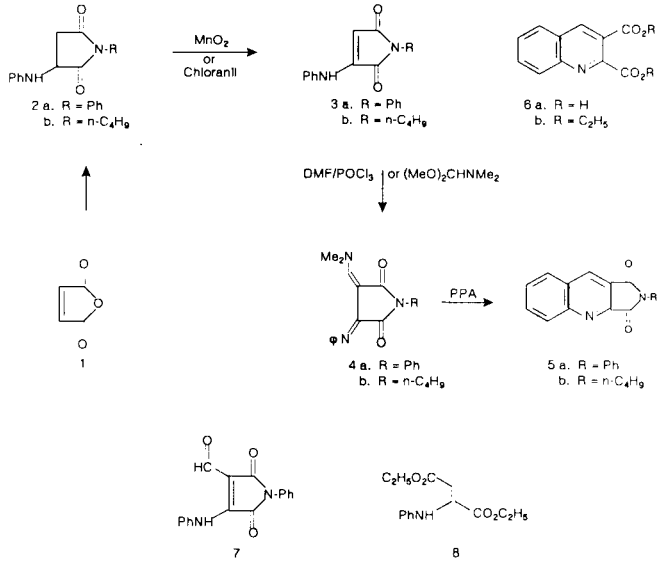
With the introduction of the new class of imidazolinone herbicides [1], 2,3-quinolinedicarboxylic acid (**6a**) has become an important intermediate. Examination of the existing procedures for making the diacid showed that neither the often-referenced Friedlander reaction [2] of 2-aminobenzaldehyde with diethyl oxalacetate to give diester **6b**, nor ozonolysis of acridine [3] to give **6a** is acceptable, due to the difficulty in preparing and storing 2-aminobenzaldehyde, the low yield of products, and the limited supply of acridine. In a recent paper [4] the use of the stable 2-nitrobenzaldehyde was described in the condensation with diethyl (diethyloxyphosphinyl) succinate to give the quinoline *N*-oxide, which was then heated with phosphorus trichloride to give the quinoline diester **6b**.

A route to **6a** that appears to have useful synthetic applications starts with the reaction of aniline with diethyl oxalacetate to provide diethyl anilinofumarate (**8**), and conversion to the quinoline diester **6b** by heating in dimethylformamide and phosphorus oxychloride [5]. We describe our attempt to prepare diacid **6a** by a related sequence, which uses the low cost starting materials, maleic anhydride and aniline. The anilinosuccinimide **2a**, which can be formed in 94% yield from maleic anhydride and two moles of aniline [6], was oxidized to the anilinomaleimide **3a** with manganese dioxide or chlornil. In an attempt to prepare the acridinimide **5a** directly from **3a** and the Vilsmeier reagent from dimethylformamide and phosphorus oxychloride at temperatures of 80-135°, only polymeric material was isolated. In other experiments we have demonstrated that this temperature range will provide good to excellent yields of diester **6b** from diethyl anilinofumarate [5a]. When **3a** was stirred with the Vilsmeier reagent in methylene chloride, a 25% yield of the iminosuccinimide **4a** was isolated from a tarry reaction mixture. The same product was formed in a considerably higher yield (77%), however, on heating **3a** with dimethyl formamide dimethyl acetal. Ring closure of **4a** in polyphosphoric acid to acridinimide **5a** and base hydrolysis, followed by acidification gave **6a** in 54% yield based on maleic anhydride.

Scheme



To determine if changing the electronic effect of the maleimide ring would allow the *n*-alkylacridinimide **5a** to be formed directly from **3a**, aniline was added to *n*-butyl maleimide and the anilinosuccinimide **2b** was oxidized with manganese dioxide to provide **3b** in good yield. However, the reaction of **3b** with dimethylformamide and phosphorus oxychloride gave mainly polymeric material, with a low yield of **4b**. As was observed with the *N*-phenyl derivative **3a**, the acridinimide **5b** could be produced from **3b** in two steps by first reacting with dimethylformamide dimethyl acetal, followed by a brief heating in polyphosphoric acid.

The fact that cyclization of diethyl anilinofumarate to diester **6b** occurs directly, whereas the analogous transformation from **3** to **5** proceeds stepwise, indicates that **4** or its protonated form is not the intermediate undergoing cyclization. Supportive of this conclusion was the observation that heating **4a** in refluxing dimethylformamide for one hour gave **5a** in only a 5% yield. By contrast, the conversion of **4a** to **5a** in polyphosphoric acid was complete

after 15 minutes at 150°. That the aldehyde **7** is first formed from **4a**, then cyclized was demonstrated by the isolation of **7** in 89% yield after stirring **4a** in warm polyphosphoric acid for five minutes, and converting **7** to **5a** in 94% yield under the same conditions used for the formation of **5a** from **4a**.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin Elmer 297 spectrophotometer. Nuclear magnetic resonance spectra were taken at 300 MHz on a Varian XL-300 NMR spectrometer, and chemical shifts are given relative to internal tetramethylsilane. Mass spectra were obtained on a Finnigan Model 4500 quadrupole mass spectrometer.

3-Anilino-*N*-phenylsuccinimide (**2a**).

A mixture of 9.8 g (0.1 mole) of maleic anhydride, 18.6 g (0.20 mole) of aniline and 75 ml of *o*-dichlorobenzene was heated at 175-180° for 1 hour. At 175° all of the solid went into solution. A Dean Stark trap was used to collect the condensate during the reaction. Cooling gave a thick precipitate, which was stirred in 50 ml of ethanol, cooled in ice and collected to give 16.6 g of colorless solid, mp 211-214.5° (lit [6] mp 211-212°); ir, 3350, 3180, 1670, 1640, 1600 cm^{-1}. Concentration of the filtrate and slurring in 50 ml of ethanol gave another 3.0 g of product. Total yield of **2a** was 74%.

3-Anilino-*N*-phenylmaleimide (**3a**).

A mixture of 1.98 g (7.5 mmoles) of anilinosuccinimide **2a**, 1.96 g (22.5 mmoles) of manganese dioxide (Aldrich brown activated) and 45 ml of toluene was refluxed for 6 hours. The mixture was filtered while hot. The resulting solid was heated in another 50 ml of boiling toluene and the mixture was filtered while hot. Cooling the combined toluene filtrates gave 450 mg of **3a** as yellow-orange needles. Concentration of the toluene solution gave another 360 mg, mp 228-233° (lit [7] mp 230-230.5°); ir, 3225, 3180 (sh), 1755 (sh), 1695, 1615, 1590 cm^{-1}.

A mixture of 1.32 g (5.0 mmoles) of **2a**, 1.22 g (5.0 mmoles) of chloranil and 30 ml of xylene was refluxed for 4 hours. The mixture was cooled to room temperature and the precipitate was collected and recrystallized from acetonitrile to give 0.86 g (65%), mp 233-235°.

3-Phenylimino-4-dimethylaminomethylene-*N*-phenylsuccinimide (**4a**).

A solution of 13.2 g (0.5 mole) of anilinomaleimide **3a**, 11.9 g (0.10 mole) of dimethylformamide dimethyl acetal and 250 ml of toluene was refluxed for 3 hours. Cooling the solution gave a dark maroon solid which was stirred in 200 ml of hot ethanol and collected. Yield of **4a**, mp 196-200.5° was 12.3 g (77%). Recrystallization from acetonitrile gave brown-gold crystals, mp 199.5-201.5° dec; ir, 1700, 1635 (sh), 1620 and 1595 cm^{-1}; ms: m/e 319 (M^+).

Anal. Calcd. for $C_{19}H_{17}N_3O_2$: C, 71.47; H, 5.33; N, 13.17. Found: C, 71.42; H, 5.56; N, 12.98.

To a solution of 0.37 g (5 mmoles) of dimethylformamide and 15 ml of methylene chloride was added dropwise with cooling (15-20°) 1.68 g (11 mmoles) of phosphorus oxychloride. The slurry was stirred at room temperature for 30 minutes and the anilinomaleimide **3a** was added as a solid. The mixture was refluxed for 3 hours and a dark maroon solution formed. The solution was cooled in ice and 20 ml of methylene chloride and 10 ml of water were added. Aqueous sodium carbonate was added until the aqueous phase was alkaline and the two layers were stirred for 15 minutes and filtered. The organic phase was separated and evaporated to give a viscous oil, which was dissolved in 40 ml of ethanol. Cooling gave 200 mg of orange solid, mp 189-195°. Evaporation of solvent and recrystallization from ethyl acetate gave another 200 mg of **4a**.

When the Vilsmeier reaction was attempted in refluxing monochlorobenzene, toluene or ethylene dichloride, only polymeric material was obtained.

N-Phenylacridinimide (**5a**).

A solution of 2.0 g of **4a** in 60 g of polyphosphoric acid was heated at 140-145° with occasional stirring for 20 minutes. The red-maroon solution was cooled and poured into 400 g of ice and water. The crude product was collected, stirred in 100 ml of hot ethanol and isolated as an off-white solid, 1.54 g (90%), mp 315-321° (lit [8], mp 322-323°); ir, 1775 (sh), 1710, 1590 cm^{-1}.

2,3-Quinolinedicarboxylic Acid (**6a**).

A mixture of 274 mg (1.0 mmole) of **5a**, 160 mg (4.0 mmoles) of sodium hydroxide in 1.5 ml of water and 10 ml of ethanol was refluxed for 3 hours. More water (10 ml) was added and ethanol was removed by distillation and the resulting solution was refluxed 2 hours. The solution was cooled in an ice bath and concentrated hydrochloric acid was added dropwise until the mixture was acidic. The thick mixture was filtered, washed with water and dried in an vacuum oven at 60°/25 inches of Hg. Weight of **6a** was 179 mg, mp 279-281° (dec with loss of carbon dioxide at 105-120°). Infrared of dried material had peaks at 1710 cm^{-1} and broad band centered at 1510 cm^{-1} with shoulders at 1610, 1595, 1560, 1535, 1495 cm^{-1}. The purity of the diacid as determined by hplc was 97%.

N-Butylmaleimide.

Reaction of *n*-butylamine with maleic anhydride to give maleamic acid was carried out according to the published method [9]. The maleamic acid was converted to *N*-butylmaleimide by a modified procedure. A mixture of 12.0 g (0.07 mole) of *n*-butylmaleamic acid, 29 ml of acetic anhydride and 2.73 g of anhydrous sodium acetate was heated at 85-90° for 30 minute. The solution was cooled to 40° and poured into 55 ml of water. The layers were stirred at room temperature for 15 minutes, then diluted to 275 ml. A dark oil precipitated. Extraction with 100 ml of methylene dichloride, then another 25 ml of methylene dichloride, and evaporation of solvent gave 9.9 g of oil; ir, 1735 (sh) and 1700 cm^{-1}.

N-Butylanilinosuccinimide (**2b**).

A solution of 9.9 g (0.065 mole) of *N*-butylmaleimide and 35 ml of acetic acid was treated with 6.51 g (0.07 mole) of aniline and the resulting solution was heated at 120° for 30 minutes. The solution was cooled and poured into 280 ml of water. The amorphous material was collected and recrystallization from isopropyl alcohol gave 9.3 g of off-white crystals, mp 97-100°; ir, 3350, 1720 (sh), 1680, 1600 cm^{-1}; ms: (ci) m/e 247.

Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.29; H, 7.32; N, 11.38. Found: C, 68.46; H, 7.28; N, 11.25.

N-Butylanilinomaleimide (**3b**).

A mixture of 2.46 g (0.01 mole) of **2b**, 2.61 g (0.03 mole) of activated manganese dioxide (Aldrich brown) and 15 ml of toluene was refluxed for 5 hours. The hot mixture was filtered and the solid was washed with 5 ml of hot toluene. Cooling the filtrate gave 2.3 g (93%) of red-orange solid. Recrystallization from isopropyl alcohol gave **3b**, mp 128-130°; ir, 3300, 1750 (sh), 1680, 1635, 1600 (sh) cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: 68.85; H, 6.56; N, 11.48. Found: C, 68.58; H, 6.45; N, 11.38.

N-Butylacridinimide (**5b**).

A solution of 244 mg (1.0 mmole) of **3b**, 238 mg (2.0 mmoles) of dimethylformamide dimethyl acetal and 5 ml of toluene was refluxed for 3 hours. Evaporation of the toluene gave a dark red-brown gum, which was heated in 6 g of polyphosphoric acid at 145-150° for 15 minutes. The solution was poured into 60 ml of cold water, and the resulting dark solid was collected and heated with 8 ml of methanol. Filtration of the hot mixture and evaporation of filtrate gave 120 mg (47%) of crude product. Recrystallization from methanol gave white crystals, mp 165-167°; ir, 1775, 1710 (sh) and 1695 cm^{-1}; ms: m/e 254 (M^+).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.87; H, 5.51; N, 11.02. Found: C, 70.78; H, 5.41; N, 10.96.

2-Anilino-3-formyl-*N*-phenylmaleimide (**7**).

A mixture of 4.0 g of **4a** and 120 g of polyphosphoric acid was heated with stirring at 80° for 10 minutes. The red-orange mixture was poured into one liter of water. Recrystallization from acetonitrile gave 3.24 g of **7** as a yellow-orange solid, mp 188-190.5°; ir: 1750 (w), 1760 (sh), 1710, 1640, 1605, 1590 cm^{-1}; 1H-nmr (deuteriochloroform): S, 9.93 (s, 1H, CHO), 7.26-7.48 (m, 10H, aromatic H).

Anal. Calcd. for $C_{17}H_{12}N_2O_3$: H, 69.86; H, 4.11; N, 9.59. Found: C, 69.95; H, 4.20; N, 9.42.

A red-brown solution formed when 2.0 g of **7** and 60 g of polyphosphoric acid was heated at 145-155° for 15 minutes. The solution was cooled and poured into 500 ml of water. The resulting solid was heated in 50 ml of hot ethanol and the slurry was filtered to give 1.77 g (94%) of **5a**.

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