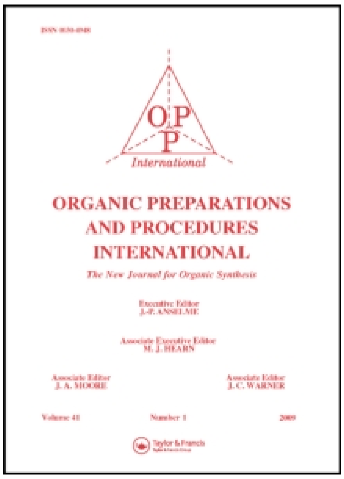

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A ONE-STEP SYNTHESIS OF 1-HYDROXY-10-METHYL-9(10H)-ACRIDINONE

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A ONE-STEP SYNTHESIS OF 1-HYDROXY-10-METHYL-9(10H)-ACRIDINONE

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(12/16/98)

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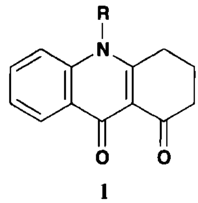
The yellow acridone alkaloid 1-hydroxy-10-methyl-9(10H)-acridinone (**4**) is found in a variety of plant species. It has been isolated from the roots of *Boenninghausenia albiflora*[1,2] and *Ruta chalepensis*[3] and also from callus cultures obtained from the meristematic cells of *Ruta graveolens*.[4] Two multistep systheses of **4** have been reported. The first is a five-step biomimetic approach involving the cyclization of an intermediate N-methylamino-2,6-dimethoxybenzophenone[5] (1.5% overall yield). The second, a four-step sequence starting from an acylmalonate, gives the product in 27% overall yield.[6]

We previously described a two-step synthesis of 10-alkyl-9-acridanones from the reaction of N-alkylisatoic anhydrides with the lithium enolate of 2-cyclohexen-1-one followed by aromatization of the intermediate 1,2-dihydroacridones.[7] It is also known that isatoic anhydrides react with the anions derived from β-ketoesters and β-diketones to form 3-carboalkoxy- or 3-acyl-4-quinolinones.[8,9] It was envisioned that a similar reaction of N-methylisatoic anhydride (**2**) with the sodium salt of cyclohexane-1,3-dione (**3**) would furnish the 1,9-acridinedione (**1**, R = CH$_3$). Subsequent substitution α to the 1-carbonyl by a suitable functional group (*e. g.* halogen or phenylselenide) would upon elimination, aromatize to produce the desired alkaloid **4**. N-Unsubstituted isatoic anhydrides have been reported to react with **3** at elevated temperature to produce **1** (R = H) in moderate yields.[10]



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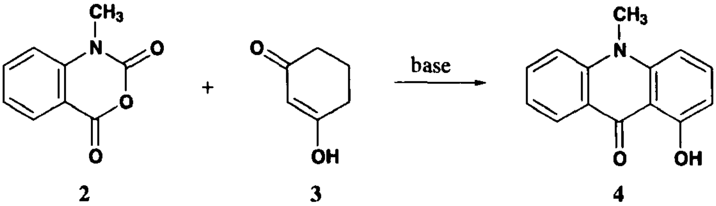
When the sodium salt of **3** was treated with N-methylisatoic anhydride (**2**) in DMF at 120° for 48 h, a single compound was isolated in 15% yield. The remainder of the reaction mixture was highly polar decomposition products. Analysis of this yellow solid it proved to be the aromatized acridone **4** not the acridinedione **1**. If the potassium salt of **3** (generated with KH in DMF) was used and the reaction heated at 110° for 18 h, the yield of **4** rose to 31%. When the potassium salt of **3** was generated with K_2CO_3 in DMSO and the reaction performed under the same conditions, the yield further increased to 45%.



EXPERIMENTAL SECTION

Commercially available reagents and compounds were purchased from Aldrich Chemical Company. Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The IR spectrum was recorded on an Analect FX-6200 spectrometer. The ^1H NMR spectrum was measured on an AC300 spectrometer. Chemical shifts are reported in ppm from internal TMS. The mass spectrum was determined on a Finnegan 4600 soectrometer.

1-Hydroxy-10-methyl-9(10H)-acridinone (4).- To a stirred suspension of K_2CO_3 (1.4 g, 0.01 mol) in 25 mL of DMSO was added cyclohexane-1,3-dione (1.2 g, 0.0107 mol). The mixture was stirred at room temperature for 1 h then N-methylisatoic anhydride (1.77 g, 0.01 mol) was added in one portion. The flask was placed in an oil bath at 70° then the temperature was raised to 110° over a period of 20 min. After stirring the mixture at 110° for 18 h, the resulting dark brown solution was poured into 100 mL of 1N hydrochloric acid. The resulting precipitate was collected, washed with water and dried in vacuo to give 1.5 g of a dark brown solid. This solid was dissolved in a minimal amount of methylene chloride and was filtered through a pad of silica gel using 2% methanol/methylene chloride as the eluting solvent. Removal of the solvent under reduced pressure gave 1.0 g (45%) of pure **4** as a yellow solid. An analytical sample was obtained by crystallization from acetone to give yellow needles, mp. 186-189°, lit[1] 191-193°. IR (KBr): 3440, 1632, 1597, 1500, 1246 cm^{-1}. MS: m/z 226 (MH^+). ^1H-NMR ($CDCl_3$): δ 8.45 (dd, J = 8.1 Hz, 1H), 7.76-7.70 (m, 1H), 7.58-7.49 (m, 2H), 7.28 (t, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 3.84 (s, 3H); the OH proton was not observed.

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ISOMERIZATION OF LONGIFOLENE TO ISOLONGIFOLENE CATALYZED BY MONTMORILLONITE CLAY

Submitted by
(05/14/97)

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During the last decade, a large number of reactions catalyzed by clays or modified clays have been reported.[1] Laszlo's group[2] has performed pioneering work in exploring the utility of clays in organic transformations. Some of the interesting reactions catalyzed by clay include nitration,[3] Michael addition,[4] Friedel-Crafts reaction[5] and oxidations[6] and these reactions are becoming quite popular in academic as well as industrial research owing to the simpler reaction conditions and eco-friendly nature. The acidic clays also have the advantage that reaction may be carried out without recourse to any special reaction vessel (a matter of great concern for an industrial scale) unlike the case with protic or Lewis acids.

Isolongifolene (**2**) is an important raw material in the synthesis of many perfumery products having interesting woody fragrances and is a prime constituent of many perfume formulations.[7,8] Existing procedures involve either reacting longifolene (**1**) with protic acids like dilute sulfuric acid[9] or with Lewis acids such as $BF_3{\bullet}Et_2O$.[7] All these methods have serious drawbacks during scale-up. Variable proportions of the rearranged products, tetralin **4** and octalin **5**, are unavoidable side-products.[10] The protic acids produce more resinous material while Lewis acids require dry reaction conditions in addition to the formation of resinous material. Although there is a report on the use of Japanese acidic clay for the isomerization of longifolene to isolongifolene at 200°, no information was