The Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 21 [1]. A Mild Process For The Preparation of 10-Alkyl-9-acridanones And It's Application To The Synthesis of Acridone Alkaloids

Gary M. Coppola* and Herbert F. Schuster

Sandoz Research Institute, Chemistry Research Department, Sandoz Pharmaceuticals Corporation, Route 10, East Hanover, N.J. 07936

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10-Substituted-9-acridanones are readily prepared by the reaction of the corresponding isatoic anhydride with the lithium enolate of 2-cyclohexen-1-one. The initially formed product, the 1,2-dihydroacridone need not be purified but can be aromatized directly with DDQ to the desired acridone. This methodology is applicable to the synthesis of acridone natural products. Two alkaloids, 1,2,3-trimethoxy-10-methylacridone (**9**) and evoxanthine (**10**), were prepared from 4,5,6-trimethoxy-*N*-methylisatoic anhydride and 6-methoxy-4,5-methylenedioxy-*N*-methylisatoic anhydride respectively. In these trioxygenated systems, palladium-on-charcoal must be used to aromatize the penultimate intermediate.

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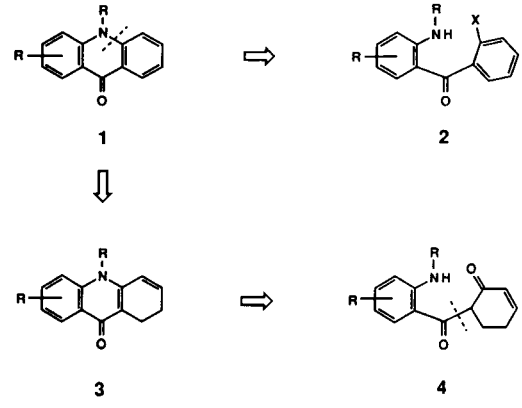
The acridines play an important role in a large variety of chemically useful substances. Compounds containing its ring system not only have found utility as synthetic dyes and pigments, whose colors nearly span the range of the entire rainbow, but also as pharmaceutical agents which possess carcinogenic, antibacterial, and antimalarial activity [2].

One specific class of acridines which we were particularly interested in was the 9-acridanone family more commonly known as the acridones. Of the many synthetic strategies reported to produce these compounds, only the cyclization of diphenylamine-2-carboxylic acids appears to have been used with the most frequency. Methods to accomplish the ring closure, however, often require rather harsh conditions such as refluxing phosphorous oxychloride followed by aqueous hydrochloric acid at 100° [3], polyphosphoric acid [4], or concentrated sulfuric acid [5]. The common theme of these reactions is the formation of an aromatic carbon-carbon bond, a rather high energy transformation. Consequently, we felt that another strategy, one that would form a carbon-nitrogen bond in the cyclizing step, would produce acridones under much more benign conditions.

Over the past several years we have developed methodology to construct 4-quinolinones under extremely mild conditions. This consists of a hetero ring opening of an isatoic anhydride with a ketone enolate followed by a dehydrative cyclization (the carbon-nitrogen bond formation) which furnishes these quinolinones in essentially one transformation [6,7]. Since the acridone system is essentially a 4-quinolinone fused to another benzene ring a similar strategy would appear feasible for the preparation of a variety of substituted acridone derivatives.

Retrosynthetically, disconnection of the acridone **1** as shown would result in precursor **2**. The proposition of now having to form an aromatic carbon-nitrogen bond by some sort of displacement of X, although plausible, would again require forcing conditions. In addition, the preparation of **2** also necessitates the use of methodology such as a Friedel-Crafts acylation to produce the benzophenone system.

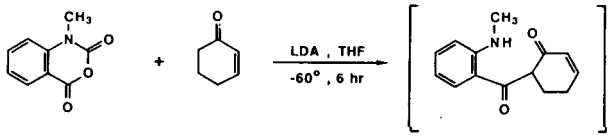


1 **2**

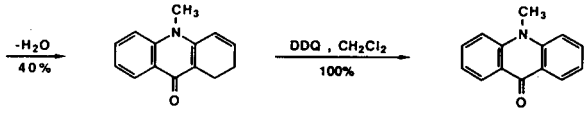
3 **4**

If, however, one of the aromatic rings of the acridone was dearomatized by removing one double bond (*e.g.* **3**), such an intermediate could easily be accessed from a dehydrative cyclization of the β-diketo species **4**. Bisection of **4** as shown gives an anthranoyl moiety (which can be provided in the form of an isatoic anhydride) and 2-cyclohexen-1-one both of which are commercially available.

Reducing theory to practice, in the simplest case, *N*-methylisatoic anhydride (**5**) is allowed to react at −60° with the lithium enolate generated from 2-cyclohexen-1-one and within six hours complete consumption of **5** has occurred. The newly formed product is assumed to be the intermediate β-diketo species **6**, however, this cannot be physically confirmed due to spontaneous cyclization during the work-up process. Consequently, only the dihydroacridone **7** is isolated. The position of the olefin is substantiated by spectral techniques.

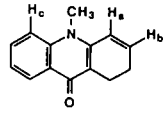


5 6



7 8a

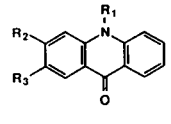
The nmr spectrum taken in deuteriochloroform provides little information about the olefinic protons. In this solvent, both protons H_a and H_b appear as a near singlet at δ 6.61. In deuteriobenzene, the olefinic protons become non-equivalent and are observed as two second-order multiplets at δ 5.65 and δ 5.51, the latter only showing a secondary long-range coupling to a methylene signal at δ 1.57. This suggests that the signal at δ 5.51 is associated with proton H_a. The aromatic proton H_c also becomes shifted upfield from the aromatic region and is observed as a doublet at δ 6.41. The assignments were corroborated by means of a DIF-NOE experiment. Irradiation of the *N*-methyl signal at δ 2.30 results in a strong positive enhancement to the olefinic proton at δ 5.51 as well as the aromatic proton at δ 6.41 thus establishing the relationship of H_a and H_c to the *N*-methyl group.



7

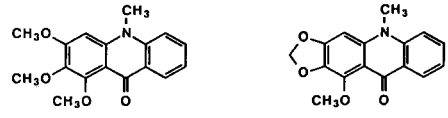
The dihydroacridone **7** is quantitatively aromatized to 10-methylacridone (**8a**) in the presence of DDQ. In practice, it is not necessary to isolate and purify **7**. Instead, the crude product can be directly oxidized with DDQ and purified at this stage. The total yield by this technique is slightly higher than the two-step procedure. Several additional derivatives were synthesized by this methodology and are listed in Table 1. The 2,3-dimethoxy and methylenedioxy derivatives were prepared as model compounds for the synthesis of two naturally occurring trioxygenated acridones.

Table 1. 10-Substituted-9-acridanones



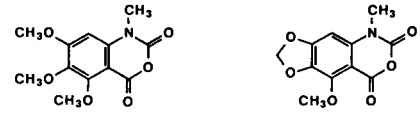
No.	R_1	R_2	R_3	yield(%)	mp(°C)(lit mp)
8a	CH_3	H	H	43	199-202 (198-199) [8]
8b	$CH_2C_6H_5$	H	H	53	176-179 (180-181) [9]
8c	CH_3	Cl	H	82	172-173 (172-173) [10]
8d	CH_3	OCH_3	OCH_3	30	191-194 (194-195) [11]
8e	CH_3	O-CH_2-O		33	260-263 (265-266) [12]

Polyoxygenated acridones occur widely in nature especially in the Australian *Rutaceae*. Among them, 1,2,3-trimethoxy-10-methylacridone (**9**) and evoxanthine (**10**) are found in a variety of plant sources. Alkaloid **9** is isolated from the leaves of *Evodia alata* [13] and the bark of *Vepris bilocularis* [14], while **10** is isolated from the bark of *Evodia xanthoxyloides* [15], *Evodia alata* [13], *Vepris bilocularis* [14], and both the roots [16] and stem bark of *Teclea grandifolia* [17].



9 10

Synthesis of these two structurally related alkaloids by our methodology necessitates the use of the corresponding trioxygenated isatoic anhydrides **11** and **12** as key intermediates. The construction of the isatoic anhydride ring system can generally be approached by two separate routes; (1) oxidation of an isatin with either chromium trioxide or peracids, (2) cyclization of an anthranilic acid with phosgene or ethyl chloroformate. When one considers possible syntheses of either of these potential starting materials it strategically narrows down to an intramolecular cyclization of an aniline derivative to give the isatin or a nitration of a benzoic acid followed by a reduction to afford the anthranilic acid. Considering the substitution pattern of the three oxygen atoms in the aromatic ring we felt that the best possible chance for success would be the isatin route since the intramolecular cyclization can only produce one cyclic product therefore precluding the risk of obtaining any isomers which may arise by the nitration route.

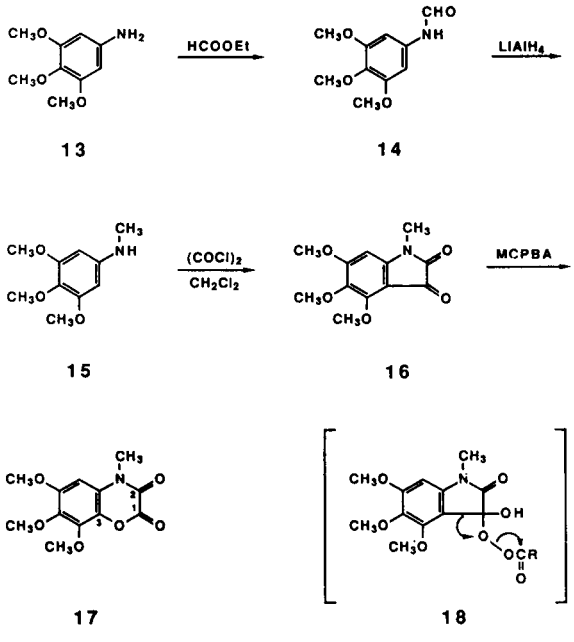


11 12

Our first target intermediate, the trimethoxyisatin **16** was synthesized starting from commercially available 3,4,-5-trimethoxyaniline (Scheme 1). Refluxing **13** with ethyl formate provides the *N*-formylated aniline **14** in 80% yield. Transformation of the formyl group to a methyl is effected quantitativley by reduction with lithium aluminum hydride. Conversion of **15** to isatin **16** occurs with

amazing facility when treated with oxalyl chloride. In fact, the aromatic ring is so activated by the three methoxy substituents that aluminum chloride is not required for cyclization to occur. The reaction is complete immediately following the mixing of the reactants. The order of addition is, however, crucial. Adding **15** slowly to oxalyl chloride produces an 81:19 mixture of the desired product **16** and a dimer resulting from the reaction of two equivalents of **15** with one equivalent of oxalyl chloride. These are readily separable by flash chromatography to give pure **16** in 77% yield. Inverse addition affords a 40:60 mixture **16** and dimer.

Scheme 1

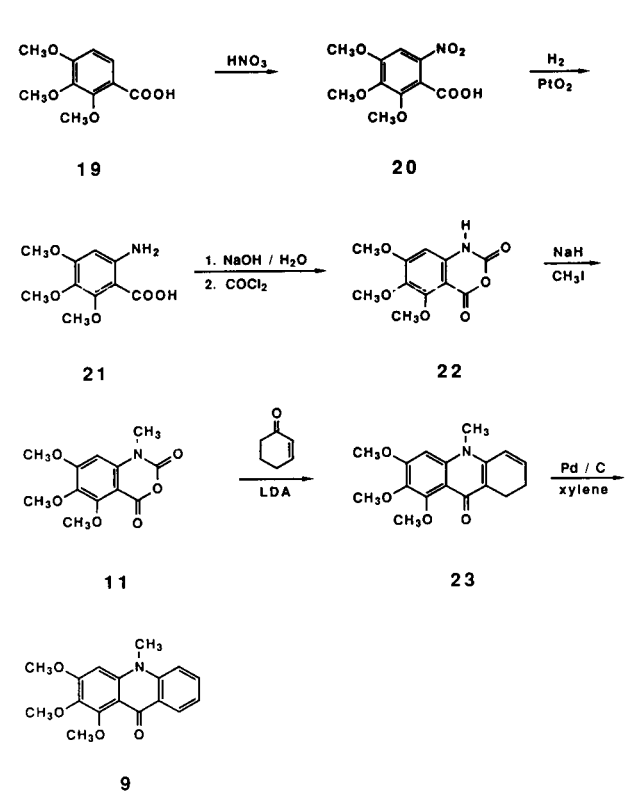


Oxidation of **16** with *m*-chloroperoxybenzoic acid proceeds smoothly and within 3 hours the reaction mixture changes color from deep red to yellow. The product, isolated in 57% yield, exhibits all the appropriate physical as well as spectral characteristics of the isatoic anhydride **11** with the exception of its carbon-13 spectrum. A major discrepancy is the position of the aromatic carbon C_3 which is directly attached to the carbonyl group of **11**. In deuteriodimethyl sulfoxide, its signal, which is usually observed between 100 and 115 ppm for an isatoic anhydride, is shifted downfield to 128.1 ppm. Furthermore, the carbonyl carbons are shifted slightly upfield to 151.9 and 150.7 ppm. This suggests that the aromatic ring is not connected to an sp^2 carbonyl carbon but rather to an oxygen atom. Therefore, the product from the oxidation of **16** is the 1,4-benzoxazine-2,3-dione **17** and not the isatoic anhydride.

This product can be rationalized as being formed by way of a Baeyer-Villiger-type rearrangement of the peroxy intermediate **18**. In this intermediate, migration of either the amide group (to give the isatoic anhydride **11**) or aryl group to produce **17** is possible. Since the migratory ability of aryl groups is increased by electron-donating substituents [18], it is not surprising that the highly electron-rich trimethoxyaryl group migrates in preference to the amide functionality.

We therefore persued the anthranilic acid route to prepare the isatoic anhydride **11** (see Scheme 2). Nitration of 2,3,4-trimethoxybenzoic acid with concentrated nitric acid occurs within 10 minutes at 0° to afford 6-nitro-2,3,4-trimethoxybenzoic acid **20** in 75% yield. The 5-nitro isomer is not formed at least to the limits of visual detection in the nmr spectrum. Reduction of the nitro group by catalytic hydrogenation gives the anthranilic acid **21** in 83% yield. Treatment of the sodium salt of **21** with phosgene provides 4,5,6-trimethoxyisatoic anhydride (**22**) in 92% yield. Methylation on nitrogen with sodium hydride and methyl iodide furnishes the desired *N*-methylisatoic anhydride **11** in 74% yield.

Scheme 2



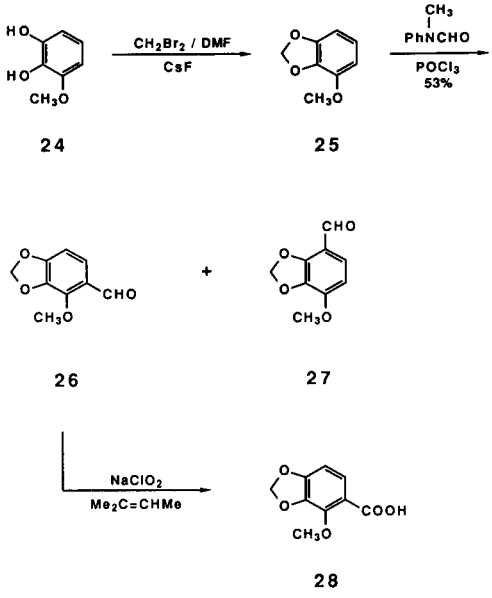
Treatment of **11** with the lithium enolate of 2-cyclohexen-1-one followed by oxidation with DDQ as described for the compounds in Table 1 surprisingly produces no acridone product. In fact, complete degradation occurs and only tar-like materials are isolated. To determine at which stage the process fails the reaction was performed in a stepwise manner. The initial reaction of **11** with the

enolate of 2-cyclohexen-1-one proceeds smoothly to produce the expected dihydro derivative **23** as a stable material in 49% yield. When aromatization is attempted with DDQ, close monitoring of the reaction reveals that within one minute conversion to a new product takes place, however, simultaneous decomposition occurs and within a short period of time, complete degradation is observed.

Therefore, the aromatization conditions must be modified in order to circumvent this problem. We found that the use of palladium-on-charcoal as a dehydrogenating agent affords the alkaloid **9** cleanly in 55% yield. Since the reaction is essentially a spot-to-spot conversion we attribute the modest yield to the adsorbance of the product on the large amount of charcoal required in the reaction.

For the preparation of evoxanthine (**10**) the synthetic sequence must begin at a more rudimentary level due to the lack of commercial availability of the properly substituted benzoic acid. The key intermediate, croweacic acid (**28**), is a known compound and has been synthesized previously. We have essentially used the procedure of Benington and Morin [19] to prepare **28** (Scheme 3), however, we have modified two of the three steps in order to increase yield and impove reproducibility.

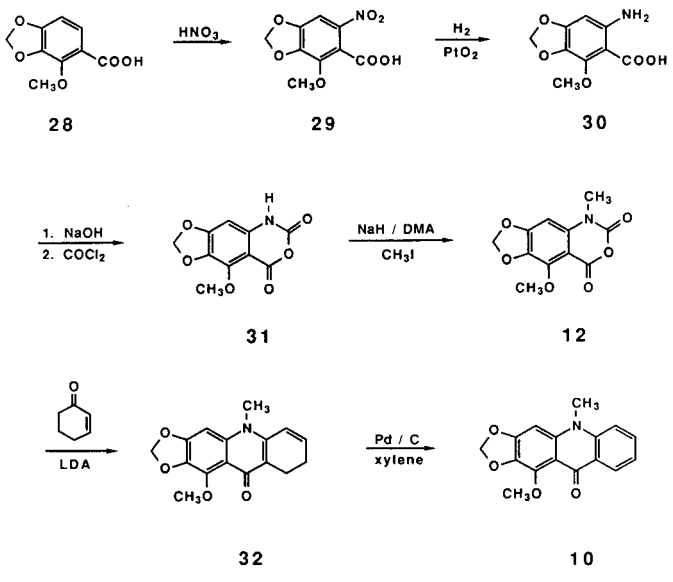
Scheme 3



The first step, the methylenation of 3-methoxycatechol (**24**), can be improved by heating **24** with dibromomethane and cesium fluoride in dimethylformamide [20]. On a 10 mmole scale, **25** is isolated in 85% yield, however, larger runs results in slightly lower yields. Formylation of **25** under Vilsmeier conditions with *N*-methylformanilide and phosphorus oxychloride produces a 3:1 mixture of 2-methoxy-3,4-methylenedioxybenzaldehyde (**26**) and 4-methoxy-2,3-methylenedioxybenzaldehyde (**27**) which is consistent with the observations of Wagner, *et. al.* [21] and Bick [27]. Oxidation of **26** to croweacic acid (**28**) is accomplished quantitatively within 30 minutes with sodium chlorite [22] in the presence of 2-methyl-2-butene [23].

Nitration of **28** occurs readily at 0° to give **29** as the sole isomer in 85% yield (Scheme 4). Catalytic hydrogenation affords the anthranilic acid derivative **30** in nearly quantitative yield. Cyclization of **30** with phosgene produces 6-methoxy-4,5-methylenedioxyisatoic anhydride (**31**) in 78% yield. *N*-methylation with methyl iodide and sodium hydride furnishes the key intermediate **12** in 88% yield.

Scheme 4



Conversion of **12** to evoxanthine (**10**) is accomplished by reaction of **12** with the enolate of 2-cyclohexen-1-one followed by dehydrogenation with palladium-on-charcoal. In this case it was found that the dihydroacridone **32** need not be purified and can be directly aromatized to the alkaloid. The overall yield for this sequence is 28% which is nearly identical to the overall yield obtained for the **11** → **23** → **9** conversion where **23** was purified prior to aromatization.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt Apparatus and are uncorrected. The infrared spectra were recorded on an Analect FX-6200 spectrophotometer. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on Jeol FX-90-Q and Joel FX-200 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 carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on either a Jeol FX-200 or a Bruker AM-500 spectrometer operating at carbon resonance frequencies of 50.1 MHz

and 125.77 MHz respectively. Sample concentrations were approximately 0.1 molar in deuterated solvent and were placed in 5 mm (od) sample tubes. Acquisition parameters used were: 220 ppm spectral width, a pulse width corresponding to a 45° pulse angle (3 μsec on the Jeol FX-200 and 3.5 μsec on the Bruker AM-500), 1.8 second pulse repetition time, and 16K (Jeol FX-200) or 64K (Bruker AM-500) time-domain points.

The starting materials 2-cyclohexen-1-one, 3,4,5-trimethoxyaniline, 3-methoxycatechol, and *N*-methylformanilide were purchased from Fluka Chemical Corporation. 2,3,4-Trimethoxybenzoic acid and *N*-methylisatoic anhydride were purchased from Aldrich Chemical Company. The *N*-methylisatoic anhydride was recrystallized from methylene chloride/methanol prior to use. Enolate generating reactions were conducted under an argon atmosphere using tetrahydrofuran which was freshly distilled over lithium aluminum hydride. Many of these reactions were only performed once, and no attempt has been made to optimize their yields.

1,10-Dihydro-10-methyl-9(2*H*)-acridinone, (1,2-dihydro-10-methyl acridinone) (**7**).

To a solution of 1.0 g (10 mmoles) of diisopropylamine in 25 ml of tetrahydrofuran (at −10°) was added 0.64 g (10 mmoles) of *n*-butyllithium (as a 1.6 *M* solution in hexane). After cooling to −78°, a solution of 1.0 g (10.4 mmoles) of 2-cyclohexen-1-one in 5 ml of tetrahydrofuran was added dropwise, and the mixture was stirred at −78° for 1 hour. To the resulting solution was added, slowly, a solution of 0.885 g (5 mmoles) of *N*-methylisatoic anhydride (**5**) in 15 ml of tetrahydrofuran, and the resulting suspension was stirred at −60° for 6 hours. The mixture was quenched with saturated ammonium chloride solution, and the mixture was extracted with methyl *t*-butyl ether (1x) and methylene chloride (1x). The combined organic extracts were dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was chromatographed on a Waters Prep-500 apparatus using ethyl acetate to elute the product, 0.43 g (40%) of **7**. An analytical sample was recrystallized from methyl *t*-butyl ether, mp 164-166°; ir (chlroform): 1625, 1577 cm^{-1}; ^1H nmr (deuteriobenzene): δ 8.60 (dd, 1H), 6.91-6.68 (m, 2H), 6.41 (d, 1H), 5.65 (dt, 1H), 5.51 (m, 1H), 2.71 (t, 2H), 2.30 (s, 3H), 1.57 (m, 2H); ^1H nmr (deuteriochloroform): δ 8.45 (dd, 1H), 7.63-7.11 (m, 3H), 6.61 (m, 2H), 3.75 (s, 3H), 2.87 (t, 2H), 2.30 (m, 2H); ms: (70 eV) m/z 212 (MH^+).

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.69; H, 6.58; N, 6.28.

10-Methyl-9-acridanone (**8a**).

To a suspension of 0.23 g (10 mmoles) of DDQ in 5 ml of methylene chloride was added a solution of 0.21 g (10 mmoles) of **7** in 4 ml of methylene chloride. The mixture was stirred at room temperature for 1 hour, then was poured into 10% aqueous sodium bicarbonate solution. The organic phase was separated and the solvent removed under reduced pressure. The residue was dissolved in a minimal amount of methylene chloride, then was filtered through a plug of silica gel using 1% methanol/methylene chloride to elute the product, 0.21 g (100%) of **8a**. An analytical sample was crystallized from methylene chloride/ethyl acetate, mp 199-202°, lit [8] mp 198-199°; ir (chloroform): 1607 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.46 (dd, 2H), 7.27-7.08 (m, 6H), 3.77 (s, 3H).

General Procedure for the Preparation of 10-Substituted-9-acridanones **8**.

To a solution of 2.0 g (0.02 mole) of diisopropylamine in 50 ml of tetrahydrofuran (at −10°) was added 1.28 g (0.02 mole) of *n*-butyllithium (as a 1.6 *M* solution in hexane). After cooling to −78°, a solution of 2.0 g (0.021 mole) of 2-cyclohexen-1-one in 10 ml of tetrahydrofuran was added dropwise, and the mixture was stirred at −78° for 1 hour. To the resulting solution was added, slowly, 0.01 mole [24] of the appropriate isatoic anhydride, either as a solution in tetrahydrofuran when soluble or directly as a solid, and the mixture was stirred at an appropriate temperature until the starting material was consumed (see individual examples below).

The mixture was quenched with saturated ammonium chloride solution and the mixture was extracted with methyl *t*-butyl ether (1x) and methylene chloride (1x). The organic solutions were combined and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was dissolved in 40 ml of methylene chloride. This solution was added to a suspension of 2.3 g (0.01 moles) of DDQ in 25 ml of methylene chloride, and after stirring at room temperature for 1 hour, the mixture was washed with 10% aqueous sodium bicarbonate solution. The solvent was removed under reduced pressure, and the crude product was chromatographed on a Waters Prep-500 apparatus (see individual examples below for mobil phase) to give the pure acridone. These results are listed in Table 1.

10-Methyl-9-acridanone (**8a**).

Reaction conditions = −60°, 6 hours; mobile phase = 1% methanol/methylene chloride. For spectra see previous example.

10-Benzyl-9-acridanone (**8b**).

Reaction conditions = −60°, 3 hours; mobile phase = ethyl acetate; crystallization solvent = methylene chloride/ethyl acetate; ir (chloroform): 1614 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.60 (dd, 2H), 7.75-7.50 (m, 2H), 7.45-7.10 (m, 7H), 5.61 (s, 2H).

3-Chloro-10-methyl-9-acridanone (**8c**).

Reaction conditions = −60°, 5 hours; mobile phase = 5% ethyl acetate/methylene chloride; crystallization solvent = methylene chloride/methyl *t*-butyl ether; ir (chloroform): 1636, 1604 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.53 (dd, 1H), 8.48 (d, J = 9 Hz, 1H), 7.85-7.13 (m, 5H), 3.77 (s, 3H).

2,3-Dimethoxy-10-methyl-9-acridanone (**8d**).

Reaction conditions −78° → room temperature, 30 minutes; mobil phase = ethyl acetate; crystallization solvent = methylene chloride/methyl *t*-butyl ether; ir (chloroform): 1614, 1598 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.57 (dd, 1H), 7.93 (s, 1H), 7.80-7.18 (m, 3H), 6.80 (s, 1H), 4.07 (s, 3H), 4.01 (s, 3H), 3.85 (s, 3H).

2,3-Methylenedioxy-10-methyl-9-acridanone (**8e**).

Reaction conditions = −78° → room temperature, 2 hours; mobile phase = 10% ethyl acetate/methylene chloride; crystallization solvent = ethyl acetate; ir (potassium bromide): 1625, 1585 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.55 (dd, 1H), 7.91 (s, 1H), 7.80-7.17 (m, 3H), 6.95 (s, 1H), 6.19 (s, 2H), 3.85 (s, 3H).

N-(3,4,5-Trimethyoxy)phenylformamide (**14**).

A mixture of 6.0 g (32.8 mmoles) of 3,4,5-trimethoxyaniline and 50 ml of ethyl formate was refluxed for 15 hours. The excess ethyl

formate was removed under reduced pressure, and the resulting oil was treated with 50 ml of hexane and 10 ml of ether. Upon standing, a solid formed. This was filtered and washed well with hexane to give 5.52 g (80%) of **14**, mp 71.5-73°, lit [29] mp 68-70°; ir (potassium bromide): 3428, 3270, 1673, 1603, 1279, 1185 cm^{-1}; ^{1} nmr (deuteriochloroform): δ 8.62 (d, 0.3H), 8.33 (d, 0.7H), 7.50 (s, broad, 0.3H, NH), 6.88 (s, 1H), 6.30 (s, 0.7H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H); ms: (70 eV) m/z 212 (MH^+).

3,4,5-Trimethoxy-*N*-methylaniline (**15**).

To a solution of 5.0 g (23.7 mmoles) of **14** in 125 ml of tetrahydrofuran (at 0-5°) was added dropwise 30 ml of a 1.0 *M* solution of lithium aluminum hydride in tetrahydrofuran. The mixture was stirred at 0° for 1 hour, then at room temperature for 2 hours. The solution was cooled to 0-5°, and was quenched by careful dropwise addition of saturated sodium sulfate solution. The insoluble inorganic salts were filtered and washed with ether. The filtrates were combined and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave 4.7 g (100%) of **15** as an orange oil. After standing at −20° for 24 hours, the oil crystallized, mp 44.5-45.5°, lit [30] mp 160-162° (hydrochloride salt); ir (neat): 3405, 1612, 1514, 1237, 1126 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 5.87 (s, 1H), 3.87 (s, 6H), 3.80 (s, 3H), 3.60 (s, 1H, NH), 2.84 (s, 3H).

1-Methyl-4,5,6-trimethoxy-1*H*-indole-2,3-dione (**16**).

To a refluxing solution of 3.0 g (25 mmoles) of oxalyl chloride in 25 ml of methylene chloride was added dropwise a solution of 4.5 g (22.8 mmoles) of **15** in 25 ml of methylene chloride. Upon complete addition, the red solution was cooled and the solvent was removed under reduced pressure. The resulting red solid was triturated with ether and dried to give 4.4 g (77%) of **16**, mp 70.5-72.0°; ir (chloroform): 3020, 1742, 1721, 1612, 1482, 1246, 1215 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 6.11 (s, 1H), 4.23 (s, 3H), 4.04 (s, 3H), 3.79 (s, 3H), 3.22 (s, 3H).

Anal. Calcd. for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.81; H, 5.53; N, 5.65.

4-Methyl-6,7,8-trimethoxy-2*H*, 1,4-benzoxazine-2,3-(4*H*)-dione (**17**).

To a solution of 6.0 g of *m*-chloroperoxybenzoic acid (80-85% pure) in 250 ml of methylene chloride was added 2.0 g (8 mmole) of **16**. After stirring at room temperature for 18 hours, the color of the solution changed from red to yellow and a precipitate formed. Addtional methylene chloride was added to obtain a solution. This solution was then washed with 5% aqueous sodium bisulfite followed by a solution of 2.8 g of sodium bicarbonate in 300 ml of water. The organic phase was dried over sodium sulfate, and the solvent was removed under reduced pressure to give the crude product. Recrystallization from methylene chloride/methyl *t*-butyl ether gave 1.2 g (57%) of **17**, mp 158-161°; ir (chloroform): 1776, 1696 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 6.43 (s, 1H), 4.04 (s, 3H), 3.97 (s, 3H), 3.92 (s, 3H), 3.61 (s, 3H); ^{13}C nmr (DMSO-d_6): δ 151.92, 150.70, 149.72, 140.98, 138.19, 128.10, 123.18, 94.64, 61.44, 60.91, 56.48, 29.58; ms: (70 eV) m/z 268 (MH^+).

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.61; H, 5.08; N, 5.18.

2,3,4-Trimethoxy-6-nitrobenzoic Acid (**20**).

To 92.5 ml of concentrated 70% nitric acid at 0° was added in portions 10.0 g (47 mmoles) of 2,3,4-trimethoxybenzoic acid (**19**). After stirring at 0° for 10 minutes, the mixture was diluted with 500 ml of cold water. Stirring was continued at 0° for 1 hour, and the resulting light orange precipitate was filtered and washed well with water to give 7.55 g of **20**, mp 155.5-157°. An additional 1.43 g of product was obtained by extraction of the aqueous filtrate with methylene chloride followed by evaporation of the organic solvent (total yield = 75%); ir (potassium bromide): 3408, 1709, 1614; ^{1}H nmr (deuteriochloroform): δ 9.55 (s, broad, 1H, COOH), 7.51 (s, 1H), 3.99 (s, 6H), 3.97 (s, 3H); ms: (100 eV) m/z 272 (MH^+).

Anal. Calcd. for $C_{10}H_{11}NO_7$: C, 46.70; H, 4.31; N, 5.45. Found: C, 46.76; H, 4.32; N, 5.22.

6-Amino-2,3,4-trimethoxybenzoic Acid (**21**).

A mixture of 6.5 g (25.3 mmoles) of **20** and 0.6 g of platinum oxide in 150 ml of ethanol was hydrogenated at 40 psi for 30 minutes. The catalyst was removed by filtration through celite, and the filtrate was evaporated under reduced pressure to give an orange oil. Addition of hexane caused the oil to crystallize. The solid was filtered and washed with hexane to give 5.36 g (83%) of **21**, mp 91.5-93°, lit [25] mp 95-96°; ir (potassium bromide): 3493, 3378, 1645, 1247 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 5.98 (s, 1H), 4.12 (s, 3H), 3.87 (s, 3H), 3.78 (s, 3H), NH_2 protons are seen as a broadening of the baseline.

Anal. Calcd. for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.16. Found: C, 53.22; H, 5.77; N, 6.30.

4,5,6-Trimethoxyisatoic Anhydride (**22**).

To a solution of 2.3 g (10.1 mmoles) of **21** in 11.0 ml of 1.0 *N* sodium hydroxide at 0° was added dropwise 11.0 ml of a 12.5% solution of phosgene in toluene. After warming to room temperature, the resulting tan precipitate was filtered and washed with water. The solid was suspended in toluene and the solvent was removed under reduced pressure. The solid was suspended in ether and was filtered to give 2.3 g (92%) of **22**, mp 247-248° dec; ir (potassium bromide): 3267, 1788, 1728, 1617, 1500, 1379; ^{1}H nmr (DMSO-d_6): δ 11.5 (s, broad, 1H), 6.44 (s, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H); ms: (100 eV) m/z 254 (MH^+).

Anal. Calcd. for $C_{11}H_{11}NO_6$: C, 52.18; H, 4.38; N, 5.53. Found: C, 52.46; H, 4.38; N, 5.34.

N-Methyl-4,5,6-trimethoxyisatoic Anhydride (**11**).

To a suspension of 0.32 g (8.0 mmoles) of sodium hydride (60% in mineral oil) in 20 ml of dimethylacetamide (under argon) was added a warm solution of 1.89 g (7.5 mmoles) of **22** in 50 ml of dimethylacetamide. After the evolution of hydrogen ceased and a clear brown solution formed, 1.5 g (10.6 mmoles) of methyl iodide was added, and the mixture was stirred at room temperature for 3 hours. The mixture was poured into 100 ml of 2 *N* hydrochloric acid/ice and was extracted into ethyl acetate (2x). The organic phases were combined and dried over magnesium sulfate. Cooling of the solution resulted in the formation of a yellow-tan solid. This was filtered to give 1.48 g (74%) of **11**, mp 165-166°; ir (potassium bromide): 1767, 1718, 1602 cm^{-1}; ^{1}H nmr (deuteriochloroform + DMSO-d_6): δ 6.34 (s, 1H), 4.00 (s, 3H), 3.99 (s, 3H), 3.86 (s, 3H), 3.55 (s, 3H); ^{13}C nmr (DMSO-d_6): δ 159.97, 154.76, 154.25, 147.95, 140.55, 138.03, 98.46, 94.34, 61.46, 60.80, 56.59, 32.01; ms: (100 eV) m/z 268 (MH^+).

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.75; H, 4.97; N, 4.89.

1,2-Dihydro-10-methyl-6,7,8-trimethoxyacridone (**23**).

To a solution of 0.55 g of diisopropylamine in 15 ml of tetrahydrofuran (at −10°) was added 0.35 g of *n*-butyllithium (as a 1.6 *M* solution in hexane). After cooling to −78°, a solution of 0.525 g of 2-cyclohexene-1-one in 3 ml of tetrahydrofuran was added dropwise and the mixture was stirred at −78° for 1 hour. To the resulting solution was added 0.7 g of **11** as a solid. The suspension was stirred at −78° for 30 minutes, then the temperature was raised to room temperature at which point a yellow solution formed. After stirring at room temperature for 90 minutes, the reaction was quenched with saturated ammonium chloride and the mixture was extracted with methyl *t*-butyl ether (1x) and methylene chloride (2x). The organic phases were combined, dried over sodium sulfate, and the solvent evaporated to give a crude oil. This oil was flash chromatographed using 2% methanol/methylene chloride to elute the product, 0.388 g (49%) of **23** as a foam. This was used directly in the next step; ir (chloroform): 1636 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.26 (s, 1H), 6.55 (s, 2H), 4.02 (s, 3H), 3.99 (s, 3H), 3.93 (s, 3H), 3.75 (s, 3H), 2.83 (m, 2H), 2.30 (m, 2H): ms: (70 eV) m/z 302 (MH^+).

1,2,3-Trimethoxy-10-methylacridone (**9**).

A mixture of 0.3 g of **23** and 1.0 g of 5% palladium-on-charcoal in 30 ml of xylene was refluxed for 2 hours. The charcoal was filtered, and the filtrate evaporated under reduced pressure to give a waxy solid. Recrystallization from ethyl acetate furnished 0.166 g (55%) of **9** as a yellow solid, mp 165-168°, lit [26] mp 168-170°; ir (chloroform): 1628, 1601 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.46 (dd, 1H), 7.72-7.08 (m, 3H), 6.55 (s, 1H), 4.05 (s, 3H), 4.01 (s, 3H), 3.92 (s, 3H), 3.80 (s, 3H).

1-Methoxy-2,3-methylenedioxybenzene (**25**).

To a solution of 1.4 g of 3-methoxycatechol in 25 ml of dimethylformamide was added 7.5 g of cesium fluoride and 1.9 g dibromomethane. After stirring at room temperature for 1 hour, then at 110-120° for 1 hour, the solvent was removed under reduced pressure. Water was added to the residue, and the mixture was extracted with methyl *t*-butyl ether. The organic phase was dried over sodium sulfate, and the solvent was removed under reduced pressure. The residual oil was dissolved in 5 ml of methylene chloride and filtered through a pug of silica gel. Evaporation of the solvent from the eluent furnished 1.3 g (85%) of **25**, mp 39-42°, lit [27] mp 40-41°; ir (chloroform): 1638, 1498, 1461, 1289, 1092 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.92-6.46 (m, 3H), 5.96 (s, 2H), 3.91 (s, 3H).

2-Methoxy-3,4-methylenedioxybenzaldehyde (**26**).

To 13.6 g (88.7 mmoles) of phosphorus oxychloride (under argon) was added dropwise 12.0 g (88.7 mmoles) of freshly distilled *N*-methylformanilide. The mixture was stirred at room temperature for 30 minutes, then 5.31 g (34.9 mmoles) of **25** was added as a solid. The mixture was heated at 100° for 2 hours then was cooled to room temperature. Water (200 ml) was added, and the mixture extracted with chloroform (3x). The organic phases were combined and dried over magnesium sulfate then the solvent was removed under reduced pressure to give 3.32 g (53%) of a 3:1 mixture of isomers. Flash chromatography of the crude oil using methyl *t*-butyl ether/hexane (6:4) elution provided 2.12 g (34%) of **26**, mp 103-104°, lit [27] mp 107-108°; ir (chloroform): 1678, 1612, 1477, 1279, 1240, 1074, 1046 cm^{-1}; ^1H nmr (deuteriochloroform): δ 10.22 (d, 1H), 7.49 (d, J = 9 Hz, 1H), 6.61 (dd, 1H), 6.06 (s, 2H), 4.16 (s, 3H).

Anal. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.47. Found: C, 59.85; H, 4.19.

In addition to the product, 0.63 g (10%) of **27** was also isolated, mp 83.5-84.5°, lit [21] mp 85-86°; ir (chloroform): 1689, 1636, 1451, 1290, 1108, 1042 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.98 (s, 1H), 7.32 (d, J = 9 Hz, 1H), 6.63 (d, J = 9 Hz, 1H), 6.16 (s, 2H), 4.01 (s, 3H).

Anal. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.47. Found: C, 60.20; H, 4.29.

2-Methoxy-3,4-methylenedioxybenzoic Acid (Croweacic Acid) (**28**).

To a stirred solution of 1.39 g (7.72 mmoles) of **26** and 50 ml of 2-methyl-2-butene in 150 ml of *t*-butyl alcohol was added dropwise a solution of 7.8 g (68.9 mmoles) of sodium chlorite and 7.4 g (53.6 mmoles) of dibasic sodium phosphate in 50 ml of water. The mixture was stirred at room temperature for 30 minutes, then the organic solvents were removed under reduced pressure. The resulting mixture was extracted with ethyl acetate and the organic phase was dried over magnesium sulfate. The solvent was removed under reduced pressure and the resulting solid was triturated with hexane/ether to give 1.47 g (98%) of **28**, mp 154.5-155.5°, lit [19] mp 153-154°; ir (potassium bromide): 3425, 1698, 1453, 1278 cm^{-1}; ^1H nmr (deuteriochloroform): δ 10.61 (s, broad, 1H, COOH), 7.77 (d, J = 9 Hz, 1H), 6.65 (d, J = 9 Hz, 1H), 6.07 (s, 2H), 4.22 (s, 3H).

2-Methoxy-3,4-methylenedioxy-6-nitrobenzoic Acid (**29**).

To 12 ml of cold (0°) concentrated 70% nitric acid was added in small portions 1.4 g (7.14 mmoles) of **28**. After stirring at 0° for 10 minutes, 70 ml of water was added and stirring was continued at 0° for 20 minutes. The resulting yellow solid was filtered then dissolved in 100 ml of ether. The solution was dried over magnesium sulfate and solvent removed under reduced pressure. The solid was triturated with hexane to give 1.47 g (85%) of **29**, mp 189.5-191°, lit [21] mp 190-192°; ir (film): 1706, 1632, 1506, 1369, 1286 cm^{-1}; ^1H nmr (deuteriochloroform + DMSO-d_6): δ 7.40 (s, 1H), 6.21 (s, 2H), 4.09 (s, 3H). The acid proton is seen as a broadening of the baseline at δ 9.23.

6-Amino-2-methoxy-3,4-methylenedioxybenzoic Acid (**30**).

A mixture of 1.31 g (5.43 mmoles) of **23** and 0.1 g of platinum oxide in 50 ml of ethyl acetate was hydrogenated at 40 psi for 2 hours. The catalyst was filtered and washed well with ethanol. The solvent from the filtrate was removed under reduced pressure to give 1.09 g (95%) of **30**, mp 148.5-149.5° dec; ir (potassium bromide): 3466, 3400, 3346, 1697, 1667, 1609, 1369 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.23 (s, 1H), 6.1 (broad, 1H), 5.98 (s, 1H), 5.87 (s, 2H), 4.16 (s, 3H); ms: (100 eV) m/z 212 (MH^+).

Anal. Calcd. for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63: Calcd. for $C_9H_9NO_5 + \frac{1}{2} H_2O$: C, 49.10; H, 4.58; N, 6.36. Found: C, 49.45; H, 4.55; N, 6.13.

6-Methoxy-4,5-methylenedioxyisatoic Anhydride (**31**).

To a solution of 1.05 g (4.97 mmoles) of **30** in 5.6 ml of 1.0 *N* sodium hydroxide at 0° was added dropwise 6.0 ml of a 12.5% solution of phosgene in toluene. After warming to room temperature, the resulting precipitate was filtered and washed with water. The

solid was suspended in toluene and the solvent was removed under reduced pressure. The solid was then triturated with ether to give 0.92 g (78%) of **31**, mp 243.5-244° dec; ir (potassium bromide): 3237, 1789, 1724, 1629 cm^{-1}; ^1H nmr (deuteriochloroform + DMSO-d_6): δ 11.37 (s, broad, 1H), 6.37 (s, 1H), 6.01 (s, 2H), 4.12 (s, 3H).

Anal. Calcd. for $C_{10}H_7NO_6$: C, 50.64; H, 2.97; H, 5.91. Found: C, 50.81; H, 2.88; N, 5.78.

6-Methoxy-4,5-methylenedioxy-*N*-methylisatoic Anhydride (**12**).

To a suspension of 0.16 g (4.0 mmoles) of sodium hydride (60% in mineral oil) in 20 ml of dimethylacetamide was added a slurry of 0.887 g (3.74 mmoles) of **31** in 30 ml of dimethylacetamide. After stirring at room temperature for 2 hours, a clear orange-brown solution formed. Then, 0.65 g (4.58 mmoles) of methyl iodide was added, and the mixture was stirred at room temperature for 30 minutes. The reaction was poured into 50 ml of cold 1 *N* hydrochloric acid, and the resulting tan precipitate was filtered and washed successively with water then ether. The solid was dried *in vacuo* at 80° for 3 hours to give 0.825 g (88%) of **12**, mp 237.5-239° dec; ir (potassium bromide): 1764, 1709, 1682, 1659, 1621, 1463 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.33 (s, 1H), 6.05 (s, 2H), 4.18 (s, 3H), 3.50 (s, 3H); ms: (100 eV) m/z 252 (MH^+).

Anal. Calcd. for $C_{11}H_9NO_6$: C, 52.60; H, 3.61; N, 5.58. Found: C, 52.04; H, 3.73; N, 5.62.

Evoxanthine (**10**).

To a solution of 325 mg of diisopropylamine in 15 ml of tetrahydrofuran (at −10°) was added 210 mg of *n*-butyllithium (as a 1.6 *M* solution in hexane). After cooling to −78°, a solution of 310 mg of 2-cyclohexen-1-one in 5 ml of tetrahydrofuran was added dropwise and the mixture was stirred at −78° for 1 hour. To the resulting solution was added 400 mg of **12** as a solid and the mixture was stirred at −78° for 30 minutes then at room temperature for 90 minutes. The resulting yellow solution was quenched with a saturated ammonium chloride then the mixture was extracted with methyl *t*-butyl ether (1x) and methylene chloride (2x). The organic phases were combined and dried over sodium sulfate, then the solvent was removed under reduced pressure to give 650 mg of **32** as a glass. This was dissolved in 20 ml of xylene and 1.5 g of 5% of palladium-on-charcoal was added. After refluxing the mixture for 1 hour, the charcoal was filtered and the filtrate evaporated to give 355 mg of a crude oil. This was flash chromatographed using 2% methanol/methylene chloride to elute the product 130 mg (28%) of **10**. An analytical sample was crystallized from ethyl acetate, mp 217-220°, lit [28] mp 217-218°; ir (chloroform): 1608, 1498, 1470, 1216 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.45 (dd, 1H), 7.72-7.10 (m, 3H), 6.65 (s, 1H), 6.02 (s, 2H), 4.17 (s, 3H), 3.77 (s, 3H).

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