The Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 9. Synthesis of 2-Arylquinoline Alkaloids

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A one-step synthesis of *N*-methyl-2-aryl-4-quinolone alkaloids is described. These compounds are readily prepared from the reaction of an *N*-methylisatoic anhydride with the lithium enolate of an acetophenone. By this method, the reaction of *N*-methylisatoic anhydride (**5**) or 5-methoxy-*N*-methylisatoic anhydride (**7**) with acetophenone produces the alkaloids *N*-methyl-2-phenyl-4-quinolone (**1**) and eduline (**2**) in 81% and 70% yield, respectively. An analogous reaction of **5** with 3,4-methylenedioxyacetophenone gives graveoline (**3**) in 63% yield whereas **7** and α-methoxyacetophenone affords japonine (**4**) in 61% yield.

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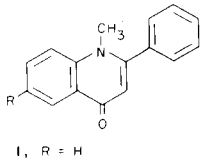
The rather elementary 2-arylquinoline alkaloids, belonging to the family *Rutaceae*, have only been sporadically discovered in nature during the past 20 years. However, compounds of this type have been found in the leaves, bark or seeds in a variety of Genera indigenous to various parts of the world such as Mexico, Argentina, Australia, Japan and the Phillipine Islands.

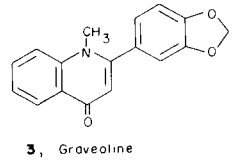
It became of interest to investigate the pharmacological profile of some of these alkaloids and, if biological activity is found, further modify the molecule in order to optimize the desired activity. It was therefore necessary to develop a general synthetic route to assemble these molecules which employs readily available starting materials, can be accomplished in a minimum number of steps, and proceeds in good yield.

Reported syntheses leading to alkaloids of this type are quite varied and range from a Conrad-Limpach type reaction (which produces quinolines by a thermal condensation of an arylamine with a β-ketoester followed by cyclization of the resulting Schiff base), to a Darzens condensation which requires an *o*-nitrobenzaldehyde and phenacyl bromide to assemble the initial framework which can subsequently be transformed to a quinoline.

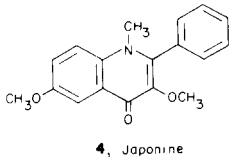
The four target alkaloids chosen for synthesis in this paper are methylated on the nitrogen of the quinoline ring and possess a carbonyl function in the 4-position. Previous synthetic routes leading to these compounds are multistep and generally did not proceed in good overall yield: 1-methyl-2-phenyl-4-quinolone (**1**) (1), 62% (4 steps); Eduline (**2**) (2), 42% (2 steps); Graveoline (**3**) (3), 9% (5 steps); and Japonine (**4**) (4), 11% (5 steps).



1, R = H
2, R = OCH_3
Eduline



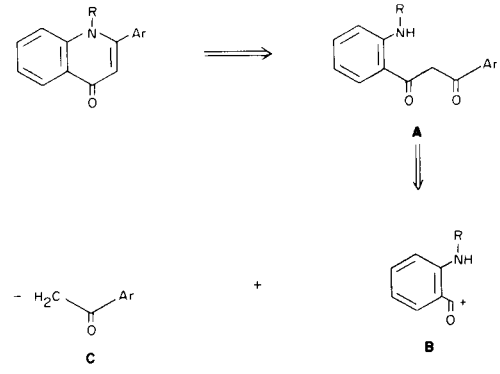
3, Graveoline



4, Japonine

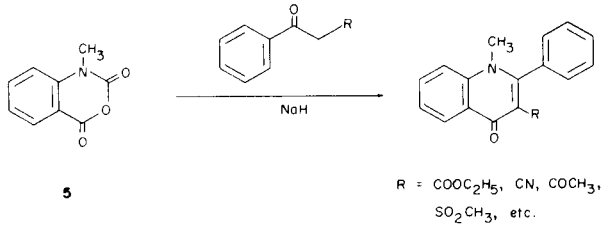
Retrosynthetic analysis (Scheme 1) indicates that the desired 2-aryl-4-quinolone can be formed by a dehydrative cyclization of a diketone species such as **A** which can, in turn, be prepared by the reaction of electrophile **B** with nucleophile **C**.

Scheme 1



The charged species **C** is the equivalent of an aromatic ketone enolate. In fact, the enolate of acetophenone has been generated successfully with lithium diisopropylamide (5) or lithium hexamethyldisilazane (6) at -78°. *N*-Methylisatoic anhydride (**5**) may be considered a synthetic equivalent for electrophile **B** where attack of the nucleophile at the C-4 carbonyl of the hetero ring (with concomitant loss of carbon dioxide) should furnish **A**. It has already been demonstrated that *N*-methyl-4-quinolones are readily accessible from the reaction of **5** with the sodium generated anions of active methylenes (7) and it was postulated that the products arose through such an

intermediate. It was therefore considered feasible that alkaloids **1-4** could be synthesized *via* intermediate **A** according to Scheme 1.

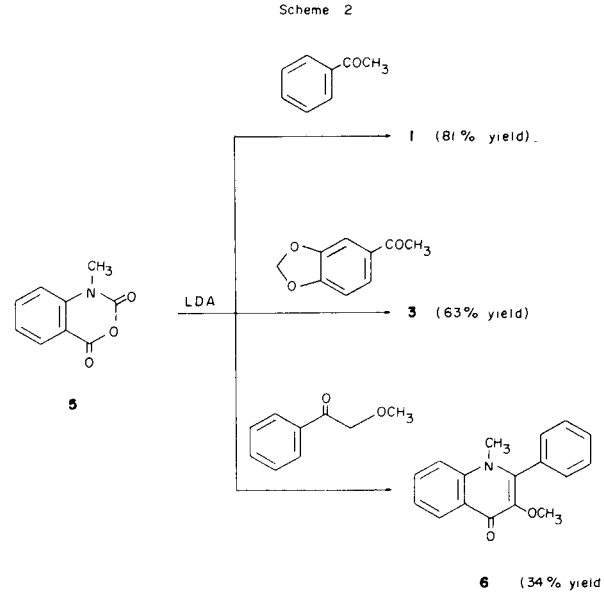


The choice of the four target alkaloids was based on the desire to synthesize the simplest of the *N*-methyl-2-aryl-4-quinolones, *e.g.*, **1**, then extend the scope of the reaction to include a nuclear substituted quinoline, **2**, then one that contains functionality in the 2-aryl moiety, **3**, and finally substitution in the 3-position of the quinoline, **4**. Demonstrating that these criteria can be met would constitute a general synthesis for these type of alkaloids.

The first in the series, *N*-methyl-2-phenyl-4-quinolone (**1**), is isolated from *Balfourodendron riedelianum* (8). According to Scheme 1, its synthesis requires the use of *N*-methylisatoic anhydride (5) and acetophenone. The enolate of acetophenone is readily generated at -65° with lithium diisopropylamide (LDA). When equimolar amounts of **5** and the above enolate are allowed to react at -65°, after acidic workup, thin layer chromatography reveals the presence of a new product plus significant quantities of unreacted starting materials. In an analogous reaction with equimolar quantities of **5** and acetophenone, but using two equivalents of LDA , the majority of **5** is consumed but the reaction is accompanied by a variety of additional products (possibly arising as a result of further deprotonation in the aromatic ring of acetophenone and the second, more nucleophilic anion, reacting with **5**). However, when two full equivalents of the acetophenone enolate are allowed to react with one equivalent of **5** at -65° for 90 minutes, analysis of the reaction mixture indicates that **5** is completely consumed and only a new product and the excess acetophenone remains. Column chromatography of the mixture furnishes the alkaloid **1** in 81% yield (Scheme 2). The intermediate, corresponding to **A** in Scheme 1, evidently is not stable and spontaneously cyclizes to give the desired product during the workup phase.

Graveoline (**3**), isolated from the Hong Kong species of *Ruta graveolens* (9), contains a 3,4-methylenedioxyphenyl group in the 2-position of the quinoline ring. This alkaloid can be synthesized in 63% yield in one step, as in the previous example, by the reaction of **5** with two equivalents of the lithium enolate derived from 3,4-methylenedioxyacetophenone. The reaction in this case is extremely rapid and

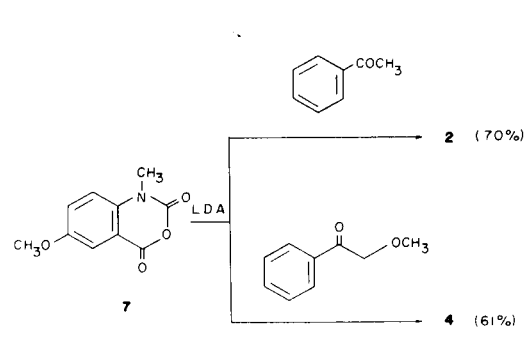
Scheme 2



is essentially complete after the addition of the *N*-methylisatoic anhydride. Thin layer chromatography of the mixture within two minutes after addition reveals the total consumption of **5**.

Eduline (**2**), a quinolone in this series with a nuclear methoxy substituent in the 6-position, is found in the seeds of the Mexican Central American fruit tree *Casimiroa edulis* (10) and also in the leaves of female *Skimmia japonica* Thunb. (11). The required 5-methoxy-*N*-methylisatoic anhydride (**7**) is readily prepared by the reaction of the corresponding unsubstituted isatoic anhydride with methyl iodide in the presence of sodium hydride (13). Reaction of **7** with acetophenone enolate requires 24 hours at -50° for completion and the product **2** is isolated in 70% yield (Scheme 3).

Scheme 3



Japonine (**4**), an interestingly substituted alkaloid, is methoxylated in both the 3 and 6-positions of the quinoline. It is isolated from the aerial parts of *Orixa japonica* Thunb. (14,15).

Prior to the attempted synthesis of **4**, it was necessary to determine if the basic framework including the 3-methoxy substituent could be assembled using the presently des-

cribed methodology. To introduce a methoxy into the 3-position of the quinoline, the required acetophenone must contain an OCH_3 in the α-position. The lithium enolate of the commercially available α-methoxyacetophenone is readily generated with LDA and, using the same stoichiometry as described in the previous examples, it reacts with **5** to produce the desired product **6** in 34% yield (Scheme 2).

It is interesting to note that upon addition of the solution of **5** to the enolate at -65°, crystallizaiton of **5** occurs and no reaction is observed even after two hours. But when the reaction mixture is allowed to warm to -40°, a solution occurs and the reaction is complete within 5 minutes. The physical data for **6** is identical with that described in the literature (4).

Being assured that structures of type **6** can be formed, an analogous reaction using the methoxyisatoic anhydride **7** was attempted. As in the case of **6**, no reaction is observed at -65° even after 24 hours (probably due to the even less soluble nature of **7** in the reaction medium). However, when the mixture is allowed to warm to room temperature, reaction occurs and, after one hour, **4** is isolated in 61% yield.

The melting points reported for japonine (**4**) are 143° for the naturally occurring product (14) and 142-143° for the previous synthetic material (4). However, the product obtained by the synthetic process described herein possesses a melting point of 165-167°. At first it was thought that crystallization from methylene chloride/ether resulted in a different crystal structure causing this discrepancy, but using the same solvent system described in the literature (methanol/ether) did not change the melting point.

Not being totally assured that the correct product was in hand, a detailed spectral investigation was undertaken. The ir spectrum (potassium bromide) of our compound shows absorptions at 1630, 1595, 1580, 1310, 1245 and 750 cm^{-1} which are characteristic of this type molecule (14). The uv spectrum (methanol) is identical with natural and synthetic japonine (4,14). The nmr spectrum (deuteriochloroform) is identical to those reported in the literature (4,14) with the exception that the signals are shifted slightly downfield by approximately 0.1 ppm (16). Even though the numerical values do not correspond exactly, every signal is actually superimposable on those of the spectrum of the synthetic material reported by Piozzi (4,17). High resolution mass spectral analysis (Table 1) reveals that the fragmentation pattern corresponds exactly to the reported values of the natural product (14).

In a recent report (18), the carbon-13 shifts of some 2-and 4-quinolones was investigated. It was decided to additionally support the structure of our synthetic **4** by its comparison with the other members of the group (**1, 2, 6**) described in this report. The shifts are in full agreement with all the model compounds and further confirm the integrity of **4** (results are listed in Table 2).

Since all spectral data are consistent with reported values and all further evidence points to structure **4**, it is our feeling that our product is indeed the alkaloid japonine.

In summary, a simple one-step synthesis of *N*-methyl-2-aryl-4-quinolone alkaloids from readily available materials is described. Although the basic reaction is the same throughout the series, each one has its own unique temperature requirements for completion of the reaction. Conditions ranging from 2 minutes at -65° (in the case of **3**) to 1 hour at room temperature (for japonine) are typical of the parameters. It should be emphasized that the majority of the reactions were only performed once and the yields reported are by no means optimized.

By the described synthetic route, other members of the 2-aryl-4-quinolone family should be able to be prepared. The reaction of isatoic anhydrides with enolates of esters, lactones, amides and lactams is presently under investigation and will be reported in subsequent publications.

Table 1

High Resolution Mass Spectrum of **4**

m/e (observed)	Melecular Formula	m/e (Calcd.)	Relative Intensities (%)
295.1172	$C_{18}H_{17}NO_3$	295.1208	100.0
294.1100	$C_{18}H_{16}NO_3$	294.1130	97.8
276.1041	$C_{18}H_{14}NO_2$	276.1024	90.7
264.1022	$C_{17}H_{14}NO_2$	264.1024	64.0
252.0976	$C_{16}H_{14}NO_2$	252.1024	28.7
248.0978	$C_{17}H_{14}NO$	248.1089	12.4
218.0766	$C_{12}H_{12}NO_3$	218.0817	5.6

EXPERIMENTAL

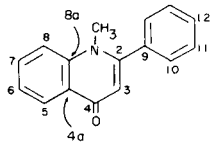
Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on Varian T-60, EM-360, and Varian XL-100 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 LKB 9000 or AEI MS-30 spetrometers. Ultraviolet spectra were recorded on a Cary 14 spectrometer.

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Varian XL-100-12 spectrometer system equipped with a Varian 620/L computer with 16K memory. The spectra were obtained at an observing frequency of 25.159 MHz. Sample concentrations were *ca.* 0.5 molar in deuteriochloroform in 10 mm (od) sample tubes. General nmr spectral and instrumental parameters employed were: Internal deuterium lock to the solvent; spectral width of 5120 Hz; a pulse width of 25 μs corresponding to a 43° pulse angle; and a pulse repetition time of 1.8 seconds. For all spectra, 8K time-domain points were used. All shifts reported are referenced to internal tetramethylsilane and are estimated to be accurate to ± 0.05 ppm.

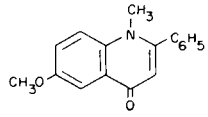
All of the described reactions are performed under a nitrogen atmo-

Table 2

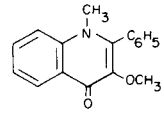
Carbon-13 Chemical Shifts for **1**, **2**, **4** and **6**



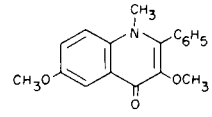
1



2



6



4

Compound	N-CH_3	C-2	C-3	C-4	C-4a	C-5	C-6	C-7
1	37.26	154.83	112.58	177.58	126.60	126.60	123.68	132.39
2	37.36	153.81	111.80	176.92	128.15	105.83	156.33	122.94
6	37.03	141.02	147.23	173.01	127.20	126.81	123.03	131.89
4	37.18	140.46	146.51	172.15	128.40	105.40	155.84	122.89

Compound	C-8	C-8a	C-9	C-10	C-11	C-12	3-OCH_3	6-OCH_3
1	116.04	141.94	135.86	128.81*	128.57*	129.65		
2	117.71	136.02	136.63	128.80*	128.69*	129.58		55.86
6	115.68	147.23	132.56	128.95*	128.79*	129.34	59.90	
4	117.46	135.01	132.63	128.75*	129.09*	129.32	59.86	55.81

Shifts marked with an * are interchangeable.

sphere using tetrahydrofuran which has been distilled over lithium aluminum hydride. Unless otherwise stated, all solutions of organic compounds are washed with saturated sodium chloride and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

N-Methyl-2-phenyl-4-quinolone (**1**).

To a solution of 2.0 g (0.02 mole) of diisopropylamine in 75 ml of dry tetrahydrofuran (at -30°) was added 1.28 g of *n*-butyllithium (0.02 mole, 1.6 *M* in hexane). After cooling to -65°, a solution of 2.4 g (0.02 mole) of acetophenone in 10 ml of tetrahydrofuran was added dropwise and the mixture was stirred at -65° for 1 hour. To this was added slowly a solution of 1.8 g (0.01 mole) of *N*-methylisatoic anhydride (**5**) in 40 ml of tetrahydrofuran (19) and the resulting suspension was stirred at -65° for 1.5 hours. The mixture was quenched with saturated ammonium chloride solution and the organic phase was separated. The aqueous layer was extracted twice with methylene chloride and then the organic phases were combined and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product, 1.9 g (81%) of **1**. An analytical sample was crystallized from ether, mp 142-145°, Lit (1) mp 143.5-144.5°.

Eduline (**2**).

Lithium diisopropylamide (0.02 mole) was prepared as in Example **1**. After cooling to -65°, a solution of 2.4 g (0.02 mole) of acetophenone in 10 ml of tetrahydrofuran was added dropwise and the mixture was stirred at -65° for 1 hour. Then a suspension of 2.07 g (0.01 mole) of **7** (13) in 50 ml of tetrahydrofuran was added slowly and the resulting mixture was stirred at -50° for 24 hours. After quenching with saturated ammonium chloride, the organic phase was separated and the aqueous phase was extracted twice with methylene chloride. The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure. The resulting solid was crystallized from acetone/ether to give 1.85 g (70%) of **2**, mp 183-186°, Lit (2) mp 187-188°; nmr (100 MHz, deuteriochloroform): δ 7.90 (d, 1, J = 3 Hz), 7.60-7.25 (m, 7), 6.26 (s, 1), 3.94 (s, 3, OCH_3), 3.60 (s, 3, N-CH_3).

Graveoline (**3**).

Lithium diisopropylamide (0.04 mole) in 150 ml of dry tetrahydrofuran was prepared as in Example **1**. After cooling to -65°, a solution of 6.6 g (0.04 mole) of 3,4-methylenedioxyacetophenone in 40 ml of tetrahydrofuran was added dropwise and the mixture was stirred at -65° for 1 hour. Then a solution of 3.6 g (0.02 mole) of **5** in 40 ml of tetrahydrofuran (19) was added slowly and the resulting solution was stirred at -65° for 15 minutes. Workup as described in Example **1** furnished a brown oil which was chromatographed on a column of silica gel using 5% isopropanol/ethyl acetate to elute the product, 3.4 g (63%) of **3**. An analytical sample was crystallized from methylene chloride/ethyl acetate, mp 207-209°, Lit (3) mp 204-205°; ir (chloroform): 1620, 1600 cm^{-1}; nmr (100 MHz, deuteriochloroform): δ 8.46 (m, 1), 7.80-7.25 (m, 3), 6.87 (m, 3), 6.26 (s, 1), 6.06 (s, 2), 3.62 (s, 3); uv (ethanol): λ max (log ϵ) 243 (4.54), 325 (4.26), 338 (4.29).

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.1; H, 4.7; N, 5.0. Found: C, 73.0; H, 4.7; N, 4.8.

Japonine (**4**).

Lithium diisopropylamide (0.01 mole) in 40 ml of dry tetrahydrofuran was prepared as in Example **1**. After cooling to -65°, a solution of 1.5 g (0.01 mole) of α-methoxyacetophenone in 10 ml tetrahydrofuran was added dropwise and the mixture was stirred at -65° for 1 hour. Then a suspension of 1.05 g (0.005 mole) of **7** (13) in 40 ml of tetrahydrofuran was added slowly. The mixture was stirred at -65° for 20 minutes, then was allowed to warm to room temperature and stirred there for 1 hour. Workup as described in Example **1** furnished an oil which was chromatographed on a column of silica gel using 7% 2-propanol/methylene

chloride to elute the product, 0.9 g (61%) of **4**. An analytical sample was crystallized from methylene chloride/ether, mp 165-167°; ir (potassium bromide): 1630, 1595, 1580, 1310, 1245, 750 cm^{-1}; nmr (100 MHz, deuteriochloroform): δ 7.95 (d, 1, J = 2.9 Hz), 7.63-7.10 (m, 7), 3.95 (s, 3), 3.65 (s, 3), 3.49 (s, 3); uv (methanol: λ max (log ε): 257 (4.53), 344 (4.02), 359 (4.06).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.2; H, 5.8; N, 4.7. Found: C, 73.5; H, 5.7; N, 4.6.

3-Methoxy-1-methyl-2-phenyl-4-quinolone (**6**).

Lithium diisopropylamide (0.01 mole) in 40 ml of dry tetrahydrofuran was prepared as in Example **1**. After cooling to -65°, a solution of 1.5 g (0.01 mole) of α-methoxyacetophenone in 10 ml of tetrahydrofuran was added dropwise and the mixture was stirred at -65° for 1 hour. Then a solution of 0.9 g (0.005 mole) of **5** in 40 ml of tetrahydrofuran (19) was added slowly and the resulting suspension was stirred at -65° for 2 hours (very little reaction occurred). The mixture was then warmed to -40°, at which point a solution occurred, and was stirred there for 15 minutes. Workup as described in Example **1** furnished the crude product which was crystallized from ether to give 0.45 g (34%) of **6**, mp 220-222°, Lit (4) mp 222-224°; ir (potassium bromide): 1610, 1585, 1305, 1215, 1115 cm^{-1}; nmr (100 MHz, deuteriochloroform): δ 8.61 (m, 1), 7.83-7.25 (m, 8), 3.66 (s, 3), 3.49 (s, 3); ms (70 eV) m/e 265 (M^+).

Acknowledgement.

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(16) This downfield shift may be attributed to a concentration effect.

(17) Copies of the nmr and uv spectra were generously forwarded to us by Professor P. Venturella, Institute of Organic Chemistry, University of Palermo, Palermo, Italy.

(18) G. M. Coppola, A. D. Kahle and M. J. Shapiro, *Org. Magn. Reson.*, **17**, 242 (1981).

(19) This solution should be kept slightly warm to prevent the *N*-methylisatoic anhydride from crystallizing out.