reflux 12 h. The methanol was removed in vacuo and the mixture was diluted with 25 mL of H_2O and extracted with three 25-mL portions of diethyl ether. The etherial extracts were concentrated to give 27 mg (0.21 mmol, 82%) of 4-methylindole: NMR ($CDCl_3$) δ 2.44 (s, 3 H), 6.43 (m, 1 H), 6.62–7.05 (envelope, 4 H), 7.3 (br s, 1 H); IR ($CDCl_3$) cm^{-1} 3480, 3410, 2940, 1590, 1510, 1465. Spectra match that of an authentic sample (Aldrich).

4-Methoxyindole. This compound was prepared as described above from 4-methoxy-*N*-tosylindole on a 0.43-mmol scale in 96% yield: NMR ($CDCl_3$) δ 3.85 (s, 3 H), 6.52 (m, 2 H), 6.71–7.20 (envelope, 3 H), 7.75 (br s, 1 H); IR ($CDCl_3$) cm^{-1} 3460, 3390, 2990, 1585, 1470. Spectra match that of an authentic sample (Aldrich).

4-Hydroxyindole. This compound was prepared as described above from 4-acetoxy-*N*-tosylindole on a 0.36-mmol scale in 83%: NMR ($CDCl_3$) δ 6.50 (m, 2 H), 6.65–7.25 (envelope, 3 H), 10.6 (br s, 2 H); IR ($CDCl_3$) cm^{-1} 3620, 3380, 1590, 1460. Spectra match literature data.[27]

5-Chloroindole. This compound was prepared as described above from 5-chloro-*N*-tosylindole on a 0.28-mmol scale in 75% yield: NMR ($CDCl_3$) δ 6.55 (m, 1 H), 6.95–7.25 (envelope, 3 H), 7.58 (br s, 1 H); IR ($CDCl_3$) cm^{-1} 3370, 1590, 1470, 1370. Spectra match that of an authentic sample (Aldrich).

Acknowledgment. This research was supported in part by grants CHE-8305468 and CHE-8614289 for the National Science Foundation. The palladium was provided under the Johnson-Matthey Metal Loan program.

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Lead Tetraacetate Mediated Oxidation of the Enamides Derived from 1-Benzyl-3,4-dihydroisoquinolines

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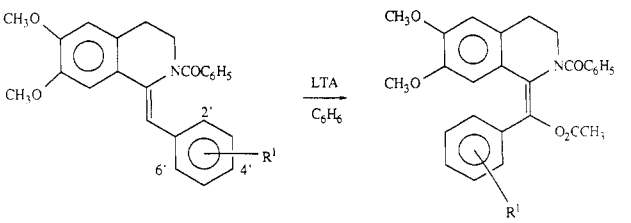
The products obtained from the lead tetraacetate (LTA) oxidation of *N*-acylbenzylidene isoquinoline enamides are a function of the type of carbonyl function in the enamide, the solvent, and the type of substitution on the benzylidene aromatic ring. The benzoyl enamides yield *Z*-β-acetoxy-substituted enamides. The ethoxycarbonyl enamides, containing electron-releasing substituents on the benzylidene ring, efficiently form oxazolones when oxidized with LTA in acetic acid. In the absence of electron-releasing substituents, ring opening occurs to form benzoin esters. When the same oxidation is conducted in benzene, the enamide double bond is converted into its diacetoxy derivative, which can undergo a variety of reactions. LTA oxidation of acetyl enamides results in cleavage of the acetyl group with ultimate formation of 1-benzoyl-3,4-dihydroisoquinolines and isoquinolines. Oxidation of the formyl enamide with LTA results in cleavage of the formyl group with formation of a variety of products. Most of these have an acetyl group in place of the original formyl and are the result of either cleavage of the benzylidene ring at the double bond, oxidation, and subsequent ring opening to a benzil or various other oxidative and rearrangement processes.

The photochemical reactions of enamides (acyl enamines) have been well studied and extensively employed in the total synthesis of various classes of alkaloids.[1,2] On the other hand, with the obvious exception of the Diels–Alder cycloadditions of enamides and dienamides,[2,3] the nonphotochemical reactivity of this grouping has been less thoroughly investigated. There are several reports on the oxidation of the enamide double bond, usually isolated instances in connection with a natural product synthesis. The enamide double bond has been oxyaminated,[4] oxidized to a variety of products with benzeneseleninic anhydride,[5] and oxidized to diketones with chromium trioxide.[6] Attempted epoxidation with peracids usually results in bond cleavage,[7] while thallium(III) oxidation can result in oxidative ring expansion.[8] Osmium tetraoxide results in formation of the glycol,[9] which can, in some instances, readily open to the hydroxy ketone.[10] Lead(IV) acetate has been reported to introduce a β-acetoxy group in steroidal enamides,[11] with the reaction occurring through the diacetoxy derivative.[9] This lead tetraacetate oxidation has been used to convert oxyprotoberberines to their acetoxy derivatives which were subsequently converted to the benzylisoquinoline alkaloids ophiocarpine and chile-

Table I



enamide	R^1	acetoxy enamide	yield, %
1	3′,4′-$(OCH_3)_2$	2	80
3	H	4	56[a]
5	4′-Cl	6	55[b]

[a] 16% recovered 3. [b] 15% recovered 5.

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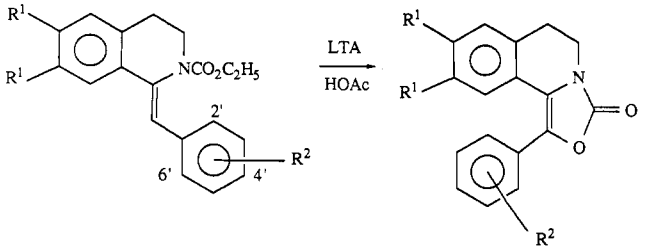
Table II. Oxidation of (Ethoxycarbonyl)benzylideneisoquinoline Enamides with Lead Tetraacetate in Acetic Acid



enamide	R^1	R^2	oxazolone	yield, %
7	OCH_3	3′,4′-$(OCH_3)_2$	8	84
9	OCH_3	3′,4′-(OCH_2O)	10	96
11	OCH_2O	3′,4′-$(OCH_3)_2$	12	71
13	OCH_3	3′,4′,5′-$(OCH_3)_3$	14	73
15	OCH_3	H	16	0

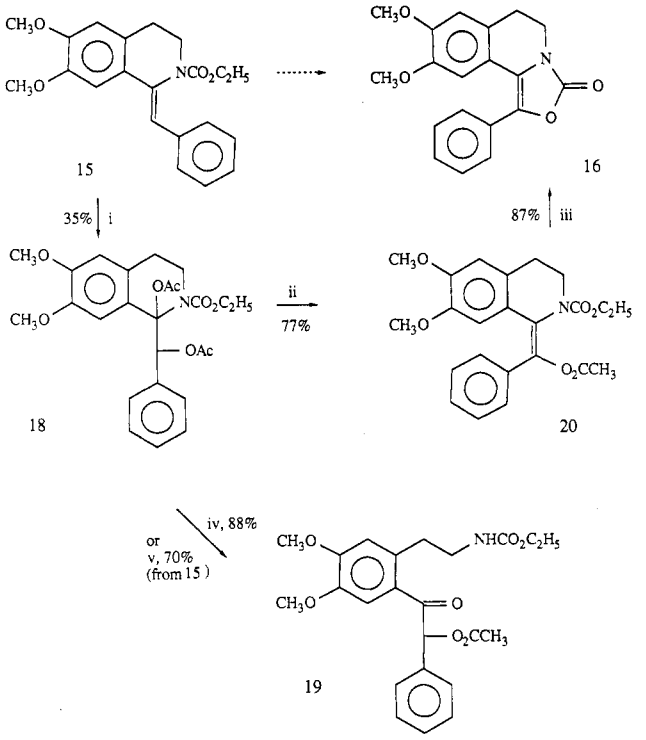
nine.[12] Our studies on the oxidation of benzylideneisoquinoline enamides arose from our interest in using functionalized enamides as an entry into the 7-oxygenated aporphine alkaloids. However, as these studies progressed, it became obvious that the product(s) of lead tetraacetate oxidation was a function not only of the substitution pattern on the benzylidene group but also of the type of carbonyl function and the solvent used for the reaction. This report is a study of the oxidation of various benzylideneisoquinoline enamides and the types of products obtained with lead tetraacetate.

Results

Benzoyl Enamides. The benzoyl benzylidene enamides, collected in Table I, are readily prepared from 1-benzyl-3,4-dihydroisoquinolines and benzoyl chloride and possess the *Z* configuration (*trans*-stilbene).[13] Oxidation of enamide **1** with dry lead tetraacetate (LTA) in benzene formed two closely moving products. The minor product was completely converted into the major product **2** upon radial thick-layer chromatography. The major product was identified as the β-acetoxy enamide **2** through its spectral properties. The stereochemistry was assigned as *Z* based on the basis of, inter alia, the strong shielding of the isoquinoline 7-methoxy group in the NMR (δ 3.33).[14] It is probable that the minor product detected in this reaction is the diacetoxy derivative which eliminates acetic acid to yield **2**. In general, the benzoyl benzylidene enamides give reaction products similar to those previously reported in the literature, namely, β-acetoxy enamides.[11,12]

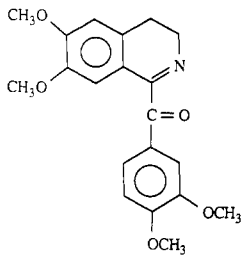
Ethoxycarbonyl Enamides. The ethoxycarbonyl benzylidene enamides, e.g., **7**, are readily prepared by reaction of the requisite 1-benzyl-3,4-dihydroisoquinoline with either ethyl chlorocarbonate or diethylpyrocarbonate.[15,16] These enamides possess the *Z* configuration. Oxidation of **7** with lead tetraacetate in acetic acid

Scheme I[a]

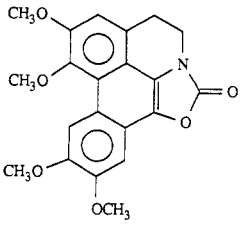


[a] Reagents: (i) $Pb(OAc)_4$/benzene; (ii) DBU, pyridine, benzene, Δ; (iii) sodium methoxide, methanol; (iv) H_2O; (v) $Pb(OAc)_4$/HOAc.

did *not* lead to the expected β-acetoxy derivative but instead furnished the oxazolone **8** in 84% yield (Table II), together with a small amount (15%) of dihydropapaveraldine (**17**). The oxazolone structure of **8** was readily



17



A

apparent from its spectral characteristics, particularly the IR and NMR. Compounds of type **8**, e.g., **16**, have been prepared by Ninomiya by a multistep sequence starting from compounds analogous to **17** by hydride reduction, two-step conversion to the oxazolidinone, and dehydrogenation to the oxazolone.[17] The oxazolones were the starting point in an abortive photochemical synthesis of the 7-oxygenated aporphines.[17,18] We have similarly found that the oxazolone **8** does not photocyclize to the phenanthrene derivative **A** (in this article, all observed, isolated, and characterized compounds are designated by number. Compounds that have not been synthesized, as **A**, or are postulated intermediates are assigned letters) under a variety of conditions. As the entries in Table II demonstrate, the LTA oxidation of the ethoxycarbonyl enamides is a general reaction for those enamides possessing electron donating substituents on the benzylidene ring. When the benzylidene ring is unsubstituted, or possesses electron-

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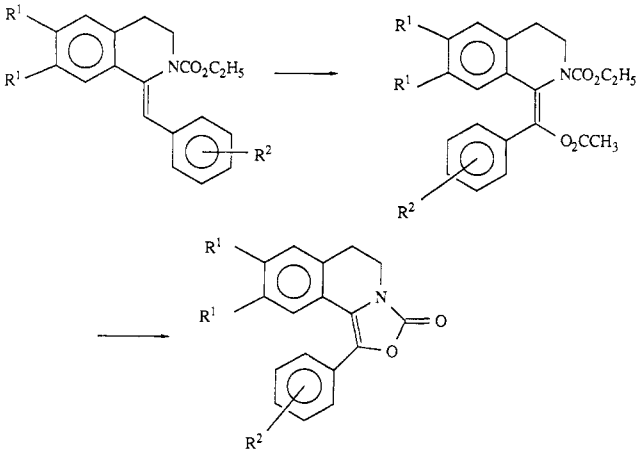
Table III. Conversion of the Ethoxycarbonyl Benzylidene Enamides to Oxazolones According to the Method in Scheme I



enamide	R^1	R^2	acetoxy enamide	oxazolone	yield, %
15	OCH_3	H	20	16	87[a]
21	OCH_2O	H	22	23	94[a]
24	OCH_3	4′-Cl		25	42[b]
7	OCH_3	3′,4′-$(OCH_3)_2$	26	8	75[a]

[a] From acetoxy enamide. [b] From enamide without isolating the acetoxy enamide.

withdrawing groups, e.g., Cl, no oxazolone is formed and the reaction takes an alternative pathway.

When enamide **15** is subjected to LTA oxidation in acetic acid, a single product is formed in high yield, (Scheme I). The product, **19**, is a substituted benzoin acetate whose structure rests on its IR spectrum, which shows a secondary carbamate, an aromatic ketone, and an ester function, and the NMR spectrum, which includes an aromatic proton deshielded by a carbonyl group, together with the methine hydrogen of the benzoin acetate. The formation of **19** proceeds through the diacetoxy adduct **18**, which undergoes ring opening to the observed product (vide infra).

Oxidation of the substituted enamides in benzene allows the isolation of the intermediate in the oxidation of **15** and also constitutes a method for preparing the corresponding oxazolones from the benzylidene enamides (Scheme I). When enamide **15** was oxidized with LTA in benzene, the proximate product, isolated by direct crystallization was the diacetoxy derivative **18**. Hydrolysis with weak acid yielded the benzoin acetate **19**. When the diacetoxy derivative **18** was treated with an organic base it formed *Z* acetoxy enamide **20**, analogous to the benzoyl derivatives (Table I). In practice, the overall yield of the acetoxy enamide from the enamide was much higher if the diacetoxy derivative was not isolated but directly subjected to elimination. Ordinarily, the *Z* isomer was formed exclusively; however, with enamide **21**, the *Z* isomer **22**, obtained in 54% yield, was accompanied by a small amount (2.5%) of its *E* isomer **27**.[14] Subsequent treatment of **20**

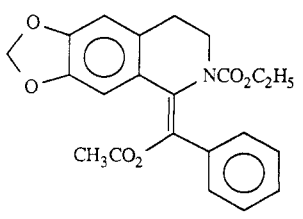
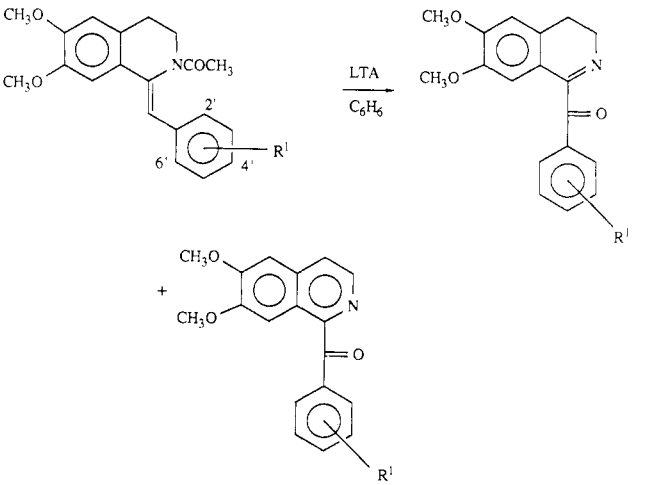


Table IV. Oxidation of the Acetyl Benzylidene Enamides to 1-Benzoylisoquinoline Derivatives with Lead Tetraacetate in Benzene



enamide	R^1	dihydroisoquinoline (yield, %)	isoquinoline (yield, %)
28	3′,4′-$(OCH_3)_2$	17 (53)	29 (36)
30	H	32 (5)	31 (61)
33	4′-Cl	34 (29)	35 (32)

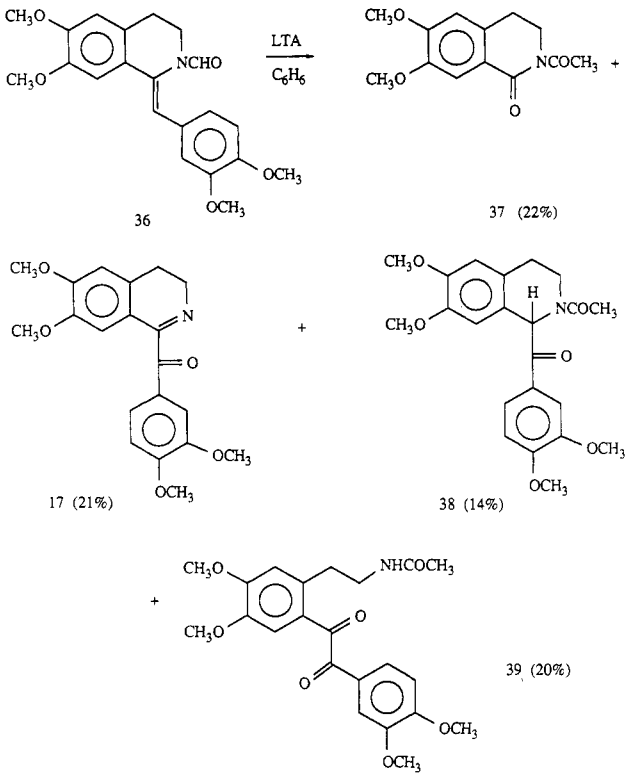
with sodium methoxide converted it into the oxazolone **16**.[17] The oxazolones, prepared by this method, are collected in Table III. It appears that all the enamides, regardless of substitution pattern on the benzylidene ring, form the diacetoxy derivative in benzene.

An attractive mechanism for the LTA in acetic acid oxidation of enamide **7** (Table II) would involve the formation of the diacetoxy derivative, elimination to the acetoxy enamide **26**, and subsequent hydrolysis of the enol acetate to the ketone, or its enol, and cyclization to the oxazolone. This possibility was examined by subjecting the β-acetoxy enamide **26** to the reaction conditions resulting in the formation of the oxazolone **8**. Under these conditions, the acetoxy enamide was recovered, having undergone what appears to be a small amount of *E*–*Z* isomerization. There was no oxazolone formed by HPLC analysis. Additionally, attempted hydrolysis of **26**, using *p*-toluenesulfonic acid, was ineffective. Therefore, the acetoxy enamide **26** is not an intermediate in formation of the oxazolone **8** from enamide **7** with LTA in acetic acid.

Acetyl Enamides. Initially, it was expected that LTA oxidation of the acetyl benzylidene enamides would furnish the β-acetoxy derivatives analogously to those obtained from the benzoyl derivatives. Actually, when the acetyl enamide **28** was oxidized with LTA in benzene, it was converted into two products, the major was the well-known dihydropapaveraldine (**17**) and the minor the equally well-known papaveraldine (**29**). The acetyl enamides studied are collected in Table IV.

Formyl Enamides. Again, the LTA oxidation of the formyl enamide **36** was expected to be straightforward. Instead, oxidation of **36** in acetic acid yielded a complex mixture of products which could be separated by careful chromatography. The structures of the products, outlined in Scheme II, bear little relation to the starting enamide. In particular, with the exception of dihydropapaveraldine (**17**), all the products have had their formyl group on the nitrogen replaced by an acetyl. The first product isolated, in order of their elution from the column, is the *N*-acetylisoquinolone **37**, which is a known compound and was compared with an authentic sample.[19] The second

Scheme II

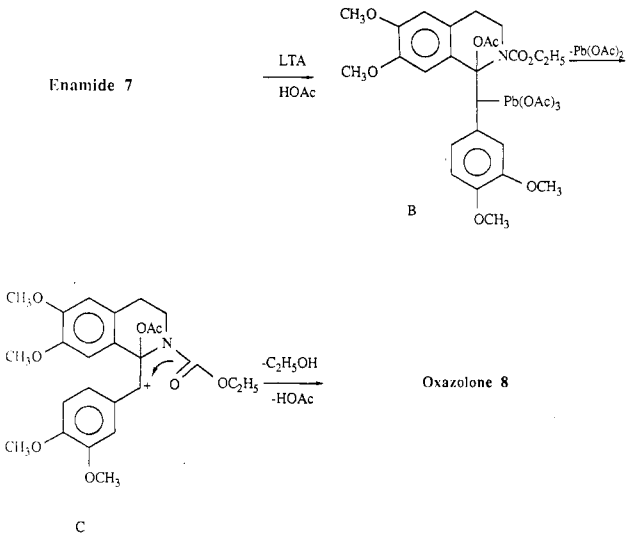


is dihydropapaveraldine (**17**). The third is the interesting compound **38**, where the enamide double bond has been converted to a ketone and the *N*-formyl group replaced by an *N*-acetyl. The characterization of **38** is based on its spectral properties. In particular, the NMR spectrum shows a C8 aromatic hydrogen deshielded by the ketone and the isoquinoline C-1 methine hydrogen as a singlet at δ 6.52. The mass spectrum was very useful in the structural elucidation showing a parent ion, cleavage of the *N*-acetyl and dimethoxybenzoyl groups, as well as the dimethoxydihydroisoquinoline ring. The last product isolated was the benzil derivative **39**, whose structure rests on its spectral data, primarily its NMR spectrum, which is qualitatively similar to that of **38**, and in particular its mass spectrum, which shows a parent, cleavage at the diketone showing both halves, and cleavage of the *N*-acetyl from the appropriate benzoyl radical ion. Because of the complexity of the reaction and the lack of useful synthetic utility, the oxidation of the formly enamides was not further pursued.

Discussion

The oxidation of olefins with LTA can lead to a variety of products, and in many cases is preparatively useful.[20,21] In many respects, the LTA oxidation of the benzylidene enamides described in this article resembles the LTA oxidation of enol ethers and esters which proceeds through diacetoxylation of the double bond.[20,22] This is particularly true of the benzoyl enamides (Table I) and the ethoxycarbonyl enamides when oxidized in benzene (Table III), where the diacetoxy intermediate was isolated (Scheme I).

Scheme III. Proposed Mechanism for the Formation of Oxazolones from Ethoxycarbonyl Benzylidene Enamides



The mechanism becomes more complicated for the ethoxycarbonyl enamides when the oxidation is conducted in acetic acid. The demonstration that the β-acetoxy enamide **26** is not an intermediate in the formation of oxazolone in acetic acid leads to the mechanism proposed in Scheme III. Addition of LTA to the enamide double bond in **7** generates the organolead derivative B, which fragments to form the carbonium ion C. Whether ion C can undergo bridging by the acetoxy group or the isoquinoline aromatic ring is unknown. However, a substantial amount of stabilization of the charge by electron-donating groups on the benzyl aromatic ring is necessary to allow trapping by the carbonyl group of the carbamate which ultimately loses both ethanol and acetic acid to yield the oxazolone. When the electron-donating substituents are not present in ion C, where a benzyl carbonium ion is present, trapping by the solvent acetic acid occurs, leading to the diacetoxy derivative with further ring opening to the benzoin derivatives, (Scheme I). It is likely that the same mechanism holds when the oxidation is conducted in benzene, but whether for solvent polarity effects, bridging or conformational reasons, trapping of the carbonium ion is not competitive with trapping by acetate. The oxidation of these enamides to oxazolones is however, a useful preparative reaction for these compounds.[23]

The oxidation of both the acetyl and formyl benzylidene enamides probably involves the solvolytic fragmentation of acyliminium intermediates. The probable mechanistic sequence for the oxidation of the acetyl enamide **28** is straightforward conversion to the β-acetoxy enamide by the sequence shown in Scheme I, followed by a second LTA oxidation to form a triacetoxy derivative. This is in equilibrium with an acyliminium ion which can undergo solvolytic removal of the acetyl group to form dihydropapaveraldine (**17**), which can be further oxidized to the isoquinoline **29**.[24] This facile second LTA oxidation of an acetoxy enamide had previously been observed in the oxidation of oxyprotoberberines.[12] The fragmentation of the acyliminium salt has little precedent, partially because the majority of research has been on cyclic compounds.[25]

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A similar mechanism is probably occurring with the formyl enamide **36**. It may be that the initially formed diacetoxy derivative is forming an acyliminium ion, where the formyl group solvolyzes to form an (α-acetoxybenzyl)dihydroisoquinoline which undergoes O → N acetyl transfer to form **38**. Compound **38** could serve as the precursor to the other products **37** and **39**, but there are other plausible pathways to these molecules, and additional speculation would be premature.

In summary, the LTA oxidation of benzylidene isoquinoline enamides is a function of the substitution pattern on the benzylidene group, the nature of the enamide carbonyl function, and the solvent in which the oxidation is conducted. The oxidations proceed through a common intermediate where the α-carbon of the enamide double bond is substituted by an acetoxy group and the β-carbon carries a positive charge. Partitioning of this intermediate then leads to the observed products. With the appropriate acyl groups, the LTA oxidation is an effective way of synthesizing β-acetoxy enamides and oxazolones. Further studies on the oxidation of enamides will be reported in due course.

Experimental Section

General Methods. Melting points were run on a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. IR spectra were recorded in KBr on a Beckman IR-12, or, alternatively, an FT-IR was obtained using a Digilab FTS-60 FT-IR spectrometer. UV spectra were run in methanol on a Beckman DK-2A or Cary-Varian 2200 spectrophotometer. NMR spectra were recorded on a Varian T-60, A-60, FT-80, or an IBM AF-270 spectrometer and were run in deuteriochloroform with tetramethylsilane as an internal standard. Mass spectra were obtained on AEI MS-30. Microanalyses were determined by the Searle Laboratories Microanalytical Service and also by the BOC Group Technical Center Microanalytical Service, under the direction of Allan Ellgren.

1-(3,4-Dimethoxybenzylidene)-2-benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (1). Enamide 1 was prepared from 3,4-dihydropapaverine[26] and benzoyl chloride in pyridine in 74% yield according to the method of Lenz.[14] Compound 1 possesses: mp 214–215 °C (lit.[27] mp 222 °C); IR 1640 cm^{-1}; UV (CH_2Cl_2) 276 nm (ϵ 21 100), 332 (20 500); NMR δ 7.18 (t, 1 H), 7.06 (s, 1 H), 7.01 (t, 2 H), 6.87 (d, 2 H), 6.73 (m, 2 H), 6.58 (d, 1 H), 6.37 (s, 1 H), 6.34 (s, 1 H), 5.14 (m, 1 H), 3.96 (s, 3 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 3.77 (s, 3 H), 3.37 (m, 2 H), 2.88 (m, 1 H); MS (EI), m/z (relative intensity) 445 (M^+, 77), 340 (M – COC_6H_5, 19), 105 (COC_6H_5, 100).

Anal. Calcd for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.81; H, 6.06; N, 2.98.

Oxidation of 1-(3,4-Dimethoxybenzylidene)-2-benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (1) with LTA. A solution of 1.00 g (2.25 mmol) of enamide 1[27] in 100 mL of dry benzene was stirred magnetically under nitrogen and 1.25 g of dry LTA added. After 20.5 h, the reaction was quenched with glycerine, washed with water and dilute sodium bicarbonate solution, and dried with sodium sulfate. Evaporation of the solvent gave a foam, which crystallized from ether to yield 900 mg, (1.79 mmol; 80%) of a 1:4 mixture of two compounds by HPLC. Radial thick-layer chromatography using 5:95 ethyl acetate/methylene chloride caused the minor component to be converted to the major *Z*-isomer **2**: mp 160–162 °C; IR 1755 cm^{-1}, 1645, 1602, 1516; UV 220 nm (end, ϵ 42 400), 256 (min, 12 600), 310 (20 300); NMR δ 7.3–7.5 (m, 5 H), 6.45–6.75 (m, 4 H), 6.25 (br s, 1 H), 4.76 (br s, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.68 (s, 3 H), 3.59 (m, 1 H), 3.33 (s, 3 H), 3.13 (br s, 1 H), 2.96 (m, 1 H), 2.09 (s, 3 H); MS, m/z (relative intensity) 503 (parent, 0.6), 445 (10.9, $-CH_3CO_2$), 444 (36.5, $-CH_3CO_2H$), 105 (100, C_6H_5CO).

Anal. Calcd for $C_{29}H_{29}NO_7$: C, 69.17; H, 5.81; N, 2.78. Found: C, 69.41; H, 5.99; N, 2.95.

1-Benzylidene-2-benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (3)[28] (2.00 g, 5.19 mmol) was oxidized in the same manner as enamide 1. After workup, the oil was crystallized from ether, containing a little ethyl acetate, to yield 1.29 g (2.91 mmol; 56%) of the *Z*-acetoxy derivative **4**: mp 182–183.5 °C; IR 1755 cm^{-1}, 1641, 1514, 1260; UV 272 nm (ϵ 16 900); NMR δ 7.53 (m, 3 H), 7.42 (m, 2 H), 7.20 (s, 5 H), 6.70 (s, 1 H), 6.15 (s, 1 H), 4.81 (br s, 1 H), 3.90 (s, 3 H), 3.64 (br s, 1 H), 3.27 (s, 3 H), 3.16 (br s, 1 H), 3.00 (br s, 1 H), 2.09 (s, 3 H). The mother liquor from above, slowly deposited 0.32 g (16%) of starting enamide **3**.

Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 72.97; H, 5.79; N, 3.52.

2-Benzoyl-1-(4-chlorobenzylidene)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (5) was prepared according to the procedure used for 1 and 3.[13] The enamide **5** showed the following: mp 223.5–225.5 °C; IR 1626 cm^{-1}, 1611, 1512, 1263; UV 214 nm (ϵ 30 300), 234 (sh, 22 800), 262 (min, 11 700), 306 (21 400), 324 (22 800); NMR δ 6.8–7.3 (m, 9 H), 6.72 (s, 1 H), 6.36 (s, 1 H), 5.13 (m, 1 H), 3.97 (s, 3 H), 3.94 (s, 3 H), 3.33 (m, 2 H), 2.88 (d, 1 H).

Anal. Calcd for $C_{25}H_{22}ClNO_3$: C, 71.51; H, 5.28; N, 3.34. Found: C, 71.70; H, 5.34; N, 3.29.

LTA Oxidation of Enamide 5. The enamide **5** (2.00 g, 4.76 mmol) was oxidized with 4 g of dry lead tetraacetate in 150 mL of dry benzene at 45 °C for 5 h and then at room temperature for 48 h. Workup as above, yielded a mixture which was flash chromatographed. Starting enamide (0.30 g) was recovered with 2:98 ethyl acetate/methylene chloride and the *Z*-acetoxy isomer **6**, 1.25 g (2.62 mmol) 55% with a 8:92 ratio of the same solvents. The acetoxy enamide **6** showed the following: mp 173–74 °C; IR 1746 cm^{-1}, 1638, 1514, 1263, 1255; UV 216 nm (ϵ 36 300), 288 (13 400); NMR δ 7.2–7.6 (m, 7 H), 6.95 (br s, 2 H), 6.69 (s, 1 H), 6.12 (s, 1 H), 4.69 (br s, 1 H), 3.92 (s, 3 H), 3.60 (br s, 1 H), 3.33 (s, 3 H), 3.11 (br s, 1 H), 2.98 (br s, 1 H), 2.07 (s, 3 H).

Anal. Calcd for $C_{27}H_{24}ClNO_5$: C, 67.85; H, 5.06; N, 2.93. Found: C, 68.28; H, 5.14; N, 2.86.

Ethyl 1-(3,4,5-Trimethoxybenzylidene)-3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinolinecarboxylate (13). A solution of 20 g (49 mmol) of the hydrochloride of 1-(3,4,5-trimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline[29] in 0.5 L of water was made strongly basic with 25 mL of 50% aqueous sodium hydroxide solution and then extracted three times with chloroform. The combined organic extracts were dried and evaporated in vacuo. The free base residue was dissolved in 250 mL of toluene and dried by refluxing under argon with a Dean–Stark trap. A solution of 10 mL of diethyl pyrocarbonate in 15 mL of toluene was added by addition funnel over 0.5 h. The dark solution was treated with decolorizing carbon, filtered by using Filter-Aid, and evaporated to an oil. Flash chromatography using 1:4 ethyl acetate/toluene yielded an oil, which could not be induced to crystallize. The NMR spectrum of this oil indicated a mixture of *E*–*Z* isomer with *E* predominating as shown by the ethyl group methyl resonances at δ 1.30 (*E*) and 0.87 (*Z*).[14] The oil was dissolved in 0.6 L of benzene, a few crystals of iodine were added, and the mixture was refluxed for 2 h. The cooled solution was extracted with sodium bisulfite solution and then dried with sodium sulfate and evaporated. The residue was crystallized from ether to yield 11.5 g of enamide **13** (25.9 mmol; 53%): mp 196.5–197.5 °C; IR 1705 cm^{-1}, 1515; NMR δ 7.33 (s, 1 H), 6.72 (s, 2 H), 6.67 (s, 1 H), 6.58 (s, 1 H), 3.96 (s, 3 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.47 (q, 2 H), 2.90 (br s, 2 H), 1.12 (t, 3 H). The remaining methylene group of the isoquinoline ethylene bridge is buried under the methoxyl group resonances at ca. δ 3.9.

Anal. Calcd for $C_{24}H_{29}NO_7$: C, 65.00; H, 6.59; N, 3.16. Found: C, 65.09; H, 6.72; N, 3.34.

Similarly prepared was ethyl 1-(3,4-dimethoxybenzylidene)-3,4-dihydro-6,7-(methylenedioxy)-2(1*H*)-isoquinolinecarboxylate (11): mp 167–168 °C; IR 1635 cm^{-1}, 1515, 1490; UV 220 nm (end, ϵ 33 000), 260 (min, 6100), 306 (sh, 17 300), 334 (24 600); NMR δ 7.20 (s, 1 H), 7.07 (s, 1 H), 7.02 (d, 1 H), 6.83 (d, 1 H), 6.68 (s, 1 H), 6.59 (s, 1 H), 5.95 (s, 2 H), 4.59 (br s, 1 H), 3.82 (s, 6 H), 3.82 (br s, 2 H), 3.1–3.2 (br m, 2 H), 2.71 (br s, 1 H), 0.76 (br t, 3 H).

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Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.53. Found: C, 66.47; H, 5.74; N, 3.75.

Ethyl 1-(4-Chlorobenzylidene)-3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinolinecarboxylate (24). 1-(4-Chlorobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline[30] (9 g, 28.5 mmol) was dissolved in 200 mL of chloroform and 25 mL of pyridine. The solution was placed under nitrogen and a solution of 15 mL of ethyl chloroformate in 50 mL of chloroform added slowly by using an addition funnel. The resulting reaction mixture was stirred overnight and then washed three times with water. The organic solution was dried with sodium sulfate and evaporated to yield 10.85 g (28.0 mmol; 98%) of the enamide **24** from ether: mp 167–169 °C; IR 1690 cm^{-1}, 1645, 1615, 1520; UV 227 nm (ϵ 19600), 257 (min, 6100), 302 (sh, 20200), 326 (25200); NMR (δ) 7.0–7.5 (m, 5 H), 6.68 (s, 1 H), 6.57 (s, 1 H), 4.20 (br m, 4 H), 3.95 (s, 3 H), 3.88 (s, 3 H), 2.87 (br s, 2 H), 0.82 (br t, 3 H).

Anal. Calcd for $C_{21}H_{22}ClNO_4$: C, 65.03; H, 5.72; N, 3.61; Cl, 9.14. Found: C, 64.83; H, 5.67; N, 3.60; Cl, 9.02.

Lead Tetraacetate Oxidation of Ethyl 1-(3,4-Dimethoxybenzylidene)-3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinolinecarboxylate (7) in Acetic Acid. Lead tetraacetate (6.25 g, 14.1 mmol) was suspended in 100 mL of glacial acetic acid. The enamide **7** (5.00 g, 12.1 mmol) was then added to this magnetically stirred suspension. The enamide took approximately 10 min to dissolve when the solution became dark red. After 20 min, the reaction was quenched with glycerine and, after the mixture was stirred for a further hour, diluted slowly with 700 mL of water. At this point, the solution was a milky yellow color, and then a compound rapidly crystallized. Filtration and drying yielded 3.50 g of the oxazolone **8**. The mother liquor was extracted with methylene chloride (3 × 150 mL). The combined extracts were washed with sodium bicarbonate, dried with sodium sulfate, and evaporated to yield 1.6 g of residue. The residue was chromatographed by using a Waters Delta Prep HPLC and eluting with an ethyl acetate/methylene chloride gradient to yield an additional 0.40 g of the oxazolone **8** (10.15 mmol; 84%) and 650 mg of dihydropapaveraldine **17** (1.8 mmol; 15%), which was identified by comparison with an authentic sample.[31] The oxazolone **8** showed the following: mp 170 °C; IR 1755 cm^{-1}, 1520; UV 220 nm (end, ϵ 32500), 236 (min, 16000), 243 (16300), 271 (min, 5900), 305 (sh, 12900), 330 (16300); NMR δ 6.65–7.25 (m, 5 H), 3.90 (s, 6 H), 3.84 (s, 3 H), 3.72 (t, 2 H), 3.63 (s, 3 H), 2.97 (t, 2 H); MS, *m/z* (relative intensity) 383 (parent, base), 312 (21).

Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.64; H, 5.44; N, 3.87.

Similarly, ethyl 1-[3,4-(methylenedioxy)benzylidene]-3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinolinecarboxylate (**9**)[16] (5.00 g, 12.6 mmol) was oxidized with 6.25 g of LTA to yield 4.43 g (12.1 mmol; 96%) of oxazolone **10**: mp 190–192 °C; IR 1760 cm^{-1}, 1610, 1510, 1500; UV 220 nm (end, ϵ 33000), 250 (13000), 273 (min, 6000), 307 (sh, 13000), 333 (16500); NMR δ 6.5–7.3 (m, 5 H), 5.98 (s, 2 H), 3.89 (s, 3 H), 3.79 (t, 2 H), 3.66 (s, 3 H), 2.96 (t, 2 H).

Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.39; H, 4.58; N, 3.83.

Ethyl 1-(3,4-dimethoxybenzylidene)-3,4-dihydro-6,7-(methylenedioxy)-2(1*H*)-isoquinolinecarboxylate (**11**) (2.00 g, 5.0 mmol) was oxidized with 3.5 g of LTA to yield 1.3 g (3.54 mmol; 71%) of oxazolone **12**: mp 176–178 °C (acetone/water); IR 1760 cm^{-1}, 1520, 1255; UV 243 nm (ϵ 18400), 271 (min, 6500), 305 (sh, 15800), 330 (17600); NMR δ 7.23 (dd, J = 8, 1.8 Hz, 1 H), 7.13 (s, 2 H), 6.90 (d, J = 8 Hz, 1 H), 6.74 (s, 1 H), 5.97 (s, 2 H), 3.94 (s, 3 H), 3.88 (s, 3 H), 3.80 (t, J = 6 Hz, 2 H), 2.98 (t, J = 6 Hz, 2 H).

Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.17; H, 4.97; N, 3.89.

Similarly, ethyl 1-(3,4,5-trimethoxybenzylidene-3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinolinecarboxylate (**13**) (5.25 g, 11.8 mmol) was oxidized with 6.5 g of LTA to give a purple solution, which turned to light orange upon glycerine quench. Workup as above yielded 3.55 g (8.60 mmol; 73%) of oxazolone **14**: mp 174.5–176.5 °C; IR 1765 cm^{-1}, 1580, 1500; UV 237 nm (min, 17300), 246 (18600), 273 (min, 5450), 333 (17700); NMR δ 7.18 (s, 1 H), 6.87 (s, 2 H), 6.72 (s, 1 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.83 (s, 6 H), 3.73 (t, 2 H), 3.65 (s, 3 H), 2.98 (t, 2 H).

Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.92; H, 5.61; N, 3.39 Found: C, 63.63; H, 5.64; N, 3.50.

Lead Tetraacetate Oxidation of Ethyl 1-Benzylidene-3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinolinecarboxylate (15) in Acetic Acid. A solution of 5.0 g (14.15 mmol) of enamide **15**[16] was dissolved in 100 mL of acetic acid and 7 g of LTA added. After 15 min, the reaction was quenched with glycerine and diluted with 50 mL of water. After standing for 16 h, it was diluted to 0.5 L with water and extracted four times with toluene. After drying with sodium sulfate, the solvent was evaporated and the residual oil flashed chromatographed by using 1:3 ethyl acetate/methylene chloride to yield 4.25 g (9.90 mmol; 70%) of the benzoin derivative **19**: mp 106.5–108.5 °C (ether/petroleum ether); IR 3440 cm^{-1}, 3305, 1735, 1690; UV 230 nm (ϵ 17600), 254 (min, 4200), 280 (7400), 295 (min, 5600), 307 (6000); NMR δ 7.32 (s, 5 H), 7.18 (s, 1 H), 6.65 (s, 1 H), 6.57 (s, 1 H), 4.05 (q, 2 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 2.70 (m, 2 H), 2.22 (s, 3 H), 1.20 (t, 3 H).

Anal. Calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.61; H, 6.43; N, 3.35.

Starting material (8%) was also recovered.

Lead Tetraacetate Oxidation of Ethyl 1-(3,4-Dimethoxybenzylidene)-3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinolinecarboxylate (7) in Benzene. The enamide **7** (10.0 g, 24.2 mmol) was dissolved in 550 mL of benzene and 5 mL of pyridine and refluxed under argon with a Dean–Stark trap to dry the solution. After the reaction was cooled, 15 g of LTA, dried by heating over refluxing acetone under vacuum, was added and the mixture stirred overnight. After any excess LTA was quenched with glycerine, the mixture was washed three times with distilled water and the benzene dried with sodium sulfate. After the addition of 100 mL of pyridine, the solution was refluxed under argon for 16 h. After cooling, the solution was washed three times with water and then dried with sodium sulfate. The solution was evaporated to give a semisolid, which was stirred with 60 mL of ether and then filtered and washed with a little petroleum ether to yield 7.20 g (15.3 mmol; 63%) of *Z*-acetoxylated enamide **26**: mp 146–148.5 °C; IR 1751 cm^{-1}, 1701, 1515, 1205; UV 240 nm (sh, ϵ 20900), 258 (min, 12300), 288 (16700), 310 (sh, 14100); NMR δ 7.04 (dd, J = 8, 1.5 Hz, 1 H), 6.99 (s, 1 H), 6.93 (d, J = 8 Hz, 1 H), 6.60 (s, 1 H), 6.44 (s, 1 H), 4.2 (br s, 2 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.3–4.0 (m, 2 H), 3.33 (s, 3 H), 2.9 (br s, 2 H), 2.13 (s, 3 H), 1.32 (t, 3 H).

Anal. Calcd for $C_{25}H_{29}NO_8$: C, 63.68; H, 6.20; N, 2.97. Found: C, 63.39; H, 6.05; N, 2.94.

Subjection of the *Z*-Acetoxy Enamide 26 to the Reaction Conditions Leading to the Formation of the Oxazolone 8. To 100 mL of glacial acetic acid were added 1.05 g of LTA and subsequently glycerine to reduce the Pb(IV) to Pb(II). Then 1 g of the *Z*-acetoxy enamide **26** was added and stirring continued for 10 min. The reaction was yellow at this time. The reaction mixture was slowly diluted with water. The milky aqueous mixture was extracted three times with methylene chloride; the organics were washed with dilute sodium bicarbonate, dried with sodium sulfate, and evaporated to 1.0 g of foam, from which 900 mg of white crystals were obtained by trituration with ether. The solid material appears to be an *E*/*Z*-mixture of the starting acetoxy enamide with the starting *Z*-isomer predominating (~10:1). Analysis was by HPLC. There was no trace of oxazolone by TLC or HPLC, and the oxazolone was well separated from the enamides.

Cyclization of the *Z*-Acetoxy Enamide 26 with Sodium Methoxide. The acetoxy enamide (1.0 g, 2.12 mmol) was suspended in 50 mL of methanol and placed under argon and 1 g of sodium methoxide added. After the reaction was stirred for 2.5 h, 2 g of citric acid was added, and then the mixture was diluted to 250 mL with water. After the mixture was stirred overnight, the precipitate was collected, washed with water, and dried to yield 610 mg (1.59 mmol; 75%) of the oxazolone **8**.

Oxidation of Ethyl 1-Benzylidene-3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinolinecarboxylate with LTA in Benzene. The benzylidene enamide **15** (5.0 g, 14.15 mmol) was dissolved in 250 mL of benzene and dried by refluxing under argon with a Dean–Stark trap. The resultant solution was cooled and placed under argon and 7.5 g of LTA added. The resultant

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suspension was stirred for 2 days, quenched with a little glycerine, and then washed with water, extracted with dilute aqueous sodium bicarbonate, and dried with sodium sulfate. After removal of the solvent, the residue was crystallized from ether to yield 2.3 g (4.89 mmol; 35%) of the diacetoxy compound **18**: mp 98–101 °C; IR 1755 cm^{-1}, 1707, 1520, 1230; UV 230 nm (sh, ϵ 6750), 253 (min, 700), 282 (3000), 287 (2900); NMR δ 7.33 (s, 1 H), 6.9–7.3 (m, 5 H), 6.55 (br s, 1 H), 6.32 (s, 1 H), 4.30 (q, 2 H), 3.97 (s, 3 H), 3.85 (s, 3 H) [2H for CH_2N are under the methoxyl resonances], 1.5–2.5 (m, 2 H), 2.24 (s, 3 H), 2.22 (s, 3 H), 1.38 (t, 3 H).

Anal. Calcd for $C_{25}H_{29}NO_8$: C, 63.68; H, 6.20; N, 2.97. Found: C, 63.96; H, 6.21; N, 3.07.

Formation of the *Z*-Acetoxy Enamide 20 from the Diacetoxy Derivative 19. A mixture of 100 mL of benzene, 10 mL of pyridine, and 1 mL of DBU (2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine) was refluxed under nitrogen with a Dean–Stark trap to dry it. After reaction was cooled, 2.0 g of **19** (4.24 mmol) was added and the solution brought to reflux for 16 h. The solution was cooled, washed with water, dried with sodium sulfate, and evaporated. The residue was flash chromatographed to yield 1.35 g (3.28 mmol; 77%) of the *Z*-acetoxy enamide **20**: mp 127–128.5 °C; IR 1760 cm^{-1}, 1705, 1610, 1510; UV 255 nm (min, ϵ 7730), 280 (10450); NMR δ 7.34 (m, 5 H), 6.53 (s, 1 H), 6.28 (s, 3 H), 4.18 (q, 2 H), 3.5–4.5 (m, 2 H), 3.82 (s, 3 H), 3.23 (s, 3 H), 2.87 (br s, 2 H), 2.10 (s, 3 H), 1.26 (t, 3 H).

Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.22; H, 6.12; N, 3.72.

Cyclization of the *Z*-Acetoxy Enamide 20 with Sodium Methoxide. The *Z*-acetoxy enamide **20** (3.5 g, 8.49 mmol) was dissolved in 125 mL of methanol under nitrogen and 5 g of sodium methoxide added. After the reaction was stirred overnight, 5 g of citric acid was added and the mixture diluted with water. After removal of the majority of the methanol on a rotary evaporator, the mixture was extracted three times with methylene chloride. The combined extracts were dried with sodium sulfate and evaporated to give a residue, which when crystallized from methanol, yielded 2.4 g (7.42 mmol, 87%) of the oxazolone **16**: mp 158–160 °C (ethanol–methylene chloride); IR 1765 cm^{-1}, 1520, 1270; UV 228 nm (end, ϵ 29800), 245 (min, 18800), 262 (26000), 286 (min, 4300), 333 (24000), 346 (sh, 20200), 362 (sh, 13500); NMR δ 7.2–7.7 (m, 5 H), 7.13 (s, 1 H), 6.72 (s, 1 H), 3.85 (m, 2 H), 3.91 (s, 3 H), 3.63 (s, 3 H), 2.98 (t, 2 H).

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.48; N, 5.48; N, 4.24.

Acetoxylation of Ethyl 1-Benzylidene-3,4-dihydro-6,7-methylenedioxy-2(1*H*)-isoquinolinecarboxylate (21) with LTA in Benzene. A solution of enamide **21**[16] (5.00 g, 12.6 mmol) in 275 mL of benzene containing 2 mL of pyridine was dried by refluxing under nitrogen with a Dean–Stark trap. The solution was cooled to 50 °C and maintained at this temperature. Then dry LTA (10 g) was added. After 16 h, the excess LTA was quenched with glycerine and the solution washed with water, dried with sodium sulfate, and evaporated. The residue, which contains primarily the diacetoxy compound, was taken up in 100 mL of pyridine containing 1 mL of acetic anhydride. After 1 h of reflux, the mixture was cooled and the solvent evaporated. The residue was flash chromatographed by using 5:95 ethyl acetate/methylene chloride to separate the geometrical isomers. The first eluted was the *E*-acetoxy enamide **27** (0.125 g, 0.31 mmol; 2.5%): mp 149–152 °C (methanol); IR 1770 cm^{-1}, 1700; UV 222 nm (ϵ 21600), 250 (min, 6700), 287 (14200), 300 (min, 13800), 310 (14200); NMR δ 7.37 (s, 1 H), 7.2–7.55 (m, 5 H), 6.63 (s, 1 H), 5.94 (s, 2 H), 2.9–4.3 (m, 4 H), 2.90 (q, 2 H), 2.16 (s, 3 H), 0.79 (t, 3 H).

Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.48; H, 5.43; N, 3.35.

The *Z*-acetoxy enamide **22** (2.7 g, 6.83 mmol; 54%), was eluted next: mp 84–88 °C (slowly from ether); IR 1760 cm^{-1}, 1710; UV 220 nm (end, ϵ 27500), 253 (min, 6700), 283 (10500), 309 (sh, 8500); NMR δ 7.30 (m, 5 H), 6.57 (s, 1 H), 6.24 (s, 1 H), 5.80 (s, 2 H), 4.17 (q, 2 H), 3.75 (br m, 2 H), 2.85 (t, 2 H), 2.08 (s, 3 H), 1.28 (t, 3 H).

Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.44; H, 5.29; N, 3.47.

Sodium Methoxide Cyclization of the *Z*-Acetoxy Enamide 22. The acetoxy enamide **22** (396 mg, 1.0 mmol) was dissolved in 20 mL of methanol and placed under nitrogen and 1 g of sodium methoxide added. After the reaction was stirred for 16 h, excess citric acid was added and the mixture diluted with water. The crystalline precipitate was filtered, washed with water, and dried to 289 mg (0.94 mmol; 94%) of the oxazolone **23**: mp 200.5–202.5 °C; IR 1765 cm^{-1}; UV 220 nm (end, ϵ 25500), 243 (sh, 10500), 258 (sh, 6100), 268 (min, 4200), 306 (11800), 314 (min, 11300), 331 (13700); NMR δ 7.3–7.7 (m, 5 H), 7.07 (s, 1 H), 6.72 (s, 1 H), 5.95 (s, 2 H), 3.79 (t, 2 H), 2.97 (t, 2 H).

Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56. Found: C, 66.95; H, 4.21; N, 4.44.

Conversion of the Chlorobenzylidene Enamide 24 to the Oxazolone 25 without Isolation of Intermediates. The enamide **24** (6.00 g, 15.5 mmol) was dissolved in 250 mL of dry benzene and 9.0 g of LTA added. After being stirred for 16 h, the reaction was quenched with glycerine, washed with water and dilute aqueous sodium bicarbonate, and dried with sodium sulfate. The benzene was evaporated and replaced with 100 mL of toluene. DBU (17 mmol, 2.59 g) was added and the solution refluxed under nitrogen for 24 h. The reaction was washed three times with water and dried with sodium sulfate and the solvent evaporated. The residue was dissolved in 125 mL of methanol and 5 g of sodium methoxide added. The reaction was quenched after 16 h with citric acid and diluted with water to yield a precipitate. The dried precipitate was flash chromatographed by using 2:98 ethyl acetate/methylene chloride to yield 2.35 g (6.57 mmol; 42%) of the oxazolone **25**: mp 171.5–173 °C; IR 1770 cm^{-1}, 1615, 1520; UV 218 nm (ϵ 30100), 245 (sh, 14100), 260 (sh, 8100), 272 (min, 3900), 311 (sh, 13200), 335 (18300); NMR δ 7.60 (d, J = 8 Hz, 2 H), 7.34 (d, J = 8 Hz, 2 H), 7.07 (s, 1 H), 6.73 (s, 1 H), 3.91 (s, 3 H), 3.81 (t, 2 H), 3.67 (s, 3 H), 2.98 (t, 2 H).

Anal. Calcd for $C_{19}H_{16}ClNO_4$: C, 63.78; H, 4.51; N, 3.91. Found: C, 63.60; H, 4.47; N, 3.90.

2-Acetyl-1-benzylidene-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (30). The enamide **30** was prepared according to the published method:[32,34] mp 152–154 °C; IR 1643 cm^{-1}, 1634, 1607, 1514; UV 224 nm (sh, ϵ 26900), 258 (min, 8700), 296 (18900), 328 (20900); NMR δ 7.47 (d, 2 H), 7.36 (t, 2 H), 7.25 (s, 1 H), 7.15 (s, 1 H), 6.79 (s, 1 H), 6.63 (s, 1 H), 5.02 (m, 1 H), 3.98 (s, 3 H), 3.90 (s, 3 H), 3.20 (m, 2 H), 2.71 (m, 1 H), 1.75 (s, 3 H).

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 73.97; H, 6.43; N, 4.30.

2-Acetyl-1-(4-chlorobenzylidene)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (33). The enamide **33** was prepared according to the published method[32,34] from the corresponding dihydroisoquinoline and acetyl chloride in pyridine and purified by flash chromatography using an ethyl acetate/methylene chloride gradient. Enamide **33** showed the following: mp 162–164.5 °C; IR 1651 cm^{-1}, 1636, 1607, 1514, 1260, 1240; UV 230 nm (ϵ 17600), 250 (min, 6000), 304 (17100), 326 (20200); NMR δ 7.42 (m, 2 H), 7.36 (m, 2 H), 7.14 (s, 1 H), 6.74 (s, 1 H), 6.64 (s, 1 H), 5.04 (m, 1 H), 3.99 (s, 3 H), 3.90 (s, 3 H), 3.17 (m, 2 H), 2.70 (m, 1 H), 1.77 (s, 3 H).

Anal. Calcd for $C_{20}H_{20}NO_3Cl$: C, 67.12; H, 5.63; N, 3.92. Found: C, 66.83; H, 5.63; N, 3.80.

Oxidation of 2-Acetyl-1-(3,4-dimethoxybenzylidene)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (28) with LTA. The enamide **28**,[32] (1.00 g, 2.60 mmol) was dissolved in 100 mL of benzene containing 0.5 mL of pyridine. The solution was dried by using a modified Dean–Stark trap and cooled to 50 °C and 5.6 g of dry lead tetraacetate (ca. 12.6 mmol) added. After the reaction was stirred magnetically at 45 °C for 3.5 h, all enamide had disappeared and two new products appeared. After the reaction was quenched with glycerine, washed with water, and dried with sodium sulfate, the benzene solution was evaporated and the residue flash chromatographed. Elution with 1:9 ethyl acetate/methylene chloride furnished 0.33 g (0.93 mmol; 36%) of papaveraldine (**29**), identical with an authentic sample,[33] and, subsequently, 0.49 g (1.37 mmol; 53%) of dihydropapaveraldine (**17**), also identical with an authentic sample.[30]

LTA Oxidation of the 2-Acetyl-1-benzylidene Enamide 30.

(32) Lenz, G. R.; Yang, N. C. *Chem. Commun.* **1967**, 1136. Gardent, J.; Thuan, L. T. LeQ. *Bull. Soc. Chim. Fr.* **1966**, 2401.
(33) Buck, J. S.; Haworth, R. D.; Perkin, W. H., Jr. *J. Chem. Soc.* **1924**, *125*, 2176.
(34) Tsatsas, G. *Ann. Pharm. Fr.* **1952**, *10*, 61.

The enamide **30** (1.00 g, 3.09 mmol) was oxidized in the same manner as enamide **28**, except the oxidation was conducted for 18 h. After similar workup, the residue was flash chromatographed by using an ethyl acetate/methylene chloride gradient to yield 0.55 g (1.88 mmol, 61%) of the known 1-benzoyl-6,7-dimethoxyisoquinoline (**31**), mp 123.5–124.5 °C (lit.[34] mp 131 °C), followed by 0.046 g (0.15 mmol; 5%) of 1-benzoyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**32**) (known as its hydrochloride salt[35]): mp 78.8–79.4 °C; IR 1668 cm^{-1}, 1568, 1514; NMR δ 8.04 (d, J = 7 Hz, 2 H), 7.61 (t, J = 7 Hz, 1 H), 7.48 (t, J = 7 Hz, 2 H), 6.96 (s, 1 H), 6.76 (s, 1 H), 3.94 (s, 3 H), 3.93 (t, 2 H), 3.79 (s, 3 H), 2.82 (t, 2 H).

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.13; H, 6.08; N, 4.58.

LTA Oxidation of the 2-Acetyl-1-(4-chlorobenzylidene) Enamide 33. The enamide **33** (0.75 g, 2.1 mmol) was oxidized in the same manner as enamide **30**. After workup, the residue was separated by using a radial thick-layer chromatograph using a methylene chloride/ethyl acetate gradient to yield 0.22 g (0.67 mmol; 32%) of 1-(4-chlorobenzoyl)-6,7-dimethoxyisoquinoline (**35**): mp 154–156 °C; IR 1659 cm^{-1}, 1586, 1506, 1267; UV 237 nm (ϵ 55000), 254 (min, 29400), 262 (30100), 312 (min, 4900), 330(5900); NMR δ 8.47 (d, J = 5.4 Hz, 1 H), 7.93 (d, J = 8.4 Hz, 2 H), 7.69 (d, J = 5.6 Hz, 1 H), 7.46 (d, J = 8.5 Hz, 2 H), 7.27 (s, 1 H), 7.16 (s, 1 H), 4.07 (s, 3 H), 4.00 (s, 3 H).

Anal. Calcd for $C_{18}H_{14}NClO_3$: C, 65.96; H, 4.31; N, 4.27. Found: C, 65.84; H, 4.36; N, 4.07.

Additionally, 1-(4-chlorobenzoyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (0.20 g, 0.61 mmol; 29%) was obtained: mp 125–126 °C; IR 1668 cm^{-1}, 1607, 1587, 1570, 1521; UV 230 nm (sh, 22400), 244 (min, 17200), 268 (29900), 320 (sh, 6300); NMR δ 7.99 (d, J = 8 Hz, 2 H), 7.46 (d, J = 8 Hz, 2 H), 6.96 (s, 1 H), 6.76 (s, 1 H), 3.94 (s, 3 H), 3.92 (t, J = 8 Hz, 2 H), 3.80 (s, 3 H), 2.81 (t, J = 8 Hz, 2 H).

Anal. Calcd for $C_{18}H_{16}NClO_3$: C, 65.55; H, 4.89; N, 4.25. Found: C, 65.65; H, 5.05; N, 4.40.

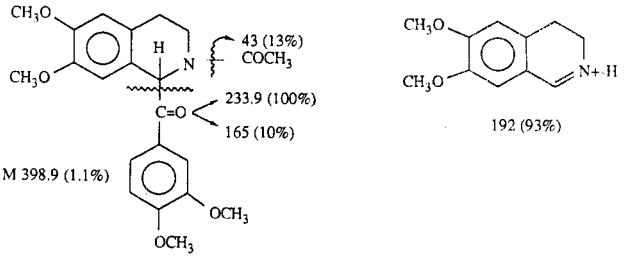
Oxidation of 1-(3,4-Dimethoxybenzylidene)-3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinolinecarboxaldehyde (36) with LTA. The enamide **36**[14,36] (4.00 g, 10.84 mmol) was added to a rapidly stirred solution of 6.22 g (11.92 mmol) of LTA in 100 mL of glacial acetic acid. After 20 min, the reaction was quenched with glycerine, diluted with water, and extracted three times with methylene chloride. The methylene chloride solution was washed with dilute sodium bicarbonate solution and then dried with sodium sulfate. TLC indicated the formation of one major, more polar, product, which could not be crystallized. Flash chromatography, however, caused the conversion of this product into several others. Elution with methylene chloride furnished 600 mg (2.41 mmol; 22%) of 2-acetyldihydroisoquinoline **37**: mp 125.5–126.5 °C (ether/hexane) (lit.[19] mp 131 °C); IR 1700 cm^{-1}; 1670, 1600, 1515; UV 229 nm (ϵ 25400), 248 (min, 4300), 272 (10000), 290 (min, 5400), 311 (8200); NMR δ 7.62 (s, 1 H), 6.69 (s, 1 H), 4.12 (t, J = 6 Hz, 2 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 2.93 (t, J = 6.2 Hz, 2 H), 2.66 (s, 3 H).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.87; H, 6.09; N, 5.21.

(35) Mahuzier, G.; Hamon, M. *Bull. Soc. Chim. Fr.* **1969**, 684, 687. Weisbach, J. A.; Kirkpatrick, J. L.; Macko, E.; Douglas, B. *J. Med. Chem.* **1968**, *11*, 752.

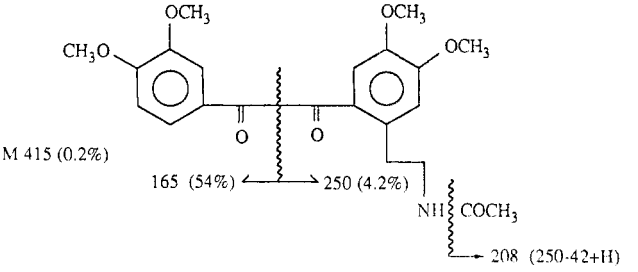
(36) Baxter, I.; Swan, G. A. *J. Chem. Soc.* **1965**, 4014.

Continued elution with 1:9 and 1:4 ethyl acetate/methylene chloride gave 800 mg (2.24 mmol; 21%) of dihydropapaveraldine (**17**), identical with an authentic sample.[31] This was followed by 600 mg (1.50 mmol; 14%) of the 2-acetyl-1-benzoyl compound **38**: mp 156.8–157.4 °C (ethyl acetate); IR 1680 (w) cm^{-1}, 1665, 1645, 1610, 1590, 1575, 1515, 1270, 1250; UV 220 nm (end, ϵ 31300), 257 (min, 8000), 278 (14200); NMR δ 7.99 (dd, J = 8.5, 1.6 Hz, 1 H), 7.64 (d, J = 1.6 Hz, 1 H), 6.97 (d, J = 8.5 Hz, 1 H), 6.82 (s, 1 H), 6.70 (s, 1 H), 6.52 (s, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.86 (s, 3 H), 3.67 (s, 3 H), 3.6–3.9 (m, 2 H), 2.96 (m, 2 H), 2.21 (s, 3 H); mass spectrum, m/z



Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 65.87; H, 6.42; N, 3.54.

After elution with ethyl acetate, a product was obtained with 5:95 methanol/chloroform, which was identified as the benzil derivative **39** (900 mg, 2.17 mmol; 20%): mp 158–166 °C (acetone/hexane): IR 3360 cm^{-1}, 1650, 1630, 1590, 1580, 1520, 1510; UV 258 nm (min, ϵ 33300), 280 (46100), 300 (min, 33800), 314 (36300); NMR δ 7.61 (d, J = 1.7 Hz, 1 H), 7.43 (dd, J = 8.3, 1.7 Hz, 1 H), 7.12 (s, 1 H), 6.92 (d, J = 8.4 Hz, 1 H), 6.87 (s, 1 H), 3.97 (s, 9 H), 3.77 (s, 3 H), 3.60 (q, J = 13.4, 3.6 Hz, 2 H, CH_2 coupled to NH), 3.24 (t, J = 7.0 Hz, 2 H), 1.97 (s, 3 H); mass spectrum, m/z



Anal. Calcd for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.06; N, 3.37. Found: C, 63.28; H, 5.94; N, 3.26.

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