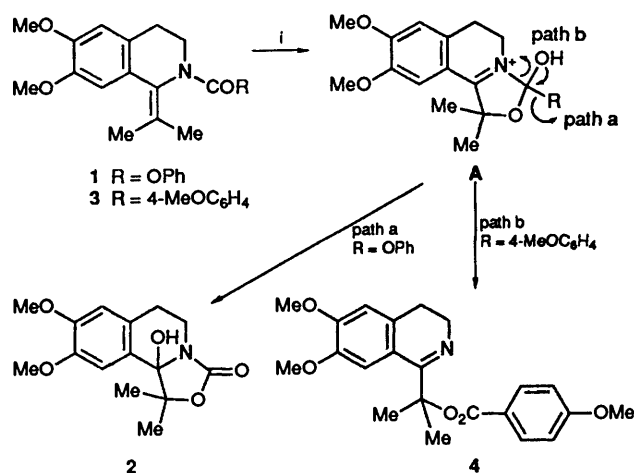


Oxidative Rearrangements of Alkyl Substituted Isoquinoline Enamides to 1-Hydroxymethyl-dihydroisoquinoline Derivatives

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Oxidation of disubstituted 1-methylenedihydroisoquinoline enamides with lead tetraacetate results in a novel N→C oxidative rearrangement whereby esters of disubstituted 1-hydroxymethyl-3,4-dihydroisoquinoline are formed. An X-ray crystallographic structural determination for 6,7-dimethoxy-1-[1-(*p*-methoxybenzoyloxy)-1-methylethyl]-3,4-dihydroisoquinoline **4** is described.

The oxidation of enamides derived from the acylation of 1-substituted dihydroisoquinolines can lead to bis-acetylation,^{1,2} heterocycle formulation² or ring expansion,^{3,4} depending on the nature of the substituents. We have previously described the oxidation of disubstituted 1-methylenedihydroisoquinolines, where the isoquinoline nitrogen is part of an urethane.⁵ For instance, oxidation of **1** (Scheme 1) with lead

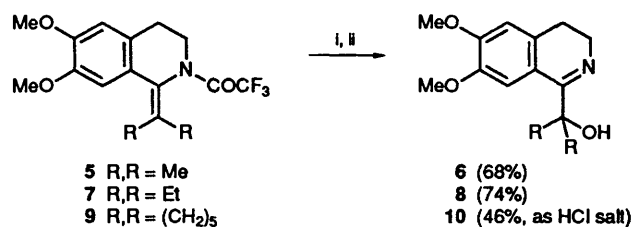


Scheme 1 Reagent: i, Pb(OAc)₄, 4 h

tetraacetate forms the hydroxyoxazolidinone **2** via the intermediate A which loses phenol to form **2** (path a). We were interested in further investigating this last series by acylating the isoquinoline nitrogen. By so doing, oxazolidinone formation would be precluded owing to the absence of a leaving group. Lead tetraacetate oxidation of these disubstituted 1-methylenedihydroisoquinolines (Scheme 1) led, unexpectedly, by way of a novel oxidative rearrangement, to esters of 1-hydroxymethyl-dihydroisoquinolines. We have taken advantage of this rearrangement to develop a convenient synthesis of these disubstituted 1-hydroxymethyl-dihydroisoquinolines.⁶

The enamide **3**, m.p. 145–147 °C, was readily prepared from 1-isopropyl-6,7-dimethoxy-3,4-dihydroisoquinoline and 4-methoxybenzoyl chloride in the presence of triethylamine.^{7,8} Oxidation of **3** (Scheme 1) with lead tetraacetate (2 equiv.) in acetic acid yielded the rearrangement product **4**, m.p. 121–122 °C, in an isolated yield of 96%. The spectral characteristics of **4** are in accord with the structure,[†] and final confirmation was secured by a single crystal X-ray analysis (Fig. 1).[‡]

Mechanistically, oxidation of **3** forms the intermediate A,



Scheme 2 Reagents: i, Pb(OAc)₄; ii, 10% K₂CO₃

the postulated common intermediate for the lead tetraacetate enamide oxidations.^{1–4} In the absence of a leaving group, intermediate A rearranges by a formal oxidative 1,3-acyl shift from nitrogen to carbon, forming the dihydroisoquinoline ester **4**. Overall, the effect is the hydroxylation of the 1-substituent in the dihydroisoquinoline used to prepare the enamide.

We have taken advantage of this reaction to develop a method for the synthesis of the difficultly accessible disubstituted 1-hydroxymethyl-dihydroisoquinolines from the parent dihydroisoquinolines (Scheme 2). For example, the enamide **5** is readily prepared from the requisite 3,4-dihydroisoquinoline and trifluoroacetic anhydride in the presence of triethylamine. Oxidation with lead tetraacetate yields the rearranged trifluoroacetate ester which is extensively hydrolysed during

[‡] Crystal Data.—C₂₂H₂₅NO₅, *M* = 383.44. Monoclinic, *a* = 23.111(6), *b* = 14.808(2), *c* = 18.484(5) Å, β = 139.85(1)°, *V* = 4079(2) Å³ (by least squares refinement on diffractometer angles for 24 automatically centred high angle reflections with 64.19° < 2θ < 88.71°, λ = 1.541 78 Å), space group *C2/c*, No. 15, *Z* = 8, *D*_x = 1.25 g cm⁻³. Clear parallelepiped. Crystal dimensions 0.25 × 0.18 × 0.40 mm, μ = 18.64 cm⁻¹.

Data Collection and Processing.—Rigaku AFC5S diffractometer, ω/2θ mode with ω scan width = (1.47 + 0.30 tanθ)°, ω scan speed = 8° – 32°/min, graphite monochromated Cu-Kα radiation; 3268 reflections measured (0° < 2θ < 120°, +*h*, +*k*, ±*l*), 3177 unique (merging *R* = 0.003), giving 1883 with *I* > 3σ(*I*). Three standards monitored every 150 reflections. No significant decay or absorption.

Structure Analysis and Refinement.—Direct methods and Fourier difference methods. Full-matrix least squares refinement of the positional and anisotropic temperature factors of all non-hydrogen atoms. Hydrogens assigned calculated positions and isotropic temperature factors 1.2 times the equivalent isotropic temperature factor of the associated non-hydrogen atom. Calculated parameters updated every two refinement cycles. The weighting scheme *w* = 1/[σ²(*F*_o) + 0.000 625*F*_o²] with σ(*F*_o) from counting statistics gave satisfactory agreement between *F*_o and *F*_c, with GOF = 1.47. The final *R* and *R*_w values were 0.045, 0.060. A final difference Fourier map displays no significant features. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre [see Instructions for Authors (1993), *J. Chem. Soc., Perkin Trans. 1*, 1993, Issue 1].

[†] All compounds were unambiguously characterized by FTIR, ¹H and ¹³C NMR, mass spectrometry, and combustion analysis.

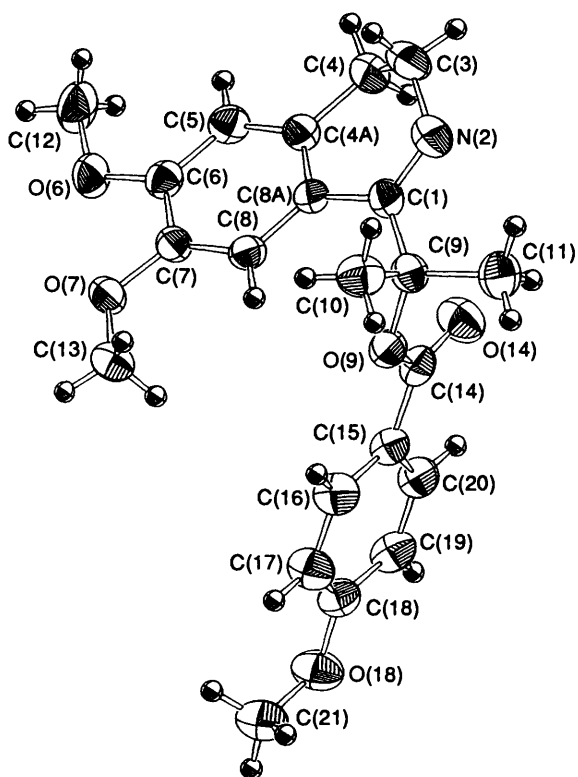


Fig. 1 Crystal structure of 6,7-dimethoxy-1-[1-(*p*-methoxybenzoyloxy)-1-methylethyl]-3,4-dihydroisoquinoline **4**

work-up. Hydrolysis is completed using potassium carbonate to yield the hydroxydihydroisoquinoline **6**. Additional examples are collected in Scheme 2.

Experimental

Typical Procedure: 1-(1-Hydroxy-1-methylethyl)-7,8-dimethoxy-3,4-dihydroisoquinoline **6**.—The trifluoroacetyl enamide **5** (3.3 g, 10 mmol) in acetic acid (15 cm³) was stirred and treated with lead tetraacetate (6.3 g, 14 mmol) for 18 h. After most of the solvent had been removed under reduced pressure the residue was partitioned between dichloromethane (50 cm³) and water (50 cm³)⁴ and solid potassium carbonate was added to it, in portions, until effervescence ceased. The organic layer was separated and the aqueous phase was extracted with dichloromethane (25 cm³). The combined organic layer and extracts were dried (Na₂SO₄) and concentrated and the residue was dissolved in a mixture of methanol and 10% aqueous potassium carbonate (4:1) and the solution stirred for 3 h to complete hydrolysis of any remaining ester. Most of the solvent was evaporated under reduced pressure and the residue was partitioned between dichloromethane and water. The organic layer was separated, dried and evaporated and the residue was chromatographed on silica gel (2.5–5.0% methanol in dichloromethane) to afford the hydroxy imine **6** as an oil (1.7 g, 68%). Kugelrohr distillation (180 °C, 0.3 mmHg) afforded pure material (Found: C, 67.6; H, 7.7; N, 5.55. C₁₄H₁₉NO₃ requires C, 67.45; H, 7.68; N, 5.62); ν_{\max} (KBr)/cm⁻¹ 1617, 1604, 1588 and 1515; δ_{H} (CDCl₃) 1.82 (6 H, s), 3.08 (2 H, t, *J* 7.8), 3.94 (3 H, s), 3.95 (2 H, t, *J* 7.8), 4.03 (3 H, s), 6.92 (1 H, s) and 7.50 (1 H, s); *m/z* 249 (M⁺, 12%).

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