Lead Tetra-acetate-mediated Oxidative Cyclizations of Isoquinoline Alkyl Substituted Methylene Urethanes (Enamides) to Isoquinoline Hydroxyoxazolidinones

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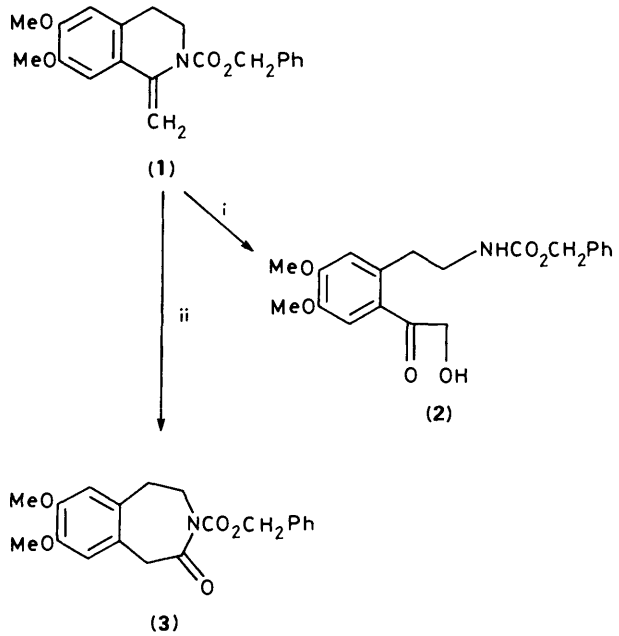
Oxidation of disubstituted 1-methylene-tetrahydroisoquinoline-2-carboxylates with lead tetra-acetate (LTA) causes a rapid oxidative cyclization to an isoquinoline hydroxyoxazolidinone. The products possess acyliminium character and the hydroxy group is readily replaced by alcohol or reduced by hydride. Cleavage of the reduced hydroxyoxazolidinone by base leads to the tertiary β-hydroxyamine. The mechanism of the LTA oxidation of various enamides is discussed in terms of a common intermediate.

The photocyclization reactions of enamides, either vinyl amides or vinyl urethanes, have been intensively investigated for over 20 years, and have led to a variety of complicated ring structures, including many natural products.[1–3] On the other hand, the ground state reactivity of these compounds, with the exception of their Diels–Alder reactivity,[3,4] has not been the subject of much attention until recently.[5] Our studies on the oxidation of enamide double bonds in the isoquinoline system have led to surprising and useful chemistry, which can be dependent on the oxidant.[6–9] The enamide double bond with β-aromatic substitution can be bis-acetoxylated or form heterocyclic ring systems upon oxidation with lead tetra-acetate.[7,8] Alternatively, as in Scheme 1, when the double bond in the isoquinoline enamide (**1**) is oxidized by osmium tetraoxide to the diol, its ring opens to the hydroxyacetophenone (**2**).[5] In contrast, lead(IV) causes a rapid oxidative rearrangement leading to benzazepinones (**3**) in high yield with unsubstituted and mono-substituted methylene groups.[9] The oxidative chemistry of the isoquinoline enamide double bonds is somewhat analogous to that of other activated double bonds. For example, oxidation of enamines with lead tetra-acetate also leads to bis-acetoxylation,[10–12] and under certain circumstances to rearrangements.[13] Similar reactivity patterns have also been observed with enol esters and ethers.[14–19] In this report, I present an extension of the studies on the oxidation of isoquinoline enamides by lead tetra-acetate. The present report describes the unexpected formation of hydroxyoxazolidinones when the fully substituted exocyclic double bonds in enamides related to compound (**1**) are oxidized by lead tetra-acetate.

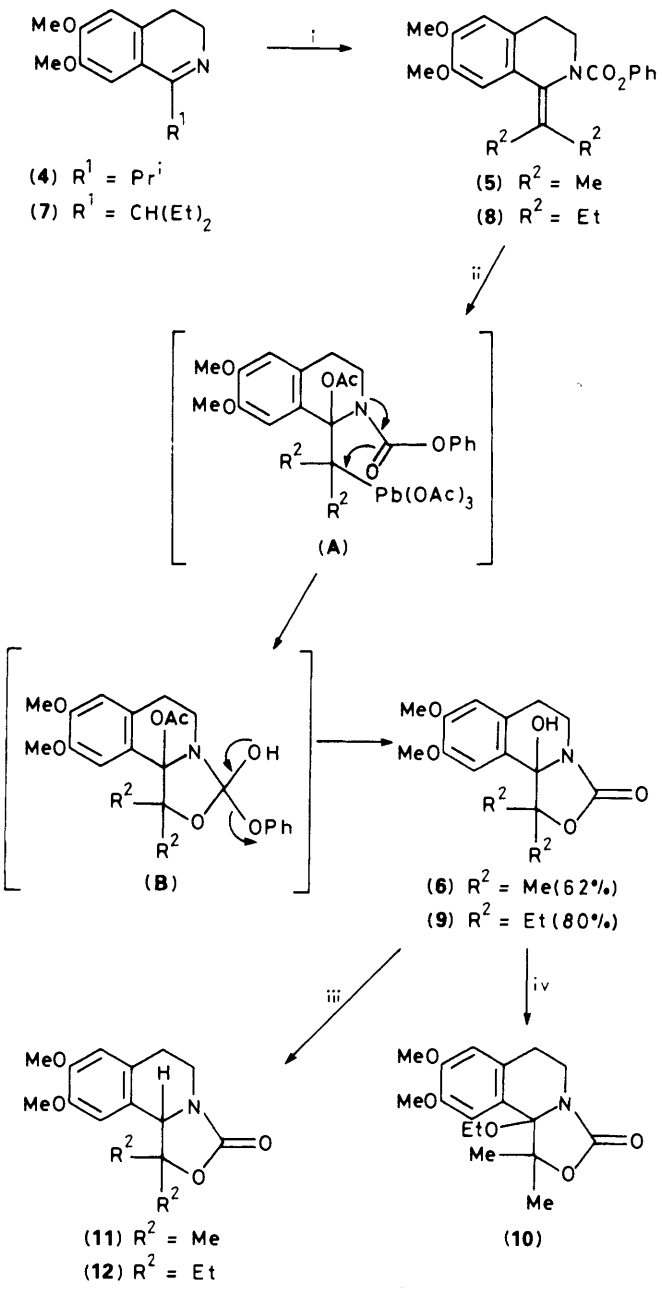
The required enamides (**5**), (**8**), and (**14**) (Scheme 2) were prepared from the appropriate 1-substituted 3,4-dihydroisoquinolines (**4**), (**7**), and (**13**) and phenyl chloroformate. The phenyl esters were used because the resultant enamides were crystalline. Oxidation of (**5**) with lead tetra-acetate (LTA) in acetic acid caused a rapid reaction leading to a single product (**6**) in good yield which was isolated by a combination of crystallization and chromatography. The product was identified as the hydroxyoxazolidinone (**6**) based on its physical and chemical properties. The i.r. spectrum indicated the presence of a hydroxyl group, and an oxazolidinone carbonyl group.[20] The ^{1}H n.m.r. spectrum of (**6**) showed loss of the phenyl ester group in (**5**), isolated chromatographically as phenol, and retention of the remaining portions of (**5**) with the methyl groups being shifted upfield due to the saturation of the double bond and ring formation. The ^{13}C n.m.r. spectrum confirmed the ring closed oxazolidinone structure shown rather than ring opening of the hydroxyoxazolidinone to the cyclic oxourethane. The mass



Scheme 1. *Reagent:* i, OsO_4; ii, $Pb(OAc)_4$

spectrum was consistent with the indicated structure with a parent ion showing the ready loss of a hydroxyl group and carbon dioxide. The structure of (**6**) (Figure) was ultimately confirmed by a single crystal *X*-ray analysis (for structural parameters, see Tables 1—3). Similarly, the enamides (**8**) and (**14**) yielded the hydroxyoxazolidinones (**9**) and (**15**) each in 80% yield upon LTA oxidation. The oxidative cyclization is not restricted to the phenylurethanes, as the methylurethane (**16**) (Scheme 3) is similarly converted into (**15**). The isoquinoline hydroxyoxazolidinone ring system is new, although the parent system, lacking the hydroxy group, has been described[21] and phenyl substituted hydroxyoxazolidinones are known.[22] However, the next higher homologue of the cyclic α-hydroxyurethane is found in the naturally occurring maytansinoids, and forms the active portion of these novel tumour inhibitors.[23]

The hydroxyoxazolidinone functionality in the oxidation products should readily undergo elimination of the hydroxy group to form an acyliminium ion similarly to the maytansinoids.[24] Accordingly, when (**6**) was dissolved in acidic ethanol, the ethyl ether (**10**) was formed in 59% yield. Additionally, all the oxidation products (**6**), (**9**), and (**15**) were smoothly and



Scheme 2. *Reagents:* i, $ClCO_2Ph$, pyridine; ii, $Pb(OAc)_4$; iii, $NaCNBH_3$; iv, EtOH, H^+

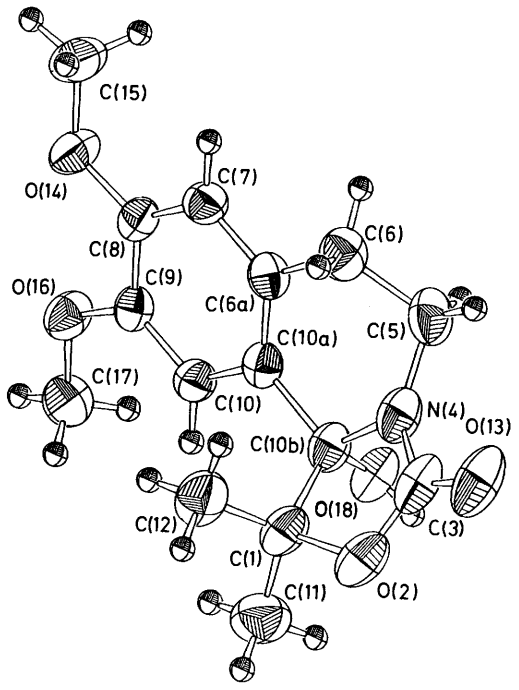


Figure. ORTEP representation of the isoquinoline hydroxyoxazolidinone (**6**)

Table 1. Fractional atomic co-ordinates with e.s.d.s for compound (**6**)

	x	*y*	*z*
C(1)	0.728 5(2)	−0.079 1(2)	0.158 6(2)
O(2)	0.677 5(2)	−0.073 1(2)	0.033 3(1)
C(3)	0.661 0(2)	0.028 5(3)	0.003 8(2)
N(4)	0.666 9(2)	0.089 1(2)	0.102 0(2)
C(5)	0.681 3(2)	0.203 0(2)	0.105 1(2)
C(6)	0.816 8(2)	0.227 2(2)	0.162 1(2)
C(6a)	0.834 0(2)	0.172 1(2)	0.281 2(2)
C(7)	0.914 9(2)	0.217 7(2)	0.371 5(2)
C(8)	0.929 4(2)	0.171 6(2)	0.482 5(2)
C(9)	0.861 1(2)	0.078 8(2)	0.506 3(2)
C(10)	0.782 5(2)	0.033 0(2)	0.417 5(2)
C(10a)	0.768 7(2)	0.078 9(2)	0.304 1(2)
C(10b)	0.677 8(2)	0.026 1(2)	0.210 3(2)
C(11)	0.671 0(3)	−0.177 8(2)	0.210 9(3)
C(12)	0.876 5(3)	−0.082 9(2)	0.158 0(2)
O(13)	0.642 2(2)	0.057 9(2)	−0.099 0(1)
O(14)	1.006 0(1)	0.210 8(1)	0.576 1(1)
C(15)	1.074 8(3)	0.305 7(2)	0.556 4(2)
O(16)	0.877 1(2)	0.042 0(1)	0.620 6(1)
C(17)	0.798 8(2)	−0.044 1(2)	0.653 9(2)
O(18)	0.554 2(1)	0.018 1(1)	0.261 8(1)

rapidly reduced with cyanoborohydride in acetic acid to yield the isoquinoline oxazolidinones (**11**), (**12**), and (**17**) in 92—100% yields. The physical properties of the reduced dimethyl compound (**11**) prepared by this method agree with published values for this compound made by an alternative method.[21] Cleavage of oxazolidinone (**17**) (Scheme 3) to the hydroxy amine (**18**) was straightforward, but required heating with base at relatively high temperatures.

The mechanism of the oxidation is outlined in Scheme 2. Oxidation of non-aryl substituted enamide double bonds ordinarily results in bis-acetoxylation, with the potential for further reaction.[25] The intermediate underlying all of the chemistry derived from LTA oxidations in the simple enamides, as well as the isoquinolines, is shown as (**A**) in Scheme 2. LTA oxidation initially introduces an acetoxy group α to the nitrogen, and the equivalent of a positive charge at the β position, which probably exists as an organolead intermediate. This intermediate (**A**) may be trapped by: (a) the aromatic ring, leading to ring expansion (*cf.* Scheme 1);[9] (b) the carbonyl group of a urethane, leading to oxazolones;[7] or (c) by external nucleophiles, such as acetate, leading to the bis-acetoxy derivative.[7] In case (c), there is the potential for bridging by the α-acetoxy group, but there is currently no evidence for this occurring. In the present case, the conformation of the intermediate (**A**) apparently does not permit participation by the isoquinoline aromatic ring, allowing trapping by the urethane carbonyl group. The intermediate (**B**) then loses phenol to form the observed product (**6**). In this respect, the oxidation is similar to that observed with mono-phenyl substitution on the exocyclic isoquinoline carbamate double bond[7] where, after

Table 2. Selected bond lengths (Å) with e.s.d.s for compound (**6**)

C(1)–O(2)	1.477(3)	C(6a)–C(10a)	1.385(3)
C(1)–C(10b)	1.551(3)	C(7)–C(8)	1.378(3)
C(1)–C(11)	1.511(4)	C(8)–C(9)	1.398(3)
C(1)–C(12)	1.510(4)	C(8)–O(14)	1.368(2)
O(2)–C(3)	1.336(3)	C(9)–C(10)	1.374(3)
C(3)–N(4)	1.342(3)	C(9)–O(16)	1.368(2)
C(3)–O(13)	1.219(3)	C(10)–C(10a)	1.401(3)
N(4)–C(5)	1.449(4)	C(10a)–C(10b)	1.521(3)
N(4)–C(10b)	1.454(3)	C(10b)–O(18)	1.418(3)
C(5)–C(6)	1.521(3)	O(14)–C(15)	1.413(3)
C(6)–C(6a)	1.512(3)	O(16)–C(17)	1.412(3)
C(6a)–C(7)	1.397(3)		

Table 3. Selected bond angles (°) with e.s.d.s for compound (**6**)

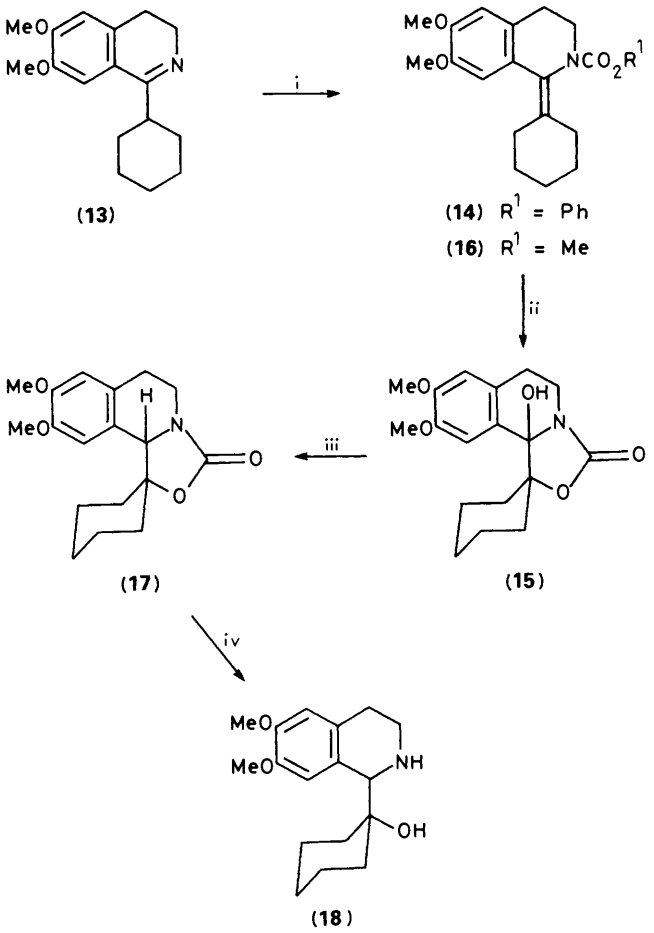
O(2)–C(1)–C(12)	107.4(2)	O(14)–C(8)–C(7)	124.9(2)
O(2)–C(1)–C(11)	106.8(2)	O(14)–C(8)–C(9)	115.2(2)
O(2)–C(1)–C(10b)	101.9(2)	C(7)–C(8)–C(9)	119.9(2)
C(12)–C(1)–C(11)	112.6(2)	O(16)–C(9)–C(10)	125.1(2)
C(12)–C(1)–C(10b)	112.4(2)	O(16)–C(9)–C(8)	115.5(2)
C(11)–C(1)–C(10b)	114.8(2)	C(10)–C(9)–C(8)	119.5(2)
C(3)–O(2)–C(1)	108.6(2)	C(9)–C(10)–C(10a)	120.8(2)
O(13)–C(3)–O(2)	122.7(3)	C(6a)–C(10a)–C(10)	119.8(2)
O(13)–C(3)–N(4)	127.1(3)	C(6a)–C(10a)–C(10b)	121.7(2)
O(2)–C(3)–N(4)	110.2(2)	C(10)–C(10a)–C(10b)	118.5(2)
C(3)–N(4)–C(5)	125.9(2)	O(18)–C(10b)–N(4)	110.5(2)
C(3)–N(4)–C(10b)	111.9(2)	O(18)–C(10b)–C(10a)	105.6(2)
C(5)–N(4)–C(10b)	121.5(2)	O(18)–C(10b)–C(1)	114.4(2)
N(4)–C(5)–C(6)	107.4(2)	N(4)–C(10b)–C(10a)	110.9(2)
C(6a)–C(6)–C(5)	109.9(2)	N(4)–C(10b)–C(1)	99.7(2)
C(10a)–C(6a)–C(7)	119.1(2)	C(10a)–C(10b)–C(1)	115.7(2)
C(10a)–C(6a)–C(6)	121.5(2)	C(8)–O(14)–C(15)	117.0(2)
C(7)–C(6a)–C(6)	119.3(2)	C(9)–O(16)–C(17)	118.1(2)
C(8)–C(7)–C(6a)	120.9(2)		

trapping by the carbonyl group, the α-acetoxy group is eliminated to form an oxazolone. In the present case, this type of elimination is not possible due to bis-substitution, and the acetoxy group exchanges during work-up for the observed hydroxy group *via* an acyliminium intermediate.

Experimental

General.—M.p.s were taken on a Thomas–Hoover Unimelt capillary apparatus and are uncorrected. I.r. spectra were recorded as KBr pellets, and u.v.–visible spectra were run in methanol unless otherwise indicated. An IBM AF-270 or a Varian Associates FT-80 n.m.r. spectrometer was used and the spectra were run in deuteriochloroform using tetramethylsilane as an internal standard. Mass spectra were obtained on an AEI-MS-30. Microanalyses were determined by the BOC Group Technical Center Microanalytical Service under the direction of Allan Ellgren.

Phenyl 1-*Isopropylidene*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*-2-*carboxylate* (**5**).—A solution of 1-isopropyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**4**)[26] (25 g, 107 mmol) in benzene (500 ml) under nitrogen was dried by refluxing using a Dean–Stark trap. After cooling, triethylamine (26.5 ml) was added, followed by the introduction of phenyl chloroformate (27.4 g, 175 mmol) in dichloromethane (25 ml). After refluxing for 3 h, the reaction mixture was cooled and the triethylamine hydrochloride filtered. The solution was washed three times with water and dried (Na_2SO_4). After removal of the solvent, the residue was triturated with ether (200 ml) and then filtered to yield the *enamide* (**5**) (31 g, 82%), m.p. 136—137.5 °C (Found: C, 71.3; H, 6.4; N, 4.0. $C_{21}H_{23}NO_4$ requires C, 71.4; H, 6.6; N, 4.0); $\nu_{max.}$ 1 712, 1 604, 1 510, and 1 199 cm^{-1}; δ_H 7.04—7.37 (5 H, m), 6.94 (1 H, s), 6.70 (1 H, s), 4.10 (1 H, m), 3.88 (6 H, s), 3.58 (1 H, m), 3.01 (1 H, m), 2.77 (1 H, m), 2.03 (3 H, s), and 1.99 (3 H, s).



Scheme 3. *Reagents:* i, $ClCO_2Ph$ or $ClCO_2Me$, pyridine; ii, $Pb(OAc)_4$; iii, $NaCNBH_3$; iv, KOH, 160 °C

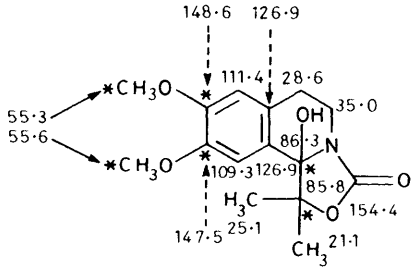
Phenyl 6,7-*Dimethoxy*-1-(3-*pentylidene*)-1,2,3,4-*tetrahydroisoquinoline*-2-*carboxylate* (**8**).—In the same manner as (**4**), 6,7-dimethoxy-1-(3-pentyl)-3,4-dihydroisoquinoline (**7**)[26] (25 g, 96 mmol) in benzene (500 ml) and triethylamine (16 ml) reacted with phenyl chloroformate (13.2 ml) to yield the enamide (**8**) (36.5 g, 100%), m.p. 105—107 °C (from CH_2Cl_2–hexane) (Found: C, 72.5; H, 7.0; N, 3.7. $C_{23}H_{27}NO_4$ requires C, 72.4; H, 7.1; N, 3.7); $\nu_{max.}$ 1 715, 1 510, and 1 200 cm^{-1}, $\lambda_{max.}$ 256 (ε 13 000) and 293 nm (5 200); $\lambda_{min.}$ 239 (10 000) and 280 nm (4 200); δ_H 7.15 (5 H, m), 6.91 (1 H, s), 6.68 (1 H, s), 3.3—4.3 (2 H, m), 3.89 (6 H, s), 2.0—3.0 (6 H, m), 1.15 (3 H, t), and 1.09 (3 H, t).

Phenyl 1-*Cyclohexylidene*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline*-2-*carboxylate* (**14**).—In the same manner as (**4**), 1-cyclohexyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**13**)[27] (21 g, 77 mmol) in benzene (500 ml) and triethylamine (12.8 ml) reacted with phenyl chloroformate (13.2 g) to yield the enamide (**14**) as a slowly crystallizing oil (20.2 g, 67%), m.p. 101—105 °C (from MeOH–H_2O) (Found: C, 73.2; H, 6.9; N, 3.5. $C_{24}H_{27}NO_4$ requires C, 73.3; H, 6.9; N, 3.6); $\nu_{max.}$ 1 715, 1 510 and 1 205 cm^{-1}; $\lambda_{max.}$ 255 (ε 14 600) and 291 nm (5 500); $\lambda_{min.}$ 239 (11 200) and 280 nm (4 600); δ_H 6.9—7.5 (5 H, m), 6.82 (1 H,

s), 6.69 (1 H, s), 3.35—4.25 (2 H, m), 3.88 (3 H, s), 3.86 (3 H, s), 2.83 (4 H, m), and 1.60 (6 H, m).

Methyl 1-*Cyclohexylidene*-6,7-*dimethoxy*-1,2,3,4-*tetrahydro*-*isoquinoline*-2-*carboxylate* (**16**).—A solution of 1-cyclohexyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**13**) (5.6 g, 20.5 mmol) in methylene dichloride (250 ml), containing di-isopropylethylamine (3.6 ml), was cooled, under nitrogen, in an ice bath. Methyl chloroformate (1.66 ml) in methylene dichloride (18 ml) was added to the cold solution by syringe through a septum. After 18 h, the solution was dark orange and any excess chloroformate was quenched with methanol (10 ml). The solution was washed three times with water, dried (Na_2SO_4) and evaporated to a viscous oil. The oil was flash chromatographed over silica using ethyl acetate–methylene chloride (5:95) as eluant to yield the non-crystalline enamide (**16**) (5.7 g, 84%) (Found: C, 68.9; H, 7.4; N, 4.4. $C_{19}H_{25}NO_4$ requires C, 68.9; H, 7.6; N, 4.2); $\nu_{max.}$($CHCl_3$) 1 685 and 1 505 cm^{-1}; $\lambda_{max.}$ 255 (ε 13 100) and 290 nm (4 700); $\lambda_{min.}$ 235 (9 750) and 280 nm (4 000); δ_H 6.81 (1 H, s), 6.67 (1 H, s), 3.87 (6 H, s), 3.65 (3 H, s), 3.4—4.1 (2 H, m), 2.0—3.0 (6 H, m), and 1.60 (6 H, br s).

1,5,6,10b-*Tetrahydro*-10b-*hydroxy*-8,9-*dimethoxy*-1,1-*dimethyl*-3H-*oxazolo*[4,3-a]*isoquinolin*-3-*one* (**6**).—The enamide (**5**) (8.0 g, 22.7 mmol) was added to a stirred suspension of lead tetra-acetate (11.1 g), dried *in vacuo* at refluxing acetone temperature, in glacial acetic acid (200 ml). After 10 min, the excess lead tetra-acetate was quenched with glycerine to yield a yellow solution. The solution was diluted with water (1.4 l) and extracted with methylene dichloride (3 × 300 ml). The organic extract was stirred with 10% aqueous sodium hydrogen carbonate (1 l) for 4.5 h. The organic layer was separated, dried (Na_2SO_4) and evaporated to an oil. Crystallization could be induced by trituration with a little ethyl acetate and slow addition of ether (50 ml) to the resultant suspension to yield the hydroxyoxazolidinone (**6**) (4.1 g). The residue, after evaporation of the mother liquor, was chromatographed on silica using an ethyl acetate gradient (1—5%) in methylene dichloride as eluant to yield phenol (0.5 g), followed by recovered starting material (1.3 g), and then by additional oxazolidinone (**6**) (0.2 g, total yield 4.3 g, 14.0 mmol, 62%), m.p. 188.5—191.5 °C (Found: C, 61.4; H, 6.5; N, 4.7. $C_{15}H_{19}NO_5$ requires C, 61.4; H, 6.5; N, 4.8); $\nu_{max.}$ 3 340, 1 740, and 1 615 cm^{-1}; $\lambda_{max.}$ 231 (ε 8 300), 279sh (3 500), 283 (3 800), and 288sh nm (3 200); $\lambda_{min.}$ 250 nm (ε 500); δ_H 6.76 (1 H, s), 6.60 (1 H, s), 3.86 (6 H, s), 3.2—3.4 (2 H, m), 1.73 (3 H, s), and 0.98 (3 H, s); δ_C([$^2H_6$]DMSO)



*Signal may be interchanged with that of similar shift

m/z 293 (M^+, 10%), 276 (M − OH, 25), 232 (M − CO_2, 26%), 207 ($C_{11}H_{13}NO_3$, 100), 178 (20), 150 (9).

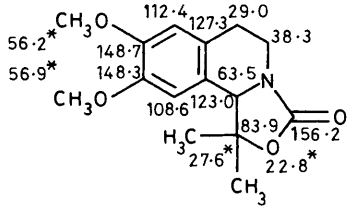
1,1-*Diethyl*-1,5,6,10b-*tetrahydro*-10b-*hydroxy*-8,9-*dimethoxy*-3H-*oxazolo*[4,3-a]*isoquinolin*-3-*one* (**9**).—To a suspension of lead tetra-acetate (13.9 g, 31.5 mmol) in glacial acetic acid (200 ml), the enamide (**8**) (10.0 g, 26.2 mmol) was added and the mixture stirred for 0.5 h. During this period, the lead salts dissolved and the solution went from colourless to yellow. After quenching with glycerine, the solution was poured into water (1 l) and extracted with methylene dichloride (4 × 200 ml). The combined extracts were stirred with 15% aqueous sodium hydrogen carbonate for 18 h. After separation, the dark yellow organic layer was treated with decolourizing carbon, then filtered through filter-aid to give a light yellow solution. The residue, after evaporation, rapidly crystallized upon trituration with ether. After subsequent dilution with hexane, the oxazolidinone (**9**) was collected (6.7 g, 20.9 mmol, 80%), m.p. 182—186 °C (from ethyl acetate–methylene dichloride) (Found: C, 63.3; H, 7.1; N, 4.3. $C_{17}H_{23}NO_5$ requires C, 63.5; H, 7.2; N, 4.4); $\nu_{max.}$ 3 410, 1 745, 1 610, and 1 515 cm^{-1}; $\lambda_{max.}$ 232 (ε 8 500), 281 (3 500), 283 (3 500), and 288 (3 150); $\lambda_{min.}$ 251 nm (ε 250); δ_H 6.83 (1 H, s), 6.59 (1 H, s), 4.0 (1 H, m), 3.87 (3 H, s), 3.85 (3 H, s), 2.5—3.5 (4 H, m), 2.17 (2 H, m), 1.20 (5 H, m), and 0.67 (3 H, t).

1,5,6,10b-*Tetrahydro*-10b-*hydroxy*-8,9-*dimethoxy*-1,1-*pentamethylene*-3H-*oxazolo*[4,3-a]*isoquinolin*-3-*one* (**15**).—(*a*) *From the phenyl ester* (**14**). The enamide (**14**) (4.35 g, 11.1 mol) was added to a rapidly stirred suspension of dry lead tetra-acetate (6.75 g) in glacial acetic acid (100 ml). Glycerine (2 ml) was added after 0.5 h and the solution was poured into water (1 l) and extracted with methylene dichloride (3 × 150 ml). The combined extracts were washed with 10% aqueous sodium hydrogen carbonate and then dried (Na_2SO_4). After evaporation, the residual oil was triturated with ethyl acetate to induce crystallization. Filtering yielded the oxazolidinone (**15**) (2.55 g). T.l.c. of the crystallization solvent indicated the presence of additional product and, as a result, it was chromatographed on silica using ethyl acetate–methylene dichloride (5:95) as eluant to yield additional (**15**) (0.40 g, total yield 2.95 g, 8.9 mmol, 80%), m.p. 180—184 °C (Found: C, 64.6; H, 7.0; N, 3.9. $C_{18}H_{23}NO_5$ requires C, 64.9; H, 7.0; N, 4.2); $\nu_{max.}$ 3 310, 1 735, and 1 520 cm^{-1}; $\nu_{max.}$ 231.5 (ε 8 500), 280 (3 500), 283 (3 600), and 288 nm (3 150); $\lambda_{min.}$ 251 nm (ε 250); δ_H 6.81 (1 H, s), 6.61 (1 H, s), 4.03 (1 H, m), 3.89 (3 H, s), 3.88 (3 H, s), 2.4—3.5 (5 H, m), and 0.8—1.9 (9 H, m).

(*b*) *From the methyl ester* (**16**). The enamide (**16**) (1.08 g, 3.26 mmol) was oxidized with lead tetra-acetate (3.8 g) in glacial acetic acid (50 ml) for 2.5 h. After the glycerine quench the solution was poured into water (750 ml) and extracted with methylene dichloride (3 × 150 ml). After extraction with 10% aqueous sodium hydrogen carbonate the organic solution was dried (Na_2SO_4) and evaporated to an oil. Trituration with ether yielded the oxazolidinone (**15**) (0.87 g, 80%).

10b-*Ethoxy*-1,5,6,10b-*tetrahydro*-8,9-*dimethoxy*-1,1-*dimethyl*-3H-*oxazolo*[4,3-a]*isoquinolin*-3-*one* (**10**).—Compound (**5**) (200 mg, 0.68 mmol) and toluene-*p*-sulphonic acid monohydrate (200 mg) were dissolved in methylene dichloride (20 ml) and absolute ethanol (2 ml). After being stirred (4 h), the yellow solution was quenched by the addition of sodium hydrogen carbonate (300 mg). As the acid was consumed, the solution went from yellow to colourless. After evaporation, the residue was flash chromatographed using ethyl acetate–methylene dichloride (3:97) as eluant to yield (**10**) as an oil. The oil was crystallized from ether at −78 °C by scratching. After dilution with hexanes, crystalline (**10**) was filtered off (130 mg, 0.40 mmol, 59%), m.p. 148.5—152 °C (Found: C, 63.4; H, 7.4; N, 4.2. $C_{17}H_{23}NO_5$ requires C, 63.5; H, 7.2; N, 4.4); $\nu_{max.}$ 1 745, 1 610, and 1 515 cm^{-1}; $\lambda_{max.}$ 232 (ε 8 000) 283.5 (4 400), and 288sh nm (3 800); $\lambda_{min.}$ 251 nm (ε 900); δ_H 6.77 (1 H, s), 6.63 (1 H, s), 4.20 (1 H, m), 3.89 (3 H, s), 3.87 (3 H, s), 3.45 (2 H, q), 3.0—3.25 (2 H, m), 2.75 (1 H, m), 1.65 (3 H, s), 1.13 (3 H, t), and 0.84 (3 H, s).

1,5,6,10b-*Tetrahydro*-8,9-*dimethoxy*-1,1-*dimethyl*-3H-*oxazolo*[4,3-a]*isoquinolin*-3-*one* (**11**).—Compound (**6**) (250 mg, 0.85 mmol) was dissolved in glacial acetic acid (25 ml) to give a yellow solution. To this magnetically stirred solution, sodium cyanoborohydride (150 mg) was added to give a rapid gas evolution and fading of the yellow colour to colourless. The solution was poured into water (250 ml) and extracted with methylene dichloride (3 × 90 ml). The combined extracts were added to 10% aqueous sodium hydrogen carbonate (0.5 l). After being stirred for 1 h, the organic layer was separated, dried (Na_2SO_4) and evaporated to afford a residue which was crystallized from ether to yield (**11**) (240 mg, 0.85 mmol, 100%), m.p. 146—148 °C (lit.,[22] 146—148 °C) (Found: C, 64.8; H, 6.8; N, 4.95. $C_{15}H_{19}NO_4$ requires C, 65.0; H, 6.9; N, 5.05); $\nu_{max.}$ 1 755 cm^{-1}; $\lambda_{max.}$ 230 (ε 8 500), 282 (3 500), 286 (3 500), and 291 nm (3 000); $\lambda_{min.}$ 252 nm (ε 340); δ_H 6.64 (1 H, s), 6.48 (1 H, s), 4.71 (1 H, s), 4.13 (1 H, m), 3.88 (3 H, s), 3.86 (3 H, s), 2.5—3.2 (3 H, m), 1.83 (3 H, s), and 0.97 (3 H, s); δ_C:



* Signal may be interchanged with that of similar shift

1,1-*Diethyl*-1,5,6,10b-*tetrahydro*-8,9-*dimethoxy*-3H-*oxazolo*-[4,3-a]*isoquinolin*-3-*one* (**12**).—In a manner similar to that for compound (**6**), the diethyl analogue (**9**) (4.00 g, 12.45 mmol) was reduced with sodium cyanoborohydride (2.5 g) in glacial acetic acid (125 ml). After work-up, the residue was crystallized from ether–light petroleum (b.p. 40—60 °C) to yield (**12**) (3.38 g, 11.1 mmol, 90%), m.p. 101—104 °C (Found: C, 66.9; H, 7.7; N, 4.6. $C_{17}H_{23}NO_4$ requires C, 66.9; H, 7.6; N, 4.6); $\nu_{max.}$ 1 740, 1 610, and 1 515 cm^{-1}; $\lambda_{max.}$ 230 (ε 8 000), 282 (3 600), and 290 nm (3 100); $\lambda_{min.}$ 253 nm (ε 260); δ_H 6.60 (1 H, s), 6.44 (1 H, s), 4.83 (1 H, s), 4.12 (1 H, m), 3.86 (3 H, s), 3.83 (3 H, s), 2.5—3.2 (3 H, m), 2.05 (2 H, q), 1.88 (2 H, q), 1.16 (3 H, t), and 0.73 (3 H, t).

1,5,6,10b-*Tetrahydro*-8,9-*dimethoxy*-1,1-*pentamethylene*-3H-*oxazolo*[4,3-a]*isoquinolin*-3-*one* (**17**).—In a manner similar to that used for the reduction of compound (**6**), compound (**15**) (1.25 g, 3.75 mmol) was reduced with sodium cyanoborohydride (0.75 g) in glacial acetic acid (125 ml) to yield (**17**) (1.09 g, 3.43 mmol, 92%), m.p. 105.5—108.5 °C (ether–hexanes) (Found: C, 68.0; H, 7.35; N, 4.4. $C_{18}H_{23}NO_4$ requires C, 68.1; H, 7.3; N, 4.4); $\nu_{max.}$ 1 750 cm^{-1}; $\lambda_{max.}$ 230 (ε 5 900), 282 (2 600), 285.5 (2 600), and 290 nm (2 300); $\lambda_{min.}$ 252 nm (ε 350); δ_H 6.61 (1 H, s), 6.50 (1 H, s), 4.60 (1 H, s), 4.13 (1 H, m), 3.87 (6 H, s), 2.5—3.2 (3 H, m), and 0.85—1.85 (10 H, m).

1-(1-*Hydroxycyclohexyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (**18**).—Compound (**17**) (1.00 g, 3.00 mmol) was dissolved in 2-methoxyethyl ether (40 ml) and ethylene glycol (5 ml) containing potassium hydroxide (3 g). The two phase system was refluxed for 3 h under nitrogen. After cooling, the mixture was poured into water (0.5 l) and extracted with methylene dichloride (3 × 200 ml). After drying (Na_2SO_4), the solvent was evaporated to an oil. Traces of remaining glycol and glycol ether were removed by heating at 95 °C *in vacuo*. The residue was triturated with ether–hexanes to yield the amino alcohol (**18**) (670 mg, 2.30 mmol, 77%), m.p. 108—111 °C (Found: C, 69.8; H, 8.75; N, 4.7. $C_{17}H_{25}NO_3$ requires C, 70.1; H, 8.65; N, 4.8); $\nu_{max.}$ 3 460, 3 100br, 3 035, and 1 530 cm^{-1}; $\lambda_{max.}$ 230 (ε 8 200), and 283 nm (3 400); $\lambda_{min.}$ 222 (ε 7 800), and 253 nm (400); δ_H 6.72 (1 H, s), 6.57 (1 H, s), 3.84 (6 H, s), 2.3—3.4 (4 H, m), and 1.0—1.8 (10 H, m).

X-*Ray Crystallographic Analysis of Compound* (**6**). *Crystal Data*.—$C_{15}H_{19}NO_5$, M = 293.32. Monoclinic, a = 10.190 5(8), b = 12.645(1), c = 11.241 2(6) Å, β = 93.073(6) Å, V = 1 446.5(2) $Å^3$ (by least squares refinement on diffractometer angles for 25 automatically centred high angle reflections, μ = 1.541 78 Å), space group $P2_1/a$ (alt. $P2_1/c$, No. 14), Z = 4, D_x 1.35 g cm^{-3}. Clear parallelepiped. Crystal dimensions 0.31 × 0.23 × 0.45 mm, μ = 8.55 cm^{-1}.

Data Collection and Processing.—AFC5S diffractometer, ω/2θ mode with ω scan width = 1.155 + 0.300 tan θ, ω scan speed 2—8° min^{-1}, graphite monochromated Cu-K_α radiation; 2 352 reflections measured (0° < 2θ < 120°, $+h$, $+k$, $+-l$), 2 237 unique (merging R = 0.005), giving 1 751 with $I > 3\sigma(I)$. 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 position and anisotropic temperature factors of all non-hydrogen atoms and of the position of the hydroxy hydrogen. The other hydrogens assigned calculated positions. All the hydrogens assigned calculated 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 $w = 1$ $[\sigma^2(F_o) + 0.000\,625F_o^2]$ with $\sigma(F_o)$ from counting statistics gave satisfactory agreement between F_o and F_c, with GOF = 1.97. The final R and R_w values were 0.038, 0.066. Programs and computers used and sources of scattering factor data are given in ref. 28.

Supplementary Material.—A full list of atomic co-ordinates, bond lengths and angles, thermal parameters, and details of least-squares planes have been deposited at the Cambridge Crystallographic Data Centre.*

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References

1 G. R. Lenz, *Synthesis*, 1978, 489.
2 I. Ninomiya and T. Naito, *Alkaloids* (*N.Y.*), 1983, **22**, 189.
3 A. L. Campbell and G. R. Lenz, *Synthesis*, 1987, 421.
4 M. Petrzilka and J. J. Grayson, *Synthesis*, 1981, 573.
5 G. R. Lenz, *Heterocycles*, 1987, **26**, 721.
6 C. R. Dorn, F. J. Koszyk, and G. R. Lenz, *J. Org. Chem.*, 1984, **49**, 2642.
7 G. R. Lenz and C. Costanza, *J. Org. Chem.*, 1988, **53**, 1176.
8 G. R. Lenz, *J. Org. Chem.*, 1988, **53**, 4447.
9 G. R. Lenz, *J. Org. Chem.*, 1988, **53**, 5791.
10 R. N. Butler, *Chem. Rev.*, 1984, **84**, 249.
11 M. Mihailović, Ž. Čeković, and L. Lorenc in 'Organic Synthesis by Oxidation with Metal Compounds,' eds. W. J. Mijs and C. R. H. I. de Jonge, Plenum Press, New York, 1986, p. 741.
12 A. G. Cook in 'Enamines: Synthesis, Structure and Reactions,' ed. A. G. Cook, Dekker, New York, 1988, p. 247.

* For details of the CCDC system, see 'Instructions for Authors (1990)', *J. Chem. Soc., Perkin Trans. 1*, 1990, Issue 1.

13 Ž. Čeković, J. Bosnjak, and M. Cvelkovic, *Tetrahedron Lett.*, 1980, 2675.
14 G. M. Rubottom, *Org. Chem.* (*N.Y.*), 1982, **5**, 1.
15 G. M. Rubottom, J. M. Gruber, and G. M. Mong, *J. Org. Chem.*, 1976, **41**, 1673.
16 G. M. Rubottom, J. M. Gruber, and K. Kincaid, *Synth. Commun.*, 1976, **6**, 59.
17 G. M. Rubottom, R. Marrero, and J. M. Gruber, *Tetrahedron*, 1983, **39**, 861.
18 G. M. Rubottom, J. M. Gruber, R. Marrero, H. D. Juve jr., and C. W. Kim, *J. Org. Chem.*, 1983, **48**, 4940.
19 R. M. Moriarty, R. Penmasta, and I. Prakash, *Tetrahedron Lett.*, 1987, **28**, 873.
20 S. Kano, Y. Yuasa, and S. Shibuya, *Synth. Commun.*, 1985, **15**, 883; *Heterocycles*, 1985, **23**, 395; S. Kano, Y. Yuasa, T. Yokomatsu, and S. Shibuya, *Chem. Lett.*, 1985, 1475.
21 S. Kano, Y. Yuasa, T. Yokomatsu, and S.Shibuya, *J. Org. Chem.*, 1983, **48**, 3835.
22 M. F. Saettone, *J. Org. Chem.*, 1966, **31**, 1959.
23 P. J. Rider and D. M. Roland, *Alkaloids* (*N.Y.*), 1984, **23**, 71; J. W. Lown, K. Majundar, A. I. Meyers, and A. Hecht, *Bioorg. Chem.*, 1977, **6**, 453.
24 H. Hiemstra and W. N. Speckamp, *Alkaloids* (*N.Y.*), 1988, **32**, 271.
25 M. Narisada, F. Watanabe, and W. Nagata, *Tetrahedron Lett.*, 1971, 3681; R. B. Boar, J. F. McGhie, M. Robinson, and D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1242.
26 P. N. Craig, F. P. Nabenhauer, P. M. Williams, E. Macko, and J. Toner, *J. Am. Chem. Soc.*, 1952, **74**, 1316.
27 V. S. Georgiev, R. P. Carlson, R. G. Vanlnwegen, and A. Khandwala, *J. Med. Chem.*, 1979, **22**, 348.
28 S. M. Evans, E. F. Ezell, and S. J. Sondheimer, *J. Crystallogr. Spectrosc. Res.*, 1989, **19**, 415.

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