# THE SYNTHESIS OF THE ISOQUINOLINE ALKALOID CALYCOTOMINE VIA FUNCTIONALIZATION OF ENAMIDE DOUBLE BONDS

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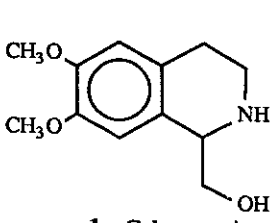
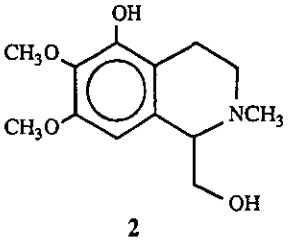
Abstract - The novel alkaloid calycotomine, a 1-hydroxymethylenetetrahydroisoquinoline, has been synthesized from 1-methyl-3,4-dihydroisoquinoline via the 2-benzyloxycarbonyl enamide derivative. Oxidation of the enamide with osmium tetroxide results in bis-hydroxylation and ring opening to form hydroxyacetophenone carbamates. Hydrogenation results in reclosure of the isoquinoline ring and further reduction yielding 1-hydroxymethylenetetrahydro-isoquinolines.

While there are a substantial number of simple tetrahydroisoquinoline alkaloids known, the presence of a 1-hydroxymethylene group in these alkaloids is a rare occurrence. Calycotomine (1) has been isolated from Calycotome, Cytisus and Acacia species in both its optically active as well as racemic forms[1]. The only other member of this family is a more highly functionalized derivative (2) found in a Mexican cactus[2]. This type of




1 Calycotomine

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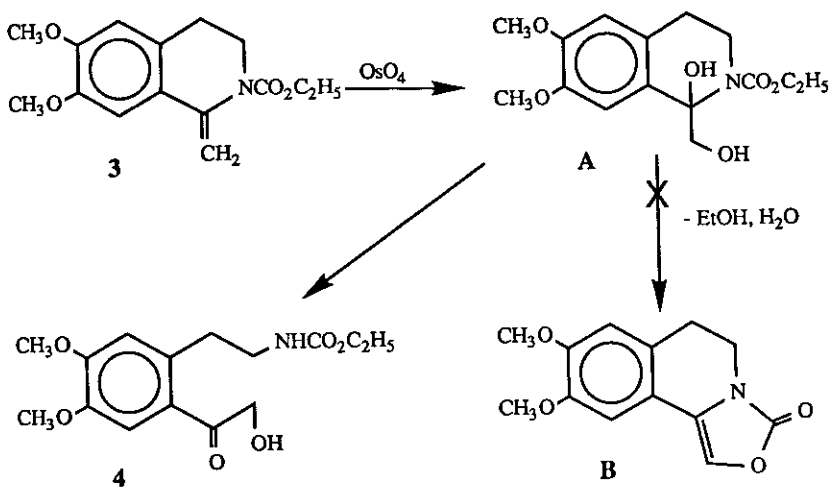
alkaloid is of interest because it represents an alternative arrangement of the aromatic amino-alcohol system found in the sympathomimetic hormone epinephrine.

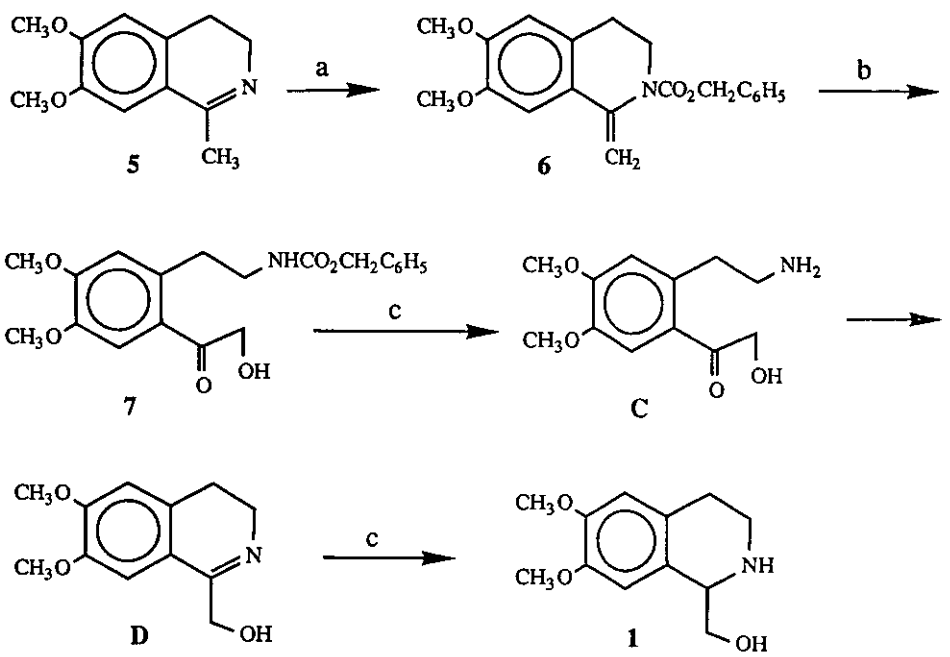
Several syntheses, including a recent enantio-selective one[3], of calycotomine have been reported[4]. These synthetic approaches have involved classical isoquinoline chemistry, Bischler-Napieralski reactions or Reissert chemistry, and have, in many cases, been plagued by troublesome steps and low yields. The ready availability of 1-methyl-3,4-dihydroisoquinolines[5] and their facile conversion into enamides[6] prompted an investigation into the conversion of the enamide grouping into an aminoalcohol. While the photochemistry of the enamides has been extensively investigated[7], the chemical reactivity has not, although the enamide double bond has been acetoxylated[8], acylated[6], brominated[9], and epoxidized[10]. This report then describes the oxidative conversion of enamides by osmium tetroxide ultimately into aminoalcohols.

**SCHEME 1**




The enamide 3, readily available from 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline and diethylpyrocarbonate[6], when treated with osmium tetroxide was expected to form the bis-hydroxy-intermediate (A) (Scheme 1), based on literature precedent.[11] This intermediate A was then further expected to undergo ring formation and dehydration to form the oxazolidinone (B), which could then be further manipulated to obtain calycotomine (1). When the enamide (3) was oxidized, using catalytic amounts of osmium tetroxide[12], the intermediate (A) underwent ring opening to form the hydroxyacetophenone derivative (4). The structure of (4) was evident from the

## SCHEME 2

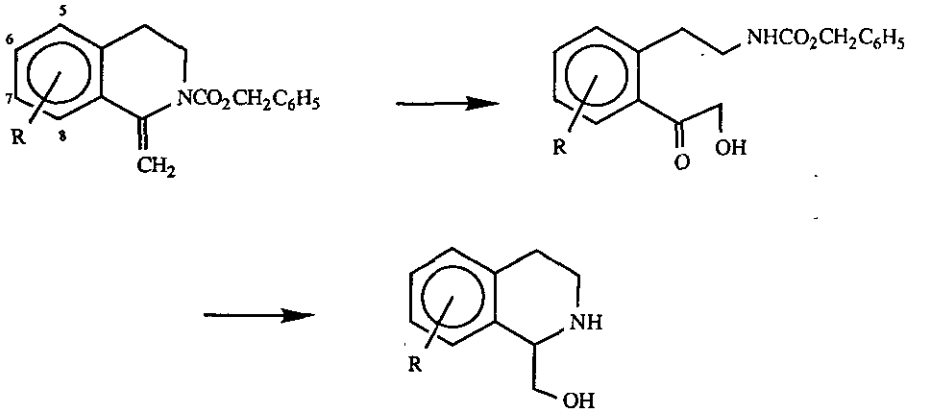



Reagents: a) N-benzyloxycarbonyloxy-5-norbornene-2,3-dicarboxamide; b) osmium tetroxide (cat.), N-methylmorpholine N-oxide; c) hydrogen, Pd/C.

retention of the ethyl carbamate function, the observation of the signal of the methylene group of the hydroxyketone at δ 4.73 in the NMR, and the ready formation of a benzoate ester. Precedent for this type of reaction is found in the acid catalyzed ring opening of enamides analogous to (3) leading to acetophenone derivatives[5]. Since ethyl carbamates require rather harsh conditions for cleavage[13], the use of compound (4) for the synthesis of calycotomine was not further investigated.

Although the use of the ethyl ester group in compound (3) led to an unexpected product (4), the simple change to a benzyl ester would enable the hydroacetophenone derviative to be used for a novel and synthetically useful synthesis of calycotomine-type alkaloids (Scheme 2). The synthetic sequence envisaged, proceeding from the benzyl carbamate ester of the hydroxyacetophenone (e.g. (7)), was a one pot reaction involving cleavage of the benzyl ester by catalytic hydrogenation, decarboxylation to the amine (C), subsequent ring closure to the dihydroisoquinoline (D) and finally reduction of the imine double

**TABLE**



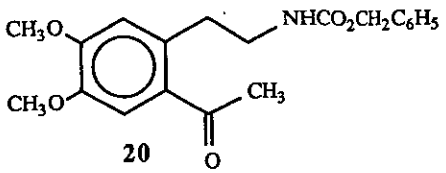

| Substitution pattern[a] | Enamide | Hydroxy-acetophenone | 1-Hydroxymethylene derivative |
|---|---|---|---|
| 6,7-$(OCH_3)_2$ | 6 | 7 (67%) | 1 (86-98%) |
| 5,6-$(OCH_3)_2$ | 8 | 9 (63%) | 10 (94%) |
| 6-$OCH_3$ | 11 | 12 (65%) | 13 (64%) |
| 6,7-$(OCH_2O)$ | 14 | 15 (74%) | 16 (73%) |
| 6,7,8-$(OCH_3)_3$ | 17 | 18 (72%) | 19 (76%)[b] |

a) isoquinoline numbering. b) hydrochloride salt.

bond to yield the 1-hydroxymethylenetetrahydroisoquinoline calycotomine (1). In the event, the readily available dihydroisoquinoline (5)[5] was converted to the requisite enamide (6) in very high yield, using a commercially available benzyloxycarbonyl transfer reagent.[14] Osmium tetroxide oxidation then gave the benzyl carbamate (7) in 67% yield.

Catalytic hydrogenation of (7) in methanol:acetic acid (9:1) smoothly converted (7) into the naturally occurring alkaloid calycotomine (1) in 86% yield, thus completing the synthesis. The overall synthetic transformation is the conversion of a methylimine into a beta-hydroxyamine.

Calycotomine and the analogs prepared, together with the enamides and hydroxyacetophenones are collected in the Table. The enamides (6) and (8) were crystalline while enamides



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(11), (14), and (17) were oily. The non-crystalline enamides were characterized by NMR and used as prepared. These non-crystalline enamides were particularly prone to hydrolysis to the acetophenone derivatives.[5] Although varying amounts of hydrolysis product, for instance (20), were observed in the oxidation of all of the enamides, they were not usually characterized.

Calycotomine (1) and its analogs were crystalline substances, with the exception of the mescaline derivative (19) which was isolated as its hydrochloride salt. The overall yields for the hydroxyacetophenone derivatives are 63-74% and for the conversion to calycotomine derivatives 64-98%, making this a useful and flexible route for these aromatic amino-alcohol derivatives.

## EXPERIMENTAL

General - Melting points were taken on a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. IR spectra of solid were run in KBr and that of oils in chloroform. A Varian Associates T-60 or FT-80 NMR spectrometer was used and the spectra were run in deuterochloroform using tetramethylsilane as an internal standard. UV spectra were recorded in methanol.

### Osmium Tetroxide Oxidation of the Ethoxycarbonyl Enamide 3.

The enamide[6](3), 5.00 gm, 19.1 mmol, was dissolved in 30 ml of acetone, containing 4 drops of triethylamine to retard hydrolysis. To this solution was added 2.84 gm, 21 mmol, of N-methylmorpholine N-oxide monohydrate, followed by 10 ml of water and 10 ml of a 0.5% solution of osmium tetroxide in tert-butyl alcohol. After stirring at rt under nitrogen for 17 h, sodium dithionite was added to destroy residual osmium tetroxide. After stirring for 4 h, the reaction mixture was filtered through filter-aid, which in turn, was washed with 250 ml of methylene chloride. The combined oraganics were washed with water, and the aqueous portion back extracted with methylene chloride. The combined organics were dried with sodium sulfate and evaporated to give a very dark oil. This residue was

flash chromatographed with ethyl acetate to yield 3.47 gm, 11.2 mmol (59%) of the hydroxyketone (4): mp 116-121°C (ethyl acetate: petroleum ether); IR 3460 $cm^{-1}$, 3345, 1685, 1663; UV 230 nm ( ε 19200), 249 (min, 2500), 275 (7600), 293 (min, 4700), 305 (5200); NMR δ 7.07 (s,1H), 6.77 (s,1H), 4.73 (s,2H), 4.09 (q,2H), 3.94 (s,3H), 3.91 (s,3H), 3.38 (distorted t,2H), 3.08 (distorted t,2H), 1.22 (t,3H).

$C_{15}H_{21}NO_6$ requires: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.74; H, 6.72; N, 4.52.

The benzoate of (4) was prepared from benzoyl chloride and pyridine, mp 85-87°C (ether: petroleum ether).

**Procedure for the Preparation of the Benzyloxycarbonyl Enamides.**

N-Methylmorpholine (5 ml) and 13.6 g (43.3 mmol) of N-benzyloxycarbonyloxy-5-norbornene-2,3-dicarboxamide (purchased from Chemical Dynamics) were added to a magnetically stirred solution of 8.87 gm (43.3 mmol) of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline[5] (5) in 200 ml of methylene chloride under nitrogen. After stirring for 3.5 h, 100 ml of 30% potassium carbonate solution was added to remove the N-hydroxy-imide. After a second carbonate treatment, the organic layer was washed three times with water, dried with sodium sulfate and evaporated. The residue was crystallized from ethyl acetate: petroleum ether to yield 13.24 gm, 39.0 mmol (90%) of enamide (6): mp 104.5-106.5°C, IR 1695$cm^{-1}$; 1515; UV 240 nm (min, ε 6300), 264 (11500), 287 (min, 4000), 303 (5900), 315 (sh,4200); NMR δ 7.31 (s,5H), 7.07 (s,1H), 6.53 (s,1H), 5.52 (s,1H), 5.37 (s,1H), 5.18 (s,2H), 3.87 (s,3H), 3.85 (s,3H), 3.84 (t,2H), 2.87 (t,2H).

$C_{20}H_{21}NO_4$ requires: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.61; H, 6.15; N, 4.07.

The 5,6-Dimethoxyenamide (8) was prepared in 79% yield: mp 60-62°C; IR 1677 $cm^{-1}$; UV 230 nm (sh, ε14800), 240 (min, 500), 272 (8600); NMR δ 7.35 (m,6H), 6.76 (d,J 9Hz,1H), 5.54 (s,1H), 5.37 (s,1H), 5.19 (s,2H), 3.86 (s,3H), 3.78 (s,3H), 3.80 (m,2H), 2.86 (t,2H).

$C_{20}H_{21}NO_4$ requires: C, 70.78; H, 6.24; N,4.13. Found: 70.43; H, 6.43; N, 3.83.

The following enamides were oils and were characterized by NMR and used as prepared:

The 6-methoxyenamide (11) (85%): δ 7.50 (d,J=8Hz,1H), 7.28 (s,2H), 6.68 (dd,J=8,3Hz,1H), 6.50 (d,J=3Hz,1H), 5.47 (s,1H), 5.35 (s,3H), 5.48 (s,2H), 3.81 (t,2H), 3.73 (s,3H), 2.80 (t,2H).

The 6,7-methylenedioxyenamide (14) (92%): δ7.35 (s,5H), 7.03 (s,1H), 6.50 (s,1H), 5.87

(s,2H), 5.37 (s,1H), 5.20 (s,1H), 5.18 (s,2H), 3.80 (t,2H), 2.73 (t,2H).

The 6,7,8-trimethoxyenamide (17) (95%): δ 7.28 (s,5H), 6.42 (s,1H), 5.98 (s,1H), 5.50 (s,1H), 5.15 (s,2H), 3.85 (s,3H), 3.82 (s,3H), 3.80 (s,3H), 3.75 (t,2H), 2.78(t,2H).

All the preceding non-crystalline enamides were isolated and purified using ethyl acetate:methylene chloride eluants with rapid flash chromatography.

**Osmium Tetroxide Oxidation of the Benzyloxycarbonyl Enamides: (6),(8),(11),(14), and (17)**

The 6,7-dimethoxybenzyloxycarbonyl enamide (6), 5.0 gm (14.7 mmol) was dissolved in 50 ml of acetone containing 5 drops of triethylamine. To the solution was added 2.5 gm of N-methylmorpholine N-oxide monohydrate (18.4 mmol) and 10 ml of 1% osmium tetroxide in tert-butyl alcohol. After adding 10 ml of water, the flask was stoppered and magnetically stirred. After stirring for further 24 h, an additional 5 ml of osmium solution was added. After a total of 27 h, the solution was poured into dilute sodium dithionite solution and extracted three times with chloroform. The chloroform solution was dried with sodium sulfate and condensed to a black oil. The oil was flash chromatographed using ethyl acetate: methylene chloride (1:1) to yield 3.65 gm of the hydroxyketone (7), 9.84 mmol (67%): mp 112-113°C; IR 3470cm$^{-1}$, 3340, 1690; UV nm (ε 19500), 249 (min, 2700), 275 (8300), 294 (min, 5000), 305 (5200); NMR δ 7.28 (s,5H), 7.02 (s,1H), 6.73 (s,1H), 5.06 (s,2H), 4.69 (s,2H), 3.87 (s,3H), 3.85 (s,3H), 3.41 (m,2H), 3.33 (t,2H).
$C_{20}H_{23}NO_6$ requires: C,64.33, H, 6.21; N, 3.75. Found: 64.72; H, 6.19; N, 4.15.

Accompanying the oxidation product, varying amounts of the hydrolysis product (20) of the starting enamide were found: 91.5-93.5°C; IR 3340cm$^{-1}$, 1685, 1665; UV 230 nm (ε 22500), 247 (min, 2500), 273 (8200), 292 (min, 4800), 303 (5300); NMR δ 7.29 (s,5H), 7.17 (s,1H), 6.69 (s,1H), 5.06 (s,2H), 3.89 (s,3H), 3.85 (s,3H), 3.43 (distorted t,2H), 3.01 (t,2H), 2.55 (s,3H).
$C_{20}H_{23}NO_5$ requires: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.46; H, 6.41; N, 3.90.

The 5,6-dimethoxyenamide (8) was similarly converted to the 5,6-dimethoxyhydroxyketone (9) (63%) with purification by flash chromatography using ethyl acetate:methylene chloride (1:4): mp 83-87°C; IR 3420 cm$^{-1}$, 1685; UV 225 nm (end, ε 14000), 244 (min, 5000), 271 (11000); NMR δ 7.40 (d,J=9Hz, 1H), 7.29 (s,5H), 6.80 (d,J=9Hz, 1H), 5.03

(s, 2H), 4.67 (s,2H) 3.92 (s,3H), 3.83 (s,3H), 2.93 (m,2H), 2.67 (m, 2H).
$C_{20}H_{23}NO_6$ requires: C, 64.33; H, 6.21, N, 3.75. Found: C, 64.01; H, 5.89; N, 3.51.

The 6-methoxy enamide (11) was converted to the 6-methoxyhydroxyketone (12) (65%) with purification by flash chromatography using ethyl acetate:methylene chloride (1:4): mp 82-84°C; IR 3470cm$^{-1}$, 3385, 1700, 1680, 1670, 1540; NMR δ7.60 (d,J=10 Hz,1H), 7.31 (s,5H), 6.78 (m,2H), 5.07 (s,2H), 4.70 (s,2H), 3.87 (s,3H), 3.50 (m,2H), 3.19 (distorted t,2H).
$C_{19}H_{21}NO_5$ requires: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.25; H, 6.23, N,4.03.

The 6,7-methylenedioxyenamide (14) was converted to the 6,7-methylenedioxyhydroxyketone (15) (74%) with purification by flash chromatography using ethyl acetate:methylene chloride (3:7): mp 97-99°C; IR 3430cm$^{-1}$, 1725, 1680, 1670, 1510; UV 231 nm (ε17600), 250 (min, 1700), 276 (4700), 290 (min, 3400), 310 (4900); NMR δ7.30 (s,5H), 7.00 (s,1H), 6.73 (s,2H), 5.03 (s,2H), 4.61 (s,2H), 3.46 (m,2H), 3.03 (t,2H).
$C_{19}H_{19}NO_6$ requires: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.57; H, 5.31; N, 3.75.

The 6,7,8-trimethoxyenamide (17) was converted to the 6,7,8-trimethoxyhydroxyketone (18) (72%): mp 75.5-77.5°C; IR 3440 cm$^{-1}$, 3360, 1690, 1655, UV 225 nm (sh, ε13800), 250 (min, 4000), 265 (4500); NMR δ 7.29 (s,5H), 6.49 (s,1H), 5.07 (s,2H), 4.54 (s,2H), 3.88 (s,3H), 3.83 (s,6H), 3.39 (q,2H), 2.68 (t,2H).
$C_{21}H_{25}NO_7$ requires: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.15, H, 6.24, N, 3.51.

**The Synthesis of Calycotomine 1 (1,2,3,4-tetrahydro-1-hydroxymethylene-6,7-dimethoxyisoquinoline).**

*A solution of 3.00 gm (2.67 mmol) of the 6,7-dimethoxyhydroxyketone (7) in 30 ml of a* 1:9 mixture of acetic acid:methanol was hydrogenated using 0.3 gm of 5% Pd/C catalyst and hydrogen at 60 psi and room temperature. During the course of 1 h, 14 psi (theoretical 17.1 psi) were consumed. The difference between the observed and theoretical hydrogen consumption is attributed to the carbon dioxide generated. The catalyst was filtered and washed with additional solvent mixture. The organics were condensed to a small volume and partitioned between chloroform and 10% potassium carbonate. The basic aqueous solution was extracted two additional times with chloroform and the combined organics treated with decolorizing carbon. After filtering through filter-aid, the solvent was removed and the residue crystallized from ether to yield 0.51 gm, 2.29 mmol (86%) of calycotomine (1).

If a continuous extraction apparatus is utilized, instead of partitioning, the yield of (1) is 98%. Calycotomine possesses: mp 131-133°C (lit.[15] 132-134°C); UV 225 nm (ε 8000), 253 (min, 500), 285(3000); NMR δ 6.55(s,2H), 3.5-4.1(m,3H), 3.05(s,6H), 3.04(m,2H), 2.66(t,2H).

Calycotomine, $C_{12}H_{17}NO_3$ requires: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.27; H, 7.59; N, 6.11.

Similarly prepared were the following calycotomine analogs:(10),(13),(16) and (19):

1,2,3,4-Tetrahydro-1-hydroxymethylene-5,6-dimethoxyisoquinoline 10 (94%): mp 136.5-137.5°C; IR 3300cm$^{-1}$; NMR δ 6.76(s,2H), 3.83(s,3H), 3.79(s3H), 3.5-4.1(m,3H), 3.01(m,2H), 2.70(m,2H).

$C_{12}H_{17}NO_3$ requires: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.53; H, 7.88, N, 6.20.

1,2,3,4-Tetrahydro-1-hydroxymethylene-6-methoxyisoquinoline 13 (64%): mp 106-108°C; UV 277 nm (ε 1800), 282 (min, 1600), 285 (1700), NMR δ 6.98(d,J=8Hz,1H), 6.73(dd,J=8,3Hz,1H), 6.62(d,J=3Hz,1H), 3.5-4.2(m,3H), 3.76(s,3H), 3.03(m,2H), 2.71(m2H).

$C_{11}H_{15}NO_2$ requires: C, 68.36; H, 7.82; N, 7.25. Found: C, 67.95; H, 7.63; N, 7.29.

1,2,3,4-Tetrahydro-1-hydroxymethylene-6,7-methylenedioxyisoquinoline (16) (73%): mp 111.5-113°C (lit.[16] 109-110°C); UV 234 nm (ε 3800), 255(min, 340), 292(4600); NMR δ 6.52(s,2H), 5.86(s,2H), 3.5-4.1(m,3H), 3.00(m,2H), 2.63(distorted t,2H).

$C_{11}H_{13}NO_3$ requires: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.79; H, 6.23; N, 6.14.

1,2,3,4-Tetrahydro-1-hydroxymethylene-6,7,8-trimethoxyisoquinoline hydrochloride (19) (76%): mp 154-156°C; UV 227 nm (sh, ε 10600), 252(min, 260), 272(900), 278.5(900); NMR ($D_2O$) δ 6.78(s,1H), 3.78 (S,9H), 3.8 -4.05(m,3H), 3.58(m,2H), 3.10(broad t, 2H).

$C_{13}H_{19}NO_4$ HCl requires: C, 53.89; H, 6.96; N, 4.83; Found: C, 53.55.; H, 6.94; N 4.88.

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