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A REVISION OF THE STRUCTURE OF THE ISOQUINOLONE ALKALOID THALFLAVINE

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Key Word Index—*Thalictrum flavum*; Ranunculaceae; structural revision; synthesis; isoquinolone alkaloid; thalflavine.

Abstract—The structure of the isoquinolone alkaloid thalflavine, originally proposed as 1-oxo-2-methyl-5-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, is revised to 1-oxo-2-methyl-5,6-methylenedioxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline, on the basis of synthesis.

INTRODUCTION

In 1970, an alkaloid named thalflavine, mp 132–133° (Me_2CO), and assigned as 1-oxo-2-methyl-5-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**1**) via a consideration of physicochemical and spectral data, was isolated from *Thalictrum flavum* L. [1]. Apparent confirmation of the validity of this assignment occurred in 1971, when oxidation ($KMnO_4$–Me_2CO) of what was then assigned as thalmelatidine (**2**), an aporphine-benzylisoquinoline dimeric alkaloid isolated from *Thalictrum minus* L. var. *elatum* Jacq. in 1970 [2], produced an isoquinolone, mp 137–139° ($CHCl_3$), identified as thalflavine (**1**) [3]. In a subsequent study, oxidation ($KMnO_4$–Me_2CO) of thalistyline, a bisbenzylisoquinoline alkaloid isolated from *Thalictrum longistylum* DC. [4, 5] and *T. podocarpum* Humb. [5, 6] in 1977, apparently produced isoquinolone **1** as colourless needles, mp 136–137° (MeOH) [4]. This isoquinolone was stated to be identical (UV, ^{1}H NMR, MS) to that obtained via oxidation of thalmelatidine [3] and to thalflavine [1]. By way of contrast, a recent communication has revised the structure of thalmelatidine to **3** [7]. This revision, which was based on extensive ^{1}H NMR studies, particularly double irradiation techniques and NOE experiments, would thus require that the structure of thalflavine be represented as **4**, since thalflavine is a direct oxidation product of thalmelatidine. It is thus not unlikely that the structures of other related bisbenzylisoquinoline alkaloids, such as thalistyline (**5**) [4], thaliracebine (**6**) [8], and thalistine (**7**) [9], each of which had been assigned a 5-methoxy-6,7-methylenedioxy-substitution because of an apparent oxidation to isoquinolone **1**, may be revised in the future to reflect a 5,6-methylenedioxy-7-methoxy-substitution. Furthermore, the structures of *N*-desmethylthalistyline (**8**) [4], *N*-methylthalistyline (**9**) [4], and thalirabine (*O*-desmethylthalistyline) (**10**) [4] may also be revised in a similar fashion because these structures had been assigned on the basis of a *N*-methylation or an *O*-methylation product of thalistyline.

RESULTS AND DISCUSSION

In order to address the ambiguities of these problems, it was decided to synthesize 1-oxo-2-methyl-5-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**1**) and its structural isomer 1-oxo-2-methyl-5,6-methylenedioxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**4**) in order to compare and contrast the physicochemical and spectral properties of these isoquinolones and to unequivocally assign the structure of thalflavine. Although an earlier study [3] had reported the synthesis of what was assumed to be isoquinolone **1**, a literature search revealed no further syntheses of isoquinolone **1** and produced no references to the synthesis of isoquinolone **4**.

The synthesis of isoquinolones **1** and **4** proceeded via well-established pathways and began with the preparation of 2-methoxy-3,4-methylenedioxybenzaldehyde and 2,3-methylenedioxy-4-methoxybenzaldehyde. Since these aldehydes were not readily available from commercial sources, they were prepared from simpler precursors utilizing established reactions. Oxidation of 2-hydroxy-3-methoxybenzaldehyde (*o*-vanillin) in aqueous sodium hydroxide by hydrogen peroxide via a modified Dakin reaction afforded pyrogallol-1-monomethyl ether [10]. Methyleneation of this ether with dibromomethane in aqueous sodium hydroxide using the phase transfer catalyst Adogen 464 [11] gave 1-methoxy-2,3-methylenedioxybenzene [12]. Vilsmeier–Haack formylation of this compound with phosphorus oxychloride and DMF [12, 13] gave a mixture of 2-methoxy-3,4-methylenedioxybenzaldehyde [12] and 2,3-methylenedioxy-4-methoxybenzaldehyde [12] which were separated by flash column chromatography. Each aldehyde was then treated separately in a conventional manner for

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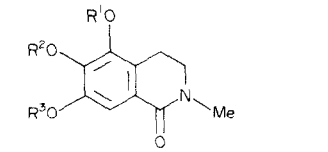
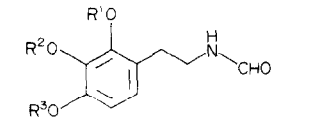
the synthesis of the respective isoquinolones [14]. Treatment of the individual aldehyde with nitromethane and ammonium acetate gave the corresponding β-nitrostyrene [13] which was reduced with lithium aluminium hydride in THF to afford the β-phenethylamine [13]. *N*-Formylation of the respective amines with formic acid gave the *N*-formyl amides **11** and **14** [14] which were subsequently cyclized to the corresponding 3,4-dihydroisoquinolines **12** and **15** via refluxing with phosphorus oxychloride [14]. Oxidation of the methiodide salts **13** and **16** of these 3,4-dihydroisoquinolines with alkaline potassium ferricyanide [14] afforded the isoquinolones **1** and **4**.

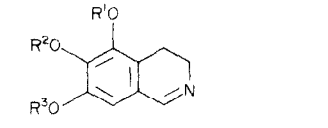
A comparison of the physicochemical and spectral properties of synthetic isoquinolones **1** and **4** with those assigned to thalflavine are shown in Table 1. An examination of the data in this table leads to the following informative observations: first, six different literature references to the mp of thalflavine are in close agreement with that of isoquinolone **4**, and considerably differ from that of isoquinolone **1**. Second, the principal UV absorption band of thalflavine [280 nm (log ε 4.13)] [4] is closer to that of isoquinolone **4** [278 nm (log ε 3.96)] than to that of isoquinolone **1** [271 nm (log ε 3.93)]. Third, the carbonyl bands in the IR spectra (KBr) of isoquinolone **1** (1645 cm^{-1}) and isoquinolone **4** (1625 cm^{-1}) are well separated. The literature values for naturally occurring thalflavine (1625 cm^{-1}) (solid/solvent-not specified) [1] and that obtained as an oxidation product of the alkaloid thalistyline [1640 cm^{-1} (KBr)] [4] differ from each other, and are intermediate to those values for isoquinolones **1** and **4**. Fourth, the ^1H NMR chemical shift for the methoxy group of naturally occurring thalflavine (δ3.84) [1] and that obtained as an oxidation product of thalistyline (δ3.92) [4] are in closer agreement with that of isoquinolone **4** (δ3.92) than that of isoquinolone **1** (δ4.00). In addition, the ^1H NMR chemical shift of the H-8 proton of naturally occurring thalflavine (δ7.32) [1] and that obtained as an oxidation product of thalistyline (δ7.40) [4] are in closer agreement with that of isoquinolone **4** (δ7.39) than that of isoquinolone **1** (δ7.60). Fifth, both isoquinolones **1** and **4** display prominent molecular ions at *m/z* 235 and very characteristic and intense fragment ions at *m/z* 192 $[M-(CH_2{=}NMe)]^+$ and 164 $[M-(CH_2{=}NMe)-CO]$ [14] in their EIMS. Most other spectral features are similar except that isoquinolone **1** exhibits a significant ion (23%) (proposed as **17**) at *m/z* 134 while the corresponding ion (proposed as **18**) for isoquinolone **4** is relatively weak (less than 5%). The higher intensity of ion **17** is attributed to the greater stability of this ion. The EIMS of thalflavine, obtained as an oxidation product of thalistyline, displayed a weak ion at *m/z* 134 (2%) [4]. These five observations prompt us to conclude that both the naturally occurring thalflavine [1] and the isoquinolone obtained as an oxidation product of the alkaloids thalmelatidine [3], thalistyline [4], thaliracebine [8], and thalistine [9] is 1-oxo-2-methyl-5,6-methylenedioxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**4**). Finally, the revision of structure of thalflavine as isoquinolone **4** would then suggest that the structures of the alkaloids thalmelatidine (**2**) [3], thalistyline (**5**) [4], *N*-desmethylthalistyline (**8**) [4], *N*-methylthalistyline (**9**) [9], thalirabine (*O*-desmethylthalistyline) (**10**) [4], thaliracebine (**6**) [8], and thalistine (**7**) [9] be changed to reflect their 5,6-methylenedioxy-7-methoxy-substitution.



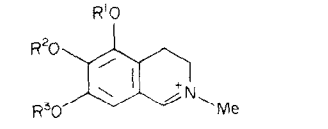
1 $R^1 = Me$; $R^2 + R^3 = CH_2$
4 $R^1 + R^2 = CH_2$; $R^3 = Me$



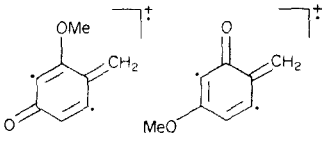
11 $R^1 = Me$; $R^2 + R^3 = CH_2$
14 $R^1 + R^2 = CH_2$; $R^3 = Me$



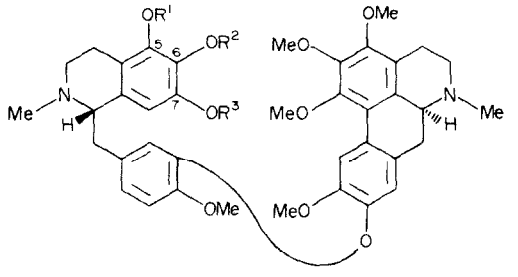
12 $R^1 = Me$; $R^2 + R^3 = CH_2$
15 $R^1 + R^2 = CH_2$; $R^3 = Me$



13 $R^1 = Me$; $R^2 + R^3 = CH_2$
16 $R^1 + R^2 = CH_2$; $R^3 = Me$



17 **18**



2 $R^1 = Me$; $R^2 + R^3 = CH_2$
3 $R^1 + R^2 = CH_2$; $R^3 = Me$

EXPERIMENTAL

General. Methods and equipment used have been described previously [15], with the exception of the utilization of a Bruker Model AF 300, Fourier Transform ^1H NMR spectrometer (300 MHz).

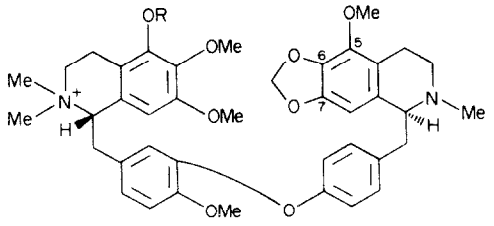
Preparation of N-[2-*methoxy*-3,4-(*methylenedioxy*)-*phenethyl*] *formamide* (**11**). β-[2-methoxy-3,4-methylenedioxy-phenyl]-Ethylamine (17 g, 0.09 mol) [13] was refluxed with HCOOH (98%) (17 ml) (0.45 mol) for 16 hr. The mixture was cooled to room temp., poured into ice-H_2O (140 ml), and extracted with C_6H_6 (5 × 100 ml). The C_6H_6 extracts were combined, washed with H_2O (500 ml), dried ($MgSO_4$), filtered and evapd to afford a brown crystalline residue (13 g, 67%). Recrystallization of this solid from petrol–C_6H_6 gave white crystals of the amide **11**, mp 85–87°, UV λ_{max}^{MeOH} nm (log ε): 276 (3.04); IR ν_{max}^{KBr} cm^{-1}: 3310, 1655, 1470, 1463, 1390, 1360, 1255, 1225, 1200, 1182, 1065, 1042, 998, 971, 935, 905, 785, 775, 750, 710, and 630; ^1H NMR (300 MHz, $CDCl_3$): δ2.77 (2H, *m*, CH_2CH_2N), 3.45 (2H, *m*,

Table 1. A comparison of the physicochemical and spectral properties of synthetic 1-oxo-2-methyl-5-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**1**) and synthetic 1-oxo-2-methyl-5,6-methylenedioxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**4**) with corresponding literature values of thalflavine

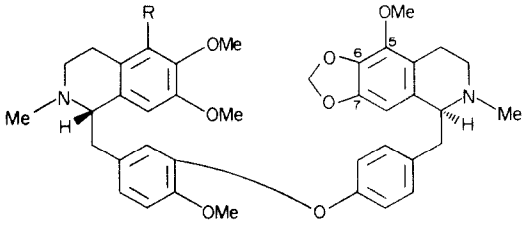
Isoquinolone **1**	Isoquinolone **4**	Thalflavine
Mp 50–52° (petrol–C_6H_6)	141–142° (petrol–C_6H_6)	132–133° (Me_2CO) [1] 136–137° (MeOH) [4] 136–137° [5] 137–139° ($CHCl_3$) [3] 140° (MeOH) [9] 140° [8]
UV λ_{max}^{MeOH} nm (log ε): 306 (sh) (3.22), 274 (3.64), 224 (4.3)	λ_{max}^{MeOH} nm (log ε): 278 (3.96), 264 (sh) (3.90), 216 (4.59)	λ_{max}^{MeOH} nm (log ε): 280 (4.13), 216 (4.64) [4]
IR ν_{max}^{KBr} cm^{-1}: 1645	ν_{max}^{KBr} cm^{-1}: 1625	1625 cm^{-1} [1] ν_{max}^{KBr} cm^{-1}: 1640, 1600, 1500, 1035, 940 [4]
^{1}H NMR ($CDCl_3$): δ3.11 (3H, *s*, NMe) 4.00 (3H, *s*, OMe) 5.97 (2H, *s*, CH_2O_2) 7.60 (1H, *s*, H-8) 2.89 (2H, *t*, J = 7.5 Hz) 3.48 (2H, *t*, J = 7.5 Hz)	($CDCl_3$): δ3.14 (3H, *s*, NMe) 3.92 (3H, *s*, OMe) 6.06 (2H, *s*, CH_2O_2) 7.39 (1H, *s*, H-8) 2.88 (2H, *t*, J = 6.8 Hz) 3.54 (2H, *t*, J = 6.8 Hz)	($CDCl_3$): δ3.13 (3H, *s*, NMe) [4] 3.92 (3H, *s*, OMe) [4] 6.03 (2H, *s*, CH_2O_2) [4] 7.40 (1H, *s*, H-8) [4] 2.86 (2H, *t*, J = 6.5 Hz) [4] 3.54 (2H, *t*, J = 6.5 Hz) [4] δ3.05 (3H, *s*, NMe) [1] 3.84 (3H, *s*, OMe) [1] 5.95 (2H, *s*, CH_2O_2) [1] 7.32 (1H, *s*, H-8) [1] 2.77 (2H, *t*, J = 7 Hz) [1] 3.95 (2H, *t*, J = 7 Hz) [1]
EIMS (cap. GC) 70 eV, *m/z* (rel. int.): 235 $[M]^+$ (100) 192 (88) 164 (65) 163 (38) 147 (5) 134 (23)	EIMS (cap. GC) 70 eV, *m/z* (rel. int.): 235 $[M]^+$ (90) 192 (100) 164 (97) 163 (2) 147 (3) 134 (3)	EIMS *m/z* (rel. int.) [4]: 235 $[M]^+$ (85) 192 (100) 164 (79) — — 134 (2) other ions include 204 (2), 149 (2), 121 (2), 119 (2), 106 (2), 91 (3), 63 (7), 44 (6) *m/z* (rel. int.) [1]: 235 $[M]^+$ (100) 192 (95) 164 (88) other ions include 150 (17), 117.5 (5)

CH_2CH_2N), 4.01 (3H, *s*, OMe), 6.48 (1H, *d*, J = 7.8 Hz, ArH), 5.92 (2H, *s*, CH_2O_2), 6.60 (1H, *d*, J = 7.8 Hz, ArH), 8.12 (1H, *s*, NCHO); ^{13}C NMR (25.15, $CDCl_3$): δ29.8, 38.6, 59.4, 100.7, 102.4, 122.6, 123.7, 136.3, 141.6, 148.1, and 161.1; EIMS (probe), *m/z* (rel. int.): 223 $[M]^+$ (18), 178 (100), 165 (95), 150 (15), 135 (11), and 120 (6).

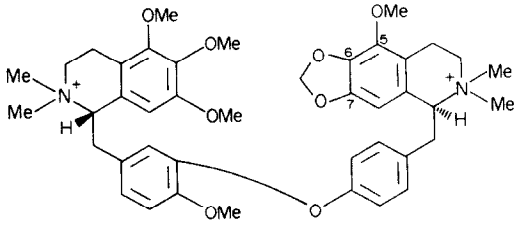
Preparation of 5-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinoline (**12**). *N*-[2-methoxy-3,4-(methylenedioxy)-phenethyl]Formamide (**11**) (12 g, 0.05 mol) was refluxed with $POCl_3$ (36 ml, 59.2 g, 0.39 mol) for 45 min. The mixture was cooled to room temp., placed in an ice bath, and ice (100 g) gradually added over a period of 10 min. The resulting soln was



5 R = Me
10 R = H



6 R = H
7 R = OH
8 R = OMe



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extracted with Et_2O (3 × 150 ml), basified with NH_4OH to pH 8–9 and re-extracted with Et_2O (5 × 150 ml). The combined Et_2O extracts were dried ($MgSO_4$), filtered, and evapd to leave a pale-brown residue (2 g, 18%) which resisted all attempts at crystallization. The residue was subsequently dissolved in EtOH (20 ml) to which was added a soln of oxalic acid (0.88 g) in EtOH (20 ml). A white ppt. of the imine oxalate formed immediately and was filtered by suction and recrystallized from hot EtOH to yield white micro-crystals of 5-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinoline (**12**) oxalate, mp 194–196°, UV λ_{max}^{MeOH} nm (log ε): 295 (4.04), 240 (sh) (4.04), and 215 (4.40); $\lambda_{max}^{MeOH+HCl}$ nm (log ε): 354 (4.21), 248 (sh) (3.95), 235 (sh) (4.15), and 220 (sh) (4.24); IR ν_{max}^{KBr} cm^{-1}: 1630, 1610, 1565, 1490, 1470, 1440, 1300, 1260, 1247, 1220, 1180, 1070, 1045, 985, 975, 930, 880, 800, 780, and 760; ^1H NMR (90 MHz, $CDCl_3$) (imine base): δ 2.68 (2H, *t*, *J* = 8.1 Hz, H-4), 3.72 (2H, *dt*, *J* = 2.7, 8.1 Hz, H-3), 4.05 (3H, *s*, OMe), 6.01 (2H, *s*, CH_2O_2), 6.57 (1H, *s*, H-8), 8.17 (1H, *s*, H-1); ^{13}C NMR (25.15 MHz, $CDCl_3$) (imine base): δ 18.6, 47.0, 59.6, 101.2, 102.2, 122.7, 123.0, 138.5, 140.0, 147.8, and 159.3; EIMS (probe), *m/z* (rel. int.): 205 $[M]^+$ (100), 204 (47), 189 (28), 178 (12), 174 (10), and 160 (8).

Preparation of 5-*methoxy*-6,7-*methylenedioxy*-3,4-*dihydroisoquinoline methiodide* (**13**). To 5-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinoline (**12**) (1.3 g, 0.006 mol) in Et_2O (15 ml) was added MeI (1.6 ml, 3.65 g, 0.026 mol) and the reaction mixture was allowed to stand for 16 hr at room temp. The yellow, crystalline mass which formed was filtered by suction, rinsed with Et_2O, and crystallized from Me_2CO to afford the methiodide salt **13** as a fine yellow powder (1.2 g, 55%), mp 206–207°, UV λ_{max}^{MeOH} nm (log ε): 342 (4.08), 240 (sh) (4.30), 217 (4.57); IR ν_{max}^{KBr} cm^{-1}: 1675, 1605, 1490, 1460, 1400, 1355, 1330, 1307, 1260, 1240, 1220, 1190, 1165, 1075, 1045, 1000, 965, 940, and 915; ^1H NMR (90 MHz, MeOH-d_4): δ 3.72 (3H, *s*, N^+Me), 4.00 (3H, *s*, OMe), 6.18 (2H, *s*, CH_2O_2), 7.00 (1H, *s*, H-8), 8.82 (1H, *br s*, H-1); ^{13}C NMR (25.15, MeOH-d_4): δ 20.7, 47.8, 50.9, 60.7, 104.7, 107.9, 119.9, 125.9, 141.7, 146.4, 150.6, and 166.3; FABMS, *m/z* (rel. int.): 220 $[M]^+$ (42) and 207 (22).

Preparation of 1-*oxo*-2-*methyl*-5-*methoxy*-6,7-*methylenedioxy*-1,2,3,4-*tetrahydroisoquinoline* (**1**). To 5-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinoline methiodide (**13**) (0.211 g, 0.0006 mol) dissolved in H_2O (12 ml) was added by dropwise addition over 45 min at a temp. of 8–10° a soln of $K_3Fe(CN)_6$ (1.12 g, 0.0034 mol) dissolved in a soln of KOH (10%) (8 ml). The reaction mixture was stirred an additional 30 min at 8–10°, allowed to warm to room temp., and shaken with Et_2O (5 × 100 ml). The Et_2O solns were combined, shaken with H_2O (2 × 500 ml), then HCl (5%) (2 × 500 ml), and finally H_2O again (2 × 500 ml). The Et_2O soln was dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to leave a viscous yellow oil which deposited crystals on standing overnight. The crystalline material was recrystallized from petrol–C_6H_6 to afford isoquinolone **1** as feathery rosette crystals (0.107 g, 75%), mp 50–52°; UV λ_{max}^{MeOH} nm (log ε): 304 (sh) (3.27), 271 (3.93), and 217 (4.36); IR ν_{max}^{KBr} cm^{-1}: 1645, 1610, 1500, 1470, 1440, 1400, 1378, 1341, 1290, 1282, 1225, 1205, 1185, 1080, 1045, 980, 958, 930, 886, 870, 798, 782, 770, 760, 745, 740, 715, and 692; ^1H NMR (300 MHz, $CDCl_3$): δ 2.89 (2H, *t*, *J* = 7.5 Hz, H-4), 3.11 (3H, *s*, NMe), 3.48 (2H, *t*, *J* = 7.5 Hz, H-3), 4.00 (3H, *s*, OMe), 5.97 (2H, *s*, CH_2O_2), and 7.60 (1H, *s*, H-8); ^{13}C NMR (25.15 MHz, $CDCl_3$): δ 21.5, 35.1, 48.0, 59.7, 101.3, 102.6, 124.0, 125.1, 138.9, 139.0, 148.0, and 164.4; EIMS (capillary GC), *m/z* (rel. int.): 235 $[M]^+$ (100), 192 (88), 164 (65), 163 (38), 134 (23); High resolution MS: *m/z* 235.0845 (observed) and 235.0845 (calculated) for $C_{12}H_{13}O_4N$.

Preparation of N-[2,3-*methylenedioxy*-4-*methoxy*-*phenethyl*] *formamide* (**14**). β-[2,3-methylenedioxy-4-methoxy-phenyl]-Ethylamine (10 g, 0.05 mol), mp 62–65°, oxalate salt mp 211–213°, prepared in a like manner to β-[2-methoxy-3,4-methylenedioxy-phenyl]-ethylamine [13], was refluxed with HCOOH (98%) (12 ml) (0.26 mol) for 22 hr. The mixture was cooled to room temp., poured into ice-H_2O (100 ml), and extracted with C_6H_6 (3 × 100 ml). The C_6H_6 extracts were combined, washed with H_2O (300 ml), dried ($MgSO_4$), filtered and evad to afford a semi-crystalline residue (5.3 g, 46%). Recrystallization of this residue from petrol–C_6H_6 afforded white crystals of the amide **14**, mp 115–116°, UV λ_{max}^{MeOH} nm (log ε): 273 (3.05); IR ν_{max}^{KBr} cm^{-1}: 3280, 1630, 1505, 1460, 1440, 1380, 1350, 1305, 1290, 1280, 1260, 1205, 1190, 1175, 1165, 1110, 1100, 1055, 1035, 978, 960, 910, 790, 750, 740, and 660; ^1H NMR (90 MHz, $CDCl_3$): δ 2.79 (2H, *m*, CH_2CH_2N), 3.54 (2H, *m*, CH_2CH_2N), 3.88 (3H, *s*, OMe), 5.96 (2H, *s*, CH_2O_2), 6.47 (1H, *d*, *J* = 8.2 Hz), 6.66 (1H, *d*, *J* = 8.2 Hz), 8.11 (1H, *s*, NCHO); ^{13}C NMR (25.15, $CDCl_3$): δ 29.0, 37.8, 56.5, 101.0, 107.6, 113.3, 122.8, 134.8, 142.7, 146.8, and 161.2; EIMS (probe), *m/z* (rel. int.): 223 $[M]^+$ (23), 178 (100), 165 (95), 150 (10), 135 (2), and 120 (11).

Preparation of 5,6-*methylenedioxy*-7-*methoxy*-3,4-*dihydroisoquinoline* (**15**). *N*-[2,3-methylenedioxy-4-methoxy-phenyethyl]Formamide (**14**) (0.6 g, 2.69 mmol) was refluxed with $POCl_3$ (9.87 g, 64 mmol) for 45 min. The mixture was cooled to room temp. and treated with ice-H_2O (30 ml). The resulting soln was extracted with Et_2O (3 × 30 ml), basified with NH_4OH to pH 8–9 and re-extracted with Et_2O (3 × 100 ml). The combined Et_2O extracts were dried ($MgSO_4$), filtered, and evaporated to

leave a crystalline residue (0.26 g, 47%). Recrystallization of this residue from C_6H_6–Me_2CO afforded colourless needles of imine **15**, mp 98–100°, UV λ_{max}^{MeOH} nm (log ε): 295 (3.94), 241 (sh) (3.98), and 226 (4.30); $\lambda_{max}^{MeOH+HCl}$ nm (log ε): 355 (4.06), 236 (sh) (4.02), and 220 (sh) (4.12); IR ν_{max}^{KBr} cm^{-1}: 1645, 1600, 1505, 1440, 1409, 1379, 1351, 1341, 1315, 1245, 1210, 1195, 1189, 1142, 1135, 1075, 1045, 1008, 975, 950, 925, 911, 901, 843, 817, 765, 741, 720, and 675; ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.64 (2H, *t*, *J* = 8.1 Hz, H-4), 3.74 (2H, *m*, H-3), 3.89 (3H, *s*, OMe), 6.03 (2H, *s*, CH_2O_2), 6.52 (1H, *s*, H-8), and 8.20 (1H, *br s*, H-1); ^{13}C NMR (25.15 MHz, $CDCl_3$): δ 18.2, 46.5, 56.8, 102.1, 108.1, 110.6, 123.4, 137.8, 142.4, 145.2, and 159.2; EIMS (probe), *m/z* (rel. int.): 205 $[M]^+$ (100), 204 (61), 189 (7), 178 (13), 174 (2), 160 (8).

Preparation of 5,6-*methylenedioxy*-7-*methoxy*-3,4-*dihydroisoquinoline methiodide* (**16**). To 5,6-methylenedioxy-7-methoxy-3,4-dihydroisoquinoline (**15**) (0.607 g, 2.96 mmol) in Me_2CO (10 ml) was added MeI (2 ml, 4.56 g, 32.1 mmol) and the reaction mixture was allowed to stand for 16 hr at room temp. The yellow crystalline mass which formed was filtered by suction, rinsed with cold Me_2CO, and crystallized from Me_2CO to afford the methiodide salt **16** as fine, yellow needles (560 mg, 55%), mp 217–219°, UV λ_{max}^{MeOH} nm (log ε): 357 (4.09) and 219 (4.37); IR ν_{max}^{KBr} cm^{-1}: 1655, 1638, 1595, 1510, 1490, 1445, 1408, 1358, 1325, 1210, 1195, 1163, 1142, 1072, 1040, 1006, 968, 937, 896, 875, 750, 740, and 680; ^{1}H NMR (300 MHz, MeOH-d_4): δ 3.73 (3H, *s*, N^+Me), 3.95 (3H, *s*, OMe), 6.25 (2H, *s*, CH_2O_2), 7.24 (1H, *s*, H-8), 8.86 (1H, *s*, H-1); FABMS, *m/z* (rel. int.): 220 $[M]^+$ (65) and 207 (15).

Preparation of 1-*oxo*-2-*methyl*-5,6-*methylenedioxy*-7-*methoxy*-1,2,3,4-*tetrahydroisoquinoline* (**4**). To 5,6-methylenedioxy-7-methoxy-3,4-dihydroisoquinoline methiodide (**16**) (0.06 g, 0.173 mmol) dissolved in H_2O (5 ml) was added by dropwise addition over 40 min at a temp. of 8–10° a soln of $K_3Fe(CN)_6$ (0.33 g, 1.00 mmol) dissolved in a soln of KOH (10%) (2 ml). The reaction mixture was stirred an additional 30 min at 8–10°, allowed to warm to room temp., and shaken with Et_2O (3 × 100 ml). The Et_2O solns were combined, shaken with H_2O (2 × 300 ml), then HCl (5%) (2 × 300 ml), and finally H_2O (2 × 300 ml). The Et_2O soln was dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to leave a crystalline residue which was recrystallized from petrol–C_6H_6 to afford colourless needles (35 mg, of isoquinolone **4**, mp 141–142°; UV λ_{max}^{MeOH} nm (log ε): 278 (3.96), 264 (3.90), and 216 (4.59); IR ν_{max}^{KBr} cm^{-1}: 2920, 2855, 1620, 1605, 1490, 1463, 1443, 1398, 1360, 1338, 1315, 1257, 1204, 1190, 1135, 1083, 1035, 975, 964, 950, 935, 895, 862, 790, 763, 740, 708, 684, and 640; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.88 (2H, *t*, *J* = 6.8 Hz, H-4), 3.14 (3H, *s*, NMe), 3.54 (2H, *t*, *J* = 6.8 Hz, H-3), 3.92 (3H, *s*, OMe), 6.06 (2H, *s*, CH_2O_2), and 7.39 (1H, *s*, H-8); ^{13}C NMR (25.15 MHz, $CDCl_3$): δ 21.1, 35.5, 48.1, 56.5, 102.4, 107.7, 113.0, 123.9, 138.0, 142.7, 144.7, and 164.5; EIMS (capillary GC), *m/z* (rel. int.): 235 $[M]^+$ (90), 192 (100), 164 (97), 163 (2), 147 (3), and 134 (3); High resolution MS: *m/z* 235.0844 (observed) and 235.0845 (calculated) for $C_{12}H_{13}O_4N$.

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