

SYNTHESIS OF THE ALKALOIDS LAURIFONINE AND LAURIFINE USING A CHLOROFORMATE-MEDIATED RING EXPANSION

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Abstract — A convenient synthesis of the reduced dibenz[d,f]azonine ring system is described affording laurifonine in 29% overall yield from homoveratrylamine. The alkaloid laurifine is also accessible in 15% overall yield (as the oxalate salt) by the same route, which employs a methyl chloroformate-induced ring expansion of an erythrinan-3-one derivative.

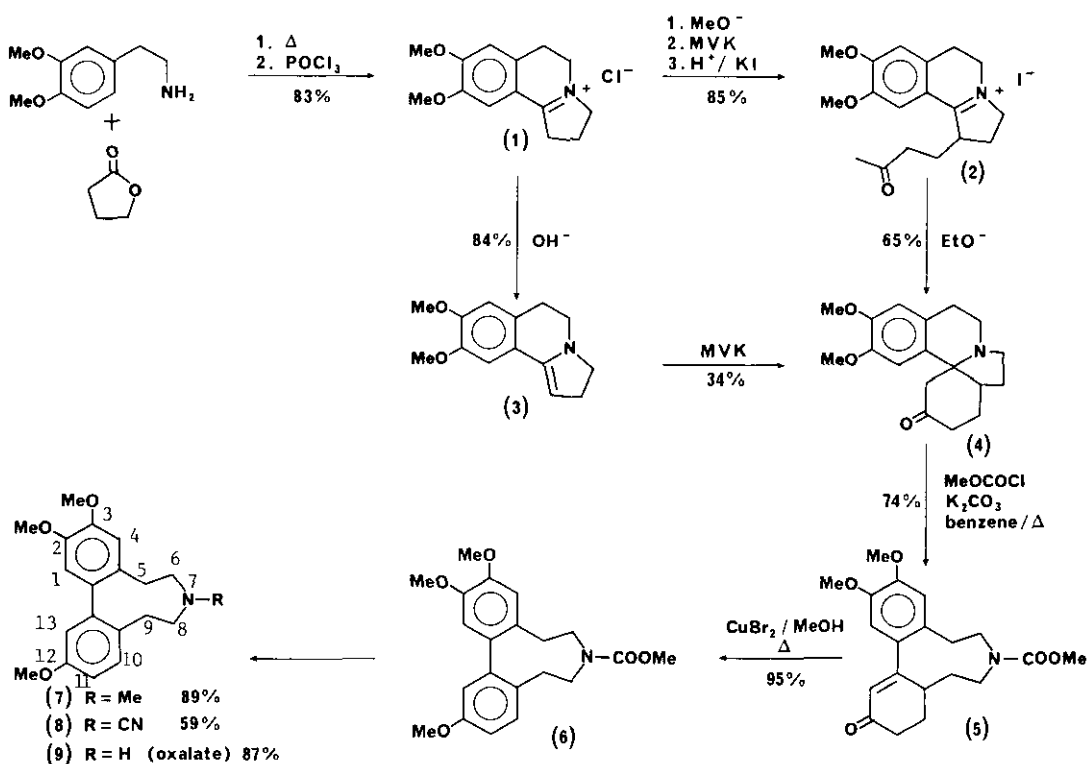
The dibenz[d,f]azonine alkaloids¹ and related derivatives² have attracted considerable synthetic attention. Amongst the alkaloids, routes to protostephanine³⁻⁷, erybidine^{8,9}, laurifonine^{10,11}, laurifine^{11,26}, laurifinine¹¹, neodihydrothebaine²⁴, and bractazonine²⁴ have been described. There is still a need for further convenient syntheses of these alkaloids and derivatives, which are of chemical, biosynthetic^{12,13,24}, and pharmacological^{5,14} interest. We now wish to report a direct synthesis of laurifonine (7) and of laurifine (9) which employs a methyl chloroformate-induced ring expansion of an erythrinan-3-one derivative²⁹.

The synthesis starts from the readily available homoveratrylamine and γ -butyrolactone which may be converted to the known erythrinan-3-one (4)^{15,16} via the iminium salt (1)^{17,18,19} and enamine (3)¹⁶ (Scheme 1). In our hands the procedure of Stevens and Wentland¹⁶ gave only a 24% overall yield of (4). Considerable improvement was made by generating the enamine (3) *in situ*, alkylating with methyl vinyl ketone (MVK), and after acid work up, isolating the keto-iminium salt (2)¹⁵. Cyclisation of this salt with sodium ethoxide yielded the erythrinan-3-one (4) in 46% overall yield. This also compares very favourably with Prelog's route¹⁵ which gives a 32% overall yield (as the picrate salt) from homoveratrylamine.

Treatment of the erythrinan-3-one (4) with methyl chloroformate²⁰ in benzene yielded the enone derivative (5) in 74% yield together with starting material (13%) and a minor product whose structure has not been fully elucidated. Aromatisation and concomitant methylation of (5) using copper(II) bromide in methanol²¹ then gave the dibenz[d,f]azonine derivative (6) in excellent

yield. Laurifonine (7) could then be obtained in high yield by reduction of (6) with lithium tetrahydroaluminate. Unfortunately, however, direct conversion of (6) into laurifine (9) could not be achieved in good yield, by any of the wide range of reagents tried²². Consequently, laurifonine was N-demethylated using the von Braun procedure to give the cyanamide (8) which was reduced (LiAlH₄) to laurifine in 52% yield from laurifonine. Thus (7) was obtained in 29% overall yield (six isolable steps) from homoveratrylamine, while (9) was obtained in 15% overall yield (eight isolable steps) as the oxalate salt.

The most direct route to laurifonine is the one via (±)-O-methylflavinantine, in which an overall yield of 63% (as the perchlorate salt) was obtained in three isolable steps from laudanosine^{9,10}. The alternative synthesis described herein, compares favourably however, with that published by Ito *et al.*¹¹, both in overall yield and number of steps; the overall yield of laurifine is also comparable with that from the latter procedure^{11,cf. also 26}.



Scheme 1

Modification of the carbamate functionality, to facilitate its removal in the presence of aromatic methyl ethers, is being investigated as well as the extension of the above synthetic scheme to the preparation of dibenz[d,f]azecine derivatives. An alkaloid containing this ring system has recently been described²³ and synthesised.²⁸

EXPERIMENTAL

Melting points are uncorrected. ^1H NMR spectra were recorded with a Jeol JNM-4H-100, a Bruker HX-270 (A.N.U.), a Bruker CXP-300 (Brisbane NMR Centre), or a Bruker AM 300 WB spectrometer and using tetramethylsilane as internal standard. Mass spectra were determined on a V.G. MM 7070F mass spectrometer. IR spectra were recorded on a Beckman IR33 spectrometer.

2,3,5,6-Tetrahydro-8,9-dimethoxypyrrolo[2,1-a]isoquinoline (3):

A solution of the iminium salt (1)^{18,19} (5.00 g, 18.7 mmol) in water (25 ml) was treated with aqueous NaOH (40%, 25 ml) and the mixture was cooled in ice. The white precipitate was filtered off and washed with ice water (20 ml). The wet solid was dissolved in CH_2Cl_2 (50 ml), dried (Na_2SO_4) and the solvent was removed in vacuo to give the enamine (3) (3.63 g, 15.7 mmol, 84%): mp 99–100°C (lit.²⁵ mp 99–100°C).

2,3,5,6-Tetrahydro-8,9-dimethoxy-1-(3-oxobutyl)-1H-pyrrolo[2,1-a]isoquinolinium Iodide (2):

To a stirred suspension of the iminium salt (1) (26.8 g, 0.10 mol) in MeCN (350 ml) at 0°, under N_2 , was added methanolic NaOMe (46.5 ml, 2.15 M). When the salt had dissolved, methyl vinyl ketone (8.50 ml, 0.105 mol) was added dropwise and the solution was allowed to warm slowly to room temperature. After 1 h the solution was again cooled to 0°C and hydrochloric acid (12.5 ml, 10 M) was added dropwise. The solvent was removed in vacuo and the residue dissolved in water (100 ml). Potassium iodide (25.0 g, 0.15 mol) dissolved in a minimum volume of water was then added and the resulting emulsion was extracted with CH_2Cl_2 (4 x 50 ml). The extracts were dried (Na_2SO_4) and evaporated in vacuo. The residue was recrystallised from EtOH to give the salt (2) as yellow prisms (36.6 g, 0.085 mol, 85%): mp 199–202°C (lit.¹⁵ mp 210–212°C, MeOH); IR (nujol): 1695, 1640, 1600, 1565, 1520 cm^{-1} ; Anal. Found: C, 50.15; H, 5.51; N, 3.25. Calcd. for $\text{C}_{18}\text{H}_{24}\text{NO}_3\text{I}$: C, 50.36; H, 5.64; N, 3.26%.

This procedure worked equally well using enamine prepared separately as described above.

15,16-Dimethoxyerythrinan-3-one (4)

The iminium salt (2) (5.80 g, 13.5 mmol) was placed in a continuous extractor and thereby slowly added to a refluxing solution of sodium (0.67 g, 29.1 mmol) in dry EtOH (60 ml) under N_2 over a period of \approx 1.5 h. Heating was continued for a further 1.5 h and the solution was then left at room temperature for 12 h. The solvent was removed in vacuo and water (10 ml) was added. Extraction with CH_2Cl_2 (3 x 20 ml), drying (Na_2SO_4) and removal of the solvent in vacuo yielded the crude base. Chromatography on silica gel (2% MeOH- CH_2Cl_2) gave the pure amino-ketone (4) which crystallised from diethyl ether as colourless needles (2.64 g, 8.8 mmol, 65%), mp 143–145°C (lit.¹⁶ mp 143–144°C).

The enamine (3) could be converted to the amino-ketone (4) directly using Stevens' procedure¹⁶ (for which precise details are unavailable) as follows:

A solution of enamine (3) (5.4 g, 23.4 mmol) in EtOH (60 ml) was treated with methyl vinyl ketone (2.27 ml, 28.0 mmol) and the solution was refluxed under N₂ for 6 h. After standing at room temperature for 12 h, work up as above yielded the amino-ketone (4) (2.42 g, 8.0 mmol, 34%).

Methyl 4,4a,5,6,8,9-Hexahydro-11,12-dimethoxy-2-oxo-2H-dibenz[d,f]azonine-7(3H)-carboxylate(5)

A mixture of the amino-ketone (4) (0.560 g, 1.86 mmol), finely ground K₂CO₃ (2.56 g, 18.6 mmol), methyl chloroformate (0.72 ml, 9.3 mmol) and dry benzene (20 ml) was refluxed with stirring under N₂ for 8 h. After stirring at room temperature for 12 h the solvent was removed in vacuo and water (20 ml) was added. Extraction with CH₂Cl₂ (3 x 20 ml), drying (Na₂SO₄) and evaporation yielded a gum which was subjected to PTLC on silica gel (1% MeOH-CH₂Cl₂) to give starting material (72 mg, 0.24 mmol, 13%) and the desired enone (5) (0.491 g, 1.37 mmol, 74%) as a gum which could not be crystallised; IR (neat): 1697, 1673 cm⁻¹; ¹H NMR (300 MHz, AM 300 WB, toluene-D₈, 100°C): δ 6.50 (s, 1H), 6.41 (s, 1H), 5.78 (d, 1H, J = 1.4 Hz), 3.54, 3.49, 3.37 3 x (s, 3H), 3.30-1.40 (complex m, 13H); MS: M⁺ 359 (100%) (accurate mass 359.1726. C₂₀H₂₅NO₅ requires 359.1732), 257 (55), 164 (45), 102 (38).

Methyl 8,9-Dihydro-2,3,12-trimethoxy-5H-dibenz[d,f]azonine-7(6H)-carboxylate(6)

The enone (5) (0.310 g, 0.86 mmol) and copper(II) bromide (1.00 g, 4.46 mmol) was refluxed for 1.5 h in MeOH (20 ml). The solution was evaporated to about 1 ml (at <30°C) and saturated ammonium chloride solution (20 ml, pH 10) was added. Extraction with CH₂Cl₂ (3 x 20 ml), drying (Na₂SO₄) and evaporation yielded pure carbamate (6) (0.304 g, 0.82 mmol, 95%) as a gum which could not be induced to crystallise; IR (neat): 1698 cm⁻¹; ¹H NMR (100 MHz, CDCl₃): δ 7.20-6.50 (m, 5H), 3.87, 3.78, 3.74, 3.50 4 x (s, 3H), 3.50-3.00 (m, 4H); 3.00-2.10 (m, 4H); MS: M⁺ 371 (95%) (accurate mass 371.1747. C₂₁H₂₅NO₅ requires 371.1732), 269 (100).

Laurifonine (7)

The carbamate (6) (0.238 g, 0.64 mmol) dissolved in dry tetrahydrofuran (15 ml) was treated with LiAlH₄ (0.30 g, 7.9 mmol) and the mixture was refluxed for 1.5 h. Work up yielded an oil which after PTLC on 0.5M KOH-silica gel (5% MeOH-CH₂Cl₂) yielded laurifonine (7) (0.186 g, 0.57 mmol, 89%) as a colourless gum which exhibited spectroscopic properties (IR, ¹H NMR-100 MHz) identical with those obtained from an authentic sample¹¹. Further proof of structure was obtained by conversion to the perchlorate salt. Recrystallisation from MeOH-diethyl ether gave colourless prisms (0.224 mg, 0.52 mmol, 92%), mp 190-192°C undepressed upon admixture with an authentic sample¹¹ of the salt.

8,9-Dihydro-2,3,12-trimethoxy-5H-dibenz[d,f]azonine-7(6H)-carbonitrile (8)

To a solution of laurifonine (7) (0.660 g, 2.02 mmol) in CH₂Cl₂ (20 ml) was added cyanogen bromide (0.60 g, 5.7 mmol). After stirring at room temperature for 24 h, evaporation in vacuo, followed by passage through silica gel (10 g, 1% MeOH-CH₂Cl₂) gave the crude cyanamide (0.56 g).

Recrystallisation from MeOH-diethyl ether yielded the cyanamide (8) (0.405 g, 1.20 mmol, 59%) as colourless diamond-shaped prisms, mp 153-154°C; IR (neat): 2200 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.16 (d, 1H, $J = 8.4$ Hz), 6.89 (dd, 1H, $J = 8.4, 2.8$ Hz), 6.71 (s, 1H), 6.705 (d, 1H, $J = 2.8$ Hz), 6.64 (s, 1H), 3.92, 3.88, 3.81 (3s, 3H each), 3.07-3.37 (m, 4H), 2.45-2.72 (m, 4H); MS: M^+ 338 (100%) (accurate mass 338.1621. $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3$ requires 338.1628), 323 (20), 269 (50). Anal. Found: C, 70.90; H, 6.59; N, 8.28. Calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3$: C, 70.99; H, 6.55; N, 8.28%.

Laurifine (9)

A mixture of cyanamide (8) (0.430 g, 1.27 mmol) and LiAlH_4 (0.40 g, 10.5 mmol) in tetrahydrofuran (20 ml) was refluxed for 2 h. Work up yielded crude laurifine (0.41 g) which was treated with oxalic acid (0.140 g, 1.40 mmol) in MeOH-diethyl ether (10 ml, 1:1), to give laurifine oxalate (0.448 g, 1.11 mmol, 87%) as colourless needles (from CH_3CN -diethyl ether), mp 192-193°C.²⁷

(Anal. Found: C, 63.00; H, 6.34; N, 3.27. Calcd. for $\text{C}_{21}\text{H}_{25}\text{NO}_7$: C, 62.52; H, 6.25; N, 3.47%). Direct comparison of the IR spectrum of the free base liberated from the oxalate salt and that from¹¹ authentic laurifine showed them to be identical, while the ^1H NMR spectrum (100 MHz) of the liberated base was in general agreement with that reported¹⁴ by Pande and Bhakuni. A 300 MHz ^1H NMR spectrum on (9) was also obtained (CDCl_3): δ 7.11 (d, 1H, $J = 8.4$ Hz), 6.87 (dd, 1H, $J = 8.4, 2.7$ Hz), 6.705 (d, 1H, $J = 2.7$ Hz), 6.69 (s, 1H), 6.66 (s, 1H), 3.92, 3.84, 3.80 (3s, 3H each), 3.00-3.15 (m, 2H), 2.55-2.90 (m, 4H), 2.20-2.35 (m, 2H).

ACKNOWLEDGEMENTS

The award of a Commonwealth Postgraduate Research Award (to C.D.) is gratefully acknowledged, together with a grant in support of this work from the Australian Research Grants Scheme.

We thank the Upjohn Company (Kalamazoo, Michigan, U.S.A.) for their support, Mr. J.C. Bignall and Mr. M. Power (Central Science Laboratory of this University) for the determination of the mass spectra, and Mr. C.J. Blake (Australian National University) and the Brisbane NMR Centre (Dr.P. Barron) for some NMR spectra. We also thank Professor L.N. Mander for providing facilities (to J.B.B.) at the Research School of Chemistry (Australian National University), where the draft of this paper was prepared and Professor K. Ito (Meijo University, Nagoya) for spectra and samples.

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Received, 23rd January, 1985