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Stereospecific Synthesis of the Cyclopenta[e]phenanthridine Ring System: Tetracyclic and Pentacyclic Analogues of Cephalotaxus Alkaloids

Martin R. Bryce* and John M. Gardiner
Department of Chemistry, University of Durham, South Road, Durham, DH1 3LE.

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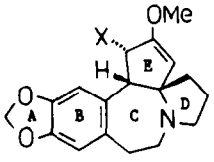
Abstract

Methylenedioxy- and dimethoxy-derivatives of the hexahydrocyclopenta[e]phenanthridine ring system, (21a) and (21b), have been synthesised stereospecifically in six steps starting from piperonal (50% overall yield) and dimethoxybenzaldehyde (27% overall yield), respectively. Piperonal was converted into nitrostyrene derivative (13a) by the known procedure; compound (13a) on reaction with butadiene sulphone afforded the butadiene cycloaddition product (14a) which reacted with methyl acrylate in base to yield nitro-ester (15a) in a stereospecific Michael addition. Reductive cyclisation of compound (15a) using zinc and hydrochloric acid gave spirolactam (16a) which was reduced with lithium aluminium hydride to yield spiropyrrolidine (18a); this compound was converted into the pentacyclic system (21a) by reaction with formaldehyde under Pictet-Spengler conditions. Thiolactam (17a), was obtained from reaction of lactam (16a) and phosphorus pentasulphide, and was methylated with methyl iodide to give lactiminium salt (19a) which reacted with sodium borohydride to yield thiolactim derivative (20a). The route to tetracyclic compound (21b) directly paralleled this sequence.

Introduction

Cephalotaxine (1) is the parent alkaloid produced by conifers of the Cephalotaxus genus which are indigenous to south east Asia.[1] Although compound (1) is biologically inactive, synthetic studies on Cephalotaxus alkaloids have attracted the attention of several research groups since the early 1970s[2-16] motivated by antileukaemic properties of naturally-occurring ester derivatives of compound (1): viz. harringtonine (2), homoharringtonine

(3), deoxyharringtonine (4) and isoharringtonine (5), the structures of which were first elucidated by Powell et al.[17] Recently, interest in these alkaloids has intensified in the light of promising results from phase II clinical trials carried out independently in the United States and in China.[2-4,18] There is impressive activity against colon 38 tumours and some P388 leukaemic lines that are resistant to ellipticine, vincristine and cytosine arabinose (Ara-C).[3]



(1) X = OH Cephalotaxine

(2) X = O-C(=O)-C(OH)(CH$_2$CO$_2$Me)-(CH$_2$)$_2$C(OH)Me$_2$ Harringtonine

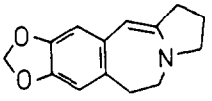
(3) X = O-C(=O)-C(OH)(CH$_2$CO$_2$Me)-(CH$_2$)$_3$C(OH)Me$_2$ Homoharringtonine

(4) X = O-C(=O)-C(OH)(CH$_2$CO$_2$Me)-(CH$_2$)$_2$CHMe$_2$ Deoxyharringtonine

(5) X = O-C(=O)-C(OH)(CH$_2$CO$_2$Me)-(CH$_2$)$_2$CHMe$_2$ Isoharringtonine

(6) X = α-Cl (N.B. Cl is syn to adjacent H)

(7) X = =O Cephalotaxinone



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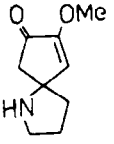

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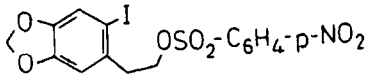

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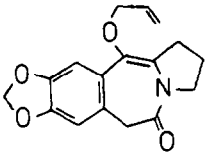


(11)

Stereospecific routes for the conversion of the pharmacologically inactive compound (1) into active harringtonines (2)-(5) have been described in detail[19] and the vast majority of synthetic variations on the structure of (1) concern modifications to the side-chain at C-3; about fifty derivatives have been characterised[20-22] and collated,[2] and seven of these are active against P388 lymphocytic leukaemia in mice.[2] The semi-synthetic derivative (6), with a chlorine atom at C-3, is notable as a derivative lacking the side-chain at C-3, that, nonetheless, shows comparable activity to harringtonine (2) in phase I trials against non-lymphocytic leukaemia.[2] The presence of three contiguous asymmetric centres and a fused azaspiro system, uncommon among natural products, makes the Cephalotaxine skeleton a

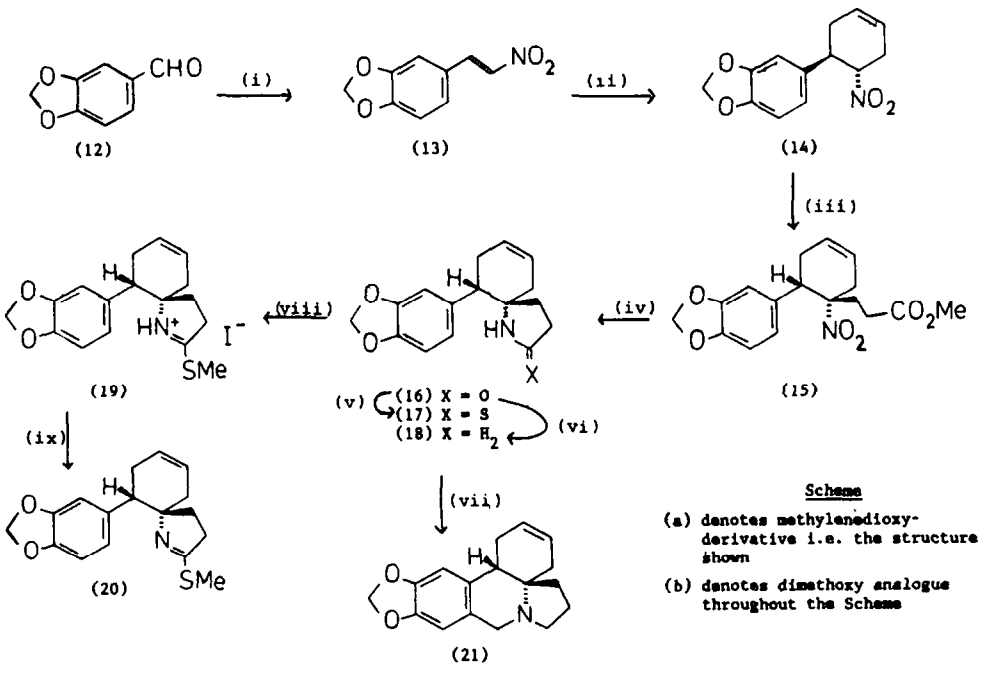
challenging target and three total syntheses have been reported. Weinreb and Auerbach synthesised intermediate (8) in four steps starting from 3,4-methylenedioxyphenylacetyl chloride and l-prolinol and then constructed cyclopentene ring E last via enamine annelation.[5,7] Semmelhack and coworkers, in a completely different approach, preformed spiro ring system (9), in eight steps starting from 2-pyrrolidone, and connected this to a suitably functionalised aromatic ring B of compound (10) and then formed azepine ring C last. They showed that hydride reduction of Cephalotaxinone (7) yielded the correct stereochemistry at C-3 of the natural product.[6,7] The third total synthesis recently reported by Hanaoka and coworkers, proceeds via Claisen rearrangement of the readily-available enol ether intermediate (11) as a key step, followed by final cyclisation to form ring E.[15] Various other partial syntheses of Cephalotaxine and model studies have been published[8-14] but none has brought the target system or any analogous pentacyclic systems clearly within short range.

Results and Discussion

We are exploring an entirely new approach towards Cephalotaxine (1) and analogues with modified pentacyclic skeletons and in a preliminary communication we have outlined our synthesis of a precursor lactam (16a) from nitrostyrene derivative (13a).[23] In this paper we extend this work and detail our route to methylenedioxy- and dimethoxy-derivatives of the cyclopenta[e]-phenanthridine ring system, (21a) and (21b), which are novel pentacyclic and tetracyclic analogues of Cephalotaxine (1). The compounds have been synthesised stereospecifically starting from piperonal (12a) and 3,4-dimethoxybenzaldehyde (12b), respectively, in the six step sequence outlined in the Scheme. The discussion below is largely restricted to the methylenedioxy compounds (12a)-(21a) except where there are notable differences in the spectroscopic properties of the dimethoxy analogues (12b)-(16b), (18b) and (19b); the thio compounds (17b), (19b) and (20b) were not prepared in the dimethoxy series.

Reaction between piperonal (12a) and the anion of nitromethane yielded (methylenedioxy)nitrostyrene derivative (13a) in accord with the literature.[24] Our method for the next step, the conversion of (13a) into (14a), represents a significant improvement over the literature procedure which reports a 72% yield from reaction of compound (13a) and a ten fold excess of butadiene:[25] we find that a five fold excess of butadienesulphone,

the well-known synthon of butadiene,[26] reacted with compound (13a) in a bomb to afford (14a) in 92% yield. In the next step, the anion α to the nitro group of compound (14a) was generated with Triton B and then trapped by addition of methyl acrylate under standard Michael conditions: a single stereoisomeric product (15a) was obtained in over 90% yield. This is the key step in setting up the stereochemistry that is retained in the title ring system (21) and it is the correct stereochemistry, as proved by X-ray analysis of derivative (17a),[23] needed for elaboration of (15) into the natural product system (1). Alkylation of the anion of nitro-compound (14a) was expected to occur with a high degree of stereoselectivity for steric reasons, with attachment of the ester side chain occurring <u>trans</u> to the bulky phenyl group on the adjacent carbon atom.



<u>Reagents, Conditions and % Yields</u>: (i) nitromethane, Na_2CO_3, methylamine hydrochloride, EtOH, 20°C, 70 h (97%). (ii) butadiene sulphone, hydroquinone, toluene, 130°C, 144 h (92%); (iii) methyl acrylate, Triton B, THF-<u>t</u>-BuOH, 20°C, 48 h (92%); (iv) Zn, HCl, EtOH, reflux, 18 h (91%); (v) P_4S_{10}, toluene, reflux 3 h (80%); (vi) $LiAlH_4$, ether, reflux, 96 h (90%); (vii) formaldehyde, 2 M HCl, reflux, 2h (75%); (viii) MeI, THF, 20°C, 12 h (87%); (ix) $NaBH_4$, THF, 20°C, 2 h (47%).

Reductive spirocyclisation of nitro-ester (15a), using activated zinc in ethanolic hydrochloric acid, occurs cleanly to furnish, in one step, γ-lactam (16a) in high yield. The lactam product (16a) was quickly identified from a combination of i.r. data, for which the ester C=O (1735 cm^{-1}) and the NO_2 absorptions of compound (15a) were replaced by lactam NH (3160 cm^{-1}) and C=O (1675 cm^{-1}) absorptions, and from ^1H and ^{13}C nmr spectra: in particular the absence of an ester OMe group in the product and the appearance of a deuterium-exchangeable NH at δ_H 7.6 and a carbonyl absorption at δ_C 178 ppm, both typical of a lactam ring. This two-step sequence, (14) → (16) represents expedient and versatile methodology[27] for the synthesis of 1-azaspirocycles with stereospecificity in the formation of the spiro centre, which is an aspect of heterocyclic synthesis of current interest.[28] For confirmation of the stereochemistry of compounds (16)-(21) a derivative of (16) was prepared that crystallised in a form suitable for X-ray analysis: this was thiolactam (17a), obtained from lactam (16a) by standard thionation using phosphorus pentasulphide.[23]

In the next step lactam (16a) was reduced to pyrrolidine derivative (18a) in high yield with lithium aluminium hydride in ether. This conversion is remarkably slow, four days at reflux being needed to complete the reaction as judged by t.l.c. and infrared spectroscopic analysis of the reaction mixture at regular intervals. Compounds (18a) and (18b) are viscous oils that even when pure as judged by t.l.c. (one spot) and ^1H and ^{13}C n.m.r. spectroscopy(250 MHz), do not always microanalyse correctly; however some samples of amine (18a) are analytically pure, and both (18a) and (18b) have been purified as their hydrochloride salts. Cyclisation of compound (18a) occurred upon reaction with formaldehyde under standard Pictet-Spengler conditions to furnish the pentacyclic compound (21a) as a stable crystalline solid. The overall yield for the six step sequence from compound (12a) → (21a) is 50%. The analogous conversion of dimethoxy-compound (12b) to the tetracyclic compound (21b) has been achieved in 27% overall yield. All analytical and spectroscopic data for the dimethoxy series are consistent with the proposed structures, in agreement with their methylenedioxy partners.

Thiolactam (17a) was smoothly methylated on reaction with methyl iodide, to afford, as expected, thioiminium salt (19a), the structure of which was supported by micro-analytical and spectroscopic data, notably the appearance

of a broad NH absorption in the i.r. spectrum along with a singlet at δ 2.7 in the ^{1}H n.m.r. spectrum (S-CH_3) and a peak at δ 198.5 in the ^{13}C n.m.r. spectrum due to the iminium carbon atom C(2). Reaction of salt (19a) with sodium borohydride in tetrahydrofuran gave lactim thioether (20a) by simple proton abstraction, the imine carbon and S-methyl protons both shifting upfield from their positions for salt (19a), to δ_C 172.3 and δ_H 2.47, respectively. However, in contrast to this, reaction of salt (19a) with either sodium borohydride in methanol, or sodium cyanoborohydride in acidic methanol, gave mixtures of products which were not investigated further. None of these hydride reactions on compound (19a) provided an alternative route to amine (18a), although it is known that other cyclic thioiminium salts are reduced by sodium borohydride and sodium cyanoborohydride to yield amines.[29]

DEPT and SFORD ^{13}C n.m.r. spectra have been obtained for thiolactam (17a) and these assist in the assignments of chemical shifts for many of the compounds in Scheme 1. The peak at δ_C 69.0 ppm for compound (17a) is clearly assigned to the spiro carbon as this peak remains a singlet in the SFORD spectrum and is absent in the DEPT spectrum. The resonance at δ_C 47.7 ppm is assigned to the benzylic carbon on the basis of its appearance as a doublet in the SFORD spectrum and as a tertiary carbon in the DEPT spectrum. The carbon atom of the methylenedioxy group is identified at δ_C 100.7 ppm for compound (17a), occurring as a triplet in the SFORD spectrum and as a secondary carbon in the DEPT spectrum. Moreover, the peak at δ_C ca. 100 ppm observed for all the methylenedioxy compounds in the Scheme is absent in the dimethoxy series and is replaced by a single peak at δ_C ca. 55 ppm from the two OMe carbons which are accidentally equivalent.

Experimental

Melting points were recorded on a Kofler hot-stage microscope apparatus and are uncorrected. Infra-red spectra were obtained on Perkin Elmer 577 and 457 spectrophotometers. N.m.r. spectra were recorded at 250 MHz using a Brucker AC 250 instrument with tetramethylsilane as internal standard. Mass spectra were run on a VG 7070E instrument operating at 70 eV.

Trans-1-(3,4-methylenedioxyphenyl)-2-nitroethene (13a) was prepared following the literature procedure[24a] from piperonal and the anion of nitromethane in 97% yield, m.pt. 161-164°C (from ethanol) (lit.[24b] 158°C).

Trans-1-(3,4-dimethoxyphenyl)-2-nitroethene (13b) prepared analogously to compound (13a) from 3,4-dimethoxybenzaldehyde, was obtained in 92% yield, m.pt. 143-144.5°C (from methanol) (lit.[30] 140°C).

Trans-4-(3,4-methylenedioxyphenyl)-5-nitrocyclohexene (14a). A mixture of compound (13a) (10.0 g, 0.05 mol), butadiene sulphone (31.0 g, 0.25 mol), hydroquinone (0.35 g) and dry toluene (150 ml) was placed in a bomb (400 ml capacity) and heated at 130°C for six days. The crude product mixture was filtered and the filtrate evaporated *in vacuo* to leave a gum which was extracted with boiling ether (ca. 500 ml). This extract was filtered and evaporated and the residue was recrystallised from methanol, with cooling to 0°C, to yield pure product (14a), light tan crystals, (11.8 g, 92%) mp 99-101°C (lit.[25] 97-99°C). Yields are not significantly reduced when the reaction is scaled up three fold.

Trans-4-(3,4-dimethoxyphenyl)-5-nitrocyclohexene (14b) was prepared analogously to (14a), from compound (13b) and butadiene sulphone, and isolated as a light tan crystalline solid, 90% yield (from methanol) mp 115-117°C. (Found: C, 63.8; H, 6.6; N, 4.8; $C_{14}H_{17}NO_4$ requires C, 63.9; H, 6.5; N, 5.3%); *m/z* 263 (EI)(M^+); υ_{max} (KBr) 3050, 2962, 2942, 2920, 2840, 1595, 1545, 1525, 1466, 1448, 1440, 1425, 1375, 1335, 1262, 1240, 1216, 1192, 1150, 1030, 862, 830, 770, 773, 715, 689, 670 and 642 cm^{-1}; $\delta_H(CDCl_3)$ 6.79-6.75 (3H, m), 5.81-5.68 (2H, m), 4.90 (1H, m), 3.85 (3H, s), 3.82 (3H, s), 3.31 (1H, m), 2.76 (2H, m) and 2.43 (2H, m); $\delta_C(CDCl_3)$ 148.8, 148.0, 132.3, 126.3, 122.3, 119.1, 111.2, 110.5, 87.2, 55.5, 43.5, 32.9 and 31.0 ppm.

4-(2-Carbomethoxyethyl)-5-(3,4-methylenedioxyphenyl)-4-nitrocyclohexene (15a) - To a stirred solution of compound (14a) (10.0 g, 0.04 mol) dissolved in a mixture of *t*-butanol (200 ml) and THF (100 ml) was added sequentially methyl acrylate (3.9 g, 0.04 mol) and *N*-benzyltrimethylammonium hydroxide (Triton B) (2.0 ml, 4 mmol). This mixture was stirred at 20°C under nitrogen for 48 h during which time the mixture darkened and some solid precipitated. The solvent was evaporated *in vacuo* and the residue extracted with ether (3 x 300 ml); the extracts were filtered and washed sequentially with (i) dilute hydrochloric acid (300 ml), (ii) 10% sodium hydroxide solution

(300 ml), (iii) water (2 x 300 ml). The ether layer was then dried ($MgSO_4$) and evaporated. Addition of cyclohexane to the resulting solid and/or recrystallisation from methanol afforded product (15a), light tan crystals, (12.3 g, 92%) mp 98-100°C (Found: C, 61.6; H, 5.7; N, 4.0. $C_{17}H_{19}NO_6$ requires C, 61.3; H, 5.7; N, 4.2%) m/z 286 (EI, M^+-NO_2) or 287 (CI), M^+ 333 absent; υ_{max} (nujol) 1735, 1530, 1352, 1315, 1250, 1210, 1180, 1170, 1030, 979, 956, 930, 899, 830, 815, 662 and 646 cm^{-1}; $\delta_H(CDCl_3)$ 6.75-6.60 (3H, m), 5.9 (2H, s), 5.8 (2H, m), 3.7 (3H, s), 3.4 (1H, d, J = 6.9 Hz), 2.8-2.1 (8H, m); $\delta_C(CDCl_3)$ 172.3, 147.6, 146.8, 133.3, 126.0, 124.0, 121.7, 108.1, 107.9, 100.9, 91.9, 51.7, 46.3, 31.9, 30.7, 28.5 and 27.5 ppm.

4-(2-Carbomethoxyethyl)-5-(3,4-dimethoxyphenyl)-4-nitrocyclohexene (15b) - This compound was prepared analogously to (15a), from (14b), and isolated in 75% yield, mp 86-89°C (from methanol). (Found: C, 62.0; H, 6.6; N, 3.5. $C_{18}H_{23}NO_6$ requires C, 61.9; H, 6.6; N, 4.0%); m/z 303 (CI, M^+-NO_2), M^+ 333 absent; υ_{max} (nujol) 1735, 1608, 1586, 1535, 1329, 1298, 1266, 1236, 1205, 1185, 1157, 1149, 1035, 1008, 980, 870, 837, 820, 773, 720 and 663 cm^{-1}; $\delta_H(CDCl_3)$ 6.76-6.74 (3H, m), 5.91-5.81 (2H, m), 3.83 (3H, s), 3.80 (3H, s), 3.67 (3H, s), 3.45 (1H, d, J = 6.3 Hz) and 2.81-2.16 (8H, m); $\delta_C(CDCl_3)$ 172.3, 148.5, 148.3, 132.0, 126.1, 123.9, 120.3, 111.3, 110.8, 91.9, 55.5, 51.7, 46.2, 31.7, 30.7, 28.5 and 27.7 ppm.

6-(3,4-Methylenedioxyphenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (16a) - Nitroester (15a) (24.5 g, 0.07 mol) was dissolved in a mixture of absolute ethanol (600 ml) and concentrated hydrochloric acid (100 ml); to this solution was added, with stirring, zinc dust (80 g) (activated by pretreatment with hydrochloric acid) in portions, causing the temperature of the mixture to rise to ca. 60°C. The mixture was then refluxed with stirring for 15 h, and while still hot, filtered in vacuo yielding a clear green filtrate which was basified with 20% aqueous sodium hydroxide solution (ca. 300 ml) and then refluxed for a further 3 h. The hot, basic solution was filtered and evaporated in vacuo nearly to dryness when the residue was dissolved in water (700 ml) and extracted into chloroform (3 x 300 ml). The organic layer was washed sequentially with (i) 10% aqueous hydrochloric acid (300 ml), (ii) 10% sodium chloride - 10% sodium carbonate solution (300 ml), (iii) water (300 ml) and then dried ($MgSO_4$) and evaporated in vacuo to yield a sticky solid, which, on washing with ether gave compound (16a) as a white

powder (9.6 g, 96% crude yield). Further washing with ether and/or acetone yielded pure compound (16a) (18.1 g, 91%) mp 179-181°C (Found: C, 71.4; H, 6.2; N, 4.7. $C_{16}H_{17}NO_3$ requires C, 70.9; H, 6.3; N, 5.2%); m/z 271 (EI), 272 (CI)(M^+); ν_{max}(nujol) 1675, 1480, 1302, 1255, 1232, 1094, 1033, 931, 852, 845, 820, 815, 766 and 691 cm^{-1}; $\delta_H(CDCl_3)$ 7.58 (NH, s), 6.81 (1H, s), 6.75 (2H, s) 5.90 (2H, s), 5.8-5.6 (2H, m) and 2.8-1.4 (9H, m); $\delta_C(CDCl_3)$ 178.0, 147.2, 146.2, 134.6, 126.9, 124.2, 121.6, 108.6, 107.8, 100.6, 59.9 (spiro-C), 47.9, 39.7, 32.1, 30.0 and 29.8 ppm.

6-(3,4-Dimethoxyphenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (16b) - This compound was prepared from (15b), analogously to compound (16a) and was isolated as a white powder in 72% yield, mp 134-136°C (from acetone). (Found: C, 71.3; H, 7.8; N, 4.4. $C_{17}H_{21}NO_3$ requires C, 71.1; H, 7.3; N, 4.9%) m/z 288 (CI), 287 (EI)(M^+); ν_{max} (KBr) 3160, 3012, 2905, 1690, 1589, 1510, 1460, 1370, 1310, 1265, 1238, 1160, 1141, 1035, 800, 767, 670 and 648 cm^{-1}; $\delta_H(CDCl_3)$ 6.83-6.81 (3H, m), 6.44 (1H, s, NH), 5.86 (1H, m), 5.70 (1H, m), 3.86 (3H, s), 3.85 (3H, s), 2.80 (1H, t, J = 7.7 Hz), 2.5-1.9 (6H, m), 1.85 (1H, m) and 1.45 (1H, m); $\delta_C(CDCl_3)$ 177.8, 148.6, 148.0, 133.3, 127.1, 124.6, 120.8, 111.4, 110.9, 59.8, 55.7, 47.8, 39.7, 32.3 and 30.0 [probably two carbons at δ 30.0, by analogy with compound (16a)].

6-(3,4-Methylenedioxy)-2-thio-1-azaspiro[4.5]dec-8-ene (17a) - To a stirred solution of lactam (16a) (1.4 g, 5.2 mmol) in dry toluene or dry benzene (100 ml) under nitrogen was added phosphorus pentasulphide (3.0 g, 6.5 mmol) and the mixture was heated at reflux for 3 h, then cooled and dilute sodium hydroxide solution added to raise the pH to ca. 9 whence a thick yellow suspension formed. The mixture was extracted into toluene-petroleum ether (bp 40-60°C) (2:1 v/v) (3 x 100 ml) and the combined extracts washed sequentially with 100 ml portions of (i) 10% sodium chloride solution, (ii) 10% sodium carbonate solution and (iii) water, and then dried ($MgSO_4$) and evaporated *in vacuo* to leave a solid which was recrystallised from toluene to afford colourless crystals of compound (17a) (1.15 g, 80%), mp 157-160°C (Found: C, 67.3; H, 6.2; N, 4.7; S, 11.6. $C_{16}H_{17}NO_2S$ requires C, 66.9; H, 5.9; N, 4.9; S, 11.2%) m/z 287 (EI), 288 (CI)(M^+). ν_{max} (KBr) 3130, 1500, 1480, 1238, 1220, 1162, 1045, 942, 858, 781 and 680 cm^{-1} $\delta_H(CDCl_3)$ 9.35 (1H, s, NH), 6.80 (1H, s), 6.75 (2H, s), 5.92 (2H, s), 5.85-5.68 (2H, m) and 2.68-1.82 (9H, m); $\delta_C(CDCl_3)$ 204.7, 147.4, 146.4, 133.7, 127.1, 123.9, 121.6, 108.6, 108.0, 100.7, 69.0, 47.7, 42.4, 38.3, 34.1 and 30.1 ppm.

6-(3,4-Methylenedioxy)-1-azaspiro[4.5]dec-8-ene (18a) - To a stirring suspension of lithium aluminium hydride (3.3 g, 86 mmol) in rigorously dried ether (distilled sequentially from sodium and lithium aluminium hydride) under nitrogen was added lactam (16a) (3.2 g, 11.8 mmol) in portions over 0.5 h at a rate sufficient to maintain gentle reflux. The reaction mixture was then heated and stirred at reflux for 4 days, then cooled and treated with water (6 ml) and 20% sodium hydroxide solution (9 ml). The mixture was warmed to room temperature, filtered and the filtrate washed sequentially with (i) 20% sodium hydroxide solution (50 ml) and (ii) water (50 ml), then dried ($MgSO_4$) and evaporated at reduced pressure to yield compound (18a) as a viscous, pale yellow oil (2.73 g, 90%) [Found: C, 75.2; H, 7.6; N, 5.04, m/z 257.13917, $C_{16}H_{19}NO_2$ requires C, 74.7; H, 7.4; N, 5.45%, m/z 257.14158]: ν_{max} (neat) 3320, 3020, 2960, 2895, 2830, 1608, 1505, 1487, 1437, 1409, 1373, 1332, 1292, 1245, 1125, 1110, 1046, 940, 870, 812, 730, 666 and 560 cm^{-1}; $\delta_H(CDCl_3)$ 6.97 (1H, s, NH), 6.8-6.7 (3H, m), 5.89 (2H,s), 5.84 (1H, m), 5.69 (1H, m), 2.94 (2H, t, J = 6.42 Hz), 2.74 (1H, t, J = 6.03 Hz), 2.4 (2H, m), 2.07 (2H, m) and 1.8-1.5 (4H, m); $\delta_C(CDCl_3)$ 147.3, 146.0, 137.8, 127.5, 126.1, 121.9, 109.0, 107.6, 100.7, 62.0, 47.2, 45.0, 37.4, 36.7, 31.6 and 24.9 ppm.

The hydrochloride salt of amine (18a) was obtained from the amine and 5 M hydrochloric acid after 0.5 h at room temperature, as a white solid, mp ca. 200°C (dec) (Found: C, 65.1; H, 6.5; N, 4.2, $C_{16}H_{20}ClNO_2$ requires C, 65.4; H, 6.8; N, 4.8%).

6-(3,4-Dimethoxy)-1-azaspiro[4.5]dec-8-ene (18b) - This compound was prepared from lactam (16b), under the same conditions as compound (18a), and isolated as an oil (yield varied between 80-90%) (Found: m/z 273.16895, $C_{17}H_{23}NO_2$ requires m/z 273.17288); ν_{max} (neat) 3020, 2940, 2895, 2830, 1587, 1506, 1445, 1260, 1235, 1145, 1033, 810, 766, 695 and 655 cm^{-1}; $\delta_H(CDCl_3)$ 7.04 (1H, s, NH), 6.87-6.74 (3H, m), 5.83 (1H, m), 5.67 (1H, m), 3.83 (6H, s), 2.90 (1H, t, J = 6.39 Hz), 2.74 (1H, t, J = 6.16 Hz), 2.45 (2H, m) and 2.13-1.47 (7H, m); $\delta_C(CDCl_3)$ 147.8, 146.9, 136.1, 127.1, 125.5, 120.4, 111.5, 110.0, 61.4, 55.2, 46.6, 44.5, 37.1, 36.1, 31.1 and 24.3 ppm.

The hydrochloride salt of amine (18b) was prepared from the amine and 5 M hydrochloric acid, white solid, mp ca. 200°C (dec) (Found: C, 65.8; H, 8.2; N, 4.3, $C_{17}H_{24}NO_2Cl$ requires C, 65.9; H, 7.8; N, 4.5%).

6-(3,4-Methylenedioxy)-2-methylthio-1-azaspiro[4.5]deca-1,8-diene hydroiodide (19a) - Thiolactam (17a) (1.53 g, 5.3 mmol) was dissolved in dry THF (130 ml) and methyliodide (6.7 g, 47 mmol) was added with stirring. The solution rapidly turned golden and a precipitate of salt (17a) began to form within 0.5 h. After stirring for 15 h at 20°C the mixture was evaporated in vacuo and the solid was washed with ether (20 ml), filtered and dried to yield compound (19a), a pale yellow solid (1.99 g, 87%) mp 185-186.5°C [Found: C, 47.5; H, 4.5; N, 3.0. $C_{17}H_{20}NSI$ requires C, 47.6; H, 4.7; N, 3.3%] υ_{max} (KBr) 3430 (broad), 3030, 2990, 2910, 2780, 1575, 1505, 1490, 1448, 1240, 1040, 930, 855, 818 and 680 cm^{-1}; $\delta_H(CDCl_3)$ 6.88-6.72 (3H, m), 5.95 (2H, s), 5.82-5.70 (2H, m), 3.4 (1H, m), 3.2 (1H, m), 2.7 (3H, s, $S\underline{CH}_3$), 2.6-1.8 (8H) m; $\delta_C(CDCl_3)$ 198.5 ($\overset{+}{C}$=N), 149.8, 149.0, 134.3, 128.4, 124.3, 123.2, 109.9, 109.5, 102.7, 77.4, 49.6, 38.7, 37.9, 33.4, 30.6 and 16.0 ppm.

6-(3,4-Methylenedioxy)-2-methylthio-1-azaspiro[4.5]deca-1,8-diene (20a) - Salt (19a) (244 mg, 0.56 mmol) was dissolved in dry tetrahydrofuran (100 ml) and sodium borohydride (38 mg, 1.0 mmol) was added. After 2 h when the solution was clear and colourless, 20% sodium hydroxide solution (75 ml) was added and two layers left to separate. The THF layer was collected, dried ($MgSO_4$) and evaporated *in vacuo* to leave a gelatinous, clear oil (80 mg, 47%) (Found: m/z 301.11435, $C_{17}H_{19}NSO_2$ requires m/z 301.11365); υ_{max} ($CDCl_3$-CCl_4) 3020, 2890, 1585, 1500, 1485, 1440, 1315, 1250, 1230, 1100 and 1045 cm^{-1}; $\delta_H(CDCl_3)$ 6.70-6.60 (3H, m), 5.90 (2H, s) 5.91-5.71 (2H, m), 2.80 (1H, m), 2.64 (1H, m), 2.47 (3H, s, S-CH_3), 2.35-2.10 (4H, m), 1.92 (1H, m) and 1.55 (2H, m); $\delta_C(CDCl_3)$ 172.3 (C=N), 147.5, 146.3, 136.5, 127.2, 125.2, 122.2, 109.3, 107.6, 100.8, 77.2, 49.6, 40.3, 38.2, 35.2, 31.1 and 13.7 ppm.

8,9-Methylenedioxy-1,4,4a,5,6,10b-hexahydrocyclopenta[c]penanthridine (21a) - Amine (18a) (3.0 g, 11.7 mmol) was added to a mixture of 37% formalin solution (60 ml) and 20% aqueous hydrochloric acid (120 ml). After 3 h at reflux the mixture was basified with 20% sodium hydroxide solution, extracted into chloroform and the chloroform extract was dried and evaporated to yield a yellow solid which was recrystallised from methanol (addition of water to a saturated methanol solution assisted crystallisation of the product) to yield compound (21a), a white solid, (2.38 g, 75%) mp 88-90°C (Found: C, 76.2; H, 7.2; N, 4.9. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%) m/z 270 (CI)(M^+); υ_{max} (KBr) 3020, 2890, 2770, 1480, 1435, 1365, 1322, 1312, 1270, 1234, 1205,

1158, 1130, 1112, 1040, 932, 845 and 656 cm^{-1}; $\delta_H(CDCl_3)$ 6.97 (1H, s), 6.66 (1H, s), 5.90 (2H, s), 5.65 (1H, m), 5.4 (1H, m), 3.93 (1H, d, J = 13.5 Hz), 3.67 (1H, d, J = 13.5 Hz), 3.10 (1H, m), 2.78-2.54 (4H, m), 1.95-1.86, 3H, m) and 1.64-1.52 (3H, m); δ_C 146.4, 145.3, 132.7, 129.6, 126.6, 123.9, 107.1, 105.6, 100.7, 61.4, 54.6, 53.3, 40.8, 36.6, 33.3, 25.5 and 23.1 ppm.

8,9-Dimethoxy-1,4,4a,5,6,10b-hexahydrocyclopenta[e]phenanthridine (21b) - By analogy with the preparation of compound (21a), amine (18b) yielded compound (21b), 65%, white powder, mp 121-124°C (from methanol-water). (Found: C, 75.4; H, 8.4; N, 4.2, $C_{18}H_{23}NO_2$ requires C, 75.8; H, 8.1; N, 4.9%); m/z 286 (CI)(M^+); υ_{max} (KBr) 1610, 1512, 1464, 1366, 1344, 1320, 1283, 1220, 1208, 1191, 1131, 1120, 1105, 1058, 861, 743 and 669 cm^{-1}; $\delta_H(CDCl_3)$ 6.70 (1H, s), 6.66 (1H, s), 5.63 (1H, m), 5.38 (1H, m), 3.91 (1H, d, J = 13.7 Hz), 3.83 (3H, s), 3.82 (3H, s), 3.75 (1H, d, J = 13.7 Hz), 3.01 (1H, m), 2.87-2.67 (3H, m), 2.54-2.47 (1H, m), 1.93-1.86 (3H, m), 1.66-1.56 (3H, m), $\delta_C(CDCl_3)$ 147.1, 146.5, 130.5, 127.7, 126.0, 123.4, 109.5, 108.1, 60.6, 55.5, 53.5, 52.0, 40.3, 35.9, 30.8, 25.1 and 22.1 ppm.

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