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MODELS OF FOLATE COENZYMES—VIII[1]

AN APPROACH TO YOHIMBANE ALKALOIDS VIA CARBON-FRAGMENT TRANSFER FROM N^5, N^{10}-METHYLENETETRAHYDROFOLATE MODELS

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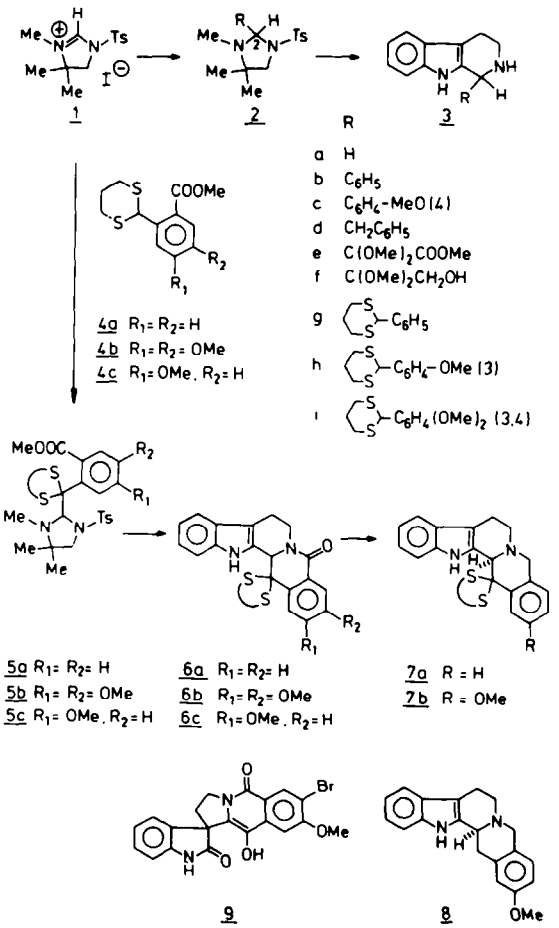
Abstract—2-Substituted 1-tosyl-3,4,4-trimethylimidazolidines, prepared by the addition of anions to 1-tosyl-3,4,4-trimethyl-2-imidazolinium iodide **1**, react with tryptamine in the presence of acetic acid to give 1-substituted β-carboline derivatives. The salt **1** reacts with anions of 2-[2-(1,3-dithianyl)]benzoates **4a–c** to give the corresponding imidazolidines **5a**, **5b** and **5c**, respectively. These transfer the substituted fragment (>CHR) to tryptamine to give pentacyclic products corresponding to the yohimbane skeleton. The product from **5c** yields, after reduction of both the amide and the dithiane function, the precursor of epi- and allo-yohimbanes.

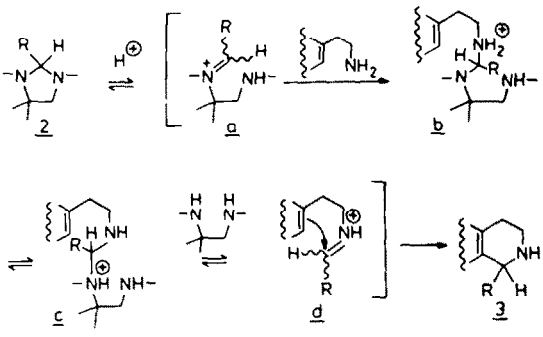
The synthesis of suitably substituted imidazolidine derivatives, which can be regarded as models of the coenzyme N^5,N^{10}-methylenetetrahydrofolate, has been described in the preceding communication.[1] Also, it has been demonstrated that such models are capable of transferring the C-2 group of the imidazolidine to appropriate nucleophiles.[1,3] In this connection, it is noteworthy that reaction of a model with both 6-aminouracil derivatives and indole,[1] led, in each case, to transfer of the methylene unit to two molecules of the heterocyclic nucleophile. This pattern of reaction suggested the opportunity of transferring C-2 with its substituents, to bifunctional nucleophiles, with the objective of synthesizing cyclic products in one practical step.[3] The present communication describes the application of the latter strategy to the synthesis of β-carboline derivatives and its extension to an approach to yohimbane alkaloids.[4]

The starting material for the synthetic methodology outlined above, is the imidazolinium salt **1** (Scheme A), which is conveniently available by the procedure developed in this laboratory.[1] Reaction of **1** with nucleophiles (R^-) gave the corresponding imidazolidine derivatives **2a–e** and **2g–i**. The unsubstituted imidazolidine **2a** was formed by careful reduction of **1** with $NaBH_4$ (1 equiv, 0°). Imidazolidines **2b–d** were obtained by addition of the appropriate Grignard reagent (RMgX) to a suspension of **1** in THF, whereas in the case of **2e** and **2g–i**, salt **1** was added to the required anions (generated by LDA or BuLi, Experimental). Imidazolidine **2f** was obtained by reduction of **2e** with $LiAlH_4$. When a mixture of **2a–i** and tryptamine was refluxed in acetonitrile, in the presence of an acid, the β-carboline derivatives **3a–i** were formed in good yield. The overall reaction represents the transfer of the RCH< fragment (of the imidazolidines) to a position between (the nucleophilic centres), C-2 and the amino group of tryptamine. The reduction of **2e** → **2f** shows that the primary imidazolidine products are capable of further transformation to new synthetically useful intermediates.

The mechanism of carbon-fragment transfer, in the synthesis of the β-carbolines (**3a–i**) is presented to Scheme B. The initial step of the transfer process is the opening of the imidazolidine ring to iminiun ion intermediate **a**. The latter undergoes a nucleophilic attack by the amino group of tryptamine, to yield **b**. Further steps of the reaction, **b** → **c** → **d**, are logical, though speculative, and involve proton transfer, followed by elimination



Scheme A.

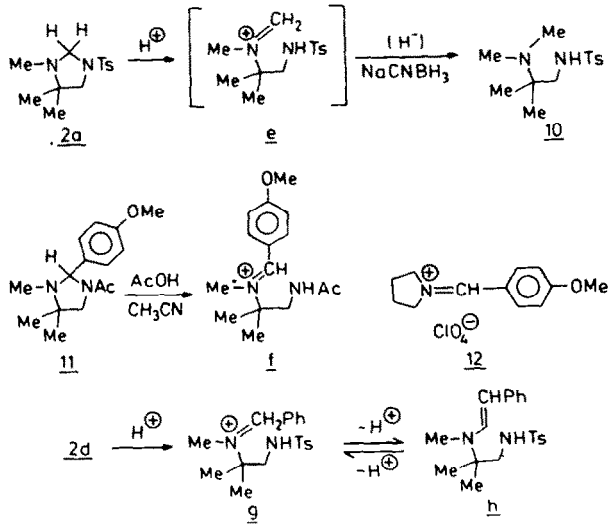


Scheme B.

of an amine moiety. The resulting iminium ion **d** cyclizes to the β-carboline **3** in a manner analogous to the Pictet–Spengler reaction.

The formation of iminium ion **a**, which involves protonation of the less basic nitrogen, but leads to the more stable cation, finds analogy in the lit.[5] and is supported by two further experiments (Scheme C). In one experiment **2a** was allowed to react with acetic acid in the presence of $NaCNBH_3$ (CH_3CN), whereupon a quantitative yield of N,N-dimethyl-N-tosyl-2,2-dimethyl-1,2-diaminoethane **10** was obtained. The formation of **10** involves ion **e** as an obligatory intermediate, which is reduced by $NaCNBH_3$.[3] In the second experiment, imidazolidine **11** was treated with acetic acid, trifluoroacetic acid or perchloric acid (in CH_3CN) at room temperature. In all three cases, a new band at 324 nm (UV spectra) was observed in the mixture. That this band originated from the iminium chromophore in **f** was attested by the presence of the same band in the spectrum of salt **12** (Scheme C).[6] Indirect evidence for an iminium intermediate was derived from the course of the reaction of **2d** with tryptamine. In the presence of acetic acid, only a low yield (~5%) of the corresponding β-carboline (**3d**) was formed. On the other hand, when trifluoroacetic acid was used as the catalyst, the yield of **3d** was increased to 80%. This difference in reactivity is rationalized on the basis of the equilibrium between the initially formed iminium intermediate (**g**, Scheme C) and the stabilized conjugated enamine **h**. It would be expected that the equilibrium **g**⇌**h** is influenced by the strength of the acid. In the presence of a weak acid, such as acetic acid, the enamine **h**, (an unproductive intermediate for the sequence of reactions described in Scheme B) would be the predominant species. Involvement of the latter in side reactions accounts for the observed low yield of **3d**. In trifluoroacetic acid, a high concentration of ion **g** would be formed, which should promote the addition of tryptamine (**a** → **b**, in Scheme B), and the resulting formation of **3d**. At this point we would like to emphasize, that although the transfer reaction (**2** → **3**) is formally analogous to the Pictet–Spengler reaction, it offers several advantages over the latter as a synthetic method. In the first instance, the sequence by which imidazolidines **2** are prepared, allows a wide variation in the nature of the substituent *R* in the "masked" aldehydes. The same aldehydes—required for the Pictet–Spengler synthesis—may be either unaccessible or accessible only with difficulty. Secondly, the imidazolidines can be prepared from the same precursor **1**, which is conveniently available, in large quantities, as a "shelf reagent". Finally, the use of non-aqueous reaction conditions provides practical advantages in terms of the execution of the reaction and its subsequent work-up.

In examining the potential of the coenzyme model approach for the synthesis of indoloquinolizidine alkaloids, attempts were made to prepare imidazolidine **2** incorporating polymethoxybenzyl substituents as the *R* moiety. These were, however, thwarted by the difficulty experienced by us in preparing the required (polymethoxybenzyl) Grignard reagents. The problem was, circumvented by introducing the benzyl groups in a masked form, in **2**, via the use of the 1,3-dithiane derivatives (e.g. **2g–i**). Transfer of the relevant carbon-fragments to tryptamine (formation of **3g-i**) occurred smoothly under the standard conditions (CH_3CN, AcOH, Δ). Encouraged by these results, we undertook the synthesis of imidazolidines, which could transfer (to tryptamine) the entire carbon-fragment required for the construction of the indoloquinolizidine skeleton. The target imidazolidines **5a–e** were prepared in good yields



Scheme C.

(>85%) by the addition of salt **1** to anions of **4a–c**. When **5a–c** were allowed to react with tryptamine (CH_3CN, AcOH, Δ), the pentacyclic indoloquinolizidine derivatives **6a–c** were obtained in one practical step. The structures of the products were attested by their spectral data (vide experimental). Further transformations of the peripheral functions followed conventional procedures. The amide group in **6a,b** was reduced by $LiAlH_4$, to give the trans quinolizidine products **7a,b**; the stereochemistry of the quinolizidine being derived from the IR spectra, which exhibited the characteristic Bohlmann bands.[8] The dithiane group in **7b** was removed by reduction (H_2/Raney-Ni) to yield the known $\Delta^{15,17,19}$-yohimbane system **8**.[9] Since **8** has been converted to epi- and allo-yohimbanes,[9] the present sequence represents a facile approach to these and related compounds. An attempt to remove the dithiane moiety in **7b**, by treatment with N-bromosuccinimide,[10] resulted in a product to which structure **9** has been assigned on the basis of spectral data (IR, NMR, exact MS).

The application of the folate model synthetic methodology to isoquinoline and other indole alkaloids is being vigorously pursued in our laboratory.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on an Unicam SP 200 or Perkin–Elmer 257 spectrometer. The absorptions are given in cm^{-1}. PMR spectra were run on a Varian Associates Model A-60, A-60D and HA-100 instruments. The chemical shifts (δ) are given in ppm using TMS as an internal standard. For the resonance signals the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Spin-spin coupling constants (J) are given in Hertz. Mass spectra were obtained with a Varian Mat-711 spectrometer. Analyses were carried out at the Microanalytical Laboratory, Department of Physical-Organic and Analytical Chemistry, Organic Chemistry Institute, T.N.O. Zeist, The Netherlands.

1-Tosyl-3,4,4-trimethylimidazolidine (**2a**)

The imidazolinium salt **1** (394 mg, 1 mmol) was dissolved in 3 ml of dry EtOH cooled to 0° and 1 equiv of $NaBH_4$ was added to the mixture. After stirring for 2 hr 1 ml of conc. NH_4Cl soln was added and the mixture extracted with $CHCl_3$. After drying ($MgSO_4$) and evaporation of the solvent, the residue was purified by chromatography (SiO_2/EtOAc). Yield: 244 mg of oil (92%). IR ($CHCl_3$): 1600 (w), 1345 (m), 1155 (s). PMR ($CDCl_3$): 0.90 (s, 6H, $C^4(CH_3)_2$), 2.10 (s, 3H, N–CH_3), 2.40 (s, 3H, $ArCH_3$), 3.15 (s, 2H, C^5CH_2), 4.10 (s, 2H, C^2CH_2), 7.40 (d, J = 8 Hz, 2H, C^3H and C^5H Ar), 7.85 (d, J = 8 Hz, 2H, C^2H and C^6H Ar).

Addition of Grignard reagents to salt **1**.[1] *Synthesis of* **2b–d**

The Grignard reagents PhMgBr, 4-(Meo)C_6H_4MgBr and $PhCH_2MgCl$, prepared from the corresponding halides, were added to a suspension of salt **1**, in THF at −60°. In case of the first two reagents the mixture was refluxed for 4 hr, whereas in case of $PhCH_2MgCl$, it was stirred at −78° (15 min) and then further at room temperature. The reactions were quenched by addition of NH_4Cl soln. Products **2b,c** were extracted with $CHCl_3$, while **2d** was extracted with EtOAc. The organic layers were washed with conc. NaCl and dried (Na_2SO_4). Evaporation of the solvent yielded crude **2b–d**. **2b** purification on a thick layer silica gel plate (eluent, EtOAc), yield the pure product. m.p. 111–112°. (29%). IR ($CHCl_3$): 1600, 1500, 1355, 1162. PMR ($CDCl_3$): 0.83, 1.13 (2 × s, 6H, $C(CH_3)_2$), 1.99 (s, 3H, NCH_3), 2.29 (s, 3H, $ArCH_3$), 3.28, 3.62, (2d, s = 10 Hz, 2H, CH_2N), 4.70 (s, 1H, N–CH–N), 6.90–7.60 (m, 9H, AR–H). **2c** (47%) purified on a thick-layer silica gel plate (eluents, cyclohexane/EtOAc, 4 : 1). IR ($CHCl_3$): 1610, 1510, 1340, 1160. PMR ($CDCl_3$): 0.82, 1.2 (2 × s, 6H, $C(CH_3)_2$), 1.95 (s, 3H, NCH_3), 2.32 (s, 3H, $ArCH_3$), 3.25 (d, J = 10 Hz, 1H, CCH–N), 3.40–3.90 (m, 4H, OCH_3, + C–CHN), 4.70 (s, 1H, N–CH–N), 6.60–7.60 (m, 8H, Ar-H). **2d**, crystallized from methanol, m.p. 123–125° (63%). IR ($CHCl_3$): 2980, 1600, 1340, 1160. PMR ($CDCl_3$): 0.33, 0.86 (2 × s, 6H, $C(CH_3)_2$), 2.53, 3.18 (2 × d, J = 11 Hz, 2H, N–CH_2), 3.12 (d, J = 3 Hz, 2H, $ArCH_2$), 4.22 (t, J = 3 Hz, 1H, N–CH–N), 7.30, 7.73 (2 × d, J = 8 Hz, 4H, $SO_2C_6H_4CH_3$), 7.25 (s, 5H, Ar–H). Found: C, 67.17; H, 7.32; N, 7.79; s, 8.78. Calc for $C_{20}H_{26}N_2O_2S$: C, 67.03; H, 7.26; N, 7.82; S, 8.94%.

1-Tosyl-2-(dimethoxycarbomethoxy)methyl-3,4,4-trimethylimidazolidine (**2e**)

4.2 g of diisopropyl amine (41.5 mmole, 5.9 ml) was dissolved in 60 ml of dry THF under nitrogen. The mixture was cooled to −78°. At this temperature 27 ml of a 1.45 N soln of *n*-butyllithium in hexane was added to the mixture and it was stirred for another 5 min. 5.6 g methyl-α,α-dimethoxyacetate dissolved in 10 ml of THF was slowly added to the mixture. After stirring for another 10 min at −78° 16.4 g of **1** (41.5 mmole) were added while the mixture was vigorously stirred. The reaction mixture was then allowed to slowly reach room temperature. Conc NH_4Cl soln was added to the resulting clear soln. The reaction mixture was concentrated to about 20 ml under reduced pressure. The residue was filtered through a column filled with silica-gel using ethylacetate as the eluent. Concentrating the filtrate yielded **2e** as a slowly crystallizing oil which could be recrystallized from methanol. Yield: 11.2 g (67%); m.p. 88–89°. IR ($CHCl_3$): 1750 (s), 1345 (s), 1160 (s); PMR ($CDCl_3$): 1.03 (broad s, 6H, $C(CH_3)_2$), 2.39 (broad s, 6H, NCH_3 and $ArCH_3$), 2.87 (s, 3H, OCH_3), 3.05 (d, J = 10.5 Hz, 1H, C^5H), 3.37 (s, 3H, OCH_3), 3.67 (s, 3H, $COOCH_3$), 3.73 (d, J = 10.5 Hz, 1H, C^5H), 5.73 (s, 1H, C^2H), 7.25 (d, J = 8 Hz, 2H, C^3H- and C^5H-Ar), 7.59 (d, J = 8 Hz, 2H, C^2H- and C^6H-Ar). Found: C, 53.94; H, 7.18; N, 7.00; S, 7.84. Calc for $C_{18}H_{28}N_2O_6S$: C, 54.00; H, 7.00; N, 7.00; S, 8.00%.

General procedure for the synthesis of compounds **2g**, **2h** *and* **2i**

30 mmole of the appropriate 2-aryl-1,3-dithiane were dissolved in 70 ml of freshly distilled THF under nitrogen. The mixture was cooled to −30° and a soln containing 1 equiv of *n*-butyllithium in hexane was added to the mixture. After stirring for about 20 min and keeping the temperature at −30 to −20°, 30 mmole of **1** was added to the mixture at −20°. The reaction mixture was kept at −20° until all the salt had dissolved. The reaction mixture was allowed to reach room temperature and then it was poured directly upon a column containing silicagel. The product was eluted from this column using ethyl acetate as the eluent. Concentrating the filtrate and recrystallization from the appropriate solvent yielded **2g–i** as white crystals.

2-[2-(1-*Tosyl*-3, 4, 4-*trimethylimidazolidinyl*)]*phenyl*-1, 3-*dithiane* (**2g**)

Yield: 10.5 g (76%), m.p. 176–177°, after recrystallization from EtOAc: hexane 1 : 2. IR ($CHCl_3$): 1600 (w), 1335 (m), 1160 (s). PMR (CCl_4): 0.85 (s, 3H, C^4CH_3), 1.02 (s, 3H, C^4CH_3), 1.50–2.70 (m, 7H, 3 × CH_2 dithiane and C^5H), 2.24 (s, 3H, $ArCH_3$), 2.42 (s, 3H, NCH_3), 3.43 (d, J = 11 Hz, 1H, C^5H), 5.00 (s, 1H, C^2H), 7.0–7.45 (m, 5H, ArH), 7.50–7.90 (m, 4H, ArH). Found C, 59.80; H, 6.54; N, 6.05; S, 20.83. Calc for $C_{23}H_{30}N_2S_3O_2$: C, 59.74; H, 6.49; N, 6.06; S, 20.78%.

2[2-(1-*Tosyl*-3,4,4-*trimethylimidazolidinyl*)]-3′-*methoxyphenyl*-1,3-*dithiane* (**2h**)

Yield: 8 g (55%); m.p. 130–131°, after recrystallization from MeOH. IR (KBr): 1595, 1570 (m), 1330 (s), 1150 (s); PMR ($CDCl_3$): 0.90 (s, 3H, C^4CH_3), 1.00 (s, 3H, C^4CH_3), 1.60–2.00 (m, 2H, C^5H_2 dithiane), 2.16 (d, J = 11 Hz, 1H, C^5H), 2.25–2.80 (m, 4H, C^4H_2 and C^6H_2 dithiane), 2.33 (s, 3H, $ArCH_3$), 2.45 (s, 3H, NCH_3), 3.46 (d, J = 11 Hz, 1H, C^5H), 3.74 (s, 3H, OCH_3), 5.14 (s, 1H, C^2H), 6.70–6.90 (m, 1H, C^6H-$ArOCH_3$), 7.05–7.55 (m, 5H, 3 × CH, $ArOCH_3$, C^3H and C^5H-Tos), 7.86 (d, J = 8 Hz, 2H, C^2H and C^6H-Tos). Found: C, 58.36; H, 6.58; N, 5.65; S, 19.47. Calc for $C_{24}H_{32}N_2S_3O_3$: C, 58.53; H, 6.50; N, 5.69; S, 19.51%.

2[2-(1-*Tosyl*-3,4,4-*trimethylimidazolidinyl*)]-3,4-*dimethoxyphenyl*-1,3-*dithiane* (**2i**)

Yield: 8.5 g (54%), m.p. 115–118°, after recrystallization from

methanol. IR (KBr): 1595, 1580 (w), 1330 (s), 1255 (s), 1150 (s); PMR ($CDCl_3$): 0.82 (s, 3H, C^4CH_3), 0.92 (s, 3H, C^4CH_3), 1.50–2.0 (m, 2H, C^5H_2 dithiane), 2.09 (d, J = 11 Hz, 1H, C^5H), 2.20–2.90 (m, 4H, C^4H_2 and C^6H_2 dithiane), 3.35 (d, J = 11 Hz, 1H, C^5H), 5.03 (s, 1H, C^2H), 6.65 (d, J = 9 Hz, 1H, C^6H-, ArOMe), 7.0–7.45 (m, 2H, C^2H- and C^5H-ArOMe), 7.31 (d, J = 8 Hz, 2H, C^3H- and C^5H-Tos), 7.75 (d, J = 8 Hz, 2H, C^2H- and C^6H-Tos). Found: C, 57.39; H, 6.60; N, 5.25; S, 18.33. Calc for $C_{25}H_{34}N_2S_3O_4$: C, 57.47; H, 6.51; N, 5.36; S, 18.39%.

β-Carboline (**3a**)

A mixture of tryptamine (160 mg, 1 mmol), imidazolidine **2a** (268 mg, 1 mmol), acetic acid (1 ml), and acetonitrile (5 ml) was refluxed for 5 hr. The solvent was removed, the residue taken up in $CHCl_3$, washed with $NaHCO_3$ soln, the organic layer dried and evaporated, whereupon a product was obtained, which was crystallized from ether. Yield: 75 mg (43%). IR (KBr): 3300, 3140. PMR (DMSO-d_6): 2.50–2.90 (m, 2H, CH_2), 3.00–3.30 (m, 2H, CH_2), 4.00 (s, 2H, $ArCH_2N$), 4.30 (s, 1H, NH), 6.95–7.60 (m, 4H, AR-H), 10.85 (s, 1H, indole NH). MS (E.I.): 172 (M^+, 40%).

1-*Phenylcarboline* (**3b**)

A mixture of the tosyl compound **2b** (1 mmol), tryptamine (1 mmol), acetic acid (1 ml) in acetonitrile (5 ml) was refluxed for 4 hr. The mixture was evaporated, the residue dissolved in $CHCl_3$, the organic layer washed with $NaHCO_3$ soln, dried and the solvent removed. The crude product was purified by chromatography over thick layer alumina plate (eluent: EtOAc), whereupon **3b** was obtained as a foam: 77 mg (31%). IR ($CHCl_3$): 3480; PMR ($CDCl_3$): 1.30 (s, 1H, NH), 2.65–3.45 (m, 4H, CH_2CH_2), 5.10 (m, 1H, ArCHN), 7.00–7.60 (m, 9H, ArH), 8.10 (s, 1H, indole NH).

1-(*p-Methoxyphenyl*)*carboline*(**3c**)

The carboline **3c** could be prepared in better yield by starting with the N-acetyl analogue of **2c**. A mixture of the acetyl compound (1 mmol), tryptamine (1 mmol), acetic acid (1 ml) in acetonitrile (5 ml) was refluxed overnight. The mixture was evaporated, the residue dissolved in $CHCl_3$, the organic layer washed with $NaHCO_3$ soln, dried and the solvent removed. The crude product was purified by chromatography over thick layer alumina plate (eluent: EtOAc), whereupon **3c** was obtained as a foam: 170 mg (60%). IR ($CHCl_3$): 3490. PMR ($CDCl_3$): 1.75 (s, 1H, NH), 2.65–3.45 (m, 4H, CH_2CH_2), 3.72 (s, 3H, OCH_3), 5.10 (m, 1H, ArCHN), 6.70–7.60 (m, 8H, Ar-H), 7.75 (s, 1H, indole NH). MS (E.I.): 278 (M^+, 100%).

1-*Benzylcarboline* (**3d**)

Tryptamine (160 mg, 1 mmol) and 358 mg of **2d** (1 mmol) were dissolved in 10 ml of dry acetonitrile. After 570 mg of trifluoroacetic acid (5 mmol) had been carefully added to the mixture, it was refluxed under nitrogen until all the starting material had disappeared (~3 hr, TLC, SiO_2/EtOAC). After the solvent had been evaporated the residue was taken up in ethyl acetate and the organic layer was washed several times with conc $NaHCO_3$ soln. Drying over Na_2SO_4 followed by evaporation of the solvent, yielded a residue which was purified by chromatography (SiO_2, EtOAC/CH_2Cl_2 1 : 1). Compound **3d** was isolated as a slightly coloured oil. Yield: 212 mg oil (80%). IR ($CHCl_3$): 3470 (m), 1600 (w); PMR ($CDCl_3$): 1.80 (broad s, 1H, N^2H), 2.50–3.50 (m, 4H, C^3H_2 and C^4H_2), 3.01 (d, J = 7 Hz, 2H, CH_2Ar), 4.33 (t, J = 7 Hz, 1H, C^1H), 6.94–7.73 (m, 10H, 9 × ArH and N^9H).

1-(*Dimethoxycarbomethoxy*)*methylcarboline* (**3e**)

Tryptamine (1.6 g, 10 mmol) and 4 g of **2e** (10 mmol) were dissolved in 40 ml of dry acetonitrile. After 5 ml of acetic acid had been added to the mixture it was refluxed until all the starting material had disappeared (~2 hr, TLC, EtOAc/SiO_2). After the solvent had been evaporated the residue was taken up in ethylacetate and the organic layer was washed with conc $NaHCO_3$ soln. Drying over Na_2SO_4 and evaporation of the solvent yielded a residue which was purified by chromatography (SiO_2, EtOAc). Yield: 2.2 g of light brown oil (73%). IR ($CHCl_3$): 3470 (m), 1750 (s); PMR ($CDCl_3$): 2.12 (s, 1H, N^2H), 2.58–3.10 and 3.25–3.40 (2m, 4H, C^3H_2 and C^4H_2), 3.31 (s, 3H, $COCH_3$), 3.49 (s, 3H, $COCH_3$), 3.68 (s, 3H, $COOCH_3$), 4.60 (broad s, 1H, C^1H), 7.0–7.60 (m, 4H, ArH), 8.53 (broad s, 1H, N^9H).

1[1-(1,1-*Dimethoxy-2-hydroxy*)]*ethylcarboline* (**3f**)

372 milligrams of **2f** (1 mmol) and 160 mg of tryptamine (1 mmol) were dissolved in 10 ml of dry acetonitrile. After 1 ml of acetic acid had been added to the mixture it was refluxed for about 2 hr until all the starting material had disappeared (TLC, SiO_2/EtOAc). After the solvent had been evaporated the residue was taken up in ethylacetate and the organic layer was washed several times with conc. $NaHCO_3$ solution. Drying over Na_2SO_4 and evaporation of the solvent yielded a residue which was purified by chromatography (SiO_2, EtOAc). Yield: 85 mg of a light brown oil (32%). IR ($CHCl_3$): 3480 (m), 2840 (w), 1570 (w), 1135 (s), 1080 (s); PMR ($CDCl_3$): 2.72–4.10 (m, 6H, C^3H_2, C^4H_2 and CH_2OH), 3.40 (s, 6H, 2 × OCH_3), 3.58 (broad s, 2H, COH and N^2H), 4.52 (m, 1H, C^1H), 6.95–7.62 (m, 4H, ArH), 8.38 (m, 1H, N^9H).

General procedure for the synthesis of compounds **3g**, **3h** *and* **3i**

The appropriate imidazolidine (1 mmol) and tryptamine (1 mmol) were dissolved in 5 ml of dry acetonitrile. After 1 ml of acetic acid had been added to the mixture it was refluxed for 48 hr. The reaction was cooled and poured carefully (CO_2 evolution) into conc. $NaHCO_3$ solution. The resulting mixture was extracted with chloroform and the organic layer dried over Na_2SO_4. Evaporation of the solvent yielded a residue which was purified by chromatography (SiO_2, EtOAc). From the eluate **3g–i** could be isolated as crystalline compounds (ethyl acetate).

1[2-(2-*Phenyl*-1,3-*dithianyl*)]*carboline* (**3g**)

Yield: 89 mg crystals (25%); m.p. 189–191°. IR ($CHCl_3$): 3450 (m), 3400 (m), 1435 (m); PMR ($CDCl_3$): 1.73 (s, 1H, N^2H), 1.83–2.05 (m, 2H, C^5H_2 dithiane), 2.53–3.05 (m, 7H, C^3H_2 and C^4H_2, C^6H_2 and C^4H dithiane), 3.20–3.45 (m, 1H, C^4H dithiane), 4.57 (broad s, 1H, C^1H), 6.98–7.60 (m, 7H, 3 ArH phenyl, 4 ArH indol), 8.0–8.18 (m, 2H, 2 ArH phenyl), 8.83 (broad s, 1H, N^9H). Exact mass, found: 366.1199. Calc for $C_{21}H_{22}N_2S_2$; 366.1174.

1[2-(2-(3-*Methoxyphenyl*)-1,3-*dithianyl*)]*carboline* (**3h**)

Yield: 214 mg slow crystallizing oil (54%); m.p. 177–179° after recrystallization from ethyl acetate. IR ($CHCl_3$): 3450 (m), 3400 (m), 1595 (m), 1575 (m). PMR ($CDCl_3$): 1.73 (s, 1H, N^2H), 1.80–2.15 (m, 2H, C^5H_2 dithiane), 2.50–3.05 (m, 7H, C^3H_2 and C^4H_2, C^4H and C^6H_2 dithiane), 3.25–3.45 (m, 1H, C^4H dithiane), 3.81 (s, 3H, $ArOCH_3$), 4.54 (broad s, 1H, C^1H), 6.80–7.65 (m, 8H, ArH), 8.87 (broad s, 1H, N^9H). Found: C, 66.55; H, 6.15; N, 6.97; S, 15.89. Calc for $C_{22}H_{24}N_2OS_2$: C, 66.80; H, 6.06; N, 7.07; S, 16.16%.

1-[2-(2-(3,4-*Dimethoxyphenyl*)-1,3-*dithianyl*)]*carboline* (**3i**)

Yield 103 mg (24%); m.p. 171–172°. IR (KBr): 3370 (s), 1590,1580 (w), 1500 (s); PMR ($CDCl_3$): 1.70–2.20 (m, 2H, C^5H_2 dithiane), 2.42 (broad s, 1H, N^2H), 2.50–3.30 (m, 8H, C^4H_2 and C^6H_2 dithiane, C^3H_2 and C^4H_2), 3.69 (s, 3H, $ArOCH_3$), 3.85 (s, 3H, $ArOCH_3$), 4.55 (broad s, 1H, C^1H), 6.70–7.65 (m, 7H, ArH), 8.80 (broad s, 1H, N^9H). Exact mass, found: 426.1436. Calc for $C_{23}H_{26}N_2O_2S_2$: 426.1436.

1 - *Tosyl* - 2 - [1 - (1,1 - *dimethoxy* - 2 - *hydroxy*)*ethyl*] - 3,4,4 - *trimethylimidazolidine* (**2f**)

Lithium aluminium hydride (20 mg, 0.5 mmol) was suspended in 5 ml of freshly distilled THF at room temperature. 400 mg of **2e** (1 mmol) was added to the mixture and during the addition a vigorous reaction took place. After the mixture had stirred for 10 min at room temp 0.1 ml of 20% NaOH soln was added while the mixture was vigorously stirred. Filtration of the granular salts and evaporation of the solvent yielded a residue which was purified by chromatography (SiO_2, EtOAc). Yield: 365 mg of oil (98%) which crystallized. M.p. 103–105°. IR ($CHCl_3$): 1600 (w), 1340 (s), 1160 (s). PMR ($CDCl_3$): 1.13 (s, 6H, $C^4(CH_3)_2$), 2.38 (s, 3H, $ArCH_3$), 2.45 (s, 3H, NCH_3), 3.12 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.45 (broad s, 2H, CH_2OH), 3.58 (d, J = 11 Hz, 1H, C^5H), 4.00 (d, J = 11 Hz, 1H, C^5H), 4.65 (broad s, 1H, C^2H), 5.50 (broad

s, 1H, OH), 7.22 (d, J = 8 Hz, 2H, C^3H and C^5HAr), 7.67 (d, J = 8 Hz, 2H, C^2H and C^6HAr). Exact mass found: 372.1746. Calc for $C_{17}H_{28}N_2O_5S$: 372.1719.

General procedure for the synthesis of compounds **5a–c**

Diisopropylamine (10 mmol) was dissolved in 5 ml of freshly distilled THF under N_2. The mixture was cooled to −78° and 0.7 ml of a 1.45 N solution of *n*-butyllithium in hexane (1 mmol) was added. After 5 min 10 mmol of the appropriate 2-phenyl-1,3-dithiane **4a–c** was added to the mixture at −78°. During this addition the color changed to orange-red. After the mixture had stirred for another 5 min 10 mmol of **1b** was added and the mixture slowly warmed to room temp (2 hr). Evaporation of the solvent yielded a residue which was purified by chromatography (for **5a**: Al_2O_3, cyclohexane/EtOAc 1:2, **5b** SiO_2 cyclohexane/EtOAc 1:2, **5c** SiO/EtOAc). Evaporation of the solvent and recrystallization from the appropriate solvent yielded **5a–c** as white crystalline compounds.

1 - *Tosyl* - 2 - [2 - (2 - *carbomethoxyphenyl*) - 1,3-*dithianyl*] - 3,4,4 - *trimethylimidazolidine* (**5a**)

Yield: 4.3 g of white crystals (82%). M.p. 138–139° after recrystallization from EtOAc/ether 1:1. IR ($CHCl_3$): 1719 (s), 1600 (w), 1300 (s), 1260 (m), 1160 (s). PMR ($CDCl_3$): complicated, probably a mixture of rotamers characteristic signals: 3.40 (s, 3H, $COOCH_3$), 5.60 (s, 1H, C^2H). Found: C, 57.38; H, 6.24; N, 5.30. Calc for $C_{25}H_{32}N_2S_3O_4$: C, 57.69; H, 6.15; N, 5.38.

1-*Tosyl*-[2-(2-*carbomethoxy*-4,5-*dimethoxyphenyl*)-1,3-*dithianyl*]-3,4,4-*trimethylimidazolidine* (**5b**)

Yield: 4.8 g (82%); m.p. 152–154° after crystallization from ether. IR ($CHCl_3$): 1710 (s), 1600 (m), 1510 (s), 1340 (m), 1270 (s), 1155 (s). PMR ($CDCl_3$): complicated, probably a mixture of rotamers. Characteristic signals: 2.40 (s, 3H, $ArCH_3$), 3.90 (broad s, 6H, $COOCH_3$ and $ArOCH_3$), 5.52 (s, 1H, C^2H). Found: C, 55.43; H, 6.41; N, 5.10. Calc for $C_{27}H_{36}N_2S_3O_6$: C, 55.86; H, 6.20; N, 4.83%.

1 - *Tosyl* - 2 - [2 - (2 - *carbomethoxy* - 5 - *methoxyphenyl*) - 1,3 - *dithianyl*] - 3,4,4 - *trimethylimidazolidine* (**5c**)

Yield: 4.2 g of white crystals (77%); m.p. 142–143° after recrystallization from EtOAc/hexane 1:4. IR($CHCl_3$): 1710 (s), 1490 (s). PMR ($CDCl_3$): complicated, probably a mixture of rotamers. Characteristic signals: 3.78 (s, 3H, OCH_3Ar), 3.86 (s, 3H, $COOCH_3$), 5.64 (S, 1H, C^2H). Found: C, 56.93; H, 6.30; N, 5.07. Calc for $C_{26}H_{34}N_2S_3O_5$: C, 56.72; H, 6.18; N, 5.09%.

14,14-*Trimethylenedithio*-21-*oxo*-Δ 15,17,19-*yohimbane* (**6a**)

Compound **5a** (350 mg, 0.67 mmol) and 107 mg of tryptamine (0.67 mmol) were dissolved in 3 ml of dry acetonitrile. After 0.7 ml of acetic acid had been added to the mixture it was refluxed for 3 hr. After the mixture was cooled the product spontaneously crystallized from the reaction mixture. Yield: 110 mg of white crystals (47%); m.p. 240–241°. IR ($CHCl_3$): 3420 (m), 1645 (s), 1600, 1580 (w). PMR ($CDCl_3$): 1.44–2.00 (m, 2H, $C^{5'}H_2$ dithiane), 2.25–2.63 (m, 3H, C^6H_2 and $C^{4'}H$ dithiane), 2.71 (m, 1H, C^5H), 2.83–3.16 (m, 3H, C^6H_2 and $C^{4'}H$ dithiane), 5.13 (m, 1H, C^5H), 5.25 (s, 1H, C^3H), 7.10–7.30 (m, 2H, ArH), 7.33–7.50 (m, 2H, ArH), 7.50–7.66 (m, 2H, ArH), 8.08–8.28 (m, 2H, ArH), 9.11 (s, 1H, N^1H). Found: N, 6.99; S, 16.31. Calc for $C_{22}H_{20}N_2OS_2$: N, 7.14; S, 16.33%.

14,14 - *Trimethylenedithio* - 17,18 - *dimethoxy* - 21 - *oxo* - Δ - 15,17,19 *yohimbane* (**6b**)

420 mg of compound **5b** (0.7 mmol) and 110 mg of tryptamine (0.7 mmol) were dissolved in 3 ml of dry acetonitrile. After 0.7 ml of acetic acid had been added to this mixture it was refluxed for 5 hr. The solvent was evaporated, the residue dissolved in chloroform, the organic layer washed with K_2CO_3 soln and dried over Na_2SO_4. Evaporation of the solvent yielded a foam from which the product could be isolated after recrystallization from ethyl acetate. These crystals contained ethyl acetate which could be removed by heating the product under reduced pressure to 120°. Yield; 120 mg of white crystals (37%). M.p. 151–155°. IR ($CHCl_3$): 3460 (m), 1638 (s), 1600 (s), 1580 (w). PMR ($CDCl_3$): 1.50–3.30 (m, 9H, $C^{4'}H_2$, $C^{5'}H_2$ and $C^{6'}H_2$ dithiane, C^6H_2 and C^5H), 4.90–5.30 (m, 2H, C^3H and C^5H), 3.92 and 4.01 (2 s, 6H, 2 × $ArOCH_3$), 7.00–7.90 (m, ArH), 9.15 (broad s, 1H, N^1H). Found: C, N, 5.79; S, 12.44. Calc for $C_{24}H_{24}N_2O_3S_2$: N, 6.19; S, 14.16.

14, 14-*Trimethylenedithio*-17-*methoxy*-21-*oxo*-Δ15, 17, 19-*yohimbane* (**6c**)

Compound **5c** (3.05 g; 5.5 mmol) and 880 mg of tryptamine (5.5 mmol) were dissolved in 20 ml of dry acetonitrile. After the addition of 5.5 ml of acetic acid to this mixture it was refluxed for 4 hr. The solvent was evaporated and the residue was disssolved in ethyl acetate. The organic layer was washed with conc $NaHCO_3$ soln, water and conc NaCl. Drying over Na_2SO_4 and evaporation of the solvent yielded a residue from which the product was isolated after crystallization from acetonitrile. Yield: 1.26 g of white crystals (54%). M.p. 204–205°. IR (KBr): 3345 (m), 1635 (s), 1600 (w). PMR ($CDCl_3$): 1.67–1.99 (m, 2H, $C^{5'}H_2$ dithiane), 2.27–2.75 (m, 4H, $C^{4'}H_2$ and $C^{6'}H_2$ dithiane), 2.92–3.13 (m, 3H, C^6H_2 and C^5H), 3.92 (s, 3H, $ArOCH_3$), 5.09 (m, 1H, C^5H), 5.23 (broad s, 1H, C^3H), 6.95–7.22 (m, 3H, ArH), 9.07 (broad s, 1H, N^1H). Found: C, 65.20; H, 5.24; N, 6.40; S, 14.95. Calc for $C_{23}H_{22}N_2O_2S_2$: C, 65.40; H, 5.21; N, 6.64; S, 15.17%.

14,14-*Trimethylenedithio*-Δ15,17,19-*yohimbane* (**7a**)

A mixture of the amide **6a** (600 mg), $LiAlH_4$ (300 mg) in 15 ml of ether (suspension) was stirred for 20 hr. Subsequently, EtOAc and NH_4Cl were added, the organic layer was dried, filtered and the solvent removed. The residue was crystallized from EtOAc/ether, but the crystalline material did not show a sharp m.p. Yield: 270 mg (47%). IR ($CHCl_3$): 3420. PMR ($CDCl_3$): 1.80–2.25 (m, 2H, $SCCH_2CS$), 2.50–3.50 (m, 8H, $S-CH_2-C-CH_2-S$, CH_2CH_2), 3.90–4.20 (m, 2H, $N-CH_2Ar$), 4.32 (s, 1H, tert.-H), 6.90-8.20 (m, 8H, Ar-H), 9.25 (s, 1H, indole NH), MS (E.I.): 378 (M^+).

14,14-*Trimethylenedithio*-17-*methoxy*-Δ15,17,19-*yohimbane* (**7b**)

A suspension of 300 mg of compound **6c** (0.71 mmol) and 140 mg of $LiAlH_4$ in 7 ml of dry ether was stirred overnight at room temp. The excess of $LiAlH_4$ was removed by adding a mixture of ethyl acetate, ethanol and a few drops of conc NH_4Cl solution to the reaction mixture carefully. The organic layer was dried over Na_2SO_4. Evaporation of the solvent yielded a residue from which **7b** could be isolated after crystallization from ethyl acetate. Yield: 190 mg of white crystals (65%); m.p. 180–181°. IR (KBr): 3410 (m), 2740, 2690 (w), 1610, 1575, 1490 (w). PMR ($CDCl_3$): 1.65–2.17 (m, 2H, $C^{5'}H_2$ dithiane), 2.33–3.30 (m, 8H, $C^{4'}H_2$ and $C^{6'}H_2$ dithiane, C^6H_2, C^5H_2), 3.75 (s, 3H, $ArOCH_3$), 3.92 (m, 2H, $C^{21}H_2$), 4.25 (s, 1H, C^3H), 6.63–7.62 (m, 7H, ArH), 9.45 (broad s, 1H, N^1H). Found: C, 67.48; H, 5.97; N, 6.62. Calc for $C_{23}H_{24}N_2OS_2$: C, 67.65; H, 5.88; N, 6.86%.

17-*Methoxy*-Δ15,17,19-*yohimbane* (**8**)

2 g of wet Ra–Ni were washed with dioxane. 190 mg of compound **7b** was dissolved in 15 ml of dry dioxane and this soln was added to the Ra–Ni described above. The resulting suspension was refluxed for 3 hr. The Ra–Ni was filtered off and the filtrate evaporated to dryness. The resulting residue was purified by chromatography (SiO_2, ether). The product could be recrystallized from a mixture of benzene and *n*-hexane, but the yellow crystals that could be collected were hygroscopic. Yield: 41 mg of yellow crystals (29%), m.p. 158–161° (lit.[9] 169°). IR ($CHCl_3$): 3470 (m), 2740, 2690 (w). PMR ($CDCl_3$): 3.88 (d, J = 13 Hz, 2H, $C^{21}H_2$) identical to lit.[9]. Exact mass, Found: 304.1580. Calc for $C_{20}H_{20}N_2O$: 304.1576.

Reaction of **6c** *with N-bromosuccinimide*

According to a procedure by Corey,[10] 50 mg of compound **6c** (0.12 mmol) was dissolved in 3 ml of a mixture of 80% CH_3CN and 20% H_2O. After the mixture had been cooled to 5°, 126 mg of N-bromosuccinimide dissolved in a mixture of 80% CH_3CN and 20% H_2O was added. After 10 min 4 ml of conc Na_2SO_3 soln and 10 ml of ethyl acetate was added. The organic layer was washed with conc $NaHCO_3$, water and conc NaCl. Drying over $MgSO_4$

and evaporation of the solvent yielded **9** as orange-red crystals. Yield: 13 mg crystals (32%), m.p. 234–235°. IR (KBr): 1670, 1700 (C=O). PMR (DMSO-d_6): 3.00 (t, J = 6 Hz, 2H, CH_2CH_2N), 4.00 (s, 3H, OCH_3), 4.67 (t, J = 6 Hz, 2H, CH_2CH_2N), 7.1–7.65 (m, 6H, Ar-H), 8.17 (d, J = 2 Hz, 1H, NH), 8.45 (s, 1H, OH). Exact mass. Found 426.0000. Calc for $C_{20}H_{15}N_2O_4Br$: 426.0216.

Reduction of **2a** *to* 1-(*N-tosyl*)-2-(*N,N-dimethyl*)-2-*methylpropane* (**10**)

The imidazolidine **2a**[1] (134 mg; 0.5 mmol) was dissolved in a mixture of acetonitrile (2 ml) and acetic acid (2 ml). $NaCNBH_3$ (30 mg, 3 equiv) was added to this solution, under nitrogen and the mixture maintained at 50° for 4 hr. The reaction mixture was brought to pH 8 by addition of Na_2CO_3 solution, sat. NH_4Cl and NaCl added and the organic product extracted with $CHCl_3$. After drying (Na_2SO_4) and evaporation of the solvent, a quantitative yield of **10**, m.p. 56–62° dec. was obtained. NMR ($CDCl_3$): δ 0.95, s (6H, CMe_2), 2.02, s (6H, NMe_2), 2.41, s (3H, Ar-Me), 2.75, s (2H, $-CH_2$), 4.05–4.45 (1H, NH, D_2O exchange), 7.28 and 7.75 d × d (4H, Ar-protons).

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