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SYNTHESES IN THE ELLIPTICINE-OLIVACINE SERIES

A POSSIBLE BIOGENETIC MODEL†

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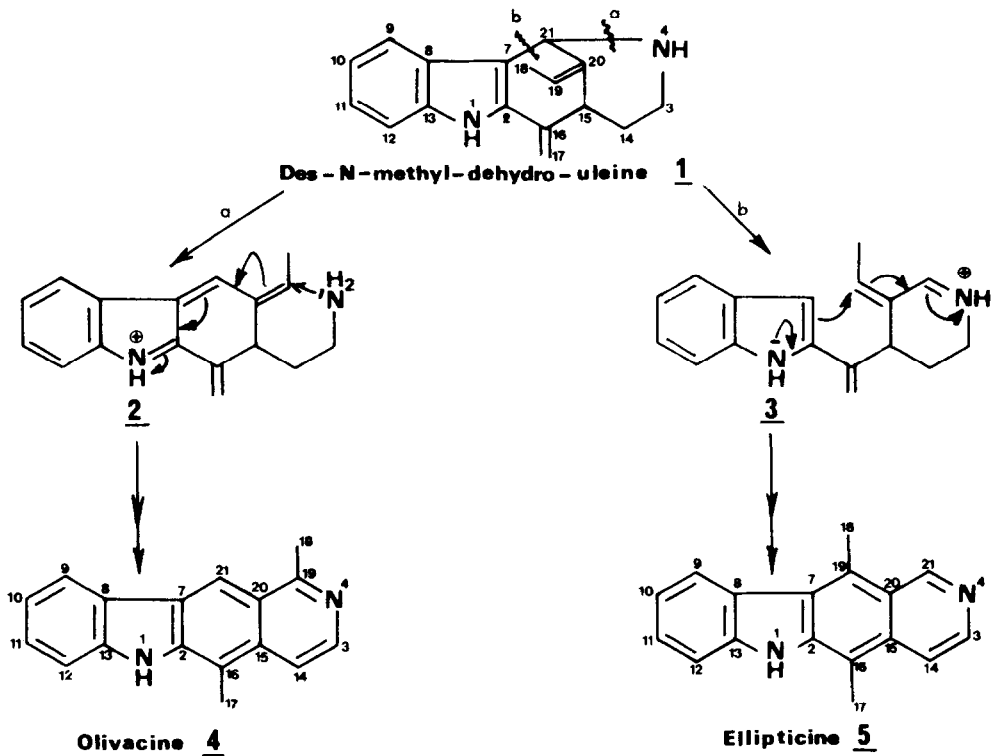
Abstract—The syntheses of the antitumor alkaloids ellipticine **5** and olivacine **4** have been achieved according to a general scheme based on the acid catalysed fragmentation of desethyl-uleine **14** into the carbazole **15**. In the initial study, **15** was synthesised from 1-benzenesulfonyl-2-lithio-indole and 4-formyl pyridine in 10 steps. A notable improvement was made with the preparation in high yield of **15** in a one-pot reaction between indole and the Δ^3 piperidine **20**. The missing carbon atoms were introduced according to a Bischler reaction on **15** to yield olivacine **4** after demethylation and aromatisation. Ellipticine was obtained in the same way from **23**.

Since the structural elucidation and the first synthesis of ellipticine **5** by Woodward,[1] a great deal of work has been devoted to the synthesis of this pyrido[4,3-*b*]carbazole alkaloid[2] due to its promising antitumor activity.[3] Much less attention has been paid to the synthesis of the isomeric alkaloid olivacine **4** which has also proved to possess potential anticancer properties.[4]

In continuation of our interest in the biomimetic synthesis of alkaloids we sought a synthetic approach to ellipticine **5** and olivacine **4** inspired by a biogenetic hypothesis. These two alkaloids exhibit unexpected structural features in comparison with their parent indole alkaloids since a three carbon chain bonds the indole nucleus and the N-4 atom instead of the two carbon atoms of the tryptophan side chain.

Potier and Janot[5] proposed an attractive hypothesis for the biogenesis of these alkaloids. Conjugated iminium salts which may often be invoked for the biogenesis of indole alkaloids[6] are key intermediates in this postulate. Thus an intramolecular Mannich type reaction of the intermediate **3** (Scheme 1) allowed biomimetic syntheses of ellipticine **5**[2,7] *via* intermediates of the aforementioned type. On the other



Scheme 1.

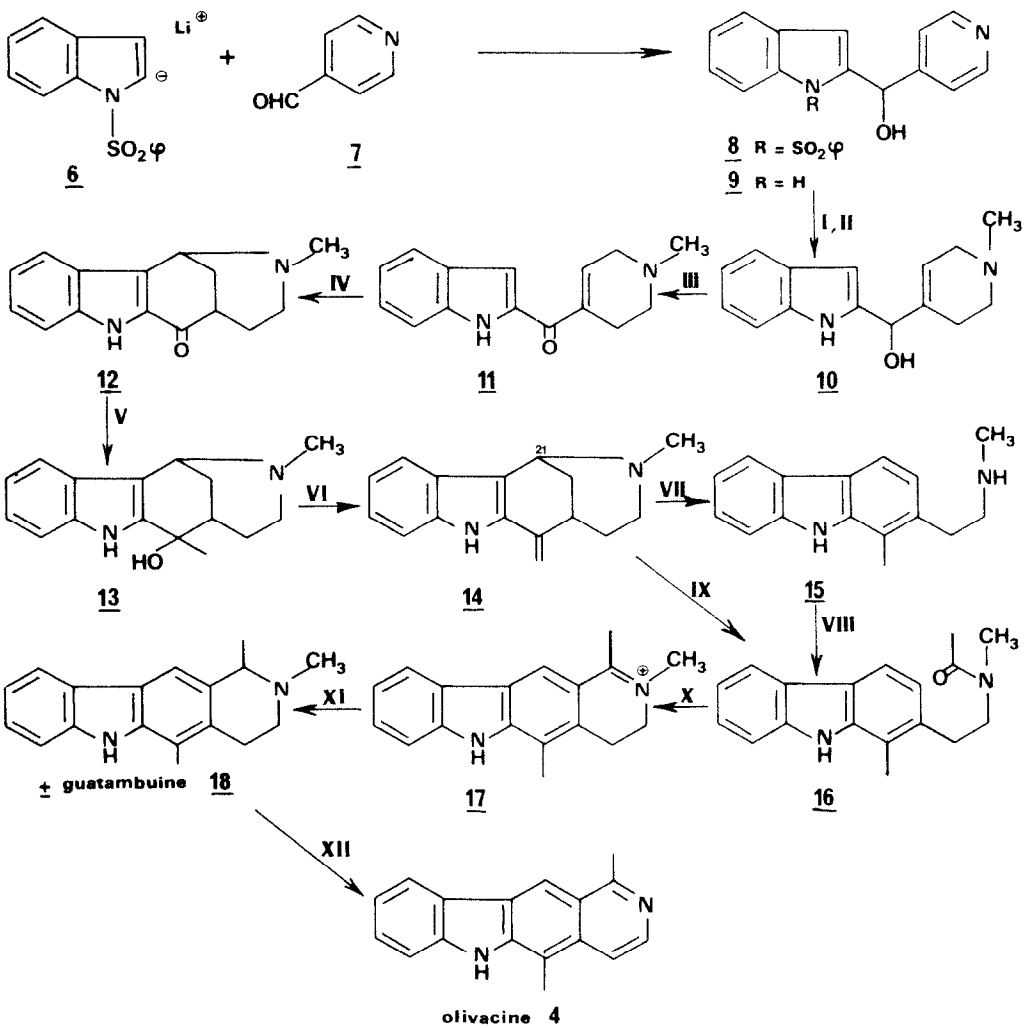
†Preliminary communication of part of this work: R. Besselièvre and H.-P. Husson, *Tetrahedron Lett* 1873 (1976). The work described comprises part of the Ph.D. Thesis of R. Besselièvre (University of Paris-Sud, 1977).

hand, the nucleophilic addition of N-4 onto the conjugated iminium ion **2** could give the olivacine skeleton.

One can imagine that intermediates **2** and **3** are formed by fragmentation of the alkaloid des-N-methyl-dehydrouleine **1**[8] according to two different pathways *a* or *b*, after protonation of N-4 or C-7 respectively (the biogenetic numbering will be used throughout this paper). Route *a* is reminiscent of the fragmentation of gramine quaternary salts previously observed.[9,10] We were able to make such a reaction on a tertiary base, in acidic medium, with the α-acylindole alkaloid ervitsine in order to make a correlation with another alkaloid.[11] Some precedent therefore did exist to favour our proposal for a possible biogenetic hypothesis for the formation of olivacine **4**.

It was our aim to prepare desethyluleine **14** (Scheme 2) to check the validity of this hypothesis and its usefulness in synthesis.

The synthetic scheme was inspired by the Joule synthesis[12] of uleine itself whose original step was the cyclisation of an α,β unsaturated ketone of type **11** into **12**. The key intermediate **9** was obtained differently on condensation of the 2-lithio derivative of benzenesulfonyl indole **6**[13] with 4-formyl pyridine **7** followed by basic hydrolysis of the protecting group.



Reagents : I, ICH_3, CH_3CN, Δ ; II, $NaBH_4$, EtOH-$CHCl_3$; III, MnO_2 , $CHCl_3$; IV, AcOH-H_2O (50,50), Δ , 10 h. ; V, CH_3Li, THF, − 8° C, 1 h. ; VI, CF_3COOH, $CDCl_3$; VII, AcOH-H_2O (50,50), Δ , 70 h. ; VIII, Ac_2O, C_6H_5N (50,50), r. t. 1 h. ; IX, AcCl, C_6H_6, Na_2CO_3, r. t. 12 h. ; X, $POCl_3$, $CHCl_3$, Δ , 10 h. ; XI, $NaBH_4$, CH_3OH ; XII, decaline, Pd 10 %/C, Δ, 24 h.

Scheme 2.

Quaternization of the pyridine nitrogen with MeI followed by $NaBH_4$ reduction yielded the tetrahydropyridine **10**. MnO_2 oxidation of **10** gave the α,β unsaturated ketone **11** (air oxidation of **10** is also effective but slower).

Cyclisation of **11** into desethyl-dasycarpidone **12** was achieved on its boiling in 50% AcOH–H_2O for 10 hr. This reaction proceeds *via* the deconjugated iminium salt coming from the conjugated enol. The exomethylene group of **14** was efficiently introduced in two high yield steps *via* the addition of MeLi to **12** followed by dehydration with CF_3COOH. This approach is more convenient than the Wittig reaction[12] whose yield is poor. Refluxing **14** in 50% AcOH–H_2O for 24 hours afforded the carbazole **15** (Y = 90%) which was acetylated to give **16** and cyclized *via* a Bischler–Napieralski reaction in a classical manner. The N-acetyl derivative **16** could also be obtained directly from AcCl treatment of **13** or **14**. $NaBH_4$ reduction of **17** led to (±)guatambuine **18** which could also be obtained by Pictet–Spengler reaction of **15** with CH_3CHO. Demethylation and dehydrogenation of **18** in boiling decalin in the presence of 10% palladium-charcoal afforded olivacine **4**.

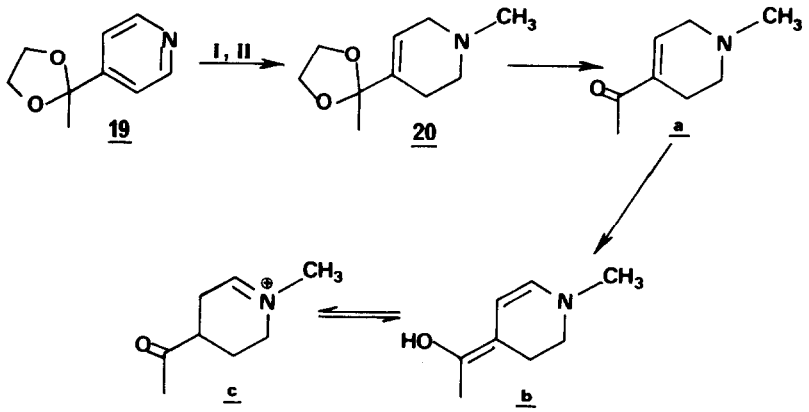
N-desmethyl-dehydrouleine **1** not being available (probably due to its sensitivity to acid treatment during extraction from the plant), it was not possible to apply the facile fragmentation reaction of **14** into **15** to the probable precursor of the guatambuine–olivacine series.

The tertiary alcohol **13** can be regarded as derived from indole and 1-methyl 4-acetyl Δ^3 piperidine *a* (Scheme 3) *via* a nucleophilic substitution on the position α to N-4 *via* an iminium ion followed by an addition on the keto group.

The piperidine **a** (Scheme 3), an equivalent of **11**, should give in acid medium **c**, which is the required intermediate for the proposed substitutions with indole. The keto group of 4-acetyl pyridine was transformed into its ethylene ketal **19**, the nitrogen was quaternarized with MeI and finally $NaBH_4$ reduction afforded **20** (overall yield 72%).

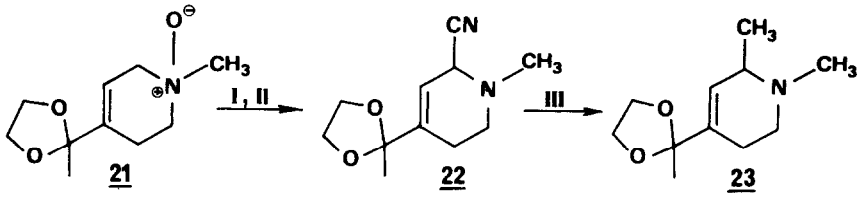
Equimolecular amounts of indole and **20** were refluxed for 56 hours in 50% AcOH–H_2O under an argon atmosphere. After work up the carbazole **15** was obtained in a one-pot reaction in 74% yield as its hydrochloride (Scheme 5).

This synthesis of **15** represents a notable improvement over the former route since there are fewer steps and the reagents are cheaper (no lithio derivative is necessary and the starting materials are commercially available). The first synthesis of 10-methoxy olivacine **28**,[14] whose structure had been



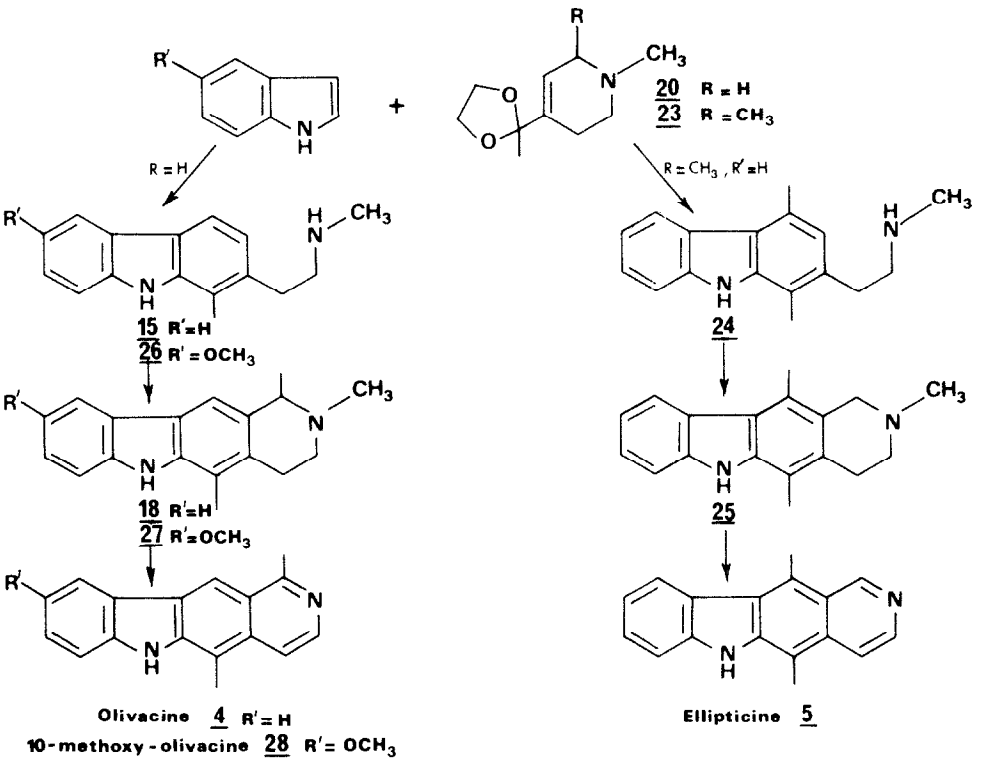
Reagents : I, CH_3I, CH_3CN ; II, $NaBH_4$, CH_3OH.

Scheme 3.



Reagents : I, $(CF_3CO)_2O$, CH_2Cl_2, 0°, 15 min. ; II, KCN, H_2O, pH4, 20 min. ; III, CH_3MgBr, THF, − 10°, 1 h.

Scheme 4.



Scheme 5.

proposed on the basis of physical data only, was achieved similarly starting from 5-OCH_3 indole (in this case the carbazole **26** was obtained in 90% yield).

The efficiency of this synthesis prompted us to adopt a similar strategy in the synthesis of ellipticine. The required Δ^3-piperidine **23** was obtained from **20** according to an original method recently developed in our laboratory[15] (Scheme 4). Trifluoroacetic anhydride treatment of the N-oxide **21** gave a conjugated iminium salt isolated as its cyano adduct **22**.

On treatment of **22** with CH_3MgBr **23** was regiospecifically prepared. Condensation of **23** with indole, in the same conditions utilized for the preparation of the carbazole **15**, gave **24** in low yield (Scheme 5). Ellipticine synthesis was achieved from **24** *via* a Pictet–Spengler cyclisation with CH_2O followed by a dehydrogenation-demethylation with 10% palladium–charcoal.

The surprisingly poor yield in comparison with the high yield of the synthesis of **15** could be explained because of a difficult Mannich reaction on the substituted intermediate iminium ion.

In conclusion we suggest a biogenetic hypothesis for the ellipticine-olivacine series and our proposal is illustrated by a model reaction in the case of olivacine.

EXPERIMENTAL

Infrared spectra (IR) were recorded in $CHCl_3$ solutions on a Perkin–Elmer 257 spectrophotometer. Infrared absorption bands are expressed in cm^{-1} using polystyrene calibration. Ultraviolet spectra (UV) were run in ethanol solution on a Bausch and Lomb Spectronic 505 spectrophotometer. ^1H nuclear magnetic resonance (NMR) spectra were recorded on a Perkin–Elmer R 12 spectrometer (60 MHz). Chemical shift data are reported in parts per million (ppm, tetramethylsilane as an internal standard, $\delta = 0$), where, s, d, dd, t, q and m designate singlet, doublet, doublet of doublets, triplet, quartet and multiplet respectively. Mass spectrometry (MS) was performed on an AEI MS 50 in the Institut de Chimie des Substances Naturelles 91190 Gif-sur-Yvette, France where the elemental analyses were also carried out. Satisfactory elemental analyses were obtained for all products described. All reactions were run under argon and freshly distilled THF was used.

1-Benzenesulfonylindol-2-yl 4-pyridyl carbinol **8**

1-Benzenesulfonyl-2-lithioindole **6** (2.57 g, 10 mmol) was prepared in THF[13] at −12° and was added slowly *via* a syringe to a THF solution of 4-pyridine-carboxaldehyde (1.1 g, 10 mmol). The resultant yellow reaction mixture was stirred at 15° for 30 min, diluted with water and then acidified (pH2) with HCl. The excess of indole was removed by extraction with ether. The aqueous phase was made alkaline with NH_4OH and extracted with $CHCl_3$. The combined $CHCl_3$ fractions were washed with water, dried over anhydrous sodium sulfate and distilled to give the crude product (2.265 g) which was crystallized from methanol (Y: 62%): m.p. 200°; $C_{20}H_{16}N_2O_3S$.

Indol-2-yl 4-pyridyl carbinol **9**

A solution of **8** (1.5 g, 4.1 mmol) in ethanol (90 ml) water (90 ml) and 10N sodium hydroxyde (20 ml) was heated at reflux for 2 hr to give **9** which was extracted with hot $CHCl_3$ after dilution of the reaction mixture with water. Concentration of the combined $CHCl_3$ fractions resulted in crystallisation. After standing overnight at 0° 0.515 g of crystals of pure **9** were filtered off (Y: 57%): m.p. 192°; $C_{14}H_{12}ON_2$; MS *m/e* (rel intensity) 224 (M^+, 100), 206 (85),

Indol-2-yl 1,2,5,6-tetrahydro-1-methyl-4-pyridyl carbinol **10**

The derivative **10** was prepared from the methiodide of **9** by $NaBH_4$ reduction as previously described.[12]

Indol-2-yl 1,2,5,6-tetrahydro-1-methyl-4-pyridyl ketone **11**

The alcohol **10** was oxidised with MnO_2 as previously described to yield the ketone **11**.[12]

Desethyldasycarpidone **12**

Desethyldasycarpidone **12** was obtained from **11** according to the procedure of Joule *et al.*[12]

Alcohol **13**

To a 1M solution of CH_3Li (3 ml) in THF (20 ml) at $-10°$ was added desethyldasycarpidone **12** (0.360 g, 1.5 mmol) in THF (36 ml) *via* a syringe. The reaction mixture was stirred at room temperature for 1 hr and then diluted with water and extracted according to the usual procedure. The crude product (0.410 g, Y ≃ 100%) was crystalline and was not recrystallized; $C_{16}H_{20}N_2O$; MS *m/e* 256 ($M^{+\cdot}$); NMR ($CDCl_3$) 1.55 (s, CH_3), 2.21 (s, N–CH_3).

Desethyluleine **14**

The dehydration of **13** into **14** was performed in an NMR tube. To a solution of **13** (40 mg, 0.16 mmol) in $CDCl_3$ three drops of CF_3COOH were added. The reaction mixture was heated at 50°. The NMR spectra showed that after 1 hr the reaction was complete. After extraction, the crude product was crystallized from benzene (quantitative yield): m.p. 213°; $C_{16}H_{18}N_2$; MS *m/e* (rel intensity) 238 $M^{+\cdot}$, 80) 195 (60), 194 (58), 181 (100); UV nm ($\log\varepsilon$) 225 (4.35), 303 (4.25), 3.10 (4.23); NMR ($CDCl_3$) 2.25 (s, NCH_3), 4.20 (t, 1 H, H-21), 4.95 (s, 1 H, H-17), 5.25 (s, 1 H, H-17).

Carbazole **15**

Method A. The carbazole **15** was prepared on refluxing **14** (40 mg) in 50% aqueous acetic acid for 24 hr. After extraction the crude product was crystallized as its hydrochloride from ethanol (35 mg, Y ≃ 90%): m.p. > 300°; $C_{16}H_{19}N_2Cl$. Base: MS *m/e* (rel intensity): 238 ($M^{+\cdot}$, 35) 195 (100), 194 (50); UV nm ($\log\varepsilon$) 239 (4.67), 249 (4.55), 260 (4.31), 295 (4.26) 326 (3.61), 339 (3.60); NMR ($CDCl_3$) 2.42 (s, NCH_3), 2.45 (s, CH_3).

Method B. The tetrahydropyridine **20** (1.83 g, 10 mmol) and indole (1.17 g, 10 mmol) in 50% aqueous acetic acid (50 ml) were refluxed for 56 hr. After extraction the amorphous carbazole (1.760 g, Y = 74%) was crystallized as its hydrochloride from methanol.

N-Acetyl derivative **16**

Method A. The alcohol **13** or desethyluleine **14** (0.2 mmol) were stirred in C_6H_6 solution in the presence of AcCl (0.6 mmol) and Na_2CO_3 (1 g) for 12 hr at room temperature. After extraction the derivative **16** was obtained as an amorphous solid (53 mg, Y = 95%); $C_{18}H_{20}N_2O$; MS *m/e* (rel intensity): 280 ($M^{+\cdot}$, 44) 207 (100), 194 (90); NMR ($CDCl_3$) exhibited two rotamers 1.82 and 2.04 (2s, CH_3), 2.44 and 2.49 (2s, NCH_3) 2.84 and 2.92 (2s, CH_3).

Method B. The secondary amine **15** (2.38 g, 10 mmol) was stirred for 1 hr in acetic anhydride–pyridine (1:1) (30 ml). After extraction the compound **16** was isolated in 95% yield.

(±) *Guatambuine* **18**

Method A. The amide **16** (2.80 g, 10 mmol) and $POCl_3$ (4 ml) were refluxed for 10 hr in $CHCl_3$. The yellow precipitate was then filtered off and washed with $CHCl_3$ (2.1 g). The crystals of the intermediate iminium salt **17** were dissolved in a mixture of $CHCl_3$ (30 ml) and CH_3OH (50 ml) and reduced with excess $NaBH_4$ at room temperature. After isolation by extraction (±) guatambuine **18** was crystallized from ethanol (1.9 g; Y: 72%): m.p. 250°; $C_{18}H_{20}N_2$ MS *m/e* (rel intensity) 264 ($M^{+\cdot}$, 8%) 263 (90%), 249 (100%); UV nm ($\log\varepsilon$) 240 (4.62), 250 (4.48), 261 (4.34), 290 (3.95), 299 (4.24), 330 (3.59), 3.40 (3.56). NMR ($CDCl_3$) 1.5 (d, J = 6.5 Hz, CH_3), 2.31 (s, CH_3), 2.48 (s, NCH_3), 3.78 (q, J = 6.5 Hz, 1 H, H-19).

Method B. To a solution of the secondary amine **15** (2.38 g, 10 mmol) in methanol (100 ml) was added 10 N HCl to make the solution strongly acidic. The solution was refluxed for 7 days and acetaldehyde (2 ml) was added every day. The reaction mixture was then extracted and the crude product (starting material and guatambuine) was purified by chromatography on a silicagel column. Elution with $CHCl_3$: methanol (98:2) gave pure guatambuine (0.88 g, Y: 33%).

Olivacine **4**

A solution of (±) guatambuine **18** (0.264 g, 1 mmol) in decalin (20 ml) was refluxed with 10% palladium–charcoal (0.250 g) for 24 hr. The reaction mixture was diluted with hexane (100 ml) and extracted with CH_3OH (5 × 20 ml). The CH_3OH extract was washed with hexane and diluted with aqueous ammonia. Half of the CH_3OH was distilled. The concentrated phase was then extracted with $CHCl_3$ (3 × 40 ml). The $CHCl_3$ extracts were washed, dried and evaporated leaving a crude product purified by elution from a silicagel column. Olivacine (0.060 g, Y: 24%) was crystallized from ether–methanol: m.p. > 300°; $C_{17}H_{14}N_2$; MS *m/e* 246 ($M^{+\cdot}$). IR superimposable on that of the natural product.

4-Acetylpyridine ethyleneketal **19**

The ketone (60 g), toluene (1.3 l), ethylene glycol (30 g) and toluene-p-sulfonic acid (20 g) were refluxed together under a Dean-Stark head for 56 hr. Further ethylene glycol (6 × 5 g) was added in small portions every 8 hr. The toluene solution was evaporated under vacuum in the presence of N ammonia solution. The aqueous solution was then extracted with $CHCl_3$. The combined $CHCl_3$ phases were washed, dried and distilled. The residue was purified by distillation (57.5 g, Y: 70%): b.p. 113° (15 mm Hg). The liquid ketal solidified at room temperature: m.p. 50°; $C_9H_{11}NO_2$; MS *m/e* 165 ($M^{+\cdot}$); NMR ($CDCl_3$) 1.61 (s, CH_3), 3.80 and 4.08 (2m, CH_2–CH_2).

Tetrahydropyridine **20**

The pyridine **19** (57.5 g) was quaternarized with CH_3I in acetonitrile (1.4 l) and the salt (m.p. 135° from benzene) was reduced with $NaBH_4$ in methanol according to usual procedures. The tetrahydropyridine was distilled b.p. 114° (17 mm Hg); overall yield: 81%; $C_{10}H_{17}O_2N$: MS *m/e* 183 ($M^{+\cdot}$); NMR ($CDCl_3$) 1.43 (s, CH_3) 2.34 (s, N–CH_3), 3.76 (m, CH_2–CH_2), 5.82 (m, 1 H).

N-Oxide **21**

A solution of **20** (5 g, 27 mmol) in 300 ml CH_2Cl_2 containing 30% EtOH was heated with 30% hydrogen peroxide (5 ml) at reflux for 70 hr. Excess peroxide was then destroyed by the addition of 10% Pd/C, stirring at reflux for 2 hr. Once the reaction mixture was free of all traces of unreacted peroxide it was filtered through a bed of celite and concentrated to give a colorless liquid (5.4 g). NMR ($CDCl_3$): 1.45 (s, CH_3) 3.15 (s, N–CH_3) 3.90 (m, CH_2–CH_2) 5.84 (m, 1 H).

2-Cyano Δ3-piperidine **22**

The N-oxide (3.5 g, 17.5 mmol) was dissolved in CH_2Cl_2 (30 ml) and stirred under an argon atmosphere at 0°. Trifluoroacetic anhydride (2 ml) was added *via* a syringe and the solution stirred for 15 min. The resulting reaction mixture was then concentrated in vacuo and reacted with an aqueous solution of potassium cyanide (5 g) in water (30 ml). The aqueous layer was quickly adjusted to pH 4.0 by addition of trifluoracetic acid. The reaction was stirred for 20 min and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were washed, dried and distilled.

A colourless oil (1.65 g, Y 45%) was obtained: MS *m/e* (rel intensity) 208 ($M^{+\cdot}$, 10), 180 (15), 121 (17), 87 (100). NMR ($CDCl_3$) 1.43 (s, CH_3), 2.49 (s, NCH_3) 3.90 (m, CH_2–CH_2), 4.1 (m, 1 H, N–CH–CN), 5.9 (1 H). IR 2222 cm^{-1} (W).

Tetrahydropyridine **23**

Methylmagnesium bromide (solution 2M in ether: 3 ml) was added slowly *via* syringe to a solution of aminonitrile **22** (1.110 g, 5.3 mmol) in THF (30 ml) which was stirred at $-10°$ under an argon atmosphere. The solution was allowed to warm up slowly to room temperature ($\sim$1 hr). The reaction was then stopped by the addition of an aqueous solution of $(NH_4)_2SO_4$ and extracted with CH_2Cl_2. The residue was purified by bulb to bulb distillation b.p. 110° (2 mm, Hg) (Y: 57%) MS *m/e* (rel intensity) 197 (M^+, 6), 182 (95), 110 (100), 87 (26). NMR ($CDCl_3$) 1.12 (d, J = 6.5 Hz, CH_3) 1.40 (s, CH_3), 2.35 (s, NCH_3), 3.85 (m, CH_2–CH_2), 5.63 (s, broad, 1 H).

Carbazole **24**

The carbazole **24** was synthesised according to the procedure used to prepare **15**. The yield after purification by preparative thick layer chromatography on silicagel was 5%. MS *m/e* (rel. intensity) 252 (M^+, 9%) 209 (21) 196 (100). NMR ($CDCl_3$): 2.40, 2.41, 2.49 (3s, CH_3).

N-methyl-tetrahydro-ellipticine **25**

As described for the preparation of **18**, **24** was reacted with 40% formaldehyde solution (Y: 53%). m.p. 215° (methanol), MS *m/e* (rel intensity) 264 (M^+, 70), 263 (100), 249 (55), 221 (80); UV nm (log ε) 229 (4.48), 240 (4.69), 249 (4.55), 262 (4.33), 285 (3.97), 295 (4.26), 317 (3.40), 327 (3.59), 340 (3.57). NMR ($CDCl_3$) 2.28 (s, CH_3), 2.49 (s, CH_3), 2.63 (s, N–CH_3). This compound was identical in all respects with the natural product.

Ellipticine **5**

Ellipticine was obtained from **25** as described for olivacine **4** from (±) guatambuine **18** (Y: 36%). The product was identical with an authentic sample of ellipticine.

Carbazole **26**

The derivative **26** was prepared according to the procedure used for **15** (method B) (Y: 90%); **26** was crystallized as its acetate m.p.: 250° (water) dec. Base $C_{17}H_{20}N_2O$; MS *m/e* (rel intensity) 268 (M^+, 32), 225 (100); NMR ($CDCl_3$) 2.45 (s, NCH_3), 2.47 (s, CH_3), 3.91 (s, OCH_3).

(±)-10-*Methoxy guatambuine* **27**

The secondary amine **26** was acetylated according to the preparation of **16** (method B) (Y: 63%) m.p. 171° (methanol) MS *m/e* (rel intensity) 310 (M^+, 44) 237 (100), 224 (96). The amide was then treated as **16** (method A) to afford (±)-10-methoxy guatambuine **27** (overall yield 76%): m.p. 95° (ethanol); $C_{19}H_{22}N_2O$; MS *m/e* (rel intensity) 294 (M^+, 4), 279 (100). All physical data were in accordance with those given by Burnell and Della Casa.[14]

10-*Methoxy olivacine* **28**

The compound **27** was dehydrogenated and demethylated according to the procedure used for olivacine **4** (Y: 52%). Physical data were identical with those of the natural product.[14]

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