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PAVINANE AND ISOPAVINANE ALKALOIDS

CORRELATION OF ABSOLUTE CONFIGURATIONS BY SYNTHESIS

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Abstract—(−)-Caryachine (**9**) and (−)-Reframoline (**10**) have been synthesised from a common intermediate; this confirms the absolute configuration in the isopavinane series deduced previously by application of the aromatic chirality rule. This also represents the first synthesis of an optically active pavinane alkaloid.

A number of alkaloids is now known[1-3] based upon the pavinane ring system (**1**). All possess N–Me groups, although the first example of this class of compounds, pavine (**1g**) is a secondary amine, and was first prepared by reducing papaverine with tin and hydrochloric acid.[4] The only method of synthesis used for the pavinane alkaloids has involved partial reduction of 1 - benzyl - 2 - methylisoquinolinium salts (**2**) to the 1,2-dihydroisoquinoline (**3**), followed by acid-catalysed cyclisation, usually with $H_3PO_4/POCl_3$ mixtures at elevated temperature (120–150°). Yields are often poor. The major side-reactions include disproportionation of the unstable enamine (**3**) into the quaternary salt (**2**) and the 1,2,3,4-tetrahydroisoquinoline (**4**),[5] elimination of the C_1-benzyl group[6] and rearrangement to the 3 - benzyl - 3,4 - dihydroisoquinolinium salt (**5**).[3,5,7,8] Early attempts[9] to establish the conditions for preferential pavinane formation or rearrangement were inconclusive; however a more extensive investigation using 2 - methyl - 1,2 - dihydropapaverine has been described.[8] The conditions used for the cyclisation of derivatives of 3 are often so severe that methylenedioxy groups are cleaved.[9] A further disadvantage of this method of synthesis of pavinanes is that 1-benzylisoquinolines with the required oxygenation pattern are sometimes inaccessible.[2,3] Further it seems that only racemic pavinanes can be prepared since it has not yet proved possible to resolve the intermediate, acid-labile 1,2-dihydroisoquinolines.[9]

Isopavinane alkaloids, based upon the ring system (**6**)[9] have been prepared[10-14] by acid-catalysed cyclisation of 1 - benzyl - 4 - hydroxy - 1,2,3,4 - tetrahydroisoquinolines (**7**, R = H or Me). These intermediates, which need not be isolated, can be obtained by hydroboration and oxidation of 1 - benzyl - 1,2 - dihydroisoquinolines (**3**),[12] by oxidation of 1 - benzyl - 7 - hydroxy - 1,2,3,4 - tetrahydroisoquinolines with lead tetraacetate,[14] or, most usefully, by acid-catalysed cyclisation of benzylaminoacetaldehyde dialkylacetals (**8**, R_5 = H or Me, R_6 = $CH_2CH(OMe)_2$).[11,13] Since the required acetals are now very readily available,[15] this route to isopavinanes is an attractive one. Additionally since 1,2-diarylethylamines (**8**, R_5 = Me, R_6 = H) can be resolved quite easily,[7] optically active isopavinanes should be accessible.

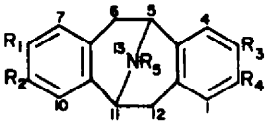
Under acid conditions a competition between cyclisation of the 4-hydroxytetrahydroisoquinolines of type 7 to yield isopavinanes, (**6**), and dehydration to 1 - benzyl - 1,2 - dihydroisoquinolines (**3**), followed by cyclisation to pavinanes (**1**) is obviously possible, and might be expected to depend upon such factors as the nitrogen substituent, the pH, and the nature and position of oxygen functions attached to the two aromatic rings. Recently we[13] reported that when the acetals (**8b** and **8e**) were treated separately with 6 N HCl at room temperature, the expected isopavinanes (**6a** and **6b**) were accompanied by the corresponding pavinanes (**1a** and **1b**), respectively. This is the first time that a pavinane cyclisation had been observed under such mild conditions.[16] We do not know at what stage the O-benzyl groups were cleaved. In one case (that of **8e**), the product of a $C_1 \rightarrow C_3$-benzyl migration was also detected. Since the mixtures of pavinanes and the isomeric isopavinanes are easily separated by column chromatography, the route is an attractive one for suitably substituted pavinanes, especially since we have now found that the benzylamino acetal (**8f**) can be cyclised to the pavinane (**1c**) in 40% yield. Only trace amounts of the isopavinane were detected. N-Methylation of **1c** with $HCHO/NaBH_4$ gave **1a**, whereas N-demethylation of **1a** to **1c** could be achieved easily by treatment with ethyl chloroformate, followed by base.[17]

The alkaloid caryachine has been isolated from Formosan *Cryptocarya chinensis* in optically active and racemic forms[18] but a distinction between structures **1a** and **1b** could not be made. Both racemates were synthesised[19] by the standard method from the preformed 1 - benzyl - 1,2 - dihydroisoquinolines: **1a** was described as a solid m.p. 239–240° and **1b** had m.p. 195–196°. The Indian workers stated that these two synthetic compounds could be distinguished from each other by small differences apparent in the IR spectra, although TLC, UV and NMR characteristics were identical. Unfortunately Natarajan and Pai did not specify the solvent used for the NMR measurements. However, it was stated that the IR spectrum of **1a** is identical with that of an authentic sample of caryachine. Our synthetic samples of **1a** and **1b** had[13] m.p. 240–241° and 206–207° respectively. The NMR spectra were recorded in several solvents when significant differences in the aromatic region were apparent. Such differences are to be expected in the light of the correlations suggested by Chen and Soine,[20] where predictive additivity rules were proposed. We find that these rules are applicable to the published spectra[21] of eschscholtzine (**1d**) and eschscholtzidine (**1e**), thus extending their scope to pavinanes containing methylenedioxy groups. The observed and predicted chemical shift values for **1a** and **1b** (in DMSO-d_6 solution) are summarised in Table 1. The NMR spectra in $CDCl_3$ do not conform to this additivity rule and a closer examination of the behaviour of **1a** and **1b** suggests that

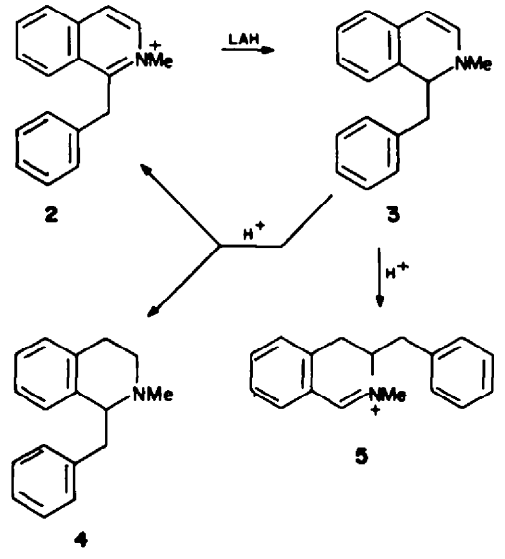
Table 1.

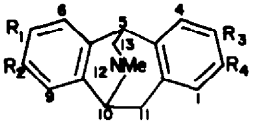
Compound in DMSO-d_6		δ-Values for aromatic H			
		H_1	H_4	H_7	H_{10}
1a	Found	6.51	6.75	6.39	6.72
	Predicted	6.54	6.78	6.36	6.70
1b	Found	6.51	6.75	6.51	6.58
	Predicted	6.54	6.78	6.48	6.57

by changing from DMSO to $CDCl_3$, a downfield shift (up to 0.1 ppm) results for aromatic protons ortho to phenolic OH, and a comparable upfield shift for protons meta to the OH group. This is in agreement with earlier studies[22] and confirms the assignments made in Table 1. Although we find that these additivity rules work well, we suggest that an anisotropic effect of the benzene rings, rather than a C–N bond inductive effect, accounts for the fact that the singlet absorptions of H_7 and H_1 are at lower

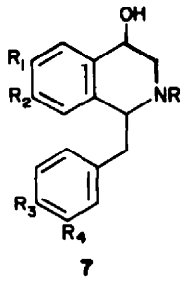


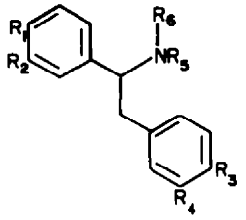
	R_1	R_2	R_3	R_4	R_5
1a	OH	OMe	O—CH_2—O		Me
1b	OMe	OH	O—CH_2—O		Me
1c	OH	OMe	O—CH_2—O		H
1d	O—CH_2—O		O—CH_2—O		Me
1e	OMe	OMe	O—CH_2—O		Me
1f	OMe	OMe	OMe	OMe	Me
1g	OMe	OMe	OMe	OMe	H



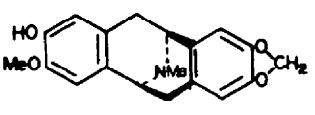


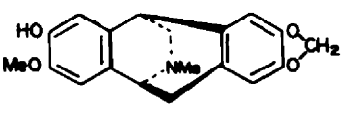
	R_1	R_2	R_3	R_4
6a	OH	OMe	O—CH_2—O	
6b	OMe	OH	O—CH_2—O	
6c	O—CH_2—O		OMe	OH





	R_1	R_2	R_3	R_4	R_5	R_6
8a	OCH_2Ph	OMe	O—CH_2—O		Me	H
8b	OCH_2Ph	OMe	O—CH_2—O		Me	$CH_2CH(OEt)_2$
8c	OMe	OMe	OMe	H	Me	H
8d	O—CH_2—O		OEt	H	Me	H
8e	OMe	OCH_2Ph	O—CH_2—O		Me	$CH_2CH(OEt)_2$
8f	OCH_2Ph	OMe	O—CH_2—O		H	$CH_2CH(OEt)_2$
8g	OCH_2Ph	OMe	O—CH_2—O		H	H
8h	OCH_2Ph	OMe	O—CH_2—O		—COOEt	H





fields than those due to H_{10} and H_4 in symmetrically substituted pavinanes.

In view of the unsymmetrical nature of the isopavine ring system it is not surprising that a set of empirical rules similar to those for pavinanes could not be found. No firm assignments could be made for the aromatic proton absorptions; in most cases they appear as three or four singlets.

We have now resolved the 1,2-diarylethylamine (**8a**) using (+)-dibenzoyltartaric acid, to give the (+)-base [$[\alpha]_D^{20}$ +87.3 (6.16% in EtOH)]. Conversion to the acetal (**8b**) was effected with bromacetal in DMF under conditions that had previously[7] been shown not to cause any racemisation. Treatment of **8b** with hydrochloric acid, and chromatography of the reaction mixture (Experimental) yielded (−)-reframoline (**10**; 16%) as a microcrystalline solid, m.p. 160°, $[\alpha]_D^{20}$ −144° (0.37% in EtOH) (lit.[23] $[\alpha]_D$ −140° (MeOH)), and (−)-caryachine (**9**; 14%) as a beige solid, m.p. 170°, $[\alpha]_D^{20}$ −251° (0.43% in EtOH) (lit.[18] $[\alpha]_D$ −270° (MeOH)). Unfortunately it has not proved possible to make a direct comparison between natural caryachine and our synthetic sample, either as the racemate or its (−)-form. However there is no doubt about the structure of our compound on the basis of the UV and especially NMR and mass spectral data. The TLC behaviour of our sample of (−)-reframoline is identical with that of the racemate synthesised previously[13] and shown there to be identical with the natural alkaloid.

The absolute configuration of (−)-caryachine has been established[9] as 5*S*, 11*S* by relation with (−)-argemonine (**1f**) of proven absolute configuration. The CD spectrum of (−)-argemonine[24] is very similar to that of our synthetic caryachine (Fig. 1). This is the first time that a synthesis of an optically active pavinane has been described.

It follows that the 1,2-diarylethylamine (+)-(**8a**) has the *S*-configuration. The ORD spectrum of (+) - *S* - 1,2 - diphenylethylamine has been reported,[25] but in view of the fact that a chromophore is directly attached to the chiral centre, care has to be exercised in extrapolating these data to derivatives such as **8a**. The work described here places the absolute configuration of **8a** beyond doubt; the CD spectrum of **8a** is very similar (Fig. 2) to

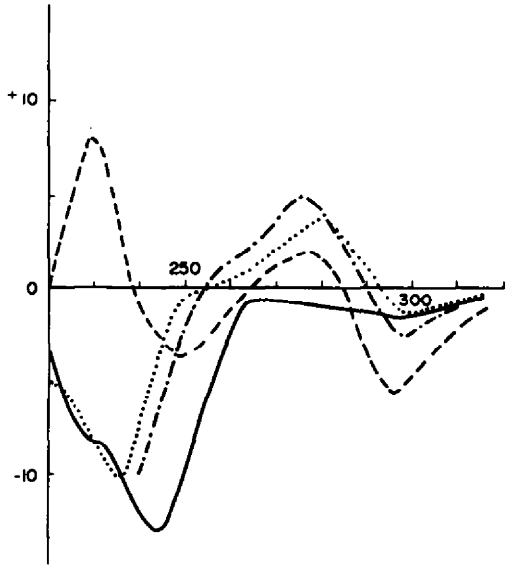


Fig. 1. CD of caryachine (**1a**) (·····); argemonine (**1f**) (–·–·–·); reframoline (**6a**) (——); and amurensine (**6c**) (– – – –).

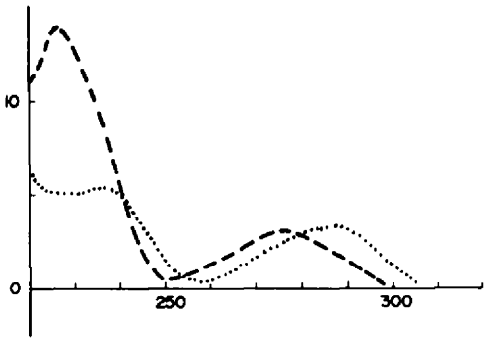


Fig. 2. CD of the diphenylethylamines **8a** (·····) and **8c** (– – – –).

that of (+)-**8c**[7] thus establishing the absolute configuration in the tri-oxygenated derivatives as well.

Since (+)-*S*-**8a** gave rise to (−)-reframoline (**6a**) as well as to (−)-caryachine (**1a**), it follows that natural reframoline has the 5*S*, 10*S*-configuration depicted in **10**. The CD spectrum of **10** is similar to that of (−)-amurensine (**6c**)[26] (Fig. 1); although our spectrum does not exhibit Davydoł splitting, it is clear that the two alkaloids possess the same absolute configuration. Shamma *et al.* had deduced a similar configuration for amurensine by an application of the aromatic chirality method,[27] which is being used increasingly in isoquinoline and other systems.[28,29] The present work offers confirmation of these deductions for the isopavinane alkaloids.

EXPERIMENTAL

M.ps are uncorrected. UV spectra are reported in nm for solns in 95% EtOH and IR spectra in cm^{-1} for Nujol mull or liquid film except where noted. Chemical shifts are expressed in ppm downfield of TMS as internal standard and mass spectra were measured on an AEI MS12 with relative peak intensities quoted as a percentage of the base peak.

Acid cyclisation of **8g**. **8g** (1.0 g) was dissolved in EtOH (25 ml) and conc HCl (25 ml) was added. The soln was left at room temp. for 2 hr then heated under reflux for a further 2 hr after which the EtOH was removed under reduced pressure. The remaining soln was diluted to 100 ml with H_2O, washed with Et_2O (2 × 30 ml), basified ($NaHCO_3$) and extracted with $CHCl_3$ (4 × 30 ml). The combined organic layers were washed with H_2O, dried ($MgSO_4$) and evaporated to give **1e** which recrystallised from MeOH as colourless prisms (264 mg, 39%), m.p. 257–8°. ν_{max} 3280, 3100–2400 broad, 1605, 1480, 1230, 1118, 920, 825; λ_{max} (ϵ) 295 (7300); λ_{max} (ϵ) (EtOH/NaOH) 300 (7600). NMR (TFA), 7.85 broad s [2] (⁺NH₂), 6.85 s [1], 6.75 s [2] and 6.57 s [1] (Ar–H), 5.94 s [1] and 5.90 s [1] (–OCH₂O–), 5.2–5.0 complex [2] (2 × –CH₂CH⁺), 3.96 s [3] (–OCH₃), 3.74 broad d [2] (J = 17 Hz) and 3.10 broad d [2] (J = 17 Hz) (2 × –CH₂CH⁺). Mass *m/e* (%), 311 [M^+] (80), 178 (100), 176 (91). (Found: C, 69.1; H, 5.6; N, 4.7. $C_{18}H_{17}NO_4$ requires: C, 69.4; H, 5.5; N, 4.5%).

N - (4' - *Benzyloxy* - 3' - *methoxybenzylidene*) - 4 - *benzyloxy* - 3 - *methoxybenzylamine*. 4 - Benzyloxy - 3 - methoxybenzaldehyde (9 g) and 4 - benzyloxy - 3 - methoxybenzylamine (9 g) were heated together with C_6H_6 (150 ml) under reflux with a Dean and Stark head for 6 hr. Evaporation of the solvent afforded the Schiff's base as a yellow gum which solidified on standing. ν_{max} 1645; NMR ($CDCl_3$), 8.24 s [1] (–CH=N–), 7.6–6.6 complex [16] (Ar–H), 5.16 s [2] and 5.11 s [2] (2 × $PhCH_2O$–), 4.69 s [2] ($ArCH_2N$=), 3.90 s [3] and 3.86 s [3] (2 × –OCH_3). (Found: C, 77.2; H, 6.4; N, 2.7. $C_{30}H_{29}NO_4$ requires: C, 77.1; H, 6.3; N, 2.8%).

α - (4 - *Benzyloxy* - 3 - *methoxyphenyl*) - β - (3',4' - *methylenedioxyphenyl*)*ethylamine* (**8g**). A soln of the above Schiff's base

(16 g) in dry DMF (275 ml) was added to a stirred slurry of NaH (2 g) in dry DMF under N_2. After stirring for 3 hr, a soln of 3,4-methylenedioxybenzyl chloride (11 g) in dry DMF (50 ml) was added dropwise (over 30 min) to the resultant dark coloured soln. The colour was rapidly discharged and the soln was stirred overnight, then the excess NaH was destroyed by dropwise addition of MeOH (50 ml). The mixture was made just acidic to litmus using glacial AcOH and the solvent was removed at 60° under reduced pressure. The residue was stirred with a mixture of C_6H_6 (250 ml) and 2 M HCl (250 ml) for 4 hr and the hydrochloride of the required amine was filtered off, washed with C_6H_6 and Et_2O then recrystallised from EtOH as colourless needles (75%), m.p. 207–8°. NMR ($CDCl_3$/DMSO), 8.7 broad s [3] ($-\overset{+}{N}H_3$), 7.6–6.4 complex [11] (Ar–H), 5.88 s [2] ($-OCH_2O-$), 5.04 s [2] ($PhCH_2O-$), 3.82 s [3] ($-OCH_3$), 3.6–3.0 complex [2] ($>CHCH_2Ar$), 4.3 m [1] ($>CHCH_2Ar$). (Found: C, 66.7; H, 5.6; N, 3.4; Cl, 8.5. $C_{23}H_{23}NO_4$·HCl requires: C, 66.8; H, 5.8; N, 3.4; Cl, 8.6%). The hydrochloride was stirred with 2 M NH_4OH (100 ml) and the base extracted into Et_2O which was dried (Na_2SO_4) and evaporated to afford a quantitative yield of the free amine as a colourless oil. NMR ($CDCl_3$) 7.6–7.0 complex [5] ($C_6H_5CH_2-$), 7.0–6.5 complex [6] (Ar–H), 5.92 s [2] ($-OCH_2O-$), 5.14 s [2] ($PhCH_2O-$), 4.06 d of d [1] (J = 9 Hz and 5 Hz) ($-CH_2CHNH_2$), 3.9 s [3] ($-OCH_3$), 2.90 d of d [1] (J = 5 Hz and 13 Hz) and 2.75 d of d [1] (J = 9 Hz and 13 Hz) ($-CH_2CHNH_2$), 1.48 broad s [2] ($-NH_2$).

N - *Carbethoxy* - *α* - (4 - *benzyloxy* - 3 - *methoxyphenyl*) - *β* - (3',4' - *methylenedioxyphenyl*) *ethylamine* (**8h**). The amine **8g** (9 g) was stirred with 2 M NaOH (60 ml) and Et_2O (10 ml), then ethyl chloroformate (6 ml) was added dropwise. The Et_2O was allowed to evaporate and the product was collected by filtration, washed with water then recrystallised from MeOH as colourless needles (72%), m.p. 117–8°. NMR ($CDCl_3$) 7.52–7.24 complex [5] ($C_6H_5CH_2-$), 7.0–6.4 complex [6] (Ar–H), 5.88 s [2] ($-OCH_2O-$), 5.09 s [2] ($PhCH_2O-$), 5.05–4.65 complex [2] (>NH) and (ArCHNH–), 4.04 q [2] (J = 7.5 Hz) ($-CH_2CH_3$), 3.80 s [3] (OCH_3), 2.93 d [2] (J = 6 Hz) ($>CHCH_2-$), 1.16 t [3] (J = 7.5 Hz) ($-CH_2CH_3$). (Found: C, 69.6; H, 6.2; N, 3.2. $C_{26}H_{27}NO_6$ requires: C, 69.5; H, 6.0; N, 3.1%).

N - *Methyl* - *α* - (4 - *benzyloxy* - 3 - *methoxyphenyl*) - *β* - (3',4' - *methylenedioxyphenyl*) *ethylamine* (**8a**). The carbamate **8h** (10 g) in dry dioxan (50 ml) was added dropwise to a stirred suspension of LAH (5 g) in boiling dioxan (300 ml). After stirring under reflux for 3 hr the excess reagent was decomposed with 20% NaOH aq (25 ml) and the mixture was filtered. The solvent was removed under reduced pressure and the residual oil was treated with 2 M NaOH (50 ml) and extracted with Et_2O (2 × 100, 1 × 50 ml). The combined extracts were dried (Na_2SO_4) and treated with HCl gas causing precipitation of the amine salt which was collected by filtration and recrystallised from EtOH as colourless needles (75%), m.p. 173–5°. NMR ($CDCl_3$/DMSO) 9.96 broad s [2] ($>\overset{+}{N}H_2$), 7.5–7.2 broad s [5] ($C_6H_5CH_2-$), 7.0–6.4 complex [6] (Ar–H), 5.86 s [2] ($-OCH_2O-$), 5.1 s [2] ($PhCH_2O-$), 3.94 s [3] ($-OCH_3$), 3.8–3.0 complex [3] ($-CH_2CH<$), 2.45 broad s [3] ($-\overset{+}{N}H_2CH_3$). (Found: C, 66.6; H, 6.2; N, 3.4; Cl, 8.3. $C_{24}H_{25}NO_4$·HCl requires: C, 67.4; H, 6.1; N, 3.3; Cl, 8.3%). The hydrochloride was stirred with 2 M NH_4OH (100 ml) and the free amine was extracted into Et_2O (2 × 100, 1 × 50 ml). Evaporation of the dried (Na_2SO_4) combined extracts afforded the required base **8a** in quantitative yield as a colourless oil. λ_{max} (*ε*) 237 (11,600), 285 (7000). NMR ($CDCl_3$) 7.6–7.1 complex [5] ($C_6H_5CH_2-$), 6.9–6.4 complex [6] (Ar–H), 5.92 s [2] ($-OCH_2O-$), 5.13 s [2] ($PhCH_2O-$), 3.88 s [3] ($-OCH_3$), 3.64 t [1] (J = 7 Hz) ($-CH_2CH<$), 2.78 d [2] (J = 7 Hz) ($-CH_2CH<$), 2.2 s [3] ($-NHCH_3$), 1.55 broad s [1] ($-NHCH_3$).

Resolution of **8a**. The racemic amine **8a** (9.8 g, 0.025 mole) and (+)-dibenzoyltartaric acid (4.71 g, 0.0125 mole) were dissolved in 95% EtOH (150 ml) and heated at reflux for a short time. The soln was diluted to 350 ml with hot EtOH, filtered while hot, then left to stand at room temp. After 72 hr the crystallised solid was collected by filtration and recrystallised twice from EtOH. Treatment of the salt with M/10 NH_4OH followed by extraction with Et_2O afforded the free amine with $[\alpha]_D^{20}$ +72.6°. The salt was reformed and further recrystallised until regenerated amine showed a constant specific rotation. The yield of (+)-**8a** was 1.5 g (31%) with $[\alpha]_D^{20}$ +87.3° (6.2% in EtOH).

(+) - N - *Methyl* - N - [*α* - (4 - *benzyloxy* - 3 - *methoxyphenyl*) - *β* - (3',4' - *methylenedioxyphenyl*) *ethyl*]*aminoacetaldehyde diethylacetal* (**8b**). Bromoacetal (1.5 g) was added portionwise over 12 hr to a stirred mixture of the (+)-amine **8a** and anhyd K_2CO_3 (0.3 g) in dry DMF (10 ml) at 100° under N_2. Examination of the reaction mixture by gc showed that no further reaction occurred after 36 hr at 100°. The mixture was allowed to cool, then was poured into H_2O (75 ml) and the product was extracted with C_6H_6 (4 × 25 ml), the combined extracts were washed with H_2O (5 × 10 ml) and evaporated. Excess reagent was removed at 60° (1 mm pressure) over 30 min and the resultant black gum was chromatographed on neutral Al_2O_3, eluting with 20% $CHCl_3$ in C_6H_6 to give **8b** as a colourless oil (68%). $[\alpha]_D^{20}$ +67.3° (1.4% in EtOH). NMR ($CDCl_3$), 7.5–7.2 complex [5] ($C_6H_5CH_2-$), 6.9–6.3 complex [6] (Ar–H), 5.82 s [2] ($-OCH_2O-$), 5.08 s [2] ($PhCH_2O-$), 4.46 t [1] (J = 5 Hz) [$-CH_2CH(OEt)_2$], 3.82 s [3] ($-OCH_3$), 3.8–2.4 complex [9] (2 × $-OCH_2CH_3$) and ($ArCH_2CH\,NCH_2-$), 2.3 s [3] ($>NCH_3$), 1.15 t [6] (J = 8 Hz) (2 × CH_3CH_2O-).

Caryachine (**9**) *and Reframoline* (**10**). The aminoacetal (+)-**8b** (400 mg) was dissolved in EtOH (25 ml) and 6 M HCl (50 ml) was added. The soln was left to stand at room temp overnight and then heated on a steam bath for 6 hr. After cooling, the soln was poured into H_2O (100 ml), washed with Et_2O (2 × 50 ml), basified ($NaHCO_3$) and extracted with $CHCl_3$ (3 × 100 ml). Evaporation of the dried (Na_2SO_4) combined extracts gave a yellow oil (170 mg) which solidified on trituration with Et_2O. TLC on silica (10% MeOH in $CHCl_3$) showed two major components with R_f values of 0.15 and 0.40, which were separated by column chromatography (SiO_2) to yield **9** and **10** respectively. **9** was obtained as a beige crystalline solid on trituration with Et_2O (35 mg, 14%), m.p. 170° (lit.[18] m.p. 175°) with $[\alpha]_D^{20}$ −251° (0.43% in EtOH) (lit.[18] $[\alpha]_D^{20}$ −270° in MeOH). λ_{max} (*ε*) 294 (9000); λ_{max} (hexane), 278, 285, 290, 295, 303. NMR ($CDCl_3$), 6.59 s [2], 6.50 s [1] and 6.43 s [1] (Ar–H), 5.87 s [1] and 5.82 s [1] ($-OCH_2O-$), 5.1 broad s [1] (–OH), 3.86 s [3] ($-OCH_3$), 4.1–3.2 complex [6] (aliphatic H), 2.53 s [3] ($>NCH_3$). Mass *m/e* (%), 326 (15), 325 [M^+] (50), 324 (34), 282 (3), 190 (100), 188 (100). High resolution: M^+-1 found: 324.1228; $C_{19}H_{18}NO_4$ requires: 324.1236. **10** was isolated as a beige crystalline solid on trituration with Et_2O (41 mg, 16%). M.p. 160° with $[\alpha]_D^{20}$ −144° (0.37% in EtOH) (lit.[23] $[\alpha]_D^{20}$ −140° in MeOH). λ_{max} (*ε*) 294 (7000), 230 sh (10,000). NMR ($CDCl_3$), 6.78 s [1], 6.73 s [1], 6.62 s [1] and 6.49 s [1] (Ar–H), 6.2 broad s [1] (–OH), 5.86 s [1] and 5.83 s [1] ($-OCH_2O-$), 3.85 s [3] ($-OCH_3$), 3.8–2.8 complex [6] (aliphatic H), 2.55 s [3] ($>NCH_3$). Mass *m/e* (%), 326 (7), 325 [M^+] (32), 324 (35), 282 (38), 190 (100), 188 (4). High resolution: M^+-1 found: 324.1231; $C_{19}H_{18}NO_4$ requires: 324.1236.

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