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HOMOISOPAVINANES—A HIGHLY PROBABLE CLASS OF PHENETHYLISOQUINOLINE ALKALOIDS

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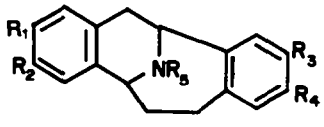
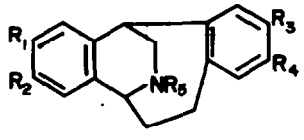
Abstract—Homoisopavinanes have been prepared by acid-catalysed cyclisation of the appropriately substituted aminoacetaldehyde dimethylacetal derivatives. The characteristic mass spectral fragmentation patterns of these homoisopavinanes is described.

In recent years a number of alkaloids has been identified that can be regarded as derivatives of 1-phenethylisoquinoline,[1–4] viz. simple 1-phenethyl-1,2,3,4-tetrahydroisoquinolines, bisphenethyltetrahydroisoquinolines, androcymbines, colchicine, homomorphinandiones, homoproaporphines, homoaporphines and homoerythrines. So far these alkaloids have been isolated from plants in the Androcymbium, Colchicum, Kreysigia, Bulbocodium, Schelhammora and Phelline families. Homoprotoberberines, although not yet known as natural products, have been synthesized,[5–7] and it is our belief that derivatives of the homopavinane (1) and homoisopavinane (2) ring systems represent highly probable examples of the phenethylisoquinoline alkaloid class. A synthesis of (±) -homoargemonine (1a) has been reported[8] by a method analogous to that used in the preparation of the naturally occuring pavinanes.[9] In this paper we describe syntheses of derivatives of the hitherto unknown homoisopavinane ring system.

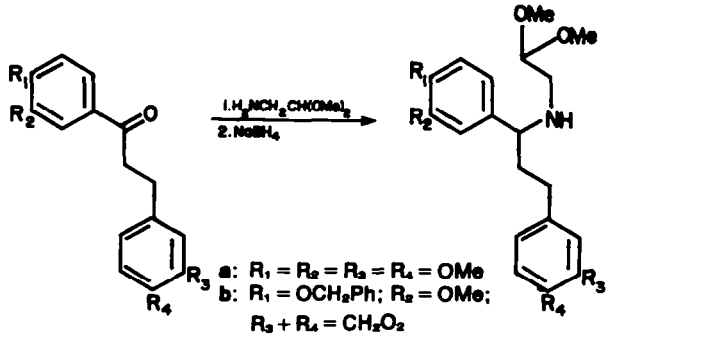


1a: $R_1 = R_2 = R_3 = R_4 = OMe$; $R_5 = Me$
1b: $R_1 = OH$; $R_2 = OMe$; $R_3 + R_4 = CH_2O_2$; $R_5 = H$



2a: $R_1 = R_2 = R_3 = R_4 = OMe$; $R_5 = H$
2b: $R_1 = R_2 = R_3 = R_4 = OMe$; $R_5 = Me$
2c: $R_1 = R_3 = R_4 = OMe$; $R_2 = OH$; $R_5 = H$
2d: $R_1 = R_2 = R_3 = OMe$; $R_4 = OH$; $R_5 = H$
2e: $R_1 = OH$; $R_2 = OMe$; $R_3 + R_4 = CH_2O_2$; $R_5 = H$

The first target was the tetramethoxy, secondary amine **2a** since, after N-methylation, a comparison with **1a** would be possible. The ketone **3a**[10] was condensed with aminoacetal and the resultant imine, without isolation, was reduced to the amino acetal derivative **4a**. Treatment of **4a** with ethanolic, aqueous HCl, under conditions used[11] successfully for the preparation of isopavinanes, yielded a brown basic oil which was found (tlc) to be a mixture of two major and several minor components. Chromatography over silica (Experimental) gave the required homoisopavinane **2a** as a beige, amorphous solid in 39% yield. It was identified by its ^{1}H NMR spectrum (only FOUR *singlets* in the aromatic region), but especially by the mass spectrum (Scheme 1). As in the case of the isopavinanes, the molecular ion and the $(M-1)^+$ ion are intense; the M^+ ion is the base peak in the case of **2a**. Also like the behaviour of isopavinanes this homoisopavinane exhibits a retro Diels–Alder fragmentation to give peak "a" at *m/e* 326. However, unlike isopavinanes, further fragmentation of "a" occurs to give the stable ion "b" at *m/e* 298. In an alternative fragmentation of the molecular ion, the single isoquinolinium



a: $R_1 = R_2 = R_3 = R_4 = OMe$
b: $R_1 = OCH_2Ph$; $R_2 = OMe$; $R_3 + R_4 = CH_2O_2$

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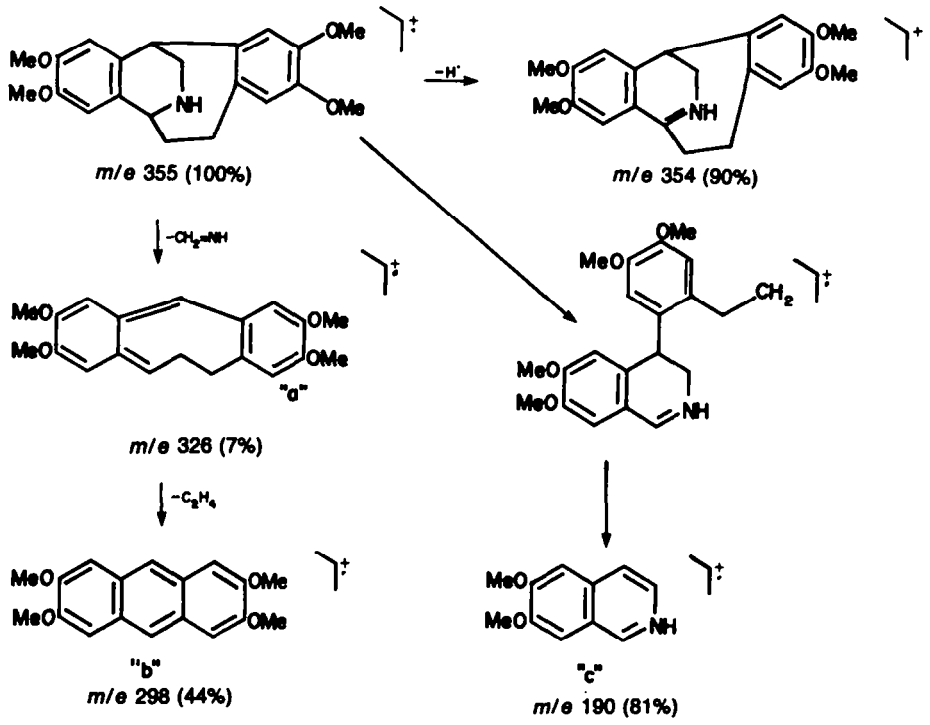
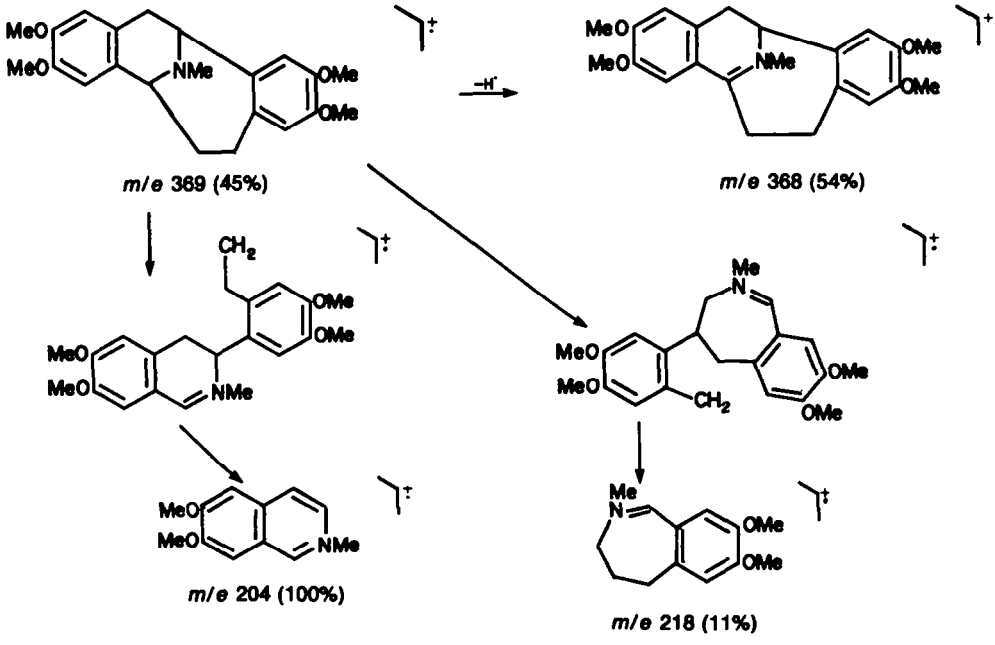


Scheme 1.

ion "c" is produced at *m/e* 190; a similar fragmentation occurs in the isopavinanes themselves. All of these fragmentations are supported by the appearance of the appropriate metastable ions. Treatment of the free base **2a** with formaldehyde, followed by reduction with $NaBH_4$, gave the N-methylhomoisopavinane **2b**. That this material is the homoisopavinane **2b** and not the homopavinane **1a** was confirmed by an examination of the mass spectrum, where fragmentations entirely analogous to those shown in Scheme 1 for **2a** were recorded. Furthermore, high resolution mass measurement of the parent ion [Found: 369.1926; $C_{22}H_{27}NO_4$ requires: 369·1940] and of the ion "b" [Found: 298·1220; $C_{18}H_{18}O_4$ requires: 298·1205] confirmed these assignments. The mass spectral data reported by Stermit and Williams (*loc. cit*) can be rationalised in terms of fragmentations similar to those exhibited by pavinanes,[12] and, summarised in Scheme 2. However, unlike pavinanes, homopavinanes can produce only one isoquinolinium ion.

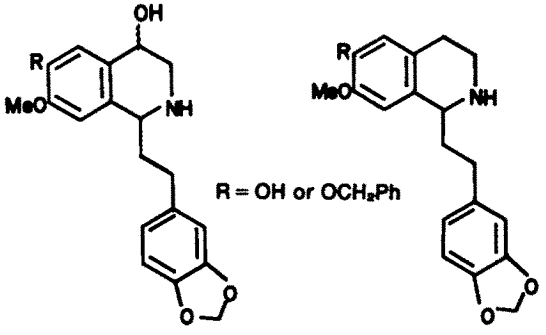
The other major component (11%) from the treatment of **4a** with HCl was isolated as a white solid, m.p. 106–108°. From the ^1H NMR and especially from the mass



Scheme 2.

spectral evidence, it was concluded that this component was a mixture of two monophenolic homoisopavinanes; all attempts to separate them failed. Phenolic functions were suggested by the observed bathochromic shift in NaOH solution. *TWO* isoquinolinium fragments were detected in the mass spectrum, one was the ion "c" at *m/e* 190, and the second, at *m/e* 176, corresponds to a monomethoxy monohydroxyisoquinolinium cation radical. Peaks at *m/e* 312 and *m/e* 284 correspond to retro Diels Alder fragmentation, but the ions corresponding to "a" and "b" are presumably isomers derived from the two different monohydroxy homoisopavinanes. The most probable structures for these compounds are **2c** and **2d**, since demethylation is most likely to occur at the methoxyl groups *para* to the position of ring-closure of **4a**.

The acid-catalysed cyclisation of **4b** was chosen for study since, on the basis of experience in the pavinane and isopavinanes series,[13] it might be anticipated that cyclisation would give rise to a mixture of the homopavinane **1b** and the homoisopavinane **2e**. In the event a mixture of bases resulted, consisting of one major component and several minor ones. The major component was isolated after chromatography as a beige solid in 63% yield. The structure was established as **2e** from UV, ^{1}H NMR and especially mass spectral data. The fragmentation pattern, proved to be entirely analogous to that of **2a** (Scheme 1) except that the anthracene derivative at *m/e* 268, analogous to "b" proved to be the base peak. The homopavinane (**1b**) was not found in the reaction mixture, presumably because the intermediate 4-hydroxy-1-phenethyltetrahydroisoquinoline (**5**) undundergoes cyclisation to **2e** more rapidly than dehydration can occur to give the 1,2-dihydroisoquinoline (**6**), the precurser of **1b**.



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EXPERIMENTAL

UV spectral data refer to EtOH solns, and IR spectra were measured on Nujol mulls. Proton NMR spectra were measured at 60 MHz or 100 MHz, and chemical shifts are expressed in ppm downfield from internal TMS. M.ps are uncorrected. Mass spectral measurements were made at low resolution on AEI MS12, and at high resolution with AEI MS 902 instruments.

N - [1,3 - *bis* (3,4 - *Dimethoxyphenyl*) *propyl*] *aminoacetaldehyde dimethylacetal* (**4a**)

The ketone **3a** [16] (6.0g) and aminoacetal (30ml) were heated under reflux in N_2 for 4 hr. The resultant soln was diluted with EtOH (100 ml) and $NaBH_4$ (1.0g) added portionwise with stirring. Stirring was continued at r.t. for 16 hr, then excess aminoacetal and EtOH removed under reduced pressure. The residue was dissolved in Et_2O(100 ml), the soln washed with H_2O(2 × 50 ml) and extracted with ice cold 2M H_2SO_4 (3 × 50 ml). After washing with Et_2O, the combined acid extracts were basified (2M NH_3 soln) and extracted with Et_2O(3 × 100 ml). Evaporation of the dried (Na_2SO_4) Et_2O soln gave the required **4a** as a colourless oil (61%), $\lambda_{max}(\epsilon)$: 235(17,200); 282(7800), ^{1}H NMR($CDCl_3$): 7·0–6·58 m [6] (6 × Ar–H); 4·4t, J = 5 Hz [1] (CH(OMe)$_2$); 3·9s and 3.85 *s* [12] (4 × Ar–OMe); 3.52t J = 7 Hz [1] (> CH–N–collapsed to singlet by irradiation at 1.96δ); 3.35 s[3] and 3.30 s[3] ($CH(OCH_3)_2$); 2.54d J = 5 Hz [2] (–CH_2–N–collapsed to singlet by irradiation at 4.4δ); 2.5t J = 7 Hz (Ar–CH_2); 2.0 m [2] (–CH_2–CH_2–N); 1·67 b.s[1] (NH–removed by D_2O). [Found: C,63·1; H,7·1; N,3·5. $C_{23}H_{33}NO_6$ requires: C,63·2; H,7·4; N,3·9%].

Acid-catalysed cyclisation of **4a**. Conc HCl (50 ml) was added to a soln of **4a** (1.0 g) in EtOH (50 ml), and the mixture was heated under reflux for 4 hr, poured into H_2O(200 ml), washed with Et_2O(2 × 50 ml), basified with conc NH_3 and extracted with Et_2O(3 × 100 ml). Evaporation of the combined dried (Na_2SO_4) Et_2O extracts left a brown oil (0.76 g). Tlc (silica/10%MeOH in $CHCl_3$) gave two major components at R_f 0·40 and 0·20 and four other spots at R_f 0·75, 0·69, 0·58 and 0·1. Column chromatography (silica/$CHCl_3$) afforded partially purified samples of the two major components. Further purification of each was achieved by preparative tlc on 1·0 mm thick SiO_2 PF_{254} layers using multiple elution with 5% MeOH in $CHCl_3$.

The component R_f 0.40 gave **2a** (39%) as amorphous solid. $\lambda_{max}(\epsilon)$: 233(13,500); 287(6600). ^{1}*H NMR*(*CDCl*$_3$): 6.75*s* [2] (2 × Ar–H); 6.57*s* [1] (Ar–H); 6.51s [1] (Ar–H); 4.46 b s [1] (CH–N); 4·02 b s [1] (Ar–CH–Ar); 3.86–3·79 four singlets [12] (4 × OMe); 2·88 b s [2] (–CH_2–N); 2·26 b s [1] (NH–removed by D_2O); 2·0 b Absorption [4] (–CH_2–CH_2–). M.S. *m/e* 355 M^+ (100%); 354(M–1)$^+$ (90%); 326(7%); 298(44%); 190(81%). m* 272·4. [Found: C, 70·1; H,7·3; N, 3·6. $C_{21}H_{25}NO_4$ requires: C, 71·0; H, 7·0; N, 3·9%]. Hydrochloride m.p. 242–244· [Found: C, 64·2; H, 6·65; N, 3·7; Cl, 9·25. $C_{21}H_{26}NO_4Cl$ requires: C, 64·4; H, 6·6; N, 3·6; Cl, 9·1%].

The second major component from the column, purified by prep tlc as above was obtained [11%] as a white solid, m.p. 106–108° λ_{max} (ϵ): 232(10,800); 287(6200). After addition of NaOH λ_{max} 232, 293 and 300. M.S. *m/e* 341(100%); 340(96%); 312(9%); 284(61%); 190(97%); 176(52%). m* 311, 285·5; 283, 106, 91 [Found: C, 69·6; H, 6·8; N, 3·85. $C_{20}H_{23}NO_4$ requires: C, 70·4; H, 6·7; N, 4·1%].

N-*Methylation of the homoisopavinane* (**2a**). The base **2a** (113 mg) was dissolved in MeOH (10 ml) and HCHO, (37–41% W/V 1 ml) added. After stirring 1 hr $NaBH_4$ (0·2 g) was added portionwise and mixture stirred at r.t. 16 hr. The soln was acidified (dil. HCl) and evaporated. The residue was dissolved in H_2O (25 ml) and made basic (NH_3 soln), then extracted with CH_2Cl_2 (2 × 25 ml). The combined extracts were washed with H_2O (12·5 ml), dried (Na_2SO_4) and evaporated to leave **2b** as a white solid (85%), λ_{max} (ϵ): 233(12,400); 285(6,700), ^{1}H NMR ($CDCl_3$); 6·77 s [2] (2 × Ar–H); 6·55 s [1] (Ar–H); 6·50s [1] (Ar–H); 4·0t [1] (CH–N); 3·92–3·76 three singlets [13] (4 × OMe + Ar–CH–Ar); 3·04 dd, J = 10 Hz, 4 Hz [1] and 2·60 dd, J = 10 Hz and 4 Hz [1] (CH–CH_2–N); 2·45 [3] (NMe); 2·3–1·6 m [4] (CH_2–CH_2). M.S. *m/e* 369 (M^+) (93%); 368(M–1)$^+$ (97%); 338(4%); 326(4%); 311(4%); 298(19%); 218(3%); 204(100%). M^+ Found: 369·1926. $C_{22}H_{27}NO_4$ requires: 369·1940. Peak at *m/e* 298, mass found: 298·1220; $C_{18}H_{18}O_4$ requires: 298·1205. Hydrochloride, colourless needles, m.p. 220–223° from acetone [Found: C, 64·2; H, 6·8; N, 3·3; Cl, 8·5. $C_{22}H_{28}NO_4$ Cl requires: C, 65·1; H, 6·9; N, 3·45; Cl, 8·75%].

1 - (3-*Methoxy* - 4 - *benzyloxyphenyl*) -3 -(3,4- *methylenedioxyphenyl*)*propen* - 1 - *one*. 3 - Methoxy - 4 - benzyloxyacetophenone (23.43 g) and 3,4-methylenodioxybenzaldehyde (13.73 g) were dissolved in EtOH (130 ml) and 2 M NaOH (20 ml) added. The required $\alpha\beta$- unsaturated ketone crystallised out almost immediately, but the mixture was left at 0° for 16 hr before the product was collected. Recrystallation from EtOH gave yellow needles m.p. 137–138° [Found: C, 77·4; H, 6·2. $C_{24}H_{20}O_4$ requires: C, 77·5; H 6·2%].

1 - (3 - *Methoxy* - 4 - *benzyloxyphenyl*) - 3 - (3,4 - *methylenedioxyphenyl*) - *propan* - 1 - *one* (**3b**). The above chalcone (5·0 g) was dissolved in glacial AcOH (150 ml) and stirred with H_2 in the presence of Adam's catalyst (200 mg) for 3 days at r.t. and

atmospheric pressure. After filtration, the soln was evaporated and the residue crystallised from EtOH to **3b** (66%) as white needles, m.p. 93·5–94° [Found: C, 77·1; H, 5·8, $C_{24}H_{22}O_4$ requires: C, 77·0; H, 5·9%]

N - [1 - *Methoxy* - 4 - *benzyloxyphenyl*) - 3 - (3,4 - *methylenedioxyiphenyl*) - *propyl*]*aminoacetaldehyde dimethyl acetal* (**4b**). The ketone **3b** (3·0 g) and amino acetal (15 ml) were heated under reflux in N_2 for 5 hr. After dilution with EtOH(50 ml), $NaBH_4$ (0·5 g) was added portionwise with stirring at rt. After 16 hr the EtOH and excess of amino acetal were removed under reduced pressure, and the residue was dissolved in Et_2O (100 ml). The soln was washed with H_2O (2 × 50 ml), then extracted with ice-cold 2 M H_2SO_4 (3 × 50 ml). The combined acid extracts were washed with Et_2O (100 ml), basified with NH_3 soln and extracted with Et_2O (3 × 100 ml). Evaporation of the combined, dried (Na_2SO_4) extracts left **4b** as a colourless oil (61%), λ_{max} (ε): 223(13,800); 234(15,800); 283(8300), ^{1}H NMR($CDCl_3$): 7·5–7·18 m[5] (C_6H_5–CH_2O); 6·9–6·4 m[6] (6 × Ar–H); 5·83 s[2] (CH_2O_2); 5·06 s [2] ($C_6H_5\underline{CH_2}O$); 4·3 t J = 5 Hz [1] (CH(OMe)$_2$); 3·83 s [3] (Ar–OMe); 3·42 t, J = 6H [1] (CH–N–collapsed to singlet by irradiation at 1·91δ); 3·28 s [3] and 3·23 s [3] (CH-O$\underline{CH_3}$)$_2$); 2·48 d, J = 5 Hz [2] (–CH_2–N–collapsed to singlet by irradiation at 4·3δ); 2·4t, J = 8 Hz [2] (Ar–CH_2); 1·91 m [2] (CH_2–CH_2); 1·52 b s [1] (NH–removed by D_2O). [Found: C, 70·0; H, 6·5; N, 3·0, $C_{28}H_{33}NO_6$ requires: C, 70·3; H, 6·75; N, 2·9%].

Acid catalysed cyclisation of **4b**. Conc HCl (50 ml) was added to a soln of **4b** (1.0 g) in EtOH (50 ml) and the mixture was heated under reflux for 4 hr, then poured into H_2O (200 ml), and the resultant soln was washed with Et_2O (2 × 50 ml). The pH of the aqueous acid soln was adjusted to 9·0 with dil. NH_3, and the mixture extracted with CH_2Cl_2 (3 × 100 ml). Evaporation of the dried (Na_2SO_4) extracts left a yellow gum. Column chromatography over SiO_2 and elution with 1% MeOH in $CHCl_3$ gave **2e** as a beige solid (63%), λ_{max} (ε): 224(7500); 291 (5300). After addition of NaOH, λ_{max} (ε): 224(9700); 245 (7600); 297 (5700), ^{1}H NMR ($CDCl_3$): 6·75 s [1], 6·72 s [1]; 6·55 s [1] and 6·50 s [1] (Ar–H's 5·90 s [2] (CH_2O_2); 5·50 b s [2] (OH + NH–removed by D_2O); 4·52 b s [1] (> CH–N); 3·95 b s [1] (Ar–CH–Ar); 3·80 s [3] (OMe); 2·90 b s [2] (CH_2–N); 2·02 b absorption [4] (CH_2–CH_2). M.S. *m/e* 325 (M^+) (71%); 324(M–1)$^+$ (73%); 296(16%); 268(100%); 190(89%); 176(83%). m* 242·5. Hydrochloride m.p. 230–232° (dec) [Found: C, 63·4; H, 5·7; N, 3·7; Cl, 9·35. $C_{19}H_{20}NO_4Cl$ requires: C, 63·1; H, 5·5; N, 3·9; Cl, 9.8%].

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