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THE SYNTHESIS OF ISOPAVINE ALKALOIDS—III[1]

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Abstract—The two isopavines (**1e** and **1f**) have been synthesised, and the former has been found to correspond to the structure of the alkaloid reframoline. The two related pavines were isolated and identified as by-products. In one case some evidence was obtained for a $C_1 \rightarrow C_3$-benzyl migration in the isoquinoline system.

Although it has proved to be impossible to distinguish between the two isopavines by spectral methods, a significant difference was observed in the UV spectra of the derived methine bases in alkaline solution.

In Part I of this series[2] we briefly reviewed the isopavine alkaloids, and listed the problems requiring solution. We described syntheses of reframidine (**1a**) and reframine (**1b**) that involved the deoxybenzoins (**2a** and **2b**). Condensation of each of these ketones with aminoacetaldehyde dialkyl acetal, followed by reduction with $NaBH_4$ gave the aminoacetals (**3a** and **3b**) which, upon treatment with mineral acid underwent double cyclisation via the 1-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines (**4a** and **4b**). N-methylation of the products completed the preparation of the required isopavines (**1a** and **1b**).

In Part II[1] we described the preparation of the two phenolic isopavines (**1c** and **1d**), and we were able to show that **1d** is identical with the alkaloid amurensine. However, since we were unable to prepare the deoxybenzoins (**2c** and **2d**), we developed an alternative, less satisfactory method involving the hydroboration and oxidation of the 1,2-dihydroisoquinolines (**10a** and **10b**). In this paper we report the syntheses of the isopavines (**1e** and **1f**), one of which is identical with the alkaloid reframoline.[3]

Two alternative methods have been used for the formation of the amine derivatives of type **3** required for the double cyclisation. In the first method, the Schiff's base (**5a**) was alkylated with 3,4-methylenedioxybenzyl chloride in the presence of NaH/DMF.[4] Hydrolysis gave the amine (**3c**), which, could not be mono-N-methylated by the usual treatment with formaldehyde and formic acid (possibly because a Pictet-Spengler reaction was occurring). However, the derived urethane (**3d**) was reduced with LAH to the required secondary amine (**3e**) which was then reacted with glycidol, followed by periodic acid. The aminoacetaldehyde (**3f**) was, without isolation, cyclised as previously described.[5] The expected 4-hydroxyisoquinoline derivative (**4e**) was not isolated; it cyclised immediately with concommitant loss of the O-benzyl group to yield the phenolic isopavine (**1e**).

The isomeric isopavine (**1f**) was obtained in a similar manner from the Schiff's base (**5b**).

The preferred method of preparation of the isopavine ring-system became possible when an alternative method[6] of preparation of the required deoxybenzoins was developed.[7] Condensation of the benzaldehyde (**6a**) with N-methylaminoacetaldehyde diethylacetal hydrochloride and KCN led to the aminonitrile derivative (**7a**) in high yield. The latter was alkylated with 3,4-methylenedioxybenzyl chloride in the presence of NaH/DMF, and the intermediate enamine (**8a**) was reduced *in situ* with $NaBH_4$ to provide the required animoacetal (**3j**). This product was contaminated by small amounts of the unalkylated aminoacetal (**7c**). Experimentally the most satisfactory procedure was to remove impurities at the end of the synthesis, rather that at this stage. A small portion of the enamine (**8a**) was hydrolysed with dilute HCl to give, in good yield, the deoxybenzoin (**2e**). Double cyclisation of **3j** was effected with 6N HCl as before.[2] The mixture of bases produced was chromatographed over alumina when the isopavine (**1e**) was obtained in 5% yield based upon **6a**. Thus, the synthesis can be effected in three isolated steps from readily available materials.

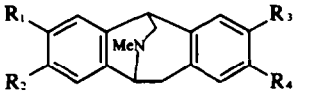
When the original mixture of bases from the double cyclisation was chromatographed over silica, a second, isomeric base wss isolated in 2% yield. An examination of the mass spectral fragmentation pattern[8] enabled the pavine structure (**9a**) to be allotted to this compound. The NMR spectrum and especially the UV spectrum[9] were each compatible with this structure. Clearly, when the intermediate 1-benzyl-4-hydroxy- 1,2,3,4-tetrahydroisoquinoline (**4e**) is formed in the initial cyclisation of **3j**, a competition between nucleophilic sustitution at C_4 by the 1-benzyl group leading to isopavine formation,[5] and dehydration to the 1,2-dihydroisoquinoline (**10c**) occurs. It has already been established[10] that 1-benzyl-1,2-dihydroisoquinolines can undergo

cyclisation to pavine derivatives under the conditions employed. An alternative reaction pathway for **10c** under mildly acidic conditions[10] involves rearrangement to the 3-benzyl-3,4-dihydroisoquinolinium salt. Although there was no clearcut evidence for this under the normal procedure, when reaction conditions most likely to favour the benzyl migration were used a very small amount of the rearrangement product was detected as the pseudo cyanide (**11g**).

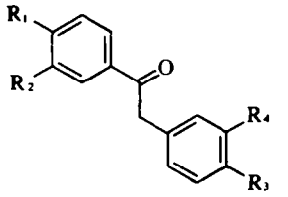
The isopavine (**1e**) which was firmly adsorbed onto the silica used in the chromatography, was removed with methanol and purified by chromatography over alumina as before.

The entire sequence of reactions was repeated using the aldehyde (**6b**), when the isopavine (**1f**) and the pavine (**9b**) were obtained in 9% and 10% yields, respectively. The pavine (**9b**) was also obtained from the sequence of reactions from the Schiff's base (**5b**). The two isopavines (**1e** and **1f**) were each O-methylated with CH_2N_2, then converted into the methiodides with MeI. The products were found to be identical with each other, and with an authentic[2] sample of reframine (**1b**) methiodide. In a similar manner the two pavines (**9a** and **9b**) were converted into the same O-methylpavine methiodide.

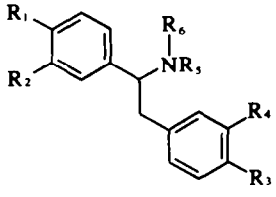
Unfortunately, when the UV (in 95% EtOH), IR (in $CHCl_3$), NMR (in $CDCl_3$, CD_3SOCD_3 and $CD_3CO\,CD_3$) and mass spectral data of **1e** and **1f** were compared, it was not possible to distinguish between the isomers, so that it would not be possible to decide which structure corresponds to that of reframoline by these methods.* Accordingly, each isomer was subjected to a Hofmann degradation, when high yields of the two methine bases (**12a** and **12b**) were obtained. The possible alternative mode



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

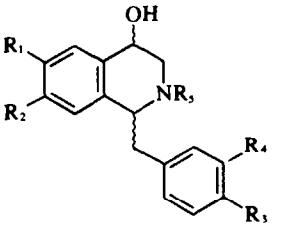


	R_1	R_2	R_3	R_4
2a	O—CH_2—O		O—CH_2—O	
2b	OMe	OMe	O—CH_2—O	
2c	O—CH_2—O		OBz	OMe
2d	O—CH_2—O		OMe	OBz
2e	OBz	OMe	O—CH_2—O	
2f	OMe	OBz	O—CH_2—O	

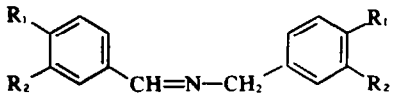


	R_1	R_2	R_3	R_4	R_5	R_6
3a	O—CH_2—O		O—CH_2—O		H	$CH_2CH(OMe)_2$
3b	OMe	OMe	O—CH_2—O		H	$CH_2CH(OMe)_2$
3c	OBz	OMe	O—CH_2—O		H	H
3d	OBz	OMe	O—CH_2—O		CO_2Et	H
3e	OBz	OMe	O—CH_2—O		Me	H
3f	OBz	OMe	O—CH_2—O		Me	CH_2CHO
3g	OMe	OBz	O—CH_2—O		H	H
3h	OMe	OBz	O—CH_2—O		CO_2Et	H
3i	OMe	OBz	O—CH_2—O		Me	H
3j	OBz	OMe	O—CH_2—O		Me	$CH_2CH(OEt)_2$
3k	OMe	OBz	O—CH_2—O		Me	$CH_2CH(OEt)_2$

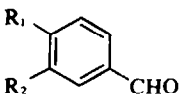
*Although we have not been able to aquire a sample of reframoline, we are indebted to Professor J. Slavic, Dept. Medical Chemistry, University J. E. Purkyne, Brno, Czechoslovakia, who kindly compared samples of **1e** and **1f** with the alkaloid by TLC on silica gel. It was established that, in three solvent systems, **1e** and reframoline exhibited identical behavior; **1f** was shown to be distinctly different.



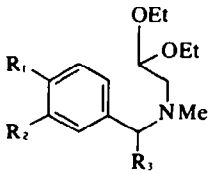
	R_1	R_2	R_3	R_4	R_5
4a	O—CH_2—O		O—CH_2—O		H
4b	OMe	OMe	O—CH_2—O		H
4c	O—CH_2—O		OBz	OMe	Me
4d	O—CH_2—O		OMe	OBz	Me
4e	OBz	OMe	O—CH_2—O		Me
4f	OMe	OBz	O—CH_2—O		Me



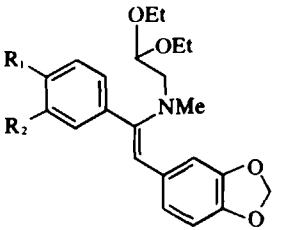
5a R_1 = OBz; R_2 = OMe
5b R_1 = OMe; R_2 = OBz



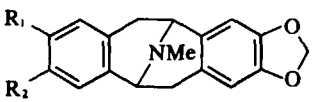
6a R_1 = OBz; R_2 = OMe
6b R_1 = OMe; R_2 = OBz



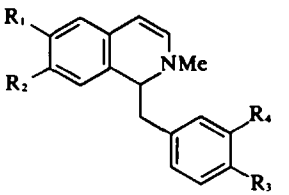
7a R_1 = OBz; R_2 = OMe; R_3 = CN
7b R_1 = OMe; R_2 = OBz; R_3 = CN
7c R_1 = OBz; R_2 = OMe; R_3 = H
7d R_1 = OMe; R_2 = OBz; R_3 = H



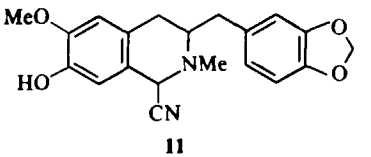
8a R_1 = OBz; R_2 = OMe
8b R_1 = OMe; R_2 = OBz



9a R_1 = OH; R_2 = OMe
9b R_1 = OMe; R_2 = OH



	R_1	R_2	R_3	R_4
10a	O—CH_2—O		OBz	OMe
10b	O—CH_2—O		OMe	OBz
10c	OBz	OMe	O—CH_2—O	
10d	OMe	OBz	O—CH_2—O	



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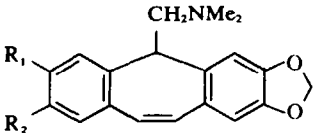

12a R_1 = OH; R_2 = OMe
12b R_1 = OMe; R_2 = OH

of elimination from each methiodide was not observed. The UV spectra (in EtOH) of **12a** and **12b** are quite similar but, as expected, the spectrum of **12a** undergoes a large bathochromic shift in alkali, whilst the UV spectrum of **12b** is almost unaffected.

EXPERIMENTAL

M.ps are uncorrected. UV spectra refer to 95% EtOH solns and IR spectra were measured on Nujol mulls unless otherwise stated. Chemical shifts are expressed in ppm downfield from internal TMS and mass spectra were measured using an AEI MS12 Spectrometer.

N-(3 - *Benzyloxy* - 4 - *methoxybenzylidene*) - 3' - *benzyloxy* - 4' - *methoxybenzylamine* (**5b**) was prepared by condensation of 3 - benzyloxy - 4 - methoxybenzylamine and **6b**, as a white crystalline solid m.p. 118–9° from EtOH, NMR ($CDCl_3$), 8·17 s[1] (CH=N), 7·58–6·67 complex[16] (Aromatic H), 5·13 s[2] and 5·10 s[2] (2 × $ArCH_2$—O), 4·65 s[2] (Ar—CH_2—N=), 3·85 s[3] and 3·82 s[3] (2 × OCH_3); ν_{max} 1640 (—C=N). (Found: C, 77·3; H, 6·3; N; 2·8. $C_{30}H_{29}NO_4$ requires: C, 77·1; H, 6·2; N, 3·0%).

α - (3-*Benzyloxy* - 4 - *methoxyphenyl*) - β - (3', 4' - *methylenedioxyphenyl*) *ethylamine* (**3g**). NaH (0·5 g) was added portionwise to a stirred soln of the above anil (4 g) in DMF (75 ml). To the resulting intense dark green soln was added 3,4-methylenedioxybenzyl chloride (2·8 g) in DMF (20 ml). The mixture was stirred at room temp for 16 h; then decomposed with MeOH. After removal of the solvents, the gummy residue was stirred with 2N HCl: benzene (50:50) for 4 h. The resultant solid contained some of the required amine, together with 2,3-6,7-bismethylenedioxy-9, 10-dihydroanthracene (0·5 g). The benzene soln when saturated with HCl gas gave the hydrochloride of **3g** (1·8 g) m.p. 247–8° (from isopropanol); NMR (CD_3SOCD_3), 8·95 broad[3] (NH_3^+), 7·70–6·37 complex[11] (Aromatic H), 5·92 s[2] (O—CH_2—O); 5·03 s[2] (Ph—CH_2—O); 3·78 s[3] (OCH_3). (Found: C, 67·0; H, 5·85; N, 3·6; Cl, 8·7. $C_{23}H_{23}NO_4$.HCl requires: C, 66·8; H, 5·8; N, 3·4; Cl, 8·6%).

N - *Carbethoxy* - α - (3-*benzyloxy* - 4 - *methoxyphenyl*) - β - (3', 4'-*methylenedioxyphenyl*) *ethylamine* (**3h**). The above amine hydrochloride (1·5 g) was suspended in 10% NaOH aq (10 ml) and ethyl chloroformate (1 ml) added dropwise with cooling. After shaking for 5 min the mixture was extracted with CH_2Cl_2 (3 × 10 ml). Removal of the dried solvent left an oil which quickly solidified (1·5 g) m.p. 137–8° from EtOH; NMR ($CDCl_3$), 7·37 broad s[2] C_6H_5—CH_2), 6·87–6·25 complex[6] (6 × Ar—H), 5·85 s[2] (O—CH_2—O); 5·07 s[2] (Ph—CH_2—O), 4·83 t[2], J = 6 Hz plus s[1] (CH_2—CH plus —NH), 4·03 q[2] J = 7·5 Hz (O—CH_2CH_3), 3·82 s[3] (OCH_3), 2·87 broad d[2] J = 6 Hz (CH_2—CH), 1·13 t[3] J = 7·5 Hz (OCH_2CH_3); ν_{max} 3340 (N—H), 1683 (NHCO). (Found: C, 69·7; H, 6·0; N, 3·0. $C_{26}H_{27}NO_6$ requires: C, 69·5; H, 6·0; N, 3·1%).

N - *Methyl* - α - (3-*benzyloxy* - 4 - *methoxyphenyl*) β - (3', 4'-*methylenedioxyphenyl*) *ethylamine* (**3i**) To a stirred suspension of LAH (1 g) in dioxan (100 ml) was added the preceding carbamate (2 g) in dioxan (10 ml). After stirring under reflux for 3 h the excess reagent was decomposed with 20% NaOH aq and the mixture was filtered. Removal of the dried ($MgCO_3$) solvent left an oil which was purified via its hydrochloride salt to give **3i** (1·8 g). NMR (CD_3SOCD_3) includes 7·60–7·30 complex[11] (Aromatic H), 5·92 s[2] (O—CH_2—O), 5·18 s[2] (Ph—CH_2—O), 3·75 s[3] (OCH_3), 2·32 s[3] (N—CH_3). Perchlorate salt m.p. 128–9° from aqueous EtOH. (Found: C, 58·3; H, 5·3; N, 2·8. $C_{24}H_{25}NO_4.HClO_4$ requires: C, 58·6; H, 5·3; N, 2·85%).

N - *Carbethoxy* - α - (3-*methoxy* - 4 - *benzyloxyphenyl*) - β - (3', 4'-*methylenedioxyphenyl*) *ethylamine* (**3d**) was obtained in an analogous series of reactions from **6a**, m.p. 129–30° from MeOH; NMR ($CDCl_3$), 7·37 broad s[5] $C_6H_5CH_2$), 7·0–6·35 complex[6] (6 × Ar—H), 5·87 s[2] O—CH_2—O), 5·08 s[2] (Ph—CH_2—), 5·00 broad s[1] (N—H), 4·85 t[1] J = 6 Hz (CH_2—CH), 4·05 q[2] J = 7 Hz (OCH_2CH_3), 3·78 s[3] (—OCH_3), 2·92 d[2] J = 6 Hz (CH_2—CH), 1·15 t[3] J = 7 Hz (OCH_2CH_3). (Found: C, 69·4; H, 6·0; N, 3·1. $C_{26}H_{27}NO_6$ requires: C, 69·5; H, 6·1; N, 3·1%).

Cyclisation to isopavine (**1f**) *and pavine* (**9b**). The amine **3i** (1·0 g) and glycidol (1·0 g) were heated together on a steam-bath for 2 h. $CHCl_3$ (30 ml) and H_2O (30 ml) were added, and the stirred soln cooled to 0°. Sodium periodate (1·4 g) in water (10 ml) was added cautiously over 5 min maintaining the temp below 5°. The aqueous phase was then adjusted to pH 8–9 by the addition of 1N NaOH, and the soln stirred for 3 h. The $CHCl_3$ layer was separated, dried and the solvent removed to leave the aminoaldehyde as an unstable orange oil (0·9 g). Conc HCl (75 ml) and EtOH (25 ml) were added and the soln was left at room temperature for 16 h. The soln was then heated under reflux for 2 h and diluted with H_2O. After washing with ether the soln was neutralised with Na_2CO_3 and the phenolic bases extracted with CH_2Cl_2 and subjected to column chromatography on alumina. Elution with $CHCl_3$ afforded **9b** (35 mg) which recrystallised as white needles from acetone m.p. 205–6°.

The alumina was extracted with MeOH (soxhlet) and the recovered material eluted from a silica column using CH_2Cl_2:EtOH:acetone, 3:2:1. The isopavine (**1f**) was obtained as a brown oil (60 mg) [(M^+ − 1) (Found: 324·1234, $C_{19}H_{19}NO_4$ requires: 324·1236)].

The analytical and spectral data for **9b** and **1f** are described later (p. 1198).

Cyclisation to the isopavine (**1e**). The sec amine **3e** was subjected to similar treatment with glycidol to yield **3f** which, without purification, was cyclised with EtOH/HCl as described above. The isopavine **1e** was obtained from a silica column as described for **1f**. Analytical and spectral data appear on p. 1197.

The corresponding **9a** was not obtained in this experiment.

N - *Methyl* - N - (α-*cyano* - 3 - *methoxy* - 4 - *benzyloxybenzyl*) *aminoacetaldehyde diethylacetal* (**7a**). N - methylaminoacetaldehydediethylacetal hydrochloride (17 g) in water (10 ml) was stirred with NaCN (8 g). **6a** (17·5 g) in MeOH (150 ml) was added over 2 h and the mixture stirred at 35° for 24 h. The reddish soln was diluted with water (500 ml) and extracted into ether (4 × 100 ml). The combined ether extracts were washed with water, dried ($MgSO_4$) and removed to give **7a** (24 g, 87%) as a reddish oil; NMR ($CDCl_3$) 7·5–6·75 complex [8] (Aromatic H), 5·10 s[2] (Ph—CH_2—O), 5·01 s[1] (CH—CN), 4·59 t[1] J = 5·3 Hz (CH_2—CH—$(OEt)_2$), 3·85 s[3] (Ar—OCH_3), 3·5 two quartets[4] J = 7·0 Hz (OCH_2CH_3)$_2$, 2·65 d[2] J = 5·3 Hz (CH_2—$CH(OEt)_2$), 2·30 s[3] (N—CH_3), 1·17 and 1·14 two triplets[6] J = 7·0 Hz (OCH_2CH_3)$_2$; ν_{max} liquid film 2215, 1598, 1510 strong, 1270, 1145, 1065, 1030; λ_{max} (ϵ) 310 sh (1260), 281 (4400), 234 (11,400); mass m/e 398 (M^+)[1%], 308[3·6%], 271[3·6%], 242[5·7%], 103[100%], 91[100%]. (Found: M^+ (398·2207) $C_{23}H_{30}N_2O_4$ requires: 398·2206).

N - *Methyl* - N - (*α-cyano* - 3 - *benzyloxy* - 4 - *methoxybenzyl*) *aminoacetaldehyde diethylacetal* (**7b**) was prepared similarly (90%); NMR ($CDCl_3$), 7·5–6·75 complex[8] (Aromatic—H), 5·16 s[2] (Ph—CH_2—O), 5·02 s[1] (>CH—CN), 4·59 t[1] J = 5·2 Hz (CH_2—CH—$(OEt)_2$), 3·89 s[3] (Ar—OCH_3), 3·55 two quartets[4] J = 7·0 Hz (OCH_2CH_3)$_2$, 2·69 d[2] J = 5·2 Hz (CH_2—CH$(OEt)_2$) 2·28 s[3] (N—CH_3), 1·20 and 1·17 two triplets[6] J = 7·0 Hz (OCH_2CH_3)$_2$; ν_{max} liquid film 2220, 1598, 1510 strong, 1265, 1140 1065, 1028; λ_{max} (ϵ) 310 sh (1310), 281 (4140); mass m/e 398 (M^+)[2%], 91[100%]; (Found: M^+ (398·2207) $C_{23}H_{30}N_2O_4$ requires 398·2206).

N - *Methyl* - N - [*α* - (3, 4-*methylenedioxybenzyl*) - 3' - *methoxy* - 4' - *benzyloxybenzyl*] *aminoacetaldehyde diethylacetal* (**3j**). Aminonitrile **7a** (16 g) in dry DMF (100 ml) under N_2 was stirred at 50° overnight with NaH (1·0 g). The blood red anion was cooled to room temp and 3,4-methylenedioxybenzyl chloride (8 g) in DMF (25 ml) was added dropwise over 6 h. The reaction was stirred for a further 24 h and the excess NaH destroyed with MeOH. The solvent was removed under 1 mm pressure, at 90° over 6 h and the crude **8a** was reduced with aqueous ethanolic $NaBH_4$ for 4 h on a steam bath. After leaving to stand overnight the solvent was removed, water added (250 ml), and the mixture extracted with ether (3 × 100 ml). The combined ether extracts were washed with 2N NaOH (2 × 50 ml) and water (2 × 100 ml), dried ($MgSO_4$) and evaporated to leave a mixture of the required **3j** contaminated with some un-alkylated **7c**. Chromatography over alumina and elution with petrol (40–60)/benzene gave a pure sample of **3j**. NMR ($CDCl_3$), 7·5–6·65 complex [11] (Aromatic H), 5·92 s[2] (—O—CH_2—O), 4·98 s[2] (Ph—CH_2—O—), 4·51 t[1] J = 5·2 Hz (—CH—CH_2—N), 3·8–2·7 complex[7] (OCH_2CH_3)$_2$ plus (Ar—CH_2—CH) 3·80 s[3] (Ar—OCH_3), 2·58 and 2·51 two doublets[2] J = 5·2 Hz (—CH—CH_2—N), 2·35 s[3] (N—CH_3), 1·15 t[6] J = 7·1 Hz (OCH_2CH_3)$_2$; mass m/e 507 (M^+)[1·8%], 372[70%], 270[51%], 242[100%], 227[100%].

Further chromatography over alumina and elution with benzene gave **7c** as an oil; NMR ($CDCl_3$) 7·5–6·5 complex[8] (Aromatic H), 5·14 s[2] (Ph—CH_2—O—), 4·64 t[1] J = 5·2 Hz (CH—CH_2—N), 3·88 s[3] (Ar—OCH_3), 3·15 s[2] (Ar—CH_2—N), 2·57 two quartets[4] J = 7·1 Hz (OCH_2CH_3)$_2$, 2·56 d[2] J = 5·2 Hz (CH—CH_2—N), 2·30 s[3] (N—CH_3), 1·20 t[6] J = 7·2 Hz (OCH_2CH_3)$_2$; mass m/e 373 (M^+)[5%], 328[6%], 270 [12%], 227[100%].

Experimentally it was found best to subject the mixture of **3j** and **7c** to the cyclisation conditions and to purify the final mixture by column chromatography.

N - *Methyl* - N - [*α*-(3, 4-*methylenedioxybenzyl*) - 3' - *benzyloxy* - 4' - *methoxybenzyl*]*aminoacetaldehyde diethylacetal* (**3k**). This was obtained, together with **7d** by an analogous method to the above procedure. The acetal **3k** was obtained as an oil. NMR ($CDCl_3$) 7·55–6·3 complex[11] (Aromatic —H), 5·84 s[2] (—O—CH_2—O), 5·13 s[2] (Ph—CH_2—O—), 4·51 t[1] J = 5·2 Hz (CH—CH_2—N), 3·8–2·65 complex[7] (OCH_2CH_3)$_2$ plus (ArCH$_2$—CH), 3·85 s[3] (Ar—OCH_3), 2·56 and 2·51 two doublets[2] J = 5·2 Hz (CH—CH_2—N), 2·25 s[3] (N—CH_3), 1·18 t[6] J = 7·1 Hz ((OCH_2CH_3)$_2$); ν_{max} ($CHCl_3$ solution) 1506, 1491, 1446, 1253; mass m/e 507 (M^-) [1%], 372[88%], 270[45%], 242[98%], 227[100%].

The amine **7d** was eluted from the alumina column with benzene as an oil. NMR ($CDCl_3$) 7·5–6·5 complex [8] (Aromatic —H), 5·14 s[2] (Ph—CH_2—O—), 4·62 t[1] J = 5·2 Hz (CH—CH_2—N), 3·84 s[3] (Ar—OCH_3), 3·50 s[2] (Ar—CH_2—N), 3·57 two quartets[4] J = 7 HZ (OCH_2CH_3)$_2$, 2·55 d[2], J = 5·2 Hz (CH—CH_2—N), 2·25 s[3] (N—CH_3), 1·18 t[6] J = 7 Hz (OCH_2CH_3)$_2$; ν_{max} ($CHCl_3$ soln) 1508, 1255, 1056, 1023; mass m/e 373 (M^+) [4·4%] 328[4·4%], 270[18·5%], 227[100%].

Cyclisation to the isopavine (**1e**) *and the pavine* (**9a**). The mixture of alkylated and unalkylated benzylamines (**3j** and **7c**) was cyclised without separation by standing overnight in 6N HCl. The soln was then heated on a steam bath for 6 h cooled, diluted with water and extracted into ether (2 × 100 ml). The aqueous soln was basified with $NaHCO_3$ and extracted into $CHCl_3$ (4 × 100 ml). The combined $CHCl_3$ extracts were washed with $NaHCO_3$, water and dried ($MgSO_4$). Evaporation of the $CHCl_3$ layer afforded a yellow solid. Chromatography on silica preparative plates, eluting with $CHCl_3$ afforded **9a** (2% based on starting **6a**). Trituration from ether afforded an off-white solid, m.p. 190–194°, NMR ($CDCl_3$), 6·59 s[2] (2 × Ar—H), 6·48 s[1] (Ar—H), 6·44 s[1] (Ar—H), 5·94 broad s[1] (OH, removed by D_2O), 5·79, 5·85 two doublets J = 1·4 Hz (O—CH_2—O), 3·83 s[3] (Ar—OCH_3), 2·52 s[3] (N—CH_3), 4·10–4·20 complex[6] (aliphatic —H); NMR (CD_3SOCD_3), 6·75 s[1] (Ar—H), 6·72 s[1] (Ar—H), 6·51 s[1] (Ar—H), 6·39 s[1] (Ar—H), 5·92, 5·87 two s broad[2] (O—CH_2—O), 3·75 s[3] (Ar—OCH_3), 2·38 s[3] (N—CH_3), 4·0–2·2 complex[6] (aliphatic H). ν_{max} ($CHCl_3$ soln) 3400–3200, 1505, 1487, 1258; λ_{max} (ϵ) 293 (9000) on the addition of NaOH λ_{max} 302; λ_{max} (hexane) resolved into 278, 284, 289, 294, 302; mass m/e 326 (M^+ + 1)[11%], 325 (M^+)[69%], 324 (M^+ − 1)[46·5%], 282[5%], 190[99%], 188[100%] (Found: C, 70·1; H, 5·9; N, 4·3. $C_{19}H_{19}NO_4$ requires: C, 70·1; H, 5·9; N, 4·3%).

The slowest fractions from the silica plate were extracted into MeOH by soxhlet and plated on alumia. Elution with $CHCl_3$ afforded **1e** (8% based on starting **6a**) as a pale yellow solid, m.p. 180–190° NMR ($CDCl_3$) 6·50 s[1] (Ar—H), 6·63 s[1] (Ar—H), 6·75 s[2] (2 × Ar—H), 5·86 and 5·82 two doublets[2] J = 1·5 Hz (OCH_2—O), 5·30–5·0 broad s[1] (—OH, removed by D_2O), 3·85 s[3] (Ar—OCH_3), 3·85–2·30 complex[6] (aliphatic H); NMR (CD_3SOCD_3), 6·89 s[1] (Ar—H), 6·81 s[1] (Ar—H), 6·72 s[1] (Ar—H), 6·58 s[1] (Ar—H), 5·90 broad s[2] (O—CH_2—O), 6·2–5·5 broad[1] (OH, removed by D_2O), 3·76 s[3] (Ar—OCH_3), 2·39 s[3] (N—CH_3), 3·8–2·3 complex[6] (aliphatic H); Part NMR (CD_3COCD_3), 6·90 s[1] (Ar—H), 6·76 s[1] (Ar—H), 6·68 s[1] (Ar—H), 6·46 s[1] (Ar—H), 5·86 and 5·83 two doublets [2] J = 1·5 Hz (O—CH_2—O); ν_{max} ($CHCl_3$ soln) 3450 sharp 3300–3000, 1602, 1505, 1485, 1370 broad, 1260, 1220 broad, 1102 1038, 934, 860; λ_{max} (ϵ) 294 (7,000), 230 sh (10,000), on the addition of NaOH λ_{max} 302; Peak resolution in hexane not as complete as with pavines **9a** and **9b**; mass m/e 325 (M^+)[27%], 324 (M^+ − 1)[26%], 282[22%], 190[100%], 188[4%], metastables 244·5, 213·5, 214, 215. The methiodide salt formed from acetone with a mole of solvent m.p. 214–18° (Found: C, 53·3; H, 5·1; N, 2·9; $C_{20}H_{22}NO_4ICH_3COCH_3$ requires C, 52·6; H, 5·4; N, 2·7%).

Cyclisation to the isopavine (**1f**) *and the pavine* (**9b**). The mixture of **3k** and **7d** was cyclised in an analogous manner to yield a solid containing the required **1f** and **9b**. The mixture was dissolved in $CHCl_3$ and stirred with SiO_2 overnight. The silica was filtered and washed with hot $CHCl_3$, and the combined $CHCl_3$ washings were evaporated to afford a gum which crystallised from acetone as **9b** (15% on starting **6b**) with 1 mole of solvent of crystallisation. (Found: C, 69·3; H, 6·3; N, 3·9; $C_{19}H_{19}NO_4$

CH_3COCH_3 requires: C, 68·9; H, 6·6; N, 3·7%). The mole of acetone was removed under vacuum at 110°, to afford crystalline pavine m.p. 206–7° NMR ($CDCl_3$) 6·67 s[1] (Ar—H), 6·60 s[1] (Ar—H), 6·44 s[2] (2 × Ar—H), 5·87 and 5·82 two doublets[2] J = 1·5 Hz (OCH_2—O), 5·4–5·1 broad s (OH, removed by D_2O), 3·77 s[3] (Ar—OCH_3), 2·53 s[3] (N—CH_3), 4·0–2·3 complex[6] (aliphatic —H); NMR (CD_3SOCD_3), 6·75 s[1] (Ar—H), 6·58 s[1], (Ar—H), 6·51 s[2] (2 × Ar—H), 5·92, 5·88 two broad s[2] (OCH_2—O), 3·69 s[3] (Ar—OCH_3), 2·39 s[3] (N—CH_3), 3·95–2·2 complex[6] (aliphatic—H); ν_{max} 2700 broad, 1603, 1527, 1490, 1241, 1230, 1109; λ_{max} (ε) 293 (9300), 225 sh (13,000), on the addition of NaOH λ_{max} 302; λ_{max} (hexane) resolved into 279, 285, 290, 295, 303; mass *m/e* 325 (M^+) [65%], 324 ($M^+ - 1$)[43%], 282[4%], 188[100%], 190[76%]. Extraction of the SiO_2 with hot MeOH and subsequent plating on alumina afforded **1f** (9% based on starting **6b**). Recrystallisation from EtOH afforded white crystals m.p. 215–16°, NMR ($CDCl_3$), 6·70 s broad[2] (2 × Ar—H), 6·62 s[1] (Ar—H), 6·46 s[1] (Ar—H), 7·2–6·8 broad[1] (OH, removed by D_2O), 5·85 and 5·80 two unresolved doublets[2] J = 1 Hz (O—CH_2—O), 3·80 s[3] (Ar—OCH_3), 2·44 s[3] (N—CH_3), 3·7–2·2 complex[6] aliphatic H); NMR (CD_3SOCD_3), 6·83 s[1] (Ar—H), 6·78 s[1] (Ar—H), 6·72 s[1] (Ar—H), 6·53 s[1] (Ar—H), 6·1–5·7 broad[1] (OH, removed by D_2O), 5·91 and 5·86 two doublets[2] J = 1 Hz (OCH_2O), 3·74 s[3] (Ar—OCH_3), 2·31 s[3] (N—CH_3), 3·8–2·2 complex[6] (aliphatic H); Part NMR (CD_3COCD_3) 6·88 s[1] (Ar—H), 6·79 s[1] (Ar—H), 6·70 s[1] (Ar—H), 6·48 s[1] (Ar—H), 5·88 and 5·84 two broad s[2] (O—CH_2—O). ν_{max} ($CHCl_3$ soln), 3450 (sharp), 3300–3000, 2300, 1602, 1506 (strong), 1485 (strong), 1368 (broad), 1260, 1220 (broad), 1102, 1038, 933, 868; λ_{max} 294 (8000), 230 sh (12,700), on the addition of NaOH λ_{max} 304; Peak resolution in hexane not as complete as with **9a** and **9b**; mass *m/e* 325 (M^+) [36·6%], 324 ($M^+ - 1$)[34·6%], 282[38·5%], 190[100%], 188[0·9%]. metastables 244·5, 213·5, 214, 215. (Found: C, 69·8; H, 6·05; N, 4·2: $C_{19}H_{19}NO_4$ requires: C, 70·1; H, 5·9; N, 4·3%).

Hofmann degradation of **1f** *to* **12b**. The methiodide of **1f**, m.p. 245° (120 mg) was heated on a steam bath for 6 h under N_2 with MeOH (10 ml) and KOH pellets (4 g). The resulting red soln was evaporated to dryness, water (5 ml) added and the soln acidified with 6N HCl, then basified with $NaHCO_3$. Extraction into ether and concentration of the ether phase afforded a pale yellow solid (90 mg). Recrystallisation from EtOH afforded a white crystalline solid m.p. 184°, NMR (CD_3SOCD_3), 6·95–6·68 complex[6] (4 × Aromatic H, plus 2 × olefinic H), 6·02 and 5·98 2 broad s [2] (O—CH_2—O), 4·12 t[1] J = 8 Hz (N—CH_2—CH), 3·80 s[3] (Ar—OCH_3), 2·07 d[2] J = 8 Hz (N—CH_2—CH), 2·01 s[6] (N—$(CH_3)_2$); ν_{max} ($CHCl_3$ soln) 3550 (sharp), 3300 (broad), 2900, 1595, 1485, 1267, 1040; λ_{max} (ε) 242 (17,400), 320 (10,440), on addition of NaOH λ_{max} 323, 260 sh mass *m/e* 339 (M^+)[9%], 281[100%] metastable 232·7. (Found: C, 70·5; H, 6·2; N, 4·1; $C_{20}H_{21}NO_4$ requires: C, 70·8; H, 6·2; N, 3·9%).

Hofmann degradation of **1e** *to* **12a**. The methiodide of **1e** was degraded to **12a** in analogous manner to give a yellow solid, melting over 152–158°. The substance, which could not be further purified, contained a small amount of the alternative methine base (by NMR). *m/e* 339 (M^+) 8%] 281[100%] metastable 232·7; ν_{max} ($CHCl_3$ solution) 3550 (sharp), 3300 (broad), 1513, 1491, 1267, 1045, 945, 876; NMR ($CDCl_3$) 6·9–6·5 complex[6] (Aromatic H plus olefinic H), 5·90 and 5·86 two doublets[2] J = 1·5 Hz (O—CH_2—O), 4·7 broad[1] (—OH, removed by D_2O), 3·96 t[1] J = 8 Hz (N—CH_2—CH) 3·84 s[3] (Ar—OCH_3), 2·6 d[2] J = 8 Hz (N—CH_2—CH), 2·1 s[6] (N—$(CH_3)_2$) λ_{max} (EtOH) 300, 320, 235 (sh). λ_{max} (EtOH/NaOH) 300, 350, 260 (sh). (Found: C, 70·2; H, 6·2; N, 3·9, $C_{20}H_{29}NO_4$ requires: C, 70·8; H, 6·2; N, 3·9%).

See Fig for UV spectra of methines **12a** and **12b**.

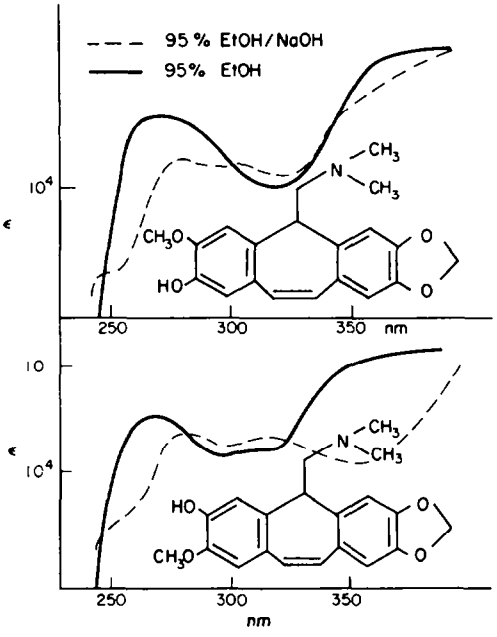

Fig 1.

(±) – *Reframine* (**1b**) *methiodide*. The isopavine **1e** (20 mg) was methylated with an ethereal diazomethane soln for 20 h. The soln was evaporated, the residue dissolved in 2N H_2SO_4 and the soln basified with NaOH and extracted with ether. The ether soln of the non-phenolic base was treated with MeI, and the ppt crystallised from MeOH (12 mg) m.p. 263–5°. A mixed m.p. with reframine methiodide m.p. 263–4°, melted at 263–265°. The IR spectrum of the product was identical with that of reframine methiodide.

The same treatment of **1f** afforded a white crystalline methiodide m.p. 262–4°, which when mixed with reframine methiodide melted at 262–4°.

The pavine (**9c**) *methiodide*. The pavines **9a** and **9b** were each methylated as described above and the methiodide salts of the products had m.p. 272–4°, undepressed upon admixture. ,

The deoxybenzoin (**2e**). The uncharacterised crude **8a** (1 g) was stirred in 6N HCl for 18 h and extracted into $CHCl_3$ (3 × 30 ml), washed with water (2 × 30 ml), and dried ($MgSO_4$). Evaporation of the solvent afforded a gum which crystallised under ether. Recrystallisation from MeOH afforded a white solid (200 mg) m.p. 98–9°; NMR ($CDCl_3$), 7·7–6·6 complex[11] (Aromatic H), 5·89 s[2] (O—CH_2—O), 5·20 s[2] (Ph—CH_2—O), 4·10 s[2] (Ar CH_2—CO), 3·89 s[3] (Ar OCH_3); ν_{max} 1668, 1602, 1591, 1275; λ_{max} (ε) 315 sh (11,000), 280 (16,000), 232 (28,400); mass *m/e* 376 (M^+)[3·3%], 241[50%], 135[18%], 91[100%], metastable 154·5. (Found: C, 73·5; H, 5·4; $C_{23}H_{20}O_3$ requires: C, 73·4; H, 5·4%).

The deoxybenzoin (**2f**). In a similar experiment **8b** gave **2f** as white crystals from EtOH, m.p. 144–5°; NMR ($CDCl_3$) 7·75–6·7 complex[11] (Aromatic H), 5·90 s[2] (O—CH_2—O), 5·17 s[2] (Ph—CH_2—O—), 4·08 s[2] (Ar—CH_2—CO), 3·90 s[3] (Ar—OCH_3); ν_{max} 1670, 1598, 1586, 1270; λ_{max} (ϵ) 320 sh (8,100), 282 (11,600), 232 (26,000); mass *m/e* 376 (M^+)[3·5%], 241[33%], 135[5·5%], 91[100%].(Found: C, 73·1; H, 5·6; $C_{23}H_{20}O_5$ requires: C, 73·4; H, 5·4%).

Pseudocyanide (**11**). A mixture of the alkylated and unalkylated acetals **3k** and **7d** (1 g) was sealed under N_2 with concentrated HCl (1 ml) and heated at 50° for 48 h. After dilution with water (10 ml) and washing with ether (2 × 10 ml) the soln was basified with $NaHCO_3$ and extracted into $CHCl_3$ (3 × 15 ml). The combined $CHCl_3$ extracts were washed with $NaHCO_3$ aq (2 × 5 ml), brine (2 × 10 ml) dried ($MgSO_4$) and evaporated to afford a yellow solid (270 mg). The mass spectrum of these crude bases showed molecular ions corresponding with pavine, isopavine and unalkylated tetrahydroisoquinoline.

To the combined $NaHCO_3$ solution was added NaCN, followed by extraction into ether (3 × 20 ml). The combined ether extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford a pale yellow solid (20 mg). λ_{max} 250 sh, 289, 316. Addition of a drop of dilute HCl to the sample gave λ_{max} 253 strong, 315, 374. Mass *m/e* 325 (M^+ − HCN), 190 (M^+ − HCN and methylenedioxybenzyl), 217/218 (M^+ − methylenedioxybenzyl). Reduction of the suspected pseudocyanide (**11**) with $NaBH_4$ in aqueous EtOH on a steam bath for 1 h, followed by workup for phenolic bases afforded an oil (10 mg), λ_{max} 294, (typical tetrahydroisoquinoline); mass *m/e* 192 (M^+ − methylene dioxybenzyl)[100%], 327 (M^+)[3%].

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