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THE SYNTHESIS OF ISOPAVINE ALKALOIDS—II[1]

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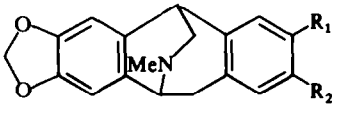
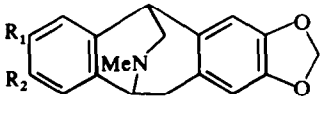
Abstract The two phenolic isopavines **1a** and **1b** have been synthesised by a method described previously[1] and the alkaloid amurensine has been shown to be identical with **1b**.

SINCE the appearance of our brief review[1] of isopavine alkaloids, a much wider review has appeared,[2] and the absolute stereochemistry of amurensine has been deduced[3] from CD measurements. The remaining uncertainties in the chemistry of this group of alkaloids concern the position of the phenolic hydroxyl group in amurensine (**1a** or **1b**) and in reframoline (**2a** or **2b**). Structure **1b** has been generally assumed for amurensine, and this would be expected if the substance is biosynthesised from reticuline. For reframoline structure **2a** is preferred since it is also directly derivable from reticuline. However, the *orientation* of substituents in the latter com-



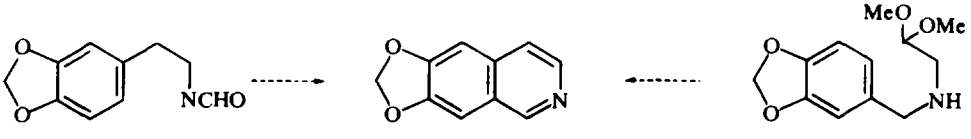
1a: R_1 = OH; R_2 = OMe
1b: R_1 = OMe; R_2 = OH
1c: $R_1 + R_2 = CH_2O_2$



2a: R_1 = OH; R_2 = OMe
2b: R_1 = OMe; R_2 = OH
2c: $R_1 = R_2$ = OMe

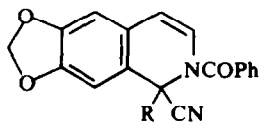
pound has been established by its methylation with CH_2N_2 to give reframine (**2c**). In this paper we describe syntheses of **1a** and **1b**.

6,7-Methylenedioxyisoquinoline (**4**), obtained either by cyclisation of the N.formylamine (**3**), followed by dehydrogenation, or, preferably, by cyclisation of the benzylaminoacetal (**5**), followed by dehydrogenation and dehydration[4] was converted[5] into the Reissert compound (**6**; R=H). This substance was then alkylated with



3 **4** **5**

4-methoxy-3-benzyloxybenzyl bromide in the presence of NaH/DMF[6] to **6**(R=4-methoxy-3-benzyloxybenzyl) and the resulting 1-benzylisoquinoline (**7a**), obtained in high yield, was N methylated and reduced with LAH to the stable 1,2-dihydroisoquinoline (**8a**). When this enamine was treated successively with B_2H_6 and H_2O_2, as previously described,[1] the 4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**9a**) was formed,



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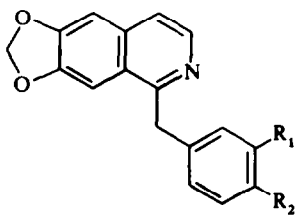
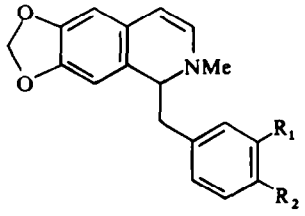
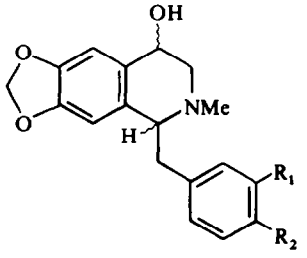


7a: $R_1 = OCH_2Ph$; $R_2 = OMe$
7b: $R_1 = OMe$; $R_2 = OCH_2Ph$



8a: $R_1 = OCH_2Ph$; $R_2 = OMe$
8b: $R_1 = OMe$; $R_2 = OCH_2Ph$



9a: $R_1 = OCH_2Ph$; $R_2 = OMe$
9b: $R_1 = OMe$; $R_2 = OCH_2Ph$

which, with 75% conc. HCl/EtOH was converted into the isopavine (**Ib**), with concomitant loss of the protecting benzyl group.

Repetition of the above sequence of reactions with (**6**) and the isomeric 4-benzyloxy-3-methoxybenzyl bromide led, *via* **7b**, **8b** and **9b** to the isopavine (**Ia**). The IR spectra (in $CHCl_3$ solution) of the synthetic samples of **Ia** and **Ib** did show some differences, but, more importantly, the IR spectrum of (**Ib**) was found to be identical with that of natural amurensine, in the same solvent. The NMR spectra (in DMSO) of (**Ib**) and amurensine were also found to be identical, differing significantly in the aromatic region from the spectrum of (**Ia**). A resolution of synthetic (**Ib**) was precluded by paucity of material, but nevertheless the spectral evidence establishes structure (**Ib**) for amurensine.

EXPERIMENTAL

M.p's are uncorrected. UV spectra refer to 95% EtOH solutions 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.

2-*Benzoyl*-1-*cyano*-6,7-*methylenedioxy*-1,2-*dihydroisoquinoline*, (**6**, R=H). Benzoyl chloride (42·2 g; 0·3 mole) was added dropwise during 2 hr to a stirred mixture of 6,7-methylenedioxyisoquinoline (17·3 g; 0·1 mole), KCN (26·0 g; 0·4 mole), CH_2Cl_2 (200 ml) and water 60 ml). After a further 16 hr stirring at room temp, the CH_2Cl_2 layer was washed with water, 10% HCl aq, water, 2N NaOH aq and finally with water. The dried CH_2Cl_2 solution was evaporated to leave a yellow oil which was crystallised from aqueous EtOH to give the Reissert compound (**6**, R=H) (14·4 g) as fine white needles, m.p. 137–138° ν^{max} cm^{-1} 1660, 1640. NMR ($CDCl_3$) 7·5, m [5] (COC_6H_5): 6·78, s [1] and 6·63, s [1] (C_5—H and C_8—H): 6·53, d[1] (J = 7 Hz) and 5·90, d [1] (J = 7 Hz) (C_3—H and C_4—H). 6·45, s [1] (C_1—H); 5·95, s [2] (CH_2O_2). (Found: C, 71·25; H, 4·06; N, 9·2 · $C_{18}H_{12}N_2O_3$ requires C, 71·06; H, 3·95; N, 9·2%).

2-*Benzoyl*-1-(3-*benzyloxy*-4-*methoxy*)*benzyl*-1-*cyano*-6,7-*methylenedioxy*-1,2-*dihydroisoquinoline*, (**6**, R = 4-methoxy-3-benzyloxybenzyl). A solution of the above Reissert compound (10·1 g) in dry DMF (40 ml)

was added to a stirred suspension of NaH (1·73 g of 50% dispersion in oil) in DMF (40 ml) at 0°, in an atmosphere of N_2. Gas was rapidly evolved and a deep red solution obtained. After 15 min a solution of 3-benzyloxy-4-methoxybenzyl chloride (10·4 g) in DMF (50 ml) was added with stirring during 30 min. Stirring was continued for 1 hr at 0° then 17 hr at room temp. After the addition of MeOH, to destroy any excess NaH, the solution was evaporated to low bulk under reduced pressure and the residue dissolved in benzene (100 ml). The resultant solution was washed with water, 2N HCl (2 × 50 ml) and water, then dried and evaporated. The residual oil crystallised when triturated with MeOH. The solid was recrystallised from MeOH to give the alkylated Reissert compound (8·3 g) as white plates, m.p. 165–166° ν^{max} cm^{-1} 1652, 1680. NMR ($CDCl_3$): 7·63–7·08, m [10] (2 × C_6H_5): 6·80, s [1] and 6·45, s [1] (C_5 - H and C_8—H): 6·83–6·35, m [3] (C_6H_3); 6·12, d (J = 8 Hz) [1] and 5·32, d (J = 8 Hz) [1] (C_3—H and C_4—H); 5·90, s, [2] (CH_2O_2): 4·88, s [2] (C_6H_5—$\underline{CH}_2$—): 3·80, s [3] (Me): 3·68, d (J = 14 Hz) [1] and 3·30, d (J = 14 Hz) [1] (Ar —$\underline{CH}_2$—) (Found: C, 74·97; H, 4·84. N, 5·36 · $C_{33}H_{26}N_2O_5$ requires C, 74·70; H, 4·94; N, 5·28%).

1-(3-*Benzyloxy*-4-*methoxy*)*benzyl*-6,7-*methylenedioxyisoquinoline* (**7a**). A solution of the above compound (6·0 g) in EtOH (100 ml) and 30% NaOH (100 ml) was refluxed for 2½ hr. After cooling and removal of EtOH, the residue was diluted with water (200 ml) and $CHCl_3$ extracted. The $CHCl_3$ solution was evaporated to leave a yellow oil which crystallised from aq EtOH to give **7a** (4·0 g) m.p. 105–106°. NMR ($CDCl_3$): 8·30, d (J = 6 Hz) [1] (C_3—H): 7·50–6·67, m [11] (11 × Ar—H): 5·92, s [2] (CH_2O_2): 4·98, s [2] (Ar—CH_2): 4·39, s [2] (Ar—CH_2): 3·75, s [3] (OCH_3). (Found: C, 75·40; H, 5·44; N, 3·57 · $C_{25}H_{21}NO_4$ requires C, 75·18; H, 5·26; N, 3·51%). Methiodide m.p. 230–232° from EtOH (Found: C, 57·92; H, 4·61. N, 2·55; I, 23·69 · $C_{26}H_{24}NO_4I$ requires C, 57·54; H, 4·44; N, 2·59; I, 23·47%).

1-(4-*Benzyloxy*-3-*methoxy*)*benzyl*-6,7-*methylenedioxyisoquinoline* (**7b**) was prepared in an analogous manner to **7a** and was obtained as a beige microcrystalline mass m.p. 130–131° from acetone ether. NM ($CDCl_3$): 8·28, d (J = 5 Hz) [1] (C_3—H): 7·67–6·58, m [11] (11 × aromatic protons): 5·85, s [2] (CH_2O_2): 4·99, s [2] (C_6H_5—CH_2): 4·40, s [2] (Ar—CH_2): 3·72, s [3] (OCH_3). (Found: C, 75·22; H, 5·31; N, 3·55 · $C_{25}H_{21}NO_4$ requires C, 75·18; H, 5·26; N, 3·51%). The intermediate Reissert (**6**,R=3-methoxy-4-benzyloxybenzyl) was obtained as solid, m.p. 158–159° from EtOH. (Found: C, 74·84; H, 4·85; N, 5·23 · $C_{33}H_{26}N_2O_6$ requires C, 74·70; H, 4·94; N, 5·28%).

(±)-*Amurensine* (**Ib**). The methiodide of **7a** was reduced with LAH in the usual way and the 1,2-dihydrosoquinoline (1·2 g) so formed was, without purification, dissolved in THF (100 ml) and treated with B_2H_6, generated externally from $NaBH_4$ (2·0 g) and $BF_3 \cdot Et_2O$ (3 ml). The THF solution was stirred until the characteristic UV spectrum of the 1,2-dihydroisoquinoline had disappeared (3–4 hr), then for a further 1 hr. A solution of 20% NaOH (50 ml) and 30% H_2O_2 (50 ml) was added with the temperature maintained at 10° or below. The two-phase system was stirred for a further 2 hr then concentrated under reduced pressure and $CHCl_3$ extracted. Evaporation of $CHCl_3$ left a yellow gum which was dissolved in EtOH (10 ml), and conc HCl (60 ml) added. The mixture was left at room temp for 16 hr, then heated under reflux for 2 hr. The solution was diluted with water (60 ml), washed with ether, basified with Na_2CO_2 aq and CH_2Cl_2 extracted. Evaporation of solvent left 300 mg of basic material from which (±)-amurensine (80 mg) was recovered as a beige solid m.p. 188–190° from EtOH. (M^+ found 325·1309 $C_{19}H_{19}NO_4$ requires 325·1313). The IR and NMR spectra of this material were superimposable upon the corresponding spectra derived from natural amurensine.

"*Isoamurensine*" (**Ia**). 1-(4-Benzyloxy-3-methoxy)benzyl-2-methyl-6,7-methylenedioxy-1,2-dihydroisoquinoline (1·7 g) when treated similarly with B_2H_6, H_2O_2 and mineral acid gave the isopavine **Ia** (400 mg) as an off-white powder m.p. 220° (dec.) from EtOH. (Found: C, 69·95; H, 5·92; N, 4·18 · $C_{19}H_{19}NO_4$ requires C, 70·15; H, 5·85; N, 4·31%).

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