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THE SYNTHESIS OF ISOPAVINE ALKALOIDS—I[1]

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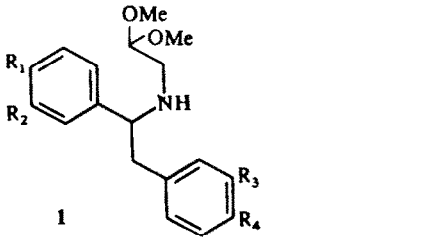
Abstract—Syntheses of reframidine (**2d**) and reframine (**2e**) by a previously described route are reported. The conversion of papaverine to O-methylthalisopavine (**2i**) constitutes a variation and represents the first recorded "hydration" of a 1,2-dihydroisoquinoline to a 4-hydroxy-1,2,3,4-tetrahydroisoquinoline. The correct structure of remrefine is confirmed. Some speculations on the biosynthesis of pavine and isopavine alkaloids are also included.

IN 1958 Battersby and Yeowell[2] showed that the compound formed by treating the benzylaminoacetal (**1**, $R_1=R_2=R_3=R_4=OMe$) with mineral acid is **2a**, and they coined the name *isopavine* for it. Recently several alkaloids have been isolated that are based upon this ring-system, *viz.* amurensine[3,4,5] (**2b**), amurensinine[4,5] (**2c**), reframidine[6] (**2d**), reframine[6] (**2e**), reframoline[6] (**2f** or **2g**) and thalisopavine[7] (**2h**). The structures were assigned from degradative and mass spectral evidence. Whereas the former can be ambiguous, the fragmentation patterns[8,9] are sufficiently well understood for mass spectrometry to be an important structural tool. The structures of amurensinine[10] (**2c**) and thalisopavine[7] (**2h**) have been confirmed by synthesis from the amino acetals (**1**, $R_1+R_2=CH_2O_2$; $R_3=R_4=OMe$) and (**1**, $R_1=R_2=R_3=OMe$; $R_4=OH$), respectively. The phenolic OH group of amurensine (**2b**) was assigned by analogy with other alkaloids isolated from the genus Papaver, and also as a result of some colour tests. The position of the phenolic grouping of reframoline is uncertain, but **2g** is probably correct. The ORD curve of the methine base derived from reframine (**2e**) is the mirror image of that obtained from amurensinine (**2c**). The absolute configurations of the isopavine alkaloids are unknown. A quaternary methosalt is also known. The Russian workers,[11] who first isolated the compound from *Roemeria refracta* and who named it ROEMREFINE, thought originally[11] that it is a pavine alkaloid, but subsequently[12,13] claimed it to be identical with the methosalt of amurensinine (**2c**).

However, Slavik *et al.*[6] named the substance REMREFINE and state that it is identical with the methosalt of reframine (**2e**). A comparison of the Russian and Czech samples of this alkaloid seems not to have been made.

As part of a wider programme in isoquinoline chemistry,[14] we are studying the syntheses of the isopavine alkaloids, and we hope to be able to settle the uncertainties outlined above. Here we describe syntheses of reframidine, reframine and O-methylthalisopavine.

The known[15] deoxypiperoin (**3**, $R+R=CH_2O_2$) was condensed with aminoacetal and the imine was, without isolation reduced with $NaBH_4$ to **1** ($R_1+R_2=R_3+R_4=CH_2O_2$). The yield was 60% from the ketone. Cyclization of this amino acetal as previously described[10] gave "norreframidine" as an amorphous



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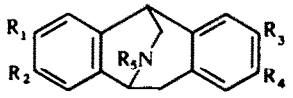
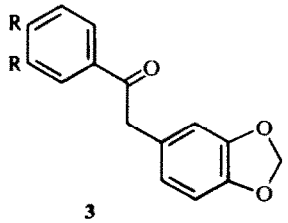


	R_1	R_2	R_3	R_4	R_5	
2a	OMe	OMe	OMe	OMe	H	isopavine
2b	O—CH_2	—O	OMe	OH	Me	amurensine
2c	O—CH_2	—O	OMe	OMe	Me	amurensinine
2d	O—CH_2	—O	O—CH_2	—O	Me	reframidine
2e	OMe	OMe	O—CH_2	—O	Me	reframine
2f	OH	OMe	O—CH_2	—O	Me	reframoline
2g	OMe	OH	O—CH_2	—O	Me	reframoline
2h	OMe	OMe	OMe	OH	Me	thalisopavine
2i	OMe	OMe	OMe	OMe	Me	

hydrochloride salt in 45% yield. N-methylation was achieved in almost quantitative yield by condensation with formaldehyde followed by reduction with $NaBH_4$. Unfortunately neither a sample of reframidine, nor copies of its IR and NMR spectra were available to us, but the NMR, and especially the mass spectra are entirely in accord with structure **2d** for the synthetic material. Interestingly, the mass spectrum exhibited a peak at *m/e* 337 equivalent to M + 14. This phenomenon, which has been observed before,[16] is



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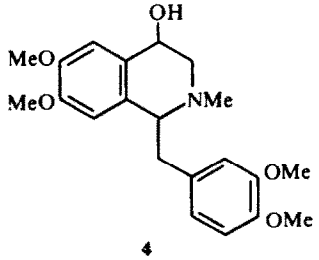

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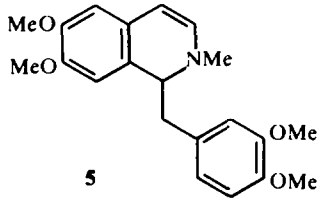
explained by partial loss of a Me radical from the molecular ion, and this is captured by another molecular ion, followed by loss of a hydrogen radical. A high resolution examination of this "M + 14" peak indicated that it has the correct molecule formula for this type of reaction to have occurred.

For the synthesis of reframine (**2e**), the required benzyl ketone (**3**, R = OMe) was prepared by the acylation of veratrole with 3,4-methylenedioxyphenylacetyl chloride. Conversion of this ketone to **1** ($R_1 = R_2 = OMe$; $R_3 + R_4 = CH_2O_2$) was achieved in 60% yield and cyclization to norreframine hydrochloride occurred in 40% yield. Methylation

as before gave (±)reframine, the spectral characteristics of which are entirely in accord with the expected structure (**2e**).

We have been able to compare the IR, NMR and mass spectral data of natural roemrefine[17] iodide with the data derived from amurensinine methiodide and reframine methiodide, and we have thereby shown conclusively that roemrefine is identical with the methosalt of reframine, as described by the Czech workers.[6]

We have suggested[1, 10] that the conversion of aminoacetals of type **1** into isopavines, under acid conditions, proceeds via the 4-hydroxy-1,2,3,4-tetrahydroisoquinolines as intermediates, but we have not been able to isolate any of them in a pure state; cyclization to the isopavine occurs too readily. 2-methyl-4-hydroxy-1,2,3,4-tetrahydropapaverine (**4**) has now been obtained by reacting 2-methyl-1,2-dihydropapaverine[18] (**5**) with diborane,[19] followed by hydrogen peroxide, under the conditions described by Elliot.[20] Using anhydrous THF, the required compound (**4**) was obtained in 60% yield, and was



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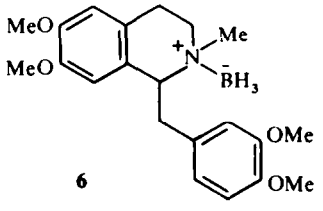

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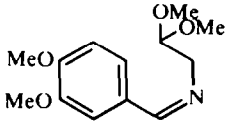
characterized as its methiodide, but in the presence of a little moisture, the only compound that could be identified was the boron complex (**6**). Trace amounts of 2-methyl-1,2,3,4-tetrahydropapaverine were also formed. When **4** was left at room temperature in contact with conc HCl for 5 days, the isopavine (**2i**) was formed and could be isolated in 30% yield. The spectral characteristics, especially NMR, were found to be identical with those reported[7] for O-methylthalisopavine (Experimental).

In another approach to the preparation of the benzylaminoacetals of type **1**, the benzalaminoacetal (**7**) was reacted with benzoyl chloride and KCN under the conditions of the Reissert reaction,[22] the amide (**8**, R = H), which was obtained in 70% yield,



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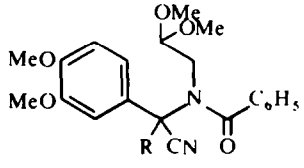

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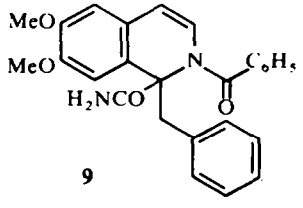

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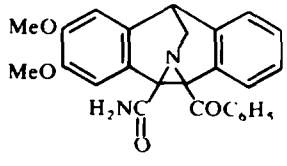

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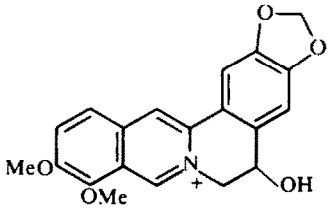
was reacted with NaH/DMF and benzyl chloride.[23] The product, (**8**, $R = CH_2C_6H_5$), when heated under reflux with 75% HCl/EtOH mixture yielded a new compound $C_{26}H_{24}N_2O_4$ (M^+ found: 428·1726; $C_{26}H_{24}N_2O_4$ requires 428·1736). The UV spectrum is very similar to that of **8** ($R = CH_2C_6H_5$) and very different from that expected for **9**. The IR spectrum exhibits absorptions attributed to —NHCO—, H_2NCO— and $C_6H_5CON<$ groups, whereas the NMR spectrum contains resonances for only *eleven* aromatic protons, thus supporting structure **10**, rather than **9** for this product. The base peak in the mass spectrum occurs at *m/e* 105 and corresponds to $^+COC_6H_5$. In the mass spectrum of **8** ($R = CH_2C_6H_5$), peaks corresponding to loss of the benzoyl and benzyl groups are almost equally strong.

No work has yet appeared on the biosynthesis of isopavine alkaloids but it is reasonable to postulate[1] that a 1-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline is a precursor. It is now established[24] that berberastine (**11**) is derived in the plant from noradrenaline and not from tyrosine, and it is possible that 4-hydroxynorlaudanosoline may be the formal precursor of a diverse group of alkaloids parallelling the compounds derivable from norlaudanosoline itself. The isolation of imenine,[25] erythrinine[26] and erythristemine[27] is significant in this context. It is almost certain that the pavine alkaloids are derived from a 1-benzyl-1,2-dihydroisoquinoline and it is tempting to suggest that 1-benzyl-4-hydroxytetrahydroisoquinolines are the precursors, especially since it has been found[29] that reticuline (**12**) is not incorporated into argemonine (**13**). If this postulate proves to be so, then it is possible that a series of 3-benzylisoquinoline alkaloids exist, since the migration of a benzyl group from C_1 to C_3 in a 1,2-dihydroisoquinoline is a facile process.[30]



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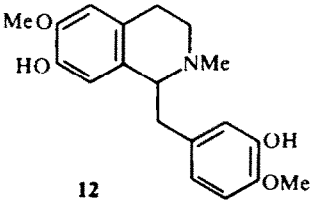

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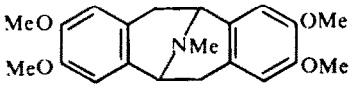

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EXPERIMENTAL

M.p. are uncorrected. IR spectra were measured as Nujol Mulls. NMR spectra were recorded at 60 MHz; chemical shifts are expressed in ppm downfield from internal TMS. Mass spectra were recorded using AEI MS12 spectrometer.

3,4-*Methylenedioxybenzyl alcohol.* $NaBH_4$ (8 g) was added portionwise to a stirred soln of piperonal (60 g) in EtOH (200 ml). After stirring for 90 min, the soln was evaporated under reduced pressure to leave a

white gum, which was taken up in chloroform (200 ml), washed with water, dried, and the solvent removed to leave the alcohol as a pale lemon viscous oil which slowly solidified to give white prisms (55 g), m.p. 49–50°, (Lit[33] 52°).

3,4-*Methylenedioxyphenylacetonitrile.* A mixture of 3,4-methylenedioxybenzyl chloride (45 g) and KCN (20 g) in DMSO (150 ml) was stirred at room temp for 3 days. The dark brown mixture was then poured into water (850 ml) and the resultant soln extracted with benzene (6 × 100 ml). After removal of the dried solvent the residual oil was distilled under reduced pressure to yield the required nitrile (37 g, b.p. 124–128°/0·5 mm) as a colourless oil which rapidly crystallized as small, water-white plates, m.p. 41–42° (Lit[34] 42°).

3,4-*Methylenedioxyphenylacetic acid.* Alkaline hydrolysis (30% NaOH, 300 ml) of the preceding nitrile (30 g) gave the required acid in 68% yield, m.p. 127° from chloroform (Lit[35] 127°).

3,4-*Methylenedioxybenzyl-3,4-dimethoxyphenyl ketone* (**3**, R = OCH_3). To a stirred soln of a veratrole (14 g) in dry CH_2Cl_2 (50 ml), a soln of $SnCl_4$ (11·5 ml) in CH_2Cl_2 (100 ml) was added. After 30 min freshly prepared homopiperonoyl chloride (from 16 g acid) in CH_2Cl_2 (100 ml) was added dropwise during 60 min; stirring was continued for a further 90 min. The complex was decomposed by heating under reflux with 50% HCl (150 ml) for 60 min. Following filtration the 2 layers were separated, and the CH_2Cl_2 layer washed with 10% NaOH aq (100 ml). Evaporation of the dried solvent left a brown oil, which upon trituration with MeOH gave the required ketone as a pale yellow solid. Recrystallization from MeOH afforded white prisms, 14·7 g (74%), m.p. 93–94°. NMR ($CDCl_3$) ppm, 7·71–6·73 m [6] (6 × Ar—H); 5·86 s [2] (O_2CH_2); 4·10 s [2] (Ar—CH_2—CO); 3·89 s [6] (2 × OCH_3); ν_{max} 1680 cm^{-1} (C=O). (Found: C, 68·2; H, 5·2. $C_{17}H_{16}O_5$ requires: C, 68·0; H, 5·3%).

Preparation of the amino acetals (**1**)

(a) 1,2-*Bis*-(3,4-*methylenedioxyphenyl*)*ethylaminoacetaldehyde dimethyl acetal* ($R_1 + R_2 = R_3 + R_4 = CH_2O_2$). Deoxypiperoin[15] (10g) and aminoacetaldehyde dimethyl acetal (50 ml) were heated together under reflux for 4 hr in an atmosphere of N_2, after which the excess solvent was removed by distillation under reduced pressure. The Schiff's Base thus produced (>C=N— 1640 cm^{-1}) was reduced to the required amino acetal with $NaBH_4$ in MeOH. The product, a golden-green oil (7·5 g), was purified by re-extraction from ice-cold 2N H_2SO_4. It was characterized as its hydrochloride salt, m.p. 190–192° ex EtOH. (Found: C, 58·3; H, 5·70; N, 3·4. $C_{20}H_{24}NO_6Cl$ requires: C, 58·5; H, 5·8; N, 3·4%).

(b) In an analogous experiment, **1** ($R_1 = R_2 = OCH_3$; $R_3 + R_4 = O_2CH_2$) was prepared from the ketone **3** (R = OCH_3). This oil was also characterized as its hydrochloride salt, m.p. 177–179° from EtOH NMR ($CDCl_3$) ppm, 10·2 broad s [2] (NH_2, removed by D_2O); 7·53 s [1]; 6·83 s [2]; 6·55 s [3] (6 × Ar—H); 5·87 s [2] (O_2CH_2); 5·1 t [1] (>CH—NH_2); 4·00 s [3] and 3·88 s [3] (2 × Ar—OCH_3); 3·45 s [3] and 3·35 s [3] (CH—(OCH_3)$_2$); 4·80–2·30 complex [5]. (Found: C, 59·0; H, 6·8; N, 3·5; Cl, 8·5. $C_{21}H_{28}NO_6Cl$ requires: C, 59·2; H, 6·6; N, 3·3; Cl, 8·3%).

Cyclization procedure. The acetal **1** ($R_1 + R_2 = R_3 + R_4 = O_2CH_2$; 5 g) was dissolved in EtOH (10 ml), and conc HCl (100 ml) was added. After 5 days the soln was evaporated to dryness. The gummy residue was triturated with acetone to give a beige solid, 1·5 g, of **2** ($R_1 + R_2 = R_3 + R_4 = O_2CH_2$; $R_5 = H_2Cl^-$). The compound could not be characterized.

Similarly **2** ($R_1 = R_2 = OCH_3$; $R_3 + R_4 = O_2CH_2$; $R_5 = H$) was prepared from the appropriate amino acetal. It was characterized as its hydriodide salt, m.p. 266–268°. (Found: C, 50·3; H, 4·4; N, 3·1. $C_{19}H_{20}NO_4I$ requires: C, 50·2; H, 4·6; N, 3·2%).

Both hydro-halide salts gave gums upon basification, neither of which could be crystallized.

(±)-*Reframidine* (**2d**). Methylation of norreframidine with formaldehyde–sodium borohydride gave (±)-reframidine as a golden oil. NMR ($CDCl_3$) ppm, 6·75 s [2]; 6·65s [1]; 6·55 s [1] (4 × Ar—H); 5·90 m [4] (2 × O_2CH_2); 2·45 s [3] (N—CH_3); 3·92–2·60 m [6] (aliphatics). Mass M^+ 323, 188 (100%), 337 (0·3%). The compound was characterized as its methiodide, m.p. 267–269° (EtOH). (Found: C, 51·5; H, 4·5; N, 3·2; I, 26·9. $C_{20}H_{20}NO_4I$ requires: C, 51·5; H, 4·3; N, 3·0; I, 27·3%).

(±)-*Reframine* (**2e**). Methylation of norreframine as above gave the title compound, N-methyl-10,11-dihydro-7,8-dimethoxy-2,3-methylenedioxy-10,5-iminomethano-5H-dibenzo[*a,d*]cycloheptatriene, as a red-brown gum. The mass spectrum of the compound was identical to that published[9] for the authentic sample. NMR ($CDCl_3$) ppm, 6·90 s [1]; 6·83 s [1]; 6·70 s [1]; 6·55 s [1] (4 × Ar—H); 5·87 q [2] J = 2 Hz (O_2CH_2); 3·90 s [6] (2 × OCH_3); 2·58 s [3] (N—CH_3). Methiodide, m.p. 272–274° (EtOH). (Found: C, 52·7; H, 5·2; N, 3·1; I, 26·1. $C_{21}H_{24}NO_4I$ requires: C, 52·4; H, 5·0; N, 2·9; I, 26·4%).

Roemrefine. The IR spectrum of roemrefine was superimposable upon that of (±)-reframine methiodide, but different from that of (±)-amurensinine methiodide.[10] The mass spectra of the three compounds were

similarly indicative that roemrefine is identical to quaternized reframine, and different from quarternized amurensinine.

4-Hydroxy-2-methyl-1,2,3,4-tetrahydropapaverine (**4**). Diborane, generated by the addition of $NaBH_4$ (2 g) in diglyme (50 ml) to a soln of BF_3 dietherate (3 g) in diglyme (100 ml), was passed, using N_2 as carrier gas, into a stirred soln of 2-methyl-1,2-dihydropapaverine (3·5 g) in THF (150 ml, distilled from LAH). After 3 hr 20% NaOH aq (50 ml) and H_2O_2 (30%, 50 ml) were added, and the soln stirred for a further 2 hr. The concentrated soln was then extracted with $CHCl_3$ (3 × 50 ml). Evaporation of the dried extracts gave a yellow gum, 3·2 g, ν_{max} cm^{-1}: 3500 (—OH), 2380 (BH_3). Re-extraction, after standing in dil HCl (100 ml) for 30 min, gave the base as an orange oil. Comparative TLC showed that the base contained a small quantity of 2-mehyl-1,2,3,4-tetrahydropapaverine. Compound **4** was characterized as its methiodide, m.p. 222–223° (MeOH). NMR (CD_3SOCD_3) ppm, 7·08 s [1] (C_5—H); 6·90–6·52 m [3] (3 × Ar—H); 6·4 d, J = 9 Hz [1] (C_4—OH, removed by D_2O); 5·7 s [1] (C_8—H); 4·86 m [2] (C_1—H, C_4—H, simplified after deuteration); 3·74, 3·70 and 3·66 s [9] (3 × OCH_3); 3·40 s [3] (C_7—OCH_3); 3·27 and 3·14 s [6] ($\overset{+}{N}(CH_3)_2$); 4·00–2·80 m [4]. (Found: C, 51·5; H, 5·8; N, 2·6. $C_{22}H_{30}NO_5I$ requires: C, 51·3; H, 5·8; N, 2·7%).

When the reaction was carried out using THF which had not been dried with LAH, the only product isolated was the borane adduct (**6**), m.p. 140–142° (EtOH). (Found: C, 67·7; H, 7·7; N, 3·9. $C_{21}H_{30}BNO_4$ requires: C, 67·9; H, 8·1; N, 3·8%).

(±) *O-Methylthalisopavine* (**2i**). Compound **4** (2 g) was subjected to the cyclization procedure as described above. The acidic soln was diluted with water, and neutralised to pH 8 with Na_2CO_3. Extraction with ether gave 0·2 g of an oil, which afforded 2-methyl-1,2,3,4-tetrahydropapaverine (0·16 g) when treated with MeOH (the mother liquors contained some isopavine). The aqueous layer was then further basified (30% NaOH, pH 11), and re-extracted with ether. Work-up as usual gave **2i** as white prisms, (0·7 g), m.p. 165–166° (MeOH). NMR ($CDCl_3$) ppm, 6·75 s [2]; 6·64 s [1]; 6·51 s [1] (4 × Ar—H); 3·84 s [9] and 3·75 s [3] (4 × OCH_3); 2·46 s [3] (N—CH_3); 4·00–2·60 m [6]. (Found; C, 70·8; H, 7·0; N, 4·1 $C_{21}H_{25}NO_4$ requires: C, 71·0; H, 7·0; N, 3·9%).

N-Benzoyl-N-(-α-cyano-3,4-dimethoxybenzyl)-aminoaceteldehyde dimethyl acetal (**8**, R = H). A soln of the benzalaminoacetal (7·8 g) in CH_2Cl_2 (50 ml) and KCN (6·2 g) in water (20 ml) was stirred whilst benzoyl chloride (7·5 ml) in CH_2Cl_2 (20 ml) was added during 90 min. After stirring for a further 30 min the layers were separated, and the CH_2Cl_2 layer washed with water, 10% HCl, water, 2N NaOH, and water. The dried soln was evaporated to give a yellow oil which crystallized when moistened with EtOH. Recrystallization from EtOH gave white needles (8·2 g), m.p. 101–102° ν_{max} 1648 cm^{-1}. NMR ($CDCl_3$) ppm, 7·45 s [5] (COC_6H_5); 7·33–6·80 m [3] (3 × Ar—H); 6·55 s [1] (CN—CH); 4·35 t, J = 5 Hz (CH_2—CH); 3·85 s [6] (2 × Ar—OCH_3); 3·23 s [3] and 3·20 s [3] ($CH(OCH_3)_2$). (Found: C, 66·2; H, 6·1; N, 7·1. $C_{21}H_{24}N_2O_5$ requires: C, 65·6; H, 6·3; N, 7·3%).

Alkylation of the "Reissert Compound". A soln of **8** (R = H, 4·42 g) in dry DMF (15 ml) was added to a stirred suspension of sodium hydride (0·65 g of a 50% dispersion in oil, washed with light petrol) in dry DMF (25 ml) at 0° under N_2. When no more H_2 was evolved (20 min), benzyl chloride (1·52 g) in DMF (25 ml) was added over 30 min. Stirring was continued for 18 hr, raising to room temp after 2 hr. After excess sodium hydride had been decomposed by the addition of MeOH, the mixture was poured into water (100 ml). The ppt (**8**, R = $CH_2C_6H_5$) was collected and recrystallized from MeOH to give a flocculent white solid (3·5 g), m.p. 182–183°, ν_{max} 1660 cm^{-1}; NMR ($CDCl_3$) ppm, 7·50–6·67 m [13] (aromatics); 4·43 t [1] J = 5 Hz (CH_2—CH); 4·20 d [1], J = 14 Hz and 3·27 d [1], J = 14 Hz (C_6H_5—CH_2); 3·80 s [3] and 3·73 s [3] (2 × Ar—OCH_3); 3·32 s [3] and 3·15 s [3] ($CH(OCH_3)_2$). (Found: C, 70·8; H, 6·2; N, 5·7. $C_{28}H_{30}N_2O_5$ requires: C, 70·9; H, 6·4; N, 5·9%).

Acid treatment of **8** (R = $CH_2C_6H_5$). A soln of **8** (R = $CH_2C_6H_5$, 1·0 g) in EtOH (25 ml) and HCl (75 ml) was heated under reflux for 2 hr. After cooling, the soln was washed with ether, diluted with water (200 ml) and basified with ammonia. Re-extraction with ether gave an orange oil (400 mg) which upon trituration with benzene gave a white amorphous solid (80 mg), m.p. 224–226°. M^+ found: 428·1726; $C_{26}H_{24}N_2O_4$ (structures **9** or **10**) requires: 428·1736; ν_{max} cm^{-1}, 3200 (NH_2), 1678, 1658; NMR (CD_3SOCD_3) ppm, 7·88 broad s [2] ($CONH_2$, removed by D_2O); 7·72–6·76 m [11] (aromatics); 3·76 and 3·73 s [6] (2 × OCH_3); 5·18–3·00 m [5].

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