View Article Online / Journal Homepage / Table of Contents for this issue

Published on 01 January 1983. Downloaded by Memorial University of Newfoundland on 08/07/2014 06:13:27.

Electrochemical Oxidation of Aromatic Ethers. Part 8. Evidence of Homogeneous Electron Transfer during the 'Low Potential' Oxidation of Laudanosine

Michael Hutchins, Malcolm Sainsbury *
School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY
David I. C. Scopes
Glaxo Group Research Limited, Ware, Herts SG12 0DJ

Photolysis of *N*-amino- and *N*-nitroso-derivatives of 1,2,3,4-tetrahydropapaverine fails to produce aryl-aryl coupled products analogous to *O*-methylflavinantine. Instead both the 1- and 2-substituents of the heterocyclic ring are cleaved to give 6,7-dimethoxy-3,4-dihydroisoquinolines and veratraldehyde, the latter being an oxidation product of the 3,4-dimethoxybenzyl radical and/or cation. From this evidence, and the results of an electrolysis experiment carried out at high dilution, it is considered that the anodic cyclisation of laudanosine to *O*-methylflavinantine proceeds through homogeneous electron transfer rather than *via* homoconjugative activation within the intermediate radical cation as proposed by other workers.

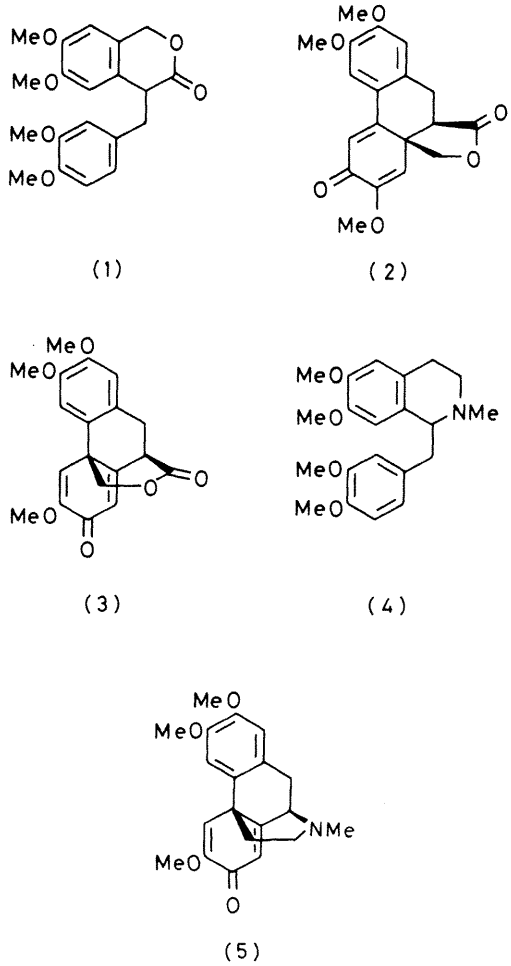
We have established [1] that the anodic oxidation of the isochromanone (1) affords the γ-lactone (2) rather than the δ-lactone (3) as previously supposed.[2,3] Since the model for the original work was the electrochemical conversion of laudanosine (4) into *O*-methylflavinantine (5),[4] this assignment has caused us to investigate the structure of this last product. However, differential nuclear Overhauser effect spectroscopy (see Experimental section) shows that the formulation of this compound is correct.†

Palmquist *et al.*[5] have already illustrated that the factors which determine alternative coupling pathways in substrates of this type are difficult to define, although clearly solvent effects are important.[6] Despite this, a mechanism which has been advanced [7] to explain the formation of *O*-methylflavinantine from laudanosine at a potential *ca.* 0.5 V less positive than that at which either of the two dimethoxylated rings are ionised is rather unusual. It requires initial electron loss from the lone pair of the basic nitrogen atom with activation of the adjacent benzenoid π-system through homoconjugation within the radical cation (6). This species is then presumed to undergo intramolecular cyclisation *via* dication intermediates, although the anode potential is not raised above its original value.

To test this proposal we decided to prepare the radical cation by non-electrochemical means and to ascertain whether or not it forms *O*-methylflavinantine under these conditions. For this purpose we have prepared several *N*-amino derivatives of 1,2,3,4-tetrahydropapaverine and subjected them to photolysis. Thus *N*-amination of papaverine with *O*-mesitylenesulphonylhydroxylamine gave the salt (7) and this upon *N'*-acetylation with acetic anhydride and *N'*-methylation with methyl iodide yielded the iodide (9). Reduction of this salt with sodium borohydride in protic media afforded the tetrahydroisoquinoline (11), although in absolute ethanol solution the corresponding 1,2-dihydroiosoquinoline (10) was obtained as a stable crystalline solid. An alternative route to the tetrahydroisoquinoline involved the initial reduction of *N*-aminopapaverinium iodide to the tetrahydroisoquinoline (13) which was then *N'*-acetylated and *N'*-methylated.

The ^{1}H n.m.r. spectrum of the tetrahydroisoquinoline (11) recorded at ambient temperature shows evidence of restricted rotation about the C-1 and N-2 bonds and all attempts to *N*-methylate the compound to the derivative (12) failed. However, the *N'*-acetyltetrahydroisoquinoline (14) is less sterically crowded and it afforded the salt (15) upon methylation.

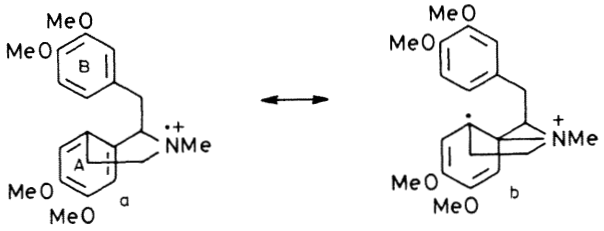
A minor by-product (4%) from the methylation of 2-acet-

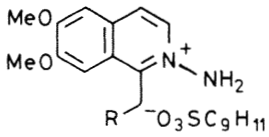


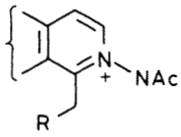
† This conclusion is confirmed by a recent crystal structure analysis (A. Dubourg, P. Briard, R. Rogues, J. D. Declerq, and G. Germain, *Acta Crystallogr., Sect. B*, 1982, **38**, 1657).

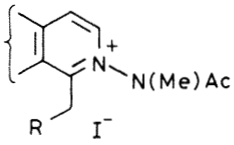
View Article Online

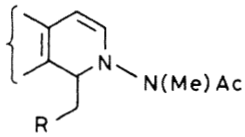
Published on 01 January 1983. Downloaded by Memorial University of Newfoundland on 08/07/2014 06:13:27.

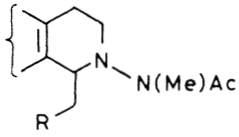


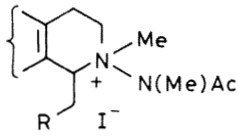


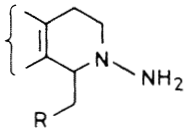


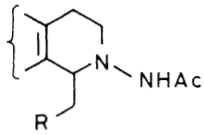


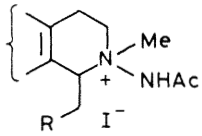






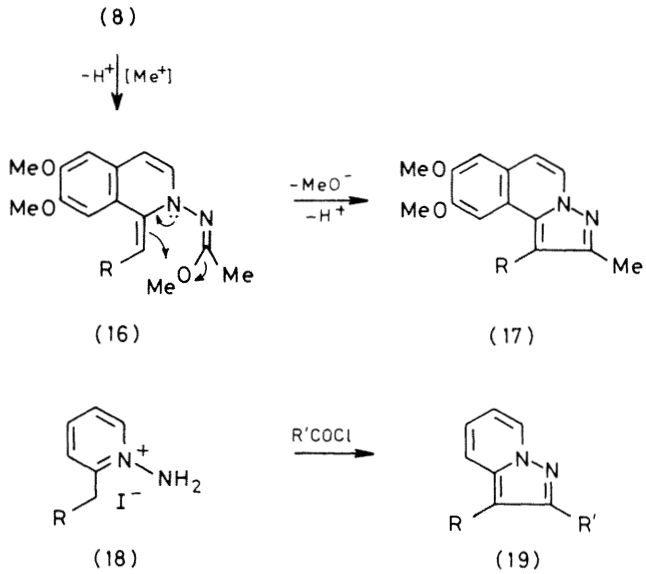






R = 3,4-$(MeO)_2C_6H_3$

amidopapaverinium ylide (8) with methyl iodide was the pyrazoloisoquinoline (17), and we assume that this compound is formed *via* the *O*-methylated intermediate (16), and indeed if diazomethane or trimethyloxonium tetrafluoroborate are used as methylating agents in place of methyl iodide the yields of the pyrazole are marginally increased. There are parallels for this type of ring closure and it is known, for example, that pyrazolo[1,5-*a*]pyridines (19) are obtained during the acylation of the pyridinium salts (18; R = H or alkyl) with acid chlorides.[8]



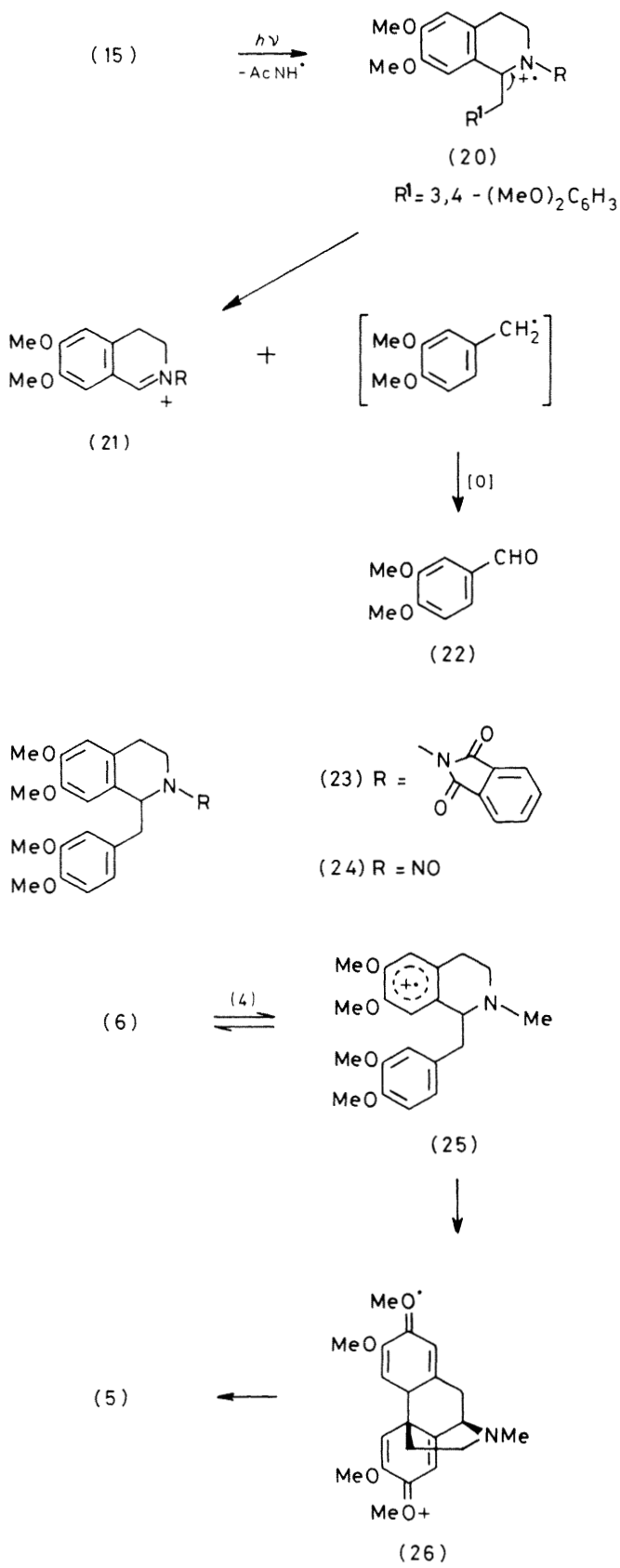
When the salt (15) was photolysed a radical cation was formed, as evidenced by e.s.r. studies (although the spectra were complex and poorly resolved), but continuous monitoring of the reaction medium did not show the presence of *O*-methylflavinantine. Instead, veratraldehyde and a 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium salt were formed, indicating that the initial radical cation (20; R = Me) underwent fragmentation as shown below. Similarly, when laudanosine (4) was oxidised at +0.6 V in very dilute solution veratraldehyde (22) and the 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium cation (21; R = Me) were produced; there was no evidence for the generation of *O*-methylflavinantine.

We have also prepared the *N*-phthalimido derivative (23) of tetrahydropapaverine but all attempts to *N*-methylate this compound failed and again we assume that steric hindrance to the approach of the various alkylating reagents used is responsible. Photolysis of this product gave only a complex mixture of products. It is known that the photolysis of *N*-nitrosamines in acidic media affords radical cations of the parent amines.[9] Thus the *N*-nitrosotetrahydroisoquinoline (24) was synthesised by treating tetrahydropapaverine with nitrous acid. The product was dissolved in methanolic hydrochloric acid and the solution irradiated with u.v. light. The *N*-demethyl derivative of *O*-methylflavinantine was not formed, however, a mixture of products being produced, the most abundant of which were veratraldehyde and 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride.

In order to accommodate the normal requirements for resonance the valence bond contributors to the hybrid must have similar energies; thus homoconjugation as implied in the species (6) is unlikely, since the two canonical forms do not meet this criterion. In one, (6a), all the ring A carbon atoms are sp^2 hybridised and aromaticity is preserved whereas in the other, (6b), one atom has tetrahedral (sp^3) symmetry and aromaticity is lost. Similarly intramolecular electron transfer from ring B is improbable since models show that effective orbital overlap between the π-system of this ring and the p-orbital on nitrogen is not possible. Thus we question the concept of aryl-aryl coupling through homoconjugative activation and suggest instead that during electrolysis in relatively concentrated solution the initial radical cation (6) may undergo homogeneous electron exchange with a second laudanosine molecule so that a new 'π'-radical cation [*e.g.* (25)] is formed which may then ring close to *O*-methyl-

View Article Online

Published on 01 January 1983. Downloaded by Memorial University of Newfoundland on 08/07/2014 06:13:27.



flavinantine *via* the species (26). Even though the ionisation potentials for the lone pair electrons on the nitrogen atom of laudanosine and the π-electrons of the benzenoid ring differ by *ca.* 0.5 V, this is a reasonable suggestion provided that the first radical cation is relatively stable and that the second decomposes into product rapidly and irreversibly. There is ample precedent for this type of process and, for example, the polarographic reduction of a number of aromatic compounds in the presence of a more easily reduced 'catalyst' was first reported by Lund *et al.*[10,*] In this work the difference between the ionisation potentials of the catalyst and the substrate was typically 0.3—0.55 V.

Experimental

U.v. spectra were recorded as solutions in 98% ethanol. I.r. data refer to Nujol mulls unless stated otherwise. ^{1}H N.m.r. spectra were recorded at 100 MHz and at 250 MHz using tetramethylsilane as an internal standard. Anode potentials were measured relative to a standard calomel electrode. Chemical ionisation (CI) mass spectrometric analyses were determined using isobutane as the ionising medium. Photolyses were performed with a Hanovia photochemical reactor using a 125-W lamp with a quartz immersion well.

O-*Methylflavinantine* (5).—This compound was prepared using the conditions described previously.[4] Its authenticity was confirmed by comparison, mixed melting point, i.r. spectroscopy and t.l.c. analysis in three solvent systems with a genuine sample (Found: C, 70.6; H, 6.8; N, 4.0. Calc. for $C_{20}H_{23}NO_4$: C, 70.7; H, 6.8; N, 4.1%). The structure of this compound was established by differential n.O.e. spectroscopy, the results of which are summarised below, together with a full ^{1}H n.m.r. spectral interpretation: δ(C_6H_6) 6.71 (1 H, s, 5-H), 6.36 (1 H, s, 8-H), 6.29 (1 H, s, 1-H), 6.00 (1 H, s, 4-H), 3.52 (3 H, s, 6-C*H*$_3$O), 3.40 (3 H, s, 7-C*H*$_3$O), 3.27 (3 H, s, C(3)-*H*$_3$O), 3.27 (3 H, s, 3-C*H*$_3$O), 3.18 (1 H, d, *J* 3.8 Hz, 10α-H), 3.02 (1 H, dd, *J* 11.5 Hz, *J* 3.8 Hz, 9β-H), 2.61 (1 H, d, *J* 11.5 Hz, 9α-H), 2.55 (1 H, m, 12*ax*.-H), 2.24 (1 H, m, 12*eq*.-H), 2.13 (3 H, s, NCH_3), 1.75 (1 H, m, 13*ax*.-H), and 1.42 (1 H, m, 13*eq*.-H).

Signal irradiated	Observed n.O.e. (%)
1-H	10-H (9.4)
4-H	5-H (17.8), 3-C*H*$_3$O (8.2)
5-H	4-H (19.9), 6-C*H*$_3$O (10.4)
8-H	7-C*H*$_3$O (10.2), 9β-H (4.0), 9α-H (2.7)

Electrolysis of Laudanosine.—Laudanosine was electrolysed at an anode potential of *ca.* +0.6 V as described in the literature,[4] except that the substrate concentration was reduced by a factor of ten. The progress of the reaction was monitored by t.l.c. analysis [*e.g.* samples were removed, basified, spotted onto silica plates and eluted with 60% ethyl acetate in light petroleum (60—80 °C)] until all the substrate had disappeared (*ca.* 2 F mol^{-1} current used). The anolyte was poured into water, the solvent (acetonitrile) partially removed by evaporation under reduced pressure, and the residual aqueous solution extracted with dichloromethane. The dry, combined extracts were evaporated and the oil which remained was then chromatographed on silica with ethyl acetate–light petroleum (60—80 °C) mixtures. Early fractions contained veratraldehyde, the structure of which was verified by physical methods and by direct comparison with an authentic sample. Veratraldehyde was also present in later fractions from the column although now increasingly contaminated with numerous other minor components.

* We are grateful to Dr. J. H. P. Utley (Queen Mary College, University of London) for drawing our attention to this work.

View Article Online

Published on 01 January 1983. Downloaded by Memorial University of Newfoundland on 08/07/2014 06:13:27.

The aqueous phase was treated with sodium borohydride, made acidic with hydrochloric acid, rebasified, and extracted with dichloromethane to yield 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (*ca.* 15%) as an oil, which slowly crystallised, m.p. 79—81 °C (lit.,[11] 83—84 °C). This compound was shown to be identical with an authentic sample formed by the reduction ($NaBH_4$) of 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium iodide, formed in turn by the methylation (MeI) of 6,7-dimethoxy-3,4-dihydroisoquinoline.[12]

A careful check was made that no *O*-methylflavinantine was formed during the reaction, both by t.l.c. analyses and by mass spectrometric analyses. In case this compound was formed as a salt, through reaction with any acid liberated during the reaction, and the extracts were made slightly basic by the addition of aqueous sodium carbonate, prior to evaporation and insertion into the mass spectrometer. The only significant molecular ion shown under these conditions was that due to veratraldehyde (*m/z* 166), although when the sample was reduced with sodium borohydride prior to mass spectrometric analysis, ions at *m/z* 168 (veratryl alcohol) and *m/z* 207 (6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline) were apparent.

N-*Aminopapaverinium Mesitylenesulphate* (7).—Papaverine (1 g) in dry dichloromethane (10 cm^3) was cooled in an ice bath and treated with an ice cold solution of *O*-mesitylenesulphonylhydroxylamine (0.63 g) in dichloromethane (6 cm^3). The pale yellow reaction mixture was stirred under a nitrogen atmosphere at 0 °C for 90 min and then poured into dry diethyl ether, whereupon the title compound separated out as a solid (1.2 g, 73.4%). Exposure of this product to air resulted in the rapid uptake of moisture, giving a hydrate which was recrystallised from ethanol, m.p. 119—120 °C; $\delta_H[(CD_3)_2SO]$ 8.56 (1 H, d, *J* 7 Hz, 3-H), 8.18 (1 H, d, *J* 7 Hz, 4-H), 8.01br (2 H, s, NH_2), 7.79 (1 H, s, 5-H), 7.71 (1 H, s, 8-H), 7.15 (1 H, s, 2-H), 6.9—6.6 (4 H, m, 5′-, 6′-H and mesitylene ring protons), 5.06br (2 H, s, CH_2), 4.00, 4.05 (6 H, 2 × s, 2 × OCH_3), 3.75, 3.68 (6 H, 2 × s, 2 × OCH_3), 3.5br (2 H, s, H_2O), 2.55 (6 H, s, 2 × CH_3, 2-, 6-mesitylene methyl protons), and 2.16 (3 H, s, CH_3, 4-mesitylene methyl protons); $\lambda_{max.}$ 228, 256, 280sh, 317, 349sh nm; $\nu_{max.}$ 3 460, 3 310, and 1 604 cm^{-1} (Found: C, 60.5; H, 6.2; N, 5.05; $C_{29}H_{34}N_2O_7S$, H_2O requires C, 60.8; H, 6.3; C, 4.9%).

1-(3′,4′-*Dimethoxybenzyl*)-6,7-*dimethoxy*-2-(N-*methylacetamido*)*isoquinolinium Iodide* (9).—*N*-Aminopapaverium mesitylenesulphonate (4 g) in 98% aqueous ethanol (15 cm) was cooled to 0 °C and acetic anhydride (5 cm^3) added. After being stirred for 20 min, the mixture was diluted with water (25 cm^3), and made basic with potassium carbonate, prior to extraction with dichloromethane (2 × 15 cm^3). The combined extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure at 20 °C to give an oil which was taken up in acetone (25 cm^3) and treated with methyl iodide (9 cm^3). The mixture was heated under reflux for 10 min to give a solid. This was collected and washed with a small volume of cold acetone (2 g, 42%). The product is unstable and decomposes when heated in a variety of solvents, although as prepared it is quite pure, m.p. 194.5—196 °C, $\nu_{max.}$ 1 700 cm^{-1}; $\delta_H[(CD_3)_2SO]$ * 8.82br (1 H, d, *J* 7 Hz, 3-H), 8.43br (1 H, d, *J* 7 Hz, 4-H), 7.89br (2 H, s, 5-, 8-H), 7.05br (1 H, s, 2′-H), 6.88br (1 H, d, *J* 8 Hz, 2′-H), 6.72 (2 H, m, 3′-, 6′-H), 4.94br (2 H, s, CH_2), 4.11, 3.96 (6 H, 2 × s, 2 × OCH_3), 3.71 (6 H, s, 2 × OCH_3), 3.66 (3 H, s, NCH_3), 2.39 (3 H, s, CH_3CO); $\nu_{max.}$ 1 700 cm^{-1}; $\lambda_{max.}$ 222, 260, and 327 (Found: C, 51.3; H, 5.4; I, 23.3; N, 5.7. $C_{23}H_{27}IN_2O_5$ requires C, 51.3; H, 5.1; I, 23.6; N, 5.2%).

The methyl sulphate salt, m.p. *ca.* 190 °C (decomp.) is obtained in similar manner if dimethyl sulphate is used in place of methyl iodide (Found: C, 54.8; H, 5.8; N, 5.5. $C_{24}H_{30}N_2O_9S$ requires C, 55.1; H, 5.8; N, 5.4%).

N-*Acetamidopapaverinium Iodide*.—When the oil (1.5 g) from the previous experiment, prior to addition of methylation agent, was treated with ethanol (5 cm^3) and 55% aqueous hydrogen iodide, the title compound gradually separated out as yellow prisms (0.6 g), m.p. 175—176 °C; $\delta[(CD_3)_2SO]$ 8.71 (1 H, d, *J* 7 Hz, 3-H), 8.45 (1 H, d, *J* 7 Hz, 4-H), 7.99, 7.95 (2 H, 2 × s, 5-, 8-H), 7.15br (1 H, s, 2-H′), 6.92 (1 H, d, *J* 8 Hz, 5-H′), 6.80br (1 H, d, 6′-H), 5.10br (2 H, s, CH_2), 4.12, 4.08 (6 H, 2 × s, 2 × OCH_3), 3.77, 3.75 (6 H, 2 × s, 2 × OCH_3), and 2.31 (3 H, s, $COCH_3$) (Found: C, 50.4; H, 4.95; N, 5.4. $C_{22}H_{25}IN_2O_5$ requires C, 50.4; H, 4.8; N, 5.3%).

1-(3′,4′-*Dimethoxybenzyl*)-6,7-*dimethoxy*-2-(N-*methylacetamido*)-1,2-*dihydroisoquinoline* (10).—6,7-Dimethoxy-1-(3′,4′-dimethoxybenzyl)-2-(*N*-methylacetamido)isoquinolinium iodide (200 mg) was suspended in absolute ethanol (4 cm^3) and sodium borohydride (14 mg) added. The mixture was stirred at room temperature for 30 min, after which time the yellow colour of the iodide salt had disappeared. Water (100 cm^3) was then added and the product extracted into dichloromethane (3 × 25 cm^3). Removal of the solvent from the dry, combined extracts gave a solid (138 mg) which was recrystallised from ethanol to afford the title compound as colourless plates (105 mg, 69%), m.p. 167—168.5 °C, $\nu_{max.}$ 1 660 and 1 620 cm^{-1}; $\lambda_{max.}$ 289 and 307 nm; $\delta_H[(CD_3)_2SO$ at 150 °C †] 6.77 (1 H, bd, *J ca.* 9 Hz, 5-H), 6.65 (1 H, s, 5- or 8-H), 6.63—6.49 (2 H, m, 2′-, 6′-H), 6.24 (1 H, s, 5- or 8-H), 6.05 (1 H, d, *J* 7 Hz, 3-H), 5.69 (1 H, d, *J* 7 Hz, 4-H), 4.68 (1 H, t, *J* 7 Hz, 1-H), 3.77, 3.75, 3.69, 3.55 (4 × 3 H, 4 × s, 4 × OCH_3), 2.79—3.00 (5 H, m, NCH_3, CH_2), and 1.89 (3 H, s, $COCH_3$).

2-*Amino*-1-(3′,4′-*dimethoxybenzyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (13).—*N*-Aminopapaverinium mesitylenesulphate (6 g) was prepared in the usual way and dissolved in 95% aqueous ethanol (80 cm^3). Sodium borohydride (2 g) was added in portions to the solution which was then evaporated and treated with 2M-hydrochloric acid. The reaction mixture was basified with sodium hydroxide and the product extracted into dichloromethane (3 × 75 cm^3). Evaporation of the combined, dry extracts afforded the title compound as a reddish oil which slowly crystallised and was eventually recrystallised from ethanol as colourless prisms (2.7 g, 72%), m.p. 112—113.5 °C, $\nu_{max.}$ 1 610 cm^{-1}; $\lambda_{max.}$ 234, 283 nm; $\delta_H(CDCl_3)$ 6.78—6.58 (3 H, m, 2′-, 5′-, 6′-H), 6.52 (1 H, s, 5-H), 6.13 (1 H, s, 8-H), 3.81 (6 H, s, 2 × OCH_3), 3.77, 3.59 (2 × 3 H, 2 × s, 2 × OCH_3), and 3.4—2.5 (9 H, m, aliphatic H + NH_2, integral height reduced by addition of D_2O to sample, then equivalent to 7 H).

2-*Acetamido*-1-(3′,4′-*dimethoxybenzyl*)-6,7-*dimethoxy*-1,2,3,-4-*tetrahydroisoquinoline* (14).—*Method 1*. 2-Amino-6,7-di-

* The ^1H n.m.r. spectrum recorded at 130 °C is considerably simplified and, for example, the ABX system of the C-1 substituent aryl protons is now clearly resolved J_{AX} 8 Hz, J_{BX} 1.5 Hz.

† At ambient temperature the ^1H n.m.r. spectrum is much more complex, indicating that there is restricted rotation about the N-2 and C-1 substituent bonds (Found: C, 67.0; H, 6.9; N, 6.85. $C_{23}H_{28}N_2O_5$ requires C, 67.0; N, 6.8; N, 6.8%).

View Article Online

Published on 01 January 1983. Downloaded by Memorial University of Newfoundland on 08/07/2014 06:13:27.

methoxy-1-(3′,4′-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (0.98 g) in 95% ethanol (14 cm^3) and acetic anhydride (3 cm^3) was stirred at room temperature for 15 min. The solvent was removed under reduced pressure and the residual oil partitioned between dichloromethane and water. Sodium carbonate was then added until the stirred mixture was neutral to litmus. The organic phase was separated, dried, and evaporated to give an oil which slowly solidified on trituration with acetone. Crystallisation from acetone gave the title compound as colourless needles (0.8 g), m.p. 138.5—139.5 °C. A further quantity of this product (0.08 g) was obtained from the mother-liquor, $\nu_{max.}$ 3 245 and 1 658 cm^{-1}; $\lambda_{max.}$ 282 nm; $\delta_H[(CD_3)_2SO]$ * 9.00, 8.43 (2 × bs, integral ratio 1/2, 1 H), 6.85—6.50 (5 H, m, ArH), 4.18 (1 H, bt, *ca. J* 7 Hz, 1-H), 3.73 (9 H, bs, 3 × OCH_3), 3.62 (3 H, bs, OCH_3), 3.33—2.60 (7 H, m, aliphatic H), 1.85, 1.70 (2 × bs, integral ratio 1/2, CH_3CO); *m/z* 400 (M^+, 2%), 339 (12), 249 (20), and 247 (100) (Found: C, 66.0; H, 7.1; N, 7.1. $C_{22}H_{28}N_2O_5$ requires C, 66.0; H, 7.05; N, 7.0%).

Method 2. 2-Acetamido-6,7-dimethoxy-1-(3′,4′-dimethoxybenzyl)isoquinolinium iodide (0.23 g), suspended in 98% ethanol (5 cm^3), was treated with sodium borohydride (0.3 g). After 45 min, the reaction mixture was acidified with 2M-hydrochloric acid, rebasified with sodium hydroxide, and extracted with dichloromethane (3 × 15 cm^3). The combined extracts were evaporated to give an oil (0.15 g), which crystallised from acetone as colourless needles (0.1 g, 57%), m.p. 138—139 °C.

1-(3′,4′-*Dimethoxybenzyl*)-6,7-*dimethoxy*-2-(N-*methylacetamido*)-1,2,3,4-*tetrahydroisoquinoline* (11).—*Method 1.* The previous compound (0.4 g), in freshly distilled dry tetrahydrofuran (22 cm^3), was treated with sodium hydride (1.04 mol equiv.). After the mixture had been stirred for 1.5 under an atmosphere of nitrogen, methyl iodide (2 mol equiv.) was introduced and the reaction mixture stirred for a further 15 min. Water (1 cm^3) was then slowly introduced, most of the solvent removed by evaporation, and the residue partitioned between brine and ethyl acetate. The organic layer was dried and evaporated to yield a pale yellow oil which was chromatographed on silica with 35% acetone in light petroleum (b.p. 60—80 °C) to give the title compound as a colourless oil, which slowly crystallised and was recrystallised from ethanol (0.17 g, 41%), m.p. 122—123 °C, $\nu_{max.}$ 1 645 cm^1; $\lambda_{max.}$ 282 nm; $\delta_H[(CD_3)_2SO]$ 6.95—6.60 (5 H, m, ArH), 4.5—4.3 (1 H, bt, *J* 5.5 Hz, 1-H), 3.8—3.5 (12 H, 4 × s, 4 × OCH_3), 3.3—2.5 (6 H, m, aliphatic H), 2.88 (3 H, s, NCH_3), 1.9 (3 H, s, CH_3CO). This spectrum is simplified by heating the sample at 120 °C (Found: C, 66.7; H, 7.3; N, 6.6. $C_{23}H_{30}N_2O_5$ requires C, 66.65; H, 7.3; N, 6.8%).

Method 2. 6,7-Dimethoxy-1-(3′,4′-dimethoxybenzyl)-2-(*N*-methylacetamido)-1,2-dihydroisoquinoline (0.1 g) in ethyl acetate (50 cm^3) was hydrogenated at 250 lb in^{-2} pressure over platinum oxide catalyst (0.01 g) for 48 h. Removal of the solvent and catalyst gave the title compound as an oil which slowly crystallised (0.085 g, 85%).

Method 3. 1-(3′,4′-Dimethoxybenzyl)-6,7-dimethoxy-2-(*N*-methylacetamido)isoquinolinium methyl sulphate (0.2 g) in 98% ethanol (10 cm^3) was treated with sodium borohydride (10 cm^3) and the mixture heated at reflux for 1 h. Water (10 cm^3) was then added and the product tetrahydroisoquinoline (14) isolated by extraction with dichloromethane (3 × 25 cm^3), followed by the work-up, yield 0.14 g (89%).

* At 180 °C the spectrum is simplified and the signals at δ 9.00 and 8.43 and at δ 1.85 and 1.70 merge into singlets at δ 8.7 and 1.80 respectively.

2-*Acetamido*-6,7-*dimethoxy*-1-(3′,4′-*dimethoxybenzyl*)-2-*methyl*-1,2,3,4-*tetrahydroisoquinolinium Iodide* (15).—The tetrahydroisoquinoline (11) (0.15 g) in warm acetone (3 cm^3) was treated with methyl iodide (1 g) and the mixture heated at reflux for 69 h. A colourless solid gradually formed and this was collected at the end of the reaction to give the title compound as an amorphous powder (0.15 g, 73.8%), m.p. 186—187 °C, $\nu_{max.}$ 3 500 and 1 700 cm^{-1}; $\lambda_{max.}$ 254, and 285sh nm; $\delta_H[(CD_3)_2SO-CDCl_3, 2:1]$ 6.94—6.45 (5 H, m ArH), 5.7 (1 H, bs, NH), 4.15—3.2 (7 H, m, aliphatic H, overlapping with singlets due to methoxy and N^+-methyl H), 3.80, 3.78, 3.66, 3.63 (4 × 3 H, 4 × s, 4 × OCH_3), 3.38 (3 H, s, N^+CH_3), and 2.18 (3 H, s, $COCH_3$); *m/z* 414.2158 (7%) [$C_{23}H_{30}N_2O_5$ (M^+ − HI) requires 414.2156], 101 (100%, $C_4H_9N_2O$). (Found: C, 50.6; H, 5.8; N, 5.2; $C_{23}H_{31}IN_2O_5$ requires C, 50.9; H, 5.8; N, 5.2%).

Photolysis of 2-*Acetamido*-6,7-*dimethoxy*-1-(3′,4′-*dimethoxybenzyl*)-2-*methyl*-1,2,3,4-*tetrahydroisoquinolium Iodide*.—The salt (50 mg) was dissolved in methanol (100 cm^3) and the solution irradiated for 3 h through a quartz immersion well with either a low- or a medium-pressure u.v. source. During the course of this time the reaction was monitored by withdrawing samples for t.l.c. and mass spectrometric and u.v. spectroscopic analyses. Although the starting material was gradually consumed (change in u.v. spectrum), there was no evidence for the production of *O*-methylflavinantine [R_F 0.2, silica 60% ethyl acetate–light petroleum (b.p. 60—80 °C)], although veratraldehyde [R_F 0.9 (same conditions)] was detected after irradiation for 15 min. At the end of the reaction the solvent was removed and half the residue partitioned between ethyl acetate and 0.2N-sodium hydroxide solution. The organic phase was evaporated and subjected to t.l.c. and mass spectrometric analyses. Again no *O*-methylflavinantine was detected, although the presence of veratraldehyde was confirmed by comparison with an authentic specimen, after the residue had been purified by chromatography on silica. The remaining crude photolysis product was dissolved in 98% aqueous ethanol and heated with sodium borohydride; after evaporation of the solvent, the residue was treated with warm 2M-hydrochloric acid, made basic with 2M-sodium hydroxide and extracted with ethyl acetate. The solvent was removed and the residue (15 mg) subjected to mass spectrometric analysis, *m/z* (EI) 207 (34%), 206 (38), 195 (29), 168 (100), 166 (32), 165 (30), 164 (67), 151 (39), and 139 (39). At low ionisation voltage (15 eV), only ions at *m/z* 207 and *m/z* 168 are observed: Found: *m/z* 207.1264. [Calc. for 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline ($C_{12}H_{17}NO_2$): *M*, 207.1259] and *m/z* 168.0787. [Calc. for veratryl alcohol ($C_9H_{12}O_3$) *M* 168.0786].

8,9-*Dimethoxy*-1-(3′,4′-*dimethoxyphenyl*)-2-*methylpyrazolo*-[5,1-a]*isoquinoline* (17).—Papaverine (1.4 g) was *N*-aminated and acetylated in the usual way. The product was then dissolved in methanol (25 cm^3) and the cooled solution treated with an excess of freshly prepared diazomethane in diethyl ether. After 12 h, the solvents were removed under reduced pressure to yield an oil which was taken up in the minimum of hot absolute ethanol (*ca.* 3 cm^3) and the solution allowed to cool overnight. The following day, the title compound was collected by filtration as a colourless crystalline solid (0.17 g, 10%). The mother liquor contained *N*-acetamidopapaverinium iodide (0.45 g, 21%). The pyrazole has m.p. 181—182 °C (ethanol), $\nu_{max.}$ (KBr) 1 502 and 1 480; $\lambda_{max.}$ 237, 256, 313, 328, and 344 nm; $\delta_H[(CD_3)_2CO]$ 8.15 (1 H, d, *J* 7.5 Hz, 5-H), 7.28, 7.23 (2 × 1 H, 2 × s, 7-, 10-H), 7.14 (1 H, d, *J* 8 Hz, 5′-H), 7.06 (1 H, d, *J* 2 Hz, 2′-H), 7.02 (1 H, dd, J_1 8 Hz, J_2 2 Hz, 6′-H), 6.98 (1 H, d, *J* 7.5 Hz, 6-H), 3.90 (2 × 3

View Article Online

Published on 01 January 1983. Downloaded by Memorial University of Newfoundland on 08/07/2014 06:13:27.

H, 2 × s, 2 × OCH_3), 3.48 (3 H, s, OCH_3), and 2.30 (3 H, s, NCH_3); *m/z* 378.1581 ($C_{22}H_{22}N_2O_4$ requires 378.1579) (Found: C, 69.8; H, 6.2; N, 7.5; $C_{22}H_{22}N_2O_4$ requires C, 69.7; H, 6.1; N, 7.4%).

6,7-*Dimethoxy*-1-(3′,4′-*dimethoxybenzyl*)-2-(N-*phthalimido*)-1,2,3,4-*tetrahydroisoquinoline* (23).—2-Amino-6,7-dimethoxy-1-(3′,4′-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (1 g and phthalic anhydride (0.41 g) were heated in a Dean-Stark apparatus with dry toluene containing triethylamine (0.04 cm^3). After 2 h, the solvent was removed to yield a pale brown gum which was chromatographed on neutral alumina, with 40% ethyl acetate in light petroleum (b.p. 60—80 °C) as eluant, thus affording the title compound as a pale yellow solid (0.84 g, 62%), which was recrystallised from ethanol, and had m.p. 142.5—144.5 °C, $\nu_{max.}$ 1 780, 1 760, and 1 715 cm^{-1}; $\lambda_{max.}$ 281 nm; $\delta_H(CDCl_3)$ 7.72 (4 H, s, protons of phthamido unit), 6.85 (1 H, bs, 2′-H), 6.65 (1 H, bd, *J ca.* 8 Hz, 6′-H), 6.62, 6.55 (2 × 1 H, 2 × s, 5-, 8-H), 4.46 (1 H, d, *J* 8 Hz, 5′-H), 5.30 (1 H, m, 1-H), 3.87, 3.82, 3.62 (12 H, 3 × s, 4 × OCH_3), 3.90—2.40 (6 H, m, remaining protons) (Found-C, 68.7; H, 6.1; N, 6.1. $C_{28}H_{28}N_2O_6$ requires C, 68.8; N, 5.8; N, 5.7%).

6,7-*Dimethoxy*-1-(3′,4′-*dimethoxybenzyl*)-2-*nitroso*-1,2,3,4-*tetrahydroisoquinoline* (24).—Tetrahydropapaverine hydrobromide (1 g) in 50% aqueous ethanol (20 cm^3) was treated with several drops of 2M-hydrochloric acid. A cold solution (*ca.* 5 °C) of sodium nitrite (0.24 g) in water (10 cm^3) was introduced into the reaction vessel and the mixture stirred for 5 min at room temperature, prior to warming to 60 °C for 20 min. During this time a colourless solid formed, which was collected, washed several times with water, and dried under reduced pressure at 60 °C to afford the title compound, m.p. 131 °C (0.66 g, 61%), $\delta_H[(CD_3)_2SO]$ 6.9—6.55 (5 H, m, ArH), 6.05—5.80 (1 H, 2 × t*, 1-H), *ca.* 4.6, 4.05 (2 H, 2 × m*, $3H_2$), 3.89, 3.82, 3.75, 3.70 (4 × 3 H, 4 × s, 4 × OCH_3), *ca.* 3.75, 2.90 (1 H, 2 × m, 4-H_{ax}, integral ratio 1 : 1), 3.40, 3.10 (2 H, 2 × m, CH_2Ar integral ratio 1 : 1), 2.65 (1 H, m, 4-H_{eq}). When the spectrum is re-run at 120 °C, the signals marked with an asterisk are sharpened but coalescence of the resonances is still not affected. In simple *N*-nitrosamines [13-15] E_a = 20—25 kcal mol^{-1}, but in our compound this barrier is much higher and a detailed analysis of the ^1H n.m.r. spectrum suggests that a mixture of diastereoisomers are present due to the chiral centre at C-1, restricted rotation with the *N*-nitroso group, and inhibition of inversion at the heterocyclic nitrogen atom; *m/z* EI (%) 342 (21), 191 (46), 151 (100); CI 373 (*M* + 1, 72). (Found: C, 64.3; H, 6.5; N, 7.5. $C_{20}H_{24}N_2O_5$ requires C, 64.5; H, 6.5; N, 7.5%).

Photolysis of 6,7-*Dimethoxy*-1-(3,4-*dimethoxybenzyl*)-2-*nitroso*-1,2,3,4-*tetrahydroisoquinoline* (24).—The nitroso compound (0.1 g) was dissolved in methanol (100 cm^3) containing concentrated hydrochloric acid (2 cm^3) and irradiated with a 125-W u.v. light source. After 13 h, during which time the progress of the reaction was carefully monitored by withdrawing samples for t.l.c., g.l.c., and mass spectrometric analysis, the solvent was removed, and the residue basified and extracted with diethyl ether. Chromatography of the extract over neutral alumina elution with diethyl ether–light petroleum (b.p. 60—80 °C) mixtures eventually afforded veratraldehyde (10 mg) and 6,7-dimethoxy-3,4-dihydroisoquinoline (5 mg); m.p. of picrate 200—201 °C (lit.,[11] 201—203 °C), identical with authentic samples, together with several multicomponent oils (total weight 25 mg). Mass spectrometric analysis of basified crude reaction mixture (EI) shows *m/z* 166 (veratraldehyde), 191 (6,7-dimethoxy-3,4-dihydroisoquinoline). CI spectrum exhibits *m/z* 167 and 192.

Acknowledgements

Michael Hutchins is the recipient of a S.E.R.C. CASE studentship in collaboration with Glaxo Group Research Ltd. The authors thank Dr. G. Klinkert for recording differential n.O.e. spectra, Dr. T. W. Bentley for a sample of *O*-methylflavinantine, and Miss A. Majeed, MSc, for experimental assistance with the anodic oxidation of laudanosine.

References

1 Part 7, P. Bird, M. Powell, M. Sainsbury, and D. I. C. Scopes, *J. Chem. Soc., Perkin Trans. 1*, preceding paper.
2 M. Sainsbury and R. F. Schinazi, *J. Chem. Soc., Perkin Trans. 1*, 1972, 718.
3 M. Sainsbury and J. Wyatt, *J. Chem. Soc., Perkin Trans. 1*, 1976, 661.
4 L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Am. Chem. Soc.*, 1973, **95**, 2651; J. R. Falck, L. L. Miller, and F. R. Stermitz, *ibid.*, 1974, **96**, 2981.
5 U. Palmquist, A. Nillson, T. Pettersson, A. Ronlán, and V. D. Parker, *J. Org. Chem.*, 1979, **44**, 196.
6 H. Klunenberg, C. Schaffer, and H.-J. Schäfer, *Tetrahedron Lett.*, 1982, **23**, 4581.
7 J. B. Kerr, T. C. Jempty, and L. L. Miller, *J. Am. Chem. Soc.*, 1979, **101**, 7338.
8 K. T. Potts, U. P. Singh, and J. Bhattacharyya, *J. Org. Chem.*, 1968, **33**, 3766.
9 Y. L. Chow, C. Colon, and S. C. Chen, *J. Org. Chem.*, 1967, **32**, 2109; M. P. Lau, A. J. Cessna, Y. L. Chow, and R. W. Yip, *J. Am. Chem. Soc.*, 1971, **93**, 3808; Y. L. Chow, *Acc. Chem. Res.*, 1973, **6**, 354.
10 H. Lund, M.-A. Michel, and J. Simonet, *Acta Chem. Scand. Ser. B*, 1974, **28**, 900. For a more recent example of a catalytic oxidative electron transfer process see S. Dapperheld and E. Steckhan, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 780. Also see S. Mazur, V. M. Dixit, and F. Gerson, *J. Am. Chem. Soc.*, 1980, **102**, 5343.
11 F. L. Pyman, *J. Chem. Soc.*, 1909, 1272.
12 E. Späth and N. Polgar, *Monatsch.*, 1929, **51**, 190.
13 H. Günther in 'N.M.R. Specktroskopie,' Thieme, Stuttgart, 1973, p. 254.
14 A. Mannschreck, H. Munsch, and A. Mattheus, *Angew. Chem.*, 1966, **78**, 751.
15 R. K. Harriss and R. A. Spragg, *Chem. Commun.*, 1967, 362.

Received 27*th December* 1982; *Paper* 2/2158