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ELECTROOXIDATIVE SYNTHESIS OF MORPHINANDIENONES FROM 1-BENZYLTETRAHYDROISOQUINOLINES[1]

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Abstract—The electrochemical oxidation of several 1-benzyl tetrahydroisoquinolines has been performed at a platinum anode in acetonitrile. Using potentiostatic conditions and a three compartment cell, the following cyclizations were accomplished on a several hundred milligram scale in the yields indicated: 6'-bromolaudanosine to O-methylflavinantine (16%), 5'-methoxylaudanosine to O-methyl-C-norandrocymbine (38%), 8-methoxylaudanosine to protostephanone (35%), norlaudanosine to N-nor-O-methylflavinantine (22%).

We have shown[2,3] that some N-methyl-tetraalkoxy-1-benzyltetrahydroisoquinolines can be electrochemically oxidized to yield morphinandienones. Because of the overall ease of synthesis of the precursors and high yield (up to 63%) of the electrochemical cyclization step, our procedure should be considered the method of choice for synthesis of certain of these complex alkaloids.

In order to widen the scope of the reaction, some extensions of the basic procedure were thought valuable.

Firstly, we had so far observed exclusively *para–para* coupling even though *ortho–para* coupling would have been possible in each case studied. If *ortho–para* coupling could be induced (for example, by the presence of a blocking group in the favored coupling position), the product would have the proper substituent placement for entry into the morphine system of alkaloids. Secondly, a number of penta-oxygenated morphinandienones (such as protostephanone) have recently been of interest in biosynthetic studies and our synthesis would make these compounds much more readily available. Finally, our first studies indicated that the N atom of the precursor and final product might not be inert to the oxidation conditions and hence yield improvements might be achieved by varying the nitrogen substituent.

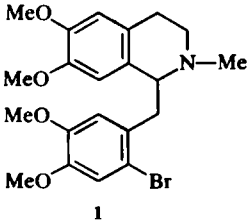
We therefore synthesized the benzylisoquinolines **1–3** and studied their anodic oxidations.

RESULTS

All oxidations were performed potentiostatically in a three compartment cell. The anode was a platinum sheet and the electrolyte was acetonitrile-lithium perchlorate. The reference electrode was Ag/0·1 M $AgNO_3$ in acetonitrile.

6'-Bromolaudanosine, **1**. From oxidation of **1** at 1·2 V, (*vs* Ag/$AgNO_3$) the only product isolated (in addition to a small amount of recovered starting material) was O-methylflavinantine, **4**, in 16% yield. Thus, the hoped for cyclization of Eq (1) did not occur, but instead loss of the bromine substituent was observed, and the product was identical to that obtained from laudanosine oxidation. The yield of O-methylflavinantine was considerably less than that found[2,3] in the case of laudanosine oxidation (52%) under these conditions.

Methoxylaudanosines, **2a** and **2b**. The oxidation of 5'-methoxylaudanosine (**2a**) was initially attempted at 1·25 V, but no alkaloidal products could be isolated. When the potential was lowered to 1·10 V, a few percent of the tetramethoxymorphinandienone **5** was obtained upon exhaustive oxi-



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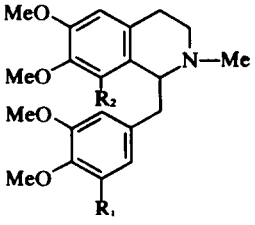
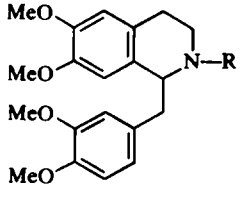
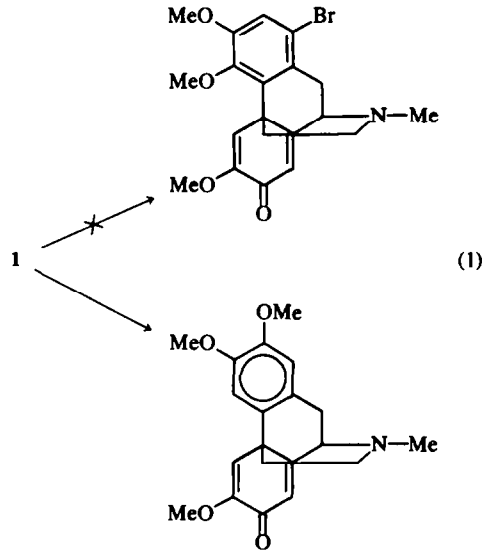


2a: R_1 = OMe, R_2 = H
2b: R_1 = H, R_2 = OMe



3a: R = H
3b: R = CHO



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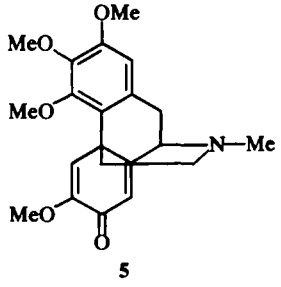
dation. Since it seemed likely that the product **5** was being oxidized during the reaction, a high speed liquid chromatography (HSLC) method for analysis of a mixture of **2a** and **5** was developed in order to



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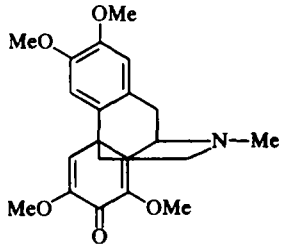
quantitatively study the effect of the amount of current passed on product yield and conversion. It was found that the percent yield of **5** increased gradually to a maximum of 38% yield when about 2 Faraday/mole of current were passed and then decreased. The yield based on reacted starting material reached a maximum of 55% at 1·0 Faraday/mole passed, with the percent yield being about 22% at that point. HSLC proved to be a rapid, useful method for analysis of this reaction.

Complete oxidation of 8-methoxylaudanosine, **2b**, at 1·23 V also yielded no alkaloidal products and only a low yield of the expected alkaloid protostephanone **6** was isolated after exhaustive oxidation at 1·10 V. However, oxidation of **2b** only until 2·0 Faraday/mole had been passed allowed isolation of protostephanone in 35% yield.

N-*substituent variations.* Norlaudanosine, **3a**, was oxidized at 1·0 V until 2 Faraday/mole of current had been passed. The N-normorphinandienone, O-methylflavinine, (**7**), was



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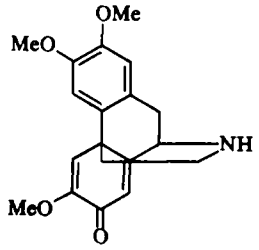
isolated in 22% yield along with a small amount of starting material and 3,4-dimethoxybenzaldehyde. Thus, for the first time in these oxidations a cleavage product (the benzaldehyde) was found.



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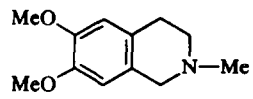
Cleavage products were the only isolable materials when N-formyllaudanosine (**3b**) was oxidized. After oxidation of **3b** and removal of solvent, the crude residue was treated with LAH in order to facilitate product isolation. The products obtained after reduction were O-methylcorypalline (**8**) and 3,4-dimethoxybenzyl alcohol. The nature of the original products formed during the oxidation was not further investigated. It was shown that treatment of the starting material **3b** with LAH yielded laudanosine as the only product.



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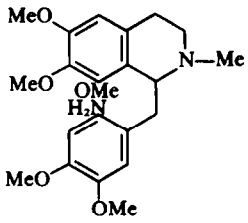
DISCUSSION

The value of these extensions of the electrochemical morphinandienone synthesis is perhaps best exemplified by the syntheses of **5** and **6**. Thus, **5** was previously[4] synthesized by a sequence which culminated in a Pschorr reaction on **10**. This last step was accomplished[4] in only 1·7% yield. Similarly, the previous synthesis of **6** was from a Pschorr reaction on **9**.

Thus, our cyclization not only proceeds in much better yield than the Pschorr reaction,[5] but does not involve the extra steps to insert the amino group needed in that reaction.



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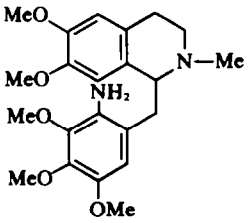

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Use of a bromine blocking group to force *ortho–para* coupling was unsuccessful, since cyclization occured at the position of the bromine group. The bromine could have been lost prior to cyclization or after, since no evidence is available for distinguishing mechanisms. One previous report[6] in the literature documented bromine loss in an aromatic coupling reaction.

The results of N-formyllaudanosine, **3b**, were unexpected. Tertiary amines are reported[7] to oxidize near 1 V and an oxidation wave appears at about 0·6 V in the cyclic voltamograms of laudanosine and its simple derivatives. Since this wave should correspond to oxidation of the non-bonded pair, the N-formyl group should raise the oxidation potential considerably. Indeed, cyclic voltammetry of **3b** revealed no oxidation wave below 1·0 V. In spite of this, oxidation of **3b** yielded only cleavage products in high yield. Very similar products were previously noted[8] in the electrooxidation of armepavine and N-norarmepavine phenoxides.

EXPERIMENTAL

General experimental details, including electrochemical procedures, were as described in detail previously.[3] Some synthetic procedures (e.g., amide formation, Bischler–Napieralski cyclization, etc) were performed essentially identically for several syntheses below, but are only described once in detail. All potentials are with reference to Ag/0·1 M $AgNO_3$ in acetonitrile.

6′Bromolaudanosine, **1**, *preparation and oxidation.* Papaverine hydrochloride (Mallinckrodt Chem. Co.) was brominated with bromine water according to the procedure[9] of Späth and Lang to give 6′-bromopapaverine in high yield (m.p. 142–143°; Lit[10] m.p. 144–145°). 6′-Bromopapaverine was methylated with MeI in MeOH to yield 6′-bromopapaverine methiodide, m.p. 240° (Lit[11] m.p. 224–225°). The methiodide was reduced with $NaBH_4$ in MeOH to yield 6′-bromolaudanosine, **1**, m.p. 124–125° (Lit[12] m.p. 128°).

6′-Bromolaudanosine was electrolyzed in acetonitrile with the usual procedure.[3] Three batches of **1** (0·40 g each) were oxidized until the current dropped to 8–10 mA (about 1 h). The combined anolytes were evaporated to near dryness, taken up in water and extracted with $CHCl_3$. The $CHCl_3$ layers were dried, evaporated, and the residue was chromatographed on neutral Al_2O_3 to yield 75 mg of recovered **1** and 140 mg (16%) of O-methylflavinantine, **4**, identified by comparison with an authentic sample.[3] No other alkaloidal products were isolated.

5′-Methoxylaudanosine (**2a**) *preparation and oxidation.* A mixture of 10·0 g of 3,4,5-trimethoxyphenylacetic acid (Aldrich Chemical Co) and 8·0 g of 3,4-dimethoxyphenethylamine (Aldrich Chemical Co) was heated (170–175°) in an oil bath for 4 h under N_2. The mixture was cooled, dissolved in benzene and then washed with 1 N HCl and 5% $NaHCO_3$. The benzene layer was dried and evaporated to yield (after crystallization from EtOH) 15·1 g of N-(3,4-dimethoxyphenethyl)-2-(3,4,5-trimethoxyphenyl) acetamide, m.p. 99·5–100·5° (Lit[13] m.p. 101–102·5). To a stirred and refluxing solution of 7·2 g of the amide in 750 ml of CH_3CN was added 21 g of $POCl_3$ over 20 min. The mixture was refluxed under N_2 for 1 h, cooled, and the solvent evaporated. The residue was dissolved in water and the soln washed with EtOAc. The basic layer was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The chloroform layer was dried and evaporated to leave the 3,4-dihydroisoquinoline as a yellow oil. This oil was immediately treated with 15 ml of MeI in 65 ml MeOH, refluxed for 3·5 h and evaporated to yield 6·2 g of 1-(3,4,5-trimethoxybenzyl) - 3,4-dihydro-6,7-dimethoxy - isoquinoline methiodide as yellow crystals. The methiodide was reduced with $NaBH_4$ in methanol to yield 6·2 g of **2a**, as a viscous oil (picrate m.p. 175°; Lit[14] m.p. 177–178°) whose NMR was consistent[14] with the structure and showed no impurities by NMR or TLC.

5′-Methoxylaudanosine, (**2a**), 300 mg, was oxidized at 1·1 V until the current dropped from 72 mA to 17 mA, and the anolyte worked up as above. Chromatography yielded a few mg of **5**, whose NMR and IR spectra were identical to that of an authentic sample.[15] Oxidations were then conducted at lower values of total current passed and, after work-up of the anolyte, the crude residue was analyzed for **2a** and **5** by HSLC.[16] Analysis was on a Waters Associate Model ALC 202 (UV detector) using an 1/4 X 3′ Corasil-C18 (Bondapak) column at 1600 psi with 7:3 MeOH–water as solvent. The results were (Faraday/mole current passed, percent yield, percent conversion): 0·5, 15, 50; 1·0, 24, 55; 2·0, 38, 43; 2·5, 34, 36. Thus optimum conversion was at 1·0 Faraday/mole and optimum yield at 2·0 Faraday/mole.

8-Methoxylaudanosine (**2b**) *synthesis and oxidation.* An equimolar mixture of 3,4-dimethoxyphenylacetic acid (Aldrich Chemical Co) and 3,4,5-trimethoxyphenethylamine (prepared by reduction of Aldrich Chemical 3,4,5-trimethoxyphenylacetonitrile according to the method of Nystrom[17]) were converted in 80% yield to N(3,4,5-trimethoxyphenethyl)-2-(3,4-dimethoxyphenyl) acetamide, m.p. 114–116° (Lit[18] m.p. 115–116°) by the procedure given for the amide above. The acetamide (19·9 g) was converted with $POCl_3$ to 1-(3,4-dimethoxybenzyl) - 3,4-dihydro-6,7,8 - trimethoxyisoquinoline as above. The dihydroisoquinoline was immediately dissolved in 50 ml MeOH, 15 ml of MeI was added and the soln was refluxed for 2 h. The soln was cooled and filtered to yield 18·6 g (83% from the acetamide) of 1-(3,4-dimethoxybenzyl) - 3,4-dihydro-6,7,8-trimethoxyisoquinoline methiodide, m.p. 163·5–165° (Lit[19] m.p. 169°). To a cooled (0°) dispersion of the methiodide in 100 ml MeOH was cautiously added excess $NaBH_4$. A vigorous, exothermic reaction occurred. The mixture was stirred for 2 h, the solvent evaporated, and the residue taken up in water. Extraction with $CHCl_3$ yielded 18 g of **2b**, as a yellow syrup.[19] The HCl salt was previously reported,[19] but without physical data or analysis. We found m.p. 175–176° for the HCl salt. (Found: C, 62·07; H, 7·52. Calcd for $C_{22}H_{30}NO_5Cl$: C, 62·33; H, 7·13%).

8-Methoxylaudanosine, **2b**, (330 mg) was oxidized at

1·08 V until 2 Faraday/mole current had been passed. The anolyte was worked up as usual and the residue chromatographed on silica gel to yield 110 mg (35%) of protostephanone, **6**, as a pale yellow syrup, whose NMR and IR spectra were identical with those of an authentic sample.[20]

Norlaudanosine, **3a**, *synthesis and oxidation.* Reaction of 10 g of N-(3,4-dimethoxyphenethyl) - 2-(3,4-dimethoxyphenyl) acetamide with 12 g of $POCl_3$ in 200 ml dry acetonitrile as above yielded 1-(3,4-dimethoxybenzyl)-3,4-dihydro-6,7 - dimethoxyisoquinoline as an oil. This oil was immediately reduced with excess $NaBH_4$ in methanol as described above to yield norlaudanosine as a colourless oil (HCl salt m.p. 215°; Lit[21] m.p. 216–216·5°).

Norlaudanosine, **3a**, (928 mg) was oxidized in 3 batches at 1·0 V until 2 Faraday/mole current was passed. The batches were combined and the anolyte worked up as usual to yield a residue which was chromatographed on silica gel. 3,4-Dimethoxybenzaldehyde (20 mg) and **3a** (32 mg) were isolated along with 195 mg (22% yield) of **7**, as a slightly yellow foam. **7** was treated with MeI in MeOH to yield O-methylflavinantine methiodide which was identical with an authentic sample prepared from O-methylflavinantine.[3]

N-*formylnorlaudanosine*, **3b**, *synthesis and oxidation.* 3,4-Dihydropapaverine hydrochloride (Aldrich Chemical Co), 1·0 g, was added to 6 ml 88% formic acid and 30 ml formamide. The mixture was refluxed 2·5 h, poured into ice, and extracted with ether. Crystallization of the residue from EtOH yielded 350 mg of **3b**, m.p. 134·5–136° (Lit[22] m.p. 136°). **3b** was also prepared by reacting **3a** with formic acid.

Compound **3b**, 550 mg, was oxidized at 1·10 V until the current reached 10 mA and the anolyte was worked up as usual. The residue shows IR bands at 1660 and 1605 cm^{-1} which were not typical of morphinandienones. To aid in identification of products (e.g., reduce any N-CHO groups remaining to N-Me), the residue was reduced with excess LAH in THF at room temp. After work-up, the residue was chromatographed on silica gel to yield 200 mg of 3,4-dimethoxybenzyl alcohol (as compared with an authentic sample from Aldrich Chemical Co) and 240 mg of a brown oil. The latter crystallized from hexane to give yellow rosettes whose NMR spectrum was identical to that reported[23] for O-methylcorypalline. A sample was sublimed to yield a white powder, m.p. 69–71° (Lit[24] m.p. 69–71°). A second, unidentified, trace alkaloid was observed on TLC, but its R_f value was different from that of laudanosine and from that of the LAH reduction product of O-methylflavinantine. Reduction of **3b** with LAH yielded only **3a**. Thus no starting material or or O-methyl-N-formylflavinine had been present in the original anolyte residue.

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