(*E*)-*N*-[2-(Phenylmethylene)cyclohexyl]-2-furanmethanamine Maleate (10). A solution of compound **8** (7 g, 0.025 mol) in 100 mL of THF was added to a solution of LAH (7 g) in 200 mL of THF, and the mixture was refluxed 6 h. It was cooled in ice and decomposed in succession with 7 mL of H_2O, 7 mL of 15% NaOH, and 21 mL of H_2O. The mixture was stirred 1 h and filtered and the filtrate dried ($MgSO_4$) and concentrated. The residue (5 g) was dissolved in ether, extracted with cold 10% HCl (3 × 20 mL). The acid extract was basified with 20% NaOH, extracted with ether, and worked up as usual[5] to give 1.3 g of yellow oil. The "neutral" component was examined by TLC only. The basic fraction was converted to the maleate. It was crystallized from MeOH–ether: mp 162–163 °C; UV (EtOH) λ_{max} 241 nm (ϵ 16 050); mass spectrum, *m/e* 267; IR 2800, 2720, 2620, 2560, 2480 (NH/acid OH), 1705 (C=O), 1640, 1620, 1525 (C=C/CO_2^-/NH_2^+), 1395, 1365, 1215, 1155, 805, 750, 700 (C–O/other) cm^{-1}; ^1H NMR (Me_2SO-d_6) [the pattern of CHN suggests that $NHCH_2$–furan group is axial] δ 1.4–2.2 (CH_2's, cyclohexyl), 4.2 (NCH_2C=CHCH=CHO), 3.8 (CHN, equatorial), 6.6 (C=CH-CH=CHO), 6.6 (CH=C), 6.05 (HOOCCH=CHCOOH), 7.3 (C=CHCH=CHO), 7.3 (Ph's).

Anal. Calcd for $C_{18}H_{21}NO{\cdot}C_4H_4O_4$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.64; H, 6.75; N, 3.84.

(*E*)-*N*-Methyl-*N*-[2-(phenylmethylene)cyclohexyl]-2-furanmethanamine (3). A solution of compound **10** (1.1 g, 0.0041 mol) in 10 mL of ethyl formate was refluxed 23 h and concentrated. The residue was dissolved in ether, washed with 10% HOAc (3 × 10 mL) and saturated $NaHCO_3$, and worked up as usual.[5] The resulting *N*-formyl compound (0.86 g) showed a reasonable IR and NMR: HR mass spectrum; found 295.15867, calcd for $C_{19}H_{21}NO_2$ 295.15721.

A solution of the *N*-formyl compound in 10 mL of ether was added to a solution of LAH (0.9 g) in 25 mL of ether and refluxed 18 h. It was cooled and decomposed as described above. The residue was dissolved in 1% MeOH–$CHCl_3$, filtered through a short column of silica gel, and concentrated to give 0.54 g of compound **3**, which showed one spot on TLC (silica gel 5% MeOH–$CHCl_3$): GC (1% QF-1 column) t_r 4.52 min; 97.33%; UV (EtOH) 229 nm (sh, ϵ 11 650), λ_{max} 242 nm (ϵ 12 450); IR 2790 (N–C–H), 1655, 1600, 1575, 1495 (C=C), 1150, 1015, 1005, 740, 735 700 (C–O/other) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–2.1 (CH_2's cyclohexyl), 2.25 (CH_3N), 2.5 (CH_2CH=C), 2.86 (CHN, equatorial), 6.2, 6.3 (C=CHCH=CHO), 6.46 (CH=C), 7.25 (Ph's), 7.36 (C=CHCH=CHO); HR mass spectrum, found 281.176939, calcd for $C_{19}H_{23}NO$, 281.177953.

Registry No. **2**, 105206-07-3; **3**, 105229-44-5; **4**, 105206-08-4; **5**, 105307-21-9; **6**, 105229-45-6; (*E*)-**7**, 105206-09-5; (*Z*)-**7**, 105206-14-2; **8**, 105206-10-8; **9**, 105206-11-9; **10**, 105206-13-1; **10** (*N*-formyl deriv), 105206-15-3; 2-benzoylcyclohexanone, 3580-38-9; *N*-methylfurfurylamine, 4753-75-7; 2-furoyl chloride, 527-69-5.

Electrosynthesis in a Beaker: An Efficient Route to Morphinandienones Avoiding Potentiostats for Control of Electrode Potentials

T. William Bentley* and Stephen J. Morris

Department of Chemistry, University College of Swansea, Singleton Park, Swansea SA2 8PP, Wales, U.K.

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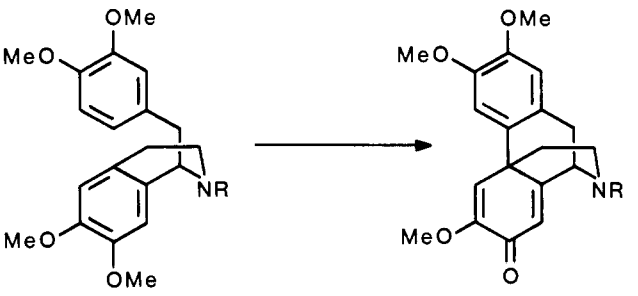
Reproducible electrosyntheses require control of the electrode potentials; potentiostats achieve this directly, but extra apparatus and specialized techniques are then required.[1a] Indirect control of electrode potentials can be carried out with much simpler apparatus, if the resistance of the solution and either the applied voltage or the current is controlled.[1b] We illustrate this general approach by the electrosynthesis of *O*-methylflavinantine (**4**) from laudanosine (**2**), which has previously been carried out at constant electrode potential.[2,3] It is a mechanistically complex process,[2c,e] and the product **4** is oxidized at an electrode potential only 0.1 V above that of the starting material **2**.[2f] Consequently, it provides a severe test of the scope of electrosynthesis by indirect control of electrode potentials.

Scheme I



(1) R = H (2) R = Me (3) R = H (4) R = Me

Results

In our most detailed studies we investigated the conversion of (±)-laudanosine (**2**) to (±)-*O*-methylflavinantine (**4**) in acetonitrile containing aqueous HBF_4 (Scheme I). This electrochemical reaction is reported to produce a yellow oil,[2,3] but we obtained a white crystalline product in over 70% isolated yield after flash chromatography. Analysis (^1H NMR, HPLC) of crude electrolysis mixtures showed higher yields, and a control experiment showed that about 10% loss of material occurred on the chromatographic column.

Experiments carried out at constant electrode potential showed decreasing currents as the reaction proceeded.[4] Currents for subsequent constant-*current* electrolyses were those continuing to flow after passing 1.1 equiv of electricity under optimum conditions for controlled-*potential* electrolysis (electrode potential 1.03–1.1 V, reference 0.1 M Ag^+/Ag). Therefore, in the constant-current experiments, the electrode potential will be less than or at most equal to the potential applied in corresponding controlled-potential experiments. Consequently overoxidation should be minimized. Experiments at constant current (but otherwise under the same reaction conditions and geometrical arrangement of the electrodes) gave virtually the same yields (ca. 80%) as the constant-potential experiments but required 50% longer electrolysis times. However, constant-current experiments were successful (ca. 70% yield) at higher concentrations of substrate (0.1 M) than the constant-potential experiments, which gave good yields below 0.02 M substrate but gave a dark intractable

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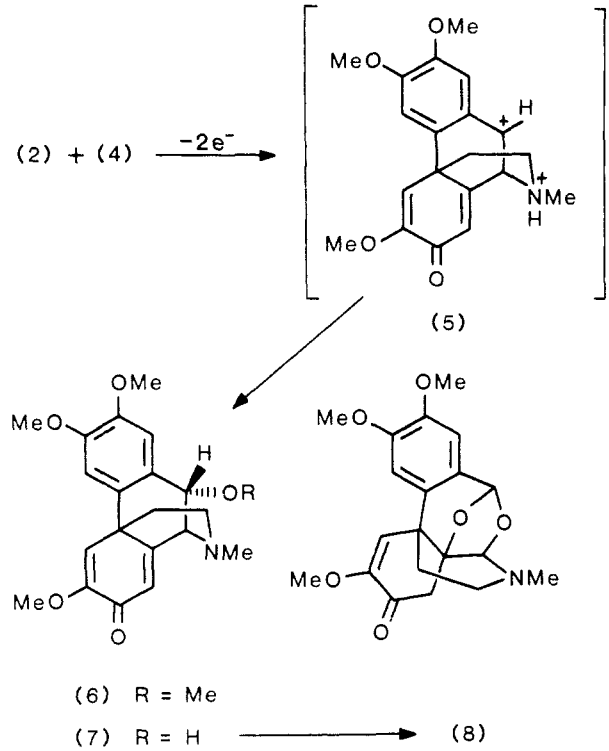
Scheme II



product for 0.1 M substrate. Some intractable materials were formed in all of the electrolyses, presumably by intermolecular reactions of cationic intermediates.

Chromatography following a 6-g scale electrooxidation gave the minor (ca. 2% yield) methoxylated side product **6** (Scheme II), which was fully characterized after it had been obtained in 14% yield by the prior addition of 1% methanol to the electrolysis medium. This product may be formed by reaction between methanol, produced in the demethylation step leading to the cyclohexadienone ring, and the carbocation **5**. Although methanol is more nucleophilic than water,[5] trapping of the cation by some of the unprotonated water would also be expected. This would lead to the 10α-hydroxy compound **7**, which may be present (undetected) in small quantities or it may undergo cleavage to other products.[2f] The stereochemical assignment for **6** and **7** is based on ^{1}H NMR.[2f,4] Direct formation of the cation **5** probably occurs in the deliberate oxidation of *O*-methylflavinantine at higher oxidation potentials to give **7** and a cyclic acetal **8**,[2f] but we obtained minute yields (TLC evidence only) of the side product **6** by direct oxidation of *O*-methylflavinantine (**4**) at the lower oxidation potential used for the oxidation of laudanosine.[6]

According to a novel mechanistic proposal,[2b] the cyclization (**2** → **4**) can occur at low oxidation potentials after removal of an electron from nitrogen. This was unsuccessful both in our hands and others.[7] The influence of solvent was examined. We obtained 80% yields of *O*-methylflavinantine (**4**) by constant-current electrooxidation of laudanosine in acetone. Reaction conditions were the same as for acetonitrile, but more electricity was required (2.75 faradays/mol). Norlaudanosine (**1**) tetrafluoroborate was also oxidized (55% yield) in acetonitrile to *O*-methylnorflavinantine (**3**) from which alkyl and acyl derivatives of **3** can readily be obtained.[4]

Discussion

The success of the electrosynthesis (Scheme I) probably depends on the following factors: (a) the desired products **3** and **4** are less easily oxidized than the starting materials ($\Delta E_{1/2} \sim 0.1$ V[2f]); (b) rapid discharge of H^+ at the cathode acts as a buffer by preventing the accumulation of H^+ ions (formed at the anode) and also reduces the probability that either products or starting materials are reduced at the cathode; (c) the nitrogen atom of the amine is protected from oxidation by protonation (see also ref 8). Aqueous HBF_4 appears to be superior to the heterogeneous reaction with sodium bicarbonate,[2c,d] which probably does not fully protonate the amine because there is a small residual amine oxidation peak in cyclic voltammetry.[4] Alternatively conversion of the amine nitrogen to amide successfully protects the amine from oxidation by Tl(III),[9,10] which converts *N*-acylreticulines to the corresponding dienones.[9] Other workers have carried out direct oxidations of *N*-acyl derivatives; e.g., electrooxidation of *N*-(trifluoroacetyl)-1-benzyltetrahydroisoquinolines (similar to **2**) in acetonitrile/methanol gives the corresponding morphinandienones, whereas the rearranged neospirodienones were formed in acetonitrile alone.[11]

The electrical parameters for electrolysis are related by eq 1,[1c] in which V is the applied voltage, i is the current, and $(E_B - E_A)$ is the difference in electrode potentials (E)

$$V = (E_B - E_A) + iR \quad (1)$$

between the two electrodes A and B. To obtain reproducible results without a potentiostat controlling E_B or E_A, it is necessary to control the resistance of the solution (R) at the beginning of the electrolysis, so that either V or i gives a satisfactory guide to $(E_B - E_A)$. The resistance (R) depends on the size of the electrodes, their distance apart, the surrounding solvent, temperature, and concentrations of substrates and added salts.

The electrosynthesis of morphinandienones is more complex and less easy to reproduce than other electrosyntheses in a beaker. In addition to the above variables, the purity of the solvent appears to be particularly important. Purification removes unwanted nucleophiles, which would interfere with the required electrochemical pathway by intercepting cationic intermediates. A useful and very sensitive guide to the suitability of a batch of acetonitrile for electrosynthesis is its specific conductivity.

Conclusion

Morphinandienones **3** and **4** are now readily available by electrosynthesis. Even for this complex reaction the important experimental variables can be adequately controlled by the current (or the applied voltage) and the geometrical arrangement of the electrodes, along with other routine variables in organic chemistry (purity and con-

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(6) If formation of significant amounts of the cation **5** at the lower electrode potential requires the concurrent electrooxidation of laudanosine, the mechanism may involve an electron transfer in homogeneous solution between *O*-methylflavinantine (**4**) and a reactive intermediate formed by oxidation of laudanosine (**2**). This would also account in part for the importance of concentration of laudanosine in optimising reaction yield.

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centration of materials and temperature). Specialized apparatus and techniques (e.g., potentiostats and use of reference electrodes) are not required.

Experimental Section

Flash column chromatography[12] was performed on silica gel (Merck Art 9385). Laudanosine (now available from Aldrich) and norlaudanosine were prepared by standard methods.[2,4]

Constant-Current Electrolysis of (±)-Laudanosine (2) to *O*-Methylflavinantine (4). To a 250-cm^3 beaker containing acetonitrile (149 cm^3), purified as described below, and 50% aqueous HBF_4 (5.7 M, 0.75 cm^3) was added (±)-laudanosine (1.07 g, 3.0 mmol). Two square platinum foil electrodes (7.3 cm^2/face) were then placed 3.0 cm apart, and a direct current of 50 mA (V = 3.5 V) was passed through the magnetically stirred solution, initially at room temperature and without enforced cooling, for 3.5 h (2.2 faradays/mol). The acetonitrile was removed under reduced pressure, a 5% aqueous solution of sodium bicarbonate was then added (to pH 8–9), and the solution was extracted with methylene chloride (3 × 30 cm^3). After isolation, the remaining brown gum was purified by flash column chromatography with elution by 7% v/v methanol/dichloromethane, and the product 4 was crystallized from acetone: yield 0.77 g (75%); mp 159–160 °C (lit.[13] mp 158–160 °C); starting material (ca. 10%) recovered by further elution.

This synthesis was repeated in 65% yield (HPLC) using 10 cm^3 of solution in a test tube with 1 cm^2 electrodes 1 cm apart. A current of 7 mA was passed for 1.8 h, so that the current/unit area of electrode was the same as for the larger scale experiments. A good commercial grade of acetonitrile was used without further purification—see below.

Larger Scale Oxidation. Isolation of 10α-Methoxy-*O*-methylflavinantine (6). The reaction was performed in 1-L beaker containing acetonitrile (800 cm^3), laudanosine (5.71 g, 0.016 mol), and 50% aqueous HBF_4 (4 mL). The electrodes were concentric pieces of platinized titanium (Marstons Excelsior Ltd., Wolverhampton), 15 cm × 5 cm. The anode was made into a cylinder of fine mesh, held in its circular shape by fine platinum wire, and almost completely surrounded by the sheet cathode at a distance of about 0.5 cm. Constant-current (150 mA) or controlled-potential (1.03 V, reference 0.1 M Ag^+/Ag, initial current 400 mA) electrolyses of the stirred solution gave high yields of crystalline dienone [4: 4.2–4.4 g (77–82%], a small amount of recovered laudanosine [0.1–0.4 g (2–7%)], and a faster eluting dienone containing four OCH_3 signals in the ^1H NMR; yield 0.10 g (2%). Smaller scale electrolyses of 0.02 M 2 in acetonitrile containing added methanol gave higher yields of the new dienone 6. Yields: 14% (with 1% $MeOH/CH_3CN$), 16% (with 5% $MeOH/CH_3CN$), and 11% (with 10% $MeOH/CH_3CN$). The product was isolated by flash column chromatography (elution by 2% methanol/dichloromethane) and was recrystallized twice from benzene and then from acetone: mp 178.5–180.0 °C; IR, ν_{max} 1625, 1647, 1675 cm^{-1}; NMR, δ 3.90 (2), 3.80, 3.46 (4 × 3 H, s, CH_3O), 4.59 and 3.75 (1 H, sharpened by decoupling, J = 1 Hz); other decoupling experiments consistent with previous assignments for amurine;[14] mass spectrum, m/e 371 (M^+, base beak), 356, 340, 313. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 68.0; H, 6.6; N, 3.7.

Purification of Solvents for Electrosynthesis. Acetonitrile (Aldrich) was purified in 5-kg batches by heating under reflux with phosphorus pentoxide (30 g) for 1 h. It was then fractionally distilled through a triple-pass fractionating column (Widmer, 3 × 24 cm), collecting only the middle 70% fraction for immediate use and recycling the remainder. After the acetonitrile had been recycled up to three or four times, the background current during electrosyntheses became too high (water hydrolyzes some of the nitrile, but most of this water could have been removed in a preliminary step with calcium hydride or silica gel[15]). The specific conductivity at 25.0 °C of the middle 70% of distillate was 3.4 × 10^{-7} Ω^{-1} cm^{-1} (good commercial grades, e.g., Fisons HPLC, are within this specification *before* purification), and corresponding values of other fractions were as follows: original supply (9.6), first 15% of distillate (23.6), four times recycled (13.4); lit.[15] 0.7–1.5 × 10^{-7} Ω^{-1} cm^{-1} (extensive purification). Acetone (A.R., 5 L) was passed through a column of anhydrous potassium carbonate and was then fractionally distilled as described above (specific conductivity of middle 70%, 0.72 × 10^{-7} Ω^{-1} cm^{-1}; original supply, 1.89).

Equipment. Electrosyntheses in a beaker do not necessarily require glass/metal seals,[1c] but White[16] described how a simple platinum/glass seal could be made. We used similar platinum/glass seals but avoided the use of mercury for electrical contact between the electrode and the connections to the voltage source,[16] by spot-welding copper/nickel braid directly to the platinum wire that supported the platinum sheet electrode. The electrodes were cleaned regularly by immersing them in concentrated nitric acid.

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Registry No. (±)-2, 1699-51-0; (±)-4, 22169-18-2; (±)-6, 104910-83-0.

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Factors Influencing the Competitive Rates of Free Radical Addition of Ethyl 2-Bromo Carboxylates to Selected Alkene Pairs[1]

Vahid Ghodoussi, Gerald Jay Gleicher,* and Mark Kravetz

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

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Ever since Kharasch and his co-workers first observed the anti-Markovnikov addition of hydrogen bromide to alkenes,[2] explanations as to why free radicals prefer to add to the less substituted end of a carbon–carbon double bond have been of two general types. The first, which will be referred to as the "electronic effect", is formulated in terms of a favored generation of more highly substituted carbon radicals. The vast majority of textbooks of elementary organic chemistry still promote this rationale.[3] The second general explanation will be termed a "steric effect". Tedder and Walton have most strongly drawn attention to the fact that all radicals, irrespective of their electrophilic or nucleophilic character, will prefer to attack the more accessible or less hindered end of the double bond.[4] Giese has generated much support for this view,[5] and a recent paper

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