Electrooxidative Cyclization of 1-Benzyltetrahydroisoquinolines. A Novel Nonphenol Coupling Reaction[1]

L. L. Miller,*[2] F. R. Stermitz, and J. R. Falck[3]

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521. *Received September 26, 1972*

Abstract: (±)-Laudanosine was oxidized at platinum in a three-compartment cell at 1.1 V in acetonitrile at 0° in the presence of Na_2CO_3. Either lithium perchlorate or tetramethylammonium tetrafluoroborate was the background electrolyte. *O*-Methylflavinantine was isolated from the anolyte in 52% yield. Similar oxidation of (±)-*O*-benzylcodamine, (±)-*O*-benzylpseudocodamine, (±)-*O*-benzyllaudanine, and (±)-*O*-benzylpseudolaudanine yielded *O*-methylflavinantine, *O*-benzylflavinantine, *O*-benzylisoflavinantine, and 2,3-dimethoxy-6-benzyloxymorphinandienone, respectively. Oxidation of (±)-laudanosine in the presence of equal molar bis(acetonitrile)palladium(II) chloride enhanced the *O*-methylflavinantine yield to 63%.

Phenolic oxidative coupling reactions[4] have long held a prominent position in the synthesis of complex alkaloids from relatively simple precursors and in biogenetic theories. In the main, synthetic oxidations have been accomplished with inorganic oxidants although some enzymatic oxidations have followed from the report[5] of work with a crude enzyme extract. Yields have generally been quite low from these syntheses and they are usually acceptable methods only when small amounts of alkaloids are needed to confirm structures or when one is interested in biosynthetic pathways. For example, a number of morphinandienones[6a] have been synthesized using phenolic oxidations although other methods,[6b] such as the Pschorr reaction or photochemical coupling reactions, are more often employed. The natural rarity of morphinandienones and difficult synthetic methods have not made them generally available although some pharmacological activity[7] has been indicated.

We wish to report here a novel electrochemical oxidation synthesis of morphinandienones in high yield starting from easily available and *nonphenolic* tetrahydrobenzylisoquinoline precursors. This should now be considered the method of choice for the synthesis of these complex alkaloids.

Results

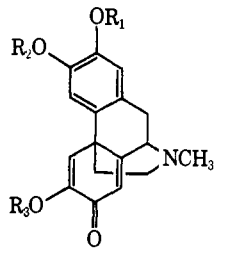
Electrooxidation of Laudanosine (10a). Cyclic voltammetric studies were conducted in a two-compartment cell in which the $Ag|AgNO_3$ reference electrode solution was separated by a glass frit from the platinum anode and cathode solution. Using either tetramethylammonium tetrafluoroborate or lithium perchlorate as electrolyte, (±)-laudanosine (**10a**) revealed waves at 0.63, 0.81, 1.13, 1.30, and 1.47 V. Though the presence of Na_2CO_3 is necessary for high yields of morphinandienone, its presence in the voltammetric cell did not change the voltammogram.

On a preparative scale, (±)-laudanosine (200 mg) was oxidized at a platinum electrode in acetonitrile under several conditions. In all cases, a three-compartment cell separating the cathode, anode, and $Ag|AgNO_3$ reference electrode solutions was utilized. Product **11a** was formed in several reactions, the most successful being carried out at 1.1 V in the presence of sodium carbonate at 0° with either lithium perchlorate or tetramethylammonium tetrafluoroborate as the electrolyte.[8] The current dropped smoothly from 110 to 8 mA in 70 min passing a total of 2.0 mF. Evaporation of the acetonitrile, followed by addition of chloroform and water and separation of the chloroform soluble products by preparative tlc on silica gel gave in 52% yield[9] a component whose uv, nmr, and ir spectra were identical with those of *O*-methylflavinantine (**11a**).[10] This product was also isolated[11] from an oxidation carried out at 0.63 V, but the current was low. If the oxidation was performed at 1.30 V, other alkaloidal products were formed in addition to **11a**.

We were prompted, by Chapman's use[12] of palladium(II) chloride in the intramolecular phenolic oxidative coupling of carpanone and the ability of this reagent to complex with tertiary amines, to examine its influence on this reaction. When the above oxidation was performed on an equimolar mixture of laudanosine (**10a**) and bis(acetonitrile) palladium(II) chloride,[13] the yield of **11a** was enhanced to 63%.

The voltammograms for the 1-benzyltetrahydroisoquinolines and the morphinandienones are very similar and indicate that the morphinandienones might not survive exhaustive electrolysis in high yield. Overoxidation is, in fact, often a problem in coupling reac-

(1) Presented in part at the First Rocky Mountain Regional American Chemical Society Meeting, Colorado State University, Fort Collins, Colo. Preliminary communication: L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Amer. Chem. Soc.*, **93**, 5941 (1971).
(2) Alfred P. Sloan Fellow.
(3) National Science Foundation Trainee.
(4) W. I. Taylor and A. R. Battersby, Ed., "Oxidative Coupling of Phenols," Marcel Dekker, New York, N. Y., 1967.
(5) S. M. Bocks, B. R. Brown, and A. H. Todd, *Proc. Chem. Soc., London*, 117 (1962).
(6) (a) K. L. Stuart, *Chem. Rev.*, 71, 47 (1971), and references cited therein; (b) T. Kametani and K. Fukumoto, *J. Heterocycl. Chem.*, **8**, 341 (1971).
(7) R. A. Raffauf, unpublished results quoted in ref 6a.
(8) Tetramethylammonium tetrafluoroborate interfered with the alkaloid visualization technique and its use was discontinued in favor of lithium perchlorate. No detectable change in yield resulted.
(9) In all the oxidations reported here, a second unidentified alkaloidal fraction accounted for the majority of the remaining product balance.
(10) We thank Professor T. Kametani for copies of the ir, nmr, and uv spectra of *O*-methylflavinantine.
(11) L. L. Miller and V. Ramachandran, unpublished results.
(12) O. L. Chapman, M. R. Engel, J. P. Springer, and J. C. Clardy, *J. Amer. Chem. Soc.*, **93**, 6696 (1971).
(13) A sample of bis(acetonitrile)palladium(II) chloride was kindly provided by Professor L. S. Hegedus.



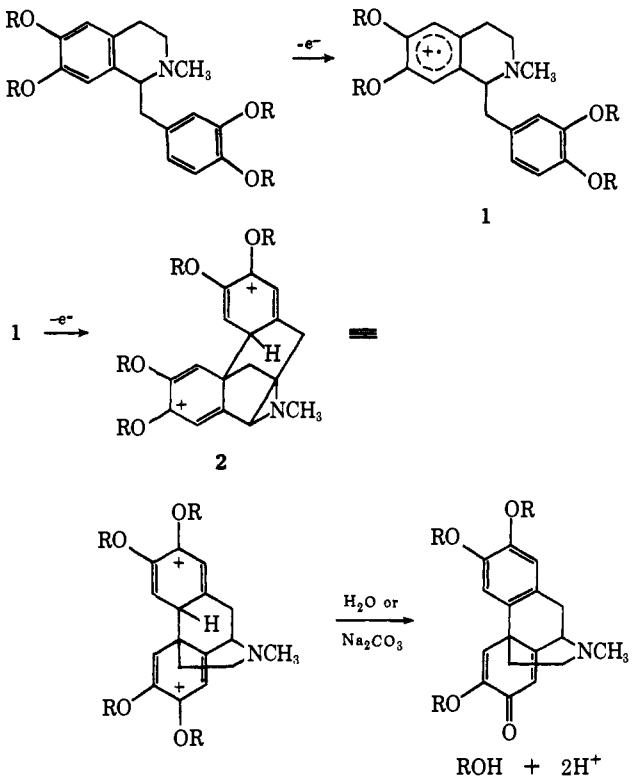
	R_1	R_2	R_3
11a,	CH_3	CH_3	CH_3
b,	CH_3	CH_2Ph	CH_3
c,	CH_3	CH_3	CH_2Ph
d,	CH_2Ph	CH_3	CH_3

Figure 1. Morphinandienone alkaloids.

tions and may in part be circumvented in this case because of the insolubility of the morphinandienones in acetonitrile.

Scheme I shows a mechanistic rationale for the formation of the morphinandienone product. First, oxidation of the 1-benzyltetrahydroisoquinoline to a cation radical **1**, followed by cyclization and loss of another electron forms **2**. Loss of a proton and rearomatization of the initial benzyl moiety and alkyl cleavage from the initial isoquinoline aromatic ring forms the final morphinandienone product. The oxidative cleavage of alkyl groups from suitable alkyl phenyl ethers has analogy,[14] but the timing of electron loss, cyclization, and cleavage as well as the cleavage mechanism remain unelucidated.[15]

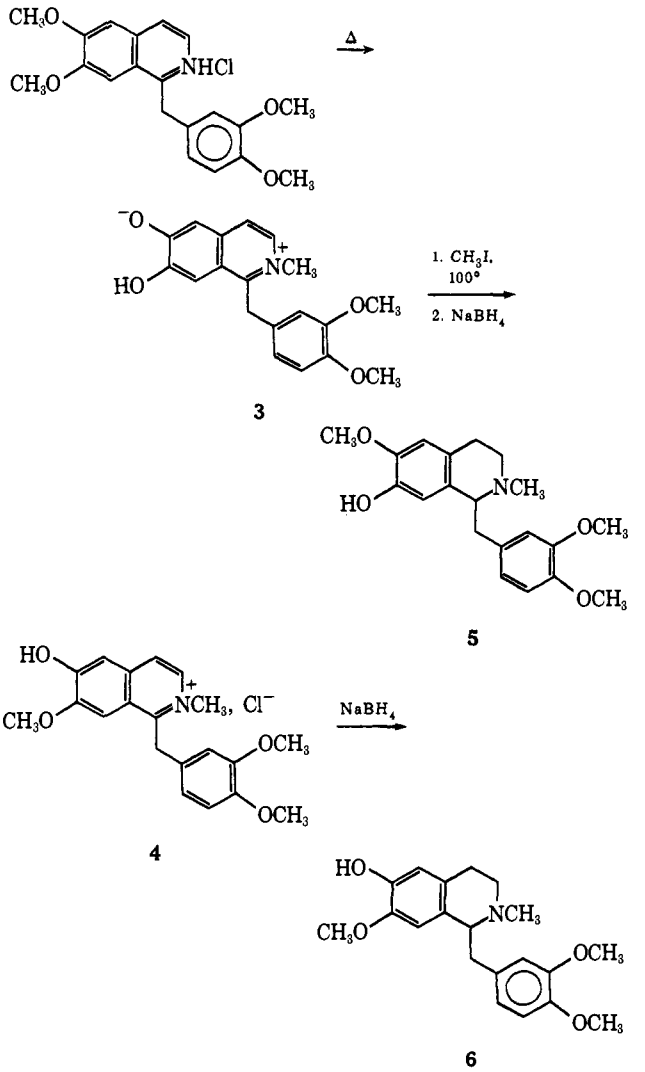
Scheme I



Electrooxidation of Laudanosine Benzyl Ethers. In order to study the generality of this reaction, several laudanosine benzyl ethers were prepared and oxidized. If the cyclization proceeded in an analogous manner to that described above, oxidation of *O*-benzylpseudocodamine (**10b**), *O*-benzylcodamine (**10c**), *O*-benzylpseudolaudanine (**10d**), and *O*-benzyllaudanine (**10e**) would provide *O*-benzylflavinantine (**11b**), *O*-methylflavinantine (**11a**), 2,3-dimethoxy-6-benzyloxymorphinandienone (**11c**), and *O*-benzylisoflavinantine (**11d**), respectively. Removal of the benzyl group in *O*-benzylflavinantine (**11b**) and *O*-benzylisoflavinantine (**11d**) would then provide entry to the naturally occurring phenolic analogs. Similar treatment of 2,3-dimethoxy-6-benzyloxymorphinandienone (**11c**) would provide an α-diketone. This structural entity has been proposed by Kametani[16] as a model system in the study of sinomenine-type alkaloids. A forum for the influence of the substituent to be cleaved at the C-7 position would be provided by comparison of oxidation data of *O*-benzylcodamine (**10c**) and laudanosine (**10a**).

An attractive synthesis of the required starting materials **5** and **6** is shown in Scheme II. When papaverine hydrochloride is heated at its melting point for several minutes, a separable mixture of the phenol betaine protopapaverine (**3**) and the salt norpapaverinium betaine hydrochloride (**4**) is formed.[17,18] Proto-

Scheme II



(14) L. Papachoudo, J. Bacon, and R. N. Adams, *J. Electroanal. Chem.*, **24**, Appendix 1 (1970); V. D. Parker and L. Eberson, *Tetrahedron Lett.*, 1449 (1972); N. I. Bruckner and N. L. Bauld, *J. Org. Chem.*, **36**, 4045 (1971); D. H. Hey, G. H. Jones, and M. J. Perkins, *J. Chem. Soc. D*, 998 (1971).

(15) Work on these and other mechanistic questions is now in progress.

(16) T. Kametani, T. Sugahara, H. Yagi, K. Fukumoto, B. R. Pai, and R. Charubala, *J. Chem. Soc. C*, 624 (1970).

(17) F. R. Stermitz and J. N. Seiber, *Tetrahedron Lett.*, 1177 (1966), and references cited therein.

Table I. Comparison of Electrochemical and Literature Morphinandienone Syntheses *via* Pschorr Reaction

Substrate	Product	Electrolysis yield, %	Lit. yield, %
Laudanosine (**10a**)	*O*-Methylflavinantine (**11a**)	52	1.4–2.0[a]
Laudanosine–PdCl (**10a**)	*O*-Methylflavinantine (**11a**)	63	1.4–2.0[a]
O-Benzylpseudocodamine (**10b**)	*O*-Benzylflavinantine (**11b**)	53	8.4[b]
O-Benzyllaudanine (**10e**)	*O*-Benzylisoflavinantine (**11d**)	43	10.0[c]
O-Benzylcodamine (**10c**)	*O*-Methylflavinantine (**11a**)	53	1.4–2.0[a]
O-Benzylpseudolaudanine (**10d**)	2,3-Dimethoxy-6-benzyloxy-morphinandienone (**11c**)	44	8.0[d]

[a] T. Kametani, K. Fukumoto, F. Sato, and H. Yagi, *J. Chem. Soc. C*, 520 (1969). [b] T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *ibid.*, 1063 (1969). [c] T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. Pharm. Bull.*, **17**, 2245 (1969). [d] T. Kametani, T. Sugahara, H. Yagi, K. Fukumoto, B. R. Pai, and R. Charubala, *J. Chem. Soc.C*, 624 (1970).

papaverine may be transformed into its methiodide derivative by heating in a sealed tube with methyl iodide. Reduction of protopapaverine methiodide and norpapaverinium betaine hydrochloride (**4**) with sodium borohydride gives the tetrahydro derivatives (±)-codamine (**5**) and (±)-pseudolaudanine (**6**), respectively. Benzylation of (±)-pseudolaudanine (**6**) *via* the phenolate ion gave (±)-*O*-benzylpseudolaudanine (**10d**) in good yield. However, a similar reaction on (±)-codamine gave only a poor yield of (±)-*O*-benzylcodamine (**10c**). This isomer was, therefore, prepared by the method described below.

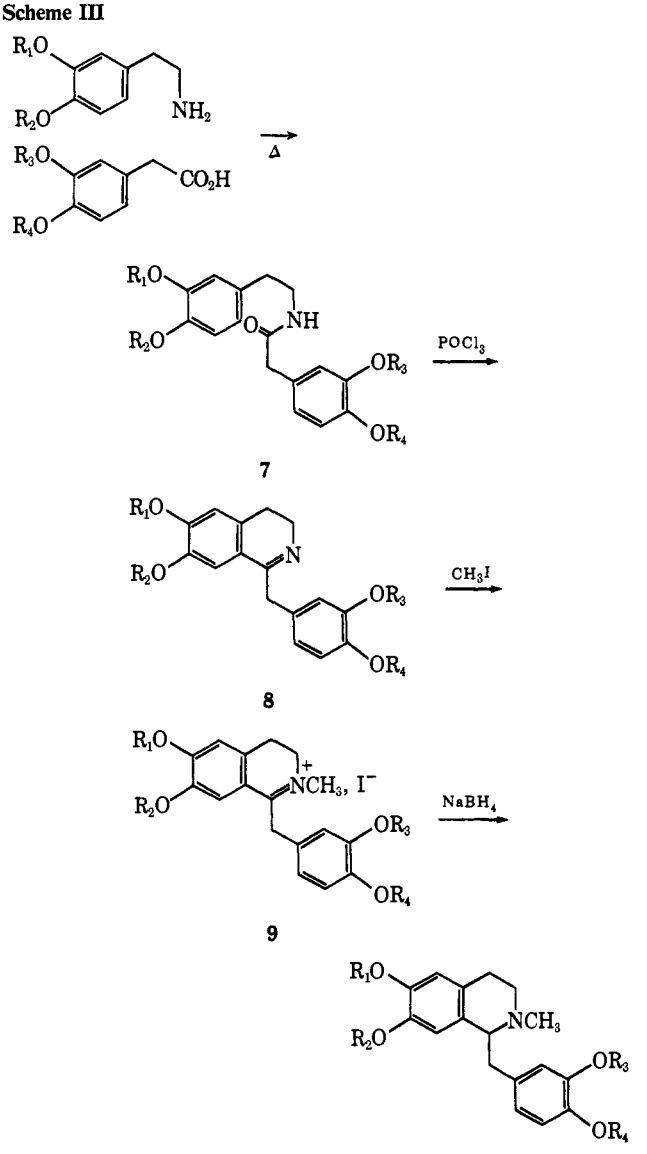
The benzyl isomers **10b**, **10c**, and **10e** were synthesized by the methods outlined in Scheme III. Condensation of the appropriately substituted phenethylamine and phenylacetic acid gave the amide **7** in high yield. Bischler–Napieralski cyclization of the amide **7** with phosphorus oxychloride in refluxing acetonitrile afforded the 3,4-dihydroisoquinoline **8**. When treated with methyl iodide, **8** formed the methiodide salt **9** in excellent yields. Subsequent reduction of the methiodide salt **9** with sodium borohydride gave the appropriate 1-benzyltetrahydroisoquinoline **10**.

Cyclic voltammetry studies on the laudanosine benzyl ethers were performed analogously to the method above. The voltammograms were similar to laudanosine, except for the absence of the 1.30 V peak.

The results from the electrooxidations are tabulated in Table I along with yields for the final coupling reaction *via* the Pschorr reaction. These data represent in some cases at least an order of magnitude or greater increase in yield over previously reported methods. In addition, extended syntheses and tedious separation from other alkaloidal products are not required.

Since the same yield of **11a** was obtained from *O*-benzylcodamine (**10c**) and laudanosine (**10a**) it seems that the identity of the C-7 substituent has little influence on the course of the cyclization. Closer examination of this question is in progress.[19]

Scheme III



	R_1	R_2	R_3	R_4
a	CH_3	CH_3	CH_3	CH_3
b	CH_3	CH_3	CH_3	CH_2Ph
c	CH_3	CH_2Ph	CH_3	CH_3
d	CH_2Ph	CH_3	CH_3	CH_3
e	CH_3	CH_3	CH_2Ph	CH_3
f	CH_3	CH_3	OH	CH_3

Discussion

It should be emphasized that this electrooxidative coupling reaction is especially novel and useful in that the substrates are not phenolic. Controlled potential oxidation employing the powerful, but selective oxidant, the anode, has eliminated the necessity for utilizing easily oxidized phenolates. In addition, the use of phenol ethers may provide a specificity for carbon–carbon coupling which is not found in phenol oxidations. The wide and variable oxidation power of the anode is an important attribute *vis-à-vis* the usual chemical oxidant. By controlling the potential one can perform selective oxidations and, indeed, can selectively oxidize certain functionalities. In particular,

(18) B. K. Cassels and V. Deulofeu, *Tetrahedron, Suppl. 8*, II, 485 (1966).

(19) L. L. Miller and G. Yost, unpublished results.

electrochemistry allows us to oxidize nonphenolic materials (ferricyanide will oxidize phenolate ions but will not affect aryl ethers).

Bobbitt and coworkers have investigated the electrooxidation of phenolic benzyltetrahydroisoquinolines and have observed intermolecular coupling and cleavage reactions.[20,21] Although the causes for the differences in some of these reactions are not entirely explicable, control over the oxidation pathway by the most easily oxidized moiety in the molecule is a first consideration. In the molecules of interest, there are three groups, two aromatic rings and the amine, to be considered. If there is a phenoxide present, this will usually provide the most easily oxidized center and the chemistry will involve that group. This is clearly indicated in Bobbitt's results where coupling to phenolic rings occur.[20]

Some phenolic morphinandienones have been produced in biogenetic type syntheses by inorganic oxidants. In comparison, however, this method suffers from very disappointing yields and often leads to complex product mixtures. A common side reaction is the unproductive formation of C–O–C coupled products not observed in this electrooxidative cyclization. In at least one case, poor yields were attributed to the fact that the morphinandienone product itself seemed to be more rapidly oxidized than the substrate.[22] As of yet, radical producing enzymes such as peroxidase and tyrosinase have been unsuccessful.

The adaptability to both phenolic and nonphenolic substrates as well as control over the coupling mode has given wide popularity[6] to the Pschorr-type synthesis involving decomposition of diazonium salts. Again, however, this method (see Table I) suffers from poor yields (rarely is 10% achieved and 1–4% is typical) as well as producing complex product mixtures. In addition, other deficiencies in the method are apparent. Firstly, the need for several additional synthetic steps to prepare the appropriate aminoisoquinoline lowers overall yield. Secondly, during the reduction of the nitroisoquinoline to the aminoisoquinoline, side reactions such as debenzylation occur, necessitating separation from by-products. Thirdly, during diazotization, the acidic environment could attack acid sensitive functionality.

Other synthetic methods[6] for morphinandienones generally are a modification upon an existing morphine skeleton. Such methods are obviously limited by the supply and suitability of available material. In comparison with the above-discussed methods, our electrochemical synthesis of morphinandienones appears straightforward and contains few limitations. We are presently extending it to other substituted cases. The general utility of the system is seen in a recent application[23] to a related polycycle.

Experimental Section

All melting point determinations are uncorrected, open capillary measurements using a Thomas-Hoover capillary melting point apparatus. Infrared spectra were recorded on either a Perkin-Elmer Model 457 or 337 grating spectrometer utilizing a polystyrene film reference; mass spectra were recorded on an AEI MS-12. Ultraviolet spectra were recorded in ethanol solution on a Perkin-Elmer Model 402. Either a Varian Associates A-60A or T-60 recorded nuclear magnetic resonance (nmr) spectra. Chemical shifts were measured relative to tetramethylsilane in deuteriochloroform solution, unless otherwise noted.

Analytical thin layer chromatography (tlc) was performed with tlc plates 250 μ thick (silica gel F_{254} precoated, abrasive resistant plates) distributed by Brinkman Instruments Inc. Development of the plates was with 3:2 benzene–methanol. For preparative tlc work, tlc plates of 2000-μ thickness from the same distributor were used. Visualization of the alkaloids was performed by spraying the entire analytical plate, or the edges of the preparative plate, with an aqueous solution of iodoplatinic acid reagent.

The normal technique used for isolating compounds from the preparative tlc plates was to scrape off the area corresponding to the alkaloid, then, after grinding the material, to extract the silica gel for 24 hr with chloroform in a Soxhlet extractor.

General Electrolysis Procedure. Preparative oxidations were conducted in a three-compartment cell (which separated the anode, cathode, and reference electrode solutions by glass frits) in conjunction with a Wenking Model 70 HV1/90 potentiostat and Exact Model 126 Signal generator. The anode was a stationary platinum sheet (total area 6.25 cm^2). The anode compartment has an approximate 150-ml volume in which solutions were agitated by means of a magnetic stir bar. A stainless steel sheet served as the cathode. A 0.1 *N* $AgNO_3$ solution in acetonitrile in contact with a Ag wire served as the reference; all potentials are given *vs.* this reference. The entire cell was maintained at ice bath temperature and under a nitrogen atmosphere.

All cyclic voltammetric studies and preparative electrolyses were conducted in Kodak <0.1% water grade acetonitrile, which had been distilled twice from P_2O_5 with nitrogen bleed and stored over molecular sieves under inert atmosphere until used.

Either G. F. Smith anhydrous lithium perchlorate or Aldrich Chemical Co. tetramethylammonium tetrafluoroborate was used as background electrolyte. Sufficient electrolyte was added to the anode and cathode compartments to have an approximately 0.1 *M* solution in electrolyte. For preparative oxidations, solid anhydrous Baker AR sodium carbonate was added to the anode compartment prior to electrolysis. In the absence of sodium carbonate, the anolyte became acidic during the oxidation with a drastic decrease in morphinandienone yield. Electrolyte and carbonate were used as received.

A general description of the preparative oxidation is as follows. Approximately 7×10^{-4} mol of substrate was added to the cell filled with purified acetonitrile and a large excess of sodium carbonate. The potential was maintained at 1.10–1.05 V, with initial currents generally 100–80 mA. The background in these potential ranges was less than 1 mA. Electrolysis was usually discontinued when the current dropped to 8–10 mA, which generally took 1–1.5 hr. The anolyte was then removed, stripped under vacuum to near dryness, then taken up in water, and extracted with chloroform. The combined organic layers were dried with anhydrous sodium carbonate, filtered, concentrated under vacuum, and then placed on a preparative tlc plate. The plate was developed first with ethyl acetate, dried, and then developed with 3:2 benzene–MeOH. Visualization of the alkaloidal component with iodoplatinic acid reagent and Soxhlet extraction yielded the final product.

Materials. (±)-Laudanosine (10a). Laudanosine was purchased from P&B Chemical Co. Unless the commercial sample was recrystallized from alcohol, low currents due to considerable electrode fouling hampered the oxidation.

Some laudanosine was prepared by $NaBH_4$ reduction of papaverine methiodide; the methiodide was prepared by reaction of papaverine-free base (available from Mallinckrodt Chemical Co. as the hydrochloride) with methyl iodide. After crystallization from alcohol, mp 115° (lit.[24] 115°) was obtained.

***N*-(3,4-Dimethoxyphenethyl)-2-(3-methoxy-4-benzyloxyphenyl)-acetamide (7b).** An equal molar mixture of 6.43 g of 4-benzyloxy-3-methoxyphenylacetic acid and 3.55 g of 3,4-dimethoxyphenethylamine was heated (170–175°) in an oil bath for 4 hr under a nitrogen atmosphere. The reaction product was cooled and dissolved in ethyl acetate, and the solution was washed with 1 *N* HCl and then with 5% $NaHCO_3$. The organic layer was dried and evaporated to give 7.70 g of **7b**. A specimen was crystallized from a mixture

(20) J. M. Bobbitt and R. C. Hallcher, *Chem. Commun.*, 543 (1971).
(21) J. M. Bobbitt, K. H. Weisgraber, A. S. Steinfeld, and S. G. Weiss, *J. Org. Chem.*, 35, 2884 (1970).
(22) D. H. R. Barton, D. S. Bhakuni, R. James, and G. W. Kirby, *J. Chem. Soc. C*, 128 (1967).
(23) M. Sainsbury and R. F. Schniazi, *J. Chem. Soc., Chem. Commun.*, 718 (1972).
(24) R. Willstratten and W. Muller, *Ann.*, 1221 (1905).

of 1:1 EtOAc–EtOH to give white microneedles, mp 114–116° (lit.[25] 113–115°).

1-(3-Methoxy-4-benzyloxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (8b). To a stirred and refluxing solution of 6.16 g of **7b** in 100 ml of dry acetonitrile was added 12.6 g of $POCl_3$ over 15 min. The reaction mixture was refluxed under nitrogen for 1 hr and cooled, and the solvent evaporated. The residue was dissolved in EtOAc and the solution washed with saturated $NaHCO_3$, dried, and evaporated yielding 5.5 g of **8b** as a yellow syrup. This product was used in the next step without further purification due to suspected instability.

1-(3-Methoxy-4-benzyloxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline Methiodide (9b). The above 3,4-dihydroisoquinoline **8b** was taken up in 3.5 ml of methanol to which 10 ml of MeI was added. After refluxing for 2 hr, the reaction mixture was evaporated. No attempt was made to purify this product. The yield of **9b** was quantitative as shown by tlc analysis.

(±)-*O*-Benzylpseudocodamine (10b). The crude methiodide **9b** was dissolved in 250 ml of MeOH and 1.1 g of $NaBH_4$ was added cautiously giving a very exothermic reaction. Removal of the solvent, after stirring for 2 hr at room temperature, gave a residue which was admixed with water and extracted with chloroform. The combined organic extracts were dried and evaporated to yield 4.98 g of **10b** as a pale yellow syrup. The product was taken up in a minimum amount of ethanol and kept at 0° for 24 hr. Filtration gave a white feathery product, mp 70–72° (lit.[26] 70–72°).

***N*-(3-Methoxy-4-benzyloxyphenethyl)-2-(3,4-dimethoxyphenyl)-acetamide (7c).** A mixture of 12.6 g of 3-methoxy-4-benzyloxyphenethylamine and 9.7 g of 3,4-dimethoxyphenylacetic acid was reacted according to the procedure given for the preparation of **7b**, to afford 19.6 g of **7c**. A specimen recrystallized from a mixture of EtOAc–EtOH afforded colorless needles, mp 127° (lit.[27] 125°).

1-(3,4-Dimethoxybenzyl)-3,4-dihydro-6-methoxy-7-benzyloxyisoquinoline (8c). Reaction of 19.6 g of **7c** with 25 g of $POCl_3$ in 400 ml of dry CH_3CN according to the procedure given for the preparation of **8b** gave 16.1 g of yellow oil which was used in the next step without further purification.

1-(3,4-Dimethoxybenzyl)-3,4-dihydro-6-methoxy-7-benzyloxyisoquinoline Methiodide (9c). The above 3,4-dihydroisoquinoline **8c** was treated with 25 ml of MeI according to the procedure given for the preparation of **9b**. The yield was quantitative as shown by tlc analysis.

(±)-*O*-Benzylcodamine (10c). The crude methiodide **9c** was reduced with 3.0 g of $NaBH_4$ according to the procedure given for the preparation of **10b** to afford 12.5 g of **10c** as a colorless oil. **10c** was previously reported[28] without spectral data. Structure confirmation was by hydrolysis to (±)-codamine as given below.

Hydrolysis of (±)-*O*-Benzylcodamine (10c). A specimen of *O*-benzylcodamine (**10c**) was hydrolyzed to the phenolic analog by the method of Marsh and Goodman.[29] A solution of 0.2 g of **10c** in 25 ml of CF_3CO_2H was allowed to stand at room temperature for 3.5 hr, then was evaporated. The residue was freed from traces of CF_3CO_2H by three treatments with 25 ml of benzene, each solution being evaporated to dryness. The residue was partitioned between 20-ml portions of 1 *N* aqueous NaOH and EtOAc. The combined alkaline extracts were adjusted to pH 8 with 3 *N* HCl and extracted with $CHCl_3$. The combined organic layers were dried and evaporated to give 0.13 g (87%) of **5** as a colorless oil whose nmr and tlc characteristics were identical to literature values.[30]

***N*-(3,4-Dimethoxyphenethyl)-2-(3-benzyloxy-4-methoxyphenyl)-acetamide (7e).** A mixture of 7.44 g of 3-benzyloxy-4-methoxyphenylacetic acid and 4.98 g of 3,4-dimethoxyphenethylamine was reacted according to the procedure given for the preparation of **7b** to give 8.9 g of **7e**. An analytical sample was crystallized from alcohol, mp 111.5–112.5° (lit.[31] 111.5–112.5°).

1-(3-Benzyloxy-4-methoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (8e). Reaction of 13.8 g of **7e** with 22 ml of $POCl_3$ in 700 ml of CH_3CN according to the procedure given for the preparation of **8b** gave **8e** in 90% yield as a golden oil which was used in the next step without further purification.

1-(3-Benzyloxy-4-methoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline Methiodide (9e). The above 3,4-dihydroisoquinoline **8e** was treated with 30 ml of MeI according to the procedure given for the preparation of **9b**. No attempt was made to purify this product. The yield of **9e** was quantitative as shown by tlc analysis.

(±)-*O*-Benzyllaudanine (10e). The methiodide salt **9e** (12.6 g) was reduced with 4 g of $NaBH_4$ in 300 ml of MeOH according to the procedure given for the preparation of **10b**. An analytical sample crystallized from ethanol as white spindles: mp 90.5–91.5°; nmr[32,33] δ 2.51 (3 H, s, NCH_3), 2.56–3.34 (7 H, m), 3.63 (3 H, s, OCH_3), 3.87 (6 H, s, OCH_3), 5.09 (2 H, s, CH_2Ph), 6.08 (1 H, s), 6.58 (1 H, s), 6.67–6.80 (3 H, m), 7.38 (5 H, s, ArH of benzyl moiety). Structure confirmation was by hydrolysis to (±)-laudanine as given below.

(±)-Laudanine (10f). Treatment of 0.3 g of **10e** with 30 ml of CF_3CO_2H by the procedure given for the hydrolysis of **10c** gave **10f** as white prismatic crystals, mp 164–165° (lit.[34] 164–165°).

Papaverine Hydrochloride Fusion Reaction. Papaverine hydrochloride (30.0 g) was fused with constant stirring in an oil bath preheated to 235° under a nitrogen atmosphere. When the fusion was complete, the temperature was reduced to 215–220° until bubbling ceased (about 15 min). The flask was heated for an additional 10 min and cooled, and the melt taken up in 300 ml of ethanol. The ethanol solution was chilled (0°) overnight. Filtration gave 7.25 g (28%) of yellow solid protopapaverine (**3**), mp 259–265° (lit.[18] 287–288°).

Evaporation of the ethanolic mother liquor gave a dark brown gum which was taken up in a minimum amount of $CHCl_3$. After cooling overnight at 0°, filtration gave 4.25 g (14%) of norpapaverinium betaine hydrochloride as a cream-colored powder, **4**, mp 219–223° (lit.[18] 229–230°).

Protopapaverine Methiodide. Protopapaverine (**3**) (6 g) was heated at 100° with 20 ml of MeI in a sealed tube for 5 hr. The tube was then cooled and broken, and the unreacted MeI evaporated. The residue was dissolved in hot water, the solution filtered, and the filtrate evaporated to dryness repeatedly with several portions of absolute ethanol to give a yellow foam whose spectral characteristics were identical to a known sample.[17,18]

(±)-Codamine (5). The above protopapaverine methiodide was reduced with 6.0 g of $NaBH_4$ in MeOH by the procedure given for the preparation of **10b** to yield a dark yellow oil. This oil was partitioned between 50-ml portions of 1 *N* aqueous NaOH and EtOAc. The combined alkaline extracts were adjusted to pH 8 with 3 *N* HCl and extracted with $CHCl_3$. The combined organic layers were dried and evaporated to give **5** as a colorless oil whose nmr and tlc properties were identical with the specimen obtained from hydrolysis of *O*-benzylcodamine (**10c**) which was prepared by another route.

Benzylation of (±)-Codamine (5). Codamine (**5**) (0.3 g) in 20 ml of dry DMF was added to a stirring solution of 38 mg of NaH in 5 ml of dry DMF under a nitrogen atmosphere. After stirring for 1 hr, 110 mg of benzyl chloride was added and stirring continued for an additional 5 hr. Quenching with H_2O and extraction with ether gave a light yellow oil. This oil was taken up in EtOAc and washed with 2 *N* NaOH solution. The organic layer was dried and evaporated to yield a pale yellow oil. Nmr analysis showed a <10% yield of *O*-benzylcodamine (**10c**).

(±)-Pseudolaudanine (6). Norpapaverinium betaine hydrochloride (**4**) (5.0 g) was reduced with $NaBH_4$ to yield 3.30 g of viscous yellow oil. This oil was partitioned between 30-ml portions of 1 *N* aqueous NaOH and EtOAc. The combined alkaline extracts were adjusted to pH 8 with 3 *N* HCl and extracted with $CHCl_3$. The combined organic layers were dried and evaporated to give a colorless oil; picrate (EtOH) mp 162° (lit.[18] 162–163°).

Benzylation of (±)-Pseudolaudanine (6). Pseudolaudanine (2.0 g) was allowed to react with NaH and benzyl chloride in the manner described in the benzylation of (±)-codamine (**5**) to give 1.9 g (76%) of **10d** as a colorless syrup. After the mixture was allowed to stand in ethanol at 0° for 24 hr, filtration gave **10d** as a white feathery

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solid: mp 81–82°; nmr δ 2.59 (3 H, s, NCH_3), 2.62–3.20 (7 H, m), 3.64 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 5.13 (2 H, s, CH_2Ph), 6.14 (1 H, s), 6.58–6.83 (4 H, m), 7.42 (5 H, s, ArH of benzyl moiety).

Anal. Calcd for $C_{27}H_{31}NO_4$: C, 74.8; H, 7.21; N, 3.23. Found: C, 74.17; H, 7.29; N, 3.07.

(±)-*O*-Methylflavinantine (11a). (i) Laudanosine (200 mg) was oxidized at 1.10 V in the manner described above to give **11a** as a yellow oil in 52% yield: nmr δ 1.93 (2 H, m), 2.44 (3 H, s, NCH_3), 2.49–3.66 (5 H, m), 3.82 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 6.30 (1 H, s), 6.53 (1 H, s), 6.70 (1 H, s), 6.95 (1 H, s); ir (KBr) 1670, 1645, 1625 cm^{-1}; uv max 240 and 283 nm. These data correspond with authentic spectra supplied by Professor T. Kametani.[10]

(ii) Electrolysis in the described fashion of 340 mg of *O*-benzylcodamine (**10c**) at 1.04 V gave **11a** in 53% yield. Spectroscopic data were identical with those of the above specimen.

(iii) Following the described oxidation method at 1.09 V, an equal molar mixture of 321 mg of laudanosine (**10a**) and 242 mg of bis(acetonitrile)palladium(II) chloride yielded **11a** in 63% yield whose spectroscopic properties were identical with those of the above specimen.

(±)-*O*-Benzylflavinantine (11b). **10b** (259 mg) was electrolyzed at 1.05 V in the prescribed manner to yield **11b** as a colorless glass in 53% yield based on quantitative conversion to the methiodide salt. Nmr and ir of the free base compared favorably with literature values:[35] ir ($CHCl_3$) 1660, 1640, 1620 cm^{-1}; nmr δ 1.80 (2 H, m), 2.52 (3 H, s, NCH_3), 2.60–3.52 (5 H, m), 3.65 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 5.18 (2 H, s, CH_2Ph), 6.13 (1 H, s), 6.34 (1 H, s), 6.70 (1 H, s), 6.80 (1 H, s), 7.40 (5 H, s, Ar H of benzyl moiety).

The methiodide salt was recrystallizated from EtOH to a constant melting point of 203–204° (lit.[35] 208–210°); HCl salt, mp 239–240° dec.

2,3-Dimethoxy-6-benzyloxymorphinandienone (11c). **10d** (350 mg) was oxidized in the described manner at 1.10 V to give **11c**[16] in 44% yield: nmr δ 1.84 (2 H, m), 2.42 (3 H, s, NCH_3), 2.58–3.50 (5 H, m), 3.67 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 5.06 (2 H, s, CH_2Ph), 6.33 (1 H, s), 6.40 (1 H, s), 6.45 (1 H, s), 6.62 (1 H, s), 7.28 (5 H, s, ArH of benzyl moiety); ir (neat) 1660, 1640, 1620 cm^{-1}; methiodide salt, mp 227° (lit.[16] 225–227°).

(±)-*O*-Benzylisoflavinantine (11d). **11d** was obtained in 43% yield after 240 mg of **10e** was oxidized at 1.05 V in the prescribed manner: nmr[32] δ 1.86 (2 H, m), 2.44 (3 H, s, NCH_3), 2.48–3.65 (5 H, m), 3.80 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 5.12 (2 H, s, CH_2Ph), 6.30 (1 H, s), 6.40 (1 H, s), 6.72 (1 H, s), 6.88 (1 H, s), 7.37 (5 H, s, ArH of benzyl moiety); ir[33] ($CHCl_3$) 1665, 1640, 1620 cm^{-1}.

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Nonenzymic Biogenetic-Like Olefinic Cyclizations.[1a] Stereospecific Cyclization of Dienic Acetals[1b]

Arne van der Gen, Koenraad Wiedhaup, Johann J. Swoboda, Harmon C. Dunathan, and William S. Johnson*

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. *Received August 21, 1972*

Abstract: This paper reports the details of a basic study on a system which has proved to be useful in effecting nonenzymic biogenetic-like olefinic cyclizations. Cyclization of the trans dienic acetal **5** with stannic chloride in benzene gives, in high yield, a mixture of *trans*-octalol ethers, **11a–15a**. The predominant isomer is **12a**, particularly when nitromethane is used as the cyclization solvent (yield of **12a**, *ca.* 80%). Cyclization of the cis dienic acetal **6** gives similar results except that the bicyclic products are cis-fused. The degree of stereoselectivity with respect to the configuration of the ring fusion (cis or trans) is better than 97% for the cyclization of the acetal **5**, and 95% for the acetal **6**. The acetals **5** and **6** were prepared by the Wittig reaction of the phosphorane **8** with the keto acetal **7**. The structures and configurations of the major cyclizations were proved by degradation to the known dimethyloctalins.

This paper contains a description of the details of the basic study which led to the demonstration that the acetal function is particularly useful for initiating biogenetic-like olefinic cyclizations. Further exploitation of the system has culminated in the successful cyclization of a tetraenic acetal to yield the *D*-homosteroid nucleus,[2] an example of the stereospecific formation of six asymmetric centers in a tetracyclic product derived, in a single step, from an acyclic substrate having no centers of asymmetry.

The known susceptibility of certain unsaturated aldehydes of the citronellal type to undergo acid-catalyzed cyclization[3] prompted us to explore the possibility of using the aldehyde group to initiate polycyclization of polyolefinic systems. We first considered it essential to ascertain if unsaturated aldehydes having the olefinic bond in the 5 instead of the 6 position would also cyclize readily. The behavior of 5-methyl-5-hexenal (**1**) was therefore examined.[4] When a solution of this aldehyde in methanol containing (0.02 *N*) hydrogen chloride was allowed to stand for 2 hr at 0°, the acetal **2** was formed in quantitative yield. When this same solution was allowed to stand at room temperature, the aldehyde was completely cyclized, giving a mixture of *cis*- and *trans*-dimethoxymethylcyclohexane (**3**) and the olefinic ethers **4**. The rate of the cyclization process could readily be

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(4) Since this study was carried only to the point of demonstrating that the cyclization did in fact proceed readily, the experimental work was not rigorously refined and the details, therefore, are not reported.