Similarly, 1-phenylcyclooctene underwent hydroboration-oxidation by this procedure to produce *trans*-2-phenylcyclooctanol[8] free of isomeric material, as revealed by GC and ^{13}C examination.

The reluctance of the 9-BBN moiety to move along the carbon skeleton is probably a reflection of the smaller steric crowding in the *B*-alkyl-9-BBN, as compared with other trialkylboranes. The availability of a hydroborating reagent capable of forming thermally stable organoboranes should prove to be very complementary to the reagents previously shown to yield readily isomerizable organoboranes and should extend application of hydroboration to the solution of problems in synthesis.

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(8) The molecular formula of this compound was obtained by high-resolution mass spectroscopy. The ^1H NMR spectrum displayed absorptions at δ 1.4–2.2 (m, 13 H), 2.75 (m, 1 H), 3.9 (m, 1 H), and 7.23 (s, 5 H).
(9) Visiting Scholar, 1972–1973, on funds provided by the Maruzen Oil Co. Ltd., Osaka, Japan.
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Aporphines. 22.[1] Electrochemical Synthesis of Aporphines via Cathodic Cyclization of Iodobenzylisoquinolinium Salts

Sir:

The clinical utilization of several aporphine alkaloids for the treatment of Parkinsonism[2a] and in cancer chemotherapy[2b] has focused attention on new methods for the synthesis of such polycyclic ring systems. Nonbiogenetic syntheses of aporphines from benzylisoquinoline precursors have involved principally Pschorr cyclizations or photochemical routes.[3] Biogenetic type syntheses utilizing oxidative coupling reactions of phenols have long been recognized as a mode of carbon-carbon bond formation in the synthesis of aporphines and related compounds.[4,5] Recent studies have demonstrated that electrooxidative cyclization of the benzyltetrahydroisoquinoline alkaloid, (±)-laudanosine, gave a morphinandienone,[6] which in turn could be converted to the aporphine alkaloid (±)-glaucine.[7] We wish to report herewith a novel synthesis of aporphine **3a** and apomorphine dimethyl ether (**3c**) via cathodic cyclization of the 1-(*o*-iodobenzyl)isoquinolinium methiodides **1a** and **1b**, and to propose a mechanism which involves the formation of the intermediate tetradehydroaporphine **2**.

The iodobenzylisoquinolinium salts **1a**[8] and **1b**[9] (mp 230–235 °C) were prepared via Reissert alkylation[10] from 2-benzoyl-1,2-dihydroisoquinaldonitrile and the appropriately substituted benzyl chloride. Cyclic voltammetry of **1a** and **1b** (Figure 1) showed in the cathodic sweep, two one-electron reduction waves of which the second was entirely irreversible in the anodic sweep at peak potentials of −660 and −1256 mV for **1a** and −672 and −1072 mV for **1b** (against a silver wire reference electrode).

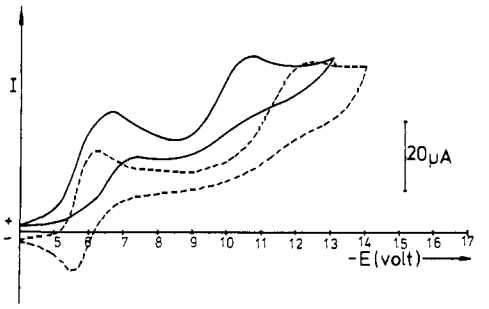
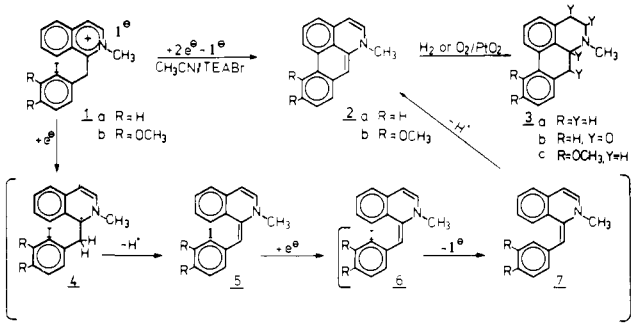


Figure 1. Cyclic voltammogram for the reduction of **1a** (- - -) and **1b** (—) 7×10^{-6} mol in CH_3CN containing 0.1 mol of tetraethylammonium bromide (TEABr). Scan rate 100 mV/s.

Scheme I



On the basis of these results, the quantitative electrolysis of **1a** and **1b** was undertaken in a two-compartment cell specially constructed for such reactions.[11] The electrolysis cell consisted of an anodic compartment with a carbon electrode, and a cathodic compartment with a mercury cathode together with a silver wire as a reference electrode. The two-cell compartments containing the electrolyte solution of TEA bromide (0.3 M) in CH_3CN were separated by a Nafion 125 membrane.[12]

One gram (2.05 mmol) of **1a** dispersed in 120 ml of 0.3 N TEA bromide in dry CH_3CN was reduced under a nitrogen atmosphere at room temperature at −1500 mV. The initial current of 120 mA dropped smoothly to 3 mA in approximately 4 h with an uptake of 398 C. (Theoretical uptake for a two-electron reduction process is 396 C.) The solution was then evaporated to dryness, dissolved in 50 ml of CH_2Cl_2 (previously flushed with argon), and chromatographed on a silica gel column (100 g) which had also been preflushed with argon. The yellow eluate was evaporated to dryness to yield 400 mg (86%) of yellow crystals of **2a**: mp 75–77 °C;[13] UV_{max}^{MeOH} (log ϵ) 228 (4.46), 275 (4.20), 300 (3.41), 339 (4.03), 352 (4.09), 404 (3.77), 427 (3.75); NMR ($CDCl_3$) 3.10 (s, 3 H), 5.68 (d, 1 H), 6.11 (s, 1 H), 6.31 (d, 1 H) and seven aromatic protons at 6.82 (d, 1 H), 7.12–7.52 (m, 4 H), 7.96 (d, 1 H), 8.21 (d, 1 H); mass spectrum *m/e* (%) 231 (100, M^+), 216 (91), 189 (23), 135 (72).

Catalytic hydrogenation of **2a** in methanolic HCl with PtO_2 (100 mg) gave aporphine hydrochloride (**3a**·HCl, 88%): mp 258–259 °C dec (lit.[14] 255 °C, 252–254 °C[8]) identical with an authentic sample.[15] When the catalytic reduction of **2a** was carried out with deuterium in CH_3OD with several drops of DCl in D_2O, a product **3b** (mp 258–259 °C dec) was isolated whose mass spectrum indicated that partial aromatic deuteration had also taken place.[16] The mass spectrum exhibited a series of peaks 4–8 mass units higher than the M^+ (235) ion of the hydrogenated compound **3a**. Fragments arising from sequential elimination of hydrogen or deuterium, CH_3, and

retro-Diels-Alder elimination were identical with the hydrogenated product **3a**. The NMR spectrum ($CDCl_3$) of **3b** showed peaks at 2.54 (s, 3 H), 2.60–3.32 (m, 7 H), the aromatic protons appear at 7.00–7.76 (m, 7 H).

The voltammogram shows that the formation of **2** proceeds via two one-electron reduction steps. We suggest that the first electron uptake leads to the formation of a relatively stable radical **4** leading to the sequence **5** → **6** → **7** → **2a**.

We believe this to be the first demonstration of an intramolecular cathodic cyclization of a benzylisoquinolinium salt, involving the intermediacy of an aryl radical, generated from an aryl halide.

In order to evaluate the potential of this new aporphine synthesis for the preparation of methoxy-substituted aporphines, (±)-10,11-dimethoxyaporphine (**3c**) was prepared from **1b**. Thus 300 mg (0.55 mmol) of **1b** gave after electrolysis 120 mg (74%) of an oil **2b**: UV_{max}^{MeOH} (log ε) 238 (4.51), 269 (4.11), 278 (4.14), 340 (4.09), 353 (4.18), 395 (3.69), 417 (3.74), 445 (3.71); NMR ($CDCl_3$) 3.00 (s, 3 H), 3.76 (s, 3 H), 5.56 (d, 1 H), 5.97 (s, 1 H), 5.23 (d, 1 H), the aromatic protons appear at 6.76 (d, 1 H), 6.98–7.34 (m, 3 H), 8.92 (d, 1 H). Without further isolation, **2b** was converted directly to **3c** with PtO_2 (25 mg) in MeOH containing a few drops of concentrated hydrochloric acid. Two molar equivalents of hydrogen were rapidly absorbed. The product was converted to the free base, and also to the hydroiodide salt, mp 262 °C dec oil bath (lit.[17] 282 °C dec (dta)); UV, NMR, and mass spectrum were identical with those of (−)-apomorphine dimethyl ether hydroiodide.[17] The high-yield conversions of **1** → **3** constitute the most efficient direct route to aporphines reported to date.

Studies are currently underway to explore the scope and mechanism of the electroreductive cyclization of benzylisoquinolines to aporphines.

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Oligomerization Stereochemistry of Vinyl Monomers. 2. Effect of Ion Pair Structure on the Methylation Stereochemistry of 1,3-Di(2-pyridyl)butane Anion

Sir:

There has been considerable interest in stereoselective alkylation reactions of Li compounds in recent years and much understanding of these reactions has been gained. However, a systematic investigation of the effect of cation on such reactions involving ionic species appears not to have been made. We now wish to report such a study dealing with the methylation stereochemistry of 1,3-di(2-pyridyl)butane[2] (**2′**) that shows dramatic and interesting effects of cation and its state of coordination.

Anion **2** was prepared by metalation of ethylpyridine using BuLi or alkali salts of α-methyl styrene tetramer[3] in THF followed by slow in vacuo distillation of vinyl pyridine onto a stirred solution of **1** at −78 °C (Scheme I). Methylation was similarly carried out by an in vacuo distillation of CH_3I onto a solution of **2** at temperatures below 0 °C. The methylation products, **3′**, were distilled (bp 102–106 °C (0.15 mm Hg)) after extraction and analyzed by NMR (*meso*-**3′**: δCH_2 1.77 and 2.25, J_{ab} = 13.3 Hz; δCH 2.80, $J_{ac} = J_{bc}$ = 7.1 Hz; δCH_3 1.25, J_{cd} = 6.7 Hz; *rac*-**3′**: δCH_3 = 1.19, J_{cd} = 7.0 Hz). Product ratios were determined by comparison of CH_3 doublet intensities of the meso compound and the racemic mixture. The results are shown in Table I and demonstrate the effect of cation size and coordination on the reaction stereochemistry. The methylation stereoselectivity shows a decrease with increasing cation size, the Li and Na salts being highly selective, while methylation of the Rb salt leads to approximately equal

Scheme I