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Electrochemistry of Natural Products. V. Intramolecular Coupling of Phenolic Alkaloid Precursors[1]

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Received August 9, 1974

Intramolecular coupling of some diphenols by electrochemical oxidation is reported. Specifically, 1-(4-hydroxyphenylethyl)- and 1-(4-hydroxy-3-methoxyphenylethyl)-7-hydroxy-6-methoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinolines have been coupled to the corresponding dienones in yields of 20–40% and *N*-acyl-*N*-norreticulines have been coupled to *N*-acyl-*N*-norpallidines in yields of about 18%. Attempts to couple *N*-benzylphenylethylamines to alkaloids of the Amaryllidaceae type were not successful.

The important role played by phenol coupling in alkaloid biosynthesis has been thoroughly documented and reviewed.[3] In general, attempts to carry out phenol coupling reactions in vitro have been only partially successful, mainly owing to low yields caused by overoxidation. In an attempt to develop a more specific oxidizing system, we have been exploring controlled potential, electrochemical oxidation. Intermolecular coupling reactions have been carried out in good yields (50–95%) and our work has recently been summarized.[4] In this paper, we would like to report our more limited success with intramolecular coupling of diphenols. Such electrochemical reactions do not appear to have been previously reported. Although diphenols have not been coupled electrochemiccally before, their methyl ethers have been coupled recently[5] with considerable success. Yields have been high, and the reactions have been remarkably clean. Although these reactions have the greater potential as useful synthetic methods, the coupling of diphenols is more relevant to biosynthesis and biomimetic synthesis of natural products.

The 1-Phenylethyltetrahydroisoquinolines. The compounds oxidized were **7** and **8**, which were prepared (Scheme I) by the method generalized by Harmon and his coworkers.[6] The actual reactions used, however, are substantially different from those previously recorded[7-9] in that the side chain double bond is left in place until the final debenzylation step (**6** to **7** and **8**). Using this sequence, the intermediates were easier to crystallize and work with.

The oxidations of the hydrochlorides of **7** and **8** were carried out on a graphite felt anode in water using tetraethylammonium perchlorate as an electrolyte. The potentials were controlled at 0.7 V for **7** and at 0.8 V for **8** [as measured against a standard calomel electrode (SCE)]. The dienone **9** was obtained from **7** in 23% yield as compared with 19% using $FeCl_3$ as an oxidizing agent.[8] The two dienones, **10** and **11** (differing in the stereochemistry at the spiro ring system) were obtained in a combined yield of 36% as compared to 9% using $K_3Fe(CN)_6$[9] and 31% using $FeCl_3$.[10] The isomers, **10** and **11**, were separated as previously described,[9] but, unfortunately, there was no preponderance of one isomer. One of the isomers is the alkaloid kreysiginone.[10]

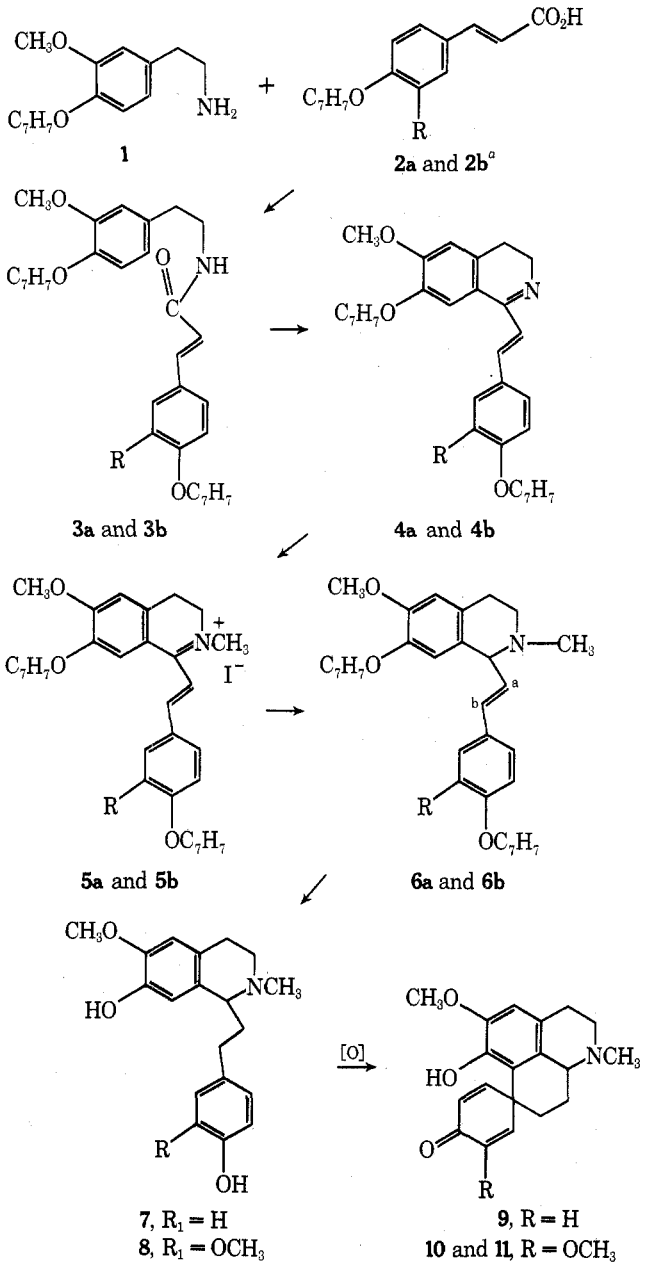
The Acyl Reticuline Derivatives. The oxidative ring closure of reticuline (**12**, Scheme II) to a dienone skeleton, **16**, and thence to morphine has been one of the major goals in alkaloid synthesis for many years. Although **16** was obtained once in very low yield,[11] the more usual product has been the isomeric dienone, **17**, albeit also in low yields (0–4%). The work has been well summarized.[3c]

Attempts to oxidize reticuline (**12**) and its nor derivative, **13**, electrochemically have yielded no isolable products and the starting material was destroyed either by extensive overoxidation or by some sort of fragmentation process.[12] Thus, the *N*-carbethoxy (**14**) and the *N*-carbobenzyloxy (**15**) derivatives of norreticuline were chosen for oxidation studies. Compound **14** was prepared from reticuline dibenzyl ether[13] and **15** was prepared from reticuline itself[14] by acylation. Compounds **12** and **13** were prepared by a general Bischler–Napieralski synthesis.[14]

Experimental conditions for the oxidation of **14** were explored extensively. The optimum conditions were found to be oxidation on a graphite felt anode in 50% aqueous *tert*-butyl alcohol with 4 molar equiv of potassium *tert*-butoxide and an equivalent amount of palladium chloride.[5d,15] The current was controlled at 0.2 V vs. SCE, and the oxidations were performed under nitrogen at 20° for a time equivalent to a two-electron oxidation. Under these conditions, the dienone **18** was obtained in a yield of 15.5%, corrected to 18% by recovery of starting material. Yields were lower in aqueous acetonitrile with tetraethylammonium perchlorate as electrolyte, at higher or lower temperatures, at higher or lower potentials, and in the absence of palladium chloride. Compound **18** was methylated to **20** with diazomethane, but all attempts to remove the carbethoxy group by hydrolysis or reduction failed to yield isolable products.

Although **18** and **20** were not crystalline, they gave satisfactory analyses and had spectroscopic properties corresponding to the structures. Both **18** and **20** had strong molecular ion peaks at *m/e* 385 and 399, respectively, with strong peaks corresponding to loss of ethyl, carbethoxy, and CH_2NCO_2Et. The uv spectra showed maxima at 283 and 236 nm in agreement with a cross-conjugated α-methoxycyclohexadienone structure[16] and lacked a strong peak at 300 nm expected from any aporphine system.[3e] The ir spectra show three bands at 1665, 1635, and 1615 cm^{-1}

Scheme I

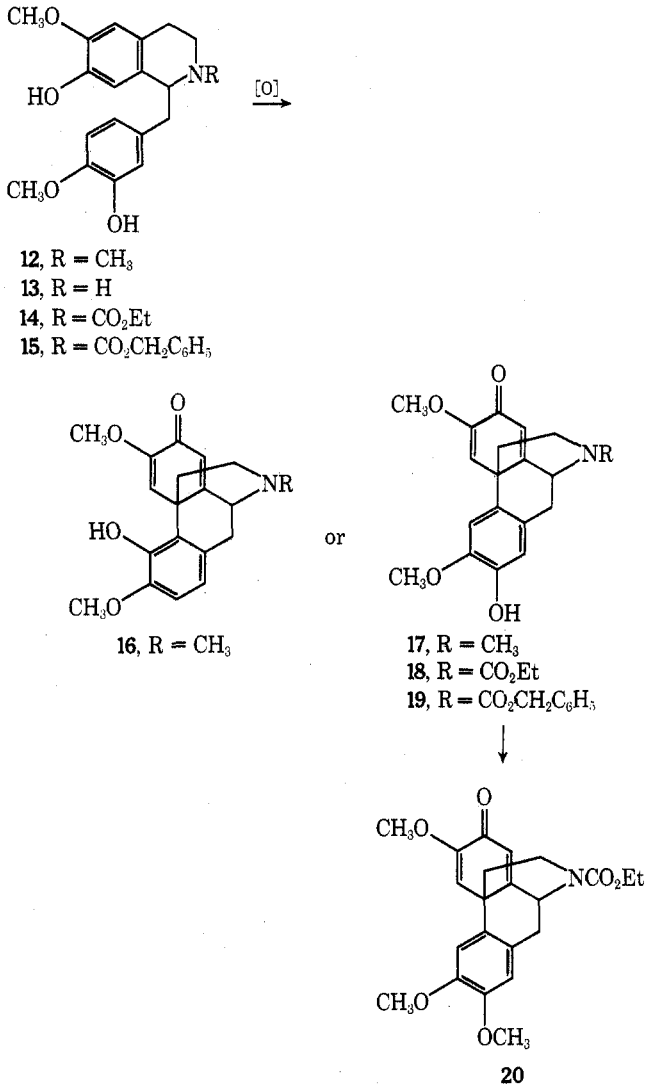


[a] In the a series R = H; in the b series, R = OCH_3.

thought[17] to be characteristic of the methoxydienone system as well as the expected amide carbonyl and hydroxyl absorptions. The NMR spectra showed the expected number of methyl groups for both compounds and four singlets in the region δ 6.3–6.9 corresponding to the aromatic protons and the olefinic protons.[18] Structures such as **16** would be expected to show an AB pattern in this region.

When it appeared that the carbethoxy group of **18** could not be easily removed, attention was shifted to the carbobenzyloxy derivative, **15**, in anticipation that the blocking group could be removed by hydrogenation. Compound **15** was oxidized under the same conditions as described for **14** except that palladium chloride was not used and the potential was kept at a minimum to yield 20 mA of current (0.0–0.024 V vs. SCE). The yield of dienone, **19**, was 10%, corrected to 11% for recovered starting material. The mass spectrum of **19** had a weak molecular ion peak at *m/e* 447 and strong peaks at *m/e* 356 and 312 corresponding to loss of the benzyl group and the carbobenzyloxy group. The uv

Scheme II



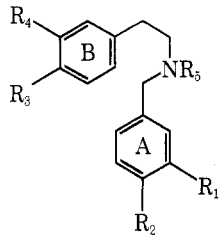
and ir spectra of **19** were quite similar to those of **18** and **20**. The NMR spectra showed the expected methyl and benzyl peaks and three singlet peaks in the aromatic olefinic region δ 6.3–6.8. However, one of these corresponded to two protons.

The Amaryllidaceae Alkaloid Precursors. A number of alkaloids appear to be formed in nature from the coupling of diphenolic benzylphenylethylamines.[3a] Intramolecular coupling reactions in this series have been carried out successfully by Schwartz and his coworkers using such oxidizing agents as vanadium oxychloride[19] and thallium salts,[20] by Franck and Lubs using ferric chloride,[21] and by Kametani and his coworkers using various oxidizing agents.[3c] Methyl ethers of this series have been coupled electrochemically by Kotani, Takeuchi, and Tobinaga.[5f] The electrochemistry of catechol amines such as dopamine and its derivatives has been studied extensively by Adams and his coworkers.[22]

Several compounds, **21–25** (Scheme III), were chosen for study. They fall in two general groups. Compounds **21** and **22** contained two adjacent phenol groups in ring B. It was reasoned that the diphenol should be easily oxidized to an ortho quinone which could add either the nitrogen of the amine or the other phenolic ring (ring A) as postulated by one of the several theories of phenol coupling.[1,3a] Compound **22**, with the methylenedioxy group was prepared to avoid any difficulties caused by the ring A phenol in **21**.

The syntheses of these new compounds are given in the Experimental Section. Unfortunately, electrochemical oxidation of **21** and **22** under various conditions produced extensive electrode coating, extensive polymerization, and no isolable products.

Scheme III



	R_1	R_2	R_3	R_4	R_5
21,	H	OH	OH	OH	H·HCl
22,	$-OCH_2O-$		OH	OH	H·HCl
23,	OCH_3	OH	OH	H	H·HCl
24,	OCH_3	OH	OH	H	$COCF_3$
25,	H	OH	OH	OCH_3	H·HCl
26,	H	OH	OH	OCH_3	$COCF_3$
27,	OCH_3	OH	OH	OCH_3	H·HCl
28,	OCH_3	OH	OH	OCH_3	$COCF_3$
29,	$-OCH_2O-$		OH	H	H·HCl
30,	$-OCH_2O-$		OH	H	$COCF_3$

The second set of compounds, **23–28,** contained only one phenol group in each ring. Preliminary oxidation studies of the known compound **23**[23] indicated extensive decomposition, probably due to fragmentation.[12] To avoid this problem, the nitrogen of the remaining three compounds, **24–26,** was blocked with the trifluoroacetyl group so successfully used by Schwartz.[19] Compound **23** and its *N*-trifluoroacetyl derivative **24** are known[25] and the syntheses of compounds **25–28** are detailed in the Experimental Section.

Electrochemical oxidation of the three amides **24, 26,** and **28** failed to yield any intramolecularly coupled products, either by isolation or, in the case of **24,** by comparison of the reaction mixtures with known compounds[26] by TLC. The oxidations were carried out on graphite felt anodes in 10% aqueous acetonitrile using KCl or tetraethylammonium perchlorate (0.1 *N*) as electrolyte. The pH was kept at about 9 by periodic additions of ammonium hydroxide. When the current fell off rapidly, it was assumed to be due to electrode coating, and a new anode was introduced.

The products isolated in each case were mixtures of dimers. The mixtures, analyzed as such, gave correct analytical data for carbon, hydrogen, and nitrogen. When the mixtures were methylated, the resulting mixed ethers could be resolved. These, in turn analyzed correctly and showed mass spectral data corresponding to carbon–carbon linked dimers. Although coupling is presumed to have been ortho and para to the phenol groups, none of the products were crystalline, and structural assignments are tenuous.[2]

Compound **30** was not oxidized appreciably under the conditions used: 0.4 V at pH 9 and 0.75 V at pH 7.

Discussion and Summary

Several generalizations arise from this work. First, it appears that electrochemical oxidation of phenols is much better for intermolecular coupling reactions than for intramolecular coupling, although in the phenethylisoquinoline series and the benzylisoquinoline series, it is as good as or better than chemical oxidation. This is in sharp contrast to the intramolecular coupling of aromatic ethers[5] where electrochemical methods have given superb results. The necessity for acylation in the benzylisoquinoline series and the improved yields over Franck's work[18,27] (18% as opposed to 4% for the coupling reaction) would seem to be in agreement with two of Franck's postulates: that a surface assists the reaction (he used silica) and that the electron pair from the nitrogen interferes with the reaction.

Finally, it should be recognized that these results are the best obtainable on the *presently available electrode surfaces.* A portion of our research program is directed toward the development of new and modified surfaces,[28] and it is anticipated that these compounds will be used as model substances for their exploration.

Experimental Section[29]

The Cinnamides, 3. A mixture of **1**[30] (22 g, 0.086 mol) and **2a**[31] (20 g, 0.08 mol) was heated under N_2 at 180–190° for 3 hr. The mixture was cooled, dissolved in $CHCl_3$, washed (10% HCl followed by 10% NaOH and water), dried (K_2CO_3), and evaporated to a brown powder which crystallized from MeOH–ether to give 29 g (69%) of **3a,** mp 187–189°.

Anal. Calcd for $C_{32}H_{31}NO_4$: C, 77.86; H, 6.33; N, 2.84. Found: C, 77.67; H, 6.21; N, 3.09.

In a similar manner, **3b** was prepared in 85% yield and melted at 166–167°.

Anal. Calcd for $C_{33}H_{33}NO_5$: C, 75.69; H, 6.35; N, 2.68. Found: C, 75.31; H, 6.27; N, 2.92.

The 3,4-Dihydroisoquinolines, 4. A mixture of **3a** (11.0 g), phosphorus oxychloride (25 ml), and dry benzene (250 ml) was heated under reflux for 2.5 hr and poured into 1 l. of hexane. The brownish powder which precipitated was collected by filtration, washed with ether, and crystallized from EtOH to give 10.5 g (93%) of the hydrochloride of **4a** as yellow prisms, mp 105–107°.

Anal. Calcd for $C_{32}H_{29}NO_3$·HCl: C, 75.04; H, 5.88; N, 2.73. Found: C, 75.57; H, 5.65; N, 2.59.

The hydrochloride of **4a** was suspended in benzene and basified with NH_4OH. The benzene layer was dried (K_2CO_3) and evaporated to a syrup which was crystallized from ether–hexane to afford the free base, mp 135–136°. The base was used in the next step without extensive purification.

In an analogous manner, the hydrochloride of **4b** was obtained in 81% yield and melted at 164–166°.

Anal. Calcd for $C_{33}H_{31}NO_4$·HCl: C, 73.12; H, 5.95; N, 2.58. Found: C, 72.74; H, 6.21; N, 2.43.

The free base **4b** melted at 116–117°.

The Methiodides, 5. The dihydroisoquinoline **4a** (8 g) dissolved in 20 ml of MeOH was treated with 15 ml of CH_3I and allowed to stand for 2 hr. The excess solvent was removed to give a reddish residue which crystallized from MeOH–ether to give 7.0 g (67%) of **5a** as yellow prisms, mp 143–144°. In the same manner **5b** was obtained from **4b** in 93% yield and melted at 117–118°. The compounds were not analyzed.

The *N*-Methyltetrahydroisoquinolines, 6. Sodium borohydride (2.8 g, 0.075 mol) was added in small portions to a stirred solution of 6.5 g (0.01 mol) of **5a** in 500 ml of MeOH. Evaporation of the solvent gave a residue which was decomposed with water and partitioned between water and benzene. The benzene was washed (H_2O), dried (K_2CO_3), and evaporated to a colorless syrup which crystallized from ether–hexane to give 4.5 g (86%) of **6a,** mp 92–93°: NMR ($CDCl_3$) δ 7.22 (d, J = 9 Hz, 2, aromatic), 6.92 (d, J = 9 Hz, 2, aromatic), 6.62 (broad s, 2, aromatic), 6.47 (d, J = 15 Hz, 1, H_a), 5.83 (two d's, J = 15 and 8.5 Hz, 1, H_b) 5.09, 5.01 (each s, each 2 H, $OCH_2C_6H_5$), 3.85 (s, 3, OCH_3), 2.42 (s, 3, NCH_3).

Anal. Calcd for $C_{33}H_{33}NO_3$: C, 80.62; H, 6.77; N, 2.85. Found: C, 80.55; H, 6.74; N, 3.13.

In an identical manner, **5b** was converted (95%) to **6b,** mp 141–142°: NMR ($CDCl_3$) δ 6.63 (2, broad s, aromatic), 6.46 (1, d, J = 15 Hz, H_a), 5.83 (1, pair of doublets, J = 15 and 8.5 Hz, H_b), 5.18, 5.02 (each 2, s, $OCH_2C_6H_5$), 3.77 (6, s, OCH_3), 2.42 (3, s, NCH_3).

Anal. Calcd for $C_{34}H_{35}NO_4$: C, 78.28; H, 6.76; N, 2.69. Found: C, 78.64; H, 6.82; N, 2.43.

The Free Phenols, 7 and 8. Compound **6a** (4 g) in 200 ml of EtOH was hydrogenated at 40–45 psi over 3 g of 5% palladium on carbon for 20 hr. The catalyst was removed by filtration, and the solution was evaporated to a colorless powder which was crystallized from ether–hexane to give 1.9 g (72%) of **7** as colorless nee-

dles, mp 161–162° (sintered at 101°) (lit.[32] mp 159–160°).

In an identical manner, **6b** was debenzylated to yield, after crystallization from chloroform–hexane, 79% of **8**, mp 100–102° (sintered at 91°).[33]

Oxidation of 7. The hydrochloride prepared from 200 mg of **7** was dissolved in 200 ml of water containing 3 g of tetraethylammonium perchlorate. The solution was oxidized in a two-compartment system[34] using a graphite felt anode (Union Carbide WDF, 10 × 10 cm) and a platinum cathode. The potential was controlled at +0.7 V vs. SCE[35] for 4 hr. The mixture was removed from the cell, and the graphite anode was shredded in a Waring blendor with MeOH. The graphite fibers were removed by filtration and washed several times with MeOH. The collected filtrates and the cell contents were concentrated to about 20 ml, basified with ammonia, and extracted three times with $CHCl_3$. The $CHCl_3$ extracts were washed (H_2O), dried ($MgSO_4$), and evaporated to a brownish residue which was separated by preparative TLC [$CHCl_3$–acetone–CH_3OH (5:4:2)]. The top zone yielded 22 mg of starting material. The second zone gave 41 mg (23% corrected for recovered starting material) of **9** as colorless prisms, mp 248–249° dec (lit.[8] mp 248–249°). Compound **9** was also prepared by ferric chloride oxidation of **7**.

Oxidation of 8. The hydrochloride prepared from 450 mg of **8** was oxidized at +0.8 V for 12 hr, and the products were isolated as described for **7**. The top zone from preparative TLC yielded 160 mg of starting material. The second zone yielded 105 mg (36%) of a mixture of two dienones **10** and **11**. The dienones were separated by fractional crystallization from benzene. Further crystallization from benzene yielded 32 mg of pure (±)-kresiginone, mp 195° dec (lit.[7] mp 190–192 and 193–195°).[9] Crystallization of the other fraction from benzene–ether gave 35 mg of the isomeric dienone, mp 206–207° (lit.[9] mp 156–158° and 202°).[10] Both dienones were identical with samples prepared by ferric chloride oxidation of **8**.[10]

***N*-Carbethoxynorreticuline (14).** 1-(3-Benzyloxy-4-methoxybenzyl)-7-benzyloxy-6-methoxy-*N*-carbethoxy-1,2,3,4-tetrahydroisoquinoline[13] (3 g) was hydrogenated at 40 psi over 1.2 g of 5% Pd on carbon in 200 ml of EtOH. The catalyst was removed by filtration, and the filtrate was concentrated to yield 2.1 g (98%) of a colorless glass: NMR ($CDCl_3$) δ 6.64 (m, 5, aromatic), 5.15 (m, 1, H-1), 3.80 (s, 6, 2 OCH_3), 2.90 (m, 4, H on C-3 and C-4), 1.08 (t, 3, CH_3).[36]

Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.12; H, 6.46; N, 3.62. Found: C, 65.37; H, 6.36; N, 3.44.

***N*-Carbobenzyloxynorreticuline (15).** *N*-Norreticuline[14] (3 g, 9.5 mmol) was dissolved in 200 ml of $CHCl_3$ and 6 ml of triethylamine. The mixture was cooled to 10–15° during the dropwise addition of 8 g (47 mmol) of carbobenzyloxychloride and allowed to stir at room temperature for 1 hr. The $CHCl_3$ was removed, and the residue was crystallized from EtOH to give 4.1 g (60%) of *N*-carbobenzyloxy-3,7-dicarbobenzyloxy-4,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline, mp 92–94°. This derivative was not characterized, but was allowed to stir for 1 hr at room temperature in 30 ml of EtOH containing 1.25 g of sodium hydroxide. The solvent was evaporated, and the residual sodium salt was dissolved in water, washed ($CHCl_3$), acidified (HCl), and extracted ($CHCl_3$). The $CHCl_3$ extract was dried ($MgSO_4$) and evaporated to yield 1.6 g (62%) of crystalline **15**: mp 86–88° from EtOH; NMR ($CDCl_3$) δ 7.30 (m, 5, aromatic), 6.60 (m, 5, aromatic), 3.78 (s, 6, 2 OCH_3), 2.95 (m, 4, C-3 and C-4).

Anal. Calcd for $C_{26}H_{27}NO_6$: C, 69.44; H, 6.01; N, 3.12. Found: C, 69.27; H, 5.81; N, 2.95.

Oxidation of 14. Compound **14** (200 mg) was dissolved in 125 ml of H_2O and 125 ml of *tert*-butyl alcohol containing 2.8 g of potassium *tert*-butoxide and 0.090 g of palladium chloride.[37] The mixture was electrolyzed in a two-compartment cell like the one described for **7** and **8** at +0.2 V (vs. SCE) for 30 min. The average current was 100 mA, and the temperature was held at 20°. The felt anode was blended and extracted as described above, and the combined electrolyte and washings were acidified to pH 4 (HCl) and extracted several times ($CHCl_3$). The $CHCl_3$ extract was dried ($MgSO_4$) and evaporated to a residue which was dissolved in $CHCl_3$–MeOH (2:1) and applied to three preparative TLC layers. The layers were developed with benzene–acetone (3:1). The top zone yielded 26 mg of starting material. The second zone yielded 33 mg (18% corrected) of noncrystalline dienone **18**, which showed only one spot on TLC. The spectral properties were: NMR ($CDCl_3$) δ 6.85 (s, 1, C-5), 6.70 and 6.40 (singlets, 2, aromatic), 6.35 (s, 1, C-8), 5.18 (s, 1, phenol); mass spectrum M^+ *m/e* 385; uv max (MeOH) 283 nm (ε 11,200), 236 (16,100); ir (film) 1665, 1635, 1615 cm^{-1}.

Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.50; H, 5.97; N, 3.63. Found: C, 65.27; H, 5.91; N, 3.48.

The dienone was methylated with diazomethane (prepared from *N,N'*-dimethyl-N,N'-dinitrosoterephthalamide) in MeOH–dioxane (1:1) to yield **20** as a glass: NMR ($CDCl_3$) δ 6.86 (s, 1, C-5), 6.70 (s, 1, aromatic), 6.37 (m, 2, C-8 and aromatic), 3.92, 3.85, 3.80 (3 singlets, 9, OCH_3); mass spectrum M^+ *m/e* 399.

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.19; H, 6.30; N, 3.53. Found: C, 66.30; H, 6.28; N, 3.27.

Oxidation of 15. Compound **15** (200 mg) was oxidized in the same electrolyte and cell as used for **14**, except that no palladium chloride was used. The potential was controlled at +0.2 V for 38 min, and the reaction was carried out at room temperature. The products were isolated in the same manner as described for **14** to yield 2 mg of starting material and 22 mg (11%) of **19** as a glass: NMR ($CDCl_3$) δ 7.35 (m, 5, aromatic), 6.85 (s, 1, C-8), 6.72 (s, 1, aromatic), 6.4 (s, 2, aromatic and C-5), 5.2 (s, 2, $CH_2C_6H_5$), 3.95 and 3.84 (2 singlets, 6, 2OCH_3); uv (MeOH) 283 nm (ε 9400) and 236 (14,800).

Anal. Calcd for $C_{26}H_{29}NO_6$: C, 69.79; H, 5.59; N, 2.81. Found: C, 69.83; H, 5.81; N, 3.13.

Preparation of 21. 3-Hydroxybenzaldehyde (4.88 g, 0.04 mol) and homoveratrylamine (7.24 g, 0.04 mol) were dissolved in 200 ml of EtOH and hydrogenated at 25 psi over 200 mg of prereduced PtO_2. The white solid which precipitated during reduction was dissolved in more solvent, the catalyst was removed by filtration, and the filtrate was concentrated. The product precipitated to give, after collection, 5.1 g (45%) of *N*-(3-hydroxybenzyl)homoveratrylamine, mp 145–146°.

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.08; H, 7.32; N, 4.88. Found: C, 70.80; H, 7.32; N, 4.82.

The dimethyl ether was demethylated by heating 300 mg with 6 ml of light yellow 45% HI at 80° under nitrogen until the methyl iodide was evolved.[38] The mixture was then heated to 121° until most of the HI was distilled and then evaporated to dryness under vacuum. The crystalline HI salt (95% yield) was stirred with freshly prepared but moist solid AgCl (from 10 ml of 0.5 *M* $AgNO_3$ and HCl) with a spatula until the yellow solid AgI formed. Water (10 ml) was added and the mixture was filtered. Removal of the water under vacuum followed by addition of absolute EtOH and evaporation gave an oil which eventually crystallized to give 0.190 g of **21**, mp 163–165°.

Anal. Calcd for $C_{15}H_{18}NO_3Cl$: C, 60.91; H, 6.09; N, 4.74; Cl, 12.01. Found: C, 60.91; H, 6.17; N, 4.86; Cl, 12.26.

Preparation of 22. Piperonal (1.5 g, 0.01 mol), 3,4-dihydroxy-β-phenylethylamine (1.9 g, 0.01 mol), and sodium acetate (0.82 g, 0.01 mol) were dissolved in 200 ml of EtOH and hydrogenated at 25 psi over 100 mg of prereduced PtO_2. The mixture was acidified (HCl) and filtered; the filtrate was concentrated under vacuum; and the residue was crystallized from H_2O to give 1.7 g (55%) of **22**, mp 240–242°.

Anal. Calcd for $C_{16}H_{18}NO_4Cl$: C, 59.26; H, 5.56; N, 4.32. Found: C, 59.08; H, 5.67; N, 4.51.

Preparation of 25. A mixture of 3-hydroxybenzaldehyde (4.27 g, 0.035 mol), 4-benzyloxy-3-methoxy-β-phenylethylamine (7.61 g, 0.03 mol), and 0.8 g of *p*-toluenesulfonic acid in 300 ml of benzene was heated under a Dean-Stark tube until no more H_2O came off. The solvent was removed, and the residue was taken up in 50 ml of MeOH and reduced with 3 g (0.078 mol) of sodium borohydride over 0.5 hr. The solvent was removed, and the residue was dissolved in 50 ml of H_2O, acidified (HCl), basified (NH_4OH), and extracted with $CHCl_3$. The $CHCl_3$ extract was concentrated to a residue, dissolved in MeOH, acidified (HCl), and hydrogenated at 40 psi over 5 g of 5% Pd on carbon. Filtration of the mixture and concentration of the filtrate yielded 8.1 g (80%) of **25**, mp 183–185°.

Anal. Calcd for $C_{16}H_{20}NO_3Cl$: C, 62.03; H, 6.46; N, 4.52. Found: C, 61.97; H, 6.55; N, 4.67.

Preparation of 26. A mixture of 1 g of **25**, 5 ml of dry pyridine, and 10 ml of trifluoroacetic anhydride was stirred at room temperature for 4 hr, diluted with 50 ml of EtOAc, and washed (first with 100 ml of 3 *N* HCl and then with H_2O). The organic layer was evaporated to a residue which was dissolved in 150 ml of MeOH–H_2O (10:1) and stirred for 24 hr. The solution was diluted with 200 ml of H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was dried (Na_2SO_4) and evaporated to a residue. The residue was triturated with hexane and cooled in Dry Ice–MeOH. The precipitated amide was collected and reprecipitated from MeOH–H_2O to yield a partially crystalline solid **26**, mp 51–55°.

Anal. Calcd for $C_{18}H_{18}NO_4F_3$: C, 58.53; H, 4.88; N, 3.79. Found: C, 58.80; H, 5.06; N, 4.05.

Preparation of 27 and 28. Compound **27** was prepared from benzylisovanillin[39] and 3-methoxy-4-benzyloxy-β-phenylethylamine[30] in a manner directly analogous to the preparation of **25** and **26** to yield **27** (88%), mp 186–188° (free base of **27**, mp 95–97°), and **28**, mp 77–78°.

Anal. Calcd for **27** free base, $C_{17}H_{21}NO_4$: C, 67.32; H, 6.93; N, 4.62. Found: C, 67.07; H, 6.95; N, 4.45.

Anal. Calcd for **28**, $C_{19}H_{20}NO_5F_3$: C, 57.14; H, 5.01; N, 3.51. Found: C, 56.86; H, 5.20; N, 3.64.

Preparation of 29 and 30. Compound **29** was prepared from piperonal and tyramine by the method used for **25** except that the debenzylation by hydrogenolysis was not necessary. Compound **29** was obtained in 92% yield and melted at 216–218°.

Anal. Calcd for $C_{16}H_{18}NO_3Cl$: C, 62.44; H, 5.85; N, 4.55. Found: C, 62.24; H, 5.81; N, 4.64.

In a manner analogous to the preparation of **26**, **29** was trifluoroacetylated to **30** (95%), mp 91–95°.

Anal. Calcd for $C_{18}H_{16}NO_4F_3$: C, 58.85; H, 4.36; N, 3.81. Found: C, 59.14; H, 4.48; N, 3.94.

Oxidation of 24.[25] Compound **24** (0.74 g) was oxidized in 200 ml of CH_3CN–H_2O (10:1) containing KCl (0.1 *N*) at +0.7–0.8 V (vs. SCE) in a two-compartment system on a graphite felt anode. The oxidation showed a low current, about 10 mA, and required 7.5 hr. The anode compartment was kept at a pH of about 9 by dropwise addition of NH_4OH. The anode was blended and extracted as described for **7**. The combined washings and electrolyte were evaporated to the aqueous portion and extracted ($CHCl_3$). The $CHCl_3$ extract was dried ($MgSO_4$), evaporated to dryness, and separated into three major fractions by preparative TLC [benzene–acetone (3:1)]. The top zone yielded 0.30 g of starting material. The middle zone yielded 22 mg of a material of unknown structure, but which was not intramolecularly coupled product. The most polar zone yielded 0.220 g of a mixture (by NMR) of two products.

Anal. Calcd for $C_{36}H_{34}N_2O_8F_6$: C, 58.69; H, 4.62; N, 3.74. Found: C, 58.55; H, 4.60; N, 3.76.

The mixture was methylated as described above for **18**, and the mixture was separated by preparative TLC [double development with benzene–acetone (20:1)] into two noncrystalline ethers (total overall yield of 15%). Each of these gave correct analyses and had molecular ion peaks at 792 corresponding to the addition of four methoxy groups, thus mandating a carbon–carbon dimer.

Oxidation of 26. The oxidation of **26** was carried out in the same way as **24** except that tetraethylammonium perchlorate was used as an electrolyte. The products were isolated as described for **24** to yield starting material, tars, and a mixture of at least two dimers.

Anal. Calcd for $C_{36}H_{34}N_2O_8F_6$: C, 58.69; H, 4.62; N, 3.74. Found: C, 59.39; H, 4.62; N, 3.74.

After methylation of the mixture, only one compound was isolable (overall yield 15%). It was not crystalline, but gave a correct microanalysis and showed the expected molecular ion at 792 for a tetramethylated carbon–carbon dimer.

Oxidation of 28. The oxidation of **28** was carried out exactly as described for **26**. The major zone of dimers gave the following analysis.

Anal. Calcd for $C_{38}H_{38}N_2O_{10}F_6$: C, 57.29; H, 4.77; N, 3.52. Found: C, 57.42; H, 4.70; N, 3.31.

After methylation of the mixture, only one compound was isolable (overall yield 12%). It was not crystalline, but gave a correct microanalysis and showed the expected molecular ion at 852 for a tetramethylated carbon–carbon dimer.

Registry No.—**1**, 22231-61-4; **2a**, 6272-45-3; **3a**, 56113-93-0; **3b**, 56113-94-1; **4a**, 56113-95-2; **4a** HCl, 56113-96-3; **4b**, 56113-97-4; **4b** HCl, 56113-98-5; **5a**, 56113-99-6; **5b**, 56114-00-2; **6a**, 56114-01-3; **6b**, 56114-02-4; **7**, 56114-03-5; **7** HCl, 56114-04-6; **8**, 56114-05-7; **8** HCl, 30242-74-1; **9**, 30816-29-6; **10**, 30040-57-4; **11**, 56192-84-8; **13**, 13168-51-9; **14**, 55869-76-6; **15**, 56114-06-8; **18**, 37729-28-5; **19**, 56114-07-9; **20**, 56114-08-0; **21**, 56114-09-1; **22**, 56114-10-4; **24**, 26668-50-8; **25**, 56114-11-5; **26**, 56114-12-6; **27**, 7239-28-3; **27** free base, 22231-53-4; **28**, 56114-13-7; **29**, 56114-14-8; **30**, 40135-88-4; 1-(3-benzyloxy-4-methoxybenzyl)-7-benzyloxy-6-methoxy-*N*-carbethoxy-1,2,3,4-tetrahydroisoquinoline, 56114-15-9; carbobenzyloxychloride, 501-53-1; *N*-carbobenzyloxy-3,7-dicarbobenzyloxy-4,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 56114-16-0; diazomethane, 157-22-2; 3-hydroxybenzaldehyde, 100-83-4; homoveratrylamine, 120-20-7; *N*-(3-hydroxybenzyl)homoveratrylamine, 32372-76-2; piperonal, 120-50-7; 3,4-dihydroxy-β-phenylethylamine, 51-61-6; trifluoroacetic anhydride, 407-25-0; tyramine, 51-67-2.

References and Notes

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(2) Taken in part from the M.S. Thesis of R. S. Ware and the Ph.D. Dissertation of K. N. Chiong, University of Connecticut, 1973.

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