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Electrochemistry of Natural Products. IV. Electrochemical and Chemical Oxidative Dimerization of 1,2-Dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline[1]

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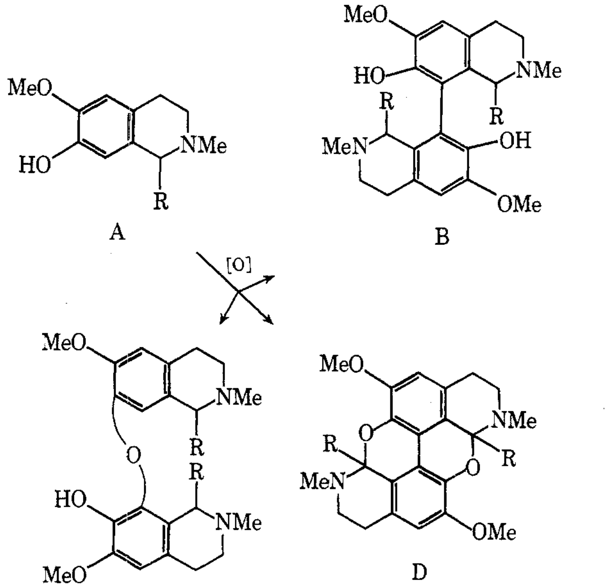
Racemic 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (1) has been oxidatively coupled by controlled-potential electrolysis in excess base to yield one (3) of three possible isomers of the carbon–carbon dimer. The reaction was carried out at +0.16 V (vs. SCE) in wet acetonitrile at a graphite felt anode with tetraethylammonium perchlorate as an electrolyte. Other reaction conditions gave the same stereochemical results in poor yields. During the oxidation, only molecules of 1 having the same configuration at C-1 coupled with each other to form product (*R* with *R* and *S* with *S*). Furthermore, only one of two possible rotational isomers was formed. The structure of the single product was established by the chemical [$K_3Fe(CN)_6$] and electrochemical oxidation of racemic 1 and its enantiomers. Additional products of the chemical oxidation are described.

In a previous paper of this series,[2] we studied the electrochemical and catalytic oxygenation of 1-alkyl-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (A) and established the general structures of the products as B, C, and D (Scheme I). All three products were formed as mixtures of stereoisomers, but only B could be resolved into its components. The centers of chirality at C-1 of B (when R = CH_3) and the newly formed center caused by restricted biphenyl rotation lead to the possible formation of three sets of enantiomers: **2**, **3**, and **4**, designated as *RS*, *SS* rotamer A, *SS* rotamer B, and their enantiomers, respectively (Scheme II). All three isomers of B (R = CH_3) were obtained from the catalytic oxygenation of A (R = CH_3) although specific stereochemical structures were not established. When the electrooxidation of 1 was carried out in acetonitrile solution,[3] only one of the three possible isomers of B was obtained. In this paper, we would like to describe the structure elucidation of the single stereochemical product and to discuss the implications of its formation.

Scheme I



Structures of the Three Carbon–Carbon Dimers 2, 3, and 4. Three dimers were isolated from the catalytic oxygenation of racemic **1** over a Pt catalyst: two crystalline compounds melting at 132–134 and 222–224° and one noncrystalline glass, all of which had characteristic spectral properties.[2] The general structures of the three dimers were confirmed in the present work by equilibrating them via oxygenation over platinum on carbon[2] of **3** to give a mixture of bis-3,4-dihydroisoquinolinium salts[5a] (the open form of a type D compound). The mixture was reduced with $NaBH_4$ to give a mixture of compounds **2**, **3**, and **4**, shown by direct chromatographic comparison.

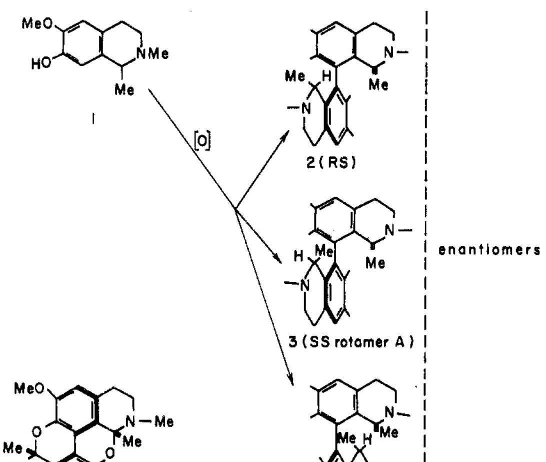
Electrooxidation of racemic **1** under a variety of conditions yielded only the isomer melting at 226–227°.[4] Of the three dimers, only **3** and **4** have the same configuration at C-1 of both isoquinoline rings. Since oxidation of the separated enantiomers of **1** (both *R* and *S*) yielded the enantiomers of the same products as obtained from racemic **1**, the single electrochemical product must be **3** or **4**, and must result from the coupling of identical stereoisomers of **1**. Oxidation of the separated enantiomers of **1** with $K_3Fe(CN)_6$ (which is not stereospecific)[5] yielded the appropriate enantiomers of **3** and **4** having the melting points of the two crystalline isomers (132–134[6] and 224–226°). Since both of these products must have identical configurations in the isoquinoline rings, the third noncrystalline dimer from the catalytic oxygenation of racemic **1** must have structure **2**. When the NMR spectra of the two crystalline dimers were measured in deuterated dimethyl sulfoxide, the C–CH_3 protons appeared at δ 0.71 for the compound melting at 226–227° and at δ 1.17 for the one melting at 132–134° (as compared with δ 1.22 in **1**). Molecular models of the two possibilities show that the CH_3 in **3** is located on top of the benzene ring whether the methyl group is axial or equatorial. In **4**, the methyl group is well away from the benzene ring when in the axial position but fairly close to it when

Table I. Oxidation of Racemic 1 and Its Enantiomers

Substrate, method	Products % yield (% conversion[a]) 2	3	4	C, R = CH_3	D, R = CH_3	C–C/ C–O–C[b]	Potential, V vs. SCE
rac-1							
$K_3Fe(CN)_6$[c] in NH_4OAc	11.4	8.3	4	2.8	1.8	8.5	
Electrolytic							
Excess NaOMe							
1 compartment		40.8 (44.4)		24.3 (26.5)		1.7	+0.16
2 compartment		68.9 (76.9)		6.8 (7.7)		10	+0.04
Sodium salt							
1 compartment		31.9 (32.9)		16.8 (17.8)		1.8	+0.01
2 compartment		41.1 (44.6)		22.2 (24.1)		1.8	+0.01
Neutral							
1 compartment		18.5 (24.7)		22.9 (30.4)		0.8	+0.22
2 compartment		47.0 (58.0)		14.8 (18.3)		3.1	+0.24–0.36
Hydrochloride							
1 compartment		10.1 (17.9)		13.8 (24.0)		0.7	+0.8
2 compartment		13.8 (17.4)		8.7 (11.6)		1.6	+0.6–0.8
Excess HCl[d]							
1 compartment		8.4 (21.3)		15.3 (31.6)	8.7 (19.7)	0.5	+1.16
2 compartment		11.1 (18.1)		8.0 (13.9)		1.4	+0.68
(*R*)-(+)-1							
$K_3Fe(CN)_6$ in NH_4OAc		17.4 (18.3)	20.9 (22.2)	4.4 (4.7)	1.7 (1.8)	8.6	
Electrolytic							
Excess NaOMe in two compartments		65.5 (87.3)		6.2 (8.3)		10	+0.16
(*S*)-(−)-1							
$K_3Fe(CN)_6$ in NH_4OAc		25.9 (27.8)	23.5 (25.5)	6.1 (6.6)	2.3 (2.7)	8.0	
Electrolytic							
Excess NaOMe in two compartments		62.2 (71.8)		5.5 (6.3)		10	+0.16

[a] Corrected for recovered starting material. [b] This ratio is the sum of the conversion yields of 2, 3, and 4 divided by C, R = CH_3. [c] Previous chemical oxidations of this compound are summarized in ref 5. [d] Oxidized in 0.1 N HCl.

Scheme II



equatorial. Since the NMR shift is very much like starting material for 4, it seems reasonable to assign structure 4 to the low-melting isomer with the less shielded methyl group. It would also follow that the methyl group is more likely to be in a pseudoaxial position in both compounds, a good possibility in such a sterically hindered situation. Thus, the product of the electrochemical oxidation is 3. The chiroptical properties of the enantiomers of both 3 and 4 have been studied[7] and found to be in general agreement with the assigned structures. It should be noted, however, that the assignments are based entirely on spectral properties and are not really definitive in a chemical sense.

Preparation and Resolution of 1. The racemic benzyl ether of 1 was prepared by a Bischler–Napieralski sequence as described by Strukov.[8] Treatment of this ether with di-*p*-toluoyl-*d*-tartaric acid and crystallization from ethanol yielded the less soluble salt of the *R* isomer. Similar treatment of the partially resolved bases recovered from the *d*-tartaric acid reaction with di-*p*-toluoyl-*l*-tartaric acid yielded the crystalline salt of the *S* base. The two salts had identical melting points and opposite rotations and were decomposed and debenzylated to yield the enantiomers of 1. These enantiomers had identical properties and equal and opposite rotations and ORD curves. The absolute configuration of the enantiomers was established by methylation to yield carnegine (6,7-dimethoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline) of known configuration.[9]

Potassium Ferricyanide Oxidation of 1 and Its Enantiomers. Racemic 1 was oxidized with $K_3Fe(CN)_6$ in an NH_4OAc system to yield the products shown in Table I. All three isomers of B (2, 3, and 4, R = CH_3) were separable and were characterized. Although C surely exists as a mixture of diastereomers, they could not be separated. A low yield of the polycyclic ether D (R = CH_3) was also obtained.[5] Corresponding oxidation of the enantiomers of 1 yielded the enantiomers of 3 and 4, presumably one enantiomer of C (R = CH_3), and an optically active form of D (R = CH_3).[10]

Electrolytic Oxidation of 1 and Its Enantiomers. The oxidations were carried out under various conditions and yielded the products shown in Table I. Except for the acid oxidations, the solvent was wet acetonitrile and the electrolyte was tetraethylammonium perchlorate. Graphite felt anodes and platinum cathodes were used as previously described.[3] As portions of other work, the effect of platinum anodes[2,11a] and carbon paste anodes[11b,11c] in this reaction were studied. In both cases, very low yields of carbon–carbon dimer were isolated. Isomer 3 was the only carbon–carbon dimer isolated from *any* of the electrochemical reactions. The absence of isomers 2 and 4 was shown by direct comparison of the NMR spectra of the crude reaction mixtures with those of the pure isomers and by direct TLC comparison using wedge-shaped layers. Attempts were made to equilibrate the isomers **2**, **3**, and **4** at 30° in aqueous acetonitrile containing electrolyte and acid or base, but no change was observed. Only in the case of the acid oxidations was any of compound D (R = CH_3) obtained.

The enantiomers of **1** were oxidized under the optimum conditions (excess NaOMe) found for racemic **1** with the results shown in Table I.

Discussion

Three aspects of the data in Table I merit discussion: the stereoselectivity of the reaction; the variation of the ratio of carbon–carbon to carbon–oxygen–carbon dimers under various conditions; and the general mechanism of the electrolytic oxidation. The stereochemistry will be considered first since it may well underlie a discussion of the other aspects.

The stereochemical results of this work can best be explained as arising from a surface reaction, presumably at or near the electrode surface. While it seems logical to assume that electrochemical reactions are surface phenomena, this has not usually been thought to be the case. Most of the electrochemical reactions studied for stereochemical reasons have been reductions as recently summarized by Fry,[12] although oxidation has received attention from Eberson and Nyberg.[13] In all of this work as well as in recent experiments concerning asymmetric induction in electrochemical systems,[14] only a partial control has been attained, and there has been some controversy about whether electrochemical reactions involve surfaces at all.

It is generally accepted[15] that the electrode surface is covered with a more or less highly ordered system of solvent molecules and solvated electrolyte ions known as the *electric double layer* or more recently the *electrified interface*. This coating may extend into the solvent as much as 50 Å and is covered in turn with a second layer known as the *diffuse layer* which may extend another 100 Å.[13] Reactions can be visualized as taking place in the outer regions of these layers where the actual electrode surface would play a minimal role or in the inner region where the surface may play a major role. Thus, in order to observe surface phenomena similar to those found in catalytic hydrogenation, substrate molecules would have to show an attraction for the electrode surface sufficiently strong to penetrate the double layer before reaction. In the reactions described in this paper, the attraction between electrode and substrate should be quite strong, at least in base solutions. The working electrode, the anode in this case, is positively charged and the isoquinoline substrate (**1**) is an extremely electron-rich system with two oxygens (one an anion), an aromatic ring, and one nitrogen. Furthermore, the electron-rich centers or *binding sites* are spread over the whole molecule so that the molecule should be arranged in a plane parallel to the surface. This has, in fact, been shown for some of our isoquinoline molecules by Braun and Stock[16] using solid graphite electrodes and methylene blue as a standard. It has recently been shown that adsorption of aromatic rings to the anode plays a role in the product distribution from the Kolbe reaction,[17] and amine adsorption has been used extensively by Weinberg to explain reaction products.[18] Such an explanation is less valid in acid, but, as shown in Table I, the experimental conditions and results are also quite different in acid. Higher potentials must be used and the overall yields are relatively low. It should be noted that the best yields of carbon–carbon dimers are obtained in strong base where the phenol is present as an anion.

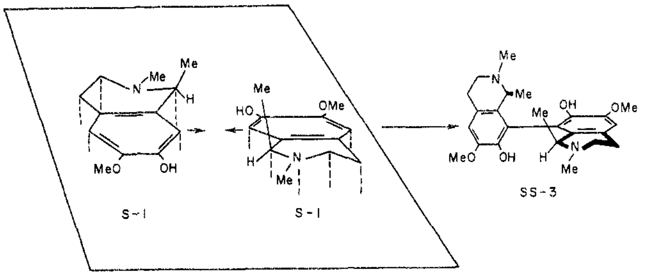


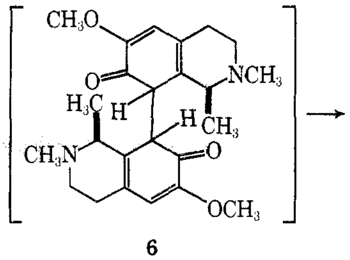
Figure 1. Oxidative coupling of (*S*)-**1** to *SS*-rotamer A, **3**.

If one assumes a surface reaction of molecules in a near-planar conformation, the electrolytic oxidation of **1** to **3** can be easily explained. Two facts must be accommodated: only molecules having the same configuration at C-1 can couple to form carbon–carbon dimers; and of the two possible configurations around the biphenyl bond (**3** and **4**), only one is formed. Reasoning from experience in catalytic hydrogenation, one would assume that the isoquinoline molecules would be adsorbed to the surface with the C-1 methyl group sticking up as shown in Figure 1. Under these conditions, only molecules having like configurations can come close enough together for carbon–carbon coupling to take place at C-8. When molecules having unlike configurations at C-1 are involved, a serious methyl–methyl interference prevents reaction. Thus, either **3** or **4** should result from the coupling of **1**.

The formation of **3** rather than **4** requires more subtle argument. On the basis of steric reasoning alone, one might expect **4** to be formed since the two methyl groups would then be pointed away from one another and would be in a separate quadrant of the molecule (assuming that the benzene rings are perpendicular to one another and that the molecule is bisected by two planes through them). In the actual product, **3**, the methyl groups face one another in the same quadrant. The formation of **3** can be explained superficially[1a] if one assumes that the isoquinoline rings are not completely parallel with the surface, but are tilted so that the more planar aromatic ring is closer to the surface than the aliphatic heterocyclic ring (Figure 1). If coupling takes place from these tilted conformations and rotation around the biphenyl bond is forbidden after coupling, **3** will be formed exclusively.

It has been pointed out by a reviewer, however, that such a superficial view may not be correct. The following rationale is a blend of his ideas and ours. The intermediate arising from the coupling of **1** will have either structure **6** or **7** depending upon whether the coupling is free radical (**6**) or ionic (**7**) (see below). If **6** is formed first, it must go by suc-

21 →



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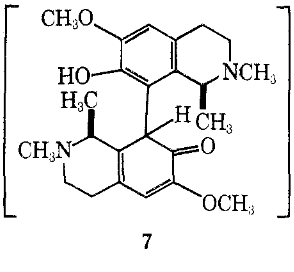
6



→ 3

7

cessive deprotonation to **7** and to **3**. The exact nature of this deprotonation would determine the structure of **3**. Since the stereospecificity is lost when the oxidation is carried out in solution with ferricyanide (which should also proceed through intermediates **6** and **7**), it seems that the surface or its coatings must still play a role in the deprotonation. If the protons are removed from the intermediate from the surface side of the dimer while it is in place on the surface, or is just leaving, the product should be **3**, possibly owing to the superficial "tilting" argument given above. Since the electrode would be expected to contain base sites, either methoxide ions or water molecules, in its double layer (see above), such a deprotonation is quite plausible. This deprotonation by surface adsorbed base sites could then explain a stereospecific removal of protons and would be tantamount to arguing that deprotonation takes place from a least hindered side. If the "tilting" argument is rejected, it could be rationalized that the conformation of intermediate **7** is such as to produce **3** when the proton is least hindered and most subject to removal. From a study of the Dreiding models of **7**, this would be quite reasonable.

The question of whether carbon–carbon (B) or carbon–oxygen–carbon dimers (C) are formed has been quite important in natural systems[19] where both do occur, but generally not simultaneously. In chemical systems[5c] attempts have been made, with limited success, to find experimental conditions leading to one type of bonding or the other. In electrochemical systems, we have observed in simple isoquinoline systems[2] that steric hindrance around the bond being formed plays a strong role in product distribution. Furthermore, in simple isoquinoline systems (ref 2 as compared with this paper) and in 1-benzylisoquinolines[20] we have found that carbon–carbon dimers are formed predominantly but not exclusively in wet acetonitrile systems whereas the reverse is true in aqueous systems. From the arguments presented above, it is reasonable to assume that carbon–carbon dimer formation is a surface reaction. As a corollary, one might assume that carbon–oxygen–carbon dimer formation might take place away from the surface. If this were true, no stereochemistry would be involved and one should obtain both isomers of the carbon–oxygen–carbon dimer (C) owing to the two asymmetric centers when R is a substituent other than hydrogen. Although such isomers were not obtained when R = CH_3 (probably owing to the difficulties of the separation), they were obtained when R = benzyl[20] or when R = ethyl.[2] Thus, it seems fairly reasonable to assume that carbon–carbon dimers are surface products and carbon–oxygen–carbon dimers are not. Some type of adsorption, or lack thereof, which is controlled by solvent factors appears to be involved.

The mechanism of phenol coupling has generally been assumed[19,21] to be a radical coupling reaction. Radical intermediates have been observed by electron spin resonance and coupled products have been obtained. McDonald and Hamilton[22] have categorized the various radical processes which might take place, but they have also suggested that biosynthetic coupling processes may take place by concerted migrations of electron pairs. Ronlán and his co-workers[23] have made a detailed study of the electrochemical oxidation of phenols and have found that phenoxonium ions, as formed by loss of two electrons, seem to explain the results best. The phenoxonium ions attack a neutral molecule to form a coupled product[23a] or can react with a convenient nucleophile such as hydroxide to form hydroxydienones.[23b]

Since our isoquinoline substrates are quite similar to natural substrates and there should be a similarity between enzyme-surface reactions and electrode-surface reactions, we believe that the carbon–carbon coupling as shown in Figure 1 takes place by a two-electron migration process. The carbon–oxygen coupling (to form C) may take place by a similar two-electron migration, or it may be a radical coupling reaction.

Finally, we would like to suggest that stereoselective electrochemical reactions are more likely to take place under the following conditions. First, oxidations should be more promising than reductions since one has a possible electrostatic attraction between the positively charged anode and the type of electron-rich molecules which are likely to undergo oxidation in the first place. Furthermore, most of the molecules dealt with in organic chemistry have π electron systems in double bonds or aromatic rings[17] and oxygen or nitrogen atoms with their free pairs of electrons. Second, stereoselective reactions are more likely to take place with polyfunctional molecules where there are a number of binding sites spread over the molecule to help penetrate the double layer and to bring about a tight, highly oriented conformation on the electrode. Finally, of course, the molecule must be sufficiently complex that a preferred type of adsorption will take place.

Experimental[24] Section

Resolution of the Benzyl Ether of 1. A solution of 2.702 g of (−)-*O,O*-di-*p*-toluoyl-*d*-tartaric acid in 20 ml of ethanol was combined with 2.079 g of racemic benzyl ether[8] in 200 ml of ethanol. The crystalline precipitate which formed was collected by filtration and recrystallized from methanol to give 0.960 g (40%) of the tartrate of the *R* isoquinoline (as shown later) as colorless needles, mp 177–178°, $[\alpha]^{22}\mathrm{D}$ −68.7° (*c* 1.0, methanol).

Anal. Calcd for $C_{39}H_{41}NO_{10}$: C, 68.36; H, 6.03; N, 2.04. Found: C, 67.97; H, 6.09; N, 2.01.

The mother liquor from the preceding experiment was evaporated to dryness, basified with 10% aqueous KOH, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried (K_2CO_3), and evaporated to yield 1.1 g of pale yellow gum. This gum was dissolved in 100 ml of ethanol and treated with 1.35 g of (+)-*O,O*-di-*p*-toluoyl-*l*-tartaric acid dissolved in 10 ml of ethanol. The crystalline compound which formed was collected by filtration and recrystallized from methanol to give 1.1 g (46%) of the tartrate salt of the *S* isomer of the isoquinoline as colorless needles, mp 177–178°, $[\alpha]^{22}\mathrm{D}$ +69.4° (*c* 1.0, methanol).

Anal. Found: C, 68.05; H, 6.05; N, 1.89.

The tartrates were decomposed by suspending them in benzene (3 g in 200 ml) and basifying with 10% aqueous KOH. The benzene layer was washed (H_2O), dried (K_2CO_3), and evaporated to yield a colorless gum. The *R* isomer was obtained in quantitative yield and had a rotation of $[\alpha]^{22}\mathrm{D}$ +30.1° (*c* 1.0, methanol). The *S* isomer was obtained in 82% yield and had a rotation of $[\alpha]^{22}\mathrm{D}$ −29.7° (*c* 1.0, methanol).

(*R*)- and (*S*)-1,2-Dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (1). The optically active benzyl ethers (1.0 g) were dissolved in 10 ml of ethanol, and 10 ml of concentrated HCl was added. The mixture was heated under reflux for 1.5 h and evaporated to dryness. The residue was basified with NH_4OH and extracted with $CHCl_3$. The extract was washed (H_2O), dried ($MgSO_4$), and evaporated to a residue which was crystallized from acetone to give the optically pure enantiomers of **1**. The *R* isomer was obtained in 58% yield as colorless needles: mp 182–183°; $[\alpha]^{22}\mathrm{D}$ +29.2° (*c* 1.0, $CHCl_3$); ORD (*c* 1.0, $CHCl_3$) $[\phi]$ (λ, nm) +130° (370), 0° (335), −2320° (290), +1680° (260 sh), +1770° (245), +620° (240); ir (KBr) 2950 cm^{-1} (OH); NMR ($CDCl_3$) δ 6.73 (s, 1, aromatic), 6.64 (s, 1, aromatic), 3.89 (s, 3, OCH_3), 3.57 (q, 1, *J* = 7 Hz, $C\mathbf{H}CH_3$), 2.50 (s, 3, NCH_3), 1.37 (d, 3, *J* = 7 Hz, $CHC\mathbf{H}_3$); NMR [$(CD_3)_2SO$] δ 6.57 (s, 1, aromatic), 6.53 (s, 1, aromatic), 3.72 (s, 3, OCH_3), 2.34 (s, 3, NCH_3), 1.22 (d, 3, *J* = 7 Hz, $CHC\mathbf{H}_3$).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.26; N, 6.76. Found: C, 69.37; H, 8.23; N, 6.89.

The *S* isomer was obtained in 67% yield as colorless needles: mp 182–183°; $[\alpha]^{22}\mathrm{D}$ −29.8° (*c* 1.0, $CHCl_3$); ORD (*c* 1.0, $CHCl_3$) $[\phi]$ (λ, nm) −220° (370), 0° (335), +2380° (290), −1690° (260 sh), −1880° (245), −770° (240); ir and NMR spectra were identical with those of the *R* isomer.

Anal. Found: C, 69.30; H, 8.22; N, 6.48.

The *S* isomer of **1** (0.07 g) in 2 ml of methanol–dioxane (1:1) was added to 100 ml of diazomethane solution (derived from 3.0 g of *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide). After 2 days at room temperature, the solvent was removed to yield a pale yellow residue which was dissolved in benzene, washed (10% aqueous KOH followed by H_2O), dried (K_2CO_3), and evaporated to give (*S*)-(−)-carnegine (0.06 g) as a colorless oil, $[\alpha]^{22}\text{D}$ −28.0° (*c* 1.1, ethanol) [lit.[9] $[\alpha]^{22}\text{D}$ −24.9° (*c* 4.45, ethanol)]. The base was converted to a hydrochloride, mp 209–210° (lit.[25] 210–211°). In a similar manner the *R* isomer of 1 was methylated to give (*R*)-(+)-carnegine with an opposite rotation of and identical melting point with that of its hydrochloride.

Potassium Ferricyanide Oxidation of Racemic 1. Racemic 1 (750 mg, 3.6 mmol) in 30 ml of 8% aqueous NH_4OAc and 4 ml of 1 N H_2SO_4 was added, dropwise, to 2.3 g (9 mmol) of $K_3Fe(CN)_6$ in 75 ml of 8% aqueous NH_4OAc. The mixture was stirred for 1.5 h, basified with NH_4OH, and extracted with $CHCl_3$. The extract was washed (H_2O), dried ($MgSO_4$), and evaporated to yield a gum, 470 mg, which was separated by preparative TLC (methanol–NH_4OH, 95:5, on six layers 20 cm × 20 cm × 1 mm) into six bands. The adsorbent containing bands were visualized with uv light, removed from the glass plates, and eluted with methanol. The top band yielded, after crystallization from ether–hexane, 13 mg (1.8%) of the diether D, R = CH_3: mp 201–203° (lit.[5a] 200–205°); NMR ($CDCl_3$) δ 6.64 (s, 2, aromatic), 3.88 (s, 6, OCH_3), 2.78 (s, 6, NCH_3), 1.58 (s, 6, C–CH_3); mass spectrum M^+ *m/e* 408 (calcd 408), 391 base peak.

The second band (from the top) yielded 53 mg of unchanged 1.

The third band yielded 20 mg (2.8%) of the carbon–oxygen–carbon dimer, C, R = CH_3, as a powder, mp 97–100°, from ether–hexane. The material is unquestionably a mixture of stereoisomers, but was identical spectroscopically with the previously characterized material.[2]

The fourth band yielded 60 mg (8.3%) of the carbon–carbon dimer, **3**, mp 226–227°, identical spectroscopically in all respects with the previously characterized compound.[2]

The fifth band yielded 29 mg (4%) of the carbon–carbon dimer, **2**, as a glass, again identical spectroscopically with previously characterized material.[2]

The sixth band yielded 80 mg (11%) of the carbon–carbon dimer, **4**, mp 133–135° as crystallized from hexane–ether. The compound was identical spectroscopically with the previously characterized substance.[2]

Potassium Ferricyanide Oxidation of the Enantiomers of 1. Similar oxidations of the *R* and *S* enantiomers of 1 gave the results shown in Table I. The NMR spectra of the enantiomers of the four products were identical with those of the racemic products. However, the melting points were somewhat different. For the products of the *R* isomer, they follow: 212–213° for D, R = CH_3; 109–110° for the carbon–oxygen–carbon dimer C, R = CH_3; 164–165° for **3**; and 175–178° for **4**. For the products of the *S* isomer, they follow: 209–211° for D, R = CH_3; 111° for C, R = CH_3; 162–165° for **3**; and 176–178° for **4**. Since **2** requires isoquinolines with opposite configurations at C-1, it could not be formed from the enantiomers and was not, in fact, observed.

Electrooxidation of Racemic 1 and Its Enantiomers in Excess Sodium Methoxide.[26] Racemic 1 (600 mg, 2.9 mmol) was dissolved in 115 ml of 0.1 M $NaOCH_3$ in methanol and evaporated to a slightly colored gum. This gum was dissolved in a mixture of 300 ml of CH_3CN and 10 ml of H_2O, and 4.0 g of tetraethylammonium perchlorate was added. The solution was cooled to 5–10° and oxidized in a two-compartment cell using a graphite felt anode (6 × 20 cm),[27] a platinum cathode, and an SCE reference electrode.[28] The compartments were separated by a fritted glass disk; nitrogen was continuously bubbled through the cooled mixture; and the potential was controlled at +0.04 V. The initial current of 35 mA fell to 15 mA over a period of 4 h, when TLC showed that very little starting material remained. The solution was removed from the cell, and the felt electrode was washed with methanol.[29] The reaction mixture and washings were acidified with HCl and concentrated to a pale brown gum which was subsequently basified with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed (H_2O), dried ($MgSO_4$), and evaporated to dryness. Preparative TLC was used as described previously to separate the mixture into starting material (63 mg), carbon–oxygen–carbon dimer (42 mg, 6.8%), and **3** (413 mg, 68.9%). Careful TLC of the crude reaction mixture as well as the various bands as they were removed failed to show the presence of either **2** or **4**. The yields as corrected for starting material are given in Table I.

Oxidations of the enantiomers of 1 under identical conditions gave the results in Table I. The melting points of the products were the same as those found in the ferricyanide oxidations. The optical properties of the products are as follows: for C, R = CH_3, from the *R* isomer, $[\alpha]^{22}\text{D}$ +12.0° (*c* 0.11, CH_3OH); for **3** as derived from the *R* isomer, $[\alpha]^{23}\text{D}$ −17.8° (*c* 1.0, CH_3OH), ORD (*c* 0.02, C_2H_5OH) $[\phi]$ (λ, nm) 0° (330), +80° (306), −1280° (292), +640° (271), +350° (254), +470° (246), +260° (240); for C, R = CH_3, from the *S* isomer, $[\alpha]^{22}\text{D}$ −11.2° (*c* 0.25, CH_3OH); for **3** as derived from the *S* isomer, $[\alpha]^{23}\text{D}$ +16.9° (*c* 0.25, CH_3OH), ORD (*c* 0.029, C_2H_5OH) $[\phi]$ (λ, nm) −100° (330), −270° (306), +1370° (292), −1000° (271), −650° (254), −800° (246), −600° (240).[30] The optical properties of D, R = CH_3, are discussed elsewhere.[7]

Electrooxidation of Racemic 1 under Other Conditions. The oxidations in one compartment are self-explanatory.[28] The sodium salts[28] were prepared from equimolar amounts of 1 and $NaOCH_3$ and were oxidized in CH_3CN–H_2O–TEAP as described above. In this case the drop-off of current was almost complete (38 to 2 mA) during the experiment. The reactions were stopped when the current fell to 2–5 mA or when TLC showed that starting material was essentially gone. The neutral reactions were carried out in the same system. In the neutral reactions, the potential was increased from +0.24 to +0.36 V to maintain the current at 31 mA during the 6.5-h experiment (on 400 mg of 1). The hydrochloride reactions were carried out in the same CH_3CN–H_2O–TEAP system on salts prepared with HCl gas in ether. A much higher potential was required as expected,[28] and yields were poor. The excess acid reactions were carried out in 0.1 N HCl. In all cases, the products were isolated as described, and the results are given in Table I.

Equilibration of Isomers 2, 3, and 4. Air was bubbled through a mixture of **3** (150 mg), 200 ml of MeOH, and 750 mg of 10% Pt on carbon[31] for 3 days. The catalyst was removed by filtration, and the solvent was evaporated to a brownish residue. The residue was chromatographed by MeOH–12 N HCl (10:1), and the major zone was isolated to give a crude mixture of 3,4-dihydroisoquinolinium salts. The mixture (43 mg) in 50 ml of MeOH was treated with 100 mg of $NaBH_4$ and heated to reflux for 30 min. The mixture was acidified, concentrated to dryness, and partitioned between $CHCl_3$ and basified (NH_4OH) H_2O. The $CHCl_3$ extract was washed (H_2O), dried ($MgSO_4$), and evaporated to give 22 mg of a colorless gum. Chromatography on shaped layers and direct comparison by chromatographic "spiking" showed that the gum consisted of the three isomers **2**, **3**, and **4**.

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Registry No.—*rac*-**1**, 19641-12-4; (*R*)-**1**, 35048-35-2; (*S*)-**1**, 35053-29-3; *rac*-**1** benzyl ether, 57550-06-8; (*R*)-**1** benzyl ether, 57527-65-8; (*S*)-**1** benzyl ether, 57527-66-9; (*R*)-**1** benzyl ether tartrate, 57527-67-0; (*S*)-**1** benzyl ether tartrate, 57527-68-1; **2**, 57550-07-9; *rac*-**3**, 57550-08-0; (*SS*)-**3**, 35053-14-6; (*RR*)-**3**, 35068-21-4; *rac*-**4**, 57550-09-1; (*SS*)-**4**, 35048-36-3; (*RR*)-**4**, 35048-37-4; **5**, 57550-10-4; C (R = CH_3), 19626-08-5; *rac*-D (R = CH_3), 57605-21-7; D (R = CH_3) from (*R*)-**1**, 57550-05-7; (−)-*O,O*-di-*p*-toluoyl-*d*-tartaric acid, 32634-66-5; (+)-*O,O*-di-*p*-toluoyl-*l*-tartaric acid, 32634-68-7.

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The Chiroptical Properties of Bistetrahydroisoquinoline and Polycyclic Biaryl Derivatives[1]

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The ORD and CD spectra are described for the atropisomers of 8,8′-bis-1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**2**), which were prepared by the electrochemical and chemical oxidation of (*S*)-(−)-1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**1**). The anticlinal isomer **2a**, mp 164–165°, probably has the (1*S*,1′*S*,biphenyl-*S*) configuration and gives CD curves with moderate Cotton effects while the curves of the synclinal isomer **2b**, mp 176–178°, of (1*S*,1′*S*,biphenyl-*R*) configuration vary more significantly with pH. A third product, which may result from cyclization of one of the atropisomers, probably has hexacyclic structure **3b** and is assigned the *S* configuration at both chiral centers and the *R* configuration (*P* helicity) of the biaryl chromophore based on the signs of the high-intensity Cotton effects.

The helicity of ortho-substituted biphenyls has been correlated with chiroptical properties [circular dichroism (CD) and optical rotatory dispersion (ORD)] by Mislow and his collaborators.[2–4] These workers observed that the nature of the substituents had profound effects on the chiral properties, but the inherently dissymmetric chromophore dominated the ORD and CD curves. The ortho,ortho′ substituents were then cyclized to yield bridged biphenyls of known[4a] absolute configuration and helical sense. The size of the ring and nature of the bridge determined the angle from coplanarity (angle of torsion) of the benzene rings. When the bridge stabilized the helicity and lacked additional elements of dissymmetry, the sign of the strongest Cotton effect could be related to the absolute configuration or sense of twist of the molecule.[4b] Since these first observations were made, a number of investigators have discussed the correlation of the ORD and CD spectra in a variety of systems with the helicity of the chromophore.[5,6]

The study of the chiroptical properties of biaryl derivatives produced by coupling of phenolic tetrahydroisoquinolines was undertaken to ascertain the stereochemical consequences of inducing helicity in the biaryl moiety. Since the starting monomeric species possessed a single chiral center at C-1, the dimeric products contain an additional center of dissymmetry, the biaryl, whose helical sense may be predicted from the signs of the circular dichroism Cotton effects. A doubly bridged biaryl also resulted from the electrochemical oxidation, and its helicity may be deduced from ORD and CD measurements which would suggest some steps in the mechanism for its formation.

Bobbitt and co-workers have synthesized chiral biaryl derivatives by the methods described in the accompanying paper.[7] The configurations were assigned from NMR evidence, and confirmation of the assignments was sought by the chiroptical methods described below.

The compounds were prepared by the electrochemical and chemical dimerization of 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline [(±)-**1**], and its enantiomers.[7,8] Bobbitt and co-workers[9] have shown that a bond is formed at the 8 positions, ortho to the hydroxyl