ELECTRO-OXIDATION AND ISOQUINOLINE ALKALOID BIOSYNTHESIS

James M. Bobbitt

Department of Chemistry, University of Connecticut, Storrs, Conn., U. S. A.

Phenol oxidation is one of the major organic reactions used in nature for the production of various metabolites, both primary and secondary, and is especially important in the biosynthesis of the isoquinoline alkaloids. Electro-oxidation can be more precisely controlled than any of the many known oxidation methods and, furthermore, is a heterogeneous reaction with the possibility of surface phenomena. In this article, those areas in which electro-oxidation has been, or may be, used to study biomimetic syntheses of the isoquinoline alkaloids will be summarized.

Introduction

Of all of the various aromatic ring systems which occur in natural materials, especially secondary metabolites, none are so easily oxidized as the phenol system (hydroxyl and aromatic ring)

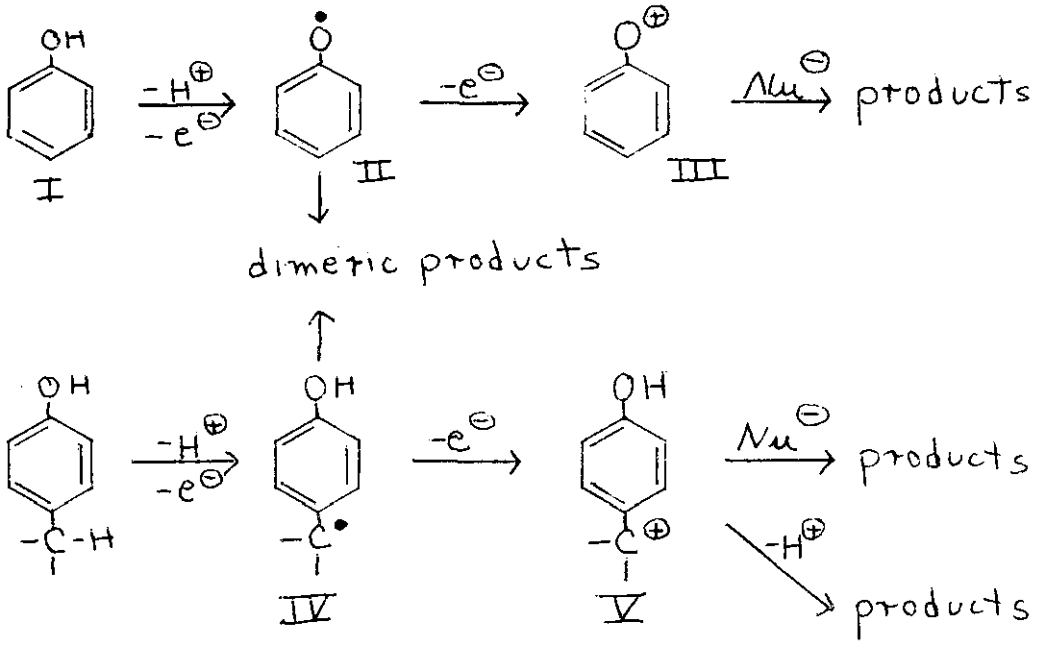
and the indole system, at least according to their half-wave potentials.[1] It is hardly surprising, then, that oxidation of these groupings is one of the major biosynthetic reactions. The special role played by phenol oxidation in nature has long been appreciated and has been well reviewed.[2,3] The isoquinoline alkaloids[4,5] are probably the major group of alkaloids whose biosynthesis is thought to involve phenol oxidation, and many attempts have been made to synthesize these molecules by <u>in vitro</u> oxidations.[6,7] These attempts have not always been successful, and, when they have been, yields have generally been low in the oxidation step. After a successful, but hardly gratifying synthesis of the trimeric isoquinoline alkaloid, pilocereine (XXXIII, R=isobutyl), by chemical [$K_3Fe(CN)_6$] coupling of the monomer, lophocerine (XXX, R=isobutyl) in about 0.3% yield,[8] we turned our attention to electro-oxidation as a more promising oxidizing system.

Controlled-potential electro-oxidations and reductions offer a number of advantages. First, one can use just enough oxidizing or reducing potential to carry out a desired, selective reaction with little fear of overoxidation and can control this potential very accurately. Of course, the method works only as long as the product is less easily oxidized or reduced than the starting material. Secondly, one can control the rate of the reaction by adjusting the electrode size and the potential, and thereby the current flow. Thirdly, one has the possibility of carrying out reactions at an interface with interesting and sometimes unpredictable results. Finally, one can carry out both oxidations and reductions in the same reaction system by simply reversing the charge on the electrodes.

There are some disadvantages. Some instrumentation, namely a potentiostat, is desirable, but several instruments have been developed in recent years and can be purchased for $1,000 - 2,000. One also loses some of the specificity associated with certain ions such as Fe^{+3}, Cr^{+3}, IO_4^-, BH_4^-, etc. since the usefulness of these reagents depends upon coordination properties and ionic sizes as well as their basic oxidation or reduction potentials. However, it is hoped that the development of new electrode systems may correct some of this. A major experimental problem involves electrode coating, either with product or with decomposition polymers. Much of this coating can be alleviated with a change of solvents or with new electrode systems.

Preparative organic electrochemistry in general[1, 9-18] and the electrolytic oxidations of phenols,[19,20] specifically, have been reviewed recently. The oxidation of phenols by one-electron oxidizing agents has been recently summarized.[21] The possible reaction paths can be very complex indeed, and a brief outline is given in Scheme I. In general, a phenol (I) may lose a proton and an electron to give a phenoxide radical (II) in which the radical is localized on the oxygen and in the o and p positions. When an alkyl group is present in the o or p position, some radical character may be developed on the benzyl carbon (IV). These radical species generally dimerize to yield products. Loss of a second electron leads to a phenoxonium ion (III) in which the positive charge is mainly on the o and p positions or, in appropriate conditions, on a benzyl carbon o or p to the phenol (V). Such phenoxonium ions generally stabilize by reacting with any available nucleophile (even another phenol ring) or by losing a proton. Both the radical and the

Scheme I



positive ion can take part in various abstraction processes.

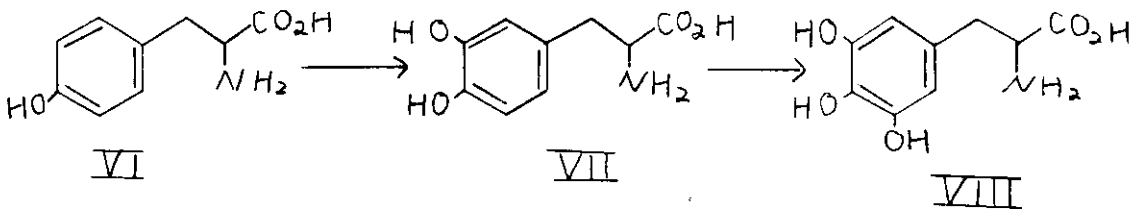
It is not completely correct to call these reactions "phenol oxidations" since the hydroxyl group of the phenol frequently emerges from the reaction unchanged. Actually, it is the aromatic ring which is made susceptible to oxidation by the strongly electron donating phenol group. When additional electron donating groups are present on the ring, oxidation becomes even easier,[1,22,23] and with electron withdrawing groups, it becomes more difficult. Half-wave potentials of p-substituted phenols have been correlated with Hammet functions.[24]

In this article, only those phenol oxidations which may have some bearing on the isoquinoline alkaloids will be considered, and for those reactions discussed, stress will be placed upon the electrochemical aspects.

Hydroxylation Reactions

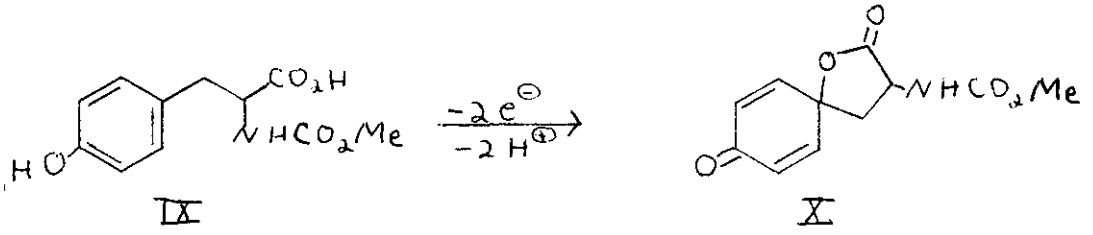
It has been well established that the isoquinoline ring and the 1-benzyl group (when it is present) of the isoquinoline alkaloids are derived biosynthetically from tyrosine (VI).[4,5,25] Such a reaction involves the addition of hydroxyl groups o to the phenol group of tyrosine to give di or trihydroxylated aromatic rings (VII or VIII). These hydroxylations may take place on tyrosine itself or on other simple metabolites.[26] Mechanistic details of these reactions are largely lacking and they are generally considered to be carried out by HO^+ "or its equivalent."

At the outset, it should be stated that tyrosine has not been hydroxylated electrochemically to give VII or VIII. However, there are some aspects of tyrosine oxidation and phenol hydroxylation



VI VII VIII

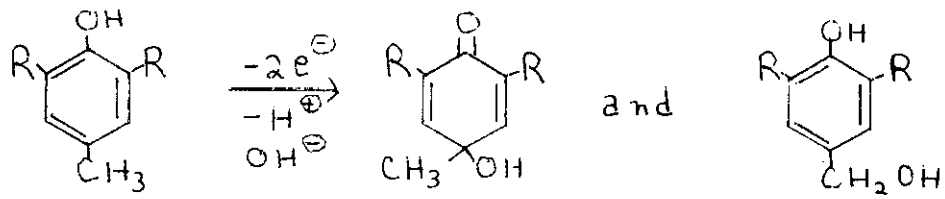
which may be of interest. Tyrosine itself was last oxidized preparatively on a PbO_2 anode by Takayama in 1933.[27] He found that tyrosine was first oxidized to p-hydroxyphenylacetic acid and then to benzoquinone and succinic acid. Under the same conditions, phenylalanine yielded no phenylacetic acid, suggesting that the phenol group of tyrosine was implicated in the oxidation of the amino acid portion. More recently, Scott, Dodson, McCapra and Meyers[28] electro-oxidized N-carbomethoxy-tyrosine (IX) to the spirolactone (X) in 15% yield. The dienone could be formed by an attack of carboxylate on an oxonium ion such as III with the charge localized in the p-position. It has not been established whether a dienone intermediate is involved in the electro-oxidative degradation of tyrosine itself, but it could show how the phenol is involved. Electro-oxidation of peptides containing tyrosine has shown some promise as a selective degradation technique.[29]



IX X

The oxidation of phenol itself generally leads to benzoquinone (probably via a hydroquinone) in good yields,[30] although Fichter had obtained dimeric and polymeric products.[31] In a recent series

of papers,[32-35] Ronlán and Parker and their coworkers have shown that (1) oxidations of phenols with no p-substituent lead to benzoquinones, (2) that when a p-substituent is present, the product is either a hydroxydienone such as XI or a hydroxymethylphenol such as XII depending upon experimental conditions, (3) that these products are almost surely produced by phenoxonium intermediates such as III and V, (4) that attack of the nucleophile (OH^- in this case) is invariably at the p-position and, finally



XI XII

(5) that the lead dioxide anode used by themselves and by Fitcher is probably acting as a chemical oxidizing agent being continuously regenerated.

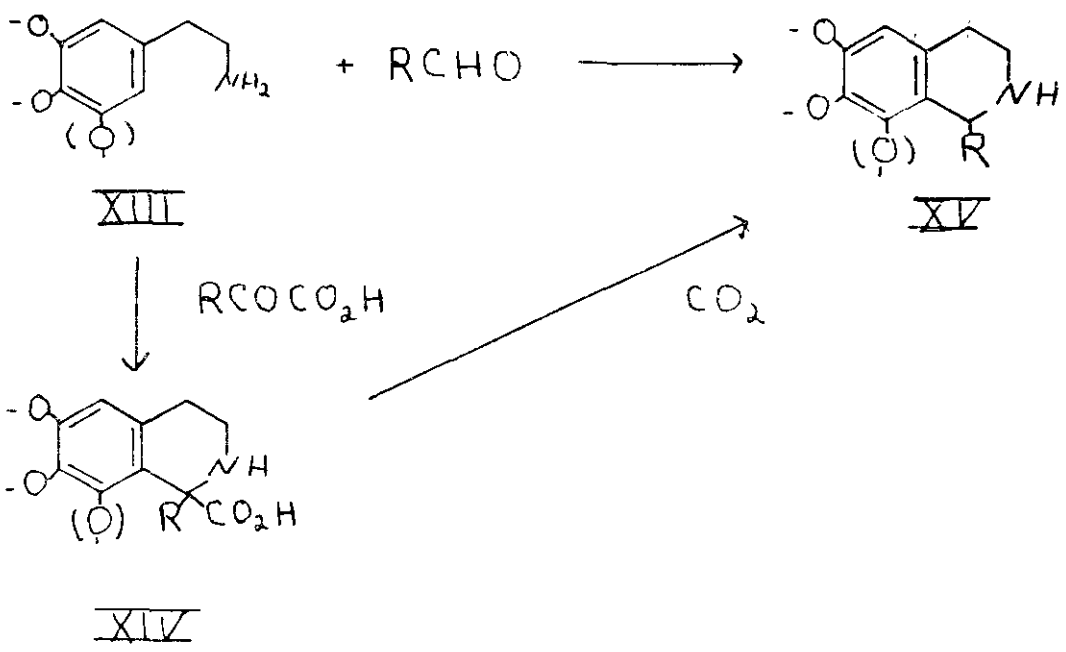
Thus it would appear unlikely that o-hydroxylation of tyrosine such as that needed for alkaloid biosynthesis can be accomplished electrochemically, at least with the present techniques. However, the phenol group may play a role in the oxidation of the amino acid portion of the molecule.

Decarboxylation Reactions

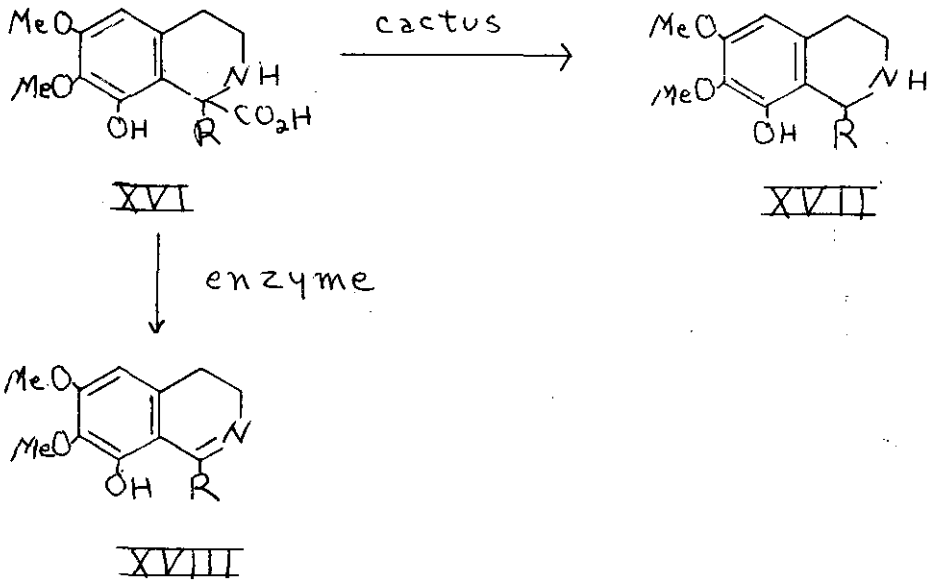
The next step in isoquinoline alkaloid biosynthesis involves the decarboxylation of the amino acids, VII and/or VIII to β-phenylethylamines to form, eventually, the isoquinoline portion of the alkaloids. It is conceivable that electro-oxidation may be applicable to this reaction, especially since tyrosine appears to be decarboxylated readily as shown above,[27] but decarboxylation is so well known in amino acid metabolism,[25] that we will not speculate.

There is, however, a possibility that oxidative decarboxylation may play a role in the following step in the biosynthesis, the ring formation. The tetrahydroisoquinoline ring is derived from two fragments, a β-phenylethylamine such as XIII and a second portion which forms C-1 and any groups attached to it (Scheme II). This second portion is thought to be either an aldehyde which would lead directly to the isoquinoline (XV) or a pyruvic acid derivative which would lead to an amino acid (XIV) requiring subsequent decarboxylation.[36] The pyruvic acid hypothesis was put forth by Hahn[37] and is somewhat more reasonable because the pyruvic acid derivatives required for alkaloid synthesis are known to be available in tissue and are far more stable than the corresponding aldehydes. However, Hahn was not able to decarboxylate XIV under any conditions which may be considered physiological, and the hypothesis was discredited.

Scheme II



It has recently been established,[38] however, that the cactus alkaloids anhalamine (XVII, R=H) and anhalonidine (XVII, R=CH_3) are indeed formed biosynthetically by way of the amino acids XVI which are also found in the plant. This established the Hahn hypothesis for the first time, although the decarboxylation of XVI was not possible under "physiological" laboratory conditions. When XVI (R=H and CH_3) were decarboxylated enzymatically, however, the products were the dihydroisoquinolines (XVIII), thus suggesting the possibility of an oxidative decarboxylation followed by some reduction step to the desired product.

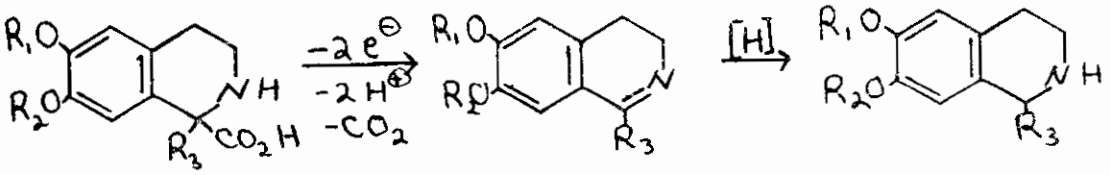


XVI XVII XVIII

We have investigated[39] the oxidative decarboxylation of some amino acids (XIX) similar to XVI on graphite felt electrodes, and have found that the reactions are extremely facile when the aromatic ring is sufficiently activated by phenol groups. In each case the dihydroisoquinoline (XX) was indicated spectroscopically (XXa was also isolated), and the product, XXI, was isolated after reduction with $NaBH_4$. Overall yields were about 80% except for XIXd. In general, when no phenol groups are present (XIXd) in the ring, decarboxylation takes place slowly at +0.6 - 0.8 v (vs. a standard calomel electrode). When one phenol group is present (XIXa, b, and c) decarboxylation takes place at 0.0 - 0.25 v. It is pertinent to note that ring closure with pyruvate (or the aldehyde) takes

place easily only when a phenol group is o or p to the point of ring closure. We are now studying the effect of the various functional groups on the reaction.

Electro-oxidative decarboxylation is, of course, quite a well known reaction.[40] It can take two paths as shown in Scheme III. If the radical dimerizes, it is the Kolbe reaction. If further oxidation takes place to yield the carbonium ion which is stabilized by reaction with a nucleophile, it is the Hofer-Moest reaction.[41] In recent years, it has become apparent that the carbonium ion reaction becomes more important when electron rich groups are in the α-position of the carboxylic acid. For example, phenylacetic acids are decarboxylated in methanol to give benzylmethylethers.[42,43] The extent of normal Kolbe coupling vs the carbonium ion reaction, in fact, has been correlated with the electron donating or withdrawing properties of various substituents in the p-position of phenylacetic acid.[44] In that study, the methoxyl group was the most strongly donating group investigated, and it led to complete carbonium ion reaction. Furthermore the potential required for the reaction was low (+1.39 v vs S.C.E. rather than +2.5 v for phenylacetic acid itself). From this, it would appear that oxidation is taking place first in the aromatic ring. This reaction has been explored in some other aromatic systems[45] and the name "pseudo Kolbe" reaction has been assigned to those instances in which the first oxidation appears to take place in the aromatic ring rather than the carboxyl group. No precise mechanism has been suggested to explain the decarboxylation reaction although one can easily see that stabilized benzyl carbonium ions must



XIX XX XXI

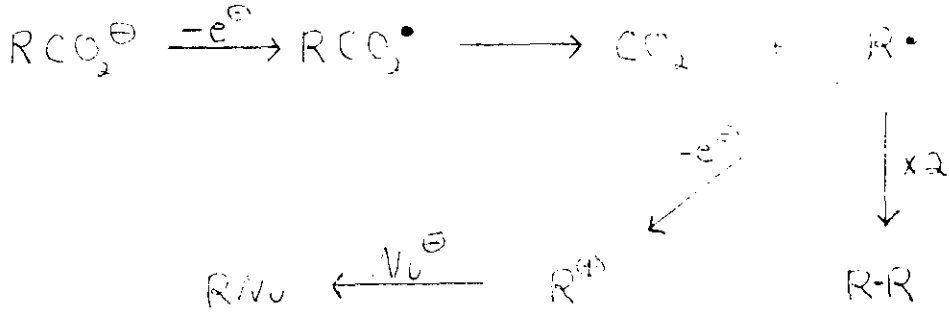
	R_1	R_2	R_3
a	H	CH_3	p-$CH_3OC_6H_4CH_2$-
b	H	CH_3	CH_3
c	CH_3	H	$C_6H_5CH_2$-
d	CH_3	CH_3	p-$CH_3OC_6H_4CH_2$-

play an important role. Thus, the oxidative decarboxylation of XIX to XX might be considered a pseudo Kolbe reaction with an extremely electron rich ring system. The electron pair on the nitrogen serves as the nucleophile. In this context, the electro-oxidative decarboxylation of simple N-acyl aminoacids has been carried out by Linstead, Shephard and Weedon.[46]

Phenol Coupling Reactions

The oxidative coupling of phenols has always been the major point of interest in biomimetic syntheses of the isoquinoline

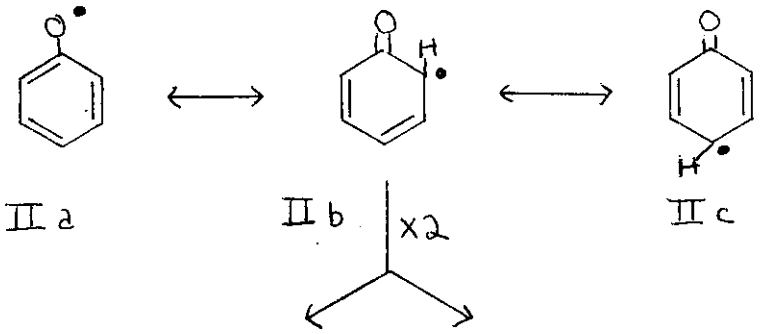
Scheme III

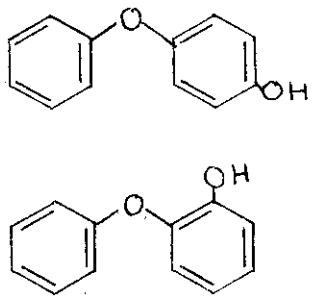


alkaloids,[4,5,6] and a number of chemical oxidizing agents have been explored.[3] The coupling reaction can be visualized as a radical coupling of II (from Scheme I) as shown in Scheme IV. Although radical coupling reactions certainly do take place as such, other mechanisms are possible.[3] In fact, there is a strong feeling that these reactions in living systems probably take place by a concerted two-electron process,[47] and all of the reactions discussed in this article could well be such. A third variation, a non-concerted two-electron oxidation involving a phenoxonium intermediate is possible,[35] and has been shown by Ronlán to take place in electro-oxidations. Finally, it is possible that one ring is oxidized to a quinone system of some type and a second aromatic system adds to it by way of a Michael reaction.[48] Such reactions have been observed in the isoquinolines by Umezawa[49] and Kupchan[50] and their coworkers.

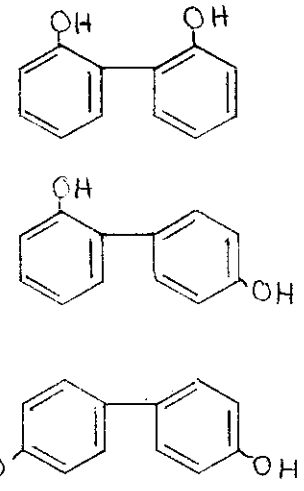
By any of the above mechanisms, two types of products are possible, carbon-oxygen-carbon dimers (from IIa and IIb or IIc) and carbon-carbon dimers (from IIb and IIc). When two phenol

Scheme IV





carbon-oxygen-carbon dimers

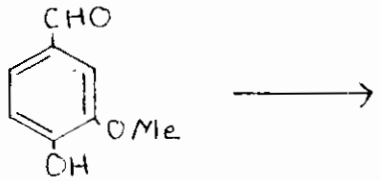


carbon-carbon dimers

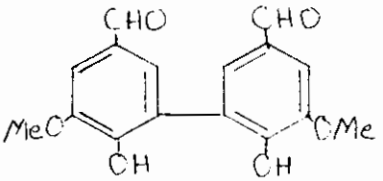
groups are present in the same molecule, intramolecular coupling may take place.

Electrochemical coupling of phenols has not been assiduously pursued until quite recently. Fichter and his coworkers[31,51] obtained carbon-carbon and carbon-oxygen-carbon dimers on lead dioxide anodes, but there is some question about whether the electrodes were actually functioning as electron-transfer agents.[34] In a classic paper, Vermillion and Pearl[52] focussed interest on this area again with an excellent, voltametric study and some preparative examples. Specifically, they coupled vanillin (XXII) to a carbon-carbon dimer, dehydrovanillin (XXIII) in about 65% yield. No carbon-oxygen-carbon dimers were reported. The first paper from our laboratory[53] on the electro-oxidation of phenolic tetrahydroisoquinolines appeared in 1966. This was followed shortly thereafter by papers from Kametani, Ohkubo, and Takano[54] and Johnston[55] on p-cresol (XXIV) and several hydroxyacetophenones respectively (XXVIII). Kametani obtained low yields of a carbon-carbon dimer (XXV), a carbon-oxygen-carbon dimer (XXVI) and Pummerer's ketone (XXVII). The latter compound was also obtained by Scott from electro-oxidation[56] but the experiment was never reported in detail. Reasonable yields (7-53%) of carbon-carbon dimers (XXIX) were obtained from the acetophenones (XXVIII). As stated above, Nilsson, Parker, and Ronlán[34] obtained mainly hydroxylation from simple phenol oxidation. They did, however, obtain some polymeric carbon-carbon linked materials and carbon-carbon dimers from 2,6-and 2,4-xylenols. In a separate paper, Ronlán[35] found that phenoxonium ions could be generated from

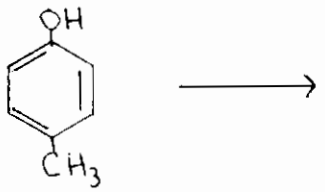
hindered phenols which would react with different phenols and anisoles to give carbon-carbon coupling.



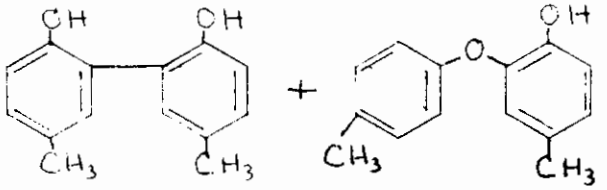
XXII



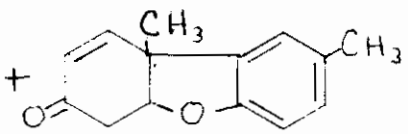
XXIII



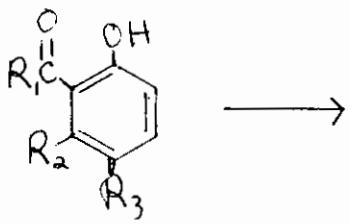
XXIV



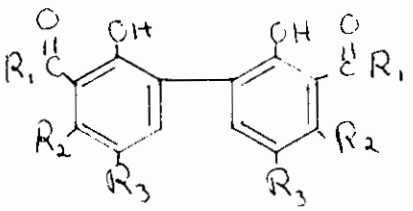
XXV XXVI



XXVII



XXVIII

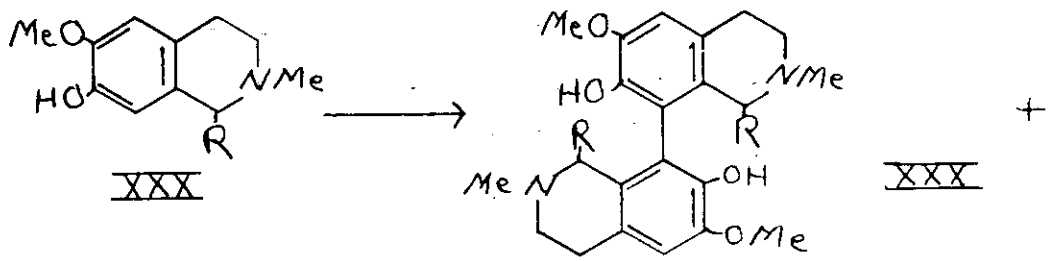


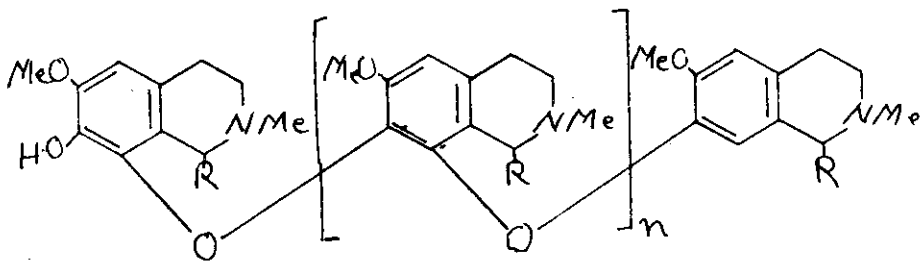
XXIX

Simple Tetrahydroisoquinolines. -- Only two coupled products derived from a simple isoquinoline (defined as an isoquinoline with only alkyl substituents) are known to exist in nature, the trimeric alkaloid pilocereine (XXXIII, R=isobutyl) and its isomer of unknown structure, piloceredine. While pilocereine has been synthesized by chemical oxidation of the monomer, lophocerine (XXX, R=isobutyl),[6,8] it has not yet been prepared by electro-oxidation.

Corypalline (XXX, R=H) and its alkyl substituents were chosen for study primarily because of their availability[57] and secondly because the oxygenation at C-6 and C-7 seemed to be much like that of the more complex alkaloids. Only corypalline is a naturally occurring material. Studies over a period of time showed[58-60] that corypalline could be dimerized electrochemically in overall yields ranging from 44 to 85% depending upon experimental conditions. Chemical and catalytic oxidations have also been carried out on corypalline (see ref. 59 for summary). In general, the product was mainly carbon-carbon dimer (XXXI, R=H) with about 5% carbon-oxygen-carbon dimer (XXXII, R=H). When R was varied from H to methyl to ethyl and the oxidations were carried out on a platinum anode in aqueous systems, the product distribution shifted toward the carbon-oxygen-carbon dimer, the ethyl derivative giving only the carbon-oxygen-carbon dimer. This was interpreted[59] as follows. The normal product in the absence of steric hindrance is the carbon-carbon dimer as it should be from theoretical considerations.[21] When a steric

Scheme V





XXXII, n = 0

XXXIII, n = 1

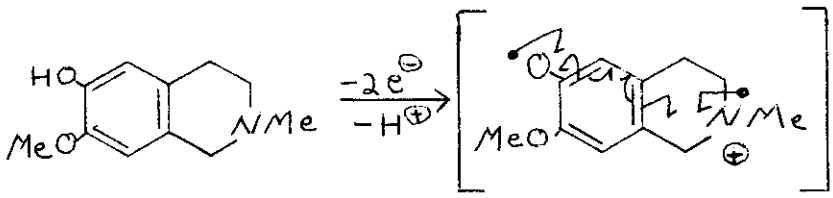
hindrance builds up around the incipient carbon-carbon bond, a carbon oxygen bond forms instead. On the other hand, when the oxidations were carried out on the sodium salts of the phenols in wet acetonitrile, the products were mainly carbon-carbon dimers, even when R was methyl (the ethyl derivative was not investigated under these conditions).

When the isomers of corypalline (XXXIV and XXXV) were oxidized in basic acetonitrile systems, it was found, contrary to expectation, that they yielded carbon-oxygen dimers (XXXVI and XXXVII respectively) with very little, if any, of the carbon-carbon dimer.[60] However, when the electrons on nitrogen were effectively removed by working in acid or by acylation (of the N-nor compounds) the products of corypalline and its isomers were all carbon-carbon dimers. Thus, it appeared that the reactions of XXXIV and XXV in base were anomalous and involved the electron pair on nitrogen. The reaction takes place at a potential of less than +0.1 v (vs. S.C.E.) which corresponds to the oxidation of the phenol group. The oxidation of tetrahydroisoquinoline rings containing methylenedioxy groups instead of phenol takes place at well over +1.0 v.[60] The mechanism shown in Scheme VI was suggested for the oxidation of XXXIV. It involves the removal of one electron from the nitrogen and one from the phenolate to give a cation diradical which is stabilized by electron migration (probably as the electrons were being removed) to an aziridinium dienone intermediate (XXXVIII) which can add phenolate to yield product. Compound XXXV can form a corresponding intermediate while corypalline (XXX, R=H) cannot. One might also propose that the phenol was oxidized to a phenoxonium ion similar to III followed, or accompanied, by internal nucleophilic

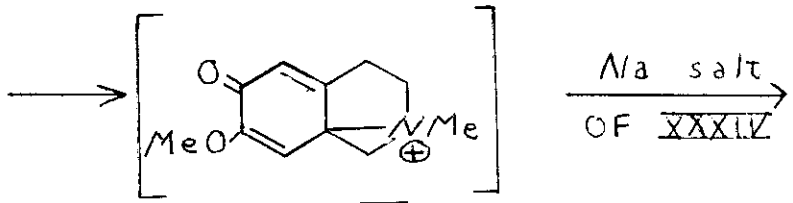
reaction. Perhaps the actual mechanism may be somewhere between these extreme possibilities. The formation of the bond on C-5 in this manner is similar to the quinone addition reactions mentioned previously[49,50] and may well explain the formation of the interesting 5,8 bond in thalidasine (see dotted line in structure).[61] If steric hindrance were an important factor in this case, the carbon-carbon dimer of XXXV should be favored since it is the least hindered diphenyl derivative of the set.

When the sodium salt of 1-methylcorypalline (XXX, R=CH_3) was oxidized in acetonitrile, a good yield of carbon-carbon dimer (69%) was obtained.[62] The reaction showed some remarkable stereochemical features. The dimerization of racemic XXX (R=CH_3) can give rise to three pairs of enantiomers (XXXIXa, b, c) due to the two chiral centers at C-1 of the isoquinoline rings and restricted rotation around the diphenyl bond (Scheme VII). In previous work all three products had been obtained from a catalytic oxygenation,[59] separated, and characterized spectroscopically, although no precise structures had been assigned. The electrolytic oxidation gave only one of the three; XXXIXb, containing the same configuration at C-1 of the two rings and the rotational configuration shown. The structures of the three enantiomers were elucidated by oxidizing optically active forms of XXX (R=CH_3); electrochemically to give XXXIXb, with $K_3Fe(CN)_6$ to give a mixture of XXXIXb and XXXIXc, and with oxygen on platinum to give all three (via racemization of C-1 before or during coupling). Thus, in the oxidative coupling reaction, only isomers having identical configurations at C-1 couple with one another, and only one of two possible rotations configu-

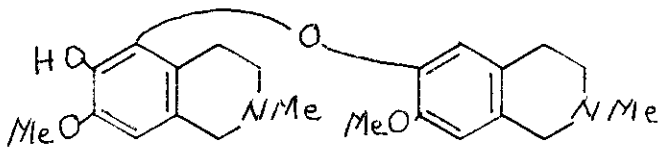
Scheme VI



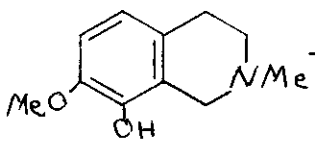
XXXIV



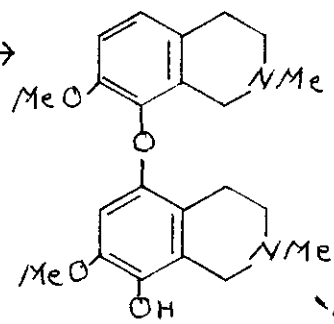
XXXVIII



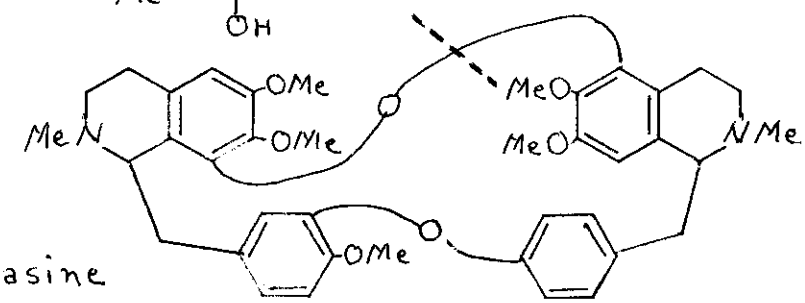
XXXVI



XXXV

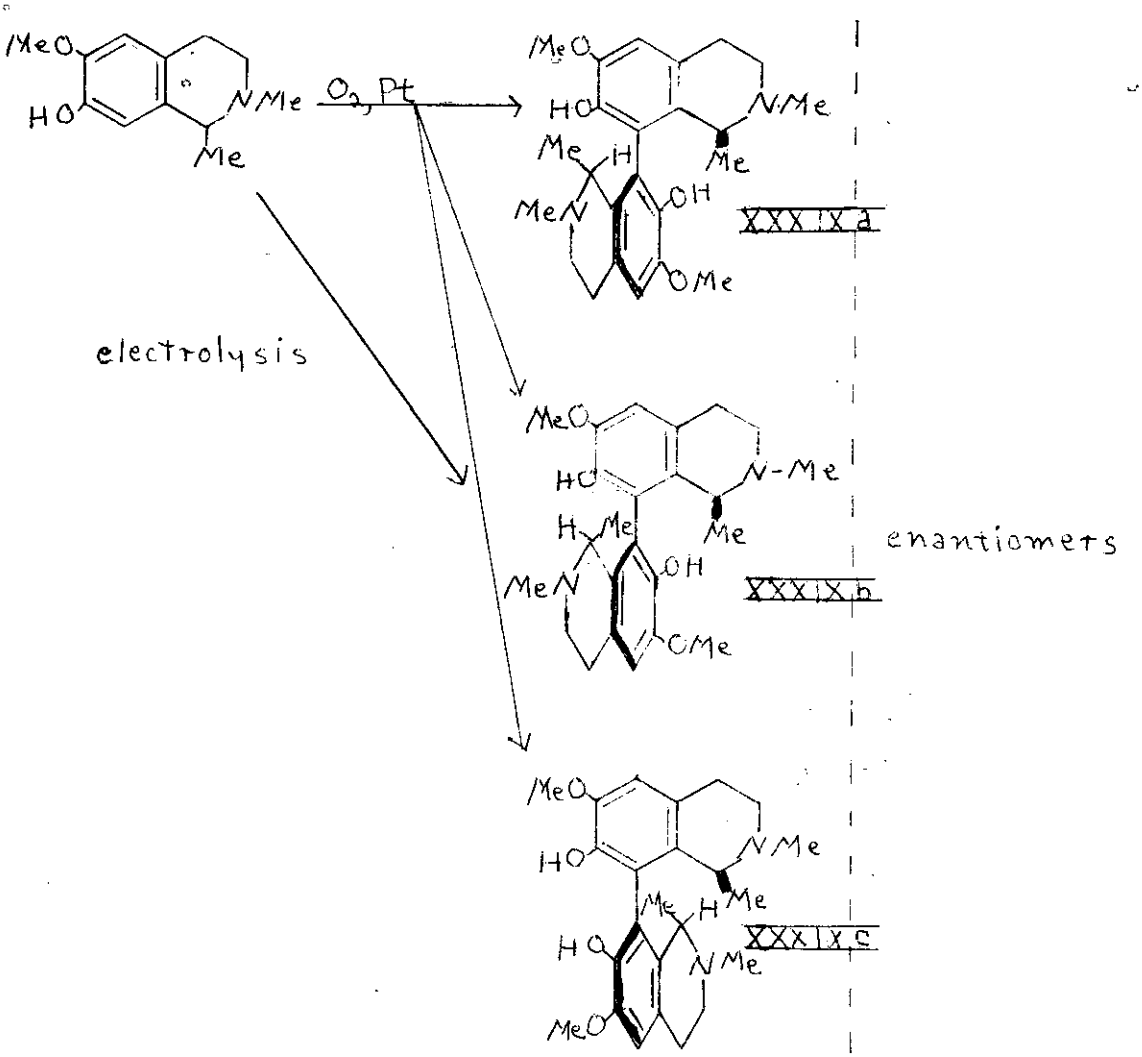


XXXVII



thalidasine

Scheme VII

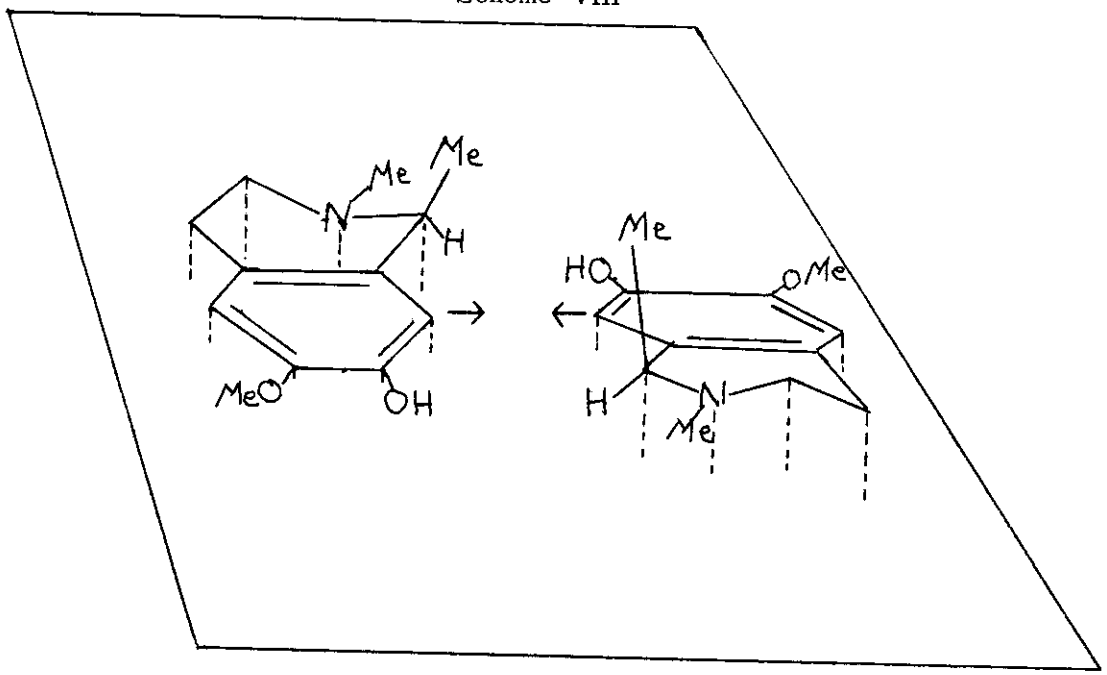

MeO
HO
NMe
Me
O2, Pt
electrolysis
H
OH
OMe
XXXIXa
XXXIXb
XXXIXc
enantiomers

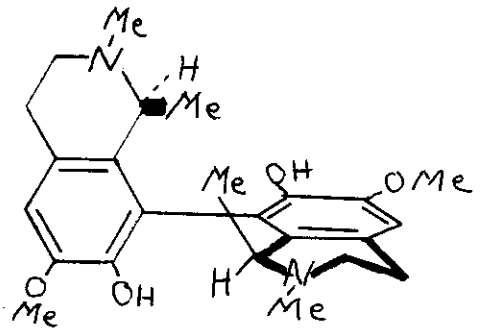
rations is formed.

These results were explained by proposing a surface mechanism in which the isoquinoline rings are adsorbed to the electrode with the methyl group at C-1 sticking up (Scheme VIII). It has been shown, by correlation with methylene blue, that the isoquinoline rings are adsorbed in a planar fashion.[63] If the molecules of XXX ($R=CH_3$) are adsorbed in this fashion and react at the surface as such, only isomers having the same configuration at C-1 can come close enough to couple at the 8-position. Coupling between unlike configurations is prevented by methyl interference. The formation of only one rotational isomer is rationalized by assuming that the isoquinoline rings are not adsorbed parallel with the surface, but are tilted with the aromatic ring being closer to the surface than the aliphatic, heterocyclic ring. If the rings are coupled in such a tilted form and lifted from the surface, the correct isomer (XXXIXb) is obtained. It is worth noting that XXXIXb is actually more hindered than XXXIXc because the methyl groups are much closer together (in the same quadrant if the rings are completely perpendicular to one another). Since the mechanism of the coupling in Scheme VIII is in some doubt, the drawing has been made simply to show how the rings must approach one another and may lie on the surface.

1-Benzyltetrahydroisoquinolines--Intermolecular Coupling.--Intermolecular coupling of benzylisoquinolines generally seems to involve carbon-oxygen-carbon coupling and can be extremely complex. Coclaurine (XL) is the main precursor of about 100 dimeric alkaloids known as the bisbenzylisoquinoline alkaloids,[4]

Scheme VIII



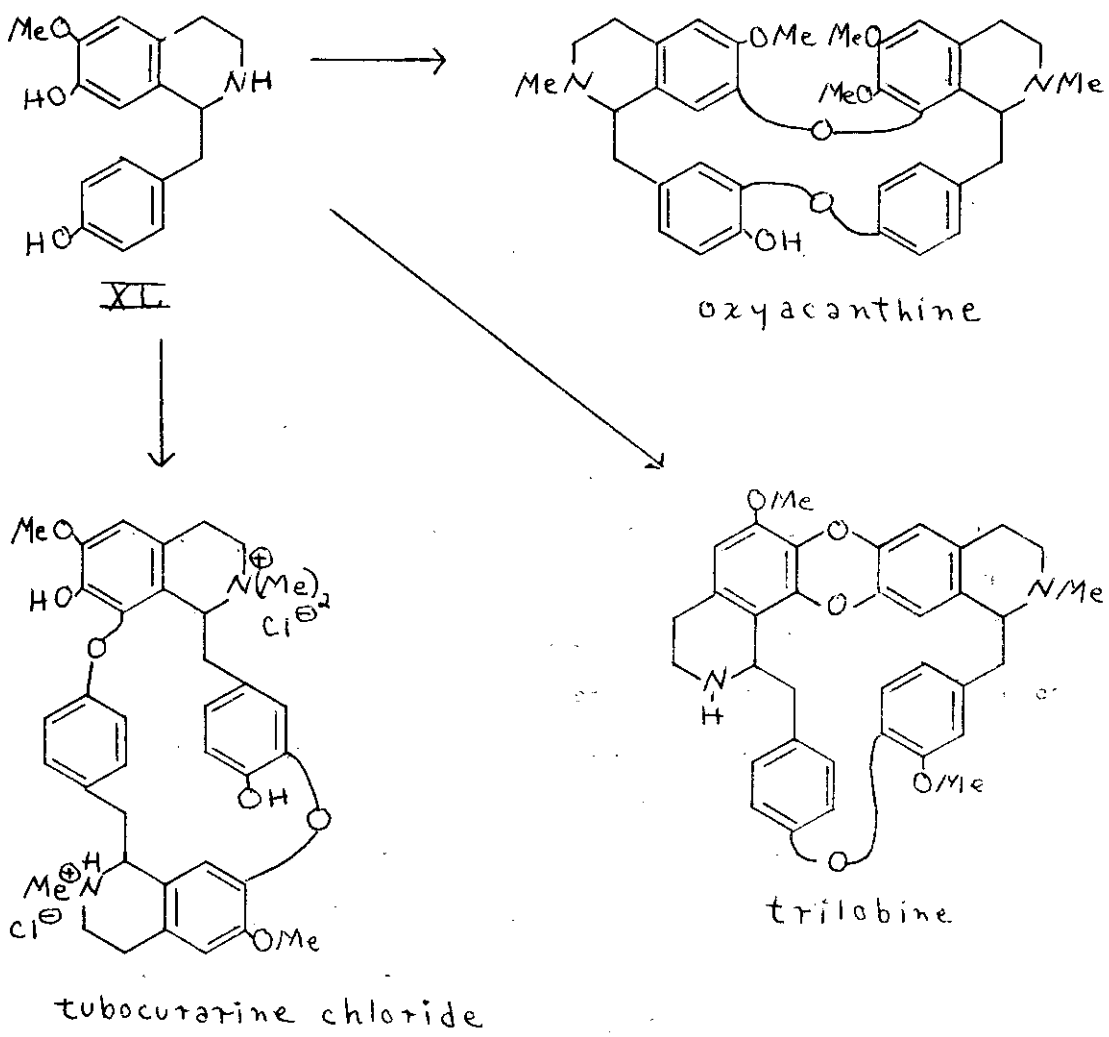


XXXIXb

three of which are shown in Scheme IX. Coupling between the isoquinoline portions is called "head-to-head" and coupling between the benzyl rings is called "tail-to-tail" coupling. Thus, oxyacanthine involves head-to-head coupling whereas tubocurarine involves head-to-tail coupling. Trilobine contains three diphenyl ethers and therefore needs three coupling reactions. Other modes of coupling are known and the natural materials have various degrees of methylation. Two model systems were studied in preparation for the actual electro-oxidation of coclaurine. These were armepavine and its derivatives (XLI) as a model for the tail-to-tail coupling and 1-benzyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline and its derivatives (XXX, R=$C_6H_5CH_2$) as a model for head-to-head coupling.

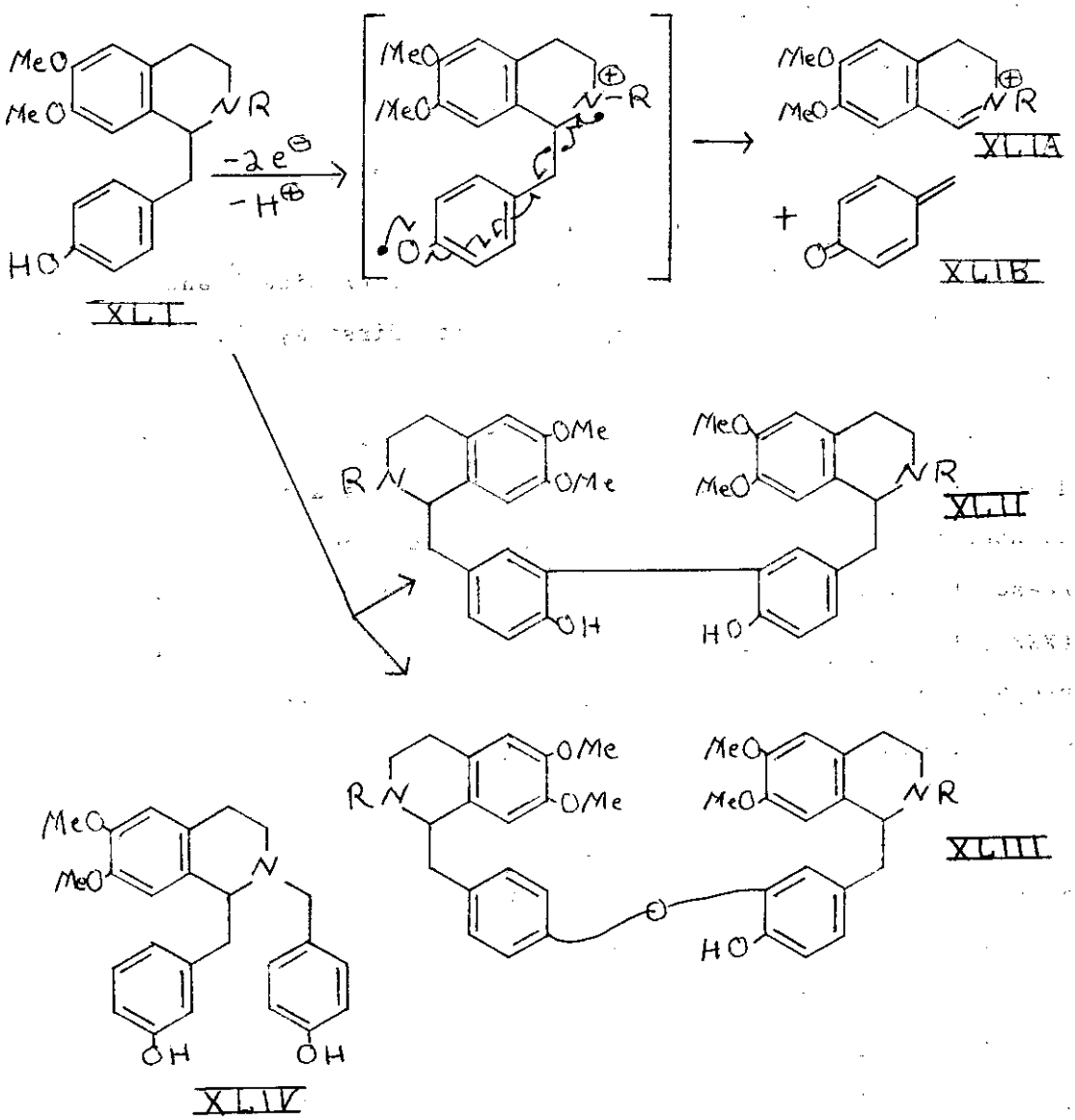
Preliminary oxidations of coclaurine and armepavine indicated a complete lack of coupling products.[64] Instead, a fragmentation of the benzyl sidechain took place resulting in the formation of a dihydroisoquinoline (XLIA) and a quinone methide (XLIB) as shown in Scheme X for armepavine itself (XLI, R=CH_3). The fragmentation is similar to the sequence used previously in Scheme VI for the oxidation of XXXIV and could take place by simultaneous oxidation of oxygen and nitrogen with a movement of electrons as shown in Scheme X. It could equally well occur by removal of two electrons through the phenol with nitrogen serving as a nucleophile again. The yield of the dihydroisoquinolinium ion (XLIA, R=CH_3) was as high as 86%. The fragmentation also took place with N-nor-armepavine (XLI, R=H) with the fortuitous result that starting material trapped the quinone methide to give XLIV in about 5%

Scheme IX


MeO
HO
NH
HO
XL
OMe MeO
MeN
MeO
NMe
OH
oxyacanthine
MeO
HO
N(Me)2
Cl⊖2
OH
Me⊕N H
Cl⊖
OMe
tubocurarine chloride
OMe
NMe
N H
OMe
trilobine

yield. This type of fragmentation was first shown to take place in enzyme oxidations[65] and provides an interesting similarity between enzyme oxidations and electro-oxidation.

Scheme X



When the nitrogen of XLI (R=H) was acylated with ethyl chloroformate, oxidation of the resulting N-carbethoxy derivative produced no fragmentation and reasonable yields of coupled products.[64] The major product was the carbon-carbon dimer XLII($R=CO_2Et$) which was benzylated, reduced with $LiAlH_4$[66] and debenzylated to yield the non-naturally occurring XLII($R=CH_3$), previously isolated from a chemical oxidation.[67] When the crude reaction mixture was treated in the same manner, the alkaloid dauricine (XLIII, $R=CH_3$) could be isolated in about 8% yield after extensive chromatography. The material was identical with synthetic dauricine[68] and its preparation in this manner represents its first synthesis by biomimetic methods.

1-Benzyl-7-hydroxy-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XXX, $R=C_6H_5CH_2$) was investigated as a model for head-to-head coupling.[69] Oxidation under various conditions gave reasonable yields (Table I) of both the carbon-carbon dimer (XXXI, $R=C_6H_5CH_2$) and the carbon-oxygen-carbon dimer (XXXII, $R=C_6H_5CH_2$). Only one carbon-carbon dimer was obtained in accord with the similar oxidation of XXX ($R=CH_3$) as described earlier.

Table I

Oxidative Coupling of XXX($R=C_6H_5CH_2$)

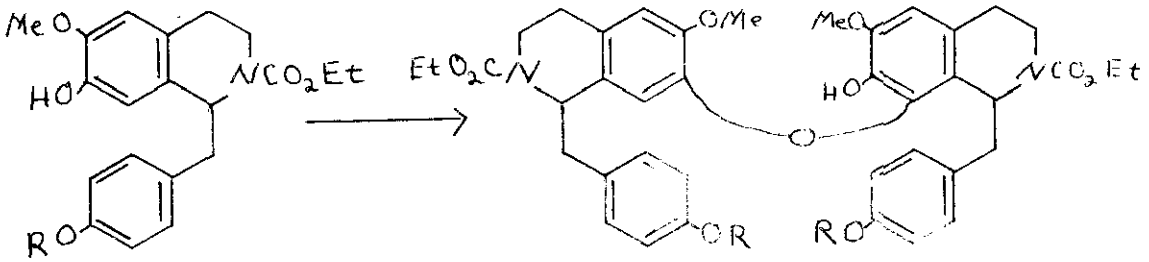
Solvent	C-C/C-O-C Ratio	Combined Yield (%)
99% CH_3CN	2.2	65
75% CH_3CN, 25% H_2O	1.1	67
50% CH_3CN, 50% H_2O	0.28	51
25% CH_3CN, 75% H_2O	0.12	51
100% H_2O	0.09	57

However, two isomers of the carbon-oxygen-carbon dimer were formed, indicating that this type of coupling is not stereoselective. The ratio of carbon-carbon to carbon-oxygen-carbon dimers was found to depend upon the solvent used in the oxidation (Table I). Acetonitrile systems tended to produce carbon-carbon dimers while aqueous systems tended to produce carbon-oxygen-carbon dimers. This same phenomenon can be seen with the simple isoquinolines (compare ref. 59 with 60), but does not seem to apply to compounds containing oxygen in the benzyl ring like coclaurine. While it is apparent that the carbon-carbon dimers are products of surface reactions, any conclusions about the carbon-oxygen-carbon dimers or the phenomenon in general would be only speculation.

At present, the oxidation of N-carbethoxycoclaurine (XLV,R=H) is under study. There is an appreciable difference between the oxidation potential needed to couple the isoquinoline portion of this molecule (about +0.2 v. as found for XXX, R=$C_6H_5CH_2$) and +0.3 v needed to couple the benzyl hydroxyl group (as found for XLI, R=CO_2Et). Thus, it should be possible to make the head-to-head coupling at one potential and then the tail-to-tail coupling at a higher potential, thereby pointing out a significant advantage of electro-oxidative coupling. The oxidation of XLV (R=H) does lead to some head-to-head carbon-oxygen-carbon dimer, but the reaction is accompanied by severe electrode coating, thus exemplifying a serious disadvantage of electrochemical reactions. For this reason, interest has now been shifted to the benzyl derivatives of XLV (R=$C_6H_5CH_2$), and yields of about 70% of the two carbon-oxygen-carbon isomers (XLVI, R=$C_6H_5CH_2$) have been

obtained on graphite felt anodes. The products have been debenzylated, and coupling reactions for the tail-to-tail reaction are underway. No carbon-carbon dimers were observed.

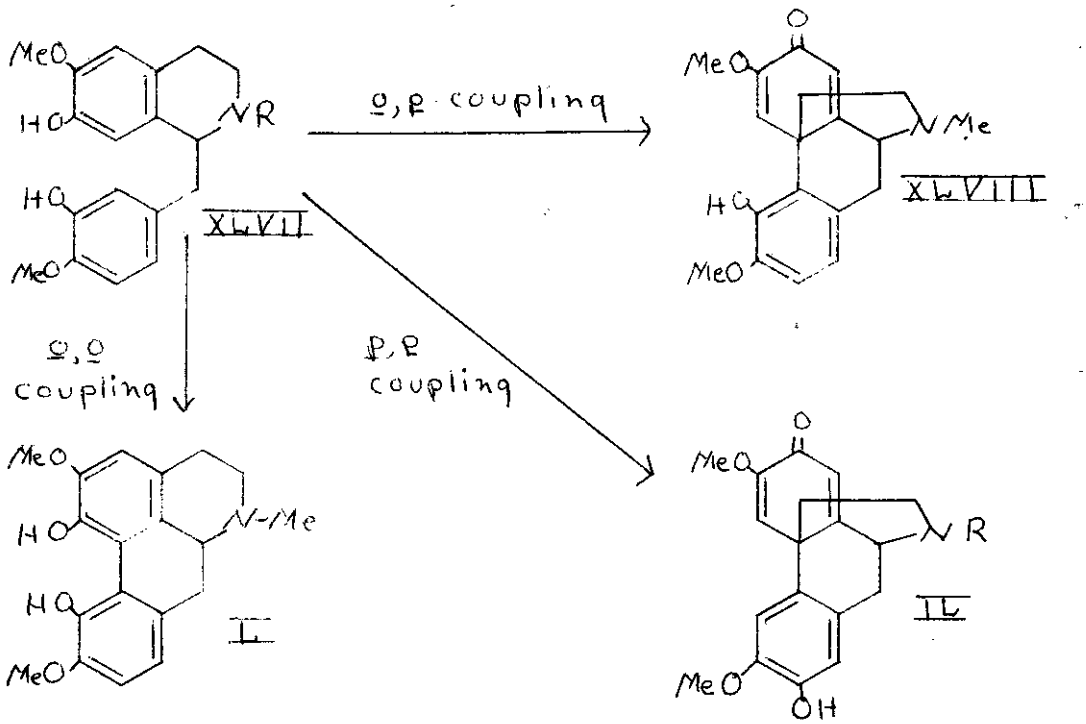
1-Benzyltetrahydroisoquinolines-Intramolecular Coupling.--When two phenol groups are present in separate rings of the same molecule, intramolecular coupling becomes a possibility. Thus, the crucial step in the biosynthesis of morphine would appear to



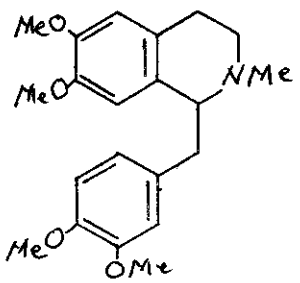
XLV XLVI

be the oxidative coupling of reticuline (XLVII, R=CH_3) to salutaridine (XLVIII) which is subsequently converted to morphine and its derivatives. In 1932, Robinson[70] first suggested the possibility of such a reaction, and, since that time, it has become almost a classic problem to bring about this reaction or reactions similar to it in the laboratory. This work has been recently reviewed.[7] However, with the exception of Barton's synthesis of XLVIII[71] in 0.024% yield, all attempts have resulted in a para coupling leading to isosalutaridine or pallidine (IL, R=CH_3).[7] Yields in the coupling step have ranged from 0 to 4%.[7,72]

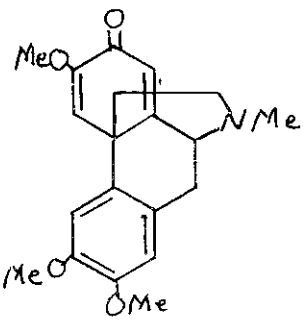
We have now managed to bring about the coupling reaction, albeit also by a para coupling, of N-carbethoxy-N-norreticuline (XLVII, R=CO_2Et) to the dienone (IL, R=CO_2Et) in about 18% yield.[73] The electro-oxidation was carried out on a graphite felt anode in basic t-butanol solution at a potential of about +0.2 v. vs. S.C.E. However, all attempts to improve the yield or to convert the dienone (IL, R=CO_2Et) to known materials have been fruitless. Although these results have not been spectacular, the answer to preparative preparation of the morphinandienone system may still



be in electrochemical oxidation. Miller, Falck and Stermitz[74] have managed to couple the methyl ethers of the benzylisoquinoline compounds to dienones in yields up to 65% (for example LI to LII). The reaction was carried out on a platinum anode in acetonitrile in the presence of palladium chloride.



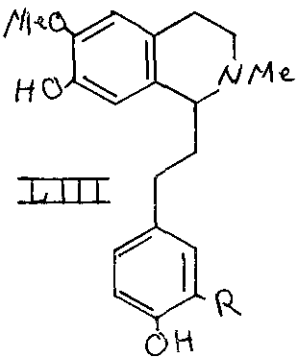
LI



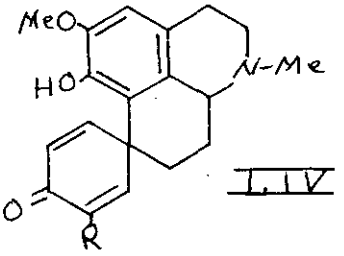
LII

Such intramolecular coupling can also produce aporphine alkaloids such as corytuberine (L), also derivable from reticuline (XLVII, R=CH_3).[5] While such products have been obtained frequently from chemical oxidations,[7] we have, as yet, seen none in the electro-oxidative work.

1-Phenylethyltetrahydroisoquinolines.--Intramolecular Coupling.--Two compounds were investigated in this series, LIII, R=H and LIII, R=OCH_3.[75] In each case, a dienone was isolated from oxidations carried out in aqueous systems on a graphite anode. The potentials used were higher than usual, being +0.7 to 0.8 v (vs S.C.E.). The yields of the two dienones (LIV, R=H and OCH_3) were 23% and 36%, respectively, and were roughly comparable to the yields from chemical oxidations.[76-78] Since LIV (R=OCH_3) has two isomers (one of which is the alkaloid kreysiginone)[78] it was hoped that the electro-oxidation would yield predominately one isomer. However, the isomers were formed in about equal proportions.



LIII

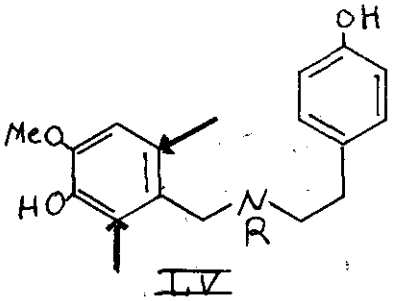


LIV

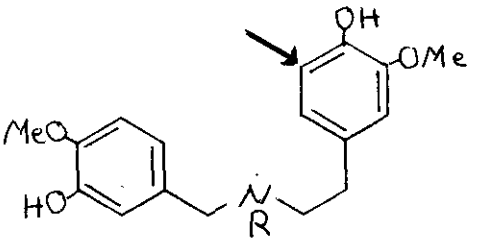
N-Benzylphenethylamine Alkaloids--Attempted Intramolecular Coupling.--An extensive series of alkaloids can be obtained by the intramolecular coupling of oxygenated N-benzylphenethyl amines,[79] and considerable progress has been made in the synthesis of the substances by chemical oxidation.[80,81] We have submitted three of these amines and their derivatives (LV, LVI, and LVII) to electro-oxidation[82] under various conditions. In cases where the nitrogen was not acylated, no products were isolable. When the nitrogen was trifluoroacetylated,[80] only dimers were isolated in yields of about 10%. Mass spectrometry of the dimers indicated that they were probably joined at the positions marked with an arrow on the structures.

Conclusions

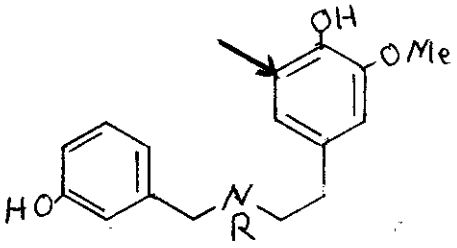
Although this work is still very much in progress, it is possible



I.V



I.VI



I.VII

to make some preliminary observations. From the viewpoint of isoquinoline alkaloid synthesis and biosynthesis, electro-oxidation produces high yields of intermolecular coupled products and mediocre yields of intramolecular coupled products. Furthermore, it may offer clues to biosynthesis, especially in regard to decarboxylation reactions. From the standpoint of preparative organic electrochemistry, the isoquinoline alkaloids present a set of polyfunctional molecules of known structure which can be used to study such reactions as phenol oxidation, oxidative decarboxylation, and stereoselective reactions. In particular, the interactions between amine groups and phenol groups have been most fruitful.

ACKNOWLEDGMENT

The author's work has been carried out with Professor J. T. Stock of this Department and has been sponsored, in part, by Grant No. GP-7601 from the National Science Foundation and Grant CA-10494 from the National Institutes of Health. The author would like to thank Dr. Alvin Ronlán of the Lund Institute of Technology (Lund, Sweden) and Dr. I. G. C. Coutts of the Trent Polytecnic Institute (Nottingham, England) for reading this manuscript and Professor Lennart Eberson of the University of Lund for his hospitality while it was being written.

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