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A Review: Synthesis of Alkaloids by Oxidative Phenol and Nonphenol Coupling Reactions

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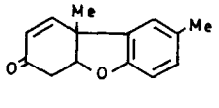
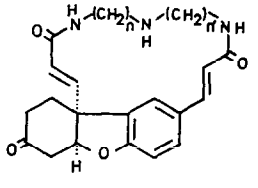
Experiments concerned with biomimetic synthesis of alkaloids by intramolecular oxidative phenol and nonphenol coupling reactions are described. Preliminary investigations of intramolecular and intermolecular oxidative coupling reactions by iron–DMF and iron–DMSO complexes, and intramolecular oxidative coupling reactions by electrochemical methods followed by biomimetic syntheses of crinine, morphinandienone, and phenanthroquinolizidine alkaloids and a new synthesis of the alkaloid colchicine are presented.

Oxidative coupling of phenols plays an important role in the biosynthesis of a wide range of natural products: tannins, lignins, melanins, pigments, antibiotics, and particularly alkaloids. Since the proposal of alkaloid biosynthesis through oxidative phenol coupling presented by Barton and Cohen (*1*) in 1957, many attempts at biomimetic or biogenetic-type syntheses of such alkaloids have been reported (*2*), and this concept has provided very fascinating challenges for synthetic organic chemists to synthesize natural products via routes which are operable or thought to be operable in nature.

Since the laboratory oxidation and coupling of phenols was first investigated by Pummerer early in this century (*3*), various coupling methods have been reported to date, which can be classified as follows: (a) oxidations with metal salts and complexes (*4*), (b) Pschorr-type reactions, (c) photochemical reactions (*5*), (d) electrochemical reactions (*6*), and (e) other chemical methods. The yields of Pummerer's ketone (I) (*7*), a crystalline oxidation product of *p*-cresol, as prepared by various reagents, are shown herein (Table 1), because the oxidation of *p*-cresol is one of the best investigated examples of phenol coupling reactions.



I



II

a: $n = 3, n' = 4$

b: $n = 4, n' = 3$

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Recently, natural products related to Pummerer's ketone, i.e., lunarine (IIa), lunaridine (IIb), and related alkaloids, were isolated from *Lunaria biennis* Moench. (*8*). The characteristic moiety of these alkaloids is obviously derived from the oxidative

TABLE 1

OXIDATION OF *p*-CRESOL

Oxidant	Yield of *I*, %	References
$K_3Fe(CN)_6$, OH^-	20	*7, 10–12*
$K_3Fe(CN)_6$, liquid NH_3	28	*13*
$FeCl_3/H_2O$	1.4	*14*
Fenton's reagent	18	*15*
$MnO_2/CHCl_3$	22	*16*
PbO_2/benzene	18	*16*
$Na_2S_2O_8$, $AgNO_3$	16	*17*
Cu(II)-*o*-toluate	3	*18*
VCl_4	trace	*19*
Electrooxidation	10	*20*
Horseradish peroxidase/H_2O_2	13.4	*21*
Polyporus versicolor (cell-free extract)	50	*22*

coupling of *p*-hydroxycinnamic acid, and the biomimetic synthesis of tetrahydrolunaridine was achieved through oxidative coupling of methyl dihydro-4-hydroxycinnamate with potassium ferricyanide (15% yield) (*9*).

This article describes a series of experiments designed to get better yields in the synthesis of alkaloids by oxidative phenol and nonphenol coupling reactions.

A. INTRAMOLECULAR AND INTERMOLECULAR OXIDATIVE PHENOL COUPLING REACTIONS BY IRON–DMF COMPLEX $[Fe(DMF)_3Cl_2][FeCl_4]$ AND IRON–DMSO COMPLEX $[Fe(DMSO)_4Cl_2][FeCl_4]$

Many transition metal salts and complexes, such as alkaline, potassium ferricyanide, ferric chloride, manganese dioxide and lead dioxide, have been used for intramolecular and intermolecular oxidative phenol coupling reactions, but the yields are frequently low. Recently, a number of new reagents have been reported which appear to give consistently high yields. Three which have proved to be particularly useful in intramolecular coupling reactions are vanadium oxychloride (*23*), tris(acetylacetonate)-manganese(II) (*24*), and thallium(III) trifluoroacetate (*25*). We attempted to discover more useful reagents for these purposes. During the investigation, we found that ferric chloride and dimethylformamide (DMF) form a very stable complex which has the molecular formula $[Fe(DMF)_3Cl_2][FeCl_4]$ and which is a good reagent for intramolecular and intermolecular phenol coupling reactions (*26*). The molecular formula of this complex was assigned on the basis of elemental analysis and visible light absorption spectra at 530 nm due to the $FeCl_4^-$ (*27*) either in the solid state or in nonaqueous solution (Fig. 1).

It is known that ferric chloride and dimethyl sulfoxide (DMSO) form an iron–DMSO complex $[Fe(DMSO)_4Cl_2][FeCl_4]$ (*28*) which is similar to the iron–DMF complex except that it differs in ligand number. We also investigated the iron–DMSO complex as an oxidizing agent and found this complex to be a good reagent like the iron–DMF complex (*29*), except that it is somewhat less useful than the DMF complex by reason of its hygroscopic character.

These iron–DMF and –DMSO complexes can be prepared very easily and stored for a long time.

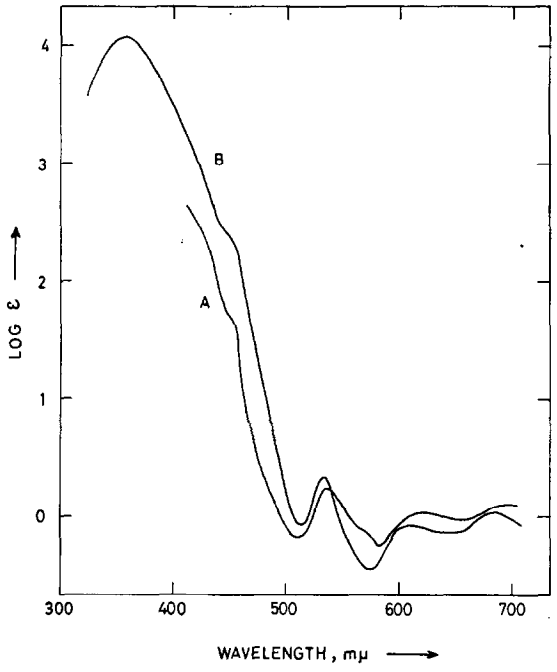


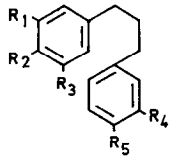
FIG. 1. Visible light absorption spectra of $[Fe(DMF)_3Cl_2][FeCl_4]$: Curve A, solid state; Curve B, in nitrobenzene.

Iron–DMF complex. To a solution of 163 g (1 mole) ferric chloride in 1.6 liter of dry ether, 110 g (1.5 mole) DMF were added with stirring. A precipitate (260 g, 95% yield) was obtained which is sufficiently pure to use directly for oxidation reactions, and can be recrystallized from methylene chloride and ethanol to give yellowish green needles, mp 220°C.

Iron–DMSO complex. To a solution of 163 g (1 mole) ferric chloride in 1 liter of dry ether, 156 g (2 mole) DMSO were added with stirring. A yellow precipitate was obtained in almost quantitative yield which can be recrystallized from chloroform and methanol to afford yellow crystalline, mp 220°C (*30*).

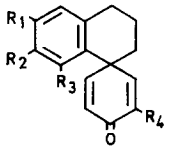
Initial investigations of intramolecular and intermolecular oxidative coupling reactions by iron–DMF complex and iron–DMSO complex were carried out with the following compounds. The reactions were usually done in either two-phase solutions with ether–water or methanol–water at 30–40°C with tenfold excess of complex. The

reaction time was varied. Oxidation of 1,3-diphenylpropanes (III) with the iron complexes was investigated as an example of intramolecular coupling reaction, giving the spirodienones (IV) in fairly good yield (Table 2). There are many alkaloids which have the spirodienone moiety and may be biosynthesized through the spirodienone.



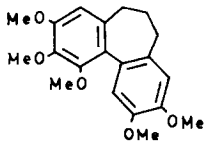
III

a: $R_1 = R_5 = OH$, $R_2 = R_3 = R_4 = OMe$
b: $R_1 = R_5 = OH$, $R_2 = R_4 = OMe$, $R_3 = H$
c: $R_1 = R_5 = OH$, $R_2 = R_3 = H$, $R_4 = OMe$
d: $R_1 = R_5 = OH$, $R_2 = R_3 = OMe$, $R_5 = H$
e: $R_1 = R_2 = R_5 = OMe$, $R_3 = R_4 = H$
f: $R_1, R_2 = OCH_2O$, $R_3 = R_4 = H$, $R_5 = OMe$
g: $R_1 = R_2 = R_3 = R_5 = OMe$, $R_4 = H$
h: $R_1 = R_2 = R_3 = R_4 = R_5 = OMe$
i: $R_1 = R_2 = R_3 = R_4 = OMe$, $R_5 = OH$



IV

a: $R_1 = OH$, $R_2 = R_3 = R_4 = OMe$
b: $R_1 = OH$, $R_2 = R_4 = OMe$, $R_3 = H$
c: $R_1 = OH$, $R_2 = R_3 = H$, $R_4 = OMe$
d: $R_1 = OH$, $R_2 = R_3 = OMe$, $R_4 = H$
e: $R_1 = R_2 = OMe$, $R_3 = R_4 = H$
f: $R_1, R_2 = OCH_2O$, $R_3 = R_4 = H$
g: $R_1 = R_2 = R_3 = OMe$, $R_4 = H$
h: $R_1 = R_2 = R_3 = R_4 = OMe$

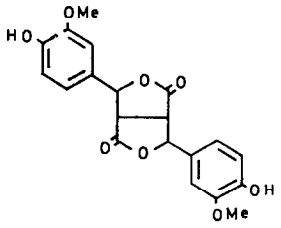


V

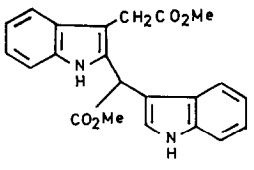
To supply additional examples, the following intermolecular coupling reactions by the iron complexes were also investigated. Oxidation of *p*-cresol afforded only Pummerer's ketone (I), and oxidation of ferulic acid produced pinoresinolide (VI), a constituent of lignin. Oxidation of methyl indole-3-acetic acid gave an unsymmetrical coupling product (VII).

TABLE 2

Oxidant	Yield of oxidation products, %						
	I	IVa	IVb	IVc	IVd	VI	VII
$[Fe(DMF)_3Cl_2][FeCl_4]$	28	91	67	39	16	35	50
$[Fe(DMSO)_4Cl_2][FeCl_4]$	7.8	67	—	—	21	33	58



VI

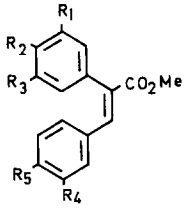


VII

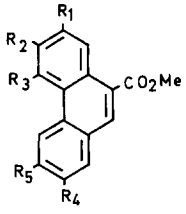
B. INTRAMOLECULAR OXIDATIVE COUPLING REACTIONS BY ELECTROCHEMICAL METHODS

Although a large number of intermolecular coupling reactions by anodic oxidation have been reported, examples of intramolecular coupling reactions are rare. One of the most typical examples in the field of natural product synthesis by electrochemical intramolecular oxidative coupling reaction is the preparation of morphinandienone alkaloids by oxidation of laudanosine, reported by Miller and his co-workers in 1971 (*31*). The electrochemical method has one obvious advantage over many known oxidation methods: One can use just enough oxidizing potential to carry out a desired reaction, and one can control this potential very accurately. Of course, the method works only as long as the product is less easily oxidized than starting material. This feature, fortified by mechanical advances in the control of potential electrolyser prompted us to investigate this method for the synthesis of natural products.

The original investigation was again carried out with 1,3-diphenylpropanes (III), and also α-phenylcinnamate (VIII), in connection with the synthesis of alkaloids which possess the phenanthrene system. Generally, electrolysis was performed as follows. Reactions were carried out in an H-type one-compartment glass cell in conjunction with a controlled potential electrolyser. All potentials were measured against a saturated calomel reference electrode, the working electrode being platinum gauze.



VIII



IX

a: $R_1 = R_2 = R_4 = R_5 = OMe$, $R_3 = H$
b: $R_1 = R_3 = H$, $R_2 = R_4 = R_5 = OMe$
c: $R_1 = R_2 = R_3 = OMe$, $R_4 = R_5 = OCH_2O$

Oxidations were carried out in commercial acetonitrile (containing a small amount of water) at room temperature with stirring at the anode site by magnetic stirrer. The concentration of reactants was approx 0.01 *M* and the supporting electrolyte was 0.1 *M*. The potential was maintained at approx 1.00–1.10 V (SCE) with initial currents of 110–120 mA. Electrolysis was usually discontinued when the current dropped to 10–20 mA, which generally took 20–45 min.

In electrolysis, results depend on the selection of electrolytes. We found that hydroboric acid afforded better results than other electrolytes in our cases. Tables 3 and 4 show some results of intramolecular coupling reactions by anodic oxidation with model compounds III and VIII, under the conditions described above. (Part of this work was reported in Refs. *38* and *48*.)

Notable results from the above experiments are as follows. (i) Conversion of IIIf to IVf shows that the methylenedioxy group survives the coupling reaction. This observation was applied in the synthesis of crinine-type alkaloids as described in a following

TABLE 3

ANODIC OXIDATION OF 1,3-DIPHENYLPROPANES (III)

Reactant III	Oxidation product IV (mp)	Electrolyte	Solvent	Yield %
e	e (95–96.5°C)	HBF_4	CH_3CN	60
			CH_3COCH_3	90
f	f (169–171°C)	HBF_4	CH_3CN	95
		Et_4NClO_4	CH_3CN	17
g	g (152–154°C)	HBF_4	CH_3CN	96
		$NaClO_4$	CH_3CN	90
		Et_4NClO_4	CH_3CN	90
h	V (109–110°C)	Et_4NClO_4	CH_3CN	90
i	h (166–168°C)	HBF_4	CH_3CN	80
a	a (245–247°C)	HBF_4	CH_3CN	60

TABLE 4

ANODIC OXIDATION OF α-PHENYLCINNAMATES (VIII)

Reactant VIII (mp)	Oxidation product IX (mp)	Electrolyte	Solvent	Yield %
a (126–128°C)	a (203–205°C)	Et_4NClO_4	CH_3CN	50
		HBF_4	CH_3CN	25
b (91–93°C)	Polymer	Et_4NClO_4 and HBF_4	CH_3CN	—
c (129–131°C)	c (156–157°C)	Et_4NClO_4	CH_3CN	45

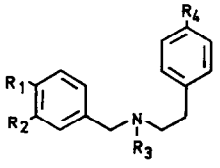
section. (ii) Conversion of IIIi and IIIa to IVh and IVa indicates that there is selectivity in the coupling position; that is, position para to the hydroxy group takes precedence over the para position of methoxy group. This result was utilized in the synthesis of the alkaloid colchicine described in the following section.

C. BIOMIMETIC SYNTHESIS OF THE ALKALOIDS D,L-OXOMARITIDINE AND D,L-OXOCRININE BY PHENOL OXIDATION AND ANODIC OXIDATION

Crinine (XIIIb) and maritidine (XIIIa), representative alkaloids of amaryllidaceae which have the 5,10-ethanophenanthridine ring system, have been synthesized by several routes (*32*, *33*) including biogenetic-type synthesis (*34–36*). We tried to synthesize these alkaloids as an application of our fundamental experiments described above.

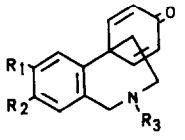
The trifluoroacetyl derivative of *O*-methylnorbelladine (Xa) was oxidized with the iron–DMF complex and iron–DMSO complex to yield a para–para coupled dienone (XIa) in 35% and 30% yields (*37*), respectively. Alkaline hydrolysis by potassium carbonate resulted in spontaneous cyclization to give normethyloxomaritidine (XIIa).

Anodic oxidation of norbelladine (Xc) in the described fashion afforded the dienone (XIc) in 60% yield (*38*). Alkaline hydrolysis of XIc gave oxo-crinine (XIIc). Other



X

a: $R_1 = OMe$, $R_2 = R_4 = OH$, $R_3 = COCF_3$
b: $R_1 = R_2 = R_4 = OMe$, $R_3 = COCF_3$
c: $R_1, R_2 = OCH_2O$, $R_3 = COCF_3$, $R_4 = OMe$
d: $R_1 = R_4 = OMe$, $R_2 = OCH_2Ph$, $R_3 = COCF_3$
e: $R_1 = R_4 = OMe$, $R_2 = OCH_2Ph$, $R_3 = H$

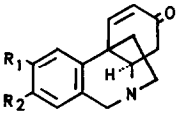


XI

a: $R_1 = OMe$, $R_2 = OH$, $R_3 = COCF_3$
b: $R_1 = R_2 = OMe$, $R_3 = COCF_3$
c: $R_1, R_2 = OCH_2O$, $R_3 = COCF_3$
d: $R_1 = OMe$, $R_2 = OCH_2Ph$, $R_3 = COCF_3$

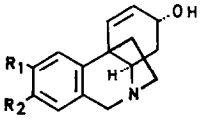
unpublished results of anodic oxidation of norbelladines are shown in Table 5. Among these, a notable experiment is the oxidation of Xe, which has a free amino group.

Comparable reports by other workers in the synthesis of this type of alkaloids describe the synthesis of XIc from X (R_1, $R_2 = OCH_2O$, $R_4 = OH$, $R_3 = COCF_3$) by



XII

a: $R_1 = OMe$, $R_2 = OH$
b: $R_1 = R_2 = OMe$
c: $R_1, R_2 = OCH_2O$
d: $R_1 = OMe$, $R_2 = OCH_2Ph$



XIII

a: $R_1 = R_2 = OMe$
b: $R_1, R_2 = OCH_2O$

oxidation with thallium(III)trifluoroacetate in 87% yield (*36*) and synthesis of XIc from Xa by oxidation with vanadium oxytrichloride in 24% yield (*35*). Transformations of XIIa and XIIc to D,L-maritidine and D,L-crinine are already known.

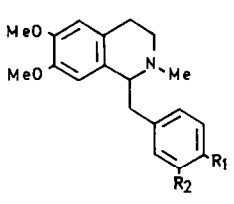
TABLE 5

OXIDATION OF NORBELLADINES (X)

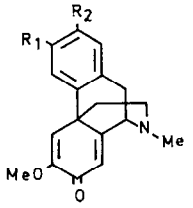
X	Oxidation method	XI (mp)	Yield %	XII (mp)	Yield %
a	$[Fe(DMF)_3Cl_2][FeCl_4]$	a (oil)	35	a (250–252°C)	
	$[Fe(DMSO)_4Cl_2][FeCl_4]$	a	30		
b	Anodic oxidation	b (159–160°C)	62	b (145–147°C)	
c	Anodic oxidation	c (181–182°C)	62	c (176–177°C)	
d	Anodic oxidation	d (167–169°C)	60		
e	Anodic oxidation	—		d (250–252°C)	50

D. BIOGENETIC-TYPE SYNTHESES OF MORPHINANDIENONE ALKALOIDS, D,L-AMURINE, D,L-FLAVINANTINE, AND D,L-PALLIDINE BY ANODIC OXIDATION

The morphinandienone alkaloid is another type which possesses a dienone system (*39*). This section is concerned with the synthesis of morphinandienone alkaloids, D,L-amurine (XVa), D,L-fravinantine (XVd), and D,L-pallidine (XVe), by electrochemical intramolecular oxidative coupling reaction of corresponding 1-benzyltetrahydroisoquinolines (XIV) (*40*). Although Miller and his collaborators have reported the synthesis of morphinandienone alkaloids, D,L-*O*-methylflavinantine (XV)



XIV



XV

a: $R_1, R_2 = OCH_2O$
b: $R_1 = OCH_2Ph, R_2 = OMe$
c: $R_1 = OMe, R_2 = OCH_2Ph$

($R_1 = R_2 = OMe$), D,L-*O*-benzylflavinantine (XVb), and D,L-*O*-benzylpallidine (XVc), by anodic oxidation of XIV (*31*), we investigated the practical synthesis of these alkaloids by anodic oxidation using hydroboric acid as electrolyte, achieving higher yields than those previously reported. The comparisons are shown in Table 6.

TABLE 6

ANODIC OXIDATION OF 1-BENZYLTETRAHYDROISOQUINOLINE (XIV)

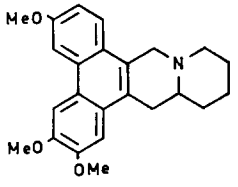
XIV	XV (mp)	Yield %	Lit best yield %
a	a (202–206°C)[a]	70 (80)[b]	1.23 (Kametani) (*41*)
b	b (142–144°C)	86 (98)	53 (Miller) (*31*)
c	c (165–167°C)	74 (90)	43 (Miller) (*31*)

[a] Melting point of methiodide.
[b] Yield based on recovered starting material.

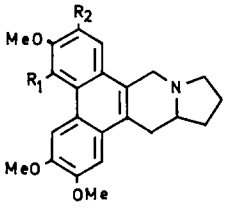
Electrolysis of XIVa in presence of hydroboric acid as electrolyte gave D,L-amurine as a colorless syrup which was identified as the methiodide. XIVb and XIVc were oxidized in the manner described before to give the spirodienones XVb and XVc. Benzyl groups in XVb and XVc were hydrolyzed by trifluoroacetic acid at room temperature (*42*) to yield D,L-flavinantine (XVd), mp 138–140°C, and D,L-pallidine (XVe), mp 120–122°C, in fairly good yield.

E. A NEW SYNTHESIS OF THE ALKALOID D,L-CRYPTOPLEURINE THROUGH ANODIC OXIDATION

The vesicant alkaloid cryptoplurine (XVI), isolated from *Cryptocarva pleurosperma* (*43*) and possessing the phenanthroquinolizidine ring system, is well known because of its interesting biological and pharmacological properties; i.e., it is mitotic poison and exhibits cytotoxic and antiviral activity. At least two of the vesicant alkaloids, tylophorine (XVIIa) and tylocrebrine (XVIIb), which have the phenanthroindolizidine ring system (*44*), along with cryptoplurine, are known to be powerful vesicants.

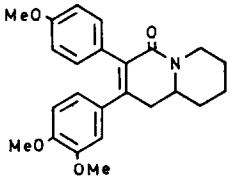


XVI

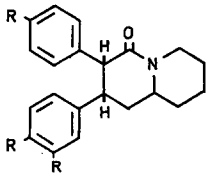


XVII

a: $R_1 = H$, $R_2 = OMe$
b: $R_1 = OMe$, $R_2 = H$

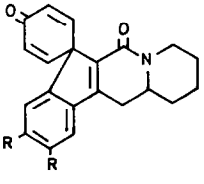


XVIII



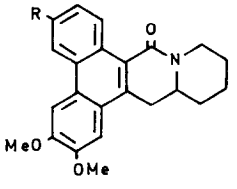
XIX

a: R = OMe
b: R = OH



XX

a: R = OMe
b: R = OH



XXI

a: R = OMe
b: R = OAc
c: R = OH

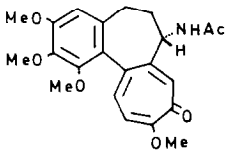
Although the total synthesis of cryptoplurine has been achieved by three groups (*45*, *46*), including the biomimetic synthesis by Pauson (*47*), development of additional synthetic methods is also necessary to make accessible a range of related compounds with a view to studying their physiological activities. Thus, we attempted to synthesize the alkaloid by electrochemical methods even though preliminary experiments involving anodic oxidation of α-phenylcinnamate did not give good results (Table 4).

The synthesis of D,L-cryptopleurine by Pauson and his co-workers features the construction of the phenanthroquinolizidine nucleus by the oxidation with manganese dioxide of the phenol XIXb (prepared from the quinolidinone XVIII by methylation followed by hydrogenation) to give the spirodienone XXb in 15–20% yield. We used their synthetic intermediate XVIII for anodic oxidation experiments. Oxidation of XVIII was carried out in acetonitrile in the presence of hydroboric acid as the electrolyte, as described, to afford the para–para coupled spirodienone (XXa) and an unexpected meta–para coupled product (XXIa) in 60% and 31% yield, respectively. Oxidation of the dihydro derivative of XVIII did not give any expected coupling product.

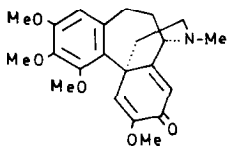
Subsequently, the spirodienone XXa was subjected to the dienone–phenol rearrangement reaction with Ac_2O–H_2SO_4, giving the acetate XXIb. XXb was hydrolysed to give XXIc, followed by methylation with diazomethane to afford XXIa in overall 80% yield from XXa. $LiAlH_4$ reduction of XXIa afforded D,L-cryptopleurine XVI in almost quantitative yield (*48*).

F. TOTAL SYNTHESIS OF THE ALKALOID COLCHICINE THROUGH AN OXIDATIVE PHENOL COUPLING REACTION

Total synthesis and biosynthesis of the alkaloid colchicine (XXII), a major alkaloid of the *Colchicum* species, has been studied extensively in the interest of chemical as well as biological and medical sciences for the past 15 years. Since the first hypothetical biosynthesis of colchicine from a chalcone was proposed by Anet and Robinson (*49*)



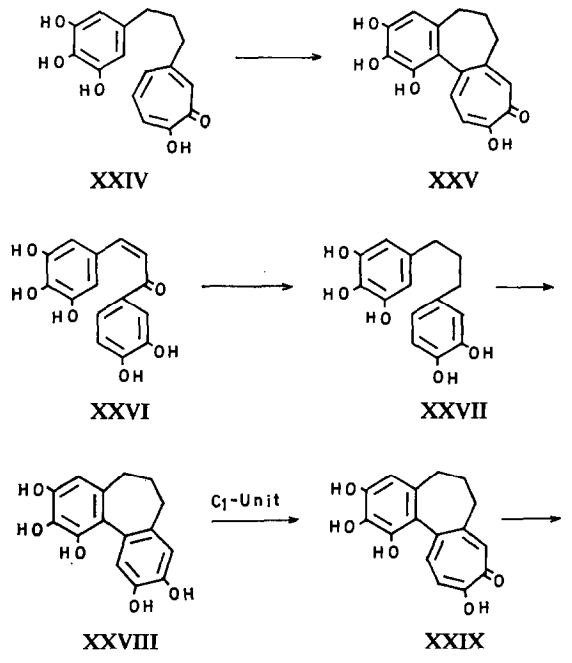
XXII



XXIII

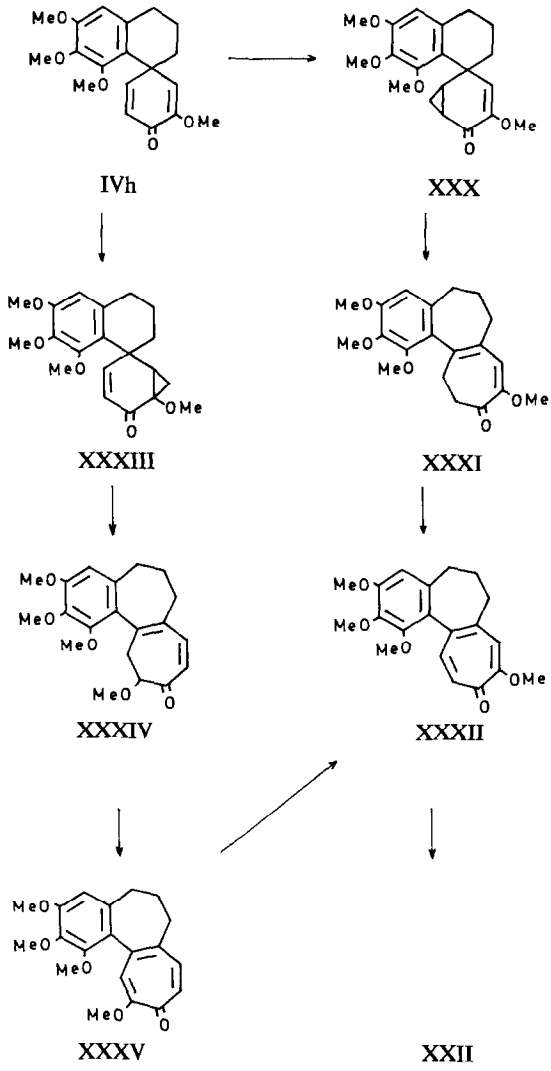
in 1950, several hypotheses based on the oxidative phenol coupling reaction have been presented (*50*). Through tracer studies in the plant, it is clear that colchicine is biosynthesized by oxidative phenol coupling of an L-phenethylisoquinoline to androcymbine (XXIII), a finding supported by the coexistence of colchicine and androcymbine in *Androcymbicum melanthioides* (*50*, *51*).

Total syntheses of colchicine have been achieved by seven groups (*50*) using with brilliant synthetic methods, including the Scott synthesis which involved $FeCl_3$ oxidative coupling of XXIV to XXV in 4–5% yield. The Anet–Robinson hypothesis for biosynthesis of colchicine from the chalcone XXVI consists of the oxidative phenol coupling of the phenol XXVII to the coupled product XXVIII, followed by C_1-unit insertion to form the tropolone ring, as shown (XXIV → XXIX). The hypothetical intermediate XXVIII could be replaced by the spirodienone IVa or IVh, now readily obtainable by the phenol oxidation or anodic oxidation of the 1,3-diphenylpropanes IIIa or IIIi. The C_1-unit insertion in IVa or IVh is much easier than in XXVIII; thus, we planned to synthesize the alkaloid starting from the spirodienone IVh. This plan

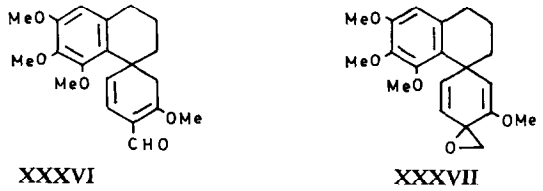


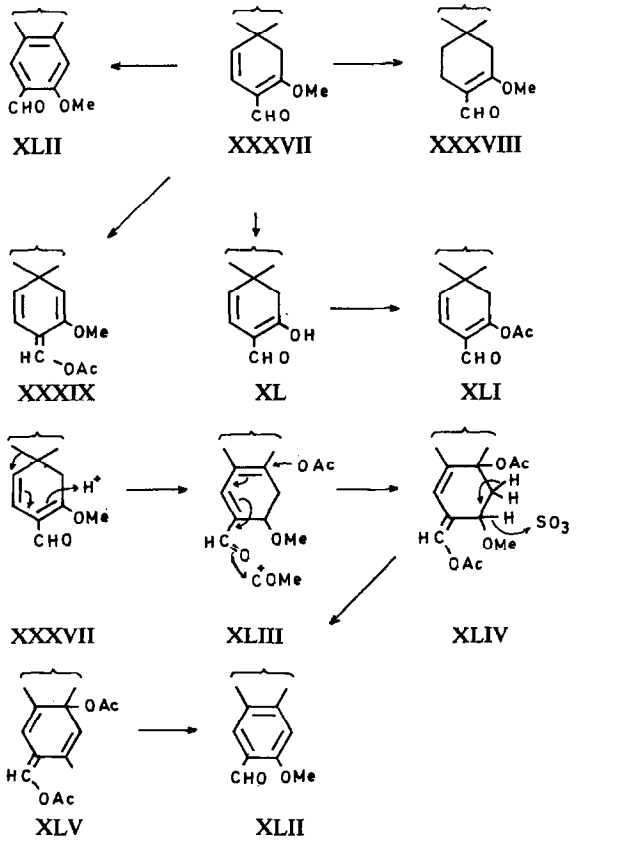
basically consisted of (a) the transformation of IVh to the α,β-unsaturated cyclopropyl ketone XXX or XXXIII by suitable methylene transfer reaction, and (b) cyclopropane ring cleavage of XXX or XXXIII to XXXI or XXXIV by ring expansion concerted with aryl migration followed by a dehydrogenation reaction of XXXI or XXXIV to give desacetamidoisocolchicine (XXXII) or desacetamidocolchiceine (XXXV). Conversion of the latter to colchicine by nitrogen insertion at the proper position had been accomplished by both van Tamelen and Eschenmoser and their co-workers (*50*); thus, the synthesis of XXXII or XXXV means completion of the synthesis of the alkaloid.

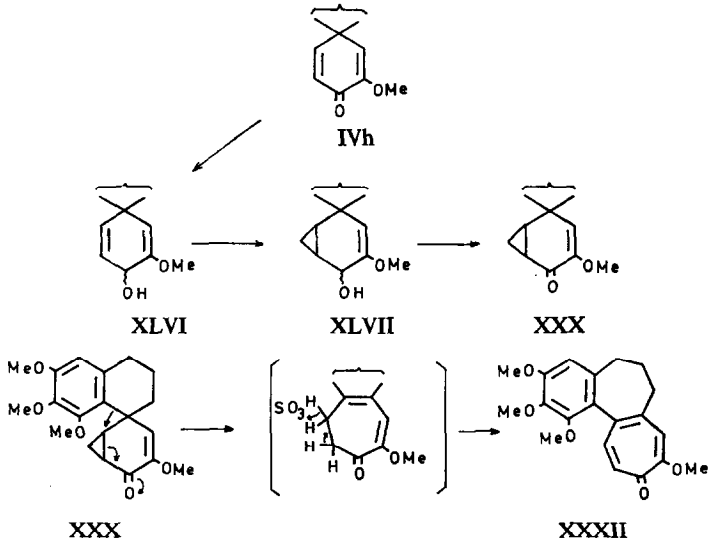
Several reagents are known to form cyclopropane rings by methylene addition to cross-conjugated dienones, namely, dimethyloxosulfonium methylide (*52*), the Simmons-Smith reagent (*53*), and diazomethane (*54*). Reaction of the spirodienone IVh with dimethyloxosulfonium methylide gave only a oxirane (XXXVI), and reaction with the Simmons-Smith reagent and diazomethane of IVh did not give any promising results. Reaction of IVh with dimethylsulfonium methylide afforded the novel product XXXVII in 90% yield. The structure of the aldehyde XXXVII was assigned on the basis of physical data and the following chemical transformations. Catalytic reduction of the aldehyde XXXVII gave a dihydro derivative XXXVIII, and reaction of XXXVII with Ac_2O-pyridine (3 : 1) afforded enol acetate (XXXIX). Treatment of either XXXVII or XXXIX with alkali yielded an acidic compound XL, which was acetylated to give the acetate XLI. Reaction of XXXVII with Ac_2O–H_2SO_4 followed by hydrolysis gave a new aldehyde XLII. A possible interpretation for the conversion of XXXVII to XLII is as follows. The aldehyde XXXVII is rearranged to XLIII by protonation and aryl migration; then acetoxylation provides the diacetate XLIV, which is oxidized by the SO_3 generated from concd H_2SO_4 and Ac_2O (*55*) to yield XLV. Subsequent hydrolysis of XLV gave an aldehyde (XLII) by elimination of acetoxy group, as shown.



The best methylene addition reaction on the spirodienone IVh was effected by the following means. Reaction of the dienol XLVI, obtained by $NaBH_4$ reduction of the spirodienone IVh, with carefully prepared active Simmons-Smith reagent (*56*), afforded XLVII in fairly good yield. Subsequently, the compound XLVII without purification was oxidized by Jones' reagent to yield the desired α,β-unsaturated cyclopropyl ketone XXX, in overall 42% yield from IVh.



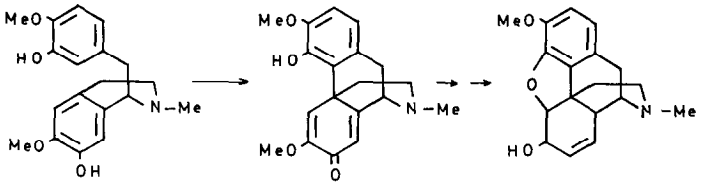

CHO OMe
OMe
CHO
OMe
CHO
XLII
XXXVII
XXXVIII
OMe
HC OAc
OH
CHO
OAc
CHO
XXXIX
XL
XLI
H+
OMe
CHO
OAc
HC O
OMe
COMe
OAc
H
H
SO3
HC
OMe
OAc
XXXVII
XLIII
XLIV
OAc
HC
OAc
CHO OMe
XLV
XLII


OMe
O
IVh
OMe
OH
OMe
OH
OMe
O
XLVI
XLVII
XXX
MeO
MeO
MeO
OMe
O
SO3H
H
H
H
O
OMe
MeO
MeO
MeO
OMe
O
XXX
XXXII

The next problem in the construction of the alkaloid is the synthesis of tropolone ring from XXX by cyclopropane ring cleavage and aryl migration followed by dehydrogenation. Treatment of XXX with Ac_2O–H_2SO_4 at room temperature for 2 hr afforded directly desacetamidoisocolchicine (XXXII). In this process, the cyclopropane ring cleavage and aryl migration, proceeding in a concerted fashion, and a novel dehydrogenation (possibly by the oxidation with SO_3, similar to the conversion of XXXVII to XLII described above) occur in one flask. In summary, the total synthesis of the alkaloid colchicine through oxidative phenol coupling reaction was completed by the route 1,3-diphenylpropane IIIa or IIIi → spirodienone IVh → cyclopropyl ketone XXX → desacetamidoisocolchicine XXXII, according to our basic plan (*57*).

Although new results, described above, in the synthesis of natural products, especially in alkaloid synthesis, by oxidative phenol and nonphenol coupling reactions were obtained, certain limitations are apparent. The coupling position in these reactions is restricted to that para to hydroxy groups in phenols and methoxy groups of the nonphenols in intramolecular reactions, and this restriction means a single coupling product as secured under the described conditions. Para–para coupling may be favorable because of steric factors due to the bulky metal molecules coordinated with the oxygen of phenols in metal complex-catalysed reactions and is favored for ionic reason due to the cation radicals being generated in anodic oxidations.

Various metabolites coupled in the ortho–ortho or ortho–para position are known in nature. An important, prototype example is the morphine alkaloid class, ortho–para coupled compounds of L-benzylisoquinolines. Barton and his collaborators (*58*)



XLVIII XLIX L

completed a particularly significant synthesis of a morphine alkaloid in 1963 (XLVIII → XLIX → L), although the yield was not higher than 1% at the oxidative coupling step. We do not have any other information on ortho–ortho or ortho–para coupling reactions, although further effort may reward those in the field.

REFERENCES

1. D. H. R. Barton and T. Cohen, *Festschr. Prof. Dr. Arthur Stoll Siebzigsten Geburtstag*, 117 (1957).
2. W. I. Taylor and A. R. Battersby, Eds., "Oxidative Coupling of Phenols." Marcel Dekker, New York, 1967; T. Kametani and K. Fukumoto, *Synthesis*, 657 (1972).
3. R. Pummerer and F. Frankfurter, *Chem. Ber.*, **47**, 1472 (1914); *Chem. Ber.*, **52**, 1416 (1919); R. Pummerer and A. Rieche, *Chem. Ber.*, **59**, 2161 (1926).
4. F. R. Hewgill, "MTP International Review of Science, Organic Chemistry Series" (W. A. Waters, Ed.), Vol. 10, p. 167. Butterworths, London, 1973.
5. T. Kametani and K. Fukumoto, *Accounts Chem. Res.*, **5**, 212 (1972).

6. J. M. Bobbitt, *Heterocycles*, **1**, 181 (1973).
7. R. Pummerer, D. Melamed, and H. Puttfarcken, *Berichte*, **55**, 3116 (1922); S. L. Cosgrove and W. A. Waters, *J. Chem. Soc.*, 1726 (1951); K. Bowden and C. H. Reece, *J. Chem. Soc.*, 2249 (1950).
8. E. W. Warnhoff, *Fortschr. Chem. Org. Naturst.* **28**, 179 (1970).
9. H-P. Husson, C. Poupat, B. Rodriguez, and P. Potier, *Tetrahedron*, **29**, 1405 (1973).
10. C. G. Haynes, A. H. Turner, and W. A. Waters, *J. Chem. Soc.*, 2823 (1958).
11. V. Arkley, F. M. Dean, A. Robertson, and P. Sidisunthorn, *J. Chem. Soc.*, 2322 (1956).
12. D. H. R. Barton, A. M. Deflorin, and O. E. Edwards, *J. Chem. Soc.*, 530 (1956).
13. T. Kametani and K. Ogasawara, *Chem. Pharm. Bull.*, **16**, 1138 (1968).
14. K. Bowden and C. H. Reece, *J. Chem. Soc.*, 2249 (1950).
15. S. L. Cosgrove and W. A. Waters, *J. Chem. Soc.*, 1726 (1951).
16. T. A. Davidson, Ph.D. thesis, Glasgow, 1962; A. I. Scott, *Quart. Rev. (London)*, **19**, 1 (1965).
17. R. G. R. Bacon, R. Grime, and D. J. Munro, *J. Chem. Soc.*, 2275 (1954).
18. W. W. Kaeding, *J. Org. Chem.*, **28**, 1063 (1963).
19. W. L. Carrick, G. L. Karapinka, and G. T. Kwiatkowski, *J. Org. Chem.*, **34**, 2388 (1969).
20. T. Kametani, K. Ohkubo, and S. Takano, *Chem. Pharm. Bull.*, **16**, 1095 (1968).
21. W. W. Westerfield and C. Lowe, *J. Biol. Chem.*, **145**, 463 (1942).
22. B. R. Brown and S. M. Bocks, "Enzyme Chemistry of Phenolic Compounds" (J. D. Pridham, Ed.), Chapter 12. Pergamon, London, 1963.
23. M. A. Schwarz, R. A. Holton, and S. W. Scott, *J. Amer. Chem. Soc.*, **91**, 2800 (1969).
24. M. J. S. Dewar and T. Nakaya, *J. Amer. Chem. Soc.*, **90**, 7134 (1968).
25. M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, *J. Amer. Chem. Soc.*, **95**, 612 (1973).
26. S. Tobinaga and E. Kotani, *J. Amer. Chem. Soc.*, **94**, 309 (1972).
27. D. W. Meek and R. S. Drago, *J. Amer. Chem. Soc.*, **83**, 4322 (1961).
28. F. A. Cotton and R. Francis, *J. Amer. Chem. Soc.*, **82**, 2986 (1960).
29. S. Tobinaga, M. Kamisato, and E. Kotani, unpublished results.
30. Described method is different from previous report (*28*).
31. L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Amer. Chem. Soc.*, **95**, 2651 (1973).
32. H. Muxfeldt, R. S. Schneider, and J. B. Mooberry, *J. Amer. Chem. Soc.*, **88**, 3670 (1966).
33. H. W. Whitlock, Jr. and G. L. Smith, *J. Amer. Chem. Soc.*, **89**, 3600 (1967).
34. M. A. Schwartz and R. A. Holton, *J. Amer. Chem. Soc.*, **92**, 1090 (1970).
35. T. Kametani and T. Kohno, *Tetrahedron Lett.*, 3155 (1971).
36. M. A. Schwartz, B. F. Rose, and B. Vishnumajjala, *J. Amer. Chem. Soc.*, **95**, 612 (1973).
37. E. Kotani, N. Takeuchi, and S. Tobinaga, *Tetrahedron Lett.*, 2735 (1973).
38. E. Kotani, N. Takeuchi, and S. Tobinaga, *J. Chem. Soc. Chem. Commun.*, 550 (1973).
39. K. L. Stuart, *Chem. Rev.*, **71**, 47 (1971).
40. E. Kotani and S. Tobinaga, *Tetrahedron Lett.*, 4759 (1973).
41. T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *J. Chem. Soc. C*, 1063 (1969).
42. J. P. Marsh, Jr. and L. Goodman, *J. Org. Chem.*, **30**, 2491 (1965).
43. E. Gellert and N. V. Riggs, *Aust. J. Chem.*, **7**, 113 (1954).
44. T. R. Govindachari, "The Alkaloid" (R. H. F. Manske, Ed.), Vol. 9, p. 517. Academic Press, New York, 1967.
45. C. K. Bradsher and H. Berger, *J. Amer. Chem. Soc.*, **79**, 3287 (1957); **80**, 930 (1958).
46. P. Marchini and B. Belleau, *Can. J. Chem.*, **36**, 581 (1958).
47. J. M. Paton, P. L. Pauson, and T. S. Stevens, *J. Chem. Soc. C*, 1309 (1969).
48. E. Kotani, M. Kitazawa, and S. Tobinaga, *Tetrahedron*, **30**, 3027 (1974).
49. R. Robinson, "The Structural Relations of Natural Products," p. 46. Clarendon Press, Oxford, 1954.
50. W. C. Wildman and B. A. Pursey, "The Alkaloids" (R. H. F. Manske, Ed.), Vol. 9, p. 407. Academic Press, New York, 1968.
51. A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *J. Chem. Soc. Perkin I*, 1741 (1972).
52. G. L. Buchanan, R. A. Raphael, and R. Taylor, *J. Chem. Soc. Perkin I*, 373 (1973).
53. J. M. Conia and J.-C. Limasset, *Tetrahedron Lett.*, 3151 (1965).

54. F. M. Dean, P. G. Jones, R. B. Morton, and P. Sidisunthorn, *J. Chem. Soc.*, 411 (1964); G. W. Krakower and H. A. Van Dine, *J. Org. Chem.*, **31**, 3467 (1966).
55. A. I. Mayers and G. Garcia-Munoz, *J. Org. Chem.*, **29**, 1435 (1964).
56. E. LeGolf, *J. Org. Chem.*, **29**, 2048 (1965).
57. E. Kotani, F. Mivazaki, and S. Tobinaga, *J. Chem. Soc. Chem. Commun.*, 300 (1974).
58. D. H. R. Bartony, G. W. Kirby, W. Steglich, and G. M. Thomas, *Proc. Chem. Soc.*, 203 (1963).