Synthesis of Morphinandienone Alkaloids
by Phenol Oxidation and the Pschorr Reaction

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1. Introduction.

Morphine, the major alkaloid of the opium poppy, *Papaver somniferum*, was isolated by Sertürner (75) in 1805 and was assigned the structure II by Gulland and Robinson (32). The structural assignment was based upon the hypothetical biogenetic theory that laudanosoline (I) undergoes oxidative coupling of the two aromatic rings to form the skeleton of morphine (II) as a result of several degradative investigations of morphine by Pschorr, Schöpf, Knorr, and Wieland.

Chart 1

(I)   (II)
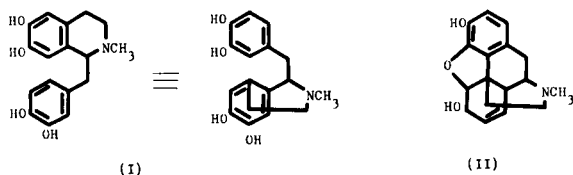
This structure III was amply confirmed by later work (22,27,31,71,76), especially by X-ray analysis of morphine by Hodgkin (59).

Chart 2

(III)
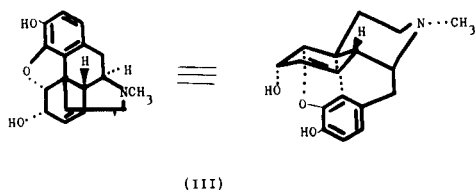
The structural determinations of morphine (II) and *Papaveraceae* alkaloids, for example, glaucine (IV), suggested a general rule that they were all related structurally to the 1-benzylisoquinolines, of which the laudanosoline (I) was an example.

Chart 3

(II)   (IV)
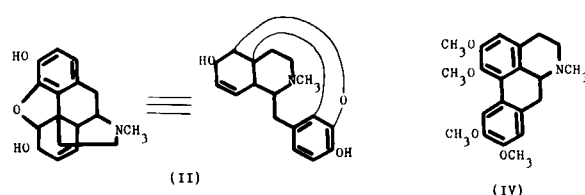
Initially, Robinson (67,68,72) postulated that morphine could be formed in the plant by oxidative coupling of a suitable benzylisoquinoline precursor. After many suggestions about the mechanism of the coupling process, the second important proposal came from Barton and Cohen (4) who postulated on the basis of the knowledge gained by the elucidation of the structure of Pummerer's ketone that the coupling step is the result of "phenol oxidation" (84). Thus, oxidation of the diphenolic base V by some one-electron transfer system could generate radicals whose coupling would yield a dienone VI, named as "morphinandienone", and then morphine could be biosynthesized through the appropriate modification of the dienone VI.

Chart 4

(V)   (VI)   (II)
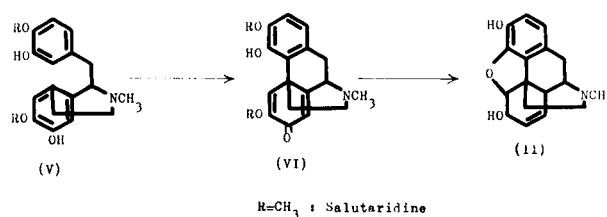
R=CH₃ : Salutaridine

In 1963, Barton (9) synthesized morphinandienone (VI, R = CH₃) and certified this dienone to be a precursor to morphine (II). Soon after this work, the isolation of

a new alkaloid, salutaridine, from *Croton salutaris* was reported by Barnes (10) and the natural substance was identical with the synthetic dienone VI. Here, the chemistry of morphinandienone alkaloids started. Previously Goto (30) had synthesized a morphinandienone type compound VII from both of the diketones VIII and IX during a structural investigation of sinomenine (X) in 1933, and floripavine (58), which was found to be identical with salutaridine, was isolated in 1935, but its structure was not determined.

Chart 5

(X)   (VIII)   (VII)

(IX)
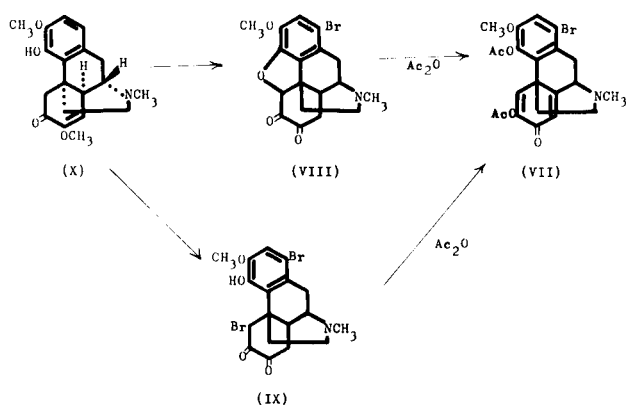
Dienone bases having the skeleton of VI are now regarded as members of a new class of the isoquinoline alkaloids designated as the morphinandienones, and the morphinandienone type compounds are key intermediates in the biogenesis not only of morphine (II) but also of sinomenine (X) and protostephanine (XI). Moreover, homomorphinandienones such as androcymbine (XII) were also found to occur naturally, and this alkaloid was shown to be a precursor to colchicine (XIII).

Chart 6

(XI)   (XII)   (XIII)
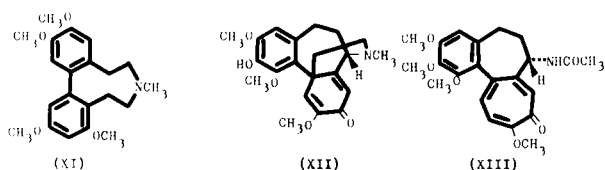
Based upon the above facts, the chemistry of the morphinandienone and homomorphinandienone type alkaloids developed with investigations of the biogenesis of some of these alkaloids. The synthesis of these alkaloids by biogenetic methods and the non-biogenetic (classic) methods is discussed in this review. At the time of writing this review, eight morphinandienone alkaloids from natural sources had been reported as well as thirteen alkaloids which correlated biogenetically with morphinandienone and four homomorphinandienone type alkaloids:

(i) Morphinandienone alkaloids: salutaridine (floripavine), sinoacutine, norsinoacutine, amurine, flavinantine, flavinine, pallidine, and O-methylflavinantine.

(ii) Alkaloids derived biogenetically from morphinandienone: 8,14-dihydrosalutaridine, 8,14-dihydronorsalutaridine, nudaurine, protostephanine, sinomenine, disinomenine, thebaine, oripavine, neopine, codeine, 10-hydroxycodeine, morphine, and pseudomorphine.

(iii) Homomorphinandienone and its related alkaloids: androcymbine, O-methylandrocymbine, kreysiginine, and alkaloid CC-12.

II. Morphinandienone Alkaloids.

(1) Salutaridine (Floripavine).

In 1957, before any tracer experiments had been reported, Barton and Cohen (4) presented a novel theory for the late stage of morphine biosynthesis applying phenol oxidation. Their proposed mechanism is shown as follows. If the intramolecular oxidative coupling of the benzylisoquinoline V is analogous to the union of p-cresol radicals XIV to form Pummerer's ketone XV (5,65), the coupling of the radicals generated by a one-electron transfer system in the plant could yield the morphinandienone VI, and the oxide bridge could then be formed by addition, as shown, to the dienone system, leading to the formation of the enone XVI. The sequence through its reduction product XVII would lead to the alkaloids thebaine (XVIII), codeinone (XIX), codeine (XX), and morphine (II). [In this mechanism, the group R represents a residue, possibly part of an enzyme face, which can be added to, or taken away from, a phenolic hydroxyl in order to provide protection adequate to ensure specific coupling of radicals.]

Chart 7

(XIV-a)   (XIV-b)   (XIV-c)

(XV)
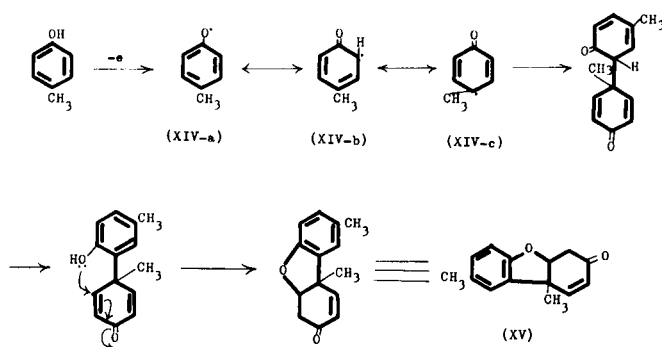
An important possible variation of this scheme was proposed by Stork (76), by Battersby (15), and by Ginsburg (28). These authors have suggested that the morphinandienone VI, formed by the phenol oxidation step, is

Chart 8

(V)

(VI)   (XVI)   (XVII)


(XVIII)   (XIX)   (XX)   (II)
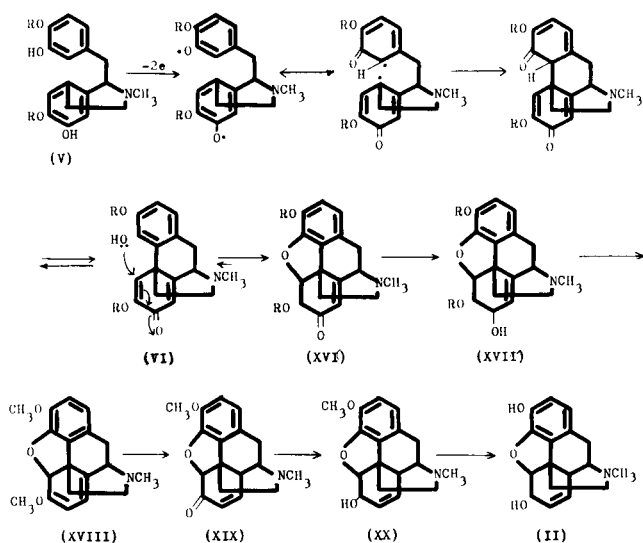
reduced to the dienol XXI rather than cyclized to the enone XVI. This could then undergo an allylic elimination as indicated, probably as the phosphate ester (X = phosphate), to give the complete pentacyclic system.

Chart 9

(VI)   (XXI)   (XVIII)
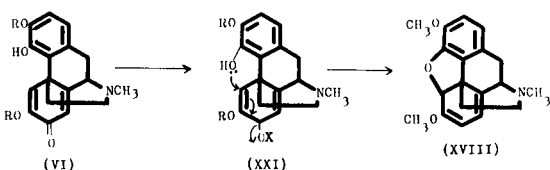
In 1963, after the dienone XXII had been synthesized from thebaine by Barton (9,10), Barnes isolated the naturally occurring substance, which exists solely in the "open" form (XXII) rather than the "closed" form (XVI) and named it salutaridine. Reduction of XXII by sodium borohydride afforded two epimeric alcohols XXIII, both of which, under extremely mild acidic conditions, were converted spontaneously at room temperature in fair yield into thebaine (XVIII). Moreover, both ^{3}H- and ^{14}C-labeled salutaridine were incorporated very efficiently without randomization of the labels into morphine (II), codeine (XX), and thebaine (XVIII). Thus, this clearly demonstrated the importance of salutaridine as a biosynthetic intermediate. The feeding experiments to the poppy plant with (±)-[3-^{14}C]-norlaudanosoline (XXIV) and [2-^{14}C] tyrosine (XXV) afforded positive evidence for the presence of salutaridine in the poppy and also for the biogenesis of this compound.
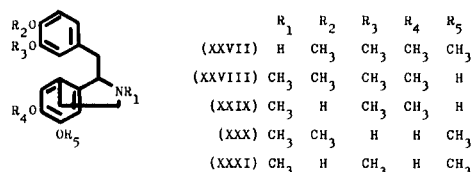
Chart 10

(XXII)   (XXIII)

β-OH : Salutaridinol-I
α-OH : Salutaridinol-II

(XXIV)   (XXV)   (XXVI)
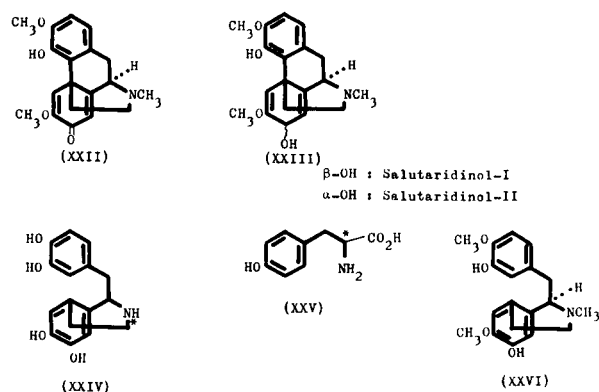
Other feeding experiments with various 1-benzyliso-quinolines (XXVII-XXXI) that do not possess the phenolic group in the correct positions for the pathway to morphine demonstrated that reticuline (XXVI) was a true precursor and phenol oxidation was a key step in this process.

The above facts show that salutaridine (XXII) is biosynthesized by the phenol oxidation of reticuline (XXVI) formed through tyrosine (XXV), norlaudanosoline (XXIV), and laudanosoline (I), and the former XXII is then converted to morphine (II).

Chart 11

|	R_1	R_2	R_3	R_4	R_5
(XXVII)	H	CH₃	CH₃	CH₃	CH₃
(XXVIII)	CH₃	CH₃	CH₃	CH₃	H
(XXIX)	CH₃	H	CH₃	CH₃	H
(XXX)	CH₃	CH₃	H	H	CH₃
(XXXI)	CH₃	H	CH₃	H	CH₃

Recently, Mndzhoyan proved floripavin, isolated from *Papaver floribundum* in 1935, to be salutaridine (XXII) by the chemical method (61).

(2) Sinoacutine and Norsinoacutine.

Chu (20) reexamined the alkaloids from Chinese *Sinomenium acutum* and isolated a new alkaloid together with sinomenine (X) and named it sinoacutine. The structure was assigned XXXII by spectroscopic methods (37) and was proved to be correct by Barton (8) by direct comparison with salutaridine (XXII).
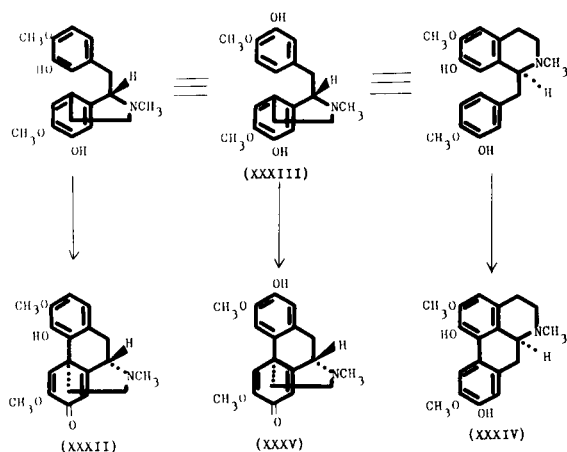
Sinoacutine (XXXII) was biosynthesized from (+)-reticuline (XXXIII) by phenol oxidation, and is a precursor in the biogenesis of sinomenine (X) (8).

Chart 12

(XXXIII)   (XXXII)   (X)
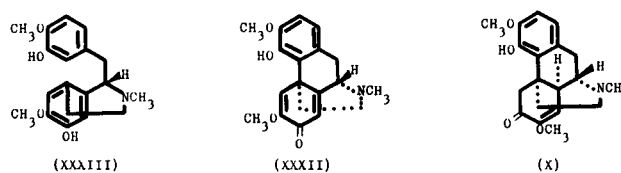
Recently, sinoacutine (XXXII) was isolated together with isoboldine (XXXIV) from *Cassytha pubescens* by Johns (38), and Kametani (40) also found sinoacutine with isoboldine (XXXIV) and pallidine (XXXV) (described later) from *Corydallis pallida* var. *tenuis*. It is interesting from a biogenetical point of view that phenol oxidation of reticuline gives sinoacutine (XXXII), isoboldine (XXXIV), and pallidine (XXXV) depending on the coupling mode.

Chart 13

(XXXIII)

(XXXII)   (XXXV)   (XXXIV)

Norsinoacutine (XXXVI) was isolated in addition to sinoacutine (XXXII), flavinantine (XXXVII), and flavinine (XXXVIII) from *Croton flavens* (78,79) and *C. balsamifera* (19,79). Stuart (80) reported that sinoacutine was biosynthesized from phenylalanine and reticuline (XXXIII), and norsinoacutine from phenylalanine.

Chart 14

(XXXVI)   (XXXVII)   (XXXVIII)
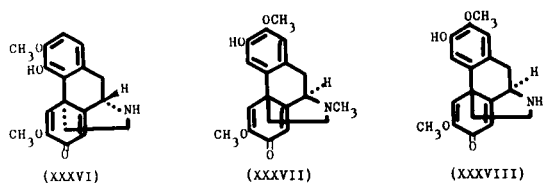
(3) Amurine, Flavinantine, Flavinine and Pallidine.

Boit isolated a new alkaloid named amurine from *Papaver nudicaule* var. *amurense*, and its structure was assigned XXXIX by Döpke (21) by chemical and spectroscopic methods after several investigations by Santavý. Flavinine and flavinantine were obtained from *Croton flavens* and assigned the structures XXXVIII and XXXVII, respectively (18,78,79).

The structural similarity of amurine and flavinantine with salutaridine suggests a close biogenetic relationship between these substances. In the light of current theories, it may be postulated that the biogenesis of amurine and

flavinantine involves *para-para* oxidative coupling of (-)-reticuline (XXVI), followed by subsequent cyclization and transmethylation of the o-methoxyphenyl in the resulting potential alkaloids, isosalutaridine (XL). This was proved by the feeding experiment with [N-^{14}C]reticuline (XXVI) to flavinantine (XXXVII) (80). Interestingly, orientaline (XLI), which could not be biogenetically transformed to salutaridine (XXII), is a further possible precursor, with subsequent formation of the bis-dienone (XLII) which would be rearranged to give flavinantine directly (80).

Chart 15

(XXVI)   (XL)   (XXXIX)

(XLI)   (XLII)   (XXXVII)
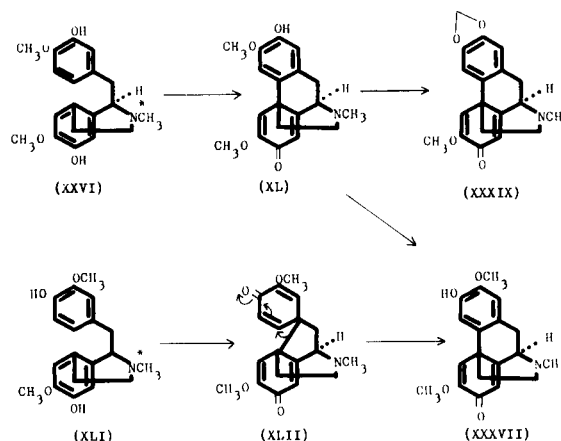
Moreover, supporting evidence for the above suggestion came from the isolation of pallidine (XXXV), an antipode of isosalutaridine (XL), from *Corydalis pallida* var. *tenuis*. Thus, Kametani (47), in the hope of finding structure of type XL, studied the basic fractions of the above plant. Pallidine was isolated in addition to sinoacutine (XXXII) and isoboldine (XXXIV). Pallidine is the first in this group of alkaloids to correspond to an actual direct *para-para* coupling product and is the enantiomer of the as yet unknown presumed intermediate in the *in vivo* conversion of reticuline (XXVI) into flavinantine (XXXVII) and amurine (XXXIX).

III. Alkaloids derived Biogenetically from Morphinandienones.

(1) Nudaurine.

Nudaurine coexists with amurine (XXXIX) in *Papaver nudicaule* var. *aurantiacum* and was assigned structure XLIII by Döpke. Nudaurine could be biosynthesized from amurine by biological reduction on the basis of its structural similarity to salutaridinol (XXIII) (21).
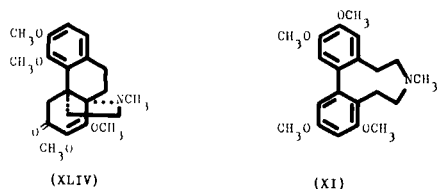
Chart 16

(XLIII)
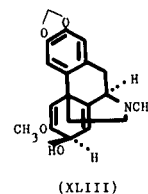
(2) Protostephanine.

Protostephanine was isolated with hasubanonine (XLIV) from *Stephania japonica* (86) and was assigned the structure XI by Takeda (82).

Chart 17

(XLIV)   (XI)

Boit (18) suggested that phenol oxidation of the bis-phenethylamine XLV, followed by reduction of the dienone XLVI and dienol-benzene rearrangement of its alcohol XLVII, afforded protostephanine (XI). On the other hand, based on the structural similarity of protostephanine (XI) with phenyldihydrothebaine (XLVIII) generated from thebaine by the action of phenyl magnesium bromide, Barton (2) suggested the following pathway; the benzyl-isoquinoline XLIX can be considered to undergo phenolic oxidation to yield the morphinandienone L, from which dienol LI could readily be derived. Rearrangement could lead to the imine LII *via* intermediate LIII, and the biological reduction would afford protostephanine (XI).

Chart 18

(XLV)   (XLVI)   (XLVII)

(XI)   (XLVIII)

(XLIX)   (L)   (LI)   (LIII)

(LII)   (XI)
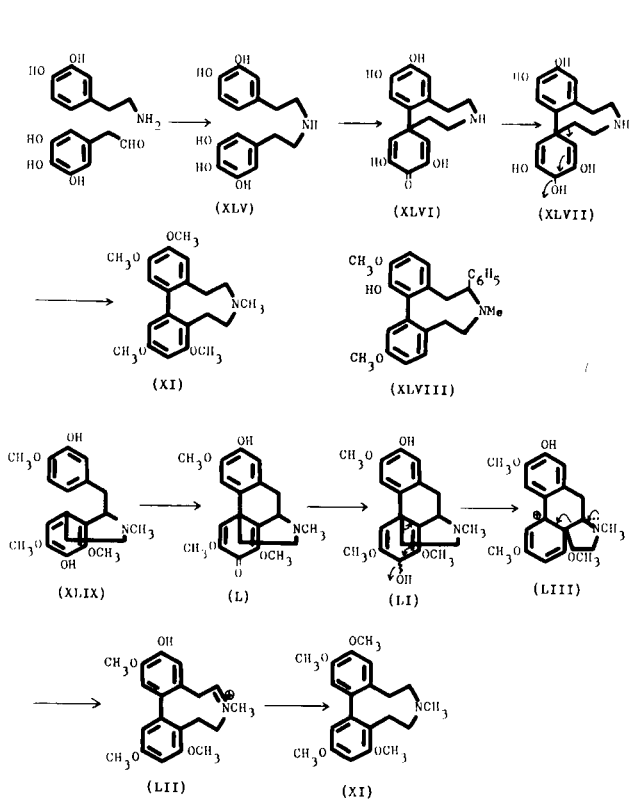
The latter theory was partially proved by the incorporation of the morphinandienone L to give protostephanine (XI) (12).

(3) 8,14-Dihydrosalutaridine and 8,14-Dihydronorsalutaridine.

Both alkaloids occur in *Croton linearis* together with crotonosine (LIII) and their structures are assigned LIV and LV, respectively (35). The former alkaloid (LIV) corresponds to an enantiomer of isosinomenine which was tentatively thought as a precursor of sinomenine (X) by Barton (12).

Chart 19

(LIII)

(LIV)   (LV)
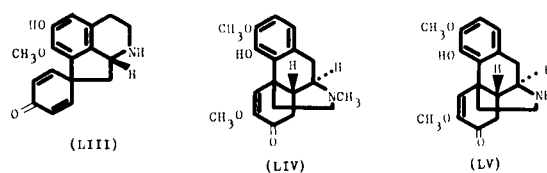
8,14-Dihydronorsalutaridine (LV) was biosynthesized from coclaurine (LVI) and norcoclaurine (LVII), and 8,14-dihydrosalutaridine (LIV) could be biosynthesized from the same precursors through the biological reduction of salutaridine (XXII) (35).
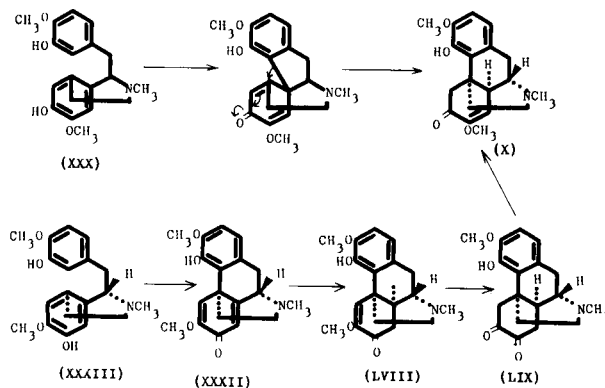
Chart 20

(LVI)   (LVII)
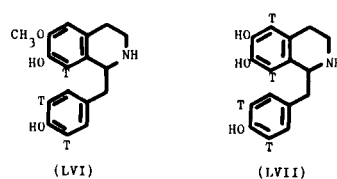
(4) Sinomenine.

Sinomenine, isolated from *Sinomenium acutum*, was assigned the structure X by Goto (29), and its biogenetic route from protosinomenine (XXX) was tentatively sug-

Chart 21

(XXX)   (X)

(XXXIII)   (XXXII)   (LVIII)   (LIX)

gested by Robinson (67,68,69,70). Recently, Barton (4) proposed another theory that (+)-reticuline (XXXIII) would first be oxidized to the morphinandienone XXXII which was an unknown compound at that time but has now been named sinoacutine. After reduction to the corresponding enone (LVIII), hydrolysis of the vinylic methyl ether, followed by methylation of diosphenol LIX to the methyl ether, would furnish sinomenine (X).

After the isolation of sinoacutine (XXXII) and the incorporation of salutaridine (XXII) into morphine (II) or thebaine (XVIII) through salutaridinol (XXIII), Barton (2) modified the latter part of the above theory; the morphinandienone (XXXII) formed by phenol oxidation of (+)-reticuline (XXXIII) would be reduced to the corresponding dienol LX, and then methylation to the methyl ether LXI, followed by hydrolysis of the vinylic methyl ether and conjugation of the ethylenic linkage from the β,γ-position (LXII) would furnish sinomenine (X).

Chart 22


(XXXII)   (LX)   (LXI)   (LXII)

(X)
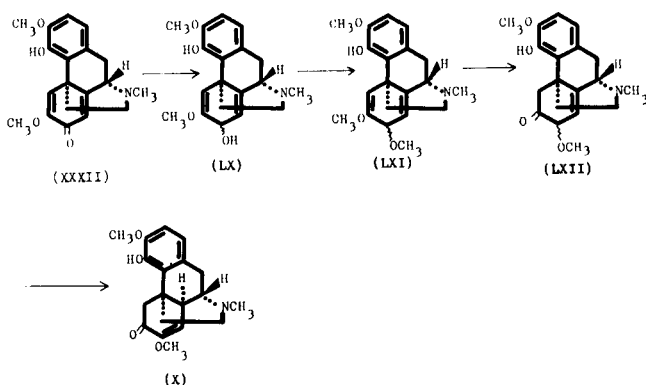
Robinson's suggestion of the above two mechanisms to sinomenine (X) was ruled out by the biosynthetic work with *Sinomenium acutum*; T-labeled protosinomenine (*cf.* XXX) was not incorporated, whereas T-labeled reticuline (*cf.* XXXIII) was incorporated to the same degree as [2-^{14}C]-tyrosine (XXV). Moreover, further support for the intermediacy of sinoacutine (XXXII) was proved by the incorporation of this into sinomenine (X) in high yield in the plant. The biosynthetic sequence (XXXIII) → (XXXII) → (X) is thus established (8), but the mechanism in the conversion of XXXII into X is still not clear.

However, T-labeled sinoacutine was not incorporated into isosinomenine (LVIII) and [1,6-OMe-^{3}H]-isosinomenine was not converted into sinomenine. Therefore, Barton postulated two possibilities to sinomenine (X) from sinoacutine (XXXII) as follows; (a) the 6-methyl group is hydrolysed first to give the diosphenol (LXIII), whose reduction would give (LXIV) and then sinomenine (X) and (b) the vinyl ether grouping of 5,6-dihydrosinoacutine (LXV) was transformed by enolization to LXVI, whose

hydrolysis, followed by methylation of demethylsino-menine (LXVII), gave sinomenine (X) (8).

Chart 23

(LXV)   (LXVI)   (X)

(XXXII)

(LXIII)   (LXIV)   (LXVII)
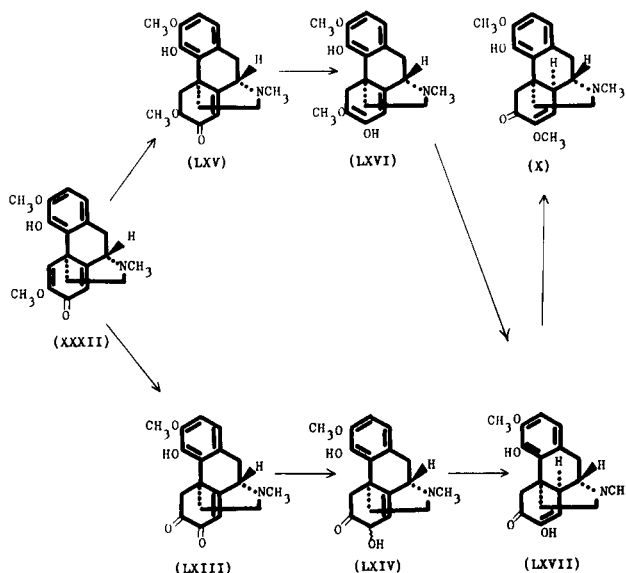
IV. Homomorphinandienones and Related Alkaloids.

(1) Androcymbine and O-Methylandrocymbine.

Ancrocymbine occurs in *Androcymbium melanthioides* together with colchicine (XIII) and melanthioidine (LXVIII) (14), and structure XII, which was established by Battersby (13) for androcymbine as the first example of a 1-phenethylisoquinoline alkaloid, was very significant from the point that it is closely related to the structure of salutaridine (XXII).

Chart 24

(XIII)   (LXVIII)

(XII)
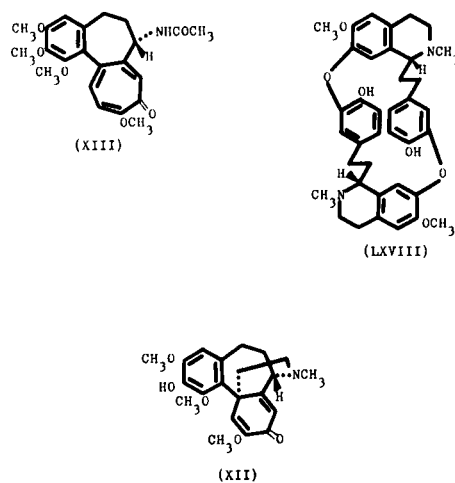
The structural similarity of androcymbine (XII) with salutaridine (XXII) indicated that the former alkaloid could be formed from the diphenolic 1-phenethyliso-quinoline LXIX in the plant. Moreover, the facts that androcymbine co-exists with colchicine, and that the absolute stereochemistry of androcymbine is shown to be the same as that of colchicine, suggest both alkaloids are biogenetically correlated (13).

The supporting evidence came from the successful incorporation of the phenethylisoquinolines LXIX and LXX into colchicine (XIII), and, further, O-methylandrocymb-ine (LXXI) was incorporated into colchicine to an unusually high extent without randomization of the label. Thus, the biogenetic route to androcymbine and colchicine was proposed by Battersby (1) as follows. Recently, O-methylandrocymbine (LXXI) was isolated from *Colchicum autumnale* (66).

Chart 25

(2) Kreysiginine and Alkaloid CC-12
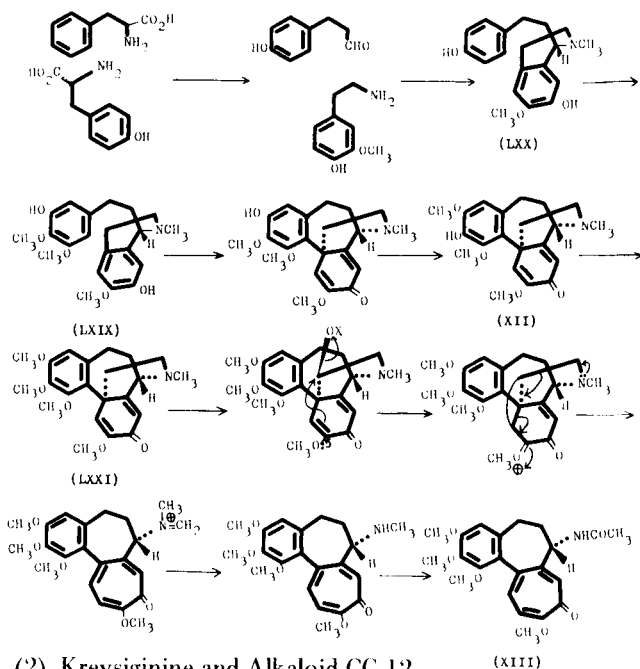
Kreysiginine has been found together with kreysigine (LXXII), kreysiginone (LXXIII), and related alkaloids, in *Kreysigia multiflora*, a member of the *Liliaceae* plant, and was assigned the structure LXXIV by X-ray analysis (16,26,34). Soon after, alkaloid CC-12, isolated from *Colchicum cornigerum*, was found to be an enantiomer of kreysiginine (16).

Chart 26
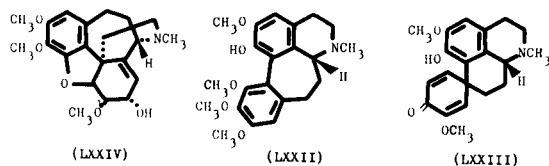
Biogenetically, the retention of an oxygenated function at the 7-position of a molecule having an oxygen bridge is in contrast to the situation which occurs in the biogenesis of morphine, but is closely similar to the biogenetic mechanism of galanthamine (LXXV).

Chart 27
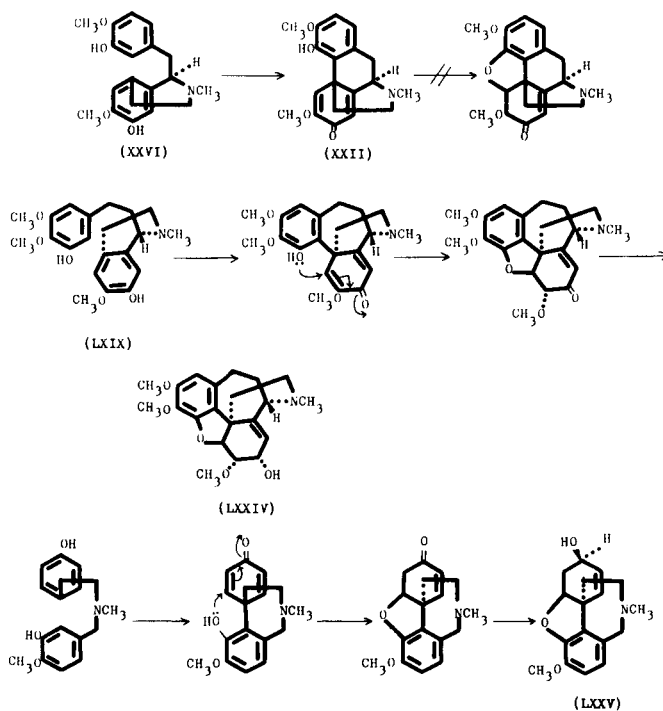
V. Biogenetic Type Synthesis.

Salutaridine (XXII) and sinoacutine (XXXII), both of which are precursors of morphine (II) and sinomenine (X), respectively, were biosynthesized by phenol oxidation of reticuline and examined before the naturally occurring substances were isolated.

Robinson (68) in 1932 suggested that laudanosoline (I) could be oxidized in a plant to the morphine type compound, and he found that the oxidation of laudanosoline (I) with chloranil in the presence of potassium acetate in ethanol afforded the dibenzopyrrocoline derivative LXXVI which was formed by the nucleophilic attack of the lone pair of electrons on nitrogen on the *o*-quinone radical LXXVII. Schöpf (72) also reported the same reaction, and Harley-Mason (33) obtained the dibenzopyrrocoline LXXVI from the alkaline ferricyanide oxidation of norlaudanosoline.

Since this type of oxidation did not afford the expected product with C-C coupling, van Tamelen called this reaction a "tantalizing possibility". In 1962, Franck (25) supposed that C-C coupling would occur by decreasing the nucleophilicity of the lone pair of electrons on the nitro-
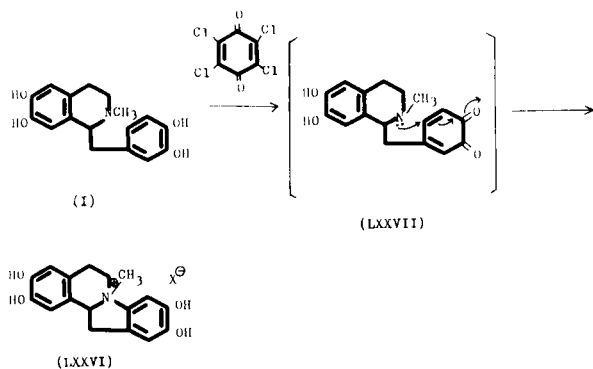
Chart 28

(I)

(LXXVII)
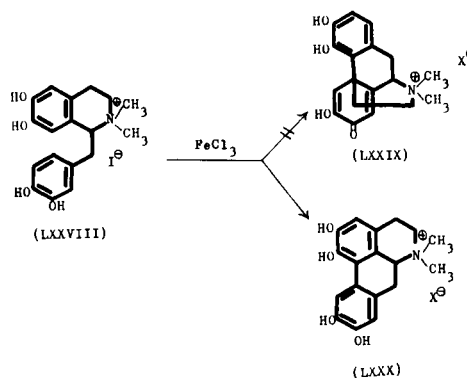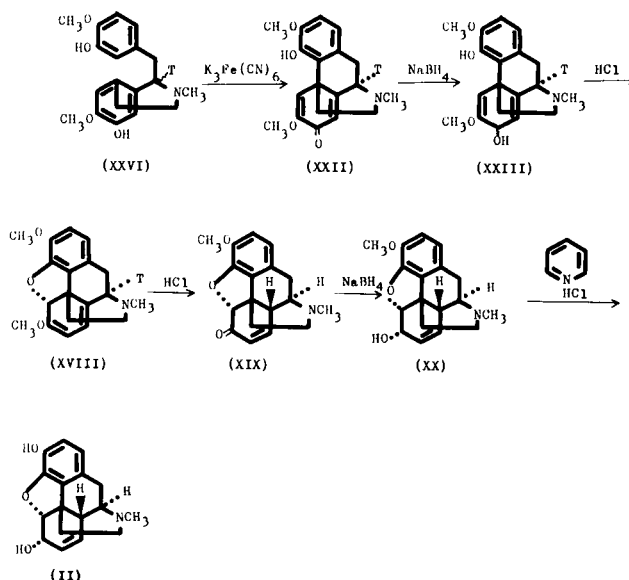
(LXXVI)

Chart 29

(LXXVIII)   FeCl₃

(LXXIX)

(LXXX)

gen, and he oxidized laudanosoline methiodide (LXXVIII) with ferric chloride, which produced not the morphine skeleton (LXXIX) but the aporphine type compound LXXX. Soon after, Barton (3,9,10) succeeded in duplicating the oxidative step in the laboratory in which the 1-benzylisoquinoline skeleton was transformed into that of the morphine alkaloids. The desired conversion was achieved with both the racemic and optically active forms of T-labeled reticuline (LXXXI), and the product was isolated by using unlabeled salutaridine as a carrier. Thus, (±)-1-[³H]-reticuline was oxidized with potassium ferricyanide and sodium bicarbonate in chloroform at room temperature to give the dienone XXII in 0.024% yield, which was reduced by sodium borohydride, followed by acidic treatment of the resulting salutaridinols (XXIII), to afford thebaine (XVIII). Thebaine (XVIII) was converted into morphine (II) through codeinone (XIX) and codeine (XX). This work constitutes a synthesis of morphine via a biogenetic pathway.

Chart 30

(XXVI)   (XXII)   (XXIII)

(XVIII)   (XIX)   (XX)

(II)

Chart 31

| (run)	(26)	Reagents		Solvent		N₂	Reaction time (hr.) temp.		Yield (%)
(1)	52 mg.	K₃Fe(CN)₆ NaHCO₃	110 mg. 200 mg.	CHCl₃ H₂O	50 ml. 100 ml.	+	1	r.t. (a)	0.024
(2)	68 mg.	MnO₂	236 mg.	CHCl₃	5 ml.	-	3	r.t.	0.011
(3)	28 mg.	KNO(SO₃)₂ AcONa	53 mg. 70 mg.	CHCl₃ H₂O	50 ml. 100 ml.	+	1	0°	0.0054
(4)	54 mg.	FeCl₃	130 mg.	H₂O	150 ml.	+	20	r.t.	0.0007

(a) r.t.: room temperature.

The transformation of reticuline into salutaridine was accomplished using the following reagents (3).

Barton (3) accounted for the low yields as follows; "even if no intermolecular coupling took place, oxidative cyclization could give several products: aporphine (isoboldine and corytuberine), pallidine and salutaridine itself. More importantly, we have found that salutaridine is oxidized more rapidly than reticuline and might therefore be largely destroyed under the conditions of its formation".

Furthermore, 8,14-dihydrosalutaridine (LIV), biosynthesized from salutaridine (35), was synthesized by the reduction of salutaridine with lithium aluminum hydride in dry tetrahydrofuran (8). In this reaction, salutaridinol -I and -II (XXIII) were also formed.

Chart 32

(XXII)

LiAlH$_4$

(XXIII)   (LIV)
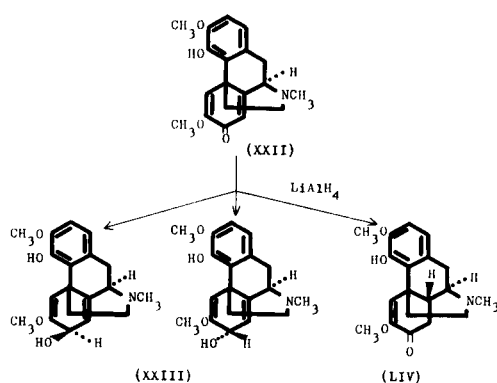
In an attempt to synthesize salutaridine (XXII) from rac-reticuline (LXXXI), Franck (23,24) oxidized reticuline with manganese dioxide on silica gel (0.08 mm. E. Merck) but obtained instead the morphinandienone XXXV in 4%

yield together with (±)-isoboldine (XXXIV) [Franck named it as isosalutaridine because the natural product had not been found, but later Kametani (47) isolated this compound and named it pallidine, the name of which is used in this review]. The fact that salutaridine could not be obtained in this reaction indicates the tendency for *para-para* coupling rather *para-ortho* coupling. Moreover, reticuline was adsorbed on the surface of silica gel during oxidation, this system plays the role of dilution in which the concentration of reticuline on the surface of the oxidant is lowered and the distance between both compounds is enlarged thus hindering the intermolecular reaction and favoring the yield of pallidine. Furthermore, Franck pointed out that the phenol oxidation in the state adsorbed on a carrier would be similar to an enzymic reaction in the cell.

Chart 33

(LXXXI)   (XXXV)   (XXXIV)
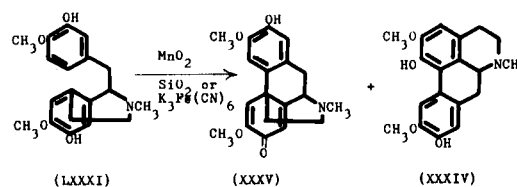
Kametani (41) oxidized reticuline (LXXXI) with potassium ferricyanide in a two-phase system consisting of 5% aqueous sodium bicarbonate and chloroform and obtained (±)-pallidine together with (±)-isoboldine. Similar treatment of (+)-reticuline gave pallidine and isoboldine (39a). The yield of pallidine may be changed by altering the reagents and reaction conditions as follows (51).

Chart 34

Reagents	Mole	Alkali	Solvent	Reaction time (hr.)	temp.	Yield (%) (XXXIV)	(XXXV)
K$_3$Fe(CN)$_6$	2.5	5% NaHCO$_3$	CHCl$_3$	1.5	r.t. (a)	+	0.2
K$_3$Fe(CN)$_6$	2.5	5% NaHCO$_3$	CHCl$_3$	1	r.t.	1.1	1.1
K$_3$Fe(CN)$_6$	2.5	5% NaHCO$_3$	CHCl$_3$	0.5	r.t.	0.4	0.95
K$_3$Fe(CN)$_6$	4	5% NaHCO$_3$	CHCl$_3$	0.25	r.t.	2	+
K$_3$Fe(CN)$_6$	4	5% NaHCO$_3$	CHCl$_3$	1	r.t.	5	3
Ag$_2$CO$_3$-celite	2.5	5% NaHCO$_3$	CHCl$_3$	1.5	r.t.	3	1
Ag$_2$CO$_3$-celite	2.5	5% NaHCO$_3$	CHCl$_3$	9	0°	+	0.5
VOCl$_3$	1		CHCl$_3$	2	r.t.	1	0.3

(a) r.t.: room temperature

Kametani (55) oxidized the diphenolic isoquinoline (LXXXII), (LXXXIII), and (LXXXIV) in order to obtain salutaridine or pallidine in good yield, but instead obtained the aporphine type compounds (XXXIV and XXXVI).

The synthesis of pallidine (XXXV) by phenol oxidation suggested the formal syntheses of amurine (XXXIX) and flavinantine (XXXIII), both of which are biogenetically equivalent to pallidine. Moreover, O-methylation of pallidine furnished O-methylflavinantine (LXXXVII), which was recently isolated from an Indian plant by Gopinath.
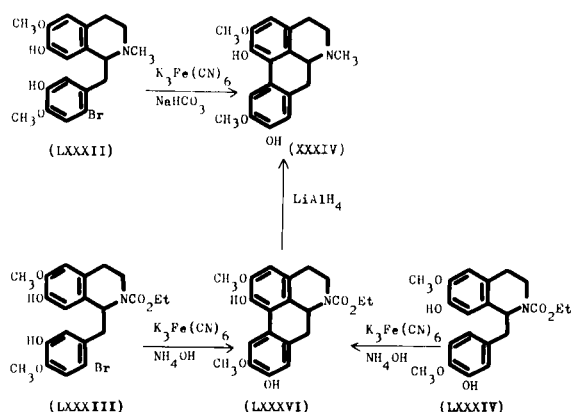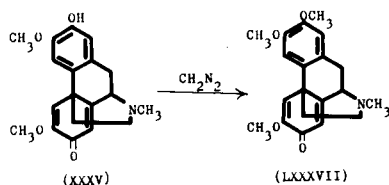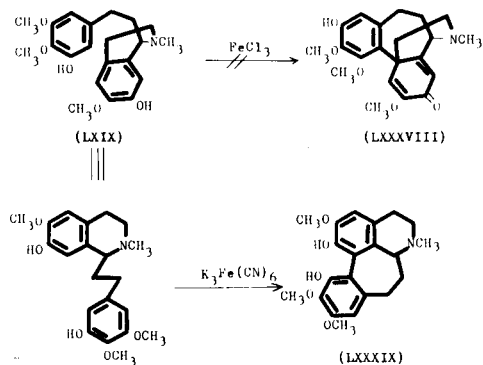
Chart 35

(LXXXII) (XXXIV)

(LXXXIII) (LXXXVI) (LXXXIV)

Chart 36

(XXXV) (LXXXVII)

The biogenetic synthesis of androcymbine (XII) using the 1-phenethylisoquinoline (LXIX) was examined (15,45) but the homoaporphine (LXXXIX) coupled at the ortho-ortho position to hydroxy group (15) was obtained instead of the androcymbine type compound LXXXVIII.

Chart 37



(LXIX) (LXXXVIII)

(LXXXIX)

However, the homomorphinandienone type compound XC was successfully sunthesised by phenol oxidation of homoreticuline (XCI) with potassium ferricyanide by Kametani (40).

Chart 38

(XCI) (XC)
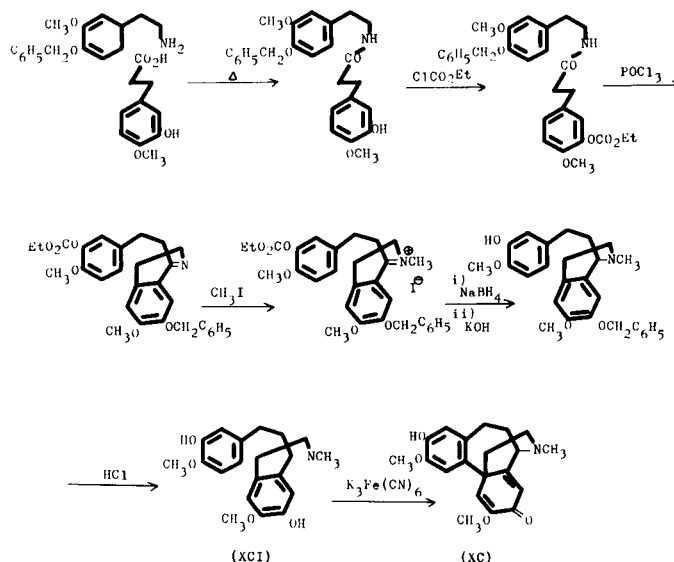
Colchicine (XIII), which could be biogenetically derived from androcymbine (XII), was synthesized by the phenol oxidation of Scott (73) and Tobinaga (45), respectively, but these routes were not in accordance with the biogenetic pattern.

Chart 39

(XLIX) (L)

(XCII) (XCIII) (XCIV) R = H
(XCV) R = CH₃

(XI)
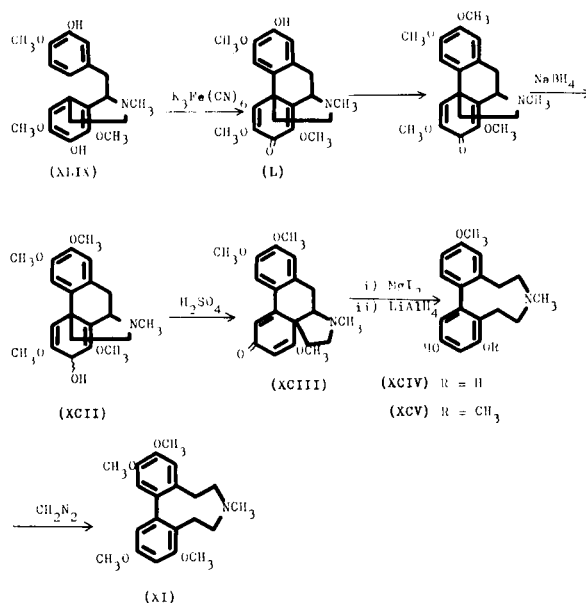
Protostephanine (XI) was biosynthesized from the morphinandienone (L), which is formed from a diphenolic isoquinoline (XLIX) in the plant. Battersby (12) succeeded in the synthesis of protostephanine by a route related to the biosynthetic pathway as follows:

The diphenolic isoquinoline XLIX was subjected to phenol oxidation with alkaline ferricyanide to afford the morphinandienone (L) together with isoboldine XXXIV. O-Methylation of this dienone L, followed by borohydride reduction, afforded the epimeric enols XCII, which were subjected to a rearrangement catalysed by sulfuric acid. Heating of the resulting dienone (XCIII) with magnesium iodide, followed by reduction with lithium aluminum hydride, gave two phenols, XCIV and XCV, which an O-methylation with diazomethane yielded protostephanine (XI).

VI. Non-Biogenetic Type Synthesis.

In 1963, Barton (3,9,10) investigated the transformation of thebaine (XVIII) into the morphinandienone, salutaridine (XXII), in order to examine whether the morphinandienone VI would be formed by phenol oxidation of reticuline (LXXXI) and would be a precursor of morphine (II), and whether this morphinandienone would be stable in the closed form (XVI).

Thebaine (XVIII) was treated with metallic sodium in liquid ammonia and the resulting dihydrothebaine-φ (phenolic dihydrothebaine) (XCVI) was acetylated with acetic anhydride in pyridine. Oxidation of the acetate XCVII with selenium dioxide and then manganese dioxide, followed by saponification, afforded salutaridine (XXII), which was stable to acids and bases. Thus the biogenesis of morphine was proved to proceed as suggested by Stork, Ginsburg, and Battersby (3,9,10).

Chart 40
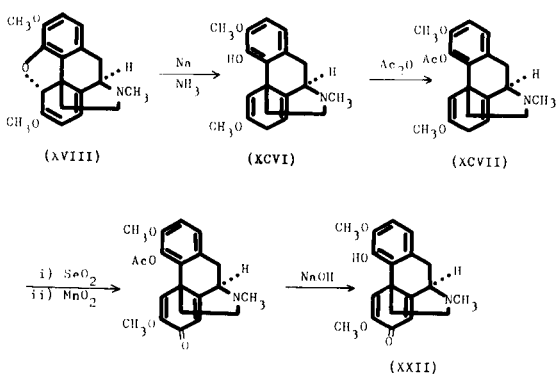
Kametani (43) successfully discovered a general synthetic method of preparing morphinandienone type alkaloids by applying the Pschorr reaction which had been used widely for the synthesis of the aporphine alkaloids.

The Pschorr aporphine synthesis is a nucleophilic reaction of the 8-position [arrow a in (XCVIII)] of the isoquinoline ring with the aromatic cation derived from 1-(2-amino-benzyl)isoquinoline (XCIX) via its diazonium salt (C). However, it is possible that the nucleophilic attack from the carbon of 8a (arrow b) and 4a (arrow c) positions to the aromatic cation could take place due to the influence of the E-effect of the alkoxy-group on the isoquinoline ring, leading to the formation of the dienone CI (6,7) or the morphinandienone CII, respectively. Moreover, the aromatic cation would react with the active methylene (arrow d) or basic nitrogen (arrow e) to form an isopavine type compound CIII or dibenzopyrrocoline (CIV), respectively (43).

Chart 41
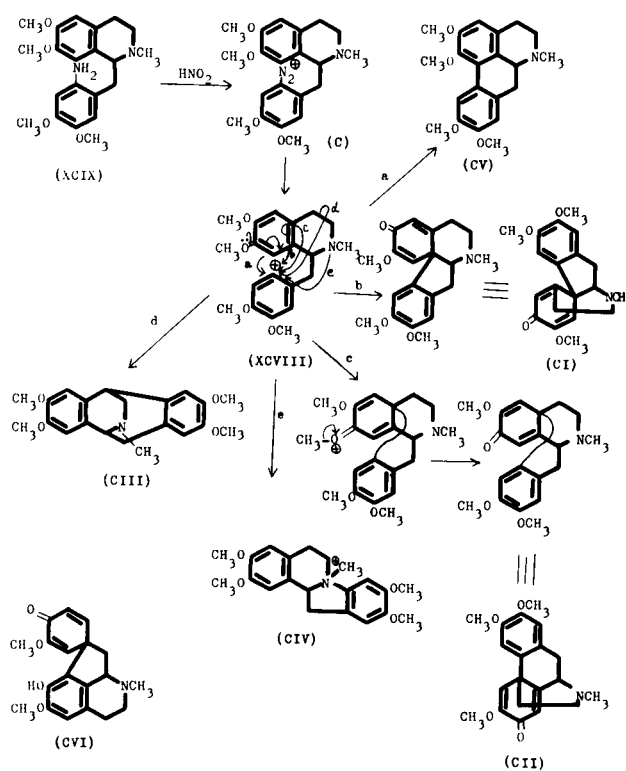
Kametani (43) diazotized 2'-aminolaudanosine XCIX with a slight excess of sodium nitrite in N-sulfuric acid, and the resulting diazonium salt (C) was decomposed thermally to give a cyclohexadienone together with laudanosine and glaucine (CV). The structure of the dienone was assigned to the morphinandienone (CII) on the basis of the following spectral evidence.

Molecular formula, $C_{20}H_{23}NO_4$, which was verified by mass spectrometry of the free base (M^+; m/e 341) and microanalysis of its methiodide, indicated the loss of one methyl group and the α-methoxylated cross-conjugated

cyclohexadienone system was well supported by its ir and uv (in methanol; λ max 238 and 282 mμ, ε 13,500 and 6,460), and mass spectra. The nmr spectrum (τ in deuterio-chloroform) showed the N-methyl and three O-methyl, two olefinic protons (3.18, 8-H and 3.73, 5-H, 1H each) and two aromatic protons as singlets. These data also indicated the loss of one methyl group and the presence of α-methoxylated cross-conjugated cyclohexadienone system.

These spectral data supported the structure of the 'morphinandienone' as well as the second dienone structure CI. However, the latter structure was ruled out by further spectral consideration and the following reactions.

The ratio of the molecular extinction coefficient at 238 and 282 mμ in the uv spectrum showed 2:1 (13,500: 6,400), which corresponded to that of morphinandienone-type compounds. Although one β-olefinic proton standing next to the methoxy group in orientalinone (CVI) reso-nanced at τ 4.08 in the nmr spectrum, no olefinic protons resonating at a higher field than τ 3.8 appeared. These facts do not support the structure for the second dienone (CI). Moreover, the above assumption was proved to be true by the synthesis of the same dienone from the second aminoisoquinoline (CVII).

Diazotization of the second aminoisoquinoline CVII, followed by thermal decomposition of the diazonium salt,
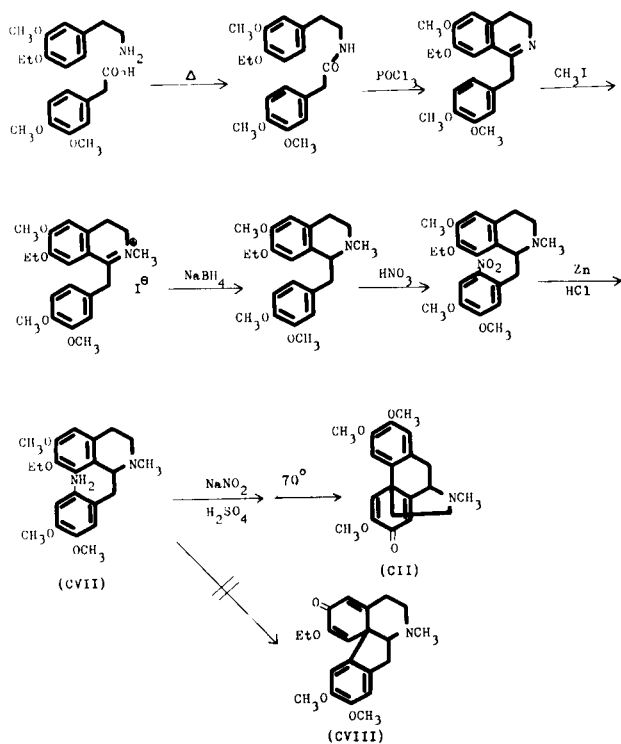
gave a cyclohexadienone in 1.4% yield, whose nmr spectrum showed three methoxy groups and no signal due to the ethyl group. If the structure of the cyclohexadienone from the first aminoisoquinoline were CI, the product from the second one would be the compound CVIII, which should be different from the product obtained from the first one.

However, the products obtained by diazotization of the two aminoisoquinolines XCIX and CVII, followed by de-composition, were proved to be identical by full spectro-scopic data (ir and nmr) and mixed m.p. determination of their methiodides. These data proved the product to be the morphinandienone type compound, (±)-O-methyl-flavinantine (CII), and the ir spectrum of the synthetic sample was superimposable on that of natural O-methyl-flavinantine, synthesised from flavinantine.

This reaction was applied to the synthesis of salutari-dine (XXII) by Kametani, and the total synthesis of morphine (II) was accomplished as follows (46).
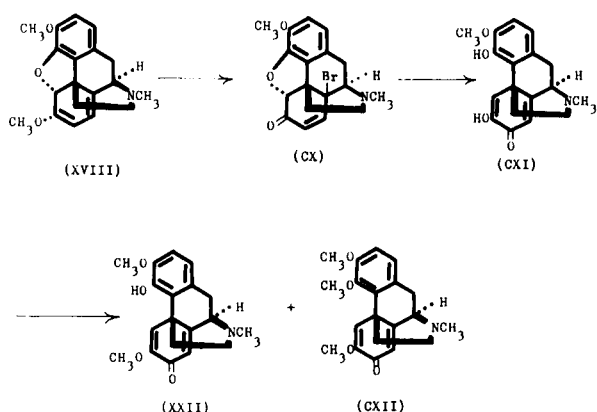
Optical resolution of (±)-2'-aminobenzylisoquinoline (CIX) was efficiently achieved via the salt of di-p-toluoyl-tartaric acid. The R-(-)-2'-aminobenzylisoquinoline (CIX-A) was diazotized with sodium nitrite and sulfuric acid, and the resulting diazonium salt was decomposed thermally without a catalyst to give salutaridine (XXII). The reduc-tion of salutaridine with sodium borohydride, followed by dehydration of the resulting epimeric salutaridinols (XXIII) in the presence of N hydrochloric acid, furnished thebaine (XVIII). Since thebaine has been converted into morphine (II) as shown in the following scheme, a formal total synthesis of morphine and its related alkaloids has been accomplished.

Chart 42

Chart 43
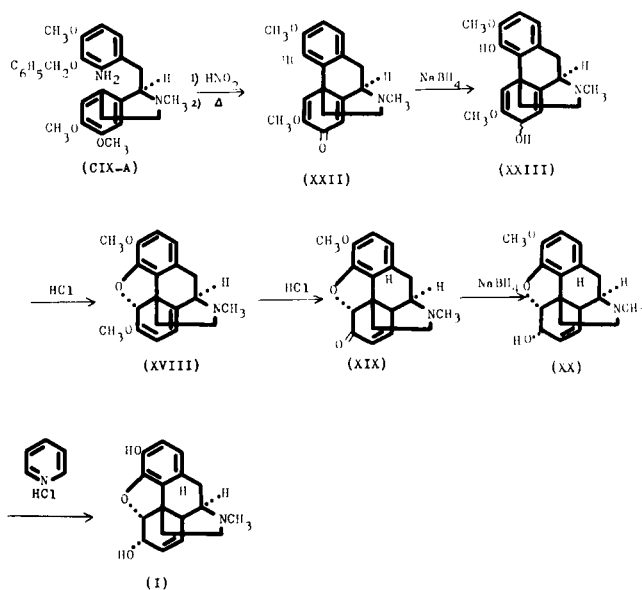
Recently, Gates (63) also prepared salutaridine (XXII) from thebaine (XVIII). 14-Bromocodeinone (CX), easily available in one step from thebaine, was dissolved in Claisen's alkali and then neutralized to give 6-O-demethyl-salutaridine (CXI), which was methylated with diazomethane to yield salutaridine (XXII) as the main product along with a trace of O-methylsalutaridine (CXII).

Chart 44

(XVIII)   (CX)   (CXI)

(XXII)   +   (CXII)

Moreover, morphine was synthesized by classic methods by Gates (27), Ginsburg (22), and Morrison (60), respectively.

S-(+)-2'-Aminobenzylisoquinoline (CIX-B), obtained by the optical resolution of the racemate (CIX) with di-p-toluoyltartaric acid, was subjected to diazotization, followed by thermal decomposition, to give sinoacutine (XXXII), which was transformed into (+)-thebaine (CXIII), an antipode of natural thebaine, via sinoacutinol (LX). Okabe (62) has recently succeeded in the conversion of natural thebaine into the enantiomer (CXIII) of sinomenine; so, the synthesis of (+)-thebaine consitutes the total synthesis of sinomenine (X) (46).

Chart 45

(CIX-B)   (XXXII)   (LX)

(CXIII)   (X)
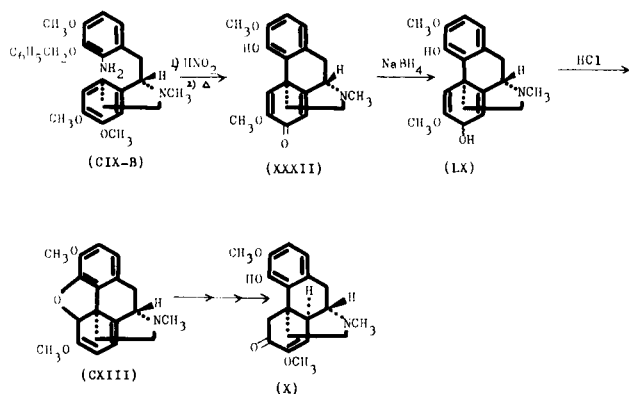
Sinomenine would be biosynthesized from sinomeninone (LXVII), formed from dehydrodiosphenol (LXIII) which would also be a key compound to the synthesis of sinomenine. As a model experiment, Kametani (52,54, 57) synthesized the dehydrodiosphenol CXIV, having the same skeleton as LXIII, via the Pschorr reaction, from the three 2'-aminoisoquinolines CXV, CXVI, and CXVII.

Furthermore, the debenzylation of the morphinandienone CXIX which was obtained by the Pschorr reaction of 2'-aminobenzylisoquinoline CXVIII followed by reduction would yield the diosphenol CXX (53).

Chart 46

(CXV)   (CXIV)   (CXVI)

(CXVII)

(CXVIII)   (CXIX)

(CXX)   (X)
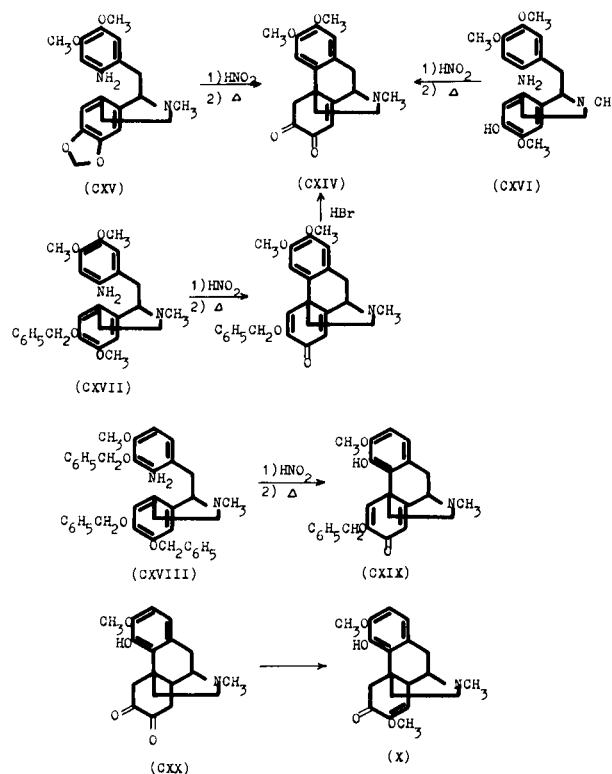
The biogenesis of amurine (XXXIX) would involve para-para oxidative coupling of (-)-reticuline (XXVI), followed by subsequent cyclization of the 2-methoxy-phenol (XL). However, amurine could not be synthesized by phenol oxidation of the reticuline in the laboratory since the structure for amurine has a methylenedioxy group at the para-position and a hydrogen at the ortho-position to the oxidative coupling site. Therefore, the Pschorr reaction is a suitable method for the synthesis of amurine. Thus, the 2'-aminobenzylisoquinolines CXXI and CXXII were independently diazotized as usual and decomposed thermally at 70° to give the same dienone, whose spectral data were superimposable on that of natural amurine (44), which corroborated the suggested structure (XXXIX) by Döpke.

Chart 47
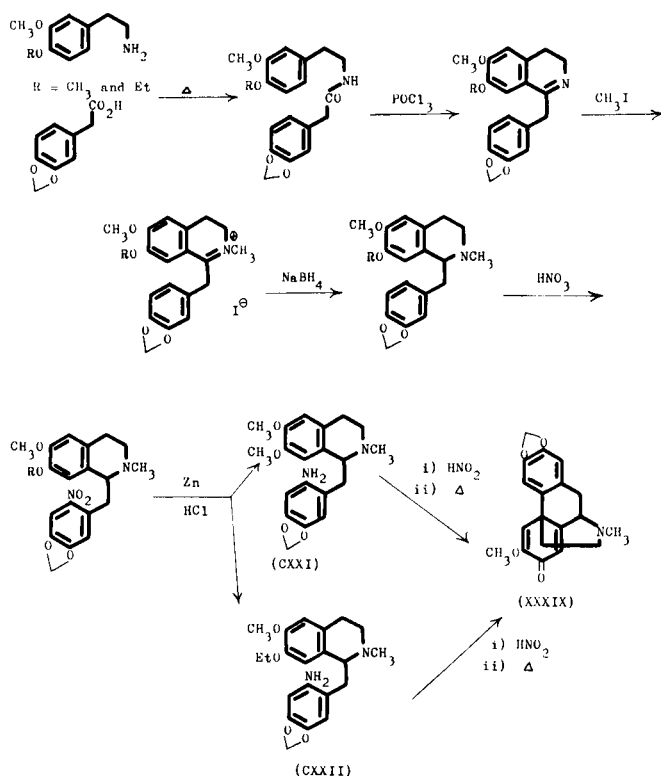
Flavinantine (XXXVII) is biosynthesized from reticuline (XXVI) by the *para-para* oxidative coupling, but the reproduction of this reaction in the laboratory would be difficult due to the fatal defect of phenol oxidation itself,

Chart 48
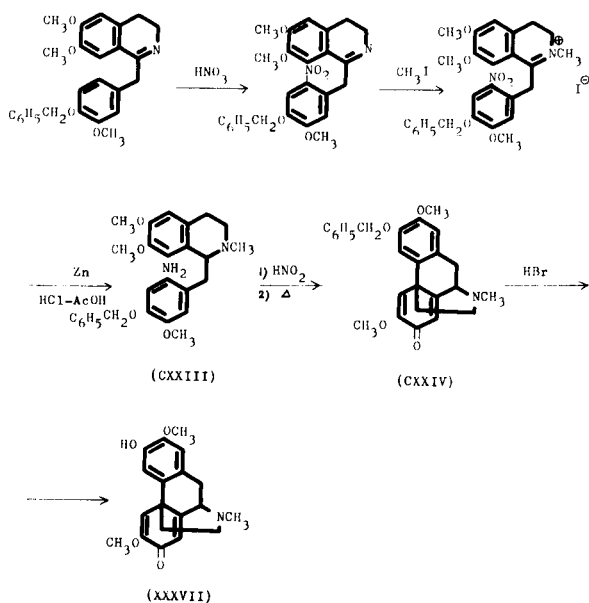
so the Pschorr reaction was applied to the synthesis of flavinantine by Kametani (56). Thus, the 2'-aminobenzyl-isoquinoline CXXIII was subjected to the Pschorr reaction, and the resulting morphinandienone CXXIV was debenzylated with 48% hydrobromic acid to afford flavinantine (XXXVII).

Pallidine (XXXV) was synthesized from 2'-amino-benzylisoquinoline (CXXV) by the same method for flavinantine (48).

Chart 49
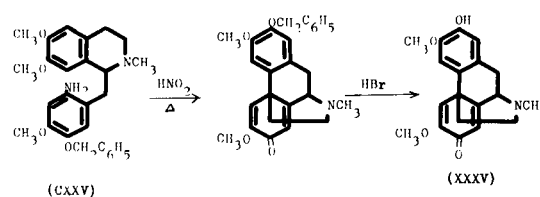
The morphinandienone CXXVI, which would be a key intermediate to protostephanine (XI) in its biogenesis and chemical synthesis, was synthesized from the 2'-amino-benzylisoquinoline CXXVII by the Pschorr reaction (12). The morphinandienone was converted into protostephanine as described above (12).

Chart 50
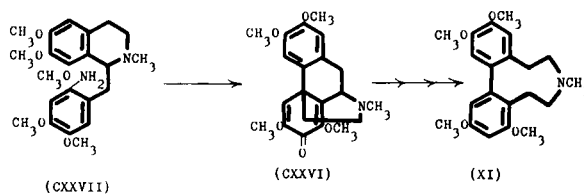
Protostephanine was synthesized by classic methods by Takeda (83) and Brossi (64), respectively.

The homomorphinandienone system CXXVIII was synthesized by the Pschorr reaction from the 2'-aminophen-ethylisoquinoline CXXIX, whose structural assignment was based upon spectral speculation and by the alternative synthesis of the second 2'-aminoisoquinoline CXXX which ruled out the other possible coupling product CXXXI (42).

Based on the above reaction the 2'-aminoisoquinoline CXXXII was subjected to the Pschorr reaction as usual to give the spiro-isoquinoline CXXXIII as a main product (49); photolytical decomposition of the corresponding diazonium salt afforded O-methylandrocymbine (LXXI), which is found naturally in Colchicum autumnale. The latter method is the first example of the annular coupling in the photolytic decomposiiton of the diazonium salt (50).
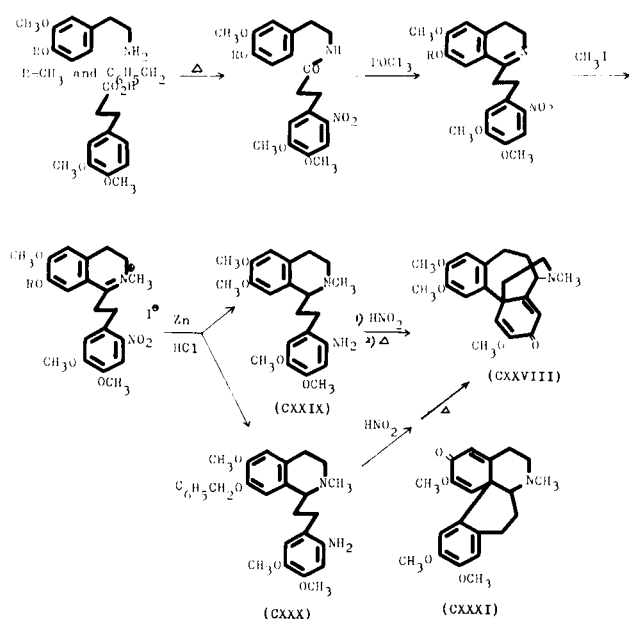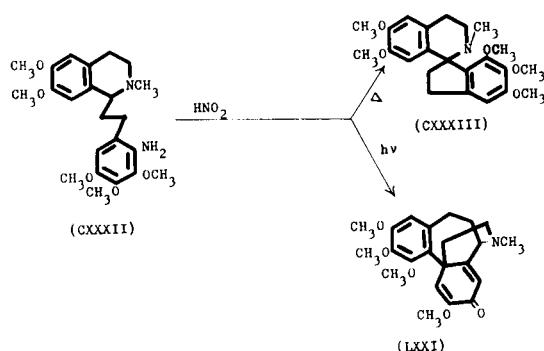
Chart 51

Chart 52

(LXXI)

Total synthesis of colchicine (XIII), derived biogenetically from androcymbine, was achieved by Eschenmoser (74), van Tamelen (87), Nakamura (81), and Woodward (88), respectively, by splendid methods.

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