SYNTHESES OF ISOQUINOLINE ALKALOIDS BY A SYSTEMATIC DESIGN

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The synthetic design of isoquinoline alkaloids from simple compounds derived by systematic retro-synthesis and transformation by either phenolic oxidation, Pschorr reaction, photolytic reaction, benzyne reaction, or thermolysis are described.

Many organic compounds found in Nature contain a heterocyclic ring system and have shown interesting physiological activity. Recently, the structure of many of these compounds was systematically determined by physical-chemical methods, such as uv, ir, nmr, ord, cd, and mass spectra, and in some cases by X-ray analysis. On the other hand, there is no routine method for the total synthesis of such natural products.

While biogenetic patterned syntheses have proved to be a most reasonable route to many natural products, its general application is often limited by the inability to direct coupling reactions as well as by poor overall yields. Thus, we have search for a more skillful synthetic design and have uncovered the following useful principle.

According to this principle, carbon-oxygen and carbon-nitrogen bonds such as C-O or C-N in the desired compound should be formed in the final step of the synthe-

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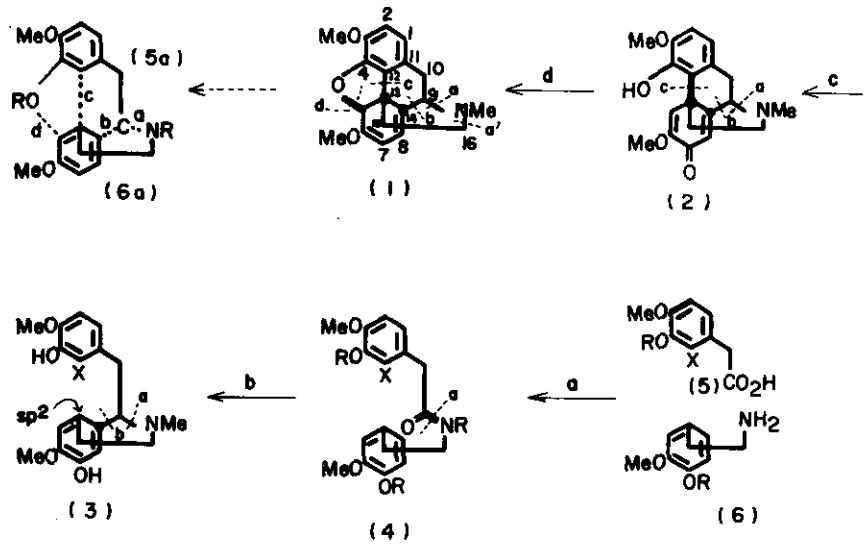
† Presented at Gordon Research Conferences in New Hampshire (June 26th, 1973) by Tetsuji Kametani.

sis and quaternary carbon atoms should be derived from sp^2 carbon atoms. This is illustrated by the synthetic design of thebaine (1), a complicated isoquinoline alkaloid.

As shown in Chart 1, thebaine (1) has two carbon-hetero atom bonds, namely, C-O and C-N, and two quaternary atoms shown as heavy dots. Now, if we cut the four bonds at a,b,c, and d, two fragnets, (5a) and (6a), are obtained. Since carbon-hetero atom cleavage occurs usually between the hetero atom and the more complicated carbon, the C-N bond is preferentially dissected at a rather than a'. Moreover, the quaternary carbon atom at C_{13} should be converted into an sp^2 carbon and thus afford the aromatic ring in fragment (6a). Based on the premise that these two fragments could be the key starting materials, the carboxylic acid (5) and the phenethylamine

Chart 1



(6) can be considered as their synthetic equivalents. Thus, condensation of (5) with (6) would effect the formation of bond (a) followed by Bischler-Napieralski reaction of the resulting amide (4) to form bond (b). Phenolic oxidative coupling of the tetrahydroisoquinoline (3) involving the sp^2 carbon atom then provides the bond formation (c) where the tetracycle (2) now contains a quaternary carbon atom. Finally, allylic dehydration of the dienol derivedfrom(2)could form bond (d) to afford thebaine (1).

Based on this principle, many isoquinoline alkaloids have been synthesized by the following key reactions which are classified according to the type of bonds that are formed.

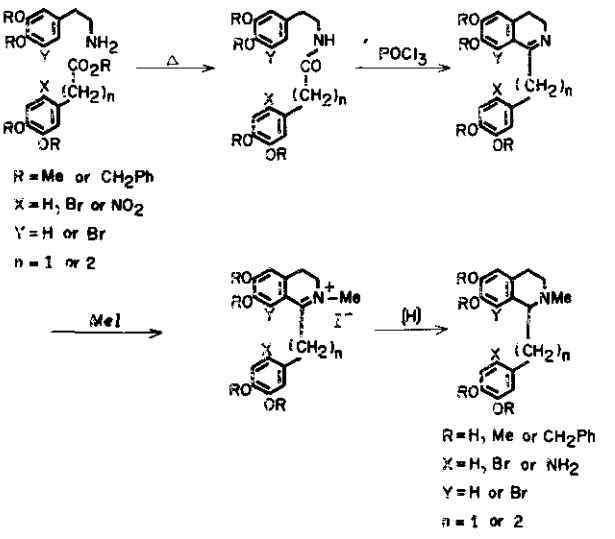
Chart 2

Key Reaction	Bond Formation
Phenolic oxidation	C−C, C−O
Pschorr reaction	C−C
Photolytic reaction	C−C
Benzyne reaction	C−C, C−N
Thermolysis	C−C, C−N

Accordingly phenolic oxidation[1] leads to bond formation between C and C or C and O, providing a biomimetic-type route to natural products, while both the Pschorr reaction[2] and the photolytic reaction[3] effect bond formation between C and C. In contrast the benzyne reaction[4] as well as the thermolytic reaction[5] induce bond formation between C and C or C and N.

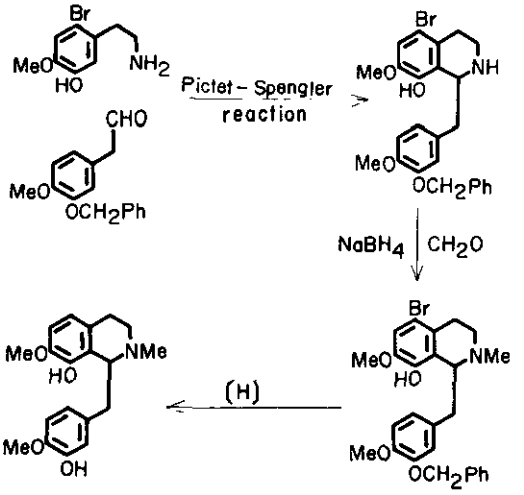
In employing these principles, the key starting materials were usually prepared by sequences which involved the Bischler-Napieralski cyclization reaction[6], thus, fusion of a phenethylamine with a carboxylic acid gave the amide which was cyclized with phosphorus oxychloride to afford the 3,4-dihydroisoquinoline followed by quaternization and reduction to furnish the desired intermediate isoquinoline.

Chart 3



In special cases such as the synthesis of cularine, the key synthetic precursors were obtained through an alternative route involving the Pictet-Spengler reaction.[7] This is illustrated in Chart 4, where the isoquinoline precursor of cularine was synthesized by blocking the usual cyclization site with a bromine atom and activation of the aromatic ring with a hydroxyl group to effect the desired condensation.[8]

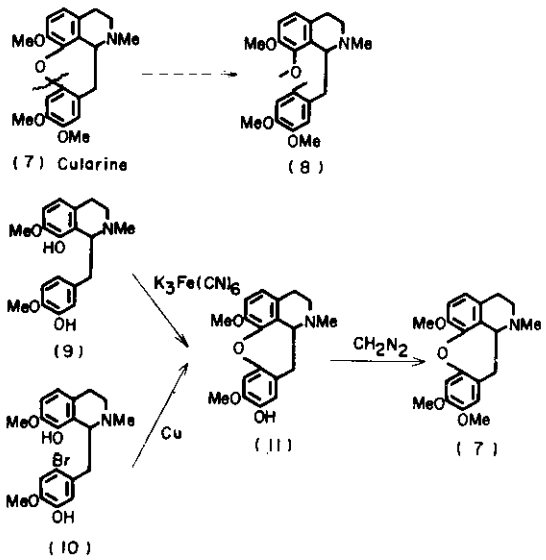
Chart 4



Considering now the synthesis of cularine (7) according to our principle (Chart 5), cleavage of the C-O bond would afford the fragment (8). Since (8) is synthetically equivalent to the diphenols (9) and (10), it could be anticipated that these would be useful precursors for the synthesis of the alkaloid (7). In fact oxidation of (9) with alkaline ferricyanide gave demethylcularine (11) which was also obtained by the Ullmann reaction of the bromo-intermidiate (10) in the presence of copper. Methylation of (11)

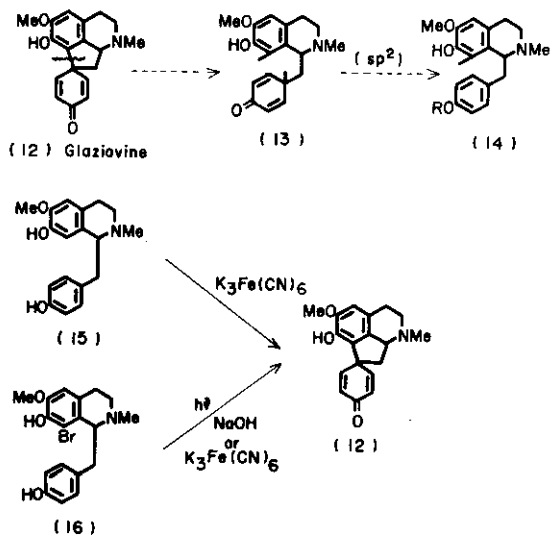
then afforded cularine (7).[8,9]

Chart 5



This concept was also applied to the synthesis of the proaporphine, glaziovine (12) (Chart 6), where the initial cleavage to the fragment (13) with a quaternary carbon

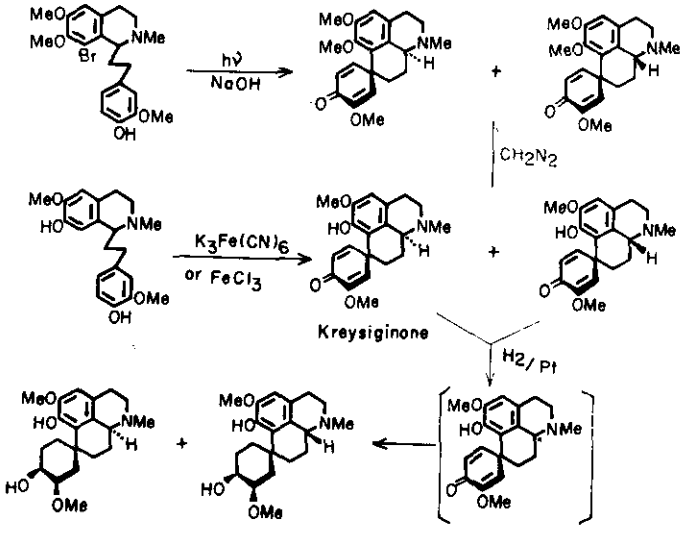
Chart 6



atom would be followed by rearrangement to yield the fragment (14) with an sp^2 type carbon. This, in turn, is synthetically equivalent to the compounds (15) and (16). Based on this reasoning, phenolic oxidation of both (15) and (16) gave glaziovine (12),[10,11] and photolysis of (16) with a Hanovia 450 W mercury lamp, equipped with a pyrex filter in an excess of sodium hydroxide, also yielded (12) in moderate yield.[11]

Similarly, photolysis of the bromo-monophenol yielded the two dienones, shown at the top of Chart 7, while phenolic oxidation of the diphenolic phenethylisoquinoline gave kreysiginone and its isomer, which were separated by fractional crystallization.[13] Although hydrogenation of the mono-phenolic dienones on palladium charcoal gave the corresponding cyclohexanone derivatives, reduction with platinum afforded a mixture

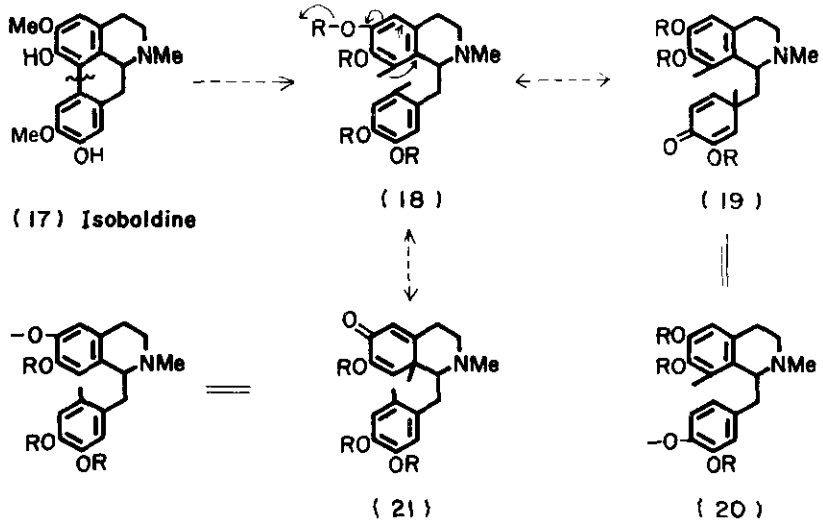
Chart 7



of the cyclohexanols in the same ratio as the dienones. This finding indicated that the homoproaporphines were absorbed on platinum catalyst in a manner whereby a hydrogen at the 6a-position was homolytically ruptured to yield an intermediate which was then hydrogenated to the cyclohexanols.[14]

In extending this concept to aporphines isoboldine (Chart 8) should cleave to form the fragment (18) which could then tautomerize to give either the fragments (19) and (20) or (21).

Chart 8

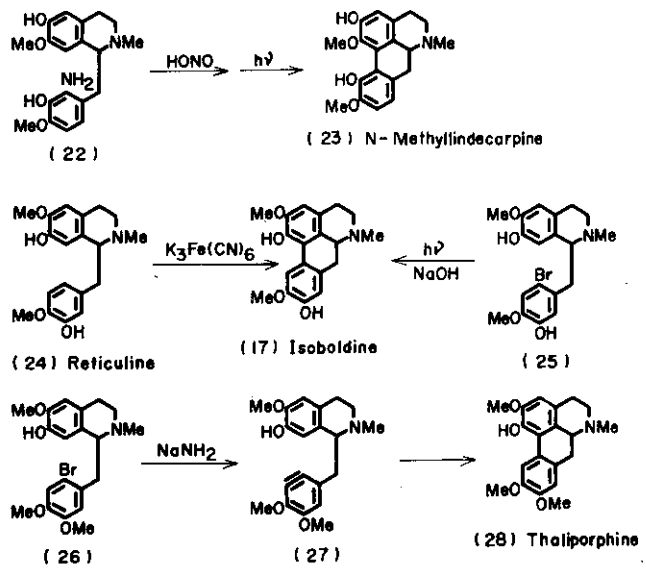


Alternatively, the fragment (18) is also synthetically equivalent with the isoquinolines (22), (24), (25), and (26), which have been used as key starting materials in the synthesis of the aporphine alkaloids (Chart 9). Since aminoisoquinoline have been previously employed in the Pschorr synthesis to give products in poor yields we

modified this reaction by thermal decomposition without catalyst or by photolytic decomposition of the diazonium salt derived from the aminoisoquinoline (22) to afford the aporphine, N-methyllindecarpine (23) in a moderate yield.[15]

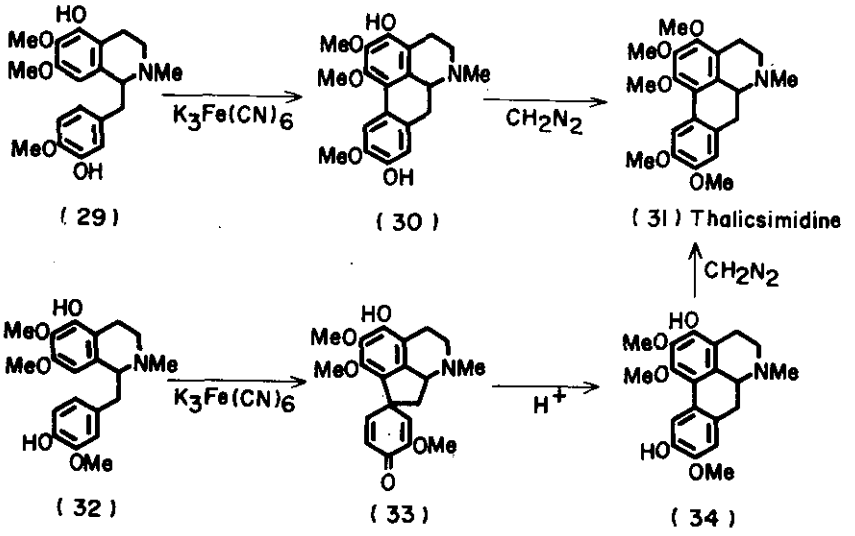
Moreover, isoboldine (17) was obtained by phenolic oxdiation of reticuline (24)[16] as well as by photolysis of the diphenolic bromoisoquinoline (25),[17] while thaliporphine was synthesized by a benzyne reaction of the phenolic bromoisoquinoline (26) with sodium amide in liquid ammonia.[18]

Chart 9



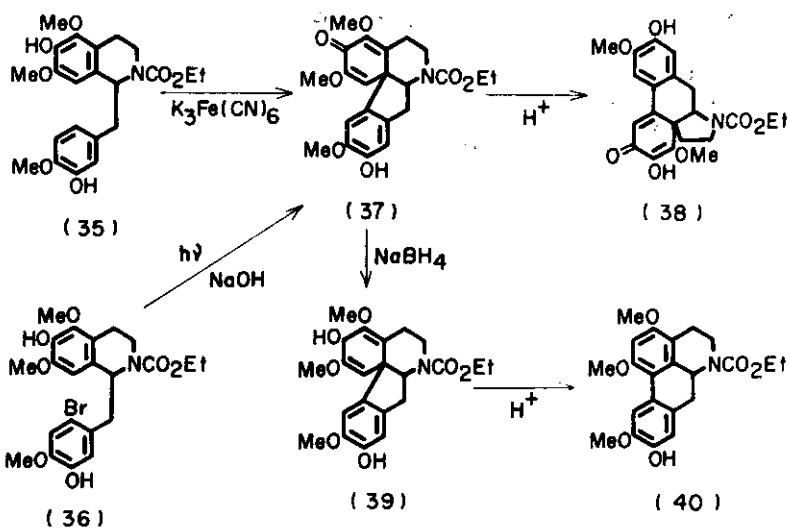
Returning now to the cleavage of isoboldine (17), the second postulated fragment (20) (Chart 8) can be considered as equivalent to the isoquinoline (32) (Chart 10). Indeed, when (32) was oxidized with potassium ferricyanide to the proaporphine (33), dienone-phenol rearrangement of (33) followed by methylation afforded the aporphine alkaloid, thalicsimidine (31), which was also obtained by phenolic oxidation of the diphenolic isoquinoline (29), equivalent to the first fragment (18) followed by methylation.[19]

Chart 10



The third fragment (21), visualized as useful for the synthesis of aporphines, (Chart 8), corresponds synthetically to the key compounds (35) and (36) (Chart 11). Based on this reasoning, the urethane (35) was converted into the dienone (37) by phenolic oxidation[20] and was also obtained from the phenolic bromo-compound (36) by photolysis.[21] However, acid rearrangement of this dienone (37) gave the enone (38) and not the expected aporphine.[20-22] Although the dienol (39), prepared from the dienone by sodium borohydride reduction, was successfully converted into the aporphine type compound (40) by "magic methyl", methyl fluorosulfonate, CH_3OSO_2F.[23]

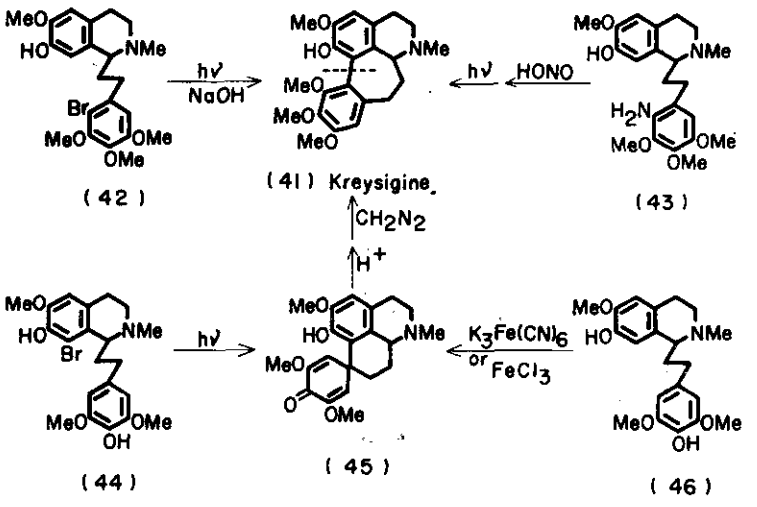
Chart II



This systematic synthesis of aporphine alkaloids was extended to include a total synthesis of the homoaporphine alkaloids, kreysigine (41) (Chart 12).

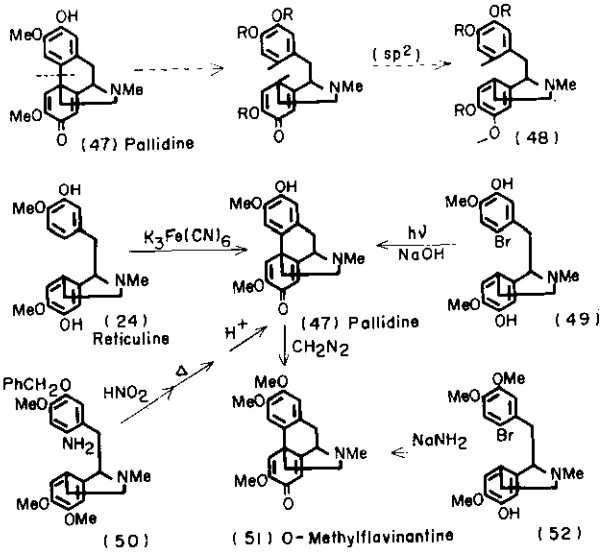
Photolysis of (42) and (43), the synthetic equivalents of the first fragment, gave directly kreysigine (41), while photolysis of (44), which belongs to the second type of fragment, afforded the homoproaporphine (45).[24,25] Moreover, the homoproaporphine (45), obtained in good yield from the diphenolic isoquinoline (46) by phenolic oxidation,[13] was transformed into kreysigine (41) by dienone-phenol rearrangement with mineral acid followed by partial methylation with diazomethane.[26]

Chart 12



In applying this cleavage principle to the morphinandienone alkaloids, scission of pallidine (47) furnishes the fragment (48) (Chart 13) which is synthetically equivalent to compounds (24), (49), (50), and (52). Experimently, the latter were converted into pallidine (47) or O-methylflavinantine by phenolic oxidation,[16] photolysis,[17,27] modified Pschorr reaction,[17,28] or benzyne reaction.[18,29]

Chart 13

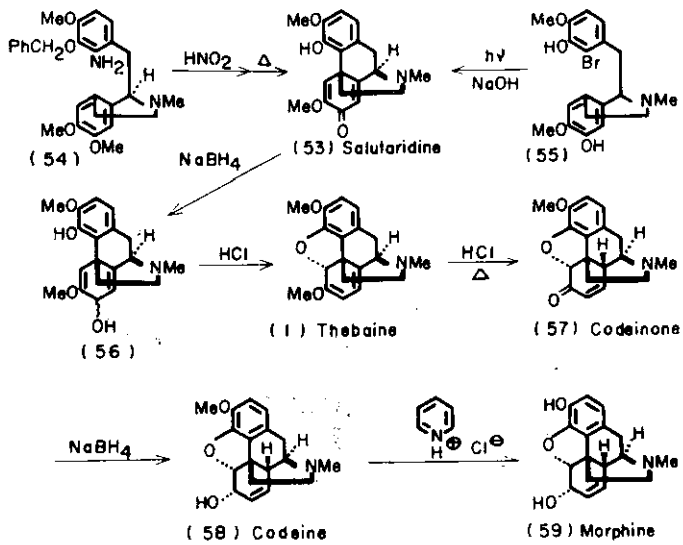


Further, by employing photolysis[30] and the modified Pschorr reaction,[31] we have synthesized other morphinandienone type alkaloids, including a formal total synthesis of morphine as shown in Chart 14.

Diazotization of the optical active aminoisoquinoline (54), followed by thermolytic decomposition without metal, gave salutaridine (53), whose racemate was also synthesized by photolysis of 2'-bromoreticuline (55). Reduction of (53) with sodium borohydride afforded salutaridinol (56) followed by treatment with dilute

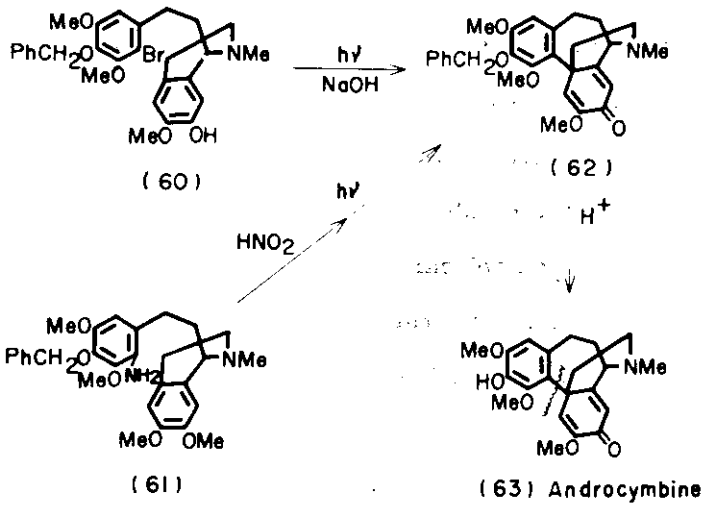
hydrochloric acid at room temperature to yield thebaine (1). Since this synthetic sequence was based on our fragmentation principle and since thebaine (1) had previously been converted into morphine (59) through codeinone (57) and codeine (58), our approach constitutes a formal total synthesis of morphine, codeine and related alkaloids.[31]

Chart 14



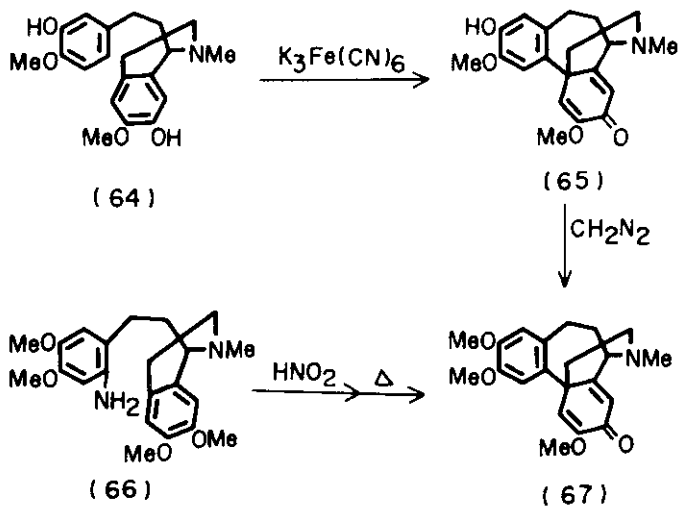
Similarly, the homomorphinandienone alkaloid androcymbine (63) (Chart 15) was synthesized from the phenolic bromoisoquinoline (60) by photolysis[32] and also from the aminoisoquinoline (61) by diazotization and photolysis followed by debenzylation of the protecting group with mineral acid.[33] It is evident that the starting materials (60 and 61) are equivalent to the fragment obtained by the cleavage line shown in androcymbine.

Chart 15



Furthermore (Chart 16), the homomorphinandienone type compounds (65 and 67)

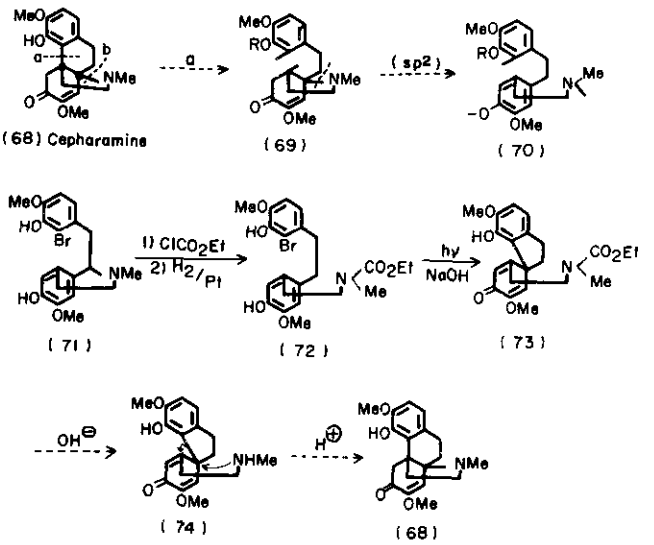
Chart 16



were obtained by phenolic oxidation of the diphenolic isoquinoline (64)[34] or by a modified Pschorr reaction of the aminoisoquinoline (66).[35]

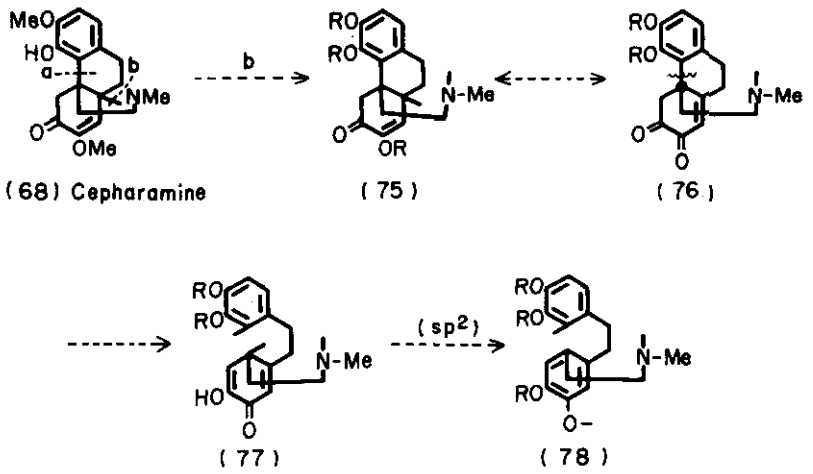
In planning the synthesis of cepharamine (68), a typical hasubanan alkaloid, we must consider the possibility that two kinds of splitting type can occur at (a) and (b) due to the presence of two quaternary carbon atoms as shown in Chart 17. If scission at (a) occurs, then the resulting fragment (69) with its quaternary carbon atom would be aromatized via an sp^2 carbon accompanied by cleavage of the C-N bond in the indolizine system to furnish fragment (70). Since the synthetic equivalent of fragment (70) is compound (72), the latter, obtained from the 2'-bromoisoquinoline (71), was irradiated to give the dienone (73). However, hydrolysis of the urethane system to the secondary amine (74) did not occur.[36] Therefore, the rearrangement of compound (74) has not yet been examined.

Chart 17



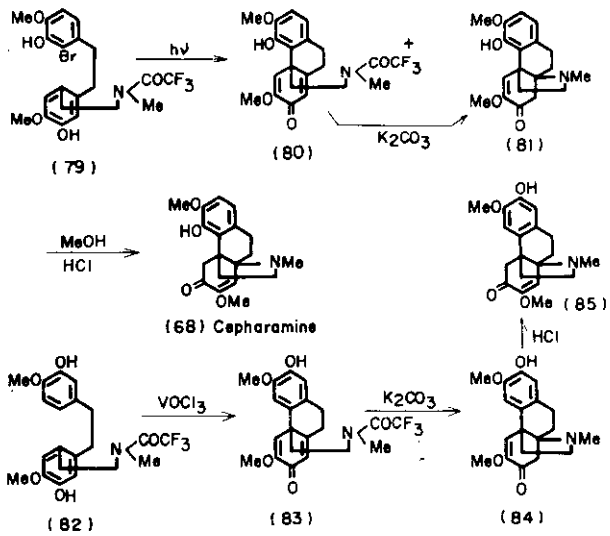
Alternatively (Chart 18), if we visualize that cepharmine (68) cleaves at (b) between the C-N bond, the resulting fragment (75) is equivalent to its tautomer fragment (76). However, since (76) still has a quaternary carbon, cleavage between the quaternary carbon and the aromatic ring provides (77) which is converted by an sp^2 carbon into fragment (78).

Chart 18



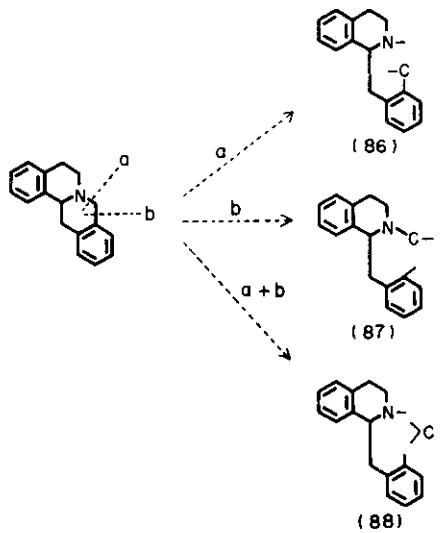
In view of the synthetic equivalency of (78) with the bromo-diphenolic amide (79) (Chart 19), the latter was subjected to photolysis to give the dienone (80) and the enone (81). Treatment of (81) with methanol in the presence of hydrogen chloride according to the procedure of Barton thus afforded cepharamine (68).[37] Moreover, phenolic oxidation of the related synthetic equivalent (82) with vanadium oxychloride gave the dienone (83) which was converted into the cepharamine analog (85) by an intramolecular Michael addition and isomerization.[38]

Chart 19



Turning our attention now to the protoberberine isoquinolines (Chart 20), these

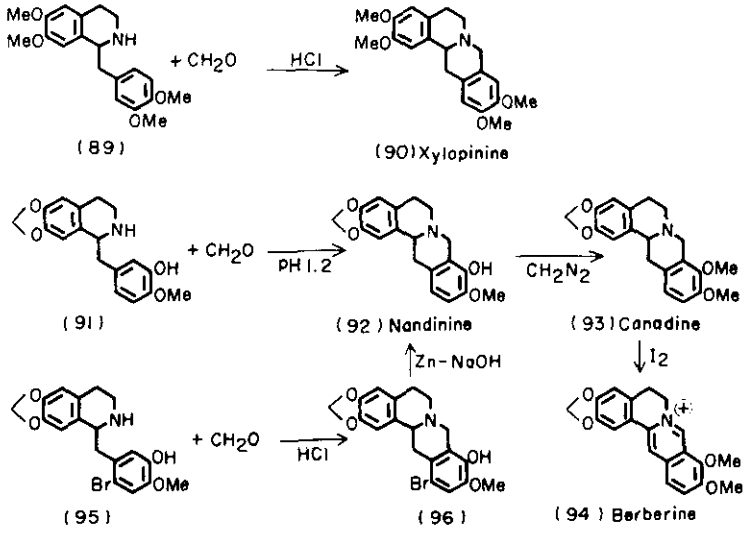
Chart 20



can be visualized as cleaving to afford the fragments (86), (87), or (88), all of which are promising intermediates for the synthesis of this type alkaloid.

In this connection (Chart 21), it is interesting that condensation of formaldehyde with the 1,2,3,4-tetrahydroisoquinoline (89), which is equivalent to fragment (88), is well known as the Mannich reaction and has been applied to the synthesis of the 10,11-disubstituted tetrahydroprotoberberines, such as xylopine (90).[7] As shown in this example, the benzyl moiety containing the methoxyl group cyclized to yield only the 10,11-disubstituted product, insted of the 9,10-disubstituted isomer which has the oxygenated pattern found in this type of alkaloid. In order to favor the formation of the 9,10-disubstituted isomers, the pH of the reaction had to be carefully

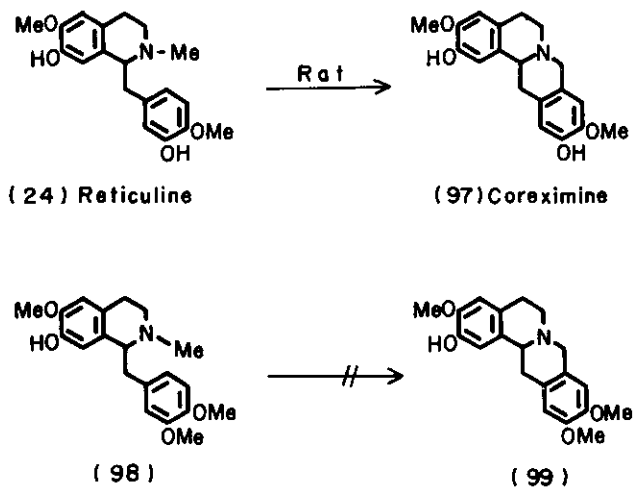
Chart 21



controlled and the alternate site of cyclization blocked by a bromine substituent. Thus, condensation of the phenolic benzylisoquinoline (91) with formaldehyde at pH 1.2 gave the 9,10-disubstituted tetrahydroprotoberberine, nandinine (92) which was converted into berberine (94) via canadine (93) in the usual manner.[39] Nandinine (92) was also obtained when the bromo-substituted phenolic precursor (95) was cyclized in the presence of mineral acid and the resulting bromo-intermediate (96) was reductively dehalogenated.[40]

Alternatively, in considering fragment (87) as a route to protoberberines (Chart 22), it would appear that the synthetic equivalent reticuline (24) would give by coupling of the N-methyl group with the benzyl moiety coreximine (97). This would be a biomimetic reaction, since, in fact, reticuline (24) is biotransformed in the rat to coreximine (97). However, experimentally it was not possible to transform the related

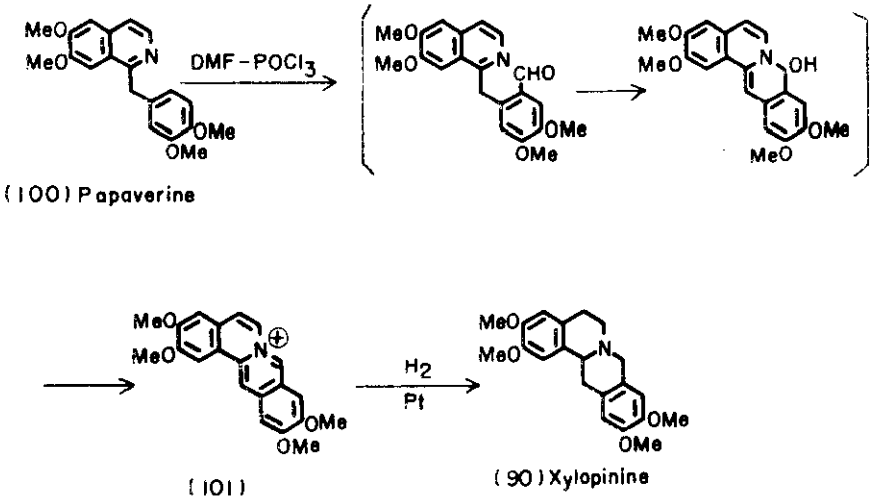
Chart 22



isoquinoline (98) by phenolic oxidation into the protoberberine (99).[42]

Finally, the synthesis of a protoberberine via the third fragment (86) was accomplished (Chart 23) by the Vilsmeier reaction of papaverine (100) to give directly the dehydroprotoberberine (101) in good yield followed by reduction in the usual manner to afford xylopinine.[42]

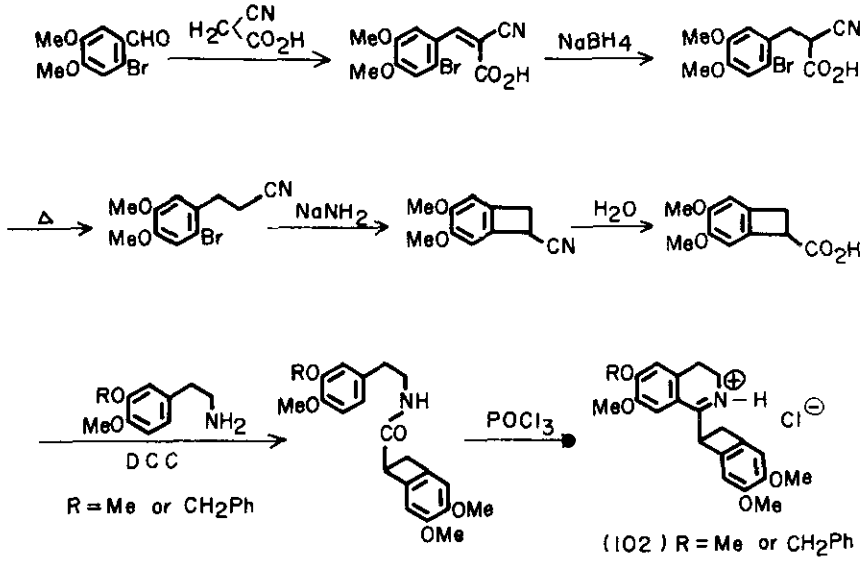
Chart 23



As extension of this approach, some protoberberine alkaloids were synthesized from the 1-benzocyclobutenyl-3,4-dihydroisoquinoline (102) which can also be considered the synthetic equivalent of the fragment (86). These benzocyclobutenes were prepared from 2-bromo-4,5-dimethoxybenzaldehyde as shown in Chart 24. Knövenagel reaction of the aldehyde with cycanoacetic acid, followed by sodium borohydride reduction and decarboxylation, gave the corresponding phenylpropionitrile which on benzyne reaction with sodium amide in liquid ammonia afforded

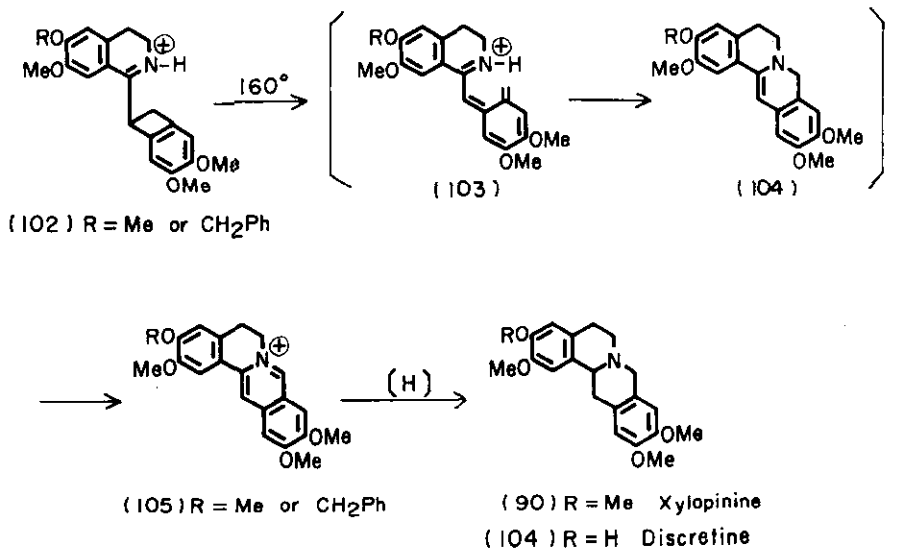
the cyanocyclobutene derivative. Hydrolysis of this nitrile with potassium hydroxide gave the carboxylic acid which was converted into the amides by reaction with the β-phenethylamines in the presence of dicyclohexylcarbodiimide followed by Bischler-Napieralski cyclization with phosphorus oxychloride to afford the desired isoquinolines as their hydrochlorides (102).

Chart 24



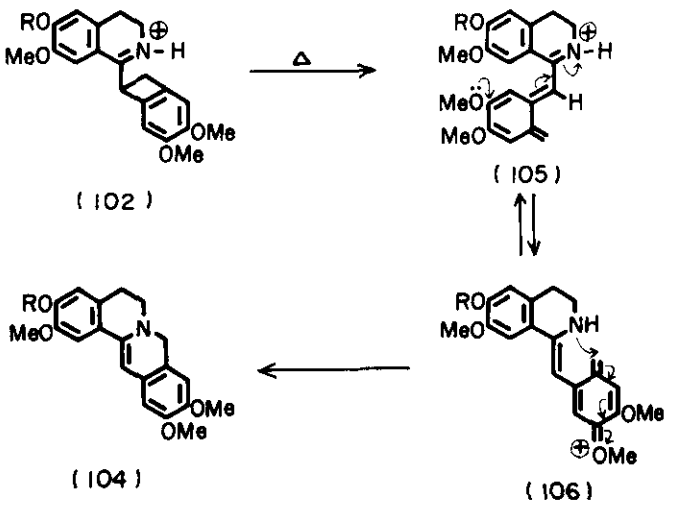
Thermolysis of these benzocyclobutene salts (102), presumably via the intermediates o-quinodimethanes (103) and the dihydroprotoberberines (104), followed by aromatization, furnished the protoberberines (105). Reduction of these compounds then afforded the alkaloids, xylopinine (90) and discretine (104).[43,44]

Chart 25



On the other hand, since thermolysis of the free base of the 3,4-dihydroiso-

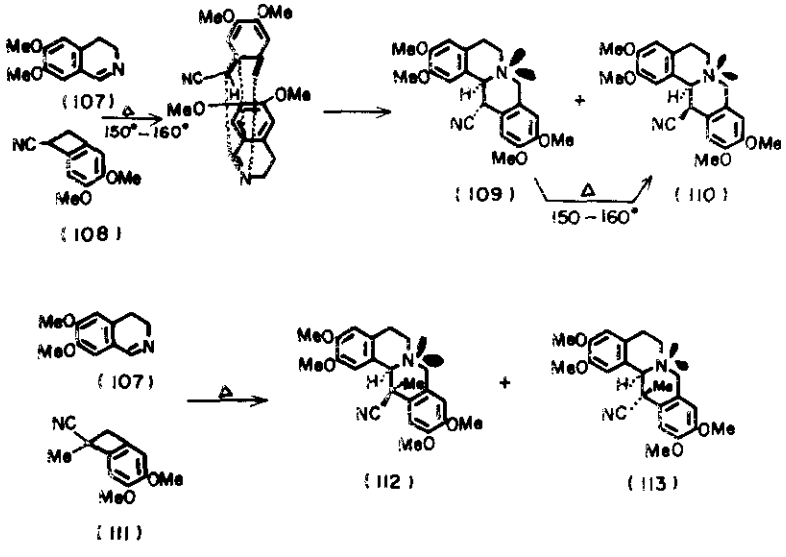
Chart 26



quinolines (102) did not yield the expected protoberberine, the following reaction mechanism provides an explanation (Chart 26). Thus, by electrocyclic reaction, the cyclobutene system forms the E-type o-quinodimethane (105) which then tautomerizes to the intermediate (106), followed by a Michael type addition of nitrogen to the endo methylene group to give the 3,4-dihydroisoquinoline (104) as the key precursor.

This successful synthesis of the protoberberine alkaloids by such an electrocyclic type reaction of the o-quinodimethane, derived from the 1-benzocyclobutenyl-3,4-dihydroisoquinoline by thermolysis, suggested (Chart 27) that the intermolecular cycloaddition of the 3,4-dihydroisoquinoline (107) with o-quinodimethanes derived from the benzocyclobutenes (108) and (111) would afford protoberberines.

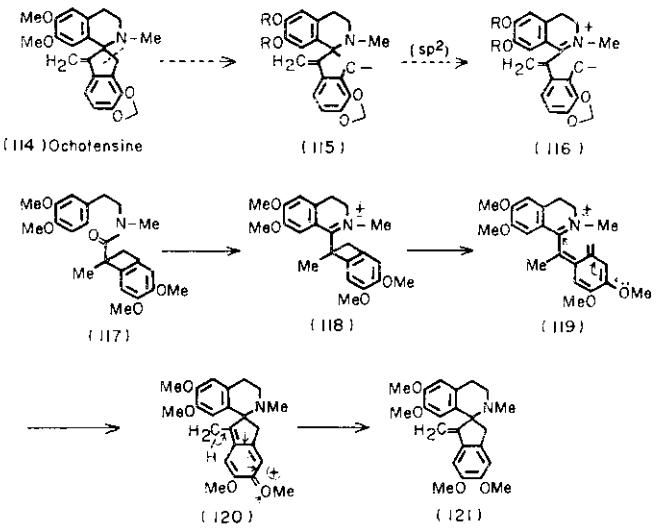
Chart 27



Indeed, this proved to be possible. Thus, a mixture of the 3,4-dihydroisoquinoline (107) and the benzocyclobutene (108) was heated at 150 - 160° to give the protoberberine (109), and, in addition, its isomer (110). The former was converted into the latter (110) by heating at 150 - 160°. The structures of both products were established by physical-chemical methods. In this reaction, the stereochemistry of the products was explained by regiospecific opening of the cyclobutene ring followed by endo addition of $4\pi + 2\pi$ cycloaddition and then epimerization. Similarly, thermal reaction of the 3,4-dihydroisoquinoline (107) with the benzocyclobutene (111) gave the regiospecific products (112 and 113) by endo addition although the ring opening occurred non-selectively.[45]

As a further example of the application of our principles of cleavage, the splitting of ochotensine (114) would give the fragment (115), which now has

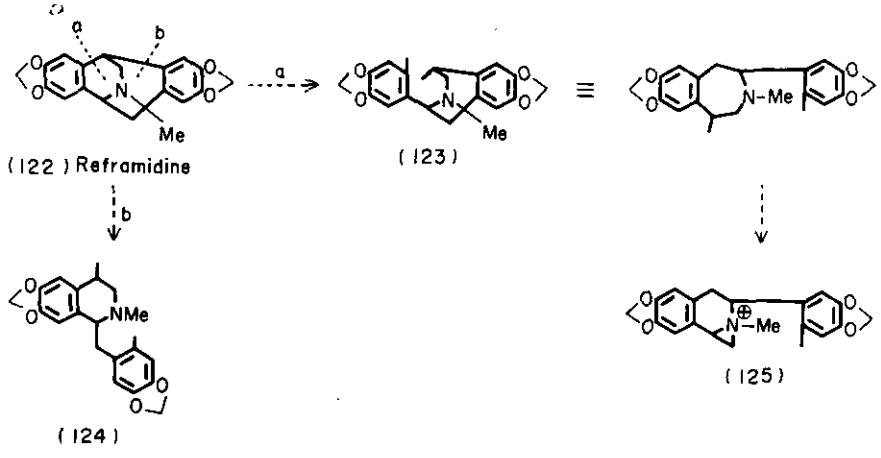
Chart 28



a quaternary carbon atom at the C-1 position in the isoquinoline system (Chart 28) which would then undergo sp^2 transformation into the fragment (116), a key precursor to ochotensine-type compounds. This promising precursor (118), synthetically equivalent to the fragment (116), was therefore synthesized by Bischler-Napieralski cyclization of the amide (117). However, the resulting 3,4-dihydroisoquinoline (118) was so unstable that it decomposed immediately to the o-quinodimethane (119) which was converted into the ochotensine-type compound (121) through the intermediate (120).[46]

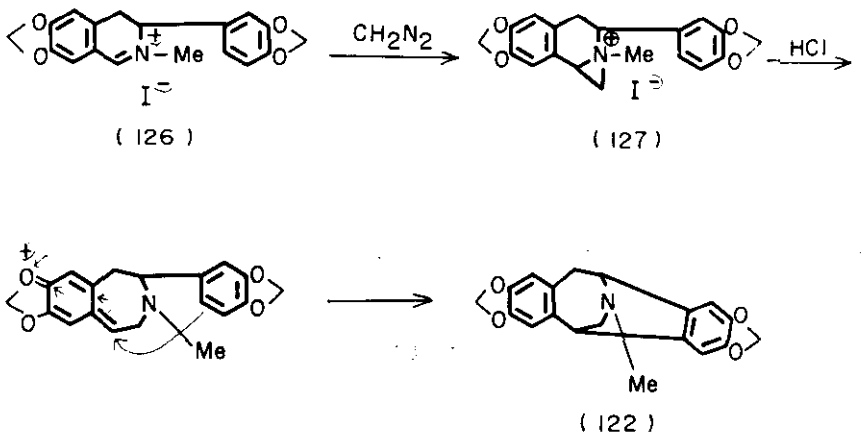
In applying the bond splitting principle to the isopavine alkaloids (Chart 29), reframidine (122) affords fragments (123) or (124) by fission at (a) or (b), respectively. While the latter fragment has been previously used for the synthesis of isopavine by acidic treatment of the 4-alkoxyisoquinoline, fragment (123) which can be considered equivalent to the aziridinium salt (125) was employed by us a key precursor in our synthesis of an isopavine alkaloid.

Chart 29



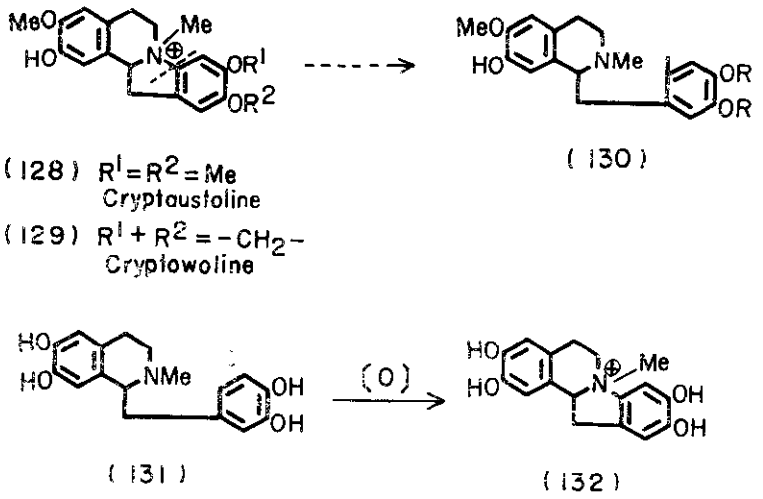
Thus (Chart 30), the aziridinium salt (127), corresponding to the fragment (125),was easily obtained by treatment of 3,4-dihydro-2-methylisoquinoline (126) with diazomethane and treated with hydrochloric acid to give reframidine (122).[47]

Chart 30



According to our theory, the dibenzopyrrocoline alkaloids, cryptaustoline (128) and cryptowoline (129), would give the fragment (130) as a synthetic intermediate (Chart 31). Indeed, the 1,2,3,4-tetrahydroisoquinoline (131), a synthetic equivalent of (130), was converted by Robinson and Schöpf by oxidative coupling into the quaternary base (132).[1]

Chart 31



(128) $R^1=R^2=Me$
Cryptaustoline

(129) $R^1+R^2=-CH_2-$
Cryptowoline

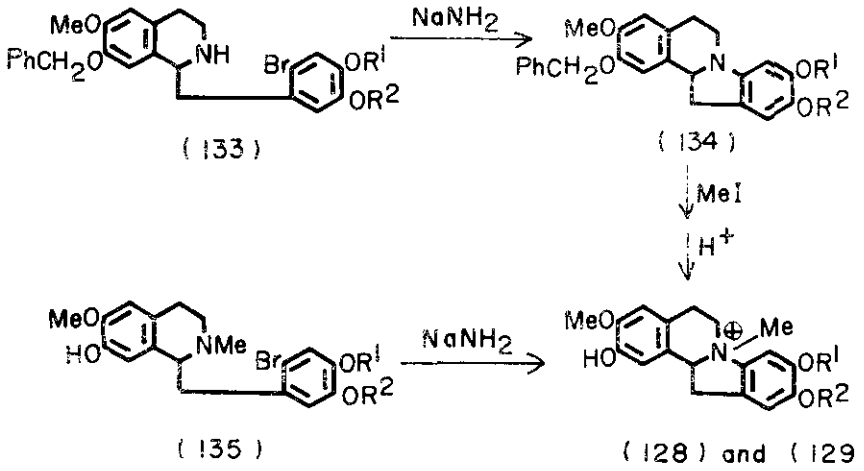
(130)

(131)

(132)

Alternatively (Chart 32), we carried out the synthesis of the dibenzopyrrocolines from 2'-bromobenzylisoquinolines which are also equivalent to the fragment (130).

Chart 32



(133)

(134)

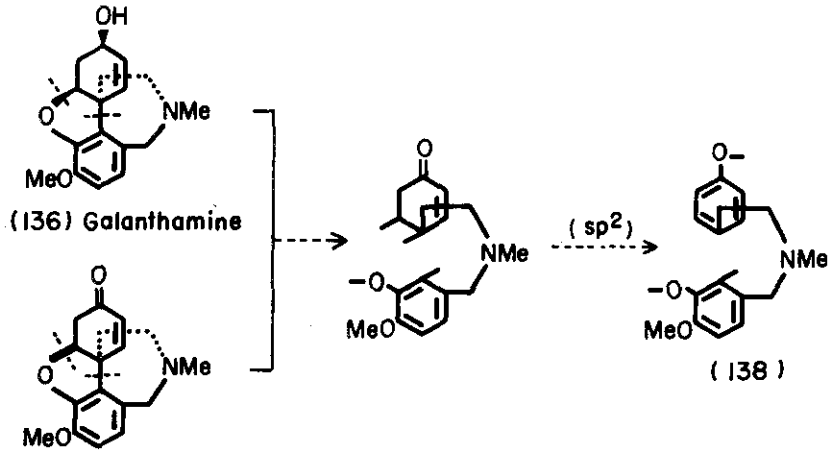
(135)

(128) and (129)

Thus, benzyne reaction of the bromo-secondary amine (133) gave the dibenzopyrrocoline(134) which was converted in the usual manner to the alkaloids, cryptaustoline (128) and cryptowoline (129), which were also obtained directly from the phenolic bromo-tertiary amine (135) by the benzyne reaction.[18,48]

Galanthamine (136) and narwedine (137), which are found in addition to crinine and its analogs in Amaryllidaceae, are split according to our principle (Chart 33) into the fragment (138). This fragment, a direct precursor of the belladine-type compound, was converted into narwedine (137) in poor yield by phenolic oxidation by Professor Barton.[1]

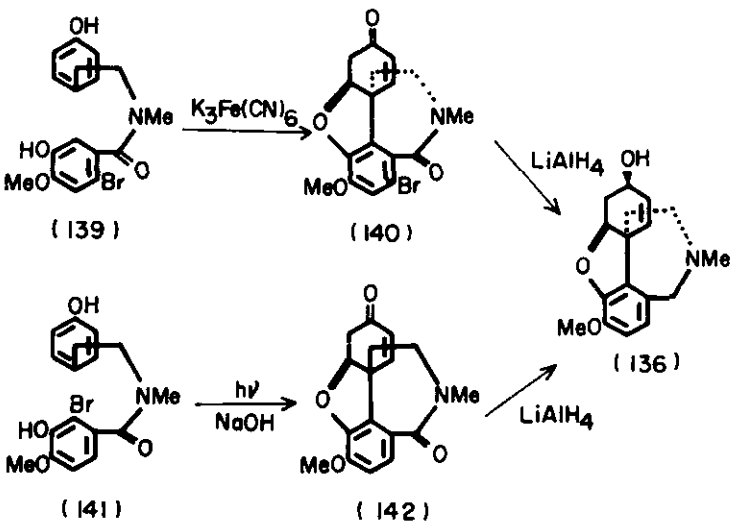
Chart 33



We also investigated a similar type of oxidative coupling but used another synthetic equivalent of the fragment (138) which was more efficient (Chart 34). For this purpose, N-(4-hydroxyphenethyl)-N-methyl-2-bromo-5-hydroxy-4-methoxybenz-

amide (139) which contains a bromine atom to inhibit the coupling para to the hydroxy-group and thus favor ortho-cyclization and an amide function to prevent the coupling of the nitrogen with the phenyl moiety was oxidized with potassium ferricyanide to give the enone (140) in 40 % yield. Reduction of this enone with lithium aluminum hydride then afforded galanthamine (136) as well as its isomer, epigalanthamine.[49] On the other hand, the bromo-amide (141), also the synthetic equivalent of the fragment (138), was photolyzed in sodium hydroxide to the enone (142), followed by reduction to also afford galanthamine.[50]

Chart 34

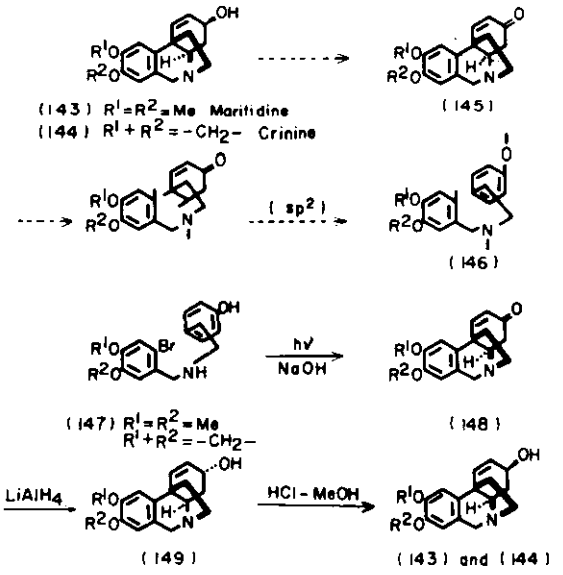


In applying the same splitting procedure to the crinine-type alkaloids (Chart 35), maritidine (143) or crinine (144) give the fragment (146). The direct equivalent of this fragment (146) is the belladine-type compound, which was already converted

by phenolic oxidation into maritidine by Professor Schwartz.[1]

In our laboratory, the bromo-amides (147), the synthetic equivalent of the fragment (146), were subjected to photolysis in the usual manner to afford the enones (148) which were reduced with lithium aluminum hydride to give the enols (149). Since these enols have previously been converted into maritidine (143) and crinine (144), our work constitutes a total synthesis of these alkaloids.[51,52]

Chart 35



ACKNOWLEDGMENTS We thank Dr. Sidney Teitel, Hoffmann-La Roche INC., Nutley, New Jersey, for his kind suggestion and also Miss Reiko Kato and Miss Chiako Yoshida for their kind help in the preparation of this manuscript.

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Received, 5th June, 1973