PARTIAL ETHER CLEAVAGE OF METHOXY AND METHYLENEDIOXY-SUBSTITUTED ISOQUINOLINE ALKALOIDS

Sidney Teitel* and Arnold Brossi

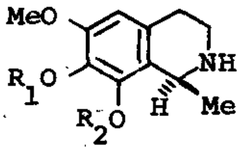
Chemical Research Department, Hoffmann-La Roche Inc.,
Nutley, New Jersey 07110, U. S. A.

A variety of polymethoxy-substituted isoquinolines have been preferentially O-demethylated with mineral acid and the procedure applied to the facile synthesis of the alkaloids corypalline (46), cherylline (48), multifloramine (51), anhalonine (2) and lophophorine (54). The method of selective O-demethylenation of methylenedioxy-dimethoxy-substituted isoquinolines with boron trichloride was utilized for the conversion of the phthalide alkaloid (-)-β-hydrastine (6) into (-)-cordrastine II (7).

Introduction

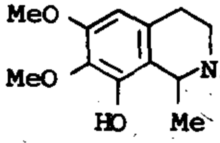
The isoquinoline alkaloids are classified into families that comprise both simple and complex structures. However, members within each family are usually closely related and often differ only at the oxygenated sites of the aromatic ring. This relationship, clearly delineated in a recent monograph by Kametani,[1] is demonstrated by the following examples. The simple isoquinoline alkaloids (+)-O-methylanhalonidine (1),

(-)-anhalonine (2), and (±)-anhalonidine (3) all have the same basic structure except for the 7,8-dimethoxy-, methylenedioxy-, and methoxy hydroxy-substituents, respectively. Similarly, the tetramethoxy benzylisoquinoline alkaloid (+)-laudanosine (4) is closely related to the dimethoxy diphenol (+)-reticuline (5) and the phthalideisoquinoline alkaloid (-)-β-hydrastine (6) differs from (-)-cordrastine II (7) only by having a methylenedioxy- instead of a dimethoxy-substituent.

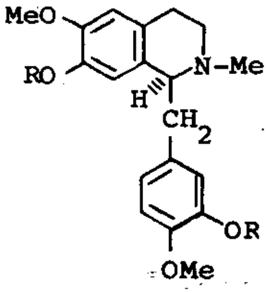


(1) $R_1=R_2=Me$

(2) $R_1+R_2=CH_2$

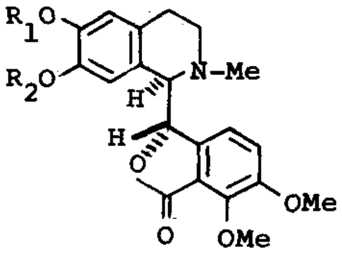


(3)



(4) R=Me

(5) R=H



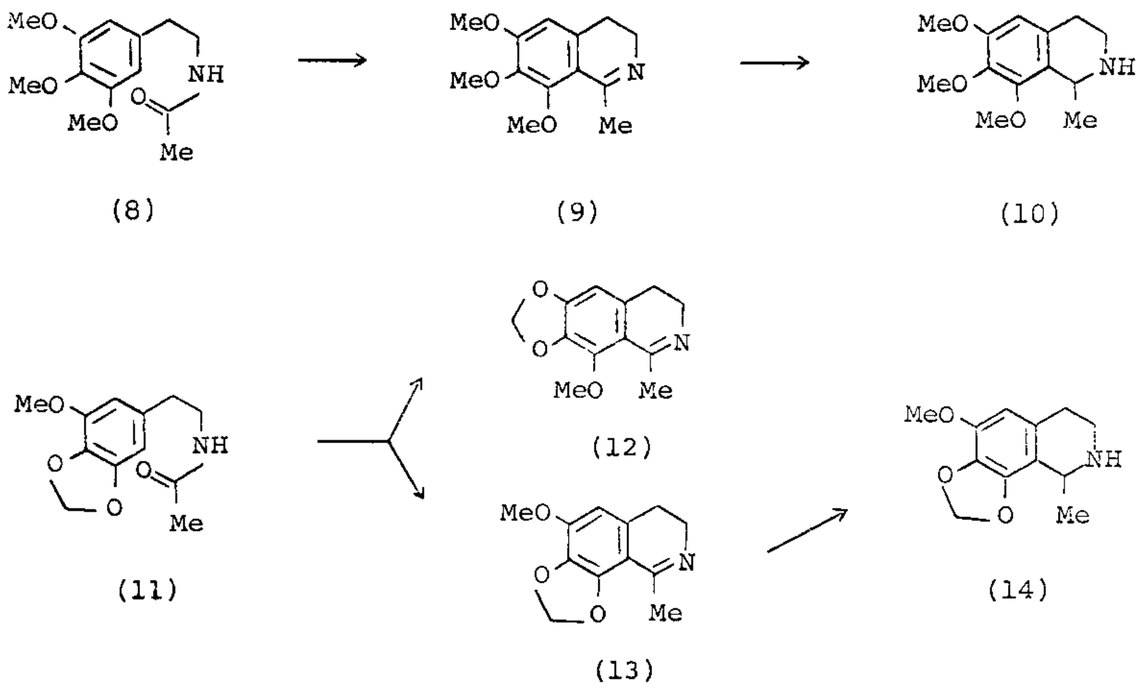
(6) $R_1+R_2=CH_2$

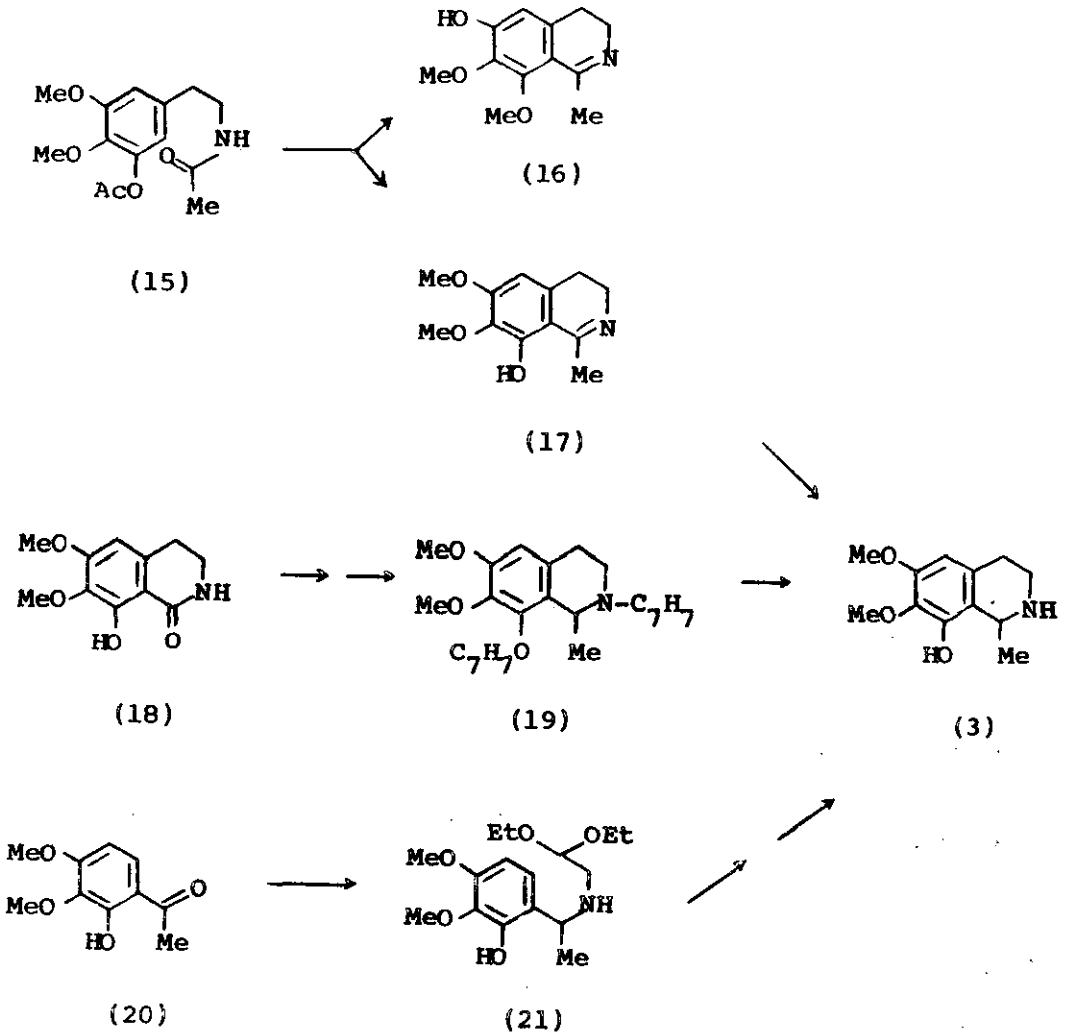
(7) $R_1=R_2=Me$

In spite of this structural resemblance, it is noteworthy that there are no general methods available whereby closely related alkaloids can be obtained from a readily accessible member. This is illustrated by considering some of the synthetic methods that have been used for the preparation of the above alkaloids as their racemates.

The simple isoquinolines (±)-O-methylanhalonidine (10), (±)-anhalonine (14), and (±)-anhalonidine (3) were initially prepared by Späth and co-workers from N-acetylmescaline (8),[2a] the methylenedioxy methoxy amide (11),[3] and the acetoxy dimethoxy amide (15),[4] respectively. While Bischler-Napieralski cyclization of (8) to the 3,4-dihydroisoquinoline (9) followed by reduction readily afforded (10), cyclodehydration of the unsymmetrically substituted amide (11) gave a mixture of the isomeric imines (12) and (13) which required separation and then reduction of (13) to yield (14). Similarly, (15) gave a mixture of (16) and (17) from which only the latter provided the alkaloid (±)-anhalonidine (3).

To circumvent isomer formation, Brossi, Schenker, and Leimgruber[5] reported the following synthesis of (3). The 8-hydroxy lactam (18), obtained from mescaline by successive treatment with ethyl chloroformate, polyphosphoric acid, and concentrated hydrochloric acid, was benzylated, reduced to the tetrahydroisoquinoline, oxidized to the imine, quaternized with benzyl bromide, reacted with methyl magnesium iodide and the resulting N,O-dibenzyloxy tetrahydroisoquinoline (19) catalytically debenzylated to afford (3). More recently, the latter was synthesized by Takido, Khanna, and Paul[6] who employed a modified Pomeranz-Fritsch reaction. 2-Hydroxy-3,4-dimethoxy-acetophenone (20), obtained by partial etherification of galloacetophenone with dimethyl sulfate, was reductively condensed with aminoacetaldehyde diethylacetal to provide the substituted benzylamine (21) which was ring-closed with acid followed by catalytic hydrogenation to (3).

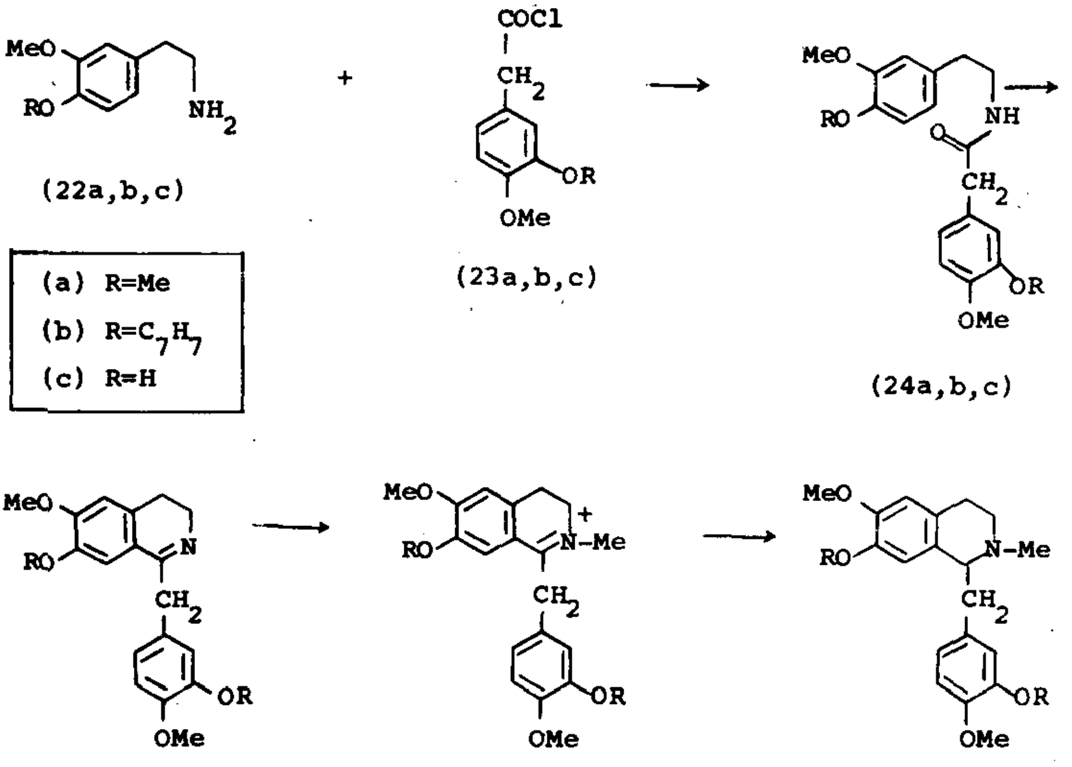




The benzylisoquinolines (±)-laudanosine (27a) and (±)-reticuline (27c) have also been synthesized by the same reaction sequences but using different intermediates. Treatment of commercially available homoveratrylamine (22a) with 3,4-dimethoxyphenylacetyl chloride (23a) gave the tetramethoxy-substituted amide (24a) which was cyclized with phosphorus pentoxide to the

3,4-dihydroisoquinoline (25a) followed by quaternization to (26a) and reduction to the tetramethoxy-substituted tetrahydroisoquinoline (27a).[7] In contrast, the synthesis of the related diphenol (±)-reticuline (27c) required not only additional steps for the preparation of the O-benzyloxy precursors (22b) and (23b) but also the removal of these protecting groups from (27b), obtained by reduction of the quaternary salt (26b).[8]

Recently, this latter sequence was simplified by the finding that some free phenols could be directly used in the Bischler-Napieralski reaction.[9] By this method, the phenolic amine (22c), obtained from vanillin by a multistep procedure, was condensed with the phenolic acid chloride (23c) to the diphenolic amide (24c) which was cyclodehydrated to the imine (25c) and then converted by reduction of the methobromide (26c) into (±)-reticuline (27c).

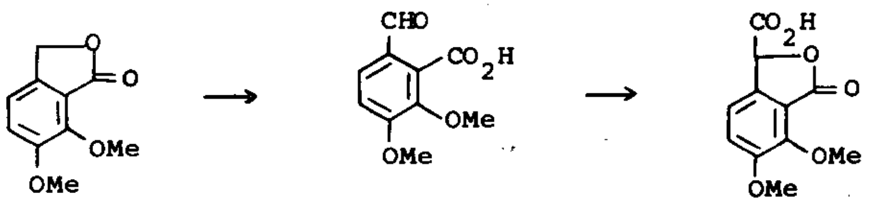


(22a,b,c) (23a,b,c) (24a,b,c)

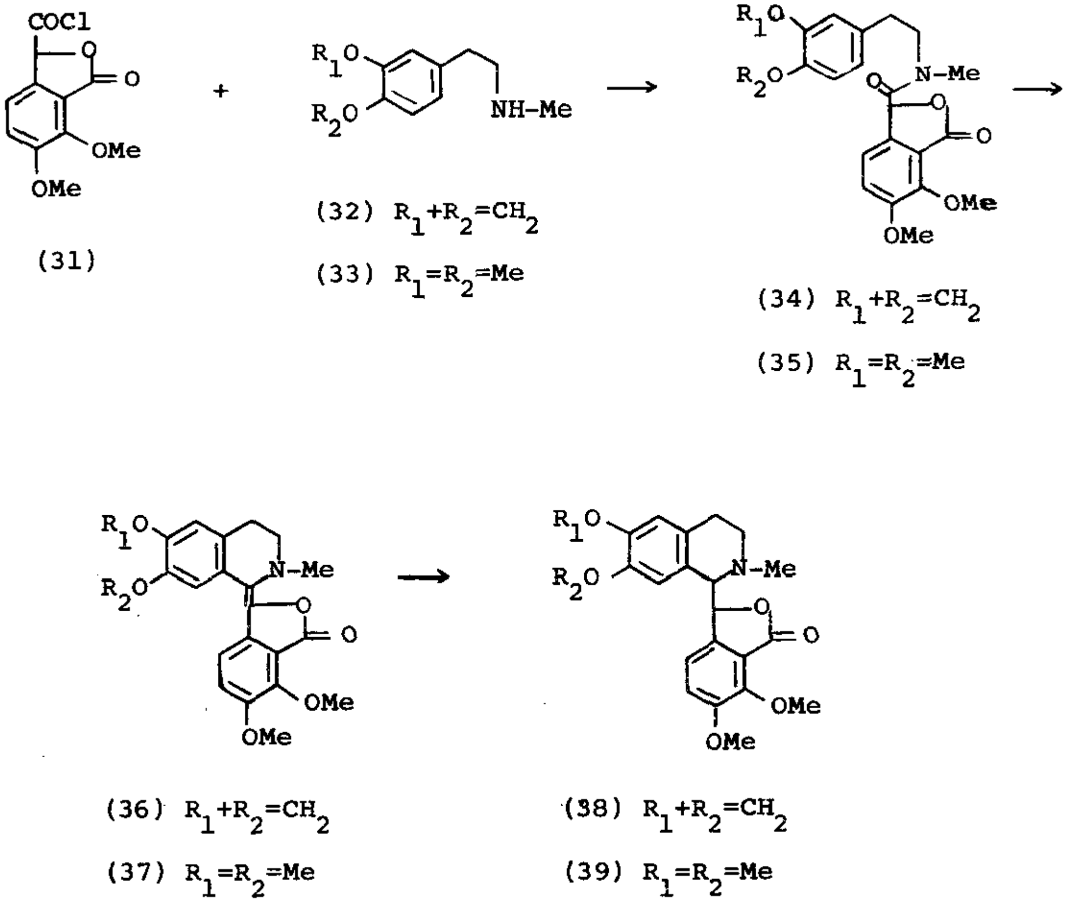
(a) R=Me
(b) R=C_7H_7
(c) R=H

(25a,b,c) (26a,b,c) (27a,b,c)

The related phthalideisoquinolines (±)-hydrastine (38) and (±)-cordrastine (39) have also been synthesized by the same reaction sequences. The necessary intermediate meconine α-carboxylic acid (30) was prepared by Perkin and Trikojus[10] by reacting 2,3-dimethoxybenzoic acid with formaldehyde and hydrochloric acid to give the dimethoxy phthalide meconine (28) which was oxidized with manganese dioxide to opianic acid (29) followed by hydrolysis of the intermediate cyanohydrin. The corresponding acid chloride (31) was transformed by Haworth, Pinder, and Robinson[11] by treatment with N-methylhomopiperonylamine (32) into the amide (34) which was ring-closed with phosphorus oxychloride; the resulting unsaturated intermediate (36) was hydrogenated to afford the dimethoxy methylenedioxy-substituted phthalide as a mixture of two diasteroisomeric hydrastines (38). Similarly, Haworth and Pinder[12] reacted the acid chloride (31) with N-methylhomoveratrylamine (33) to give the tetramethoxy amide (35) which was cyclodehydrated to (37) and catalytically reduced to afford the two racemic modifications of cordrastine (39).



(28) (29) (30)



(31)

(32) $R_1+R_2=CH_2$

(33) $R_1=R_2=Me$

(34) $R_1+R_2=CH_2$

(35) $R_1=R_2=Me$

(36) $R_1+R_2=CH_2$

(37) $R_1=R_2=Me$

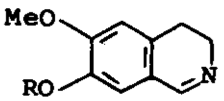
(38) $R_1+R_2=CH_2$

(39) $R_1=R_2=Me$

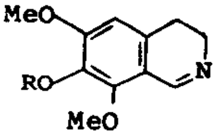
The foregoing examples illustrate that phenolic isoquinolines are less accessible than their corresponding O-methyl ethers and that the phthalideisoquinolines are only obtained as racemic diastereoisomeric mixtures. Consequently, it was of interest to consider the possibility of transforming readily available natural alkaloids or their synthetic precursors into less accessible isoquinolines. In this connection, the method of selective de-etherification appeared attractive since preferential O-demethylation with mineral acid had already been applied, in a few instances, to isoquinoline compounds.

As previously mentioned, the 8-hydroxylactam (18) was prepared from the 6,7,8-trimethoxy precursor by preferential cleavage of the methoxyl ortho to the carbonyl with mineral acid.[5] In addition, Bruderer and Brossi[13a] and Kametani, Takano, and Sasaki[13b] demonstrated that the 7-methoxyl in 6,7-dimethoxy-3,4-dihydroisoquinoline (40) and related 1-substituted derivatives was selectively cleaved with mineral acid under controlled reaction conditions to afford the monophenol (41). Similarly, the preferential scission of the 7-methoxyl in 6,7,8-trimethoxy-3,4-dihydroisoquinoline (42) to give the dimethoxy monophenol (43) was reported by Brossi, Baumann, and Borer[14] as well as by Kametani, Wagatsuma, and Sasaki.[15]

The selective O-demethylation of both imines (40) and (42) has been explained by the enhanced basicity of the 7-methoxyl due to partial loss of conjugation by preferential protonization and the concomitant reduced basicity of the 6- and 8-methoxyls due to their conjugation with the protonated imino group.[14] Indeed, 6,7-dimethoxy-3,4-dihydroisoquinoline (40) behaves as a carbinolamine and, in a manner similar to 3,4-dimethoxy-aromatic aldehydes and ketones, is selectively cleaved at the methoxyl with the highest electron density which is <u>meta</u> to the carbonyl.[16] In addition, it is generally accepted that the lability of the 7-methoxyl in the 6,7,8-trimethoxy imine is influenced by steric interactions which force the methyl of the middle methoxyl out of the plane of the benzene ring.[17] Finally, it is most likely that scission of the 7-methoxyl occurs between the methyl group and the oxygen attached to the aromatic ring since we recently found that preferential cleavage of (40) and (42) with mineral acid in ^{18}O enriched water showed no incorporation of the isotope into the corresponding O-demethylated products (41) and (43).

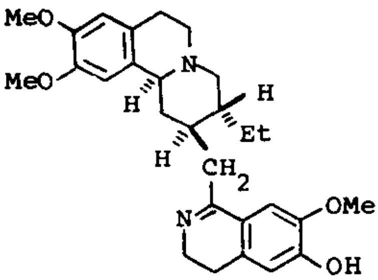


(40) R=Me
(41) R=H

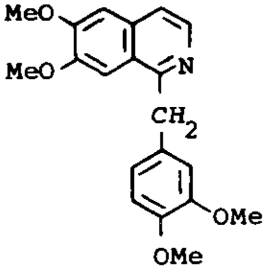


(42) R=Me
(43) R=H

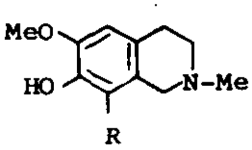
In view of the acid lability of the 7-methoxyl of the imines (40) and (42), a study was undertaken to explore its potentiality as a tool in the synthesis of phenolic isoquinoline alkaloids. In this connection, the behavior of the isomers of the 6,7-dimethoxy imine (40), the Ipecac alkaloid psychotrine (44), and the benzylisoquinoline papaverine (45) in mineral acid under controlled reaction conditions was demonstrated. The lability of the 7-methoxyl of (40) was applied to the synthesis of the simple isoquinoline alkaloid corypalline (46) and its 8-methyl derivative (47) as well as the rare Amaryllidaceae alkaloid cherylline (48). In addition, investigations of the lability of the middle of three vicinal methoxyls in model compounds and in 3,4-dihydro- and 1,2,3,4-tetrahydroisoquinolines led to facile syntheses of desmethylmescaline (49), desmethyltrichocereine (50), the homoaporphine alkaloid multifloramine (51), the monophenolic homoberbine (52), desmethylthalifendlerine (53) and the Cactus alkaloids anhalonine (2) and lophophorine (54).



(44)

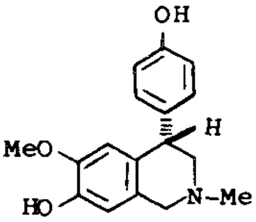


(45)

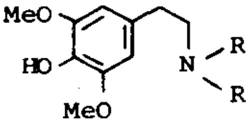


(46) R=H

(47) R=Me

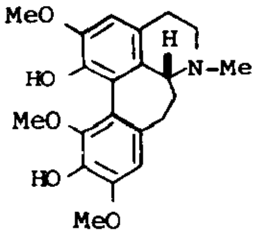


(48)

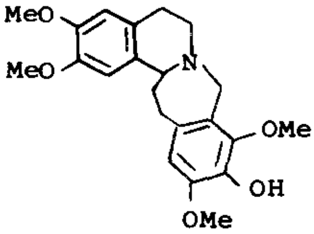


(49) R=H

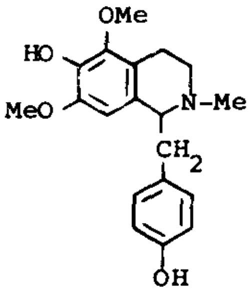
(50) R=Me



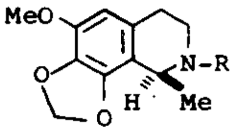
(51)



(52)



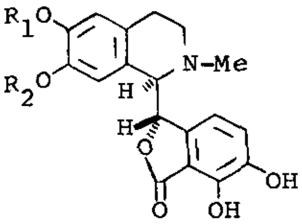
(53)



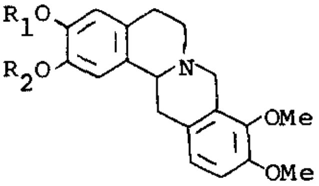
(2) R=H

(54) R=Me

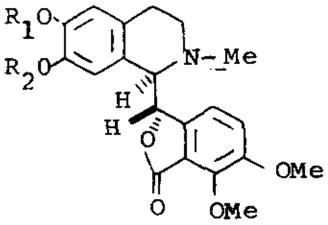
Finally, a simple transformation of commercially available (-)-β-hydrastine (6) into the related phthalide (-)-cordrastine II (7) was achieved by selective cleavage of the methylenedioxy group with boron trichloride to the diphenol (59) followed by methylation. The use of boron trichloride, based on its preferential cleavage of cyclic acetals of hexitols,[18] was prompted by the recently reported de-etherification of (6) to the tetraphenol (55) by boron tribromide.[19] The action of boron trichloride parallels that of aluminum tribromide in nitrobenzene which apparently complexed preferentially with the methylenedioxy group in the presence of methoxyls effecting cleavage of the tetrahydroberberine (57) to the corresponding diphenol (58)[20] and contrasts with that of pyridine hydrochloride which selectively cleaved both methoxyls in (6) to afford the methylenedioxy-substituted phthalide (56).[19]



(55) $R_1=R_2=H$
(56) $R_1+R_2=CH_2$



(57) $R_1+R_2=CH_2$
(58) $R_1=R_2=H$



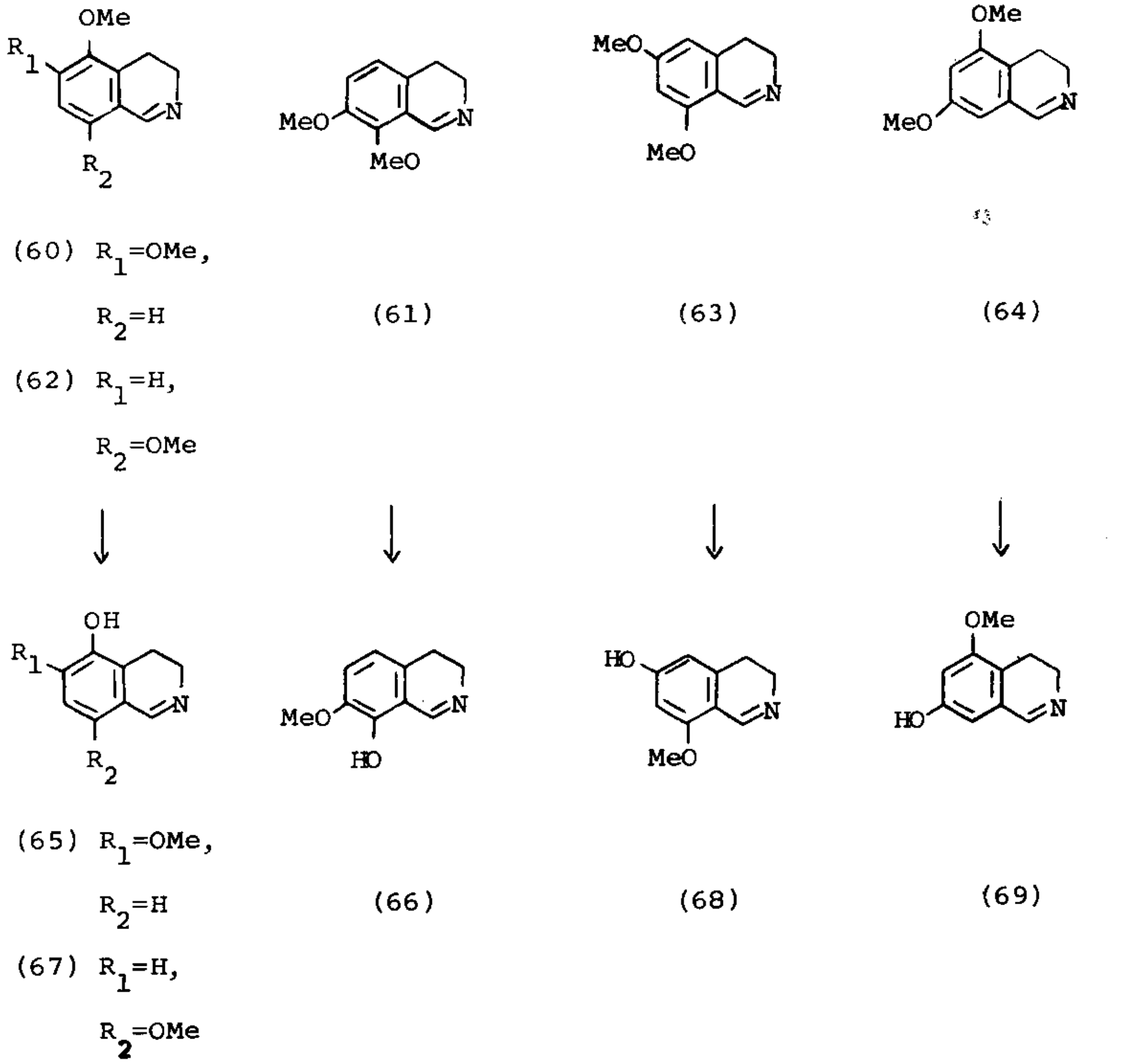
(6) $R_1+R_2=CH_2$
(7) $R_1=R_2=Me$
(59) $R_1=R_2=H$

Partial O-Demethylation of Dimethoxy-substituted 3,4-dihydroisoquinolines

Partial Cleavage of Isomeric Dimethoxy-substituted 3,4-dihydroisoquinolines[21]

In view of the preferential cleavage of 6,7-dimethoxy-3,4-

dihydroisoquinoline (40) with mineral acid to the 7-monophenol (41),[13] it was of interest to determine whether the isomeric dimethoxy-substituted dihydroisoquinolines could also be partially O-demethylated. For this purpose, the reaction conditions were optimized to favor the formation of only one main product, as visualized by thin layer chromatography, since the concentration of acid and substrate as well as the reaction temperature and



(60) R_1=OMe, R_2=H

(62) R_1=H, R_2=OMe

(61)

(63)

(64)

(65) R_1=OMe, R_2=H

(67) R_1=H, R_2=OMe

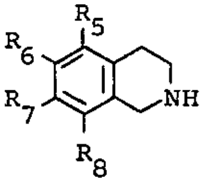
(66)

(68)

(69)

time influenced the extent of ether cleavage. Under these conditions, the 5-methoxyl of the 5,6-dimethoxy imine (60) and the 5,8-diether (62) were cleaved to give the corresponding monophenols (65) and (67) while the 6,8-dimethoxy isomer (63) and the 5,7-diether (64) afforded the 6-monophenol (68) and the 7-monophenol (69), respectively. In contrast, acid catalyzed cleavage of the 7,8-dimethoxy isomer (61) gave the 8-monophenol (66) along with a significant amount of the corresponding diphenol.

All of the isomeric dimethoxy-substituted 3,4-dihydroisoquinolines, except the 5,6-isomer (60),[22] were new and were prepared by standard methods. The 5,8-isomer (62) was obtained from 2-(2,5-dimethoxyphenyl)ethylamine[23] by N-formylation followed by Bischler-Napieralski cyclization. The isomers (61), (63), and (64) were preferably obtained by hypochlorite oxidation[24] of the corresponding tetrahydroisoquinolines (70)[25] and the heretofore unknown 6,8- and 5,7-isomers (72) and (74). The isomers (72) and (74) were conveniently prepared from the known trimethoxy-substituted precursors (71)[2a] and (73),[26] recpectively, <u>via</u> a modified Birch reduction involving the elimination of the middle of three adjacent methoxyl groups with sodium in a mixture of liquid ammonia and ethanol.[27] Alternatively, catalytic reduction of the 3-chloro-substituted isoquinoline (75)[28] also afforded the 6,8-dimethoxytetrahydroisoquinoline (72) while demethoxylation of mescaline (76) furnished 3,5-dimethoxyphenethylamine (77)[29] which was converted by N-formylation and the ring closure with phosphorus oxychloride into 6,8-dimethoxy-3,4-dihydroisoquinoline (63) in poor yield.



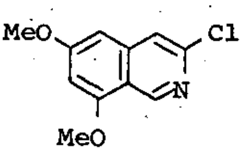
(70) $R_7=R_8=\mathrm{OMe}$

(71) $R_6=R_7=R_8=\mathrm{OMe}$

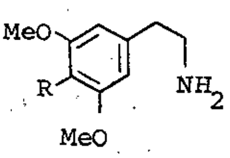
(72) $R_6=R_8=\mathrm{OMe}$

(73) $R_5=R_6=R_7=\mathrm{OMe}$

(74) $R_5=R_7=\mathrm{OMe}$



(75)



(76) R=OMe

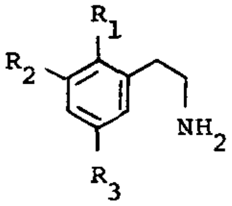
(77) R=H

All the monophenols (65)-(69) were isolated either as their crystalline bases or as mineral acid salts and characterized by physical-chemical methods. The position of the phenolic hydroxyl group was established by direct comparison with a reference compound prepared by an unequivocal route or by transformation into a known tetrahydroisoquinoline derivative.

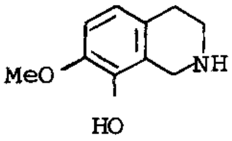
The monophenol (65) was found to be identical with 5-hydroxy-6-methoxy-3,4-dihydroisoquinoline which was prepared from 2-(2-hydroxyl-3-methoxyphenyl)ethylamine (78)[30] by N-formylation followed by cyclization with phosphorus oxychloride. In a similar manner, the phenethylamine (79), obtained from 2-benzyloxy-5-methoxybenzaldehyde,[31] was converted to the dihydroisoquinoline which by O-debenzylation with acid gave 5-hydroxy-8-methoxy-3,4-dihydroisoquinoline, identical to the monophenol (67). In contrast, the structure of (66) was readily established by reduction with sodium borohydride to the known 8-hydroxy-7-methoxytetrahydroisoquinoline (80).[26,32]

To ascertain the position of the phenolic hydroxyl of (68), it was reduced to the tetrahydroisoquinoline (81a), converted into the N-formyl derivative (81b) and reacted with 5-chloro-1-phenyl-

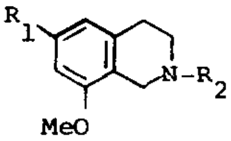
1H-tetrazole to yield the tetrazolyl ether (82). Hydrogenation of (82) in the presence of palladium removed the tetrazolyl ether group[33] and the resulting monomethoxy N-formyl derivative (83) was reduced with sodium bis(2-methoxyethoxy)aluminum hydride to a monomethoxy tertiary amine which was identical to 8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (84)[34] but not to 6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline.[35] Similarly, the monophenol (69) was transformed via (85)-(88) to a monomethoxy tetrahydroisoquinoline which was identical to 5-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (89)[36] but not to the 7-methoxy isomer.[37] Further confirmation for the presence of the 7-phenolic hydroxyl in (69) was obtained from the non-identity of the corresponding tetrahydroisoquinoline (85) to authentic 5-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline.[38]



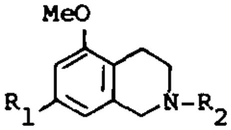
(78) R_1=OH, R_2=OMe, R_3=H
(79) R_1=OC_7H_7, R_2=H, R_3=OMe



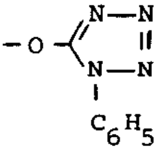
(80)



(81)-(84)



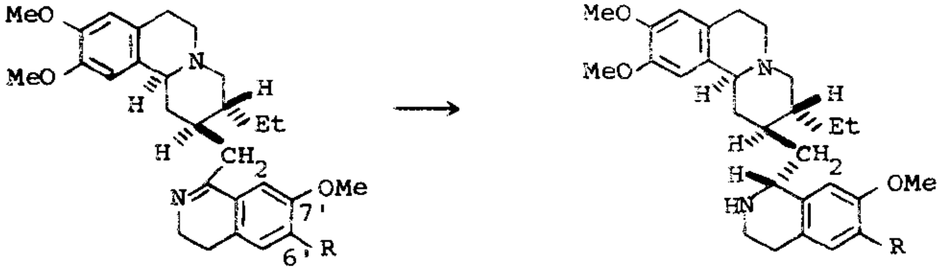
(85)-(89)

	R_1	R_2	
(81a)	OH	H	(85)
(81b)	OH	CHO	(86)
(82)		CHO	(87)
(83)	H	CHO	(88)
(84)	H	Me	(89)

Structure of Psychotrine and Cleavage of O-Methylpsychotrine[39]

In contrast to the acid lability of the 7-methoxyl in 6,7-dimethoxy-3,4-dihydroisoquinoline,[13] it has been assumed that the 6'-methoxyl in the Ipecac alkaloid O-methylpsychotrine (90), a substituted 6',7'-dimethoxy-3,4-dihydroisoquinoline, is preferentially cleaved with mineral acid to the 6'-monophenol psychotrine (44). This difference in cleavage pattern prompted the following study which confirmed the structure of (44) but not the preferential lability of the 6'-methoxyl in O-methylpsychotrine (90).

The two phenolic Ipecac alkaloids psychotrine (44) and cephaeline (91) have been related to each other by reduction.[40] Their absolute configuration has been established since O-methylation yielded O-methylpsychotrine (90)[41] and emetine (92)[40] respectively, two other Ipecac alkaloids of known absolute configuration.[42] However, the assignment of the free hydroxyl group to the 6'-position in psychotrine (44) and cephaeline (91) has not been rigidly established since it is primarily based on the assumption by Brindley and Pyman[43] that the 6'-methoxyl in O-methylpsychotrine (90) is the most labile of the four methoxyls in the molecule and is preferentially cleaved by acid hydrolysis to psychotrine (44) with a 6'-hydroxyl group. Pailer and Porschinski[44] lent support to this assumption when they subjected O-ethylcephaeline (93) to a lengthy degradation and obtained a semicarbazone which gave no melting point depression with a synthetic sample of 2-ethyl-4-ethoxy-5-methoxybenzaldehyde semicarbazone. However, the synthesis of the latter compound was ambiguous and required 6 recrystallizations to give a constant melting point.



(44) R=OH

(90) R=OMe

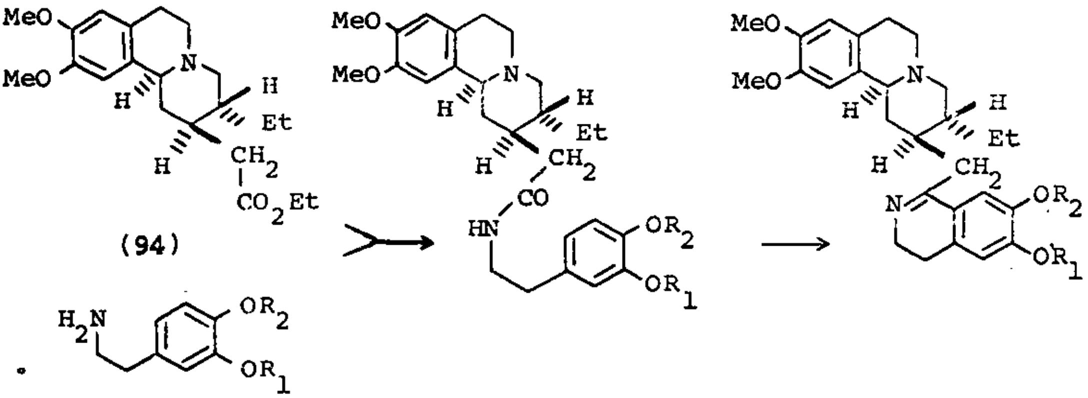
(91) R=OH

(92) R=OMe

(93) R=OEt

In view of these considerations it was of interest to rigidly establish the position of the hydroxyl group of (44) and (91) by an unambiguous synthesis of psychotrine (44) and its 6'-O-methyl-7'-O-desmethyl isomer (101) which was needed for comparison.

Condensation of the optically active tricyclic ester (94)[24] with 2-(3-benzyloxy-4-methoxyphenyl)ethylamine (95)[45] or 2-(4-benzyloxy-3-methoxyphenyl)ethylamine (96)[46] gave the benzyl ether amides (97) and (98), respectively. Cyclization of the latter with phosphorus oxychloride afforded the corresponding benzyloxy-substituted 3,4-dihydroisoquinoline derivatives (99) and (100) which were debenzylated with 20% hydrochloric acid to the phenolic bases (44) and (101), respectively. Synthetic (44) was identical in all respects to natural psychotrine and was converted by treatment with diazomethane into O-methylpsychotrine (90) which was also identical to the natural alkaloid. This definitely confirmed Brindley and Pyman's assumption that the free hydroxyl group of psychotrine (44) is in the 6'-position. Further, since (44) has been related to cephaeline (91),[41,47] this also unequivocally established the 6'-position of the free hydroxyl group of cephaeline. This was independently confirmed by Szántay and co-workers[48] who synthesized racemic (91) by a Pictet-Spengler condensation of racemic protoemetine, obtained by diisobutylaluminum hydride reduction of racemic (94), with 3-hydroxy-4-methoxyphenethylamine.



(94)

(95) $R_1=C_7H_7$, $R_2=Me$
(96) $R_1=Me$, $R_2=C_7H_7$

(97) $R_1=C_7H_7$, $R=Me$
(98) $R_1=Me$, $R_2=C_7H_7$

(99) $R_1=C_7H_7$, $R_2=Me$
(100) $R_1=Me$, $R_2=C_7H_7$
(101) $R_1=Me$, $R_2=H$

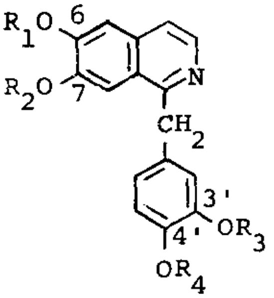
The procedure of Brindley and Pyman[43] for the hydrolysis of O-methylpsychotrine (90) with hydrochloric acid at 170° was repeated and the reaction mixture analyzed by thin layer chromatography using psychotrine (44), O-methylpsychotrine (90) and 6'-O-methyl-7'-desmethylpsychotrine (101) as comparison samples. As expected, the hydrolysis gave a rather complex mixture containing (44) and (101), as well as (90) and at least 6 other components. It is evident that, in contrast to Brindley and Pyman's postulation, selective cleavage of the methoxyl groups does not take place under these conditions.

Controlled O-Demethylation of Papaverine[49]

In contrast to the preferential cleavage of the 7-methoxyl of 6,7-dimethoxy-3,4-dihydroisoquinoline with mineral acid,[13] it has been reported that the benzylisoquinoline alkaloid papaverine (45) is partially O-demethylated to the 6,7-dimethoxy diphenol (106) by refluxing concentrated hydrochloric acid[50] and completely de-etherified to the tetraphenol papaveroline

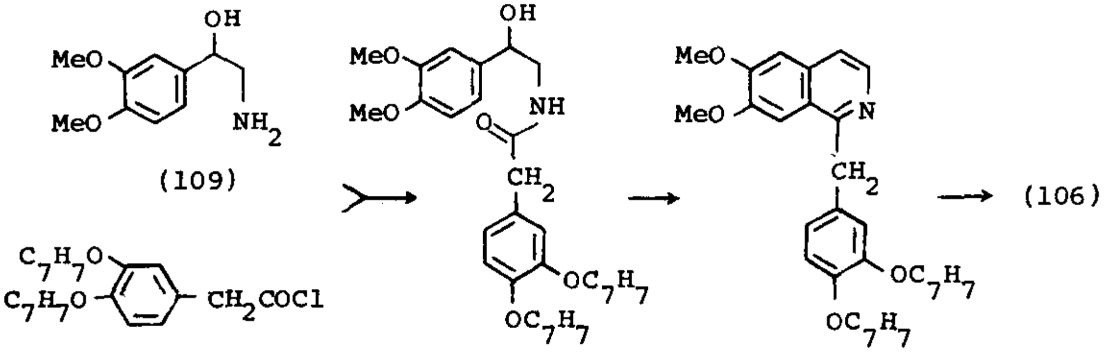
(108) by refluxing 48% hydrobromic acid.[51] It was, therefore, of interest to determine the relative lability of the methoxyls of (45) to acid catalyzed cleavage under controlled conditions.

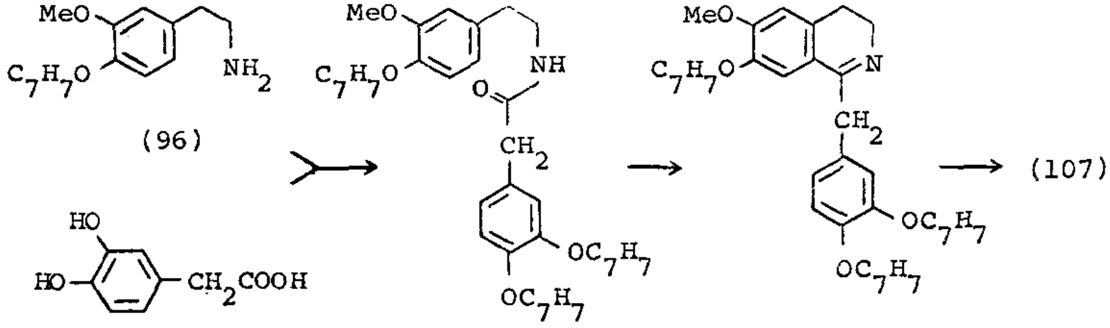
Based on these studies, the pattern of O-demethylation of (45) with mineral acid involved first the two methoxy groups of the benzylic side chain to afford a mixture of the monophenols (102) and (103) and the diphenol (106), then the methoxyl in the 7-position to form the triphenol (107), and finally the 6-methoxyl to give the tetraphenol (108). There was no evidence that the 7- or 6-methoxyl preferentially cleaved to the corresponding monophenols (104) and (105).



	R_1	R_2	R_3	R_4		R_1	R_2	R_3	R_4
(45)	Me	Me	Me	Me	(105)	H	Me	Me	Me
(102)	Me	Me	Me	H	(106)	Me	Me	H	H
(103)	Me	Me	H	Me	(107)	Me	H	H	H
(104)	Me	H	Me	Me	(108)	H	H	H	H

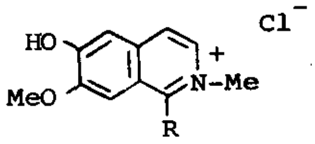
Reaction conditions for the acid catalyzed hydrolysis of papaverine (45) were optimized by thin layer chromatography using as standards authentic samples of phenols which were obtained as follows: The monophenols (102) to (105) and papaveroline (108) were prepared according to literature procedures.[51,52] The diphenol (106) was obtained by a Schotten-Baumann reaction of the hydroxy amine (109)[53] with the acid chloride (110) of 3,4-dibenzyloxyphenylacetic acid[54] to give the amide (111) which was cyclodehydrated with phosphorus oxychloride to the isoquinoline (112) and then O-debenzylated with acid. The triphenol (107) was synthesized by fusion of the benzyloxy methoxy amine (96)[46] with the diphenolic acid (113) followed by benzylation to the amide (114) which was ring-closed with phosphorus oxychloride and the resulting imine (115) dehydrogenated with palladium and debenzylated with acid.

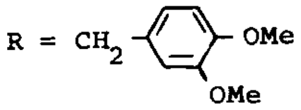


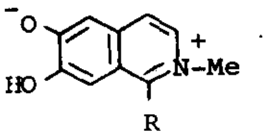


Reaction of papaverine (45) with refluxing concentrated hydrochloric acid for several hours gave a mixture of starting material and the five phenols (102), (103), (106), (107) and (108) from which the diphenol (106) could be isolated in good yield but whose physical properties differed considerably from those reported.[50] In contrast, treatment of (45) with liquid hydrogen bromide gave a 1:1 mixture of the two monophenols (102) and (103) as shown by nmr and glpc while refluxing 48% hydrobromic acid gave initially 40% of the diphenol (106) and on longer reaction time 80% of the triphenol (107). The mixture of monophenols (102) and (103) was transformed stepwise with the latter reagent to afford the diphenol (106), then the triphenol (107), and finally the tetraphenol (108).

Although these cleavage conditions provide a facile route to some of the phenols, it is interesting that the relative resistance of the 6- and 7-methoxyls of (45) to scission with mineral acid contrasts with their lability on thermal fusion of the hydrochloride of (45) to afford a mixture of the protopapaverines (116) and (117).[55]







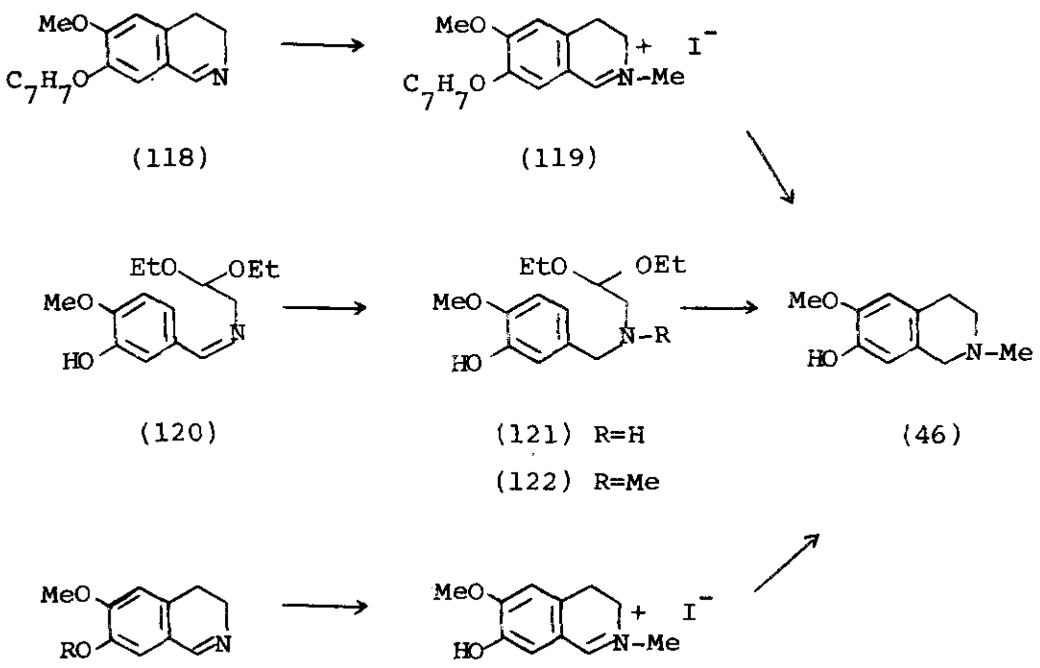
(116)

(117)

Synthesis of Corypalline[56] and 8-Methylcorypalline[57]

The simple phenolic isoquinoline alkaloid corypalline[58] (46) has been synthesized by conversion of the benzyloxy-substituted imine (118), obtained by cyclodehydration of N-formyl-4-benzyloxy-3-methoxyphenethylamine, into its methochloride (119) followed by reduction.[59] It has also been prepared by hydrogenation of the condensation product (120), obtained from isovanillin and aminoacetaldehyde diethylacetal, to form the N-benzyl derivative (121) followed by reductive condensation with formaldehyde to the tertiary amine (122), treatment with dilute mineral acid, and catalytic hydrogenation.[60]

Alternative to the above methods, a facile route to corypalline (46) has now been achieved based on the acid lability of the 7-methoxyl of 6,7-dimethoxy-3,4-dihydroisoquinoline (40).[13] Treatment of (40)[61] with 48% hydrobromic acid under controlled reaction conditions afforded 63% of the monophenolic imine (41). Catalytic hydrogenation of its quaternary methiodide (123)[62] yielded directly the alkaloid (46) in 57% overall yield.



(118)

(119)

(120)

(121) R=H

(122) R=Me

(46)

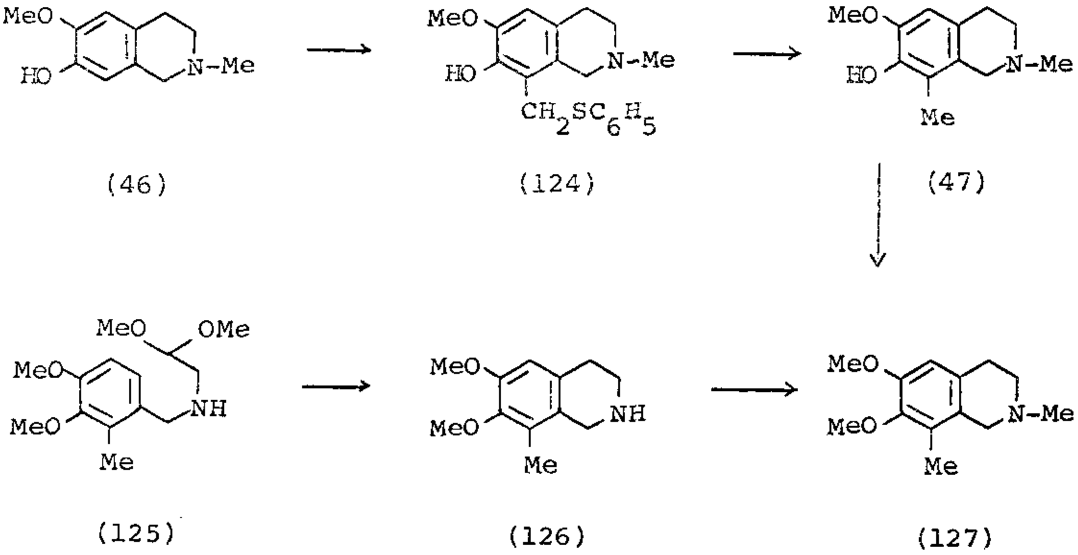
(40) R=Me

(41) R=H

(123)

As an extension of the utility of preferential O-demethylation, the now readily accessible monophenol corypalline (46) was converted into 8-methylcorypalline (47) and its O-methyl ether. This was prompted by the structural resemblance of (47) with 1-(4-methoxybenzyl)-2,8-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline, a major cleavage product of the bisbenzylisoquinoline alkaloid repanduline with potassium in liquid ammonia[63] which has been synthesized by a rather lengthy procedure.[64] In contrast, the following simple and efficient method was used to introduce an 8-methyl substituent into a 7-hydroxy-6-methoxy-tetrahydroisoquinoline and involves the thiomethylation reaction of Poppelsdorf and Holt[65] followed by reductive desulfurization of the phenyl-thiomethyl intermediate.

Reaction of corypalline (46) with formaldehyde and thiophenol provided the thio derivative (124). Treatment of (124) with excess Raney nickel in ethanol afforded directly 8-methylcorypalline (47) which was converted with diazomethane into its O-methyl ether (127). The structures of the new tetrahydroisoquinoline (124), (47), and (127), supported by physical data, were confirmed by an independent synthesis of (127). Reductive condensation of 3,4-dimethoxy-2-methylbenzaldehyde[66] with aminoacetaldehyde dimethylacetal yielded the substituted benzylamine (125) which was cyclized to the tetrahydroisoquinoline (126) followed by reductive condensation with formaldehyde to 6,7-dimethoxy-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline, identical to (127).



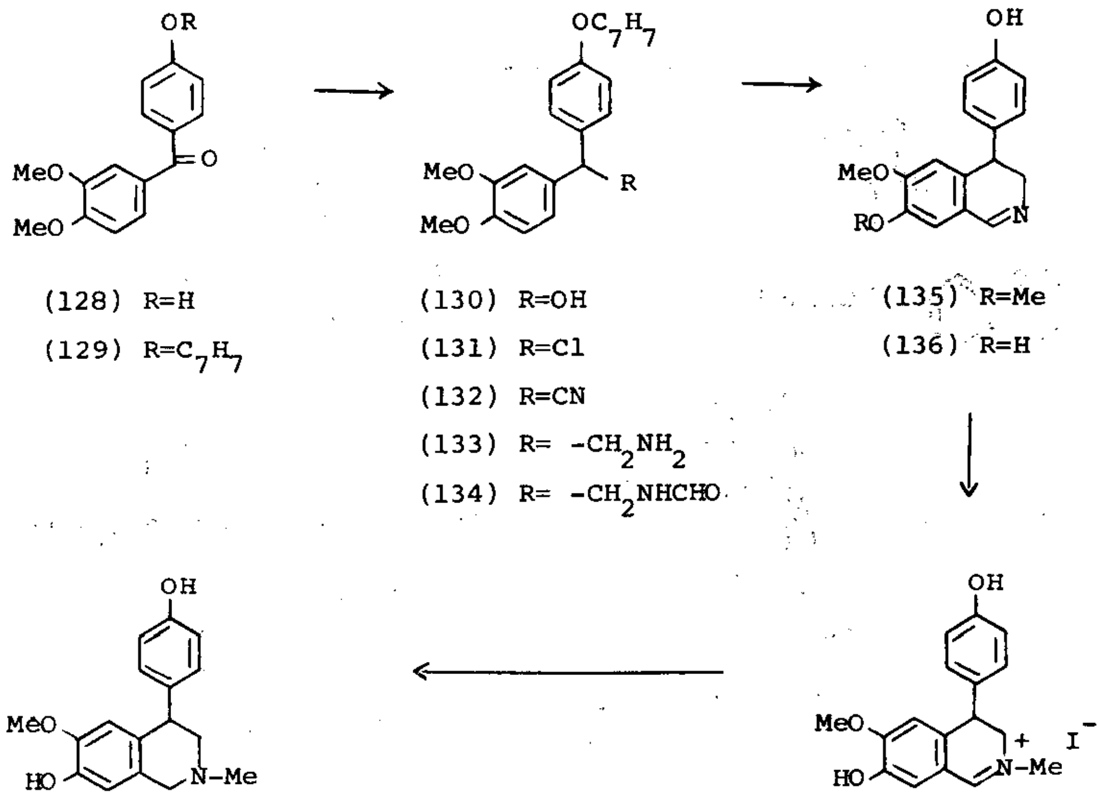
(46) (124) (47)

(125) (126) (127)

The Synthesis of Cherylline[67]

An interesting application of the preferential cleavage of the 7-methoxyl of 6,7-dimethoxy-3,4-dihydroisoquinoline[13] is given by the synthesis of cherylline (48). The latter, a 4-phenyl-substituted 1,2,3,4-tetrahydroisoquinoline and a new representative of the rare phenolic Amaryllidaccae alkaloids, was recently isolated, its structure determined and its absolute configuration established.[68] The preparation of (±)-cherylline (138) as well as the first synthesis of the natural alkaloid (48) and its unnatural isomer (149) was accomplished as follows.

Based on standard methods,[69] the benzophenone (128), obtained by condensing veratric acid and phenol in the presence of polyphosphoric acid, was converted to the benzyloxy ketone (129) and reduced to the benzhydrol (130) with sodium borohydride. Treatment of (130) with thionyl chloride yielded the chloro derivative (131) which was converted to the nitrile (132) with cuprous cyanide followed by hydrogenation in the presence of Raney cobalt to the phenethylamine (133). Bischler-Napieralski cyclization of the N-formyl derivative (134), obtained from (133) and methyl formate, followed by debenzylation with conc. hydrochloric acid at 25° gave the 6,7-dimethoxy dihydroisoquinoline (135). Selective O-demethylation of (135) with 48% hydrobromic acid at 100° for 6 hr yielded the 6-methoxy-7-hydroxy derivative (136). Sodium borohydride reduction of (137), obtained from (136) and methyl iodide, afforded (±)-cherylline (138) whose uv, nmr and mass spectra and chromatographic behavior were identical to a sample of natural cherylline.[68]



(128) R=H

(129) R=C_7H_7

(130) R=OH

(131) R=Cl

(132) R=CN

(133) R= $-CH_2NH_2$

(134) R= $-CH_2NHCHO$

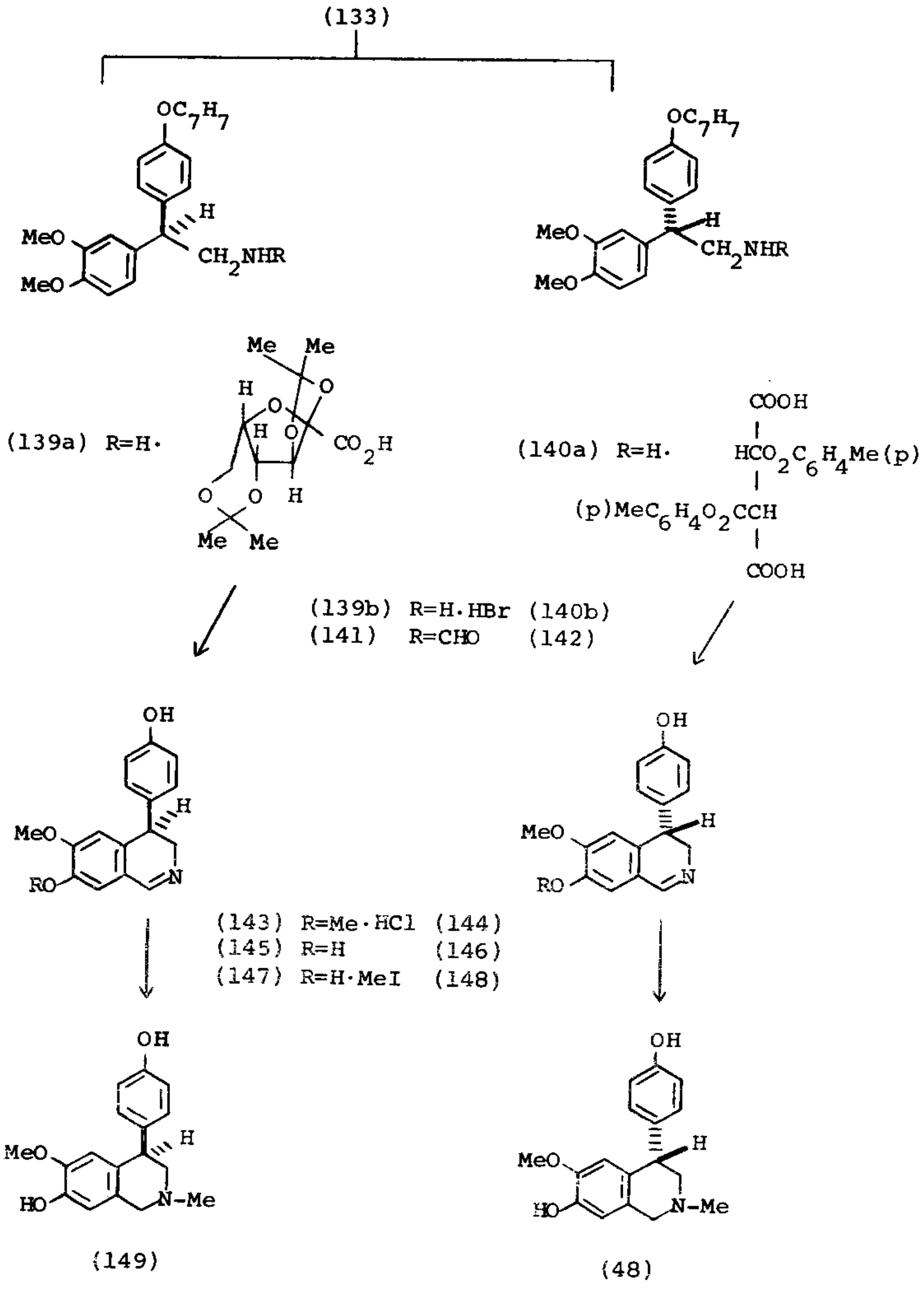
(135) R=Me

(136) R=H

(137)

(138)

The synthesis of cherylline (48) and its unnatural isomer (149) was accomplished via resolution of the (±)-phenethylamine (133). Treatment of (133) with (-)-diacetone-2-keto-L-gulonic acid[70] in isopropanol afforded the diastereomeric salt (139a). Treatment of the mother liquors (as the free base) with (-)-di-O-p-toluoyl-D-tartaric acid in acetone yielded the diastereomeric salt (140a). Each of these was converted to the corresponding crystalline hydrobromides (139b) and (140b) whose ORD and CD spectra were exact mirror images. From this point, the synthesis was carried out by the procedures described for (138). The (+)-phenethylamine (139b) gave the dextrorotatory


(133)

(139a) R=H·

(140a) R=H·

(139b) R=H·HBr (140b)

(141) R=CHO (142)

(143) R=Me·HCl (144)

(145) R=H (146)

(147) R=H·MeI (148)

(149)

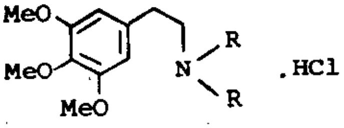
(48)

intermediates (141), (143),(145) and (147), all of which exhibited negative Cotton effects in their ORD spectra while the (-)-phenethylamine (140b) furnished the antipodes (142), (144), (146) and (148) which showed positive Cotton effects. Reduction of the quaternary intermediate (147) was accompanied by inversion of the Cotton effects and afforded unnatural cherylline (149) of R-configuration. By the same procedure (148) was converted into the (-)-tetrahydroisoquinoline (48) identical in mmp, chromatographic behavior, uv, nmr, ORD, CD and mass spectra to natural cherylline.[68]

Partial O-Demethylation of 1-(Trimethoxy-substituted) 6,7-dimethoxy-3,4-dihydro- and 1,2,3,4-tetrahydroisoquinolines

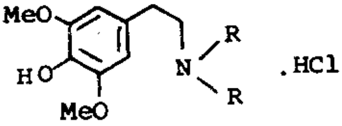
Cleavage of Mescaline[71] and Trichocereine[72] as Model Compounds

The lability of the middle of three vicinal aromatic methoxyls to mineral acid has been previously demonstrated for 6,7,8-trimethoxy-3,4-dihydroisoquinoline.[14,15] The utility of this finding was evaluated on simpler model systems. Thus, the trimethoxy-phenethylamine alkaloids mescaline (150) and its N,N-dimethyl derivative trichocereine (151) upon treatment with 20% hydrochloric acid under controlled reaction conditions afforded 64% of desmethylmescaline (49) and 74% of demethyltrichocereine (50), respectively. Evidence that scission had indeed occurred at the middle methoxyl was obtained by the identity of the cleavage product (49) to an authentic sample prepared by condensation of syringaldehyde with nitromethane followed by lithium aluminum hydride reduction.[73] Further, the product obtained by reductive condensation of (49) with formaldehyde was identical to the monophenol (50).



(150) R=H

(151) R=Me

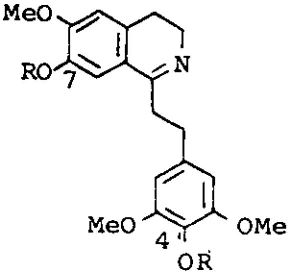


(49) R=H

(50) R=Me

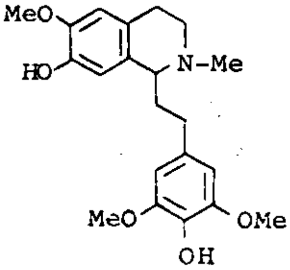
Preferential Cleavage of 1-(Trimethoxyphenethyl)-3,4-dihydro- and 1,2,3,4-tetrahydroisoquinolines[74]

The diphenolic tetrahydroisoquinoline (154), shown by Battersby and co-workers[75] to be an important precursor of the novel homoaporphine alkaloid multifloramine (51), has been synthesized by standard methods by Kametani and associates.[76] It was, therefore, worthwhile to consider preferential O-demethylation with mineral acid as an alternative route to the precursor (154). In view of the acid lability of the middle of three vicinal methoxyls[14,15,71,72] and of the 7-methoxyl in 6,7-dimethoxy-3,4-dihydroisoquinolines[13,56,67] it appeared likely that the pentamethoxy-substituted 3,4-dihydroisoquinoline (152) could be selectively cleaved at the 4',7-positions to afford the corresponding diphenol (153) which could then be readily converted into the desired tetrahydroisoquinoline (154). Based on these considerations, the action of mineral acid under controlled conditions on various 1-(3,4,5-trimethoxyphenethyl)-3,4-dihydro- and 1,2,3,4-tetrahydroisoquinolines, all obtained by standard methods,[74] was investigated.

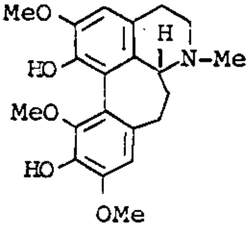


(152) R=Me

(153) R=H



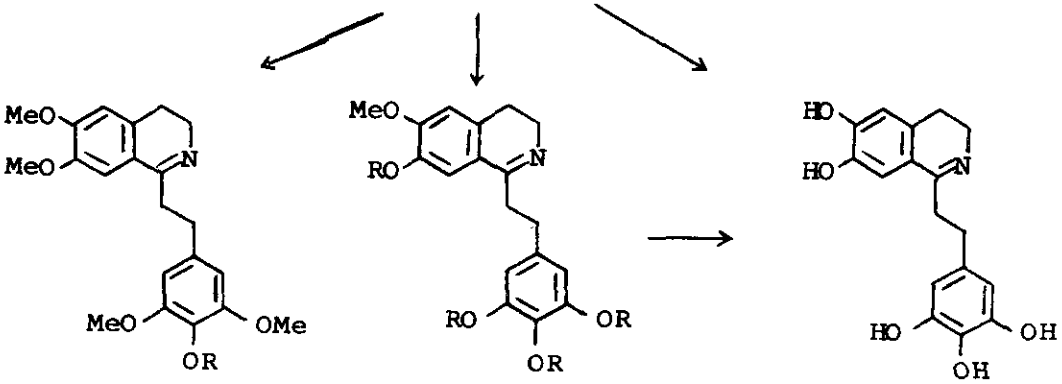
(154)



(51)

Treatment of the pentamethoxy-substituted 3,4-dihydroisoquinoline (152) with liquid hydrogen bromide cleaved the 4'-methoxy to give the monophenol (155) while 62% hydrobromic acid at 100° for 15 min. and at reflux for 2 hr gave the tetraphenol (157) and the pentaphenol (159), respectively. Based on the known greater lability of a benzyloxy function than a methoxyl to mineral acid,[77] the structures of (155) and (157) were established by their identity to the mineral acid cleavage products of the corresponding benzyloxy derivatives (156) and (158) obtained by standard methods; whereas that of (159) was confirmed by scission of the monomethoxyl of (157) with refluxing hydrobromic acid. In addition, the 4'-methoxyl of the pentamethoxy-substituted 1,2,3,4-tetrahydroisoquinoline (160) was cleaved with refluxing 20% hydrochloric acid to the corresponding monophenol (161) which was also obtained by acid catalyzed debenzylation of the monobenzyloxy derivative (162).

(152)



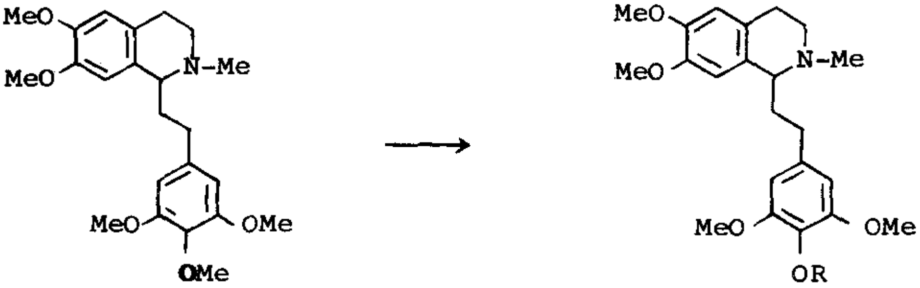
(155) R=H

(156) R=C_7H_7

(157) R=H

(158) R=C_7H_7

(159)

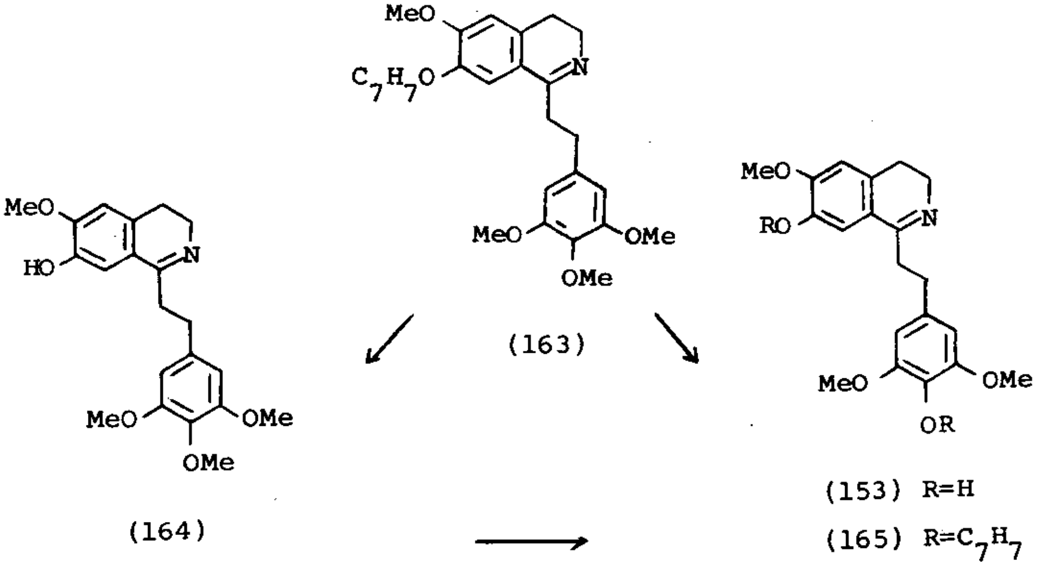


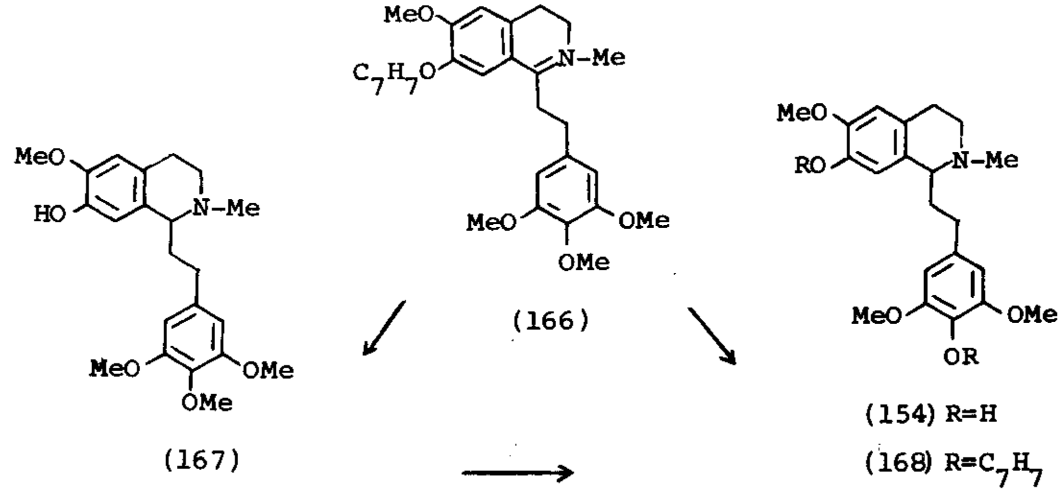
(160)

(161) R=H

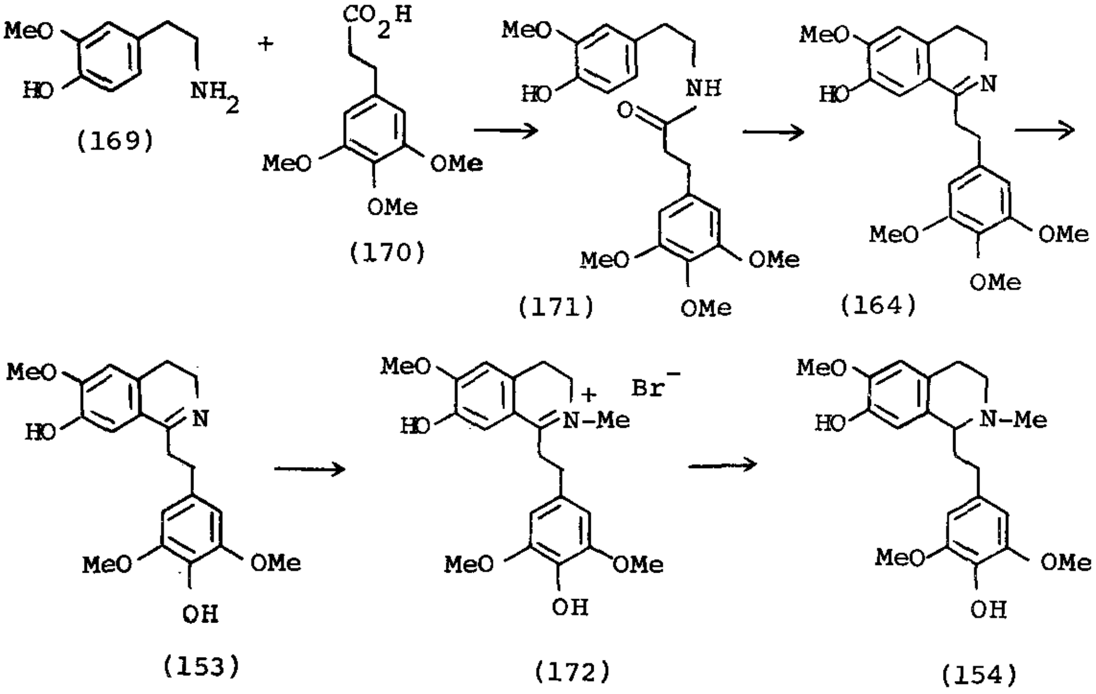
(162) R=C_7H_7

In view of this unexpected stability of the 7-methoxyl of the 3,4-dihydroisoquinoline (152), the corresponding 7-benzyloxy tetramethoxy-3,4-dihydroisoquinoline (163) was reacted with 20% hydrochloric acid under controlled conditions. At room temperature for 10 days, (163) was selectively cleaved at the benzyloxy function to afford in excellent yield the monophenol (164) while at reflux the 4',7-diphenol (153) was formed. The latter was also obtained by controlled acid hydrolysis of either the monophenol (164) or the dibenzyloxy derivative (165). In a similar manner, the 7-benzyloxy-tetramethoxy-tetrahydroisoquinoline (166) was hydrolyzed by mild treatment with 20% hydrochloric acid to the 7-hydroxy derivative (167) or under more vigorous conditions to the desired 4',7-diphenol (154). The latter was also obtained from the monophenol (167) or the dibenzyloxy intermediate (168) by controlled reaction with acid.



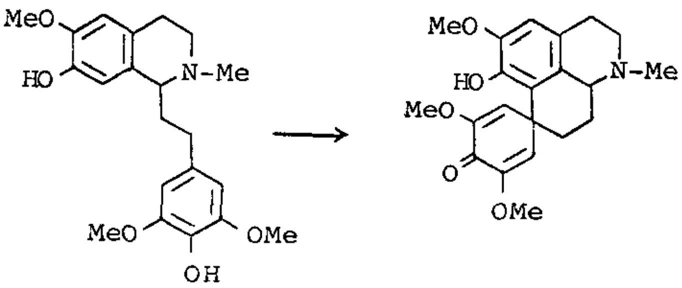


Based on the partial ether cleavage study which demonstrated that the benzyloxy and the 4'-methoxy groups were the most labile while the 6-methoxyl was the most stable to acid catalyzed hydrolysis, the diphenolic multifloramine precursor (154), previously obtained by a multistep procedure,[76] was synthesized by the following straightforward sequences. Since free phenols need not be protected in the Bischler-Napieralski reaction,[9] the hydroxy-phenethylamine[78] (169) and the trimethoxy-phenylpropionic acid (170),[79] both obtained by improved procedures, were fused to give the amide (171). Cyclodehydration of (171) with phosphorus oxychloride to the monophenolic imine (164) followed by treatment with 20% hydrochloric acid under controlled reaction conditions effected cleavage of the middle of the three methoxyls to yield the diphenolic dihydroisoquinoline (153) which was converted into the methobromide (172) and catalytically hydrogenated over platinum to the desired diphenol (154).

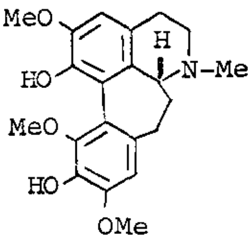


Synthesis and Absolute Configuration of Multifloramine[80]

As shown in the preceding study, the diphenolic tetrahydroisoquinoline (154), an important precursor of the novel homoaporphine alkaloid multifloramine (51),[75] was obtained by a straightforward synthesis based on preferential O-demethylation Since Kametani and co-workers[76] have reported the oxidative conversion of (154) to the dienone (173), the penultimate intermediate for racemic multifloramine, it was of interest to resolve (154) and prepare natural (-)-multifloramine (51) as well as its unnatural isomer.

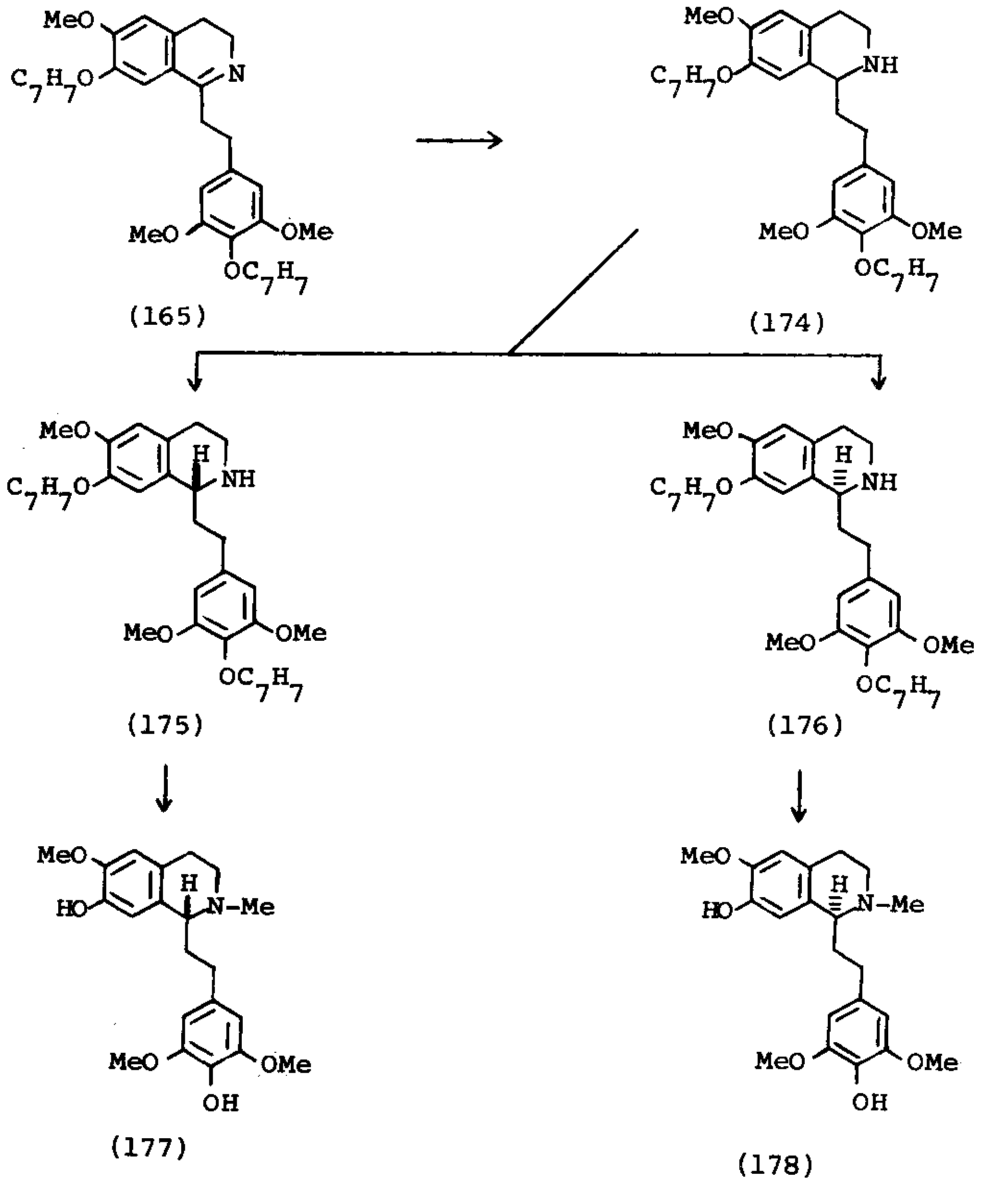


(154) (173)



(51)

Optical resolution of (154) with a number of optically active acids was unsuccessful. However, the related dibenzyloxy derivative (174), obtained from the corresponding 3,4-dihydroisoquinoline (165) by sodium borohydride reduction, was readily resolved with di-O-p-toluoyl-D-tartaric acid. Crystallization of the tartrate from acetonitrile gave the levorotatory salt of (175) whose hydrochloride was dextrorotatory. Conversion of the tartrate mother liquors to the hydrochloride followed by crystallization from acetonitrile yielded the levorotatory enantiomeric hydrochloride of (176). Reductive condensation of (175) with formaldehyde in the presence of Raney nickel resulted in simultaneous N-methylation and debenzylation to afford the levorotatory diphenol (177). Similar treatment of (176) yielded the dextro-isomer (178).



In order to determine the absolute configuration of the enantiomeric diphenols, the dextrorotatory antipode (178) was fully methylated by treatment with diazomethane to the dextrorotatory pentamethoxy-tetrahydroisoquinoline (179), isolated as its hydrobromide. The latter exhibited an ORD spectrum which was similar, but with opposite Cotton effects, to the spectrum of the hydrobromide of dimethoxytetrahydroisoquinoline (180) whose absolute configuration had been established as *R*.[81] Further, since comparison of the ORD and CD spectra of the dextro-base (179) and the *R*-levo-base (180) showed that the two compounds were mirror images of each other (Fig. 1), it followed that (179) had the *S*-configuration at its asymmetric center. Based on this assignment, the interrelated enantiomeric diphenols (177) and (178) as well as their dibenzyloxy precursors (175) and (176) possess the *R*- and *S*-configurations, respectively (Table I).

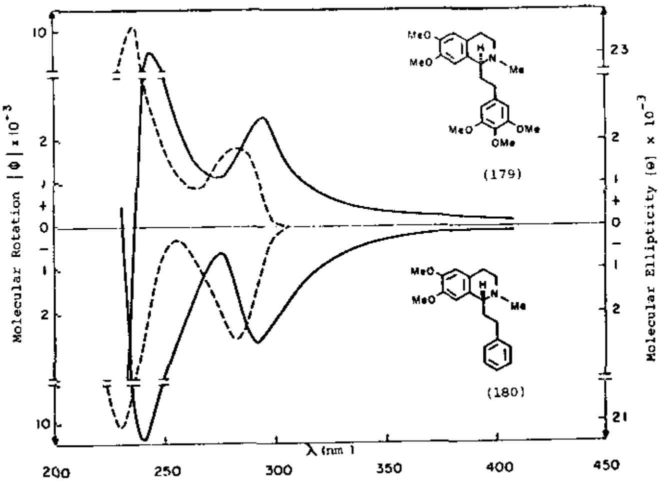
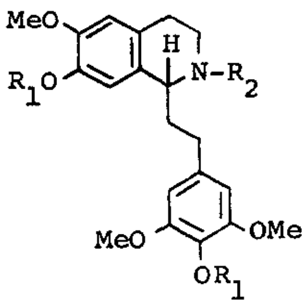


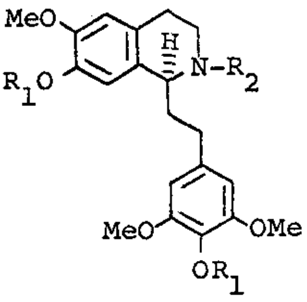
Fig. 1. ORD (-) and CD (---) Curves of (179) (c 0.1785, MeOH) and (180) (c 0.1565, MeOH).

Table 1

Configuration and Specific Rotation of Resolved Tetrahydroisoquinolines



R configuration



S configuration

Compd	Structure		Configuration	Salt		Base	
	R_1	R_2		Mp, °C	$[\alpha]^{25}_{D}$[a]	Mp or bp (mm), °C	$[\alpha]^{25}_{D}$[a]
(175)	C_7H_7	H	R	129-130[b]	-51°		
				160-161[c]	+8.0°	d	+12.8°
(176)	C_7H_7	H	S	160-161[c]	-8.0°	d	-13.0°
(177)	H	Me	R	220-222[c]	-32.0°	62-63	-27.0°
(178)	H	Me	S	220-222[c]	+32.5°	62-63	+27.0°
(179)	Me	Me	S	170-171[e]	+12.8°	220-225 (0.07)	+4.8°

[a] Determined as 1% solution in methanol.

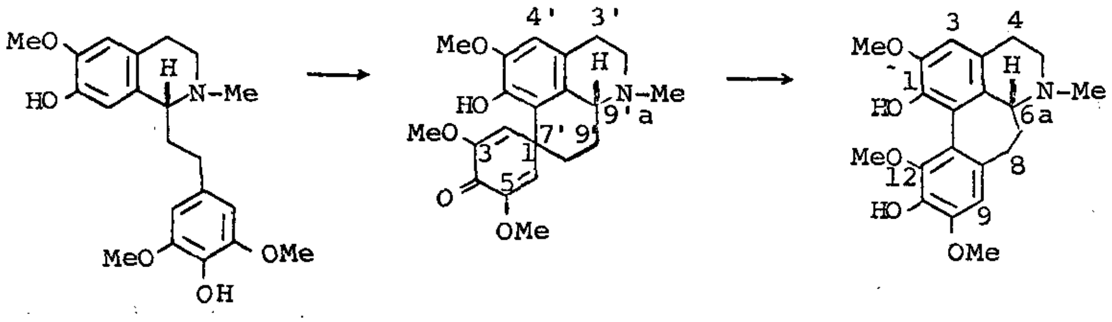
[b] Di-O-p-toluoyl-D-tartrate.

[c] Hydrochloride.

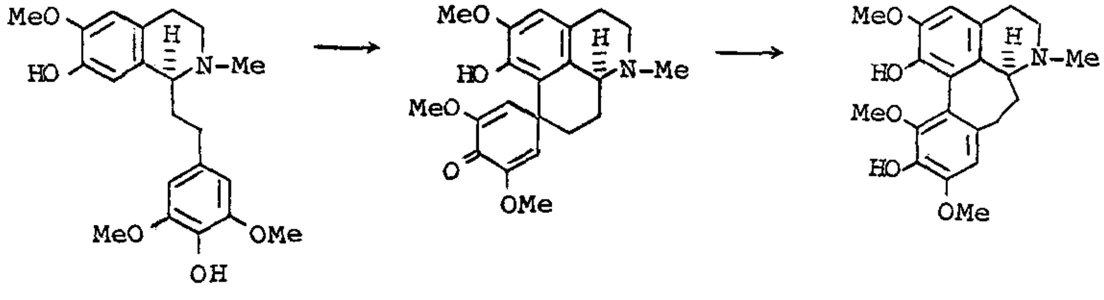
[d] Not distilled.

[e] Hydrobromide.

The isomeric diphenols (177) and (178) were transformed into the enantiomeric multifloramines (51) and (183), respectively. Oxidation of (177) with aqueous ferric chloride afforded the dienone (181) whose nmr spectrum was in excellent agreement with the chemical shifts reported for the racemic dienone.[76] Upon treatment with concentrated sulfuric acid, (181) rearranged to the levorotatory isomer of R-configuration (51), identical to the natural alkaloid[75] multifloramine by mixed melting point and optical rotation. By the same sequence of reactions, dextrorotatory unnatural multifloramine (183) was obtained from the diphenol (178) by oxidation to the dienone (182) followed by acid rearrangement (Table 2).



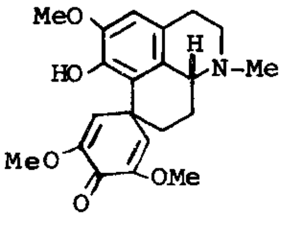
(177) (181) (51)



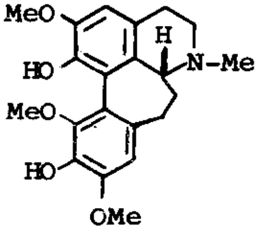
(178) (182) (183)

Table 2

Configuration and Specific Rotation of Optically Active Dienones (**A**) and Multifloramines (**B**)



A



B

Compd	Structure	Configuration	Base	
			Mp °C	$[\alpha]_D^{25}$[b]
(181)	A	*R*	243-244	-49.5°
(182)	A	*S*	241-242	+50.0°
(51)	B	*R*	215-216	-111.5°
(183)	B	*S*	214-215	+112.0°

[a] Only the *R*-configuration is represented in formula **A** and **B**.

[b] Determined as a 1% solution in methanol.

The optical rotatory dispersion spectra (Fig. 2) and the circular dichroism spectra (Fig. 3) of natural multifloramine (51) and the unnatural isomer (183) are mirror images of each other. It is of interest to note (Fig. 2) that, although (51) is levorotatory at the sodium D-line, the Cotton effects between 250 and 320 nm are dextrorotatory. In contrast, the 1-phenethyl-substituted tetrahydroisoquinolines (179) and (180) exhibited $[\alpha]_D$ values and Cotton effects of the same sign. This is probably due to the difference between a relatively rigid cyclized structure and an open-chain compound.

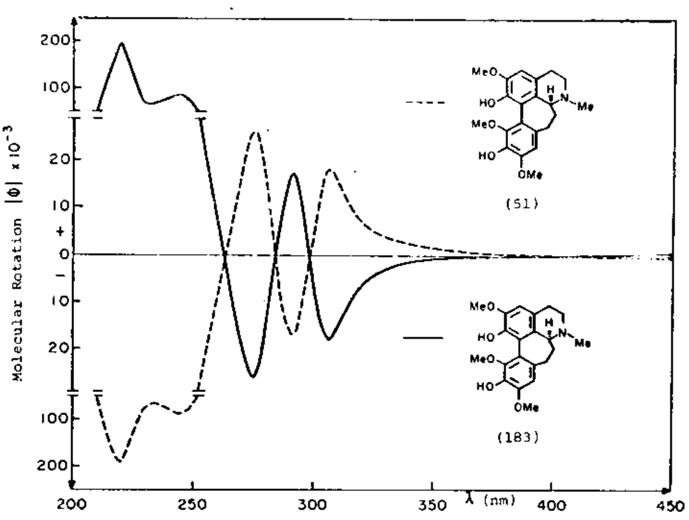


Fig. 2. ORD Curves of (51) and (183) (c 0.372, MeOH).

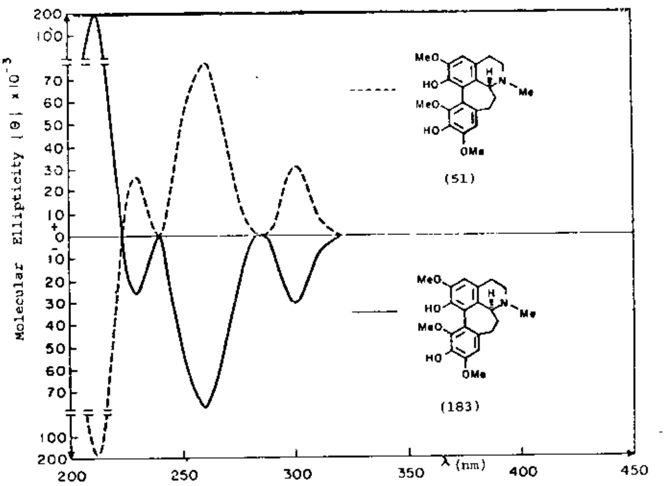
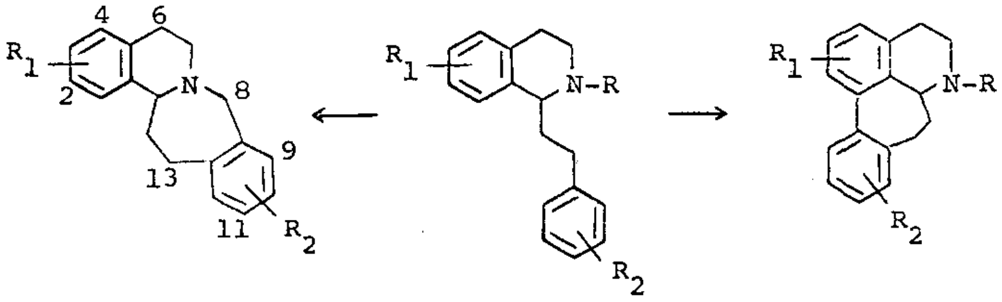


Fig. 3. CD Curves of (51) and (183) (c 0.372, MeOH).

Synthesis of 10-Hydroxy-2,3,9,11-tetramethoxyhomoberbine[82,83]

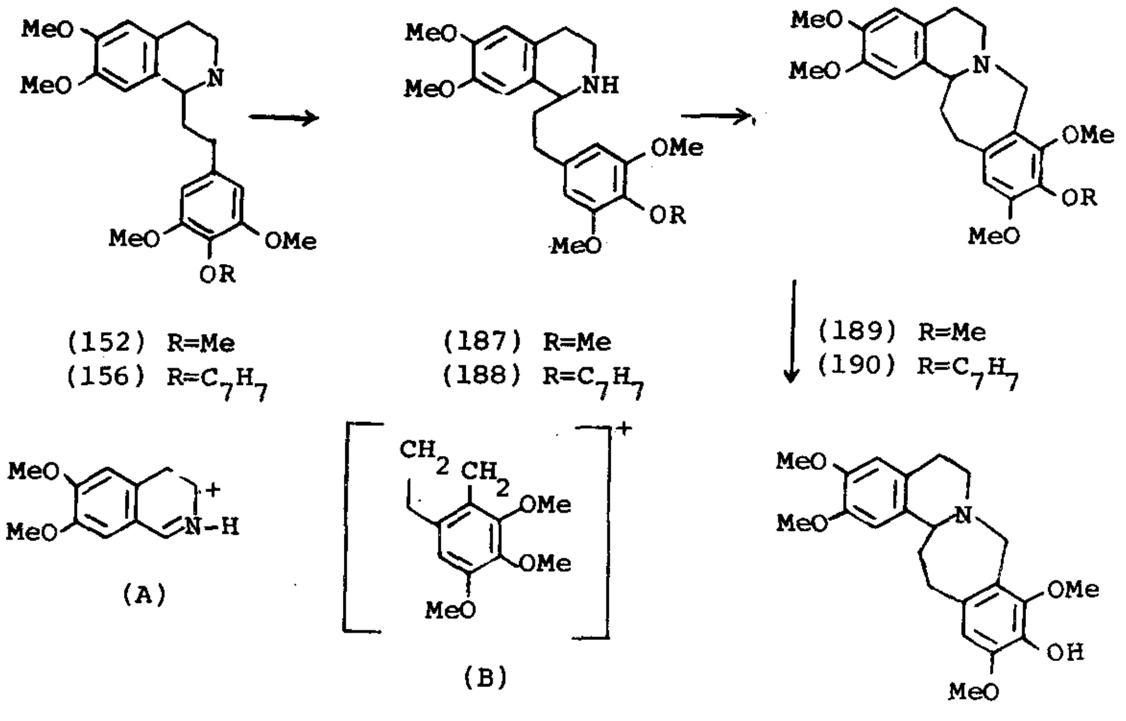
Another example of the lability of the middle of three vicinal methoxy-substituted tetrahydroisoquinolines toward mineral acid under controlled reaction conditions was provided by a study of the homoberbines (184), a new class of heterocyclic compounds which are homologs of the tetrahydroprotoberberines (berbines) but have not as yet been isolated from natural sources. However, it was of interest to synthesize a few representative homoberbines especially since they could be derived from phenethylisoquinolines (185), some of which have been shown to be biogenetic precursors of the homoaporphines (186).[75]



(184) (185) (186)

Based on the classical Mannich type reaction for the preparation of berbines, the pentamethoxy-substituted homoberbine (189) was obtained from the previously described pentamethoxy 3,4-dihydroisoquinoline (152) by sodium borohydride reduction to the corresponding tetrahydroisoquinoline (187) followed by condensation with formaldehyde in the presence of mineral acid. The mass spectrum of (189) showed the expected molecular ion (M^+) and the $(M-1)^+$ as well as main cleavage corresponding to ions (A) and (B).

Treatment of the pentamethoxy-homoberbine (189) with 20% hydrochloric acid for 2 hr at reflux effected selective scission of the middle of the three methoxyls to afford the 10-hydroxy-substituted homoberbine (191) in 64 % yield. The structure of the latter was confirmed as follows. The previously described benzyloxy-imine (156) was reduced to the tetrahydroisoquinoline (188) followed by condensation with formaldehyde in acetic acid, according to the procedure of Kametani and co-workers[84] for mineral acid sensitive functions, to the benzyloxy homoberbine (190) O-Debenzylation of (190) with acid afforded the identical monophenol (191) obtained by preferential cleavage of (189).



(152) R=Me
(156) R=C_7H_7

(187) R=Me
(188) R=C_7H_7

(189) R=Me
(190) R=C_7H_7

(A)

(B)

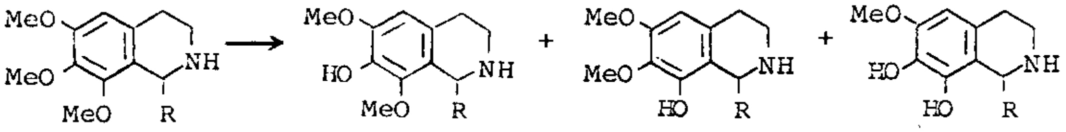
(191)

Partial O-Demethylation of 6,7,8- and 5,6,7-Trimethoxy-substituted 1,2,3,4-tetrahydroisoquinolines

Cleavage of Model Compounds[85]

The selective cleavage of the middle of three vicinal methoxyls by mineral acid under controlled reaction conditions has been demonstrated in the preceding chapter for 1-(trimethoxy-substituted) 6,7-dimethoxy-3,4-dihydro- and 1,2,3,4-tetrahydroisoquinolines and has been reported by Brossi and co-workers[14] and by Kametani and associates[15] for 6,7,8-trimethoxy-3,4-dihydroisoquinolines. It was, therefore, of interest to determine the behavior of 6,7,8- and 5,6,7-trimethoxy-substituted 1,2,3,4-tetrahydroisoquinolines toward mineral acid.

For this purpose, the simple alkaloid anhalinine (192)[2] was treated with 20% hydrochloric acid under reaction conditions optimized to favor the formation of a minimum of products as visualized by thin layer chromatography. Under these conditions, a mixture of hydrochlorides was obtained which was separated to give 60% of the starting material (192), 21% of the 7-monophenol (193),[86] 4% of the 8-monophenol anhalamine (194) hydrochloride[5,15] and 4% of the diphenolic tetrahydroisoquinoline (195) hydrochloride. Similarly, the 1-methyl-substituted alkaloid (±)-O-methylanhalonidine (196) hydrochloride[87] yielded 48% of unchanged (196), 20% of the 7-monophenol (197),[14] 5% of the 8-monophenol anhalonidine (3)[5] and 6% of the 7,8-diphenol (198).



(192) R=H (193) R=H (194) R=H (195) R=H

(196) R=Me (197) R=Me (3) R=Me (198) R=Me

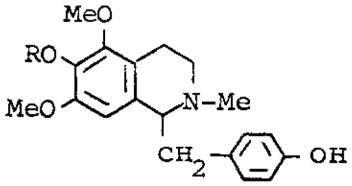
In contrast to the secondary amines (192) and (196) which formed mixtures of phenolic products that could not be avoided, the corresponding tertiary amines O-methylanhalidine (199)[88] and racemic O-methylpellotine (201)[2] when treated with 20% hydrochloric acid under the same conditions were O-demethylated at the middle methoxyl group to afford 81% of (200) and 72% of (202), respectively, as hydrochlorides. Similarly, the 5,6,7-trisubstituted tetrahydroisoquinoline (±)-thalifenderline (203) hydrochloride[89] yielded the corresponding 6-phenol (53).[90]

(199) R=H

(201) R=Me

(200) R=H

(202) R=Me



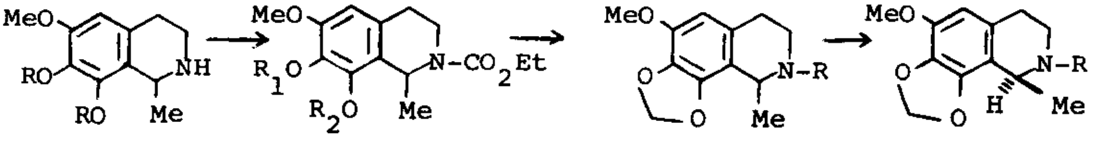
(203) R=Me

(53) R=H

Synthesis and Absolute Configuration of Anhalonine and Lophophorine[91]

The previous study on the preferential O-demethylation of 6,7,8-trimethoxy-substituted 1,2,3,4-tetrahydroisoquinolines with mineral acid demonstrated that, in contrast to the N-methyl derivatives which were selectively cleaved at the 7-methoxyl, the corresponding secondary amines gave mixtures of the 7- and 8-monophenols and the 7,8-diphenol.[85] This finding has now been utilized for a novel and simplified synthesis of two of the major cactus alkaloids, anhalonine (2) and lophophorine (54), heretofore obtained by a route (see Introduction) that formed isomeric intermediates which required separation.[3]

For this purpose, the reaction conditions previously noted for the preferential O-demethylation of (±)-O-methylanhalonidine (196) were modified by extending the treatment time with 20% hydrochloric acid to afford the key intermediate 6-methoxy-7,8-diphenol (198) in 57% yield. Reaction of (198) with ethyl chloroformate yielded the diphenolic carbamate (204) which was condensed with dibromomethane in dimethylformamide according to the procedure of Tomita and Aoyagi[92] to the methylenedioxy urethan (205). Base-catalyzed hydrolysis of (205) gave racemic anhalonine (206) whereas lithium aluminum hydride reduction of (205) afforded racemic lophophorine (207). Alternatively, (207) was obtained by reductive condensation of (206) with formaldehyde in the presence of Raney nickel catalyst. Resolution of (206) with (-)-tartaric acid according to the procedure of Späth and Kesztler[3b] afforded the alkaloid anhalonine (2)[3b,93] which was transformed by N-methylation into natural lophophorine (54).[3b,93]



(196) R=Me

(198) R=H

(204) $R_1=R_2=H$

(205) $R_1+R_2=CH_2$

(206) R=H

(207) R=Me

(2) R=H

(54) R=Me

In connection with a related study on the tetrahydroisoquinoline alkaloid (+)-O-methylanhalonidine,[91] a single-crystal X-ray analysis established that anhalonine (2) hydrobromide possesses the S-configuration (Fig. 4). This confirmed the assignment made by Battersby and Edwards[94] using the method of optical rotatory shifts wherein the negative molecular rotation of (2) and (54) decreased with increasing polarity of the solvent. The similarity of the ORD and CD spectra of (2) and (54) provided verification that lophophorine (54) possesses the S-configuration.

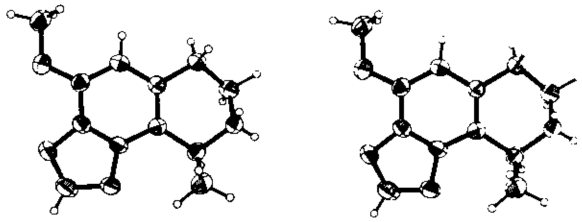
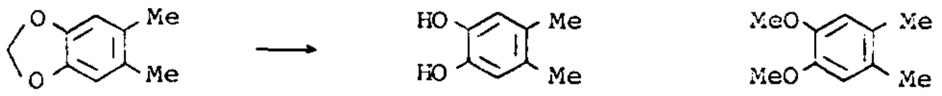


Fig. 4. Stereodrawings Illustrating the Absolute Configuration of Anhalonine (2) as Determined by X-ray Analysis of (2)HBr.

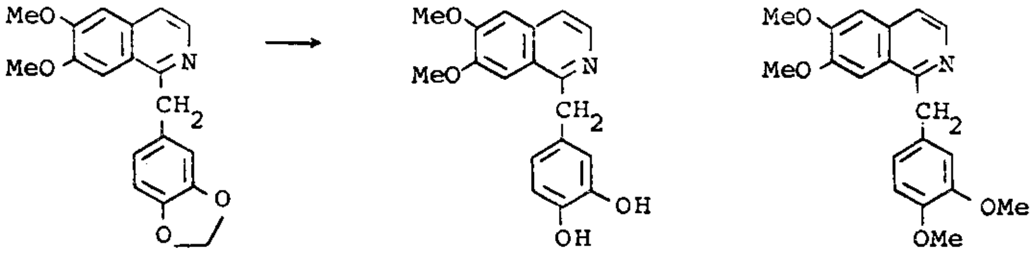
Preferential Cleavage of an Aromatic Methylenedioxy Group in the Presence of Methoxyls with Boron Trichloride[95]

In connection with recent studies on the transformation of phthalide alkaloids, it was reported that boron tribromide was an excellent reagent to effect complete O-dealkylation.[19] In contrast, it has now been ascertained that the Lewis acid boron trichloride can be used to preferentially cleave an aromatic methylenedioxy group in the presence of methoxyls. The selective action of this reagent was demonstrated on model compounds and applied to a facile synthesis of a phthalideisoquinoline.

Although boron trichloride has been utilized in the scission of cyclic acetals of hexitols[18] and in the partial de-etherification of certain podophyllotoxins,[96] it was only effective in cleaving an aromatic methylenedioxy group in the presence of aromatic methoxyls under controlled reaction conditions. The type and extent of de-etherification of model compounds treated with boron trichloride in methylene chloride was influenced by the ratio of substrate to reagent as well as the reaction temperature and time. By proper selection of conditions, cleavage of a methylenedioxy group in preference to aromatic methoxyls could be achieved. For example, treatment of the 4,5-methylenedioxy-o-xylene (208)[97] at room temperature with 1 or 2 equivalents of boron trichloride for 64 hr and 3 hr, respectively, gave the 4,5-dimethylcatechol (209)[98] in 80% yield, while ether cleavage of the 4,5-dimethoxy-o-xylene (210)[98] required higher temperatures or longer reaction times. Similarly, while the methylenedioxy-substituted isoquinoline (211)[99] and its methoxy analog papaverine (45) were converted by treatment with 2 molar equivalents of the reagent for 5 hr at room temperature into a mixture of phenolic materials, only (211) was cleanly cleaved at 4° to yield 78% of the 3',4'-O-desmethylpapaverine (106)[49] whereas (45) was recovered unchanged.

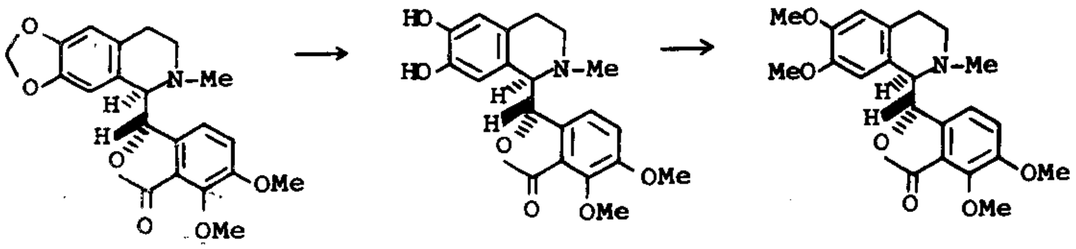


(208) (209) (210)



(211) (106) (45)

To further illustrate the synthetic applicability of preferential O-demethylenation with boron trichloride to isoquinoline alkaloids, commercially available (-)-β-hydrastine (6) was treated with 2 moles of the Lewis acid in methylene chloride at room temperature for 6 hr to afford 81% of the dimethoxy diphenol (59). Reaction of (59) with diazomethane afforded the recently described tetramethoxy phthalideisoquinoline (-)-cordrastine II (7).[19]



(6) (59) (7)

Conclusions

The utility of preferential O-demethylation with mineral acid and preferential O-demethylenation with boron trichloride as tools in the synthesis of certain isoquinoline alkaloids has been demonstrated. This approach provides a simple route to phenolic isoquinolines usually obtained by cumbersome multistep procedures. However, it is limited to specifically substituted starting materials.

A variety of simple and complicated polymethoxy-substituted 3,4-dihydro- and 1,2,3,4-tetrahydroisoquinolines have been preferentially O-demethylated with mineral acid under controlled reaction conditions. The lability of the 7-methoxyl in 6,7-dimethoxy-3,4-dihydroisoquinoline was utilized in the novel synthesis of the monophenolic alkaloids corypalline (46) and cherylline (48) and studies of the cleavage of the middle of three vicinal methoxyls resulted in the facile synthesis of the homoaporphine alkaloid multifloramine (51) and the catcus alkaloids anhalonine (2) and lophophorine (54). In addition, the potential of selective O-demethylation for further transformations was indicated by the conversion of corypalline (46) into its 8-methyl-substituted derivative (47).

However, the usefulness of preferential O-demethylation as a synthetic tool is limited not only by the necessity of empirically establishing the optimum reaction conditions for each polymethoxylated isoquinoline but also by the influence of all the substituents on the cleavage pattern. For example, whereas the 6-methoxyl in 6,7-dimethoxy-3,4-dihydroisoquinolines was the most stable to acid catalyzed hydrolysis, the preferential cleavage of the 7-methoxyl was not always possible. This was shown by the acid cleavage of the Ipecac alkaloid O-methylpsychotrine (90) which gave a complex mixture of phenols and by the lability of the methoxyls of the benzylic side chain of papaverine (45) as well as by the facile scission of the three vicinal methoxyls in 6,7-dimethoxy-1-(3,4,5-trimethoxyphenethyl)-3,4-dihydroisoquinoline (152). Further, although desmethylmescaline (49), desmethyltrichocereine (50), the monophenolic homoberbine (52), and desmethylthalifendlerine (53) were derived from their methylated precursors by preferential cleavage of the middle of the three vicinal methoxyls, controlled mineral acid treatment of the 6,7,8-trimethoxy-substituted tetrahydroisoquinolines anhalinine (192) and O-methylanhalonidine (196) gave mixtures of the 7- and 8-monophenols and the 7,8-diphenol. In contrast, the corresponding N-methyl derivatives (199) and (201) afforded the expected monophenols (200) and (202), respectively.

Finally, the preferential cleavage of a methylenedioxy group in the presence of methoxyls with boron trichloride under controlled reaction conditions was demonstrated for model compounds as well as by the facile conversion of the phthalide alkaloid (-)-β-hydrastine (6) into (-)-cordrastine II (7). This action of boron trichloride in methylene chloride, paralleling that of aluminum tribromide in nitrobenzene, provides a facile method of converting one alkaloid into another with retention of configuration. However, its general application is limited by the availability of starting materials.

References

1) T. Kametani, "The Chemistry of Isoquinoline Alkaloids", Hirokowa Publishing Co. Inc., Tokyo, and Elsevier Publishing Co., Amsterdam, 1968.

2) E. Späth, *Monatsh. Chem.*, **42**, 97 (1921); E. Späth, J. Bruck, *Ber.*, **72**, 334 (1969).

3) a) E. Späth, J. Gangl, *Monatsh. Chem.*, **44**, 103 (1923).
   b) E. Späth, F. Kesztler, *Chem. Ber.*, **68**, 1663 (1935).

4) E. Späth, *Monatsh. Chem.*, **43**, 477 (1922).

5) A. Brossi, F. Schenker, W. Leimgruber, Helv. Chim. Acta, 47, 2089 (1964).

6) M. Takido, K. L. Khanna, A. G. Paul, J. Pharm. Sci., 59, 271 (1970).

7) A. Pictet, M. Finkelstein, Ber., 42, 1979 (1909).

8) K. W. Gopinath, T. R. Govindachari, N. Viswanathan, Ber., 92, 1657 (1959).

9) S. Teitel, A. Brossi, J. Heterocycl. Chem., 5, 825 (1968).

10) W. H. Perkin, V. M. Trikojus, J. Chem. Soc., 1926, 2925.

11) R. D. Haworth, A. R. Pinder, R. Robinson, Nature, 165, 529 (1950).

12) R. D. Haworth, A. R. Pinder, J. Chem. Soc., 1950, 1776.

13) a) H, Bruderer, A. Brossi, Helv. Chim. Acta, 48, 1945 (1965).
b) T. Kametani, S. Takano, F. Sasaki, Yakugaku Zasshi, 87, 191 (1967).

14) A. Brossi, M. Baumann, R. Borer, Monatsh. Chem., 96, 25 (1965); A. Brossi, R. Borer, Monatsh. Chem., 96, 1409 (1965);

15) T. Kametani, N. Wagatsuma, F. Sasaki, Yakugaku Zasshi, 86 913 (1966).

16) A. Brossi, H. Gurien, A. I. Rachlin, S. Teitel, J. Org. Chem., 32, 1269 (1967).

17) D. Yonemitsu, H. Nakai, Y. Kanoaka, I. L. Karle, B. Witkop, J. Amer. Chem. Soc., 91, 4591 (1969); C. F. Wilcox, Jr., M. A. Seager, J. Org. Chem., 34, 2319 (1969); R. G. Wilson, D. H. Williams, J. Chem. Soc. (C), 1968, 2475.

18) T. G. Bonner, N. W. Saville, J. Chem. Soc., 1960, 2851.

19) S. Teitel, J. O'Brien, A. Brossi, J. Org. Chem., 37, 1879 (1972).

20) E. Mosettig, A. Burger, J. Amer. Chem. Soc., 52, 2988 (1930).

21) A. Brossi, S. Teitel, Helv. Chim. Acta, 53, 1779 (1970).

22) T. R. Govindachari, M. V. Lanshminantan, Proc. Indian Acad. Sci., 46A, 406 (1957) [Chem.Abst., 52, 11063 (1958)].

23) J. S. Buck, *J. Amer. Chem. Soc.*, **54**, 3661 (1932).

24) H. T. Openshaw, N. Whittaker, *J. Chem. Soc.*, **1963**, 1461.

25) G. Grethe, H. L. Lee, M. Uskokovic, A. Brossi, *J. Org. Chem.*, **33**, 494 (1968).

26) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, R. Eberman, *J. Org. Chem.*, **30**, 2247 (1965).

27) M. E. Kuehne, B. F. Lambert, *J. Amer. Chem. Soc.*, **81**, 4278 (1959).

28) J. D. White, D. S. Straus, *J. Org. Chem.*, **32**, 2689 (1967).

29) F. Benington, R. D. Morin, L. C. Clark, Jr., R. P. Fox, *J. Org. Chem.*, **30**, 2247 (1965).

30) F. A. Ramirez, A. Burger, *J. Amer. Chem. Soc.*, **72**, 2781 (1950).

31) A. Funke, *Bull. Soc. Chim. France*, **1960**, 1644.

32) G. Grethe, V. Toome, H. L. Lee, M. Uskokovic, A. Brossi, *J. Org. Chem.*, **33**, 504 (1968).

33) W. J. Musliner, J. W. Gates, Jr., *J. Amer. Chem. Soc.*, **88**, 427 (1966).

34) F. Schenker, R. A. Schmidt, W. Leimgruber, A. Brossi, *J. Med. Chem.*, **9**, 46 (1966).

35) F. Schenker, R. A. Schmidt, T. Williams, A. Brossi, *J. Heterocycl. Chem.*, **8**, 665 (1971).

36) S. Durand, X. Lusinchi, R. Moreau, *Bull. Soc. Chim. France*, **1961**, 270.

37) P. Fritsch, *Liebigs Ann. Chem.*, **286**, 1 (1895).

38) S. Teitel, A. Brossi, *J. Heterocycl. Chem.*, **7**, 1401 (1970).

39) S. Teitel, A. Brossi, *J. Amer. Chem. Soc.*, **88**, 4068 (1966).

40) F. H. Carr, F. L. Pyman, *J. Chem. Soc.*, 105, 1591 (1914).

41) F. L. Pyman, *J. Chem. Soc.*, **111**, 419 (1917).

42) A. R. Battersby, R. Binks, G. C. Davidson, *J. Chem. Soc.*, **1959**, 2704; A. R. Battersby, S. Garratt, *J. Chem. Soc.*, **1959**, 3512.

43) W. H. Brindley, F. L. Pyman, *J. Chem. Soc.*, **1927**, 1067.

44) M. Pailer, K. Porschinski, *Monatsh. Chem.*, **80**, 101 (1949).

45) M. Tomita, H. Yamaguchi, *J. Pharm. Soc. Japan,* **72**, 1219 (1952).

46) J. M. Bobbitt, T-T. Chou, *J. Org. Chem.*, **24**,1106 (1959).

47) A. R. Battersby, H. T. Openshaw, *J. Chem. Soc.*, **1949**, 59.

48) C. Szántay, L. Töke, P. Kolonitis, *J. Org. Chem.*, **31**, 1447 (1966).

49) A. Brossi, S. Teitel, *J. Org. Chem.*, **35**, 1684 (1970).

50) A. Boucherle, J. Alary, *Bull. Soc. Chim. France*, **1960**, 1222.

51) J. V. Burba, M. F. Murnaghan, *Biochem. Pharm.*, **14**, 823 (1965).

52) E. Brochmann-Hanssen, K. Hirai, *J. Pharm. Sci.*, **57**, 940 (1968).

53) N. A. Chaudhury, A. Chatterjee, *J. Indian Chem. Soc.*, **36**, 585 (1959).

54) T. Kametani, S. Kano, *J. Pharm. Soc. Japan*, **84**, 256 (1965).

55) B. K. Cassels, V. Deulofeu, *Tetrahedron Suppl.*, **8**, Part II, 485 (1966).

56) A. Brossi, J. O'Brien, S. Teitel, *Org. Prep. Procedures*, **2**, 281 (1970).

57) J. O'Brien, S. Teitel, A. Brossi, *Syn. Commun.*, **2**, 171 (1972).

58) R. H. F. Manske, *Can. J. Res.*, **15B**, 159 (1937).

59) M. Tomita, H. Watanabe, *J. Pharm. Soc. Japan*, **58**, 783 (1938).

60) J. M. Bobbitt, D. N. Roy, A. Marchand, C. W. Allen, *J. Org. Chem.*, **32**, 2225 (1967).

61) E. Späth, N. Polgar, *Monatsh. Chem.*, **51**, 190 (1929).

62) S. Akabori, *Bull. Chem. Soc. Japan*, **1**, 125 (1926).

63) J. Harley-Mason, A. S. Howard, W. I. Taylor, M. J. Vernengo, I. R. C. Bick, P. S. Clezy, *J. Chem. Soc.*(C), **1967**, 1948.

64) K. Aoki, J. Harley-Mason, *J. Chem. Soc. (C)*, **1967**, 1957.

65) F. Poppelsdorf, S. J. Holt, *J. Chem. Soc.*, **1954**, 1124.

66) A. Burger, R. D. Foggio, *J. Amer. Chem. Soc.*, **78**, 4419 (1956).

67) A. Brossi, S. Teitel, *Tetrahedron Lett.*, **1970**, 417;
A. Brossi, S. Teitel, *J. Org. Chem.*, **35**, 3559 (1970).

68) A. Brossi, G. Grethe, S. Teitel, W. C. Wildman, D. T. Bailey, *J. Org. Chem.*, **36**, 1100 (1970).

69) Y. Inubushi, H. M. Fales, E. W. Warnhoff, W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960).

70) T. Reichstein, A. Grüssner, *Helv. Chim. Acta*, **17**, 311 (1934).

71) A. Brossi, S. Teitel, *Org. Prep. Procedures*, **1**, 171 (1969).

72) S. Teitel, A. Brossi, *J. Med. Chem.*, **13**, 333 (1970).

73) F. Benington, R. D. Morin, L. G. Clarke, Jr., *J. Amer. Chem. Soc.*, **76**, 5555 (1954).

74) A. Brossi, J. Van Burik, S. Teitel, *Helv. Chim. Acta*, **51**, 1965 (1968).

75) A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, R. Ramage, *Chem. Commun.*, **1967**, 450.

76) T. Kametani, F. Satoh, H. Yagi, K. Fukumoto, *J. Org. Chem.*, **33**, 690 (1968).

77) H. Meerwein, "Methoden der Organischen Chemie (Heuben-Weyl)", E. Müller, Ed., G. Thieme, Stuttgart, Band VI/3, pp 150-151.

78) K. Kratzl, G. Billek, *Monatsh. Chem.*, **83**, 1045 (1952).

79) F. Benington, R. D. Morin, L. C. Clarke, Jr., *J. Org. Chem.*, **21**, 1545 (1956).

80) A. Brossi, J. O'Brien, S. Teitel, *Helv. Chim. Acta*, **52**, 678 (1969).

81) A. Rheiner, Jr., A. Brossi, *Experientia*, **20**, 488 (1964).

82) A. Brossi, A. I. Rachlin, S. Teitel, M. Shamma, M. J. Hillman, *Experientia*, **24**, 766 (1968).

83) A. Brossi, S. Teitel, *Helv. Chim. Acta*, **42**, 1228 (1969).

84) T. Kametani, T. Terui, H. Agui, K. Fukumoto, *J. Heterocycl. Chem.*, **5**, 753 (1968).

85) A. Brossi, S. Teitel, *Chem. Commun.*, **1970**, 1296.

86) E. Späth, H. Roder, *Monatsh. Chem.*, **43**, 93 (1922).

87) S. Karady, *J. Org. Chem.*, **27**, 3720 (1962).

88) E. P. Taylor, *J. Chem. Soc.*, **1951**, 1150.

89) T. R. Govindachari, N. Viswanathan, B. R. Pai, S. Narayanaswami, *Indian J. Chem.*, **6**, 4 (1968).

90) S. M. Kupchan, T.-H, Yang, G. S. Vasilikiotis, M. H. Barnes, M. L. King, *J. Org. Chem.*, **34**, 3884 (1969).

91) A. Brossi, J. F. Blount, J. O'Brien, S. Teitel, *J. Amer. Chem. Soc.*, **93**, 6248 (1971).

92) M. Tomita, Y. Aoyagi, *Chem. Pharm. Bull.*, **16**, 523 (1968).

93) G. J. Kapadia, N.J. Shah, T. B. Zalucky, *J. Pharm. Sci.*, **57**, 254 (1968).

94) A. R. Battersby, T. P. Edwards, *J. Chem. Soc.*, **1960**, 1214.

95) S. Teitel, J. O'Brien, A. Brossi, *J. Org. Chem.*, **37**, 3368 (1972).

96) E. Schreier, *Helv. Chim. Acta*, **47**, 1529 (1964); H. MacLean, B. F. MacDonald, *Can. J. Chem.*, **47**, 457 (1969).

97) F. Dallacker, K. W. Glombitza, M. Lipp, *Liebigs Ann. Chem.*, **643**, 67 (1961).

98) P. Karrer, E. Schick, *Helv. Chim. Acta*, **26**, 800 (1943).

99) C. Mannich, O. Walther, *Arch. Pharm.*, **265**, 1 (1927) [*Chem. Abst.*, **21**, 1462 (1927)].

Received, 14th May, 1973