RECENT CHEMICAL PROGRESS IN BERBERINE ALKALOIDS†

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Chemical progress of berberine alkaloids over the past decade has been reviewed.

I Introduction

About eighty berberine alkaloids have been isolated from the plants of Anonaceae, Berberidaceae, Convolvulaceae, Lauraceae, Menispermaceae, Papaveraceae, Ranunclaceae, and Rutaceae.[1] Since they have important biological activity,[2] a number of chemical investigations have been carried out.[3,4] We have also been interested in the field of berberine alkaloids during the past decade, and here wish to give an account of the racent chemical advances in the field of berberine alkaloids.

II Biosynthesis

On the basis of tracer experiments using various plants, it is considered that the general sequence in the biogenesis of berberine alkaloids is as follows.

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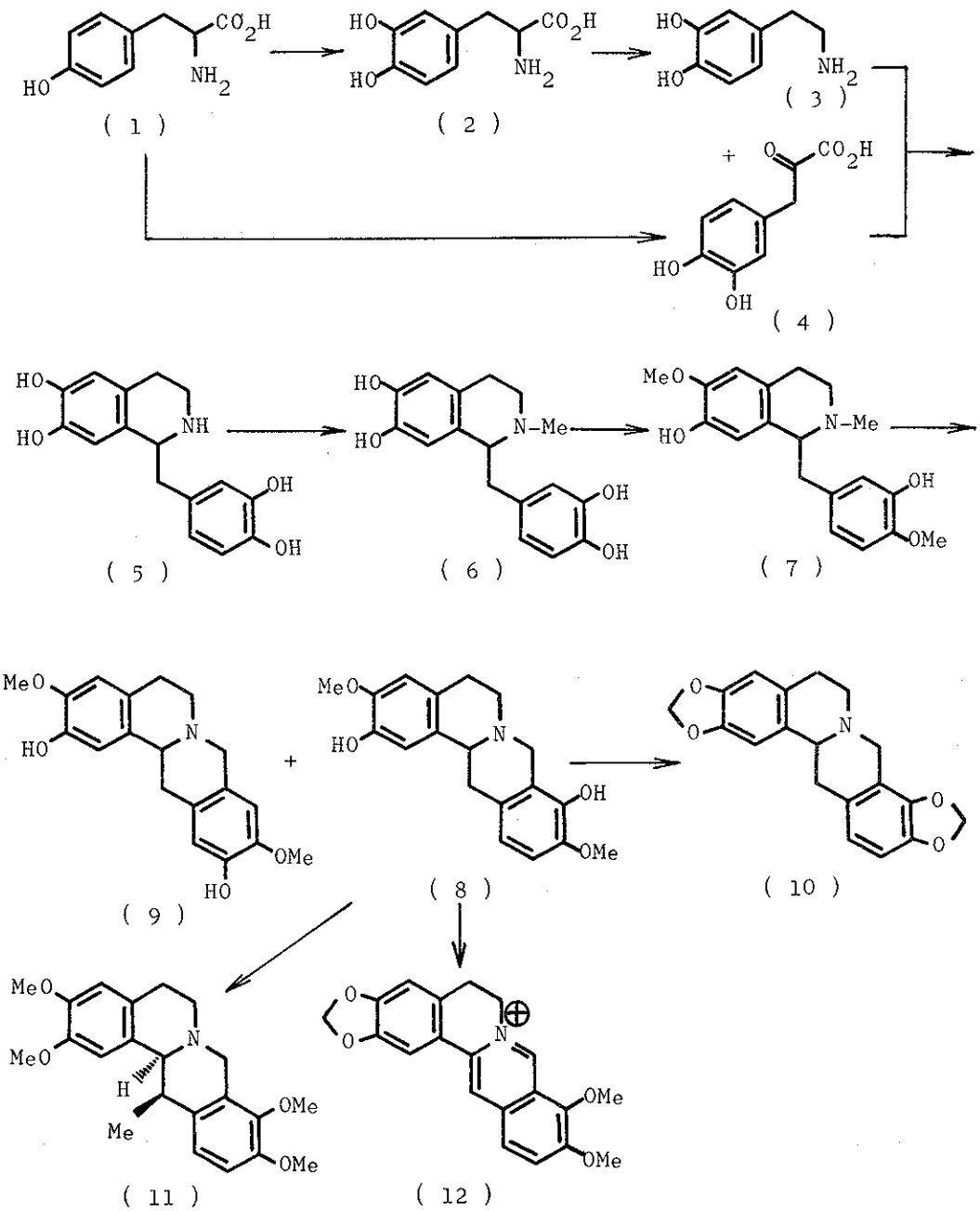
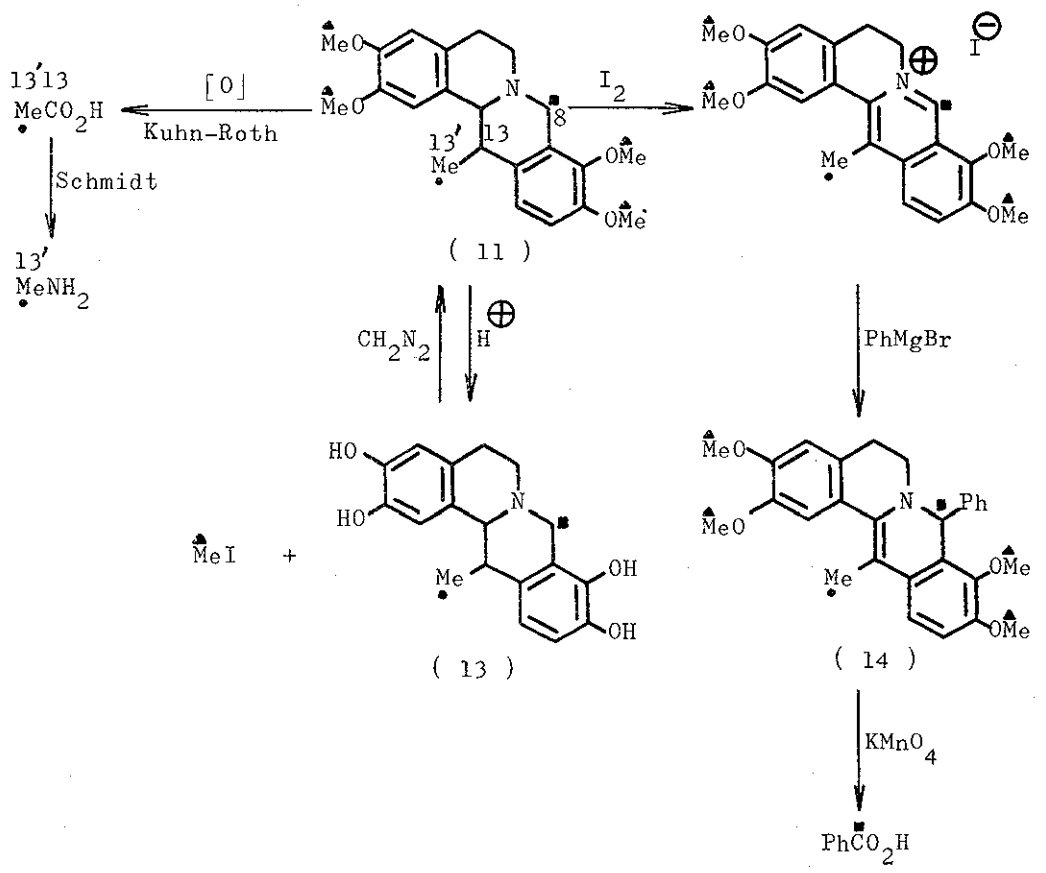
† Dedicated to Professor Tsunematsu Takemoto on the occasion of his retirement.

Scheme 1



Protoberberine alkaloids are derived from two molecules of tyrosine (1);[5-7] one molecule of tyrosine is converted to dopamine (3) via dopa (2)[7,8] and the other molecule to 3,4-dihydroxyphenyl-

Scheme 2



pyruvic acid (4).[9] Decarboxylation of the pyruvic acid (4) followed by the condensation of the resulting homoaldehyde with dopamine (3) or condensation of the two compounds, followed by decarboxylation, gave norlaudanosoline (5), which would be transformed to laudanosoline (6)[10] and reticuline (7).[11] Reticuline is known to be a

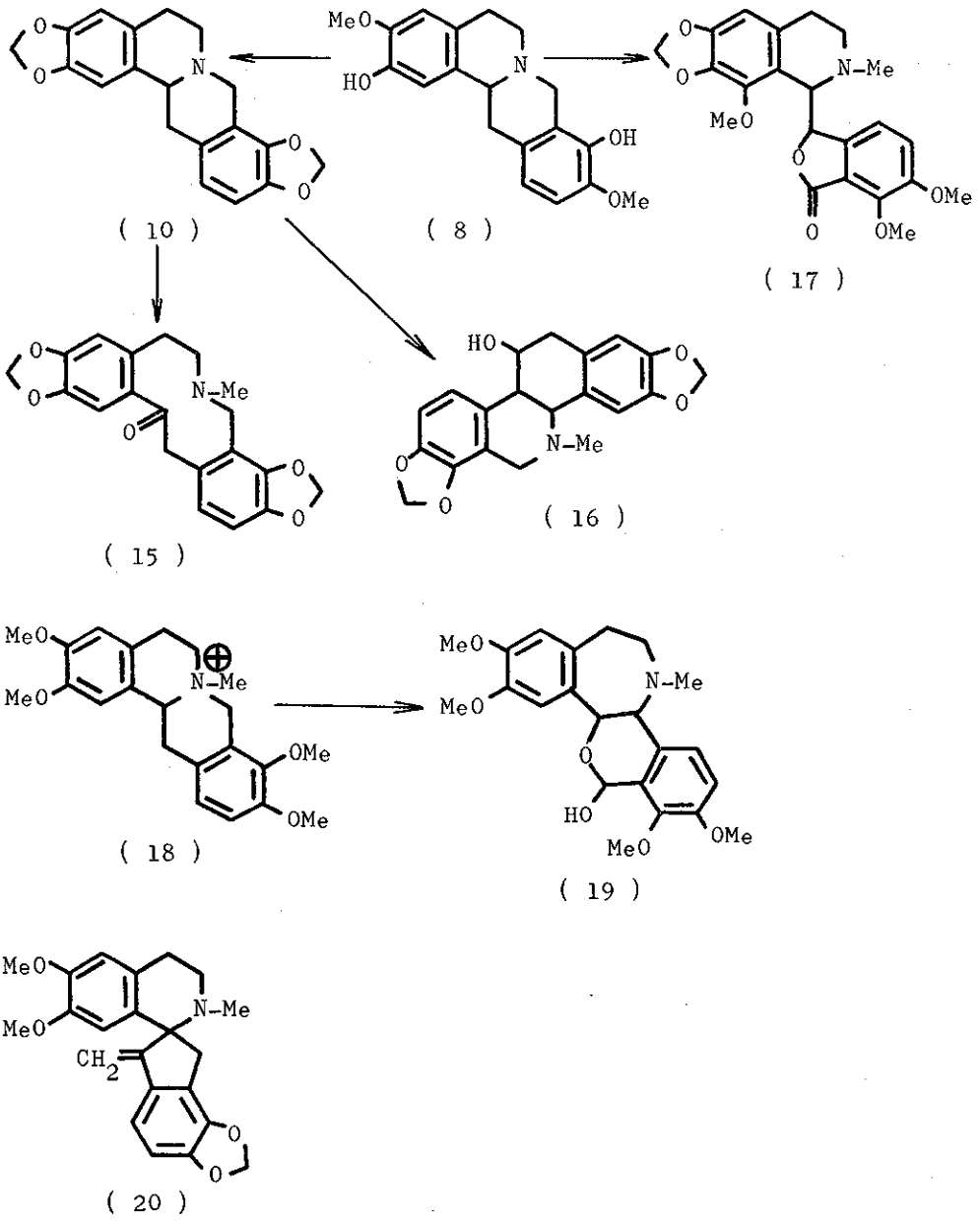
precursor of scoulerine (8),[12] coreximine (9),[13] stylopinine (10),[10] corydaline (11)[14] and berberine (12).[11] It has been furthermore proved that the (S)-isomer of reticuline is a true precursor of the berberine alkaloids,[11] and an oxidation-reduction equilibrium occurs at the stage of 1,2-dehydroreticuline.[12]

The carbon atoms of the C-8 position of the berberine alkaloids, "berberine bridge", and the methylenedioxy group originate from the S-methyl function of methionine.[15] When [methyl-^{14}C]methionine was fed to Corydalis solida, the methyl group of methionine was incorporated into the O-methyl groups, the 13-methyl group and the C(8) of corydaline (11). The labelled positions of corydaline derived from [methyl-^{14}C]methionine were clearly determined by the degradation products as shown in Scheme 2. Maintenance of the $^{3}H/^{14}C$ ratio of [methyl-^{3}H, ^{14}C]methionine within these units of corydaline proved the intact incorporation of the methyl groups. Partial loss of ^{3}H relative to ^{14}C was observed in the course of a Schmidt reaction of [2-^{3}H, 2-^{14}C]acetate.[16]

Protoberberien alkaloids could be a putative precursor of many isoquinoline alkaloids, for example, spirobenzylisoquinoline, benzophenanthridine, protopine, phthalideisoquinoline and rhoeadine alkaloids. It was substantiated that scoulerine (8) was a precursor of protopine (15), chelidonine (16) and narcotine (17).[17,18] Labelled tetrahydropalmatine methiodide (18) was incorporated with high efficiency into alpinigenine (19) in Papaver bracteatum.[19] The feeding experiment of radioactive methionine into ochotensimine (20) in Corydalis ochotensis supported the fact that corydaline (11) or its analogue is an intermediate in the biosynthesis of

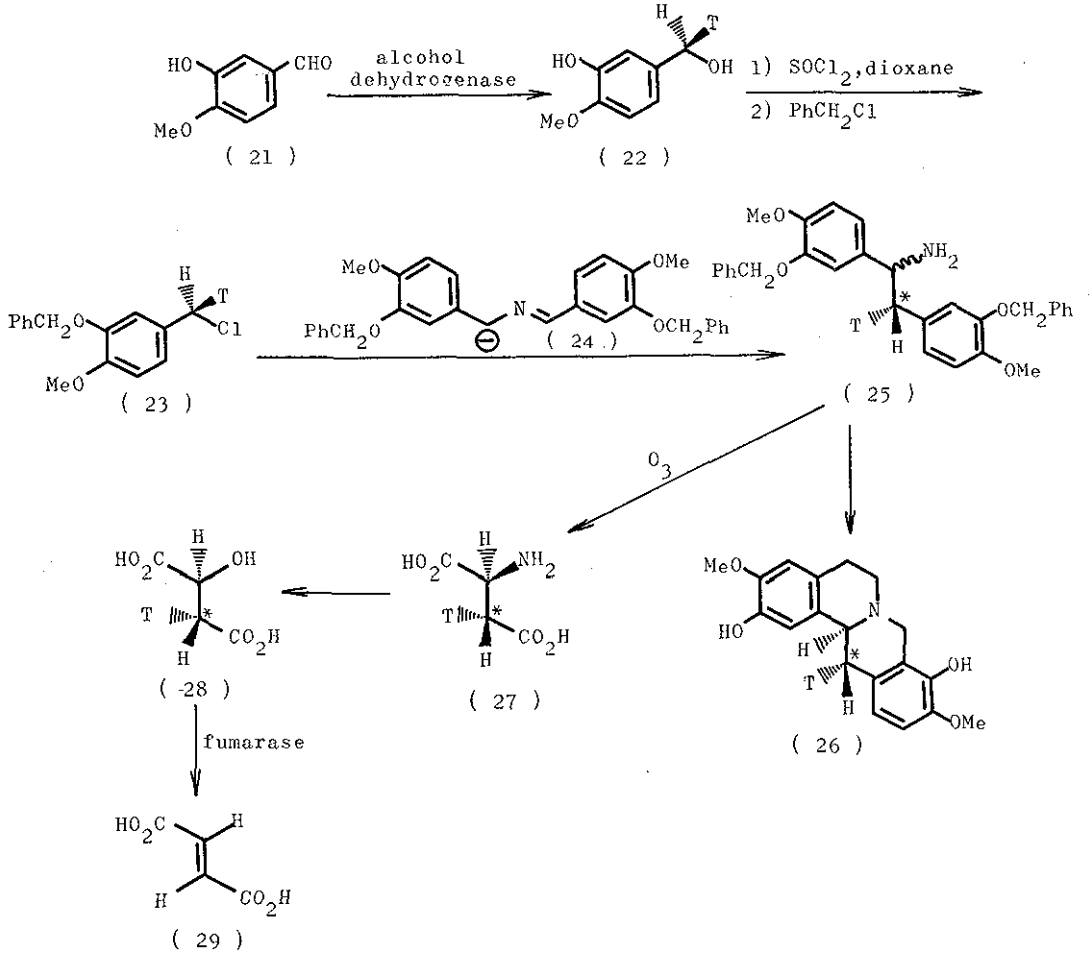
spirobenzylisoquinoline alkaloids.[16]

Scheme 3



Substances, in which prochiral centres of the type ACH_2B have been made chiral by replacement of one or the other hydrogen atom

Scheme 4



with deuterium or tritium, have been proven to be powerful tools for investigating the stereochemistry of enzyme-mediated reactions. Battersby and his coworkers developed a synthesis of scoulerine which

allowed stereospecific labelling with deuterium or tritium at C-13 position, a prochiral centre.

Isovanillin (21) was reduced with liver alcohol dehydrogenase in the presence of NAD and [1-^{3}H]cyclohexanol to the alcohol (22), which was converted into the chloride (23). The chloride (23) reacted with the symmetrical aza-allyl carbanion (24) to afford, after hydrolysis, the amine (25), which was transformed to (13R)-[13-$^{3}H_{1}$]scoulerine (26). The configurational purity of the labelled scoulerine was determined by a degradation of the amine (25) to fumaric acid (29) via malic acid (28) with fumarase.[20-22]

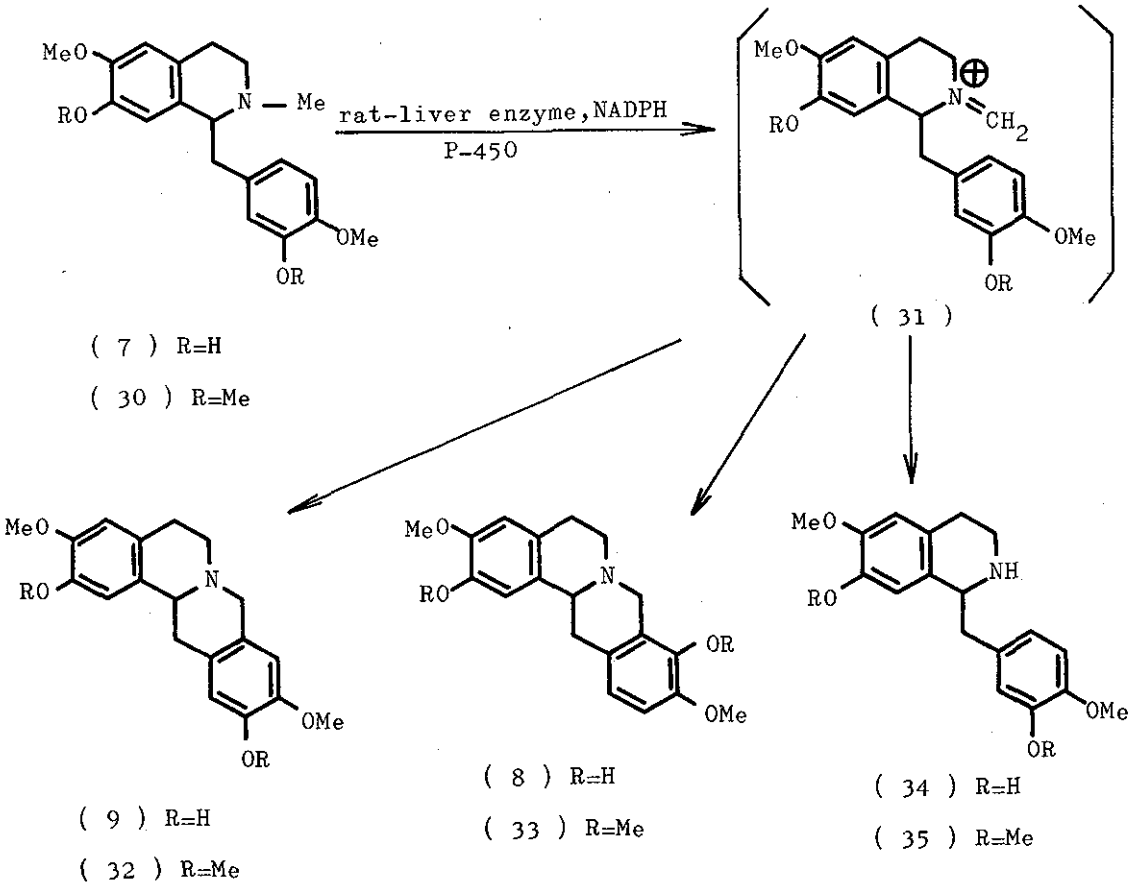
Incorporation experiments with (13R)- and (13S)-[13-$^{3}H_{1}$]-scoulerine showed that the biosynthesis of both narcotine (17) and chelidonine (16) involved a stereospecific removal of the pro-S hydrogen atom at the C-13 position of scoulerine.[22]

III Bioformation with Mannalian Tissue

In the light of the importance of reticuline (7) in the biogenesis of isoquinoline alkaloids, reticuline was fed to rats and a formation of coreximine (9) was detected by gas chromatography and mass spectrometry.[23] This finding was then confirmed by tracer experiments using a rat liver preparation. Radioactive reticuline was incorporated into coreximine (9), scoulerine (8) and norreticuline (34). Dilution of the product with two enantiomers and racemate of coreximine revealed that the coreximine formed was racemic. Laudanosine (30) was also biotransformed into xylopinine (32), tetrahydropalmatine (33) and norlaudanosine (35). The enzymatic reaction was greatly accelerated by the addition of NADPH and magnesium chloride, indicating a participation of cyto-

chrome P-450. It is apparent that the 1-benzyl-1,2,3,4-tetrahydro-2-methylisoquinoline would give rise to the immonium cation (31) which affords the tetrahydroprotoberberine by cyclisation and the

Scheme 5



N-nor-product by hydrolysis.[24]

In the course of the investigation of alcoholic addictions, Davis and coworkers found the in vivo and in vitro conversions of norlaudanosoline (5) to coreximine and related tetrahydroprotoberberines by mammalian system in the presence of S-adenosylmethionine.[25,26]

These tetrahydroprotoberberine alkaloids could be formed via laudanosoline (6) followed by the oxidative cyclisation and methylation.

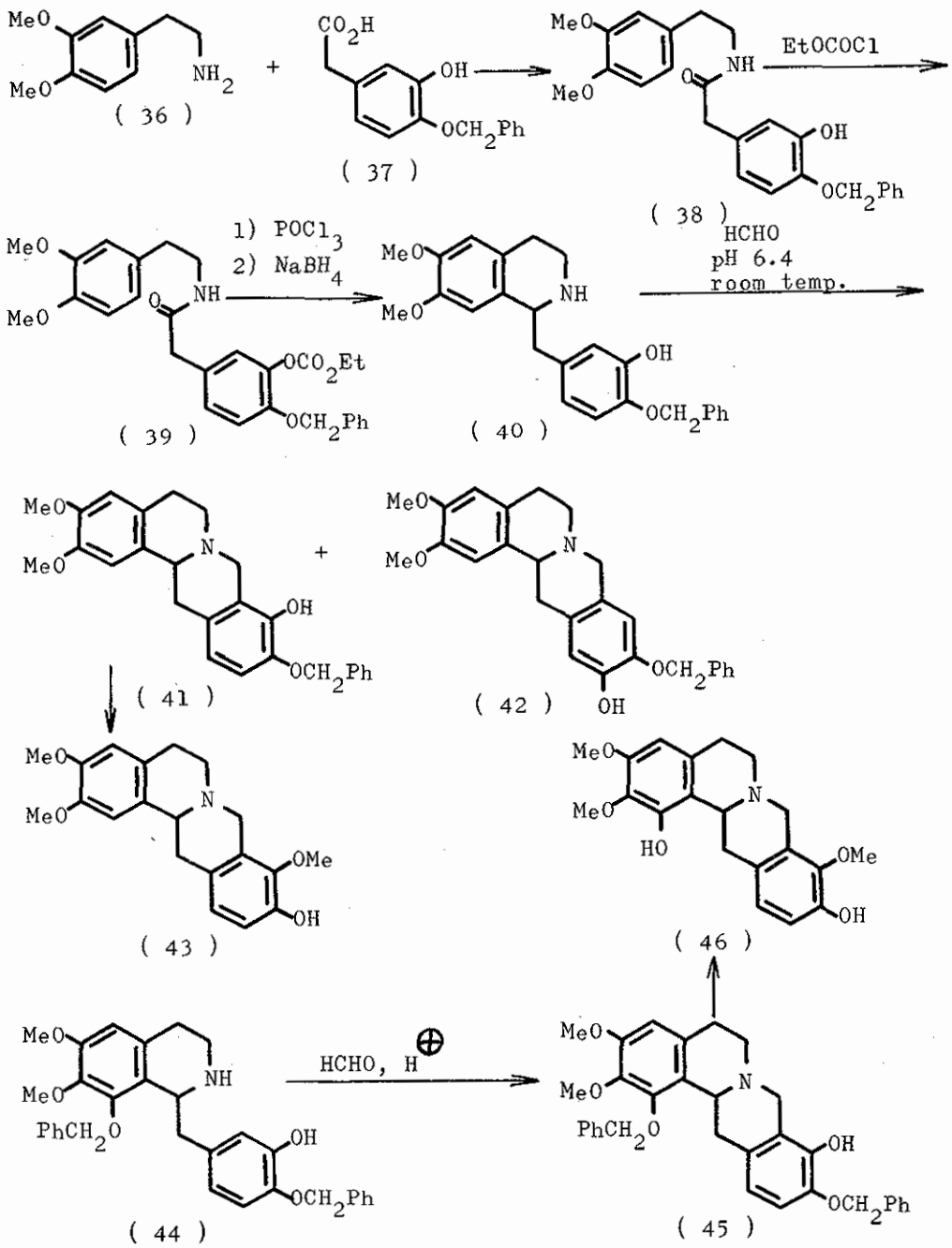
IV Syntheses of Berberine Alkaloids

1. Intramolecular Mannich Reaction

The most general synthetic method for tetrahydroprotoberberine alkaloids seems to be a Mannich reaction of 1-benzyl-1,2,3,4-tetrahydroisoquinoline with formaldehyde in the presence of acid. In general, this method gives the 10,11-substituted tetrahydroprotoberberines, but an isoquinoline, having a phenolic hydroxyl group at C-3 position of the 1-benzyl group, affords a mixture of the 9,10- and 10,11-disubstituted tetrahydroprotoberberines, whose ratio depends upon the pH of the reaction.[27-30] The substitution pattern on ring A also changes the course of the reaction, although the reason is uncertain. The synthesis of kikemanine (43), isolated from Corydalis pallida var. tenuis,[31] involved a separation of 9,10- and 10,11-isomers (41 and 42), formed at pH 6.4. If the reaction was carried out using the hydrochloride of 40 with formalin in hot ethanol, condensation occurred at the para póstion of the hydroxyl group to give only 42.[32]

However, when capaurimine (46) whose structure was corrected by us[33] and Kaneko[34] was synthesised by Mannich reaction of the phenolic isoquinoline (44), the 9,10-disubstituted tetrahydroprotoberberine (45) was predominantly obtained under the various acidic conditions.[35]

Scheme 6


MeO
MeO
NH2
(36)
+
CO2H
OH
OCH2Ph
(37)
NH
O
EtOCOCl
(38)
1) POCl3
2) NaBH4
OCO2Et
(39)
HCHO
pH 6.4
room temp.
(40)
N
(41)
(42)
OMe
(43)
HO
(46)
HCHO, H⊕
PhCH2O
(44)
(45)

The 9,10-disubstituted tetrahydroprotoberberines can be prepared cleanly via the Mannich reaction if the bromine atom is introduced as a protective group. The dibenzyloxytetrahydrobenzylisoquinoline (47) was selectively brominated to the bromide, whose debenzylation and cyclisation, followed by reductive cleavage of the halogen, afforded scoulerine (8) and tetrahydropalmatine (33). All the reaction proceeded in good yield.[36]

If a bromoisoquinoline which has no hydroxyl group at the C-3 position of the 1-benzyl group is used in the above method, the cyclisation occurs at the brominated position to give the 10,11-disubstituted compound in poor yield.

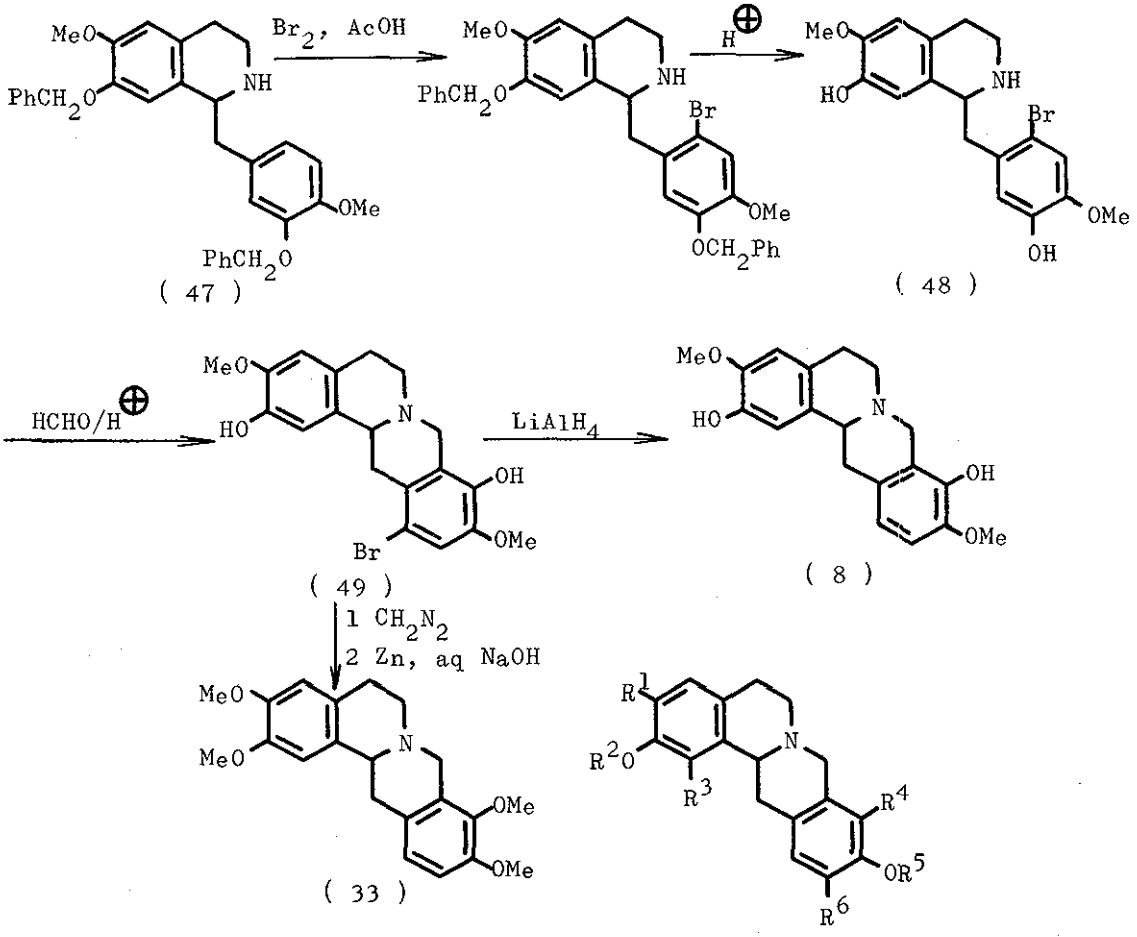
In general, mineral acids and organic acids are usually used as catalyst in the Mannich cyclisation and heating the hydrochloride of the benzylisoquinoline in alcohol also gives excellent results.

Tetrahydroprotoberberines were formed under the condition of Eschweiler-Clarke reaction using formalin and formic acid.[37-39] Therefore, in order to obtain the N-methyl-1-benzyl-1,2,3,4-tetrahydroisoquinoline, the reductive N-methylation using formaldehyde and sodium borohydride or the reduction of the 3,4-dihydroisoquinoline methiodide are recommendable.

Coreximine (9),[38,40] discretine (50),[41] canadine (51),[29,42] nandinine (52),[29,42] capaurine (53),[43] stepharotine (54),[44] caseadine (55),[45] xylopinine (32)[38] and corytenchine (56)[46] were also synthesised by application of the Mannich cyclisation.

Recently, when acetaldehyde was used instead of formaldehyde, coralydine (69),[47] O-methylcorytenchirine (59),[47] and corytenchirine (58),[48] recently isolated from Corydalis ochotensis in Taiwan,

Scheme 7



(50) R^1=OH, R^2=R^5=Me, R^3=R^4=H, R^6=OMe

(51) R^1+R^2=OCH_2, R^3=R^6=H, R^4=OMe, R^5=Me

(52) R^1+R^2=OCH_2, R^3=R^6=H, R^4=OH, R^5=Me

(53) R^1=R^4=OMe, R^2=R^5=Me, R^3=OH, R^6=H

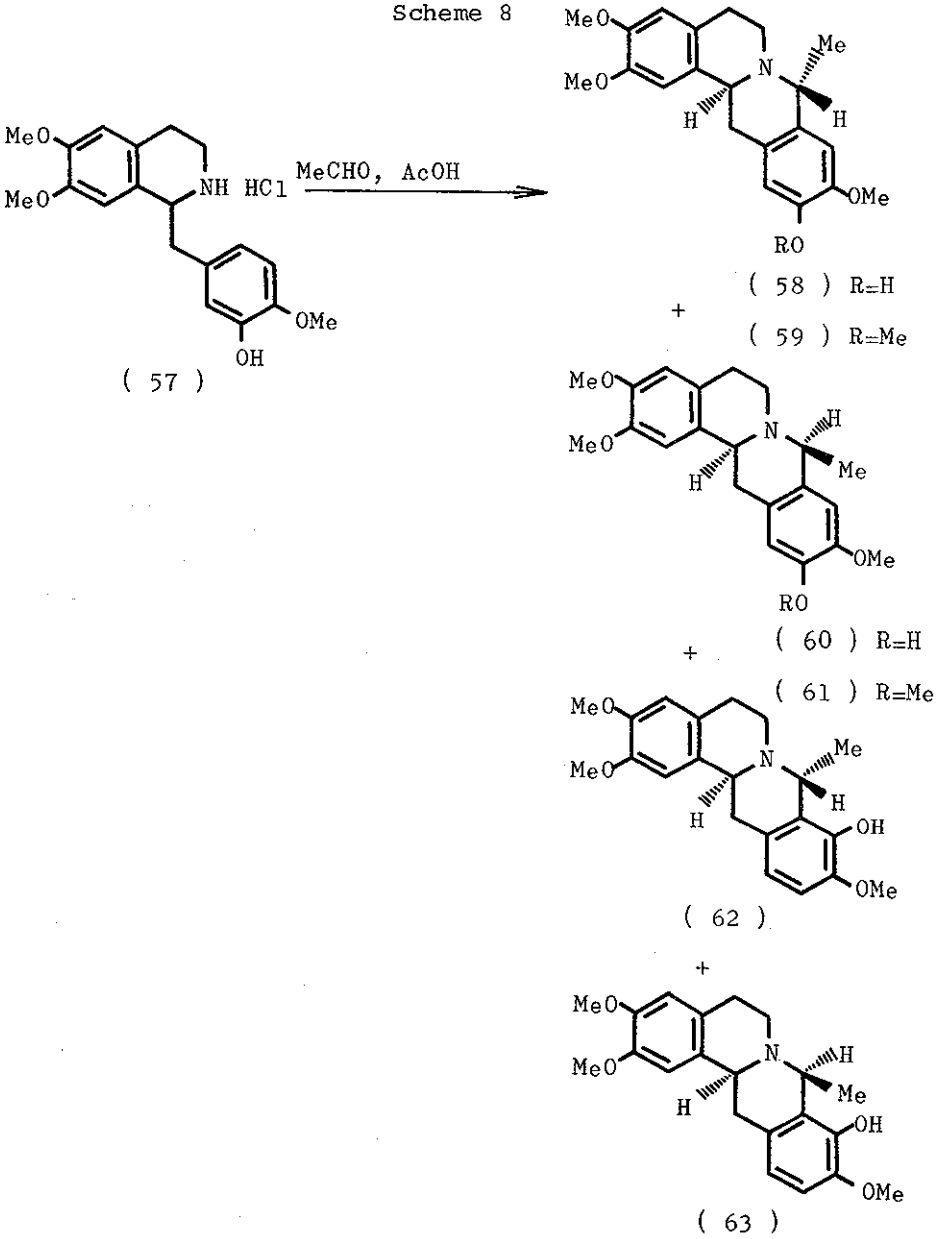
(54) R^1=R^4=OMe, R^2=R^5=Me, R^3=H, R^6=OH

(55) R^1=R^4=H, R^2=R^5=Me, R^3=OH, R^6=OMe

(56) R^1=OMe, R^2=R^5=Me, R^3=R^4=H, R^6=OH

were prepared by this method. Heating the hydrochloride of the phenolic tetrahydroisoquinoline (57) with acetaldehyde in acetic

Scheme 8



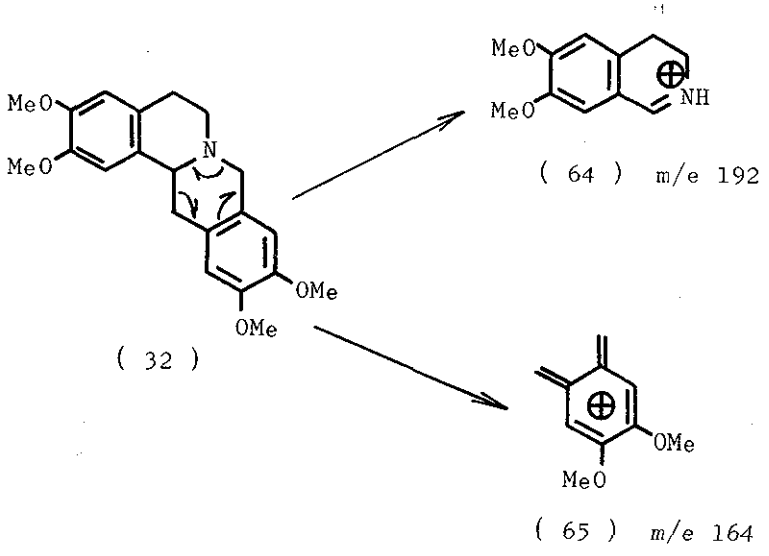
acid gave (±)-corytenchirine (58) in 45 % yield and the stereoiso-

mer (60) in 10 % yield together with a trace amount of isomers 62 and 63.[48]

2. Thermolytic Reaction

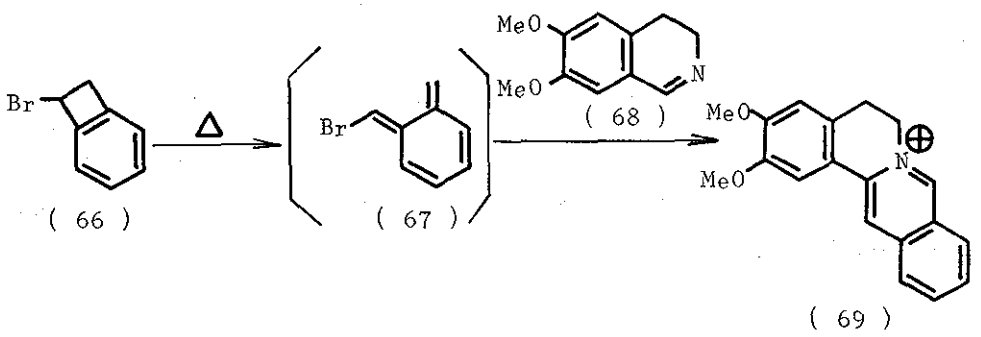
The idea of this novel method was derived from the mass spectral fragmentation pattern. The extensive applications of this to the synthesis of isoquinoline and indole alkaloids have been reviewed.[49] The mass spectral fragmentation of xylopinine (32) gave the ion (65) at m/e 164 and an alternative fragmentation with hydrogen transfer left the charge on the isoquinoline unit to give the fragment (64) at m/e 192.[50]

Scheme 9



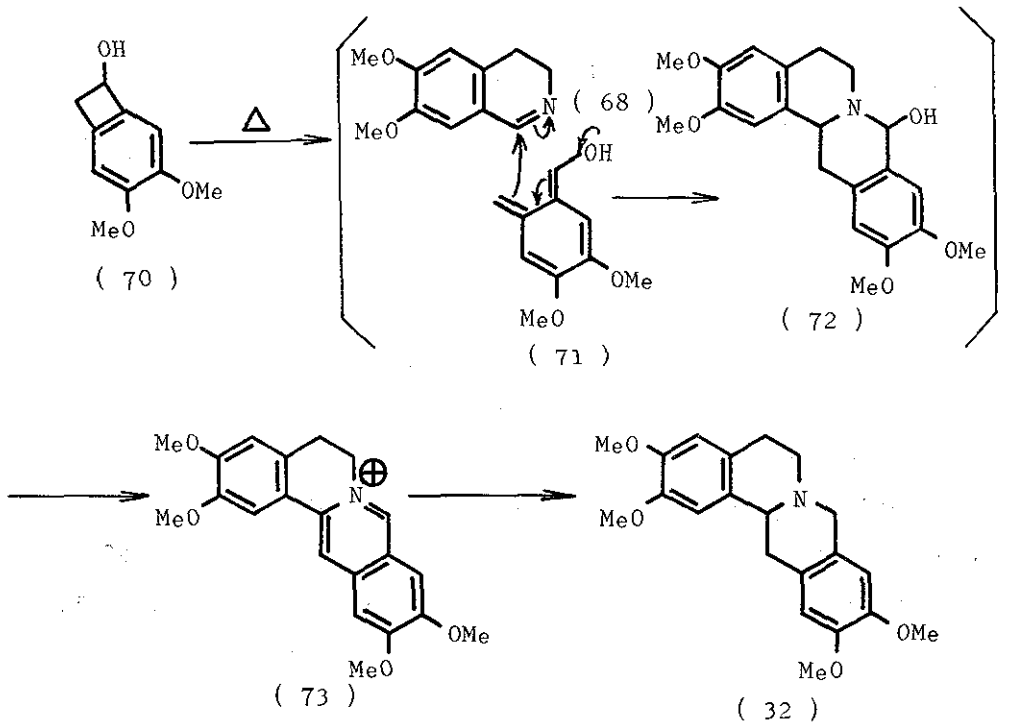
The benzocyclobutenes are ring-opened by thermolysis to the o-quinodimethanes which are equivalents of the ion (65) and could be coupled with the 3,4-dihydroisoquinoline to give the berberine alkaloids. A mixture of 1-bromobenzocyclobutene (66) and 3,4-dihydro-6,7-dimethoxyisoquinoline (68) was thus heated at 100° for 20 hr to give the desired protoberberinium salt (69).[51]

Scheme 10



Benzocyclobutenol (70) was also condensed with 3,4-dihydro-6,7-

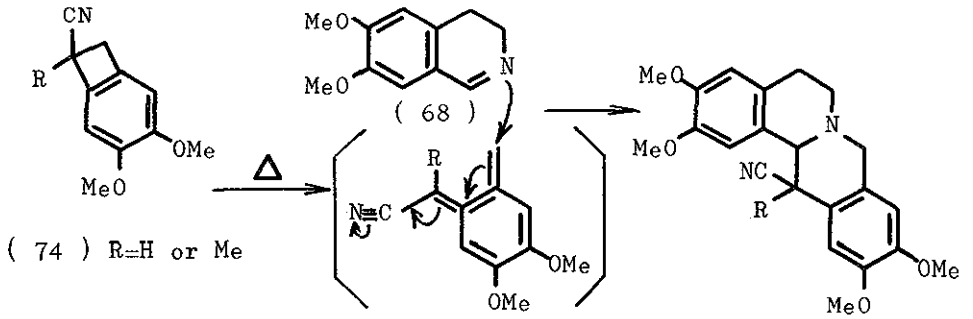
Scheme 11



dimethoxyisoquinoline (68) in benzene at 80° for 5 hr to give the protoberberinium salt (73), which on reduction furnished xylopinine (32).[52]

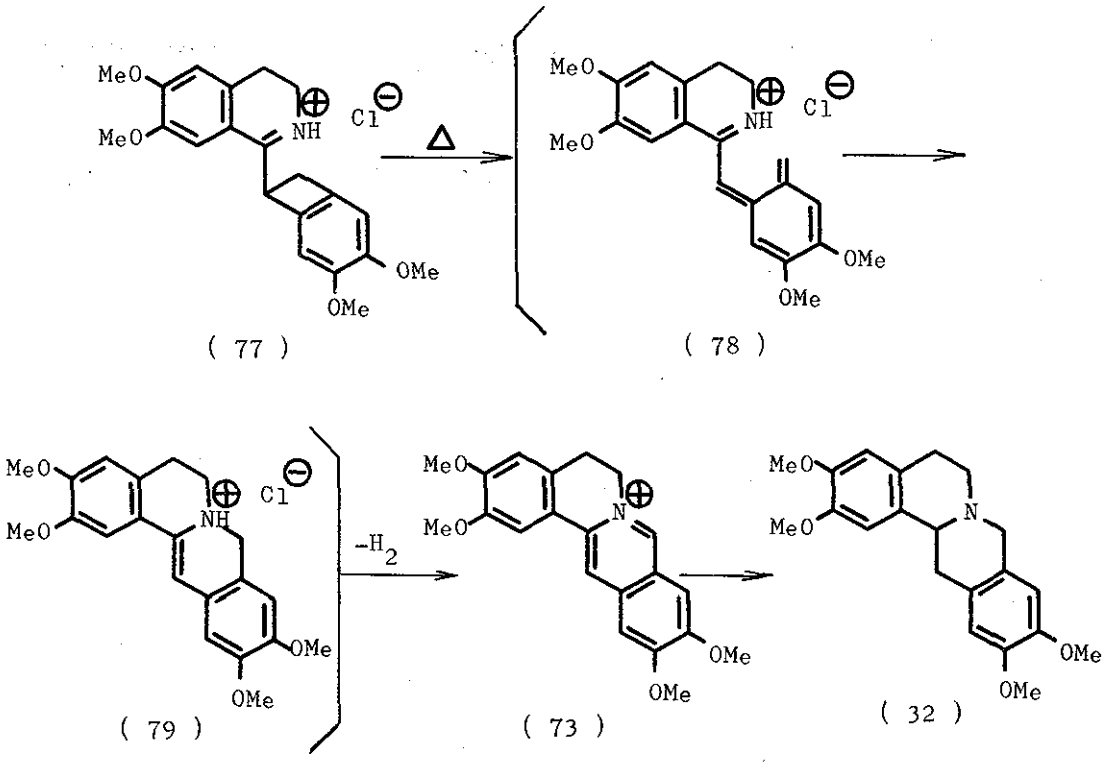
Similarly, heating the 1-cyanobenzocyclobutenes (74) with 3,4-dihydro-6,7-dimethoxyisoquinoline (68) gave the tetrahydroprotoberberines (76) in good yields.[53] These above reactions proceeded regioselectively.

Scheme 12



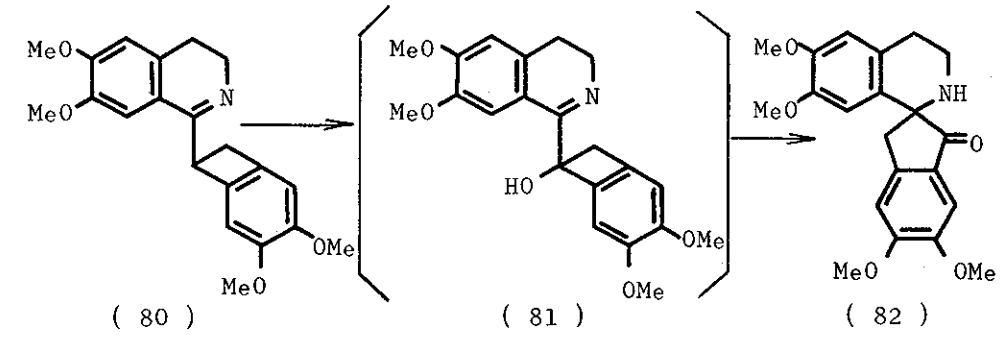
Treatment of the hydrochloride of the 1-benzocyclobutenyl-3,4-dihydroisoquinoline (77) in bromobenzene at 150 - 170° for 20 min brought about to give the protoberberine (73), reduction of which afforded xylopinine (32) in excellent yield.[54] Discretine (50)[55] and coreximine (9)[56] were also synthesised in a similar manner.

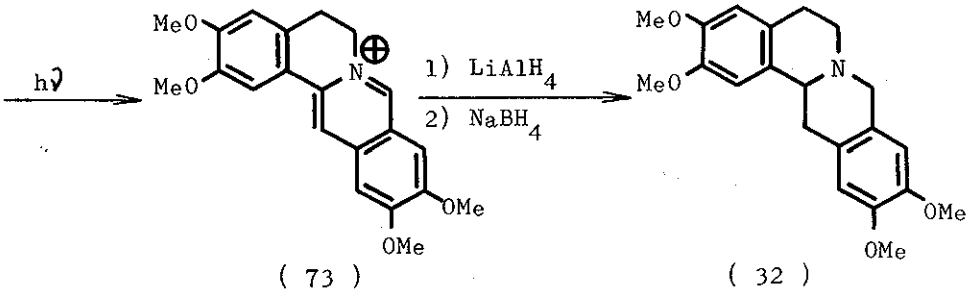
Scheme 13



When the free base of the above 1-benzocyclobutenyl-3,4-dihydroisoquinoline (80) was allowed to stand in organic solvent at room temperature for several days, interestingly the ketospiroisoquinoline (82) was obtained in high yield.[57] The reaction seems to involve an air oxidation of the 1-benzocyclobutenyl group. Since a ketospirobenzylisoquinoline had been photo-rearranged to berberinium derivative by Norish type I reaction,[58] 82 was converted into xylopinine via 73 according to this procedure.[57]

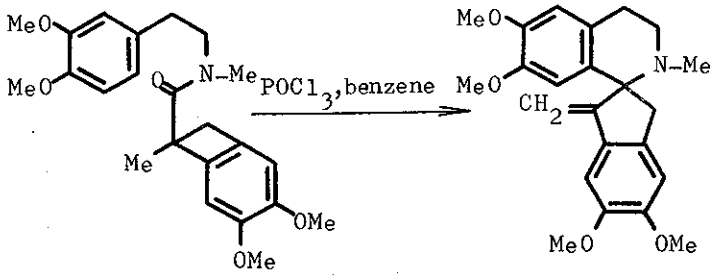
Scheme 14





On the other hand, treatment of the amide (83) with phsophoryl

Scheme 15

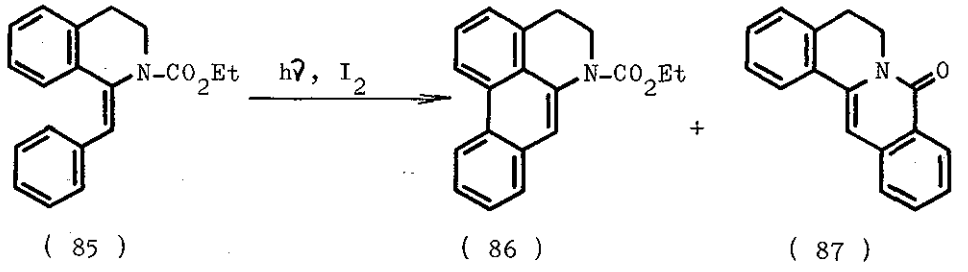


chloride in boiling benzene afforded directly the ochotensimine type compound (84).[59]

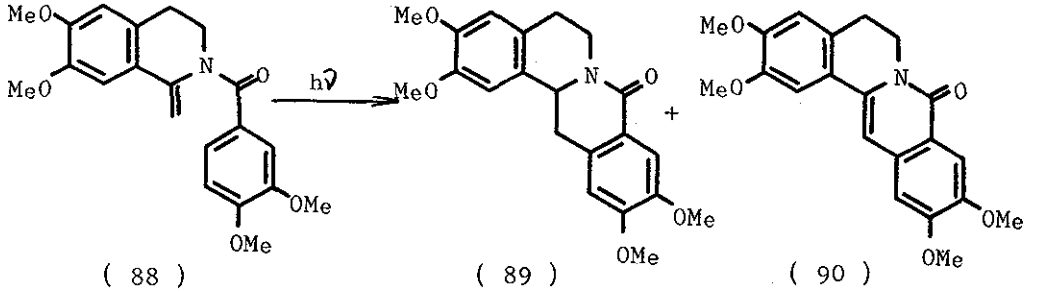
3. Photolytic Synthesis

Enamide photocyclisation provides an efficient synthetic method for berberine alkaloids.[2,60] For example, an irradiation of the carbamate (85) in the presence of iodine afforded the aporphine (86) as the major product and the berberine (87) as the minor component.[61] Photo-stimulated hexatriene-cyclohexadiene isomerisation of the enamide (88) gave the 8-oxoberberine (89) together with the corresponding dehydro compound (90) in high yield.[62]

Scheme 16



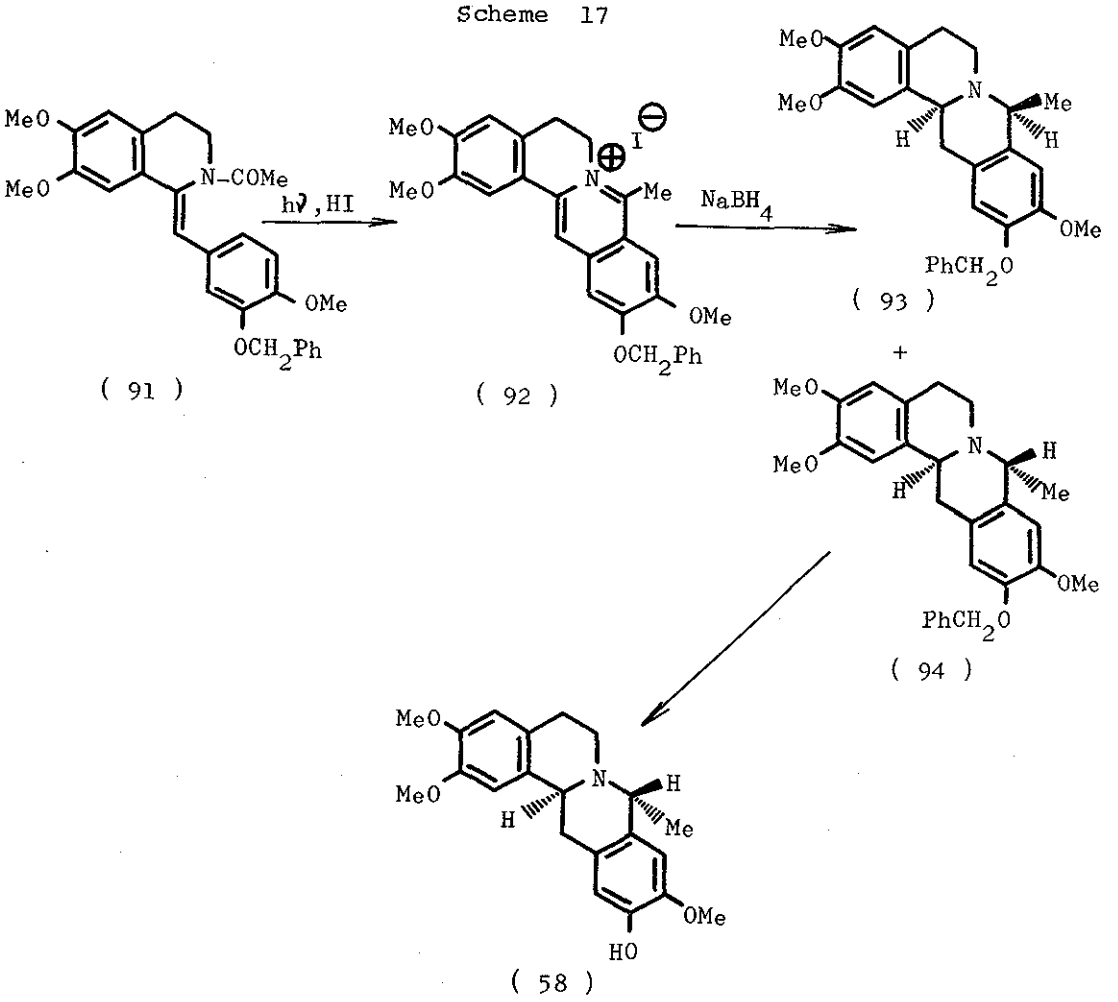
(85) (86) (87)



(88) (89) (90)

Using Lenz and Yang's method, corytenchirine (58), was synthesised as follows. (Z)-2-Acetyl-1-(3-benzyloxy-4-methoxybenzylidene)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (91) was irradiated with a high pressure mercury lamp in the presence of hydriodic acid

Scheme 17



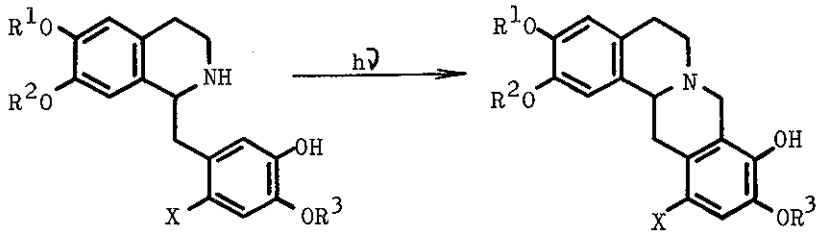
(91) (92) (93) + (94) (58)

to give the 8-methylprotoberberinium iodide (92) in moderate yield. Reduction of the quaternary salt with sodium borohydride gave the stereoisomers (93) and (94), in a ratio of 3 : 1, the latter of

which on debenzylation afforded (±)-corytenchirine (58).[48]

It was found that an irradiation of the hydrochlorides of the

Scheme 18



(48) X=Br, R^1=R^3=Me, R^2=H

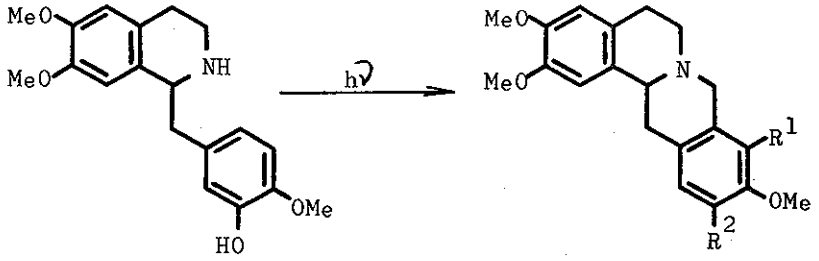
(95) X=Br, R^1+R^2=CH_2, R^3=Me

(96) X=Br, R^1+R^2=CH_2, R^3=H

(49) X=Br, R^1=R^3=Me, R^2=H

(97) X=Br, R^1+R^2=CH_2, R^3=Me

(98) X=Br, R^1+R^2=CH_2, R^3=H



(57)

(56) R^1=H, R^2=OH

(99) R^1=OH, R^2=H

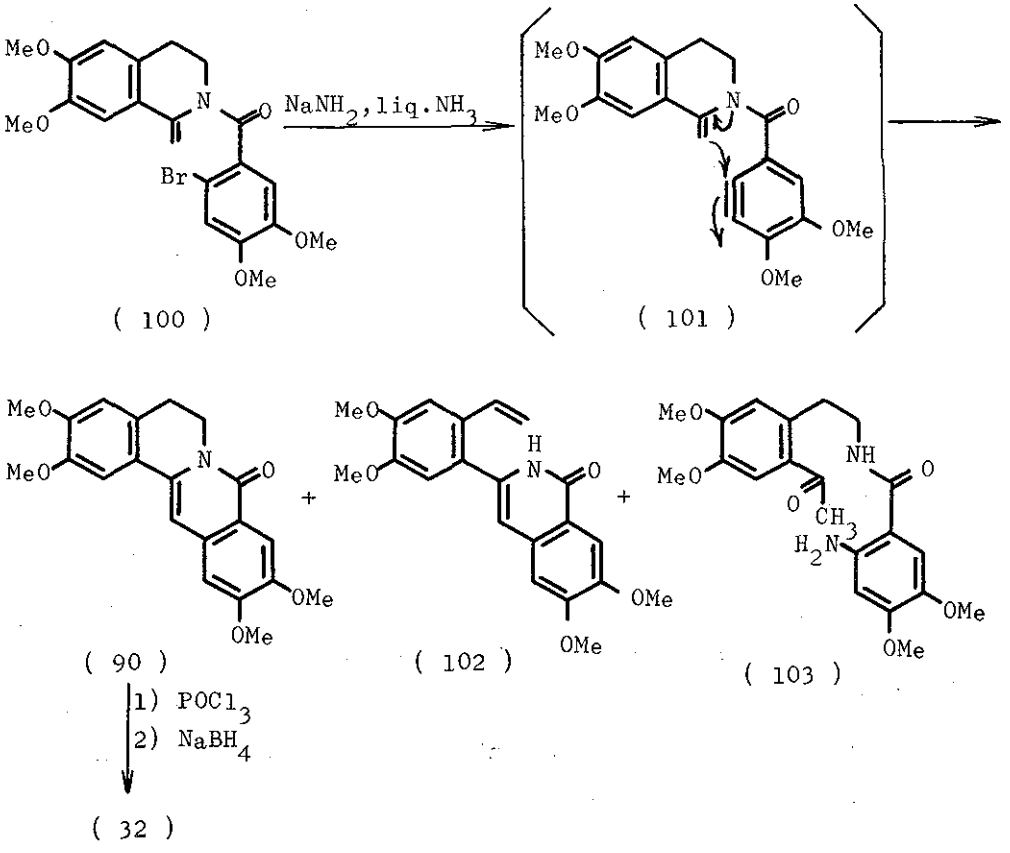
benzylisoquinoline (48, 95 and 96) containing sodium bisulphite with high pressure mercury lamp surrounded by a pyrex filter for 10 hr gave the tetrahydroprotoberberiens (49, 97, and 98) as unexpected products in addition to the required N-noraporphines. The phenolic isoquinoline (57) yielded (±)-corytenchine (56) and (±)-shefferine (99) in 4.5 and 2 % yield, respectively, under the same condition as above. The origin of the berberine bridge portion is unclear, but it could be derived from alkoxyl group,

the carbon at C-3 of isoquinoline system or methylene in benzyl residue.[63]

4. Benzyne Reaction

The benzyne reaction plays an important role in the synthesis of heterocyclic compounds. Treatment of the bromo-enamide (100) with sodium amide in liquid ammonia furnished oxoberberine (90) (15 %) and the styrene compound (102) (35 %) together with the hydrolysed product (103) (40 %). Chlorination of the oxoberberine (90) with phosphoryl chloride, followed by reduction of the chloride with sodium borohydirde, gave xylopinine (32). The benzyne

Scheme 19



intermediate (101) was postulated in the formation of the oxoberberine.[64]

V Reaction of Berberine Alkaloids

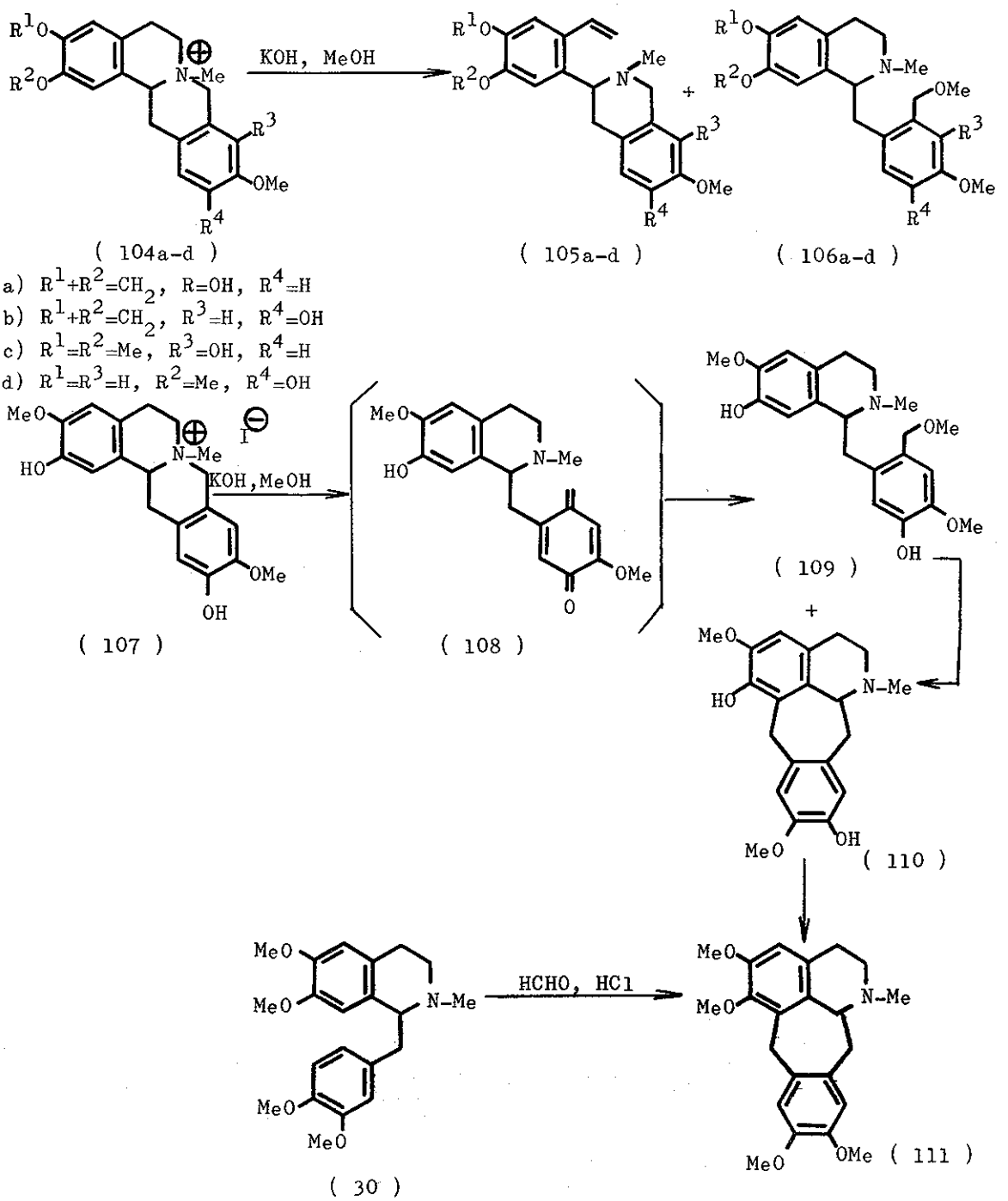
1. Alkali Treatment of Various Quaternary Salts

Hofmann degradation has been widely applied in determining the structures of alkaloids. In some cases, this reaction is a key step in the conversion of tetrahydroprotoberberines into protopine,[65] benzophenanthridine,[66,67] and pavine type alkaloids.[68]

Alkali treatment of phenolic tetrahydroprotoberberinium and dihydroprotoberberinium salts provided many interesting products through quinonoid intermediates. Refluxing the 9- or 11-hydroxytetrahydroprotoberberinium salts (104a-d) with methanolic potassium hydroxide gave the secotetrahydroprotoberberines (105a-d) in addition to the methine bases (106a-d).[69] Treatment of coreximine methiodide (107) with hot methanolic potassium hydroxide solution yielded no methine base but secoberberine (109) and the benzo[5,6]cyclohept-[1,2,3-ij]isoquinoline (110). Further treatment of the secoberberine (109) under the same basic conditions gave 110, whose O,O-dimethyl ether (111) was synthesised by the reaction of laudanosine (30) with formalin in the presence of hydrochloric acid in acetic acid.[70]

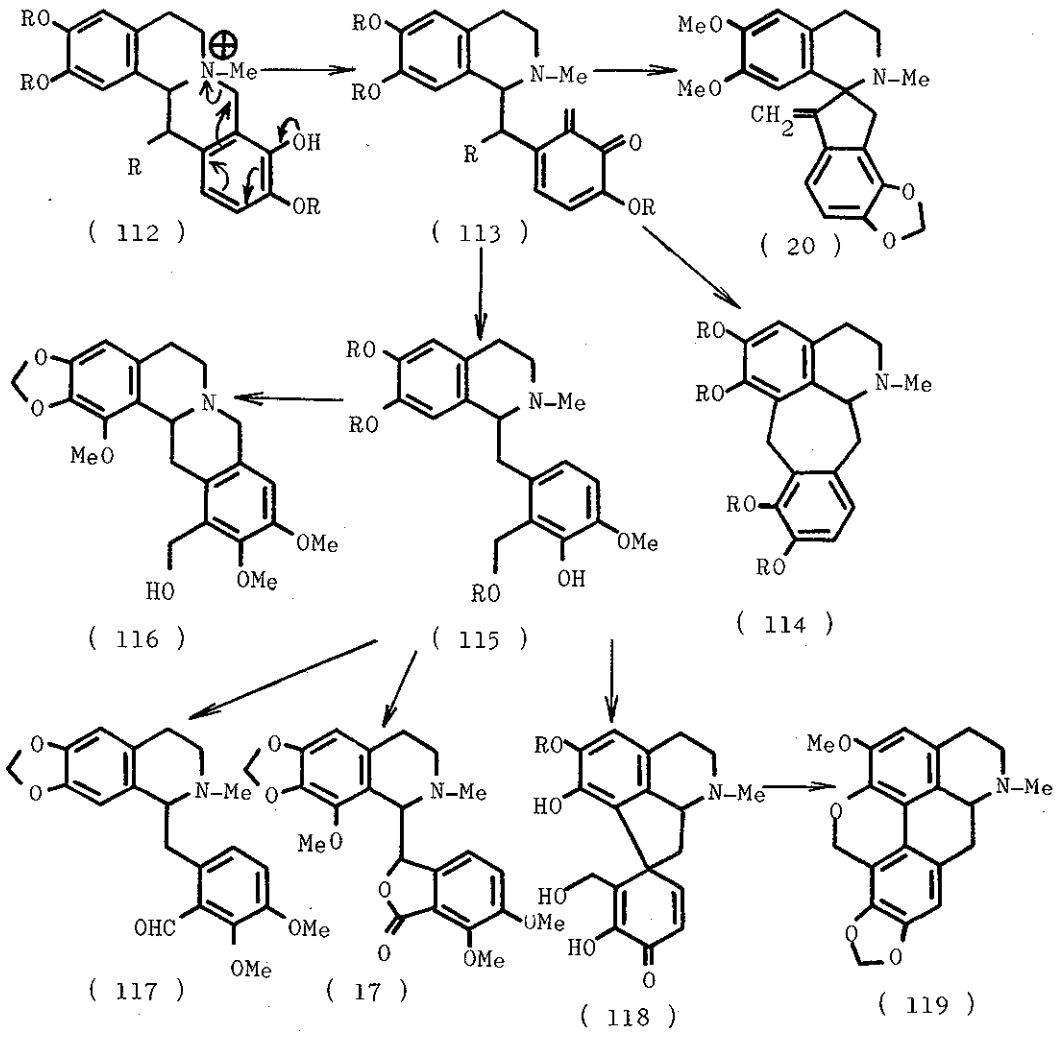
The quinonoid intermediate (113) which is apparently involved in the reaction of the phenolic quaternary salt could play an important role in the biogenesis of a number of benzylisoquinoline alkaloids. Thus nucleophilic attack on the quinonoid methylene group would generate the secoberberines (115), which could then be oxidised to mecambridine (116), narcotine (17), canadaline (117),

Scheme 20


KOH, MeOH
(104a-d)
(105a-d)
(106a-d)
a) R1+R2=CH2, R=OH, R4=H
b) R1+R2=CH2, R3=H, R4=OH
c) R1=R2=Me, R3=OH, R4=H
d) R1=R3=H, R2=Me, R4=OH
KOH,MeOH
(107)
(108)
(109)
(110)
HCHO, HCl
(30)
(111)

or the proaporphine (118). The last one (118) could then rearrange to N-demethylthaliphenine (119). On the other hand, coupling bet-

Scheme 21

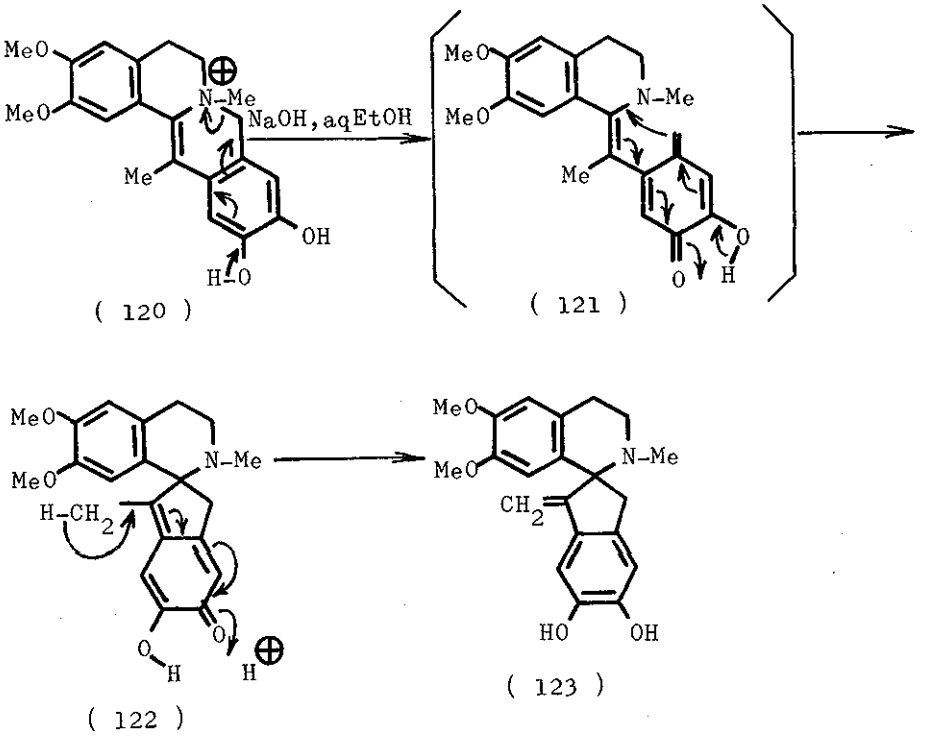


ween the quinonoid methylene group and C-1 of the isoquinoline could give the spirobenzylisoquinoline alkaloids (20).[70] The above novel benzo[5,6]cyclohept[1,2,3-ij]isoquinoline type compound (114) is expected to be a potential alkaloid, derivable from the protober-

berine alkaloids.

On the ground of the hypothesis that the spirobenzylisoquinoline

Scheme 22

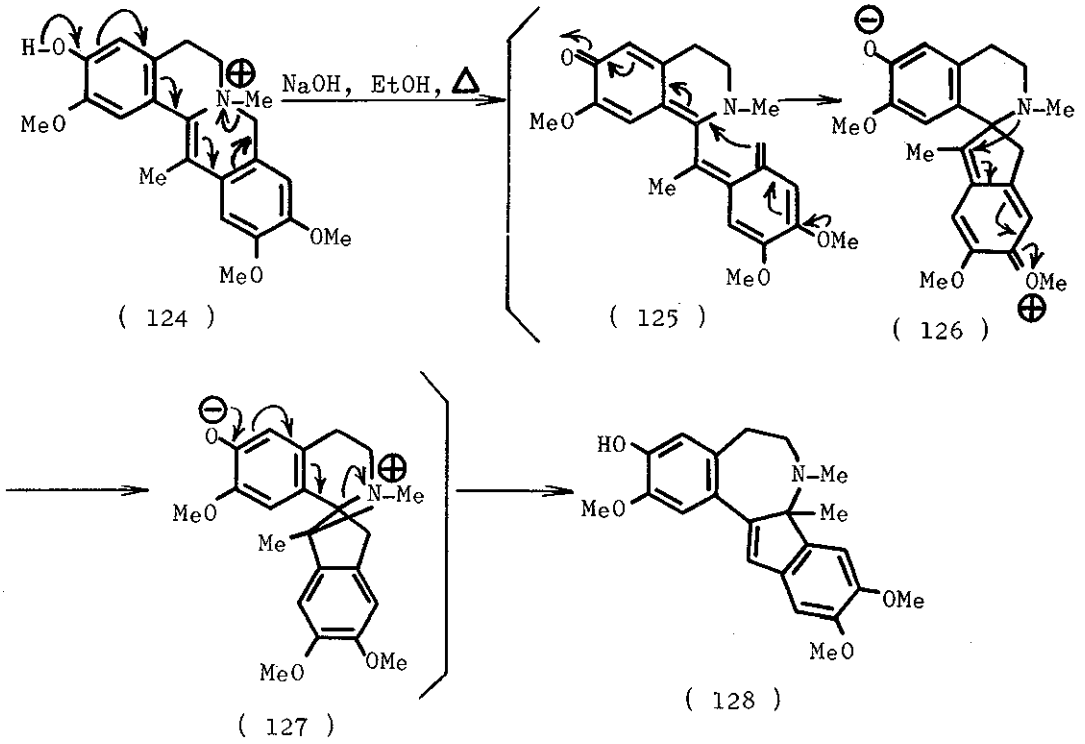


alkaloids could be biosynthesised from berberine alkaloids, Shamma and his coworkers demonstrated the chemical conversion of quaternary phenolic *dihydroprotoberberines into spirobenzylisoquinolines*.[4,71-74] Alkali treatment of enamine metho salts having dihydroxyl groups or monohydroxyl group on ring D yielded spirobenzylisoquinolines *via* quinone methides by different routes. A typical example is shown in Scheme 22.

On the other hand, the quaternary salt (124) having a hydroxyl group only on ring A interestingly gave the olefinic dihydrocyclo-

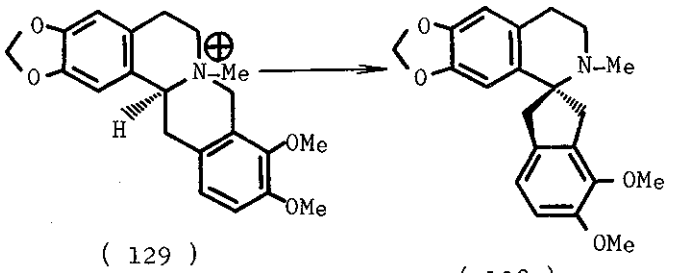
pent[b]azepine (128) by the same treatment as above.

Scheme 23



Reaction of the nonphenolic quaternary salt, for example 129, using stronger bases such as butyllithium, phenyllithium, sodium

Scheme 24

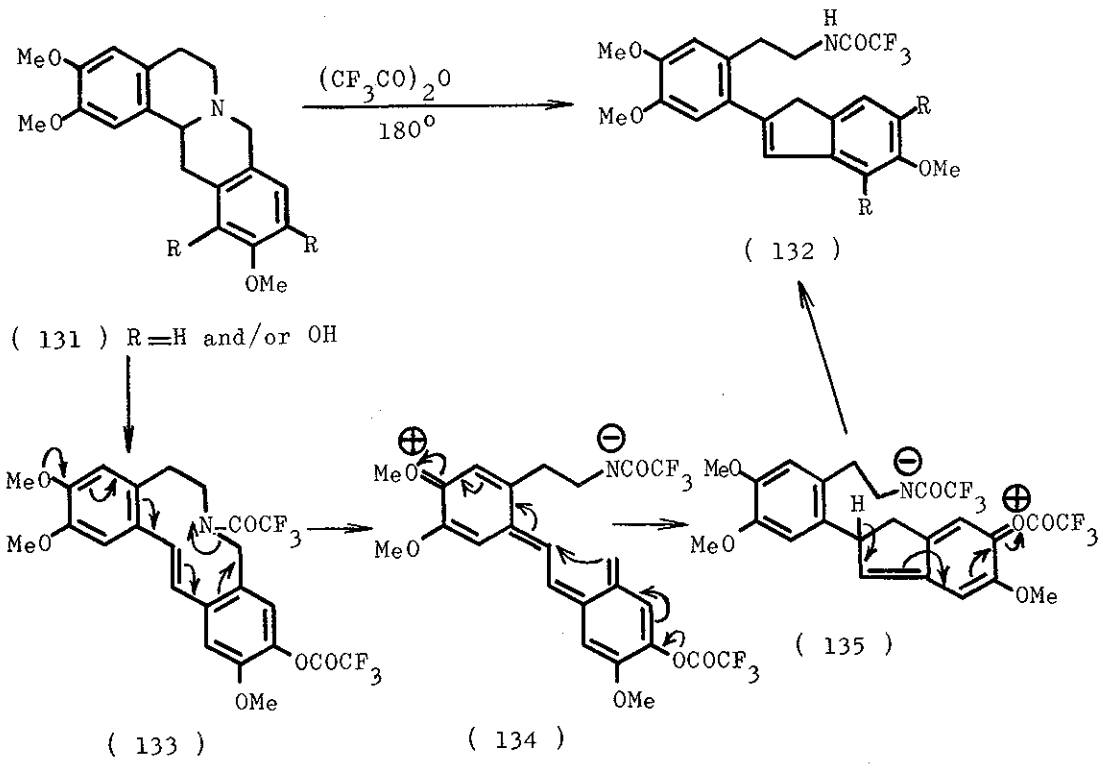


methyl sulphinyl carbanion, sodium amalgam and lithium aluminium hydride in tetrahydrofuran, causes Stevens type rearrangement to yield spirobenzylisoquinoline (130) in reasonable yield.[75,76] The chirality at C_{13a} position was shown to be retained during the reaction.[75]

2. Reaction with Trifluoroacetic Anhydride

An attempt to convert protoberberines into useful intermediates for the synthesis of spirobenzylisoquinoline and rhoeadine alkaloids led instead to the discovery of an unusual rearrangement. Phenolic compounds (131) on treatment with trifluoroacetic anhydride at 180°, gave the indene derivatives (132) in fairly good yield.[77] A possible mechanism for this transformation via the stilbene intermediate is shown in Scheme 25.

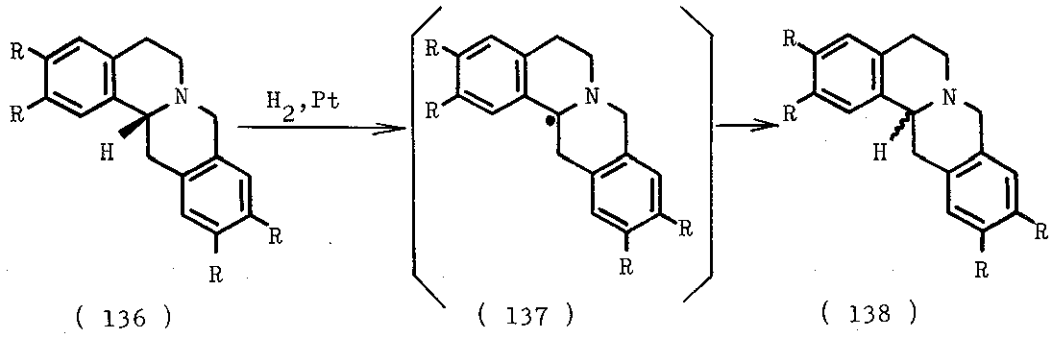
Scheme 25



3. Racemisation with Adams Catalyst

Optically active coreximine (9), tetrahydropalmatine (33) and xylopinine (32) were racemised by treatment with hydrogen in the presence of Adams catalyst. Phenolic groups appear to slow down the racemisation.[78] The reaction was extended to the racemisation of the 1-benzyltetrahydroisoquinolines.[79] It is assumed that the alkaloid is first adsorbed on the catalytic surface and that the bond between C_{13a} and hydrogen is ruptured homolytically to give a free radical (137) which is then hydrogenated to the racemate. Palladium and Raney nickel are ineffective in racemisation.[78]

Scheme 26

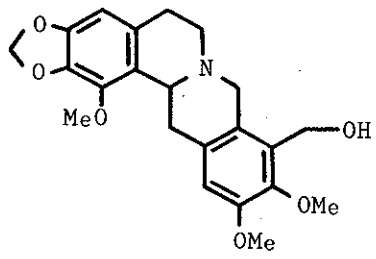


(136) (137) (138)

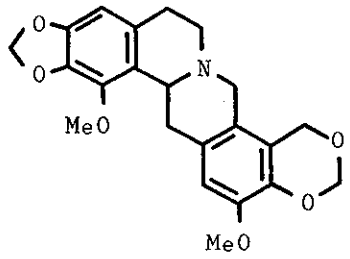
VI Mecambridine, Orientalidine and Aryapavine

Mecambridine and orientalidine, isolated from several plants of Papaver species, were initially assigned structures (139) and (140), respectively, on the basis of spectral analysis combined with some chemical degradations. Later, biogenetic consideration of these bases and uv spectral analysis of the bismethine derivatives showed that their structural assignments should be modified to 116 and 154, respectively.[80,81]

Scheme 27



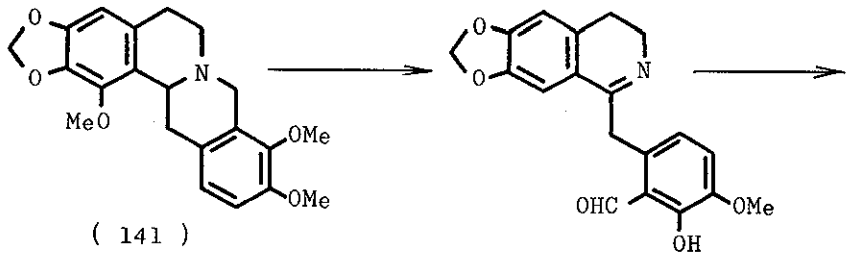
(139)



(140)

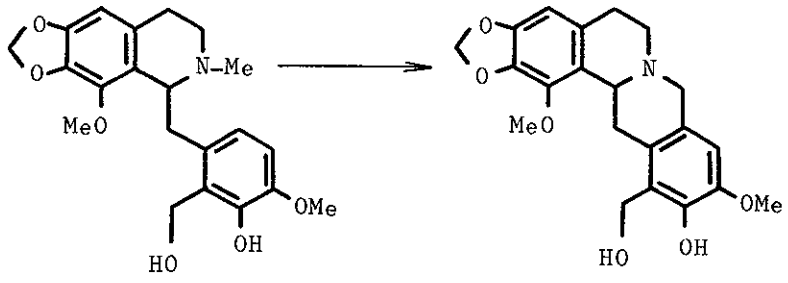
The quaternary protoberberines, PO-5 and PO-4, were isolated from the same plants as mecambridine and orientalidine. Oxidation of mecambridine and orientalidine with mercuric acetate, potassium permanganate, or chromium trioxide afforded PO-5 and PO-4, respectively. Thus PO-5 and PO-4 are the quaternary analogues

Scheme 28



(141)

(142)



(143)

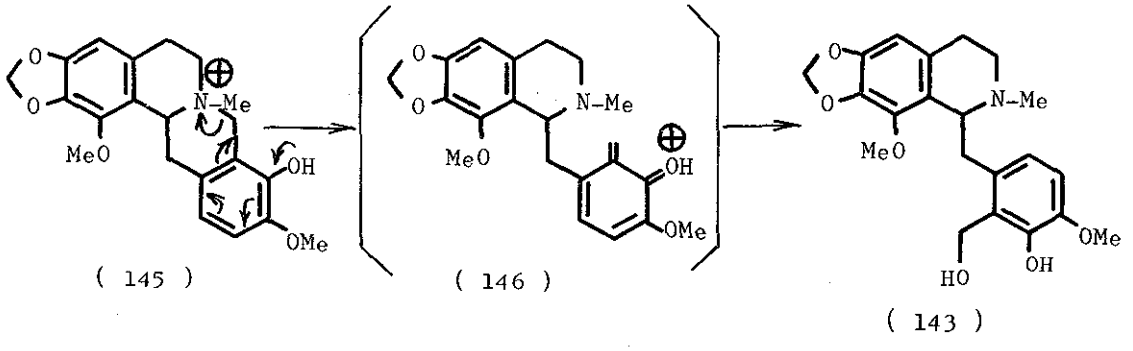
(144)

of mecambridine and orientalidine.[81,82] Recently aryapavine (144) was isolated from Papaver psedo-orientale.[83]

It was assumed that these alkaloids containing an additional carbon unit at C-12 position would be biosynthesised from tetrahydroprotoberberines. Oxidative cleavage between the N-7 and C-8 bond of a tetrahydroprotoberberine such as (141) yielded a secodihydrobenzylisoquinoline (142), which, after reduction, followed by N-methylation and oxidative recyclisation, gave the retroberberine alkaloid (144).[80]

The above hypothesis can be modified to the mechanism via the phenolic quaternary salt (145), which has already been demonstrated chemically as mentioned previously.

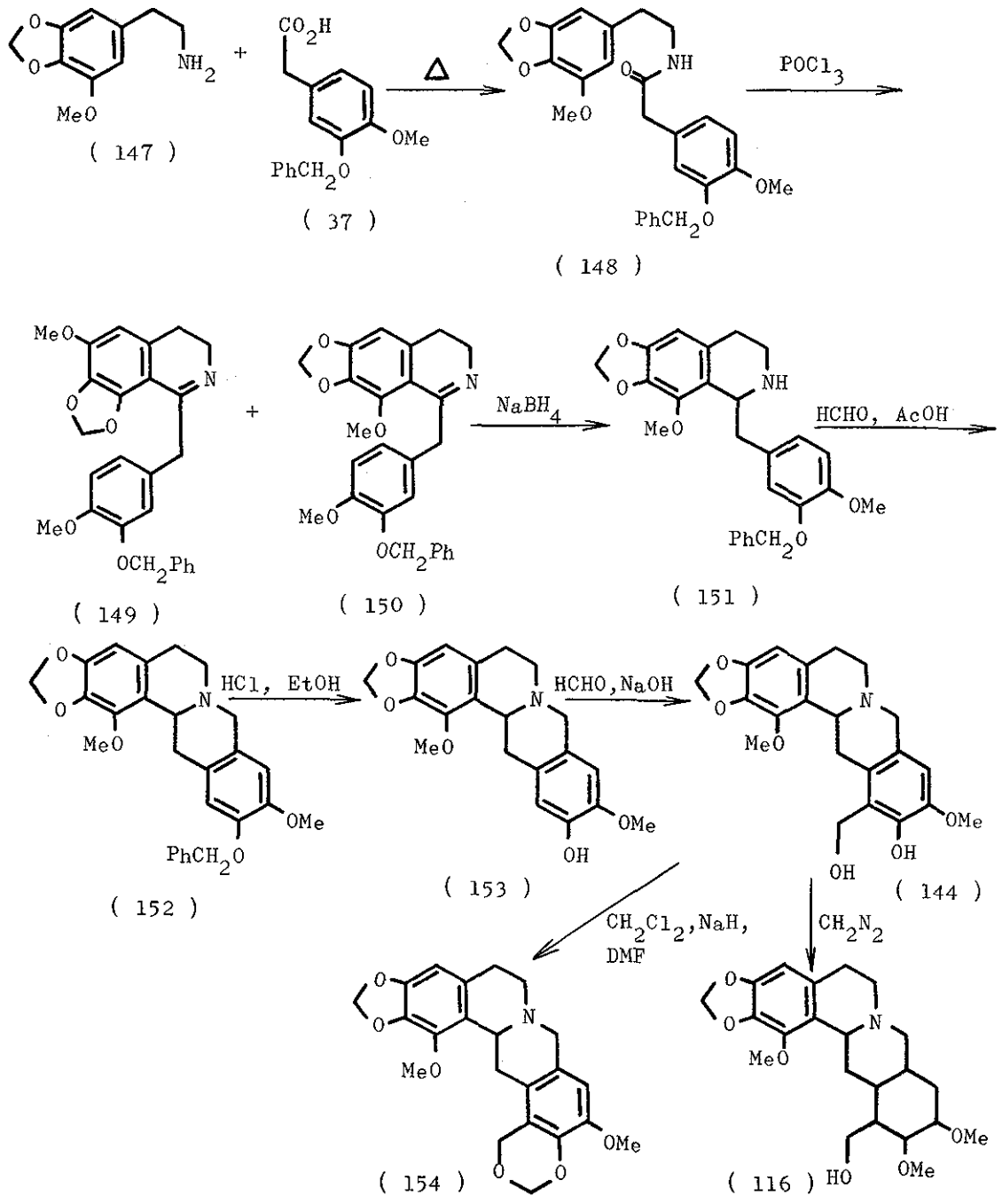
Scheme 29



(145) (146) (143)

The synthesis of aryapavine (144), mecambridine (116) and orientalidine (154) were carried out as follows. Fusion of 3-methoxy-4,5-methylenedioxyphenethylamine (147) with 3-benzyloxy-4-methoxyphenylacetic acid (37) gave the amide (148), which was cyclised with phosphoryl chloride to give two positional isomers (149 and 150). After the separation of these bases, a reduction of 150 with sodium borohydride, followed by Mannich cyclisation and debenzylation, afforded the phenolic tetrahydroprotoberberine (153). Hydro-

Scheme 30



xymethylation of 153 with formalin and 1 N sodium hydroxide gave (±)-aryapavine (144) in good yield. Methylation of 144 with diazomethane furnished (±)-mecambridine (116).[84] Treatment of 144 with methylene chloride and sodium borohydride in dimethylformamide yielded (±)-orientalidine (154).[85]

VII Stereochemistry

1. Absolute Stereochemistry

The absolute configuration of berberine alkaloids was first established chemically; ozonolysis of (-)-norlaudanosine (35) led to the amino acid derivative with the known absolute stereochemistry.[86] Mannich reaction of (-)-norlaudanosine (35) afforded (-)-xylopinine (32) [86] without racemisation at the C-1 position of tetrahydrobenzylisoquinoline.[87] In general, levorotatory tetrahydroprotoberberines have the same configuration (13a-S) as (-)-xylopinine, while dextrorotatory compound corresponds to the enantiomeric (13a-R) configuration.[4] X-Ray analysis of the hydrobromide of (-)-capaurine (53) [88] and 9-O-p-bromobenzoate of (-)-capaurimine (46)[89] revealed their absolute configuraiton to be 13a-S.

Ord measurement further assists the assignment of the absolute configuration; (13a-S)-tetrahydroprotoberberines showed two negative Cotton effects with troughs near 290 and 240 nm.[87,90]

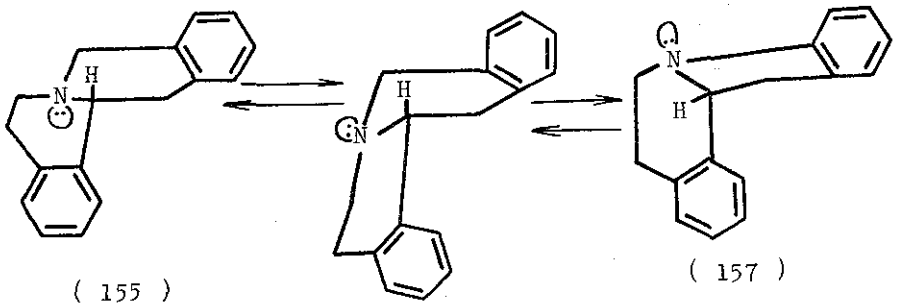
Snatzke and his group announced a useful non-empirical rule, which allows the assignment of absolute configuration of the tetrahydroprotoberberine from the ^1L_b and ^2L_a bands of the cd spectra.[91]

2. Conformation

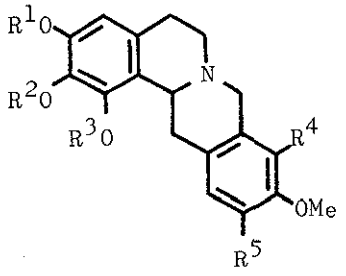
If the B and C rings of dibenzo[a,g]quinolizidine take half chair conformation, it would exist in the equilibrium of one trans (155) and two cis conformations (156 and 157) in solution, but mainly as

the thermodynamically more stable trans-quinolizidine. However, X-ray analysis of the hydrobromides of capaurine (53)[88] and iso-

Scheme 31



(155) (156) (157)



(158) R^1=R^5=H, R^2=R^3=Me, R^4=OH

(159) R^1=Me, R^2+R^3=CH_2, R^4=H, R^5=OCH_2Ph

(160) R^1=R^2=R^3=Me, R^4=OMe, R^5=H

capaurimine (158),[92] and p-bromobenzoate of capaurimine (46)[89] showed that all of them exist in the cis form (156) in the crystalline state. It was considered that an energetically unfavorable non-bonded interaction of the C-1 substituent to the C-13 hydrogens destablised the trans form.

The presence or absence of Bohlmann bands in the ir spectra in solution is utilized to distinguish the trans from cis-quinolizi-

dines.[93,94] The angular proton of the trans conformation in benzo-[a]- and indolo[b]quinolizidines resonates at a higher field than 3.8 ppm, whereas that of the cis form appears below 3.8 ppm.[95] However it is normally difficult to observe the signal due to the angular proton from the proton nmr spectra of the tetrahydroproto-berberines in deuteriochloroform, because the signals due to methoxyl groups appear around 3.8 ppm. When the proton nmr spectra were taken in deuteriotoluene, the signal due to the angular proton was shifted downfield and became visible.[96]

Cmr spectroscopy may be used as the most useful tool for determination of the conformation owing to the γ effect. The preferential conformation of the tetrahydroprotoberberine having all the substituents on both A and D rings is easily assignable by the different chemical shift of C(6) in cmr spectroscopy. Tetrahydroprotoberberines, which have a hydrogen at C-1 and 3-methoxy-1,2-methylenedioxy-derivative (159) showed the signal due to C(6) at about 51.4 ppm, even if the pattern of the substituents on rings A and D was changed, indicating the preferential trans-quinolizidine. On the other hand, the carbons at C-6 of O-methylcapaurine (160) and 1-methoxy-2,3-methylenedioxy compound (152) were observed at 48.3 and 47.1 ppm (δ from TMS), resepctively, indicating the preferential cis conformation. Capaurimine (46) showed the C(6) at 49.3 ppm, suggesting a mixture of cis and trans forms in equilibrium. It is probable that the conformation of tetrahydroprotoberberines having one substitutent at the C-1 position is governed by the degree of steric interaction between the C-1 substituent and the C-13 hydrogen.[96]

Cmr of quaternary protoberberines were measured in deuterio-

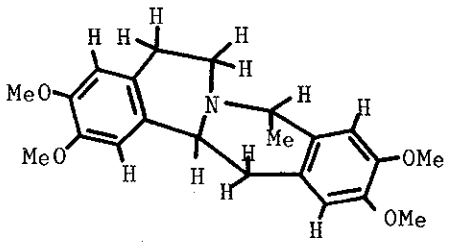
trifluoroacetic acid. Their preferential conformations were also determined by comparison of the chemical shift of C(6) and N-methyl group.[97]

It is possible, furthermore, to distinguish the difference between the 9,10- and the 10,11-disubstituted tetrahydroprotoberberines by the difference in chemical shift of C(8).[96]

Both configuration and conformation of 8-methyltetrahydroprotoberberines were made clear by analysis of cmr spectroscopy coupled with ir and proton nmr spectroscopies. The coralydine (61) series, in which the hydrogen at the C-8 and 13a positions are cis each other, exhibited Bohlmann bands in the ir and the angular proton at higher field than 3.9 ppm and the 8-methyl group at about 1.5 ppm, the resulting of which suggested that the trans-quinolizidine form (155) and the 8-methyl group would be equatorially oriented. On the other hand, the corytenchirine (58) series, in which the hydrogens at the C-8 and 13a position are trans, showed no Bohlmann bands in the ir spectra and the anqular proton at lower field than 4.11 ppm in the nmr spectra, indicating cis-quinolizidine form. The assignment of the sp^3 carbon atoms of O-methylcorytenchirine (59) and coralydine (61) of the cmr spectra is shown in Table I.

The shielding, exhibited by the carbons at C-13a and 8-methyl group of O-methylcorytenchirine, supports the one form (161) over the two possible cis-conformations.[48]

Scheme 32



(161)

Table I

Cmr chemical shifs of O-methylcorytenchirine (59) and coralydine (61) (ppm from TMS; o represents the signals where the assignments may be reversed).

	C(5)	C(6)	C(8)	C(13)	C(13a)	8-Me
O-methylcorytenchirine (59)	29.2	46.8	58.8	35.3	50.0	17.7
Coralydine (61)	29.1	46.7	58.9°	36.0	58.6°	21.3

We have reviewed some recent chemical progress in berberine alkaloids. Although the chemistry and pharmacology of berberine alkaloids have a long history, we believe from the chemical and biological importances that further efforts will be made in the field of berberine alkaloids.

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