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SYNTHESIS OF THE 1,2,3,4-TETRAHYDROISOQUINOLINES AND RELATED COMPOUNDS BY PHENOLIC CYCLISATION

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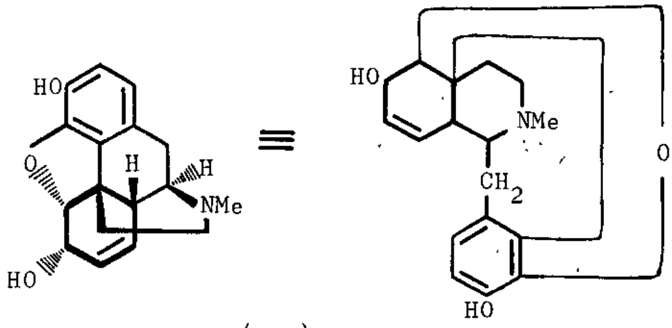
The new synthetic reaction of the 1-monosubstituted and 1,1-disubstituted 1,2,3,4-tetrahydroisoquinolines from 3-hydroxyphenethylamines and carbonyl compounds without an acidic catalyst is described.

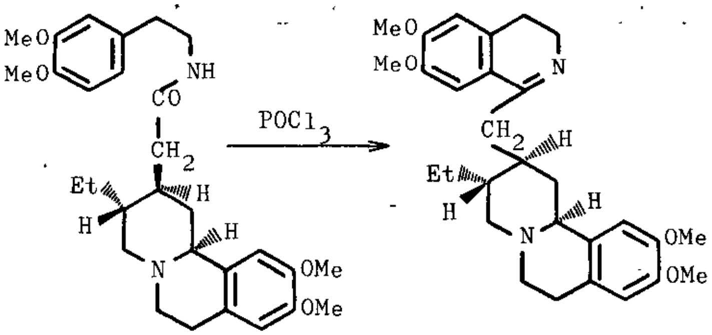
I Introduction

The chemistry of isoquinolines has a long history since an isolation of morphine (1) in 1805 by Sertürner which has an isoquinoline unit as a basic skeleton. Isoquinoline and its simple derivatives are found in coal tar, and there are many natural products having an isoquinoline ring system which we call the isoquinoline alkaloids.[1] Therefore, the synthesis of the isoquinolines as well as their reactions has been studied in details by many researchers,[2] and many synthetic methods are reported.[3] The most important and widely used synthesis is Bischler–Napieralski reaction,[4] whose application is shown in the synthesis of an alkaloid O-methylpsychotrine (2).[5]

Chart 1



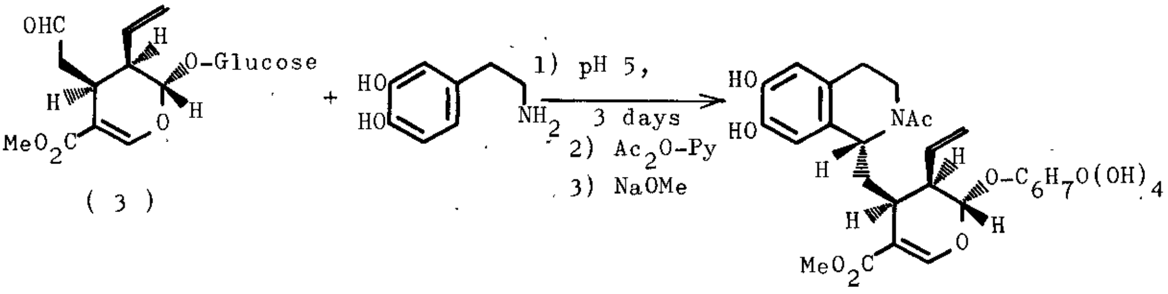
(1)



(2)

The second useful method is Pictet-Spengler reaction,[6] whose method provides a biomimetic synthesis of the isoquinoline alkaloids as shown in the formation of ipecoside (4) from secologanine (3).[7]

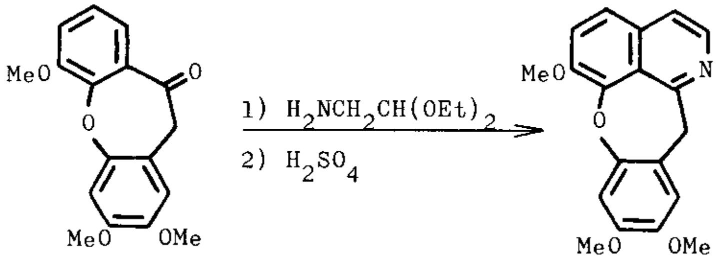
Chart 2



(4)

The third is Pomeranz-Fritsch reaction[8] as shown in the following chart,[9] and modification is reported by Bobbitt.[10]

Chart 3



In these syntheses, ring formation proceeds usually in strong acidic media, and therefore these methods could not be applied to compounds sensitive for acids. Moreover, the isoquinoline alkaloids would be biosynthesized by Pictet-Spengler type reaction from the phenolic phenethylamines and the suitable aldehydes or their equivalents, but the ring formation in Nature would occur in milder condition than a strong acidic condition used in laboratory.

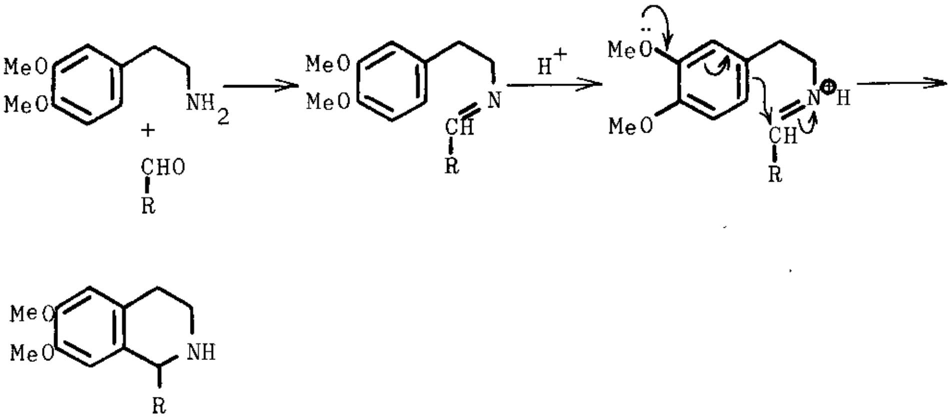
In 1968, we developed a new synthetic reaction of the 1,2,3,4-tetrahydroisoquinolines in neutral medium (without acid) from the variable 3-hydroxyphenethylamines and suitable carbonyl compounds by a modification of Pictet-Spengler reaction and proposed that this type of non-acidic reaction be called "Phenolic Cyclisation", because the phenolic hydroxy-group in the phenethylamines apparently played an important role.[11] Later, we found this reaction could proceed in a basic condition[12] and also reported a simple synthesis of 7,8-dioxygenated isoquinolines whose preparation by other methods was difficult.[13] In this article, those areas in which the phenolic hydroxy-group in the phenethylamines has played a key role in a synthesis of the isoquinoline ring system and its related compounds will be summarised.

II Synthesis of Tetrahydroisoquinolines

1. 1-Substituted tetrahydroisoquinolines from 3-hydroxy-4-methoxyphenethylamines:

The mechanism of Pictet-Spengler reaction could be explained by an aromatic substitution by electrophilic attack; the intermediate Schiff bases have been isolated and then cyclised as a separate reaction catalysed by acid.[6] A probable over-all reaction mechanism is illustrated as follows.

Chart 4



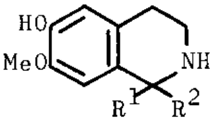
In this mechanism.acid strengthens the electrophilicity of the imine system in the Schiff base by protonation to nitrogen. Now, we supposed that this type cyclisation would proceed without acid if the electron density at the cyclisation position on the aromatic ring is extremely high. The electron density at the cyclisation site in 3-hydroxy-4-methoxyphenethylamine (5) and homoveratrylamine (6) was calculated as 1.9 and 1.1, respectively, by LCAO method, and therefore the nucleophilicity of the former phenolic amine (5) is greater than that of the latter nonphenolic amine (6).[11] Thus, the phenolic amine would afford the cyclisation product without an acidic catalyst.

On the ground of this speculation, the isoquinoline synthesis was examined by using of 3-hydroxy-4-methoxy-(5), 4-hydroxy-3-methoxy-(7), and 3,4-dimethoxyphenethylamine (6) in a neutral medium.[11]

Heating of a mixture of the phenolic amine (5) and veratraldehyde (8) in boiling ethanol gave 1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-1-(3,4-dimethoxyphenyl)isoquinoline (10), whose structure was determined on the basis of elemental analysis and spectroscopy. Condensation of the phenolic amine (5) with veratraldehyde (8) in ethanol at room temperature afforded the Schiff base (9), which was converted into the 1,2,3,4-tetrahydroisoquinoline (10) by fusion or heating in ethanol. This shows that the Schiff base (9) can be an intermediate in the formation of the 1,2,3,4-*tetrahydroisoquinoline (10) from the phenolic amine* (5) *and veratraldehyde* (8). On the other hand, 3,4-dimethoxyphenethylamine (6) and 4-hydroxy-3-methoxyphenethylamine (7) reacted with veratraldehyde (8) in boiling ethanol to give the corresponding Schiff bases (11) and (12), which could not be transformed into the tetrahydroisoquinolines (13 and 14) by fusion. These facts show that the phenolic hydroxy-group para to the site of cyclisation plays an important role in this reaction.

Thus, the key point in this cyclisation does not depend upon acidic catalyst or on the acidity of the substrates themselves but upon the electron density [1.9 in (5) and 1.1 in (6)] at the position of cyclisation, i.e., a phenolic hydroxy-group para to the cyclisation site is necessary: its electron donating effect is larger than that of a methoxy group. The simplest mechanism to explain this cyclisation is shown in the following Table I. We, therefore, proposed that this type of non-acidic cyclisation be called "Phenolic Cyclisation".[11]

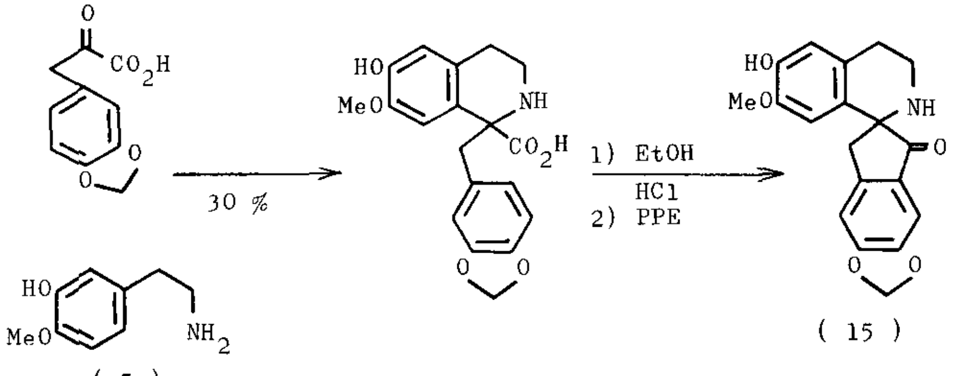
Table I



R^1	R^2	Yield(%)	Ref
4-Benzyloxyphenyl	H	72.5	11
Methyl	CO_2H	28.6	11
3,4-Dimethoxybenzyl	CO_2H	16.5	11
Cyclohexyl		31	11
Cyclopentyl		36	11
3,4-Methylenedioxybenzyl	H	21	13
Methyl	Me	25	14
Methyl	H	17	15
4-Hydroxyphenyl	H	80	15
3-Hydroxy-4-methyoxyphenyl	H	80	15
4-Benzyloxy-3-methoxyphenyl	H	80	15
3-Benzyloxy-4-methoxyphenyl	H	80	15
4-Benzyloxybenzyl	H	30~60	15
4-Benzyloxy-3-methoxybenzyl	H	30~60	15
3-Benzyloxy-4-methoxybenzyl	H	30~60	15
Pyridoxyl	H	16	16

The phenolic cyclisation of this amine (5) with several carbonyl compounds gave the corresponding 1,2,3,4-tetrahydroisoquinolines, and spiro-compounds were obtained by the reaction of the amine (5) with cycloalkanones.[11] Moreover, this amine (5) was used for the synthesis of the spirobenzylisoquinoline (15)[17] as shown in Chart 6.

Chart 6

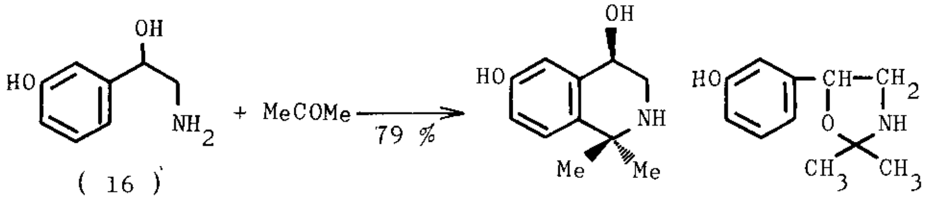


(5)

(15)

2. 1,2,3,4-Tetrahydro-4-hydroxyisoquinolines from 2-(3-hydroxyphenyl)-2-hydroxyethylamines: Similarly, condensation of novadral (16) with acetone afforded 1,2,3,4-tetrahydro-4,6-dihydroxy-1,1-dimethylisoquinoline (17),[11] but not 5-(3-hydroxyphenyl)-2,2-dimethyloxazolidine (18) whose structure was given by D'Amico, et al.[18] The structure of 17 was determined by chemical and spectroscopic method. The same reaction of the amine (16) with carbonyl compounds gave the cyclisation products as shown in Chart 7 and Table 2.

Chart 7



(16)

(17)

(18)

Chart 5

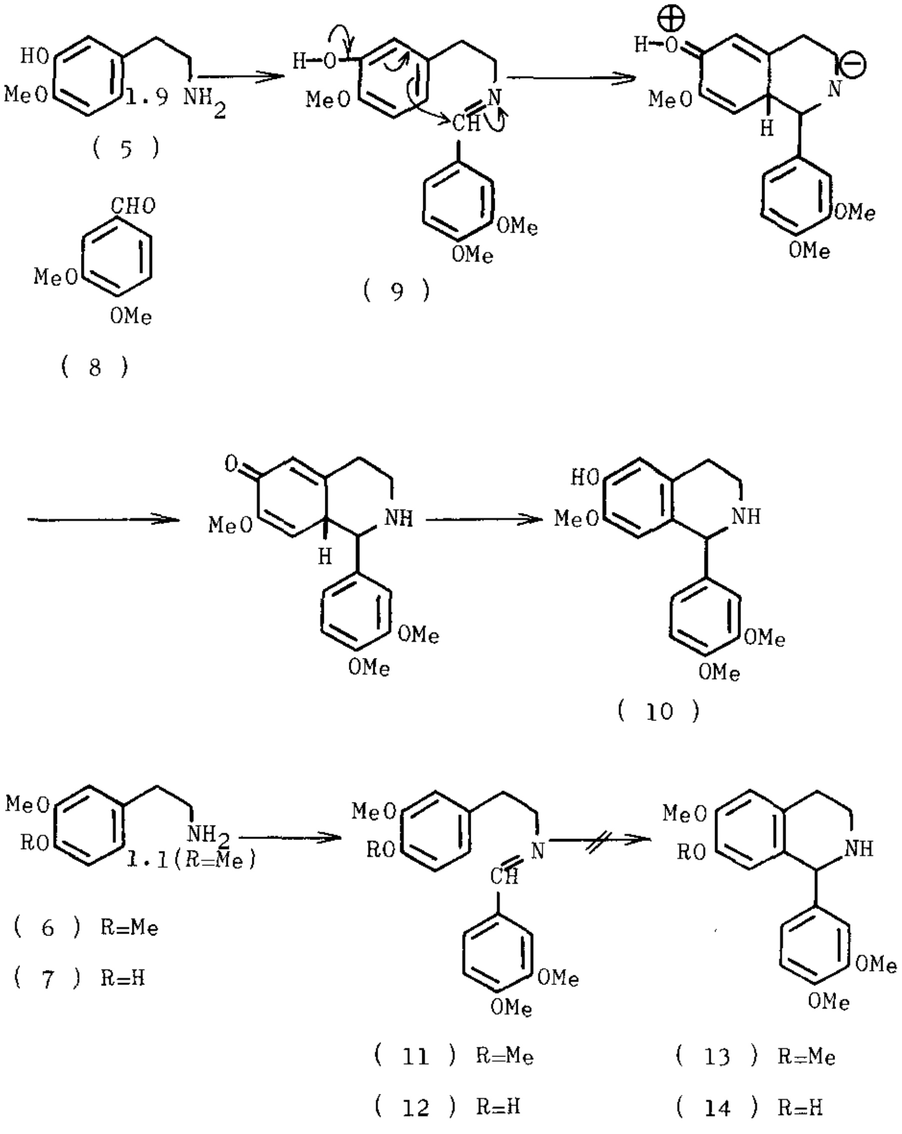
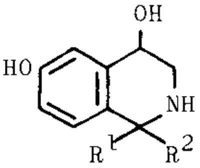
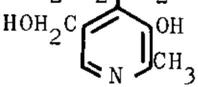

HO
MeO
1.9 NH$_2$
(5)
CHO
MeO
OMe
(8)
H–O
MeO
N
CH
OMe
OMe
(9)
H–O
MeO
N
H
OMe
OMe
O
MeO
NH
H
OMe
OMe
HO
MeO
NH
OMe
OMe
(10)
MeO
RO
NH$_2$
1.1 (R=Me)
(6) R=Me
(7) R=H
MeO
RO
N
CH
OMe
OMe
(11) R=Me
(12) R=H
MeO
RO
NH
OMe
OMe
(13) R=Me
(14) R=H

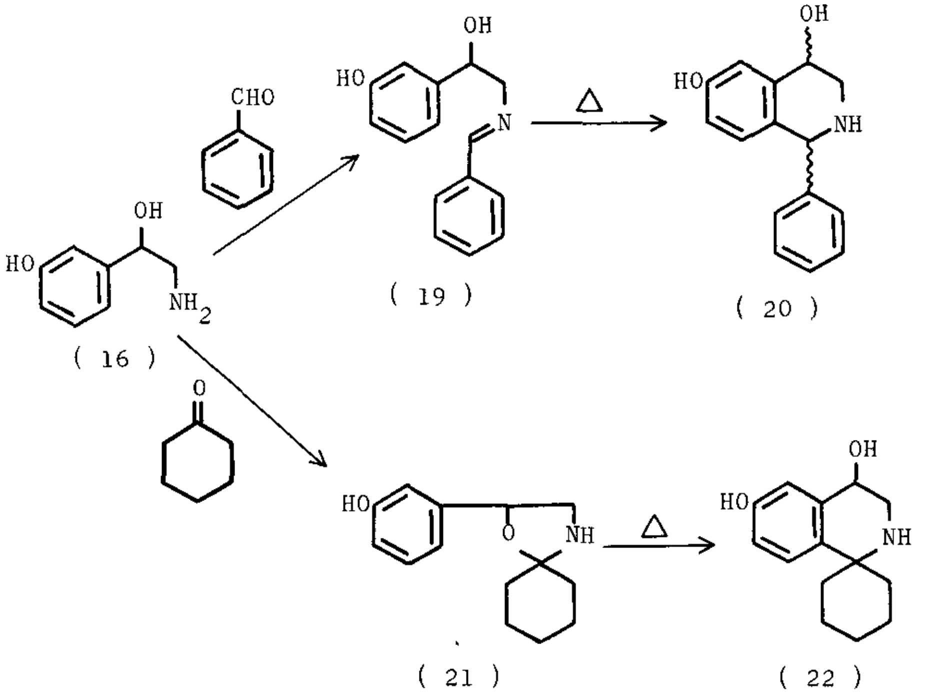
Table II



R^1	R^2	Yield(%)	Ref
C_6H_5	H	47	11,19
Me	Et	41	11
Me	C_6H_5	28	11
$-(CH_2)_5-$		22	11
$-(CH_2)_4-$		54	11
$-CH_2CH_2\underset{CH_2C_6H_5}{N}CH_2CH_2-$		69	19
$-CH_2CH_2\underset{Me}{N}CH_2CH_2-$		96	20
$-CH_2CH_2OCH_2CH_2-$		51	20
$-CH_2CH_2SCH_2CH_2-$		38	20
	H	33	16
CO_2H	H	87	21
CO_2Me	H	65	21
CO_2H	Et	80	21

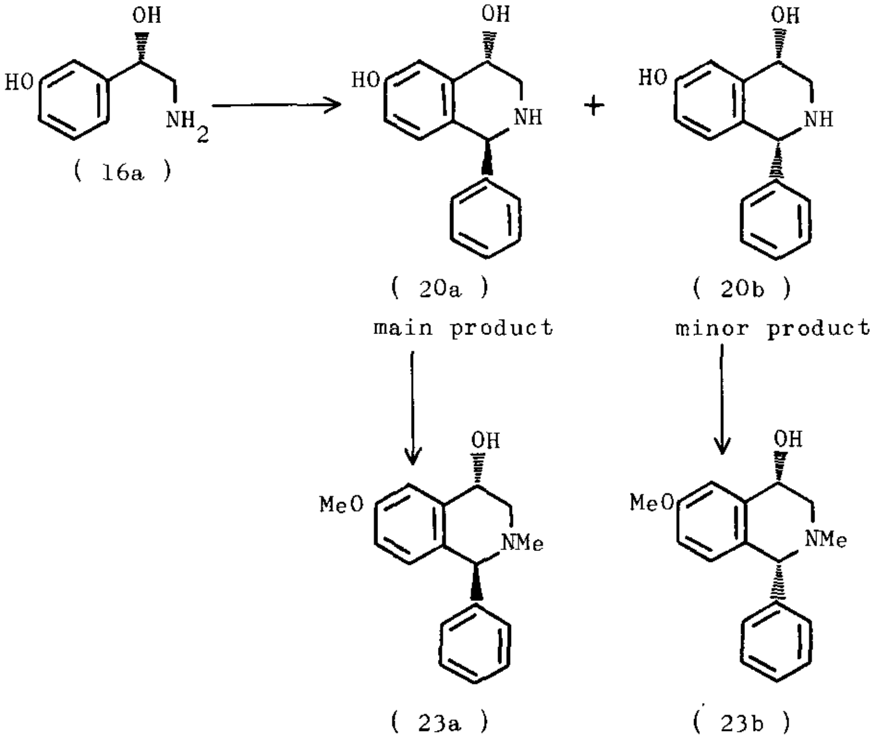
The reaction of novadral (16) with benzaldehyde in ethanol at room temperature afforded solely the Schiff base (19), which was converted into the 1,2,3,4-tetrahydroisoquinoline (20) in 53.5 % yield in boiling ethanol. Accordingly, the formation of 20 would proceed _via_ Schiff base (19). On the other hand, condensation of the amine (16) with cyclohexanone by refluxing in ethanol gave 5-(3-hydroxyphenyl)-2-spirocyclohexanooxazolidine (21), whose heating at 150° afforded the tetrahydroisoquinoline (22) in 80 % yield. This fact shows that the formation of 22 would proceed _via_ the oxazolidine (21) as an intermediate. Therefore, the route in the phenolic cyclisation in 1-(3-hydroxyphenyl)-2-aminoethanol type amine would involve the formation of isoquinoline _via_ the oxazolidine because of no stabilisation by conjugation of double bonds in case of alicyclic or aliphatic carbonyl compounds and _via_ the Schiff base because of stabilisation by conjugation of the azomethine group in case of aromatic carbonyl compounds.[19]

Chart 8



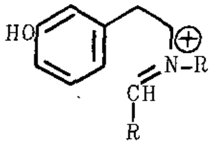
In the above reaction of novadral (16) with benzaldehyde, the diastereoisomeric mixture of products was obtained and successfully separated.[11,19] The relative configurations of the isoquinolines were determined by their n.m.r. spectral consideration on the products and their derivatives, and the absolute configuration of (1R, 4R)-1,2,3,4-tetrahydro-4-hydroxy-6-methoxy-2-methyl-1-phenylisoquinoline (23a) and its epimer, which were synthesised by cyclisation of D-(+)-novadral (16a) with benzaldehyde, followed by methylation, were also determined by their n.m.r. spectra and o.r.d. and c.d. curves.[22,23]

Chart 9



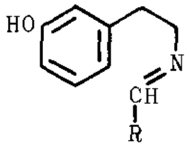
Phenolic cyclisation of a secondary amine would proceed more easily, because the intermediate, Schiff base (24) derived from a secondary amine would have stronger electrophilicity than the Schiff base (2) from a primary amine. On this hypothesis, we examined the condensation of N-methylnovadral (26) with several carbonyl compounds and obtained the expected isoquinolines as shown in Chart 10 but their yield did not increase as expected in the same condition.[20]

Chart 10

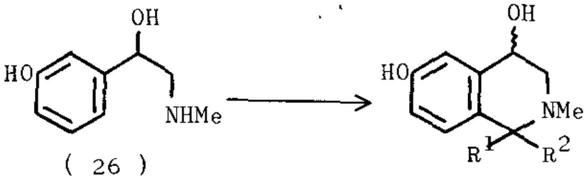


more polar

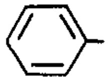
(24)



(25)

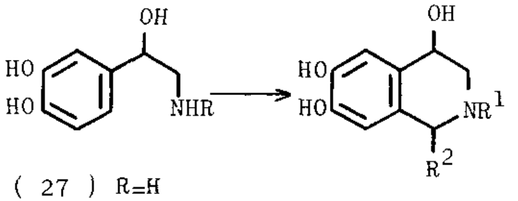


(26)

R^1	R^2	Yield(%)	Ref
Me	Me	32	20
$-(CH_2)_4-$		22	20
C_6H_5	H	46	20
Cl 	H	34	20
$C_6H_5CH_2CH_2$	H	47	20
CO_2H	H	73	21

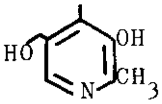
Similarly, noradrenaline (27)[16,21] and adrenaline (28)[21] gave the cyclisation products, but the reaction of 28 with dihydroxyacetic acid afforded the isoquinoline in addition to the azepine type compound (29) as shown in Chart 11.

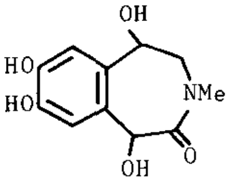
Chart 11



(27) R=H

(28) R=Me

R^1	R^2	Yield(%)	ref
H		51	16
Me	CO_2Me	26	21



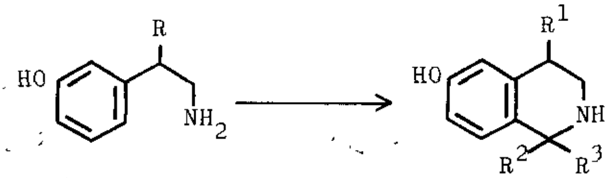
(29)

3. Reaction of 2-(3-hydroxyphenyl)ethylamines: The simple phenolic amine (30) was converted into the tetrahydroisoquinolines by carbonyl compounds in boiling ethanol,[24] and 2-methyl-(31) and 2-phenyl-2-(3-hydroxyphenyl)ethylamine (32) gave the corresponding isoquinolines (Chart 12) under fusion or reflux in 2-propanol.[25]

4. Reaction of 3-hydroxyphenylalanines: Phenolic amino acids (33)[26] and (34)[27] afforded the 3-carboxy-1,2,3,4-tetrahydroisoquinolines in good yield in the presence of ammonia and in case of this cyclisation the corresponding hydrochlorides were also used as substrates to afford the same results.

5. Cyclisation in basic medium: The above phenolic cyclisation proceeds in neutral medium, but the nucleophilic attack to the imine system would occur more easily in

Chart 12



(30) R=H

(31) R=Me

(32) $R=C_6H_5$

R^1	R^2	R^3	Yield(%)	Ref
H	$-(CH_2)_5-$		99	24
H	$-CH_2CH_2\underset{Me}{N}CH_2CH_2-$		99	24
H	$-CH_2CH_2\underset{CH_2C_6H_5}{N}CH_2CH_2-$		54	24
H	$-CH_2CH_2SCH_2CH_2-$		86	24
H	Me	Me	64	24
H	Me	Et	14	24
H	C_6H_5	H	66	24
H	C_6H_5	Me	14	24
Me	$-(CH_2)_4-$		73	25
Me	$-(CH_2)_5-$		72	25
Me	$-CH_2CH_2\underset{Me}{N}CH_2CH_2-$		94	25
Me	$-CH_2CH_2\underset{CH_2C_6H_5}{N}CH_2CH_2-$		95	25
Me	Me	Me	43	25
C_6H_5	$-(CH_2)_4-$		61	25
C_6H_5	$-(CH_2)_5-$		52	25
C_6H_5	$-CH_2CH_2\underset{CH_3}{N}CH_2CH_2-$		62	25
C_6H_5	$-CH_2CH_2\underset{CH_2C_6H_5}{N}CH_2CH_2-$		89	25

Chart 13

(33) X=H

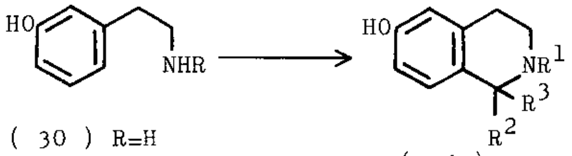
(34) X=OH

R^1	R^2	X	Solvent	Yield(%)	Ref
$-(CH_2)_5-$		H	NH_4OH	67.4	26
		H	H_2O	41.7	26
$-(CH_2)_4-$		H	H_2O	40.0	26
$-CH_2CH_2N(Me)CH_2CH_2-$		H	H_2O	78.0	26
Me	Me	H	H_2O	72.9	26
Me	CO_2H	OH	H_2O (pH 9)	88.0	27
Me	Me	OH	NH_4OH	91.0	27

a basic medium than in a neutral one due to the presence of *para* phenolic hydroxy-group to the cyclisation site. On assuming this, we investigated the isoquinoline cyclisation under basic conditions. The phenolic amine (30) was condensed with benzaldehyde with pyridine as solvent to give the expected tetrahydroisoquinoline (36) in better yield than the case of neutral condition. The same reaction with use of triethylamine as solvent afforded similar results as shown in Chart 17. Moreover, *N*-methyl-3-hydroxyphenylethylamine (35) gave the 1,2,3,4-tetrahydroisoquinoline in basic medium. Chart 14 also describes the several cyclisation products in neutral conditions.[12]

As mentioned above, phenolic cyclisation between phenethylamine or *N*-methylphenethylamine possessing the hydroxy-group at the 3-position and carbonyl compounds occurred in all media, neutral, basic, and acidic, to give the corresponding tetrahydroisoquinolines.

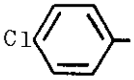
Chart 14



(30) R=H

(35) R=Me

(36)

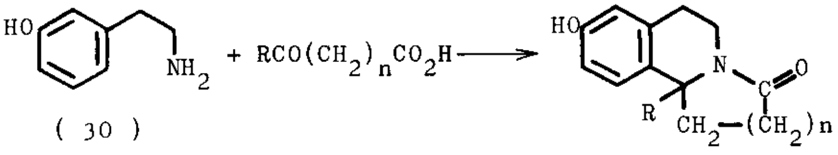
R^1	R^2	R^3	Solvent	Yield(%)
H	C_6H_5	H	Pyridine	69.4
			Et_3N	52.4
			EtOH	66.0
			EtOH-HCl	48.7
Me	C_6H_5	H	Pyridine	77.1
			Et_3N	63.1
			EtOH	82.2
			EtOH-HCl	53.0
Me		H	EtOH	77.3
Me	$C_6H_5CH_2CH_2$	H	EtOH	77.6
Me	$-(CH_2)_5-$		EtOH	48.5
Me	$-(CH_2)_4-$		EtOH	57.2

III Synthesis of Benzo[a]quinolizidines and Benzo[a]indolizidines

The simple synthesis of benzo[a]quinolizidine and benzo[a]indolizidine derivatives by phenolic cyclisation is also reported. Condensation of 3-hydroxyphenethylamine (30) with acylbutyric acid and acylpropionic acid under fusion at

150 - 200° or reflux in 2-propanol afforded the lactams (37), which were reduced with lithium aluminium hydride to give the benzo[a]quinolizine and benzo[a]-indolizidine derivatives, respectively. The configuration of these products were determined to trans by i.r. spectral consideration.[28]

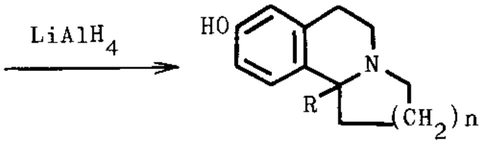
Chart 15



(30)

(37)

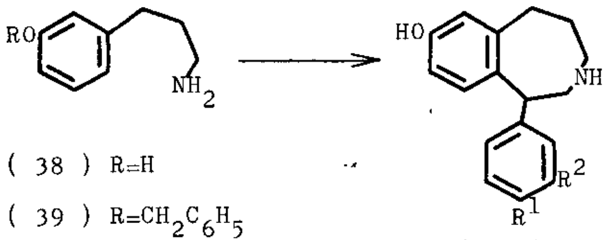
R	n	Yield (%)
Me	1	59
Me	2	51
C_6H_5	1	57
C_6H_5	2	71



IV Synthesis of Benzazepines

Phenolic cyclisation is applied to a synthesis of 2,3,4,5-tetrahydro-1H-benzazepine derivatives by the extension of this reaction. Refluxing 3-(3-aminopropyl)-phenol (38) hydrochloride with the aromatic aldehydes in butanol afforded the 2,3,4,5-tetrahydro-1H-2-benzazepines (41); however, in the corresponding reactions with the free amine the products could not be isolated, although their presence was indicated by t.l.c. 3-Benzyloxy-(39) and 3-methoxyphenylpropylamine (40) hydrochlorides did not react with the aldehydes in the same conditions. Thus, the phenolic hydroxy-group must play an important role in ring formation, indicating this reaction to be a type of phenolic cyclisation.[29]

Chart 16



(38) R=H

(39) $R=CH_2C_6H_5$

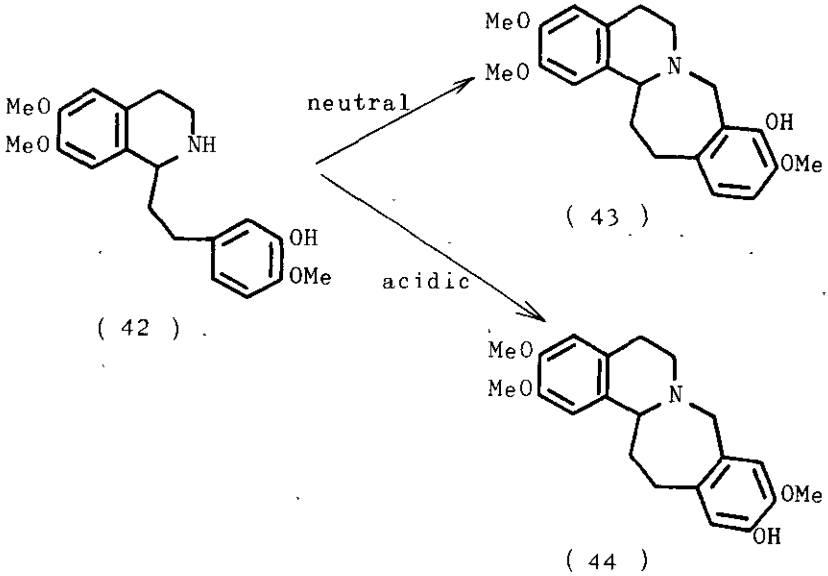
(40) R=Me

(41)

R^1	R^2	Yield (%)
H	H	22.4
MeO	MeO	5.6
$-OCH_2O-$		12.9

Interestingly, the 3-hydroxyphenethylisoquinoline (42) upon being heated with formalin in ethanol underwent phenolic cyclisation to give the ortho-cyclised homoprotoberberine (43) in 72 % yield,[30] but the Pictet-Spengler reaction of this isoquinoline (42) afforded the para-cyclised product (44).[30,31]

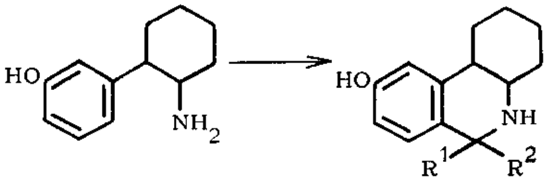
Chart 17



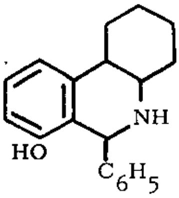
V Synthesis of Phenanthridines and Benz[c]phenanthridines

The extension of the phenolic cyclisation reaction leads to the synthesis of the phenanthridines and benz[c]phenanthridines from the appropriate phenolic amines. trans-2-(3-Hydroxyphenyl)cyclohexylamine (45) was condensed with the aliphatic carbonyl compounds to give the isoquinolines (46) cyclised at the para-position to the phenolic hydroxy-group. Two diastereoisomers (47) and (48) of the isoquinoline were obtained in the reaction with benzaldehyde, and both isomers were separated during recrystallisation. Moreover, the reaction of 45 with aromatic aldehydes gave 6-substituted phenanthridine (49) cyclised at the ortho-position to the hydroxy-group, whose structure was determined by spectroscopy. The same phenomenon was observed in the reaction of 45 with p-chlorobenzaldehyde.[32]

Chart 18



(45) (46)

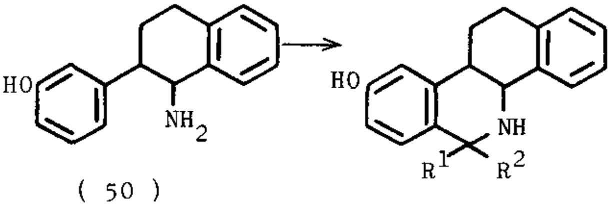


(49)

	R^1	R^2	Yield (%)
	Me	Me	67.8
	Me	Et	79.7
	$-(CH_2)_4-$		68.7
	$-(CH_2)_5-$		91.5
	$-CH_2CH_2\underset{Me}{N}CH_2CH_2-$		69.3
	$-CH_2CH_2\underset{CH_2C_6H_5}{N}CH_2CH_2-$		76.0
	p-ClC_6H_5	H	16.5
(47)	C_6H_5	H	11.0
(48)	H	C_6H_5	16.9

Similarly, cis-1-amino-1,2,3,4-tetrahydro-2-(3-hydroxyphenyl)naphthalene (50)[33] was heated with aliphatic ketones in ethanol to give the corresponding benz[a]phenanthridines (51) cyclised at the para-position to the hydroxy-group. However, in the reaction with benzaldehyde, cyclisation was found to occur not only at the para-position to give the two diastereoisomers but also the ortho-position to the phenolic

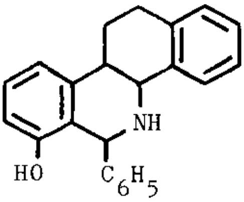
Chart 19



(50)

(51)

R^1	R^2	Yield (%)
Me	Me	12.9
$-(CH_2)_5-$		37.4
$-CH_2CH_2\underset{Me}{N}CH_2CH_2-$		76.7
C_6H_5	H	18.3
H	C_6H_5	14.6



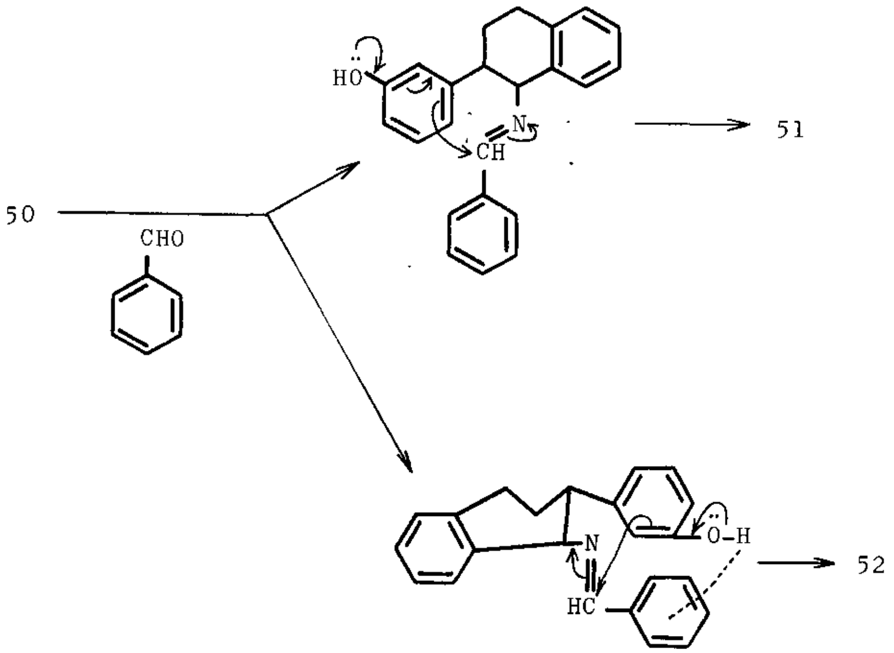
(52)

10.9 %

hydroxy-group.[34]

These ortho-cyclisation products (49) and (52) would be formed from benzaldehyde on the approach to the aldazine function to the ortho-position owing to an interaction of the phenolic hydroxy-group with π-electrons on the benzene ring in the Schiff base as shown in the formation of 52. The reaction of the amines (45) and (50) with aliphatic ketones gave selectively the usual products since the interaction between the hydroxy-group and the π-electrons of the benzene ring was absent.

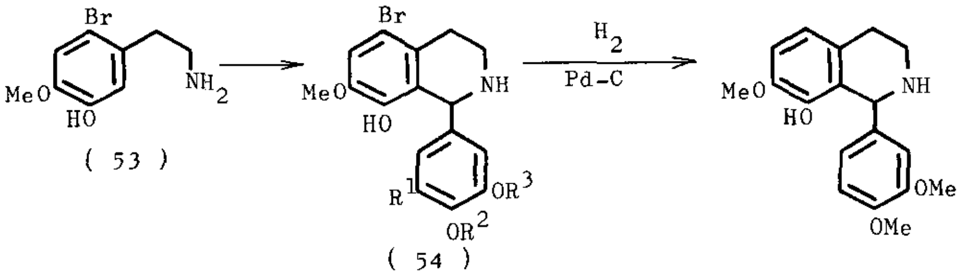
Chart 20



VI Application to Total Synthesis of Isoquinoline Alkaloids

There are many examples of the synthesis of the 6,7-dioxygenated 1-benzylisoquinolines *from 3,4-dialkoxyphenethylamines by the Bischler-Napieralski reaction*[4] and the Pictet-Spengler reaction.[6] However, these methods were not useful for the synthesis of the 7,8-dioxygenated 1-benzylisoquinolines since the cyclisation occurs preferentially at the position para to the oxygenation function. Many chemists made several unsuccessful attempts to obtain the 7,8-dioxygenated 1-benzylisoquinolines by the forgoing methods.[4,6] We also subjected the phenethylamines, whose para-cyclisation site was protected by a bromine atom, to the Pictet-Spengler reaction, in order to obtain 7,8-dioxygenated isoquinoline, but this reaction resulted in failure. However, we presumed that the cyclisation at the ortho-position to the hydroxy-group would proceed smoothly if the reactivity of the benzene nucleus were increased by

Chart 21



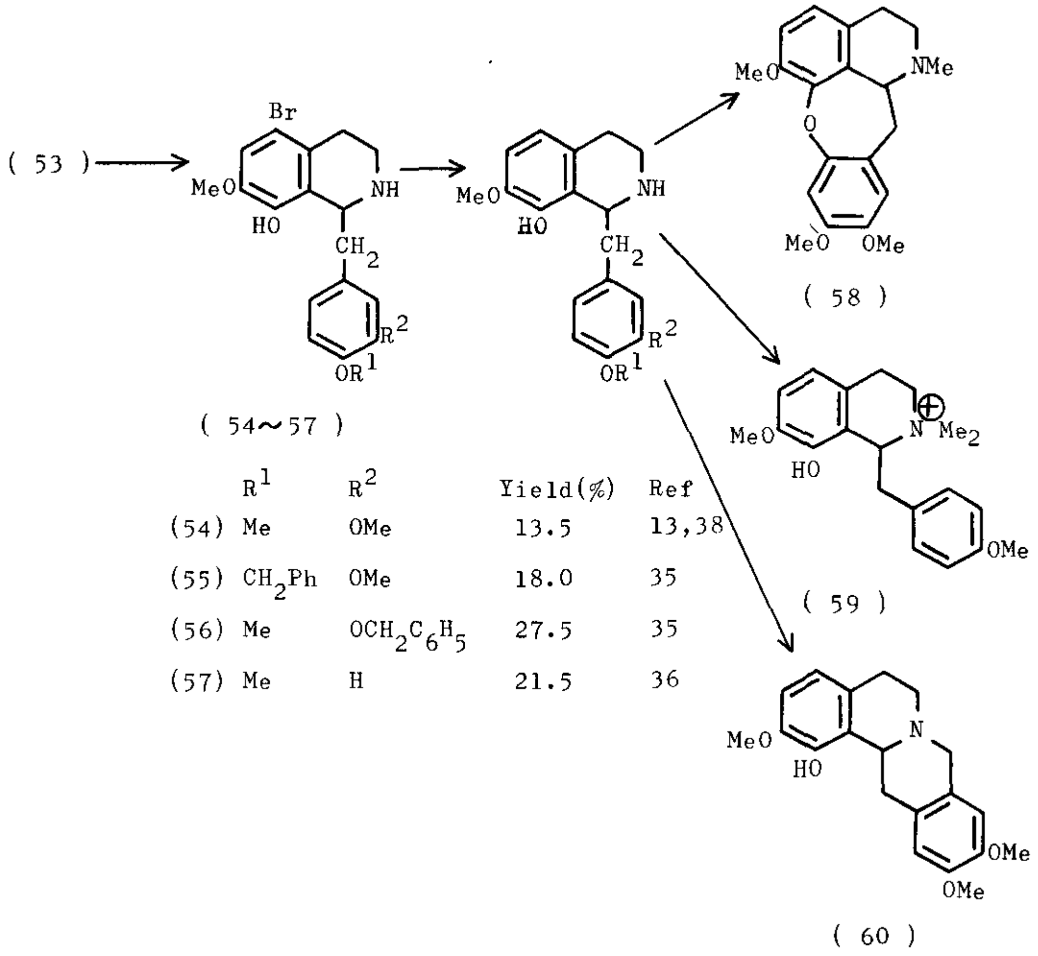
R^1	R^2	R^3	Yield (%)
H	Me	Me	53.5
OMe	Me	Me	69.2
H	Me	$CH_2C_6H_5$	28.6
H	H	Me	10.5

the presence of a phenolic hydroxy-group in the amine. Therefore, we investigated the phenolic cyclisation.

A mixture of 2-bromo-5-hydroxy-4-methoxyphenethylamine (53) and veratraldehyde in ethanol was refluxed for 7 hr to give the expected 7,8-dioxygenated isoquinolines (54), whose debromination by usual method afforded 1,2,3,4-tetrahydro-8-hydroxy-7-methoxy-1-phenylisoquinoline.[13]

On the ground of the above model experiment, the phenolic amine (53) was condensed with several phenylacetaldehydes in boiling ethanol, followed by debromination, to furnish the 1-benzylisoquinolines (55 - 57), which were converted into the alkaloids cularine (58),[35] petaline (59),[36,37] and caseadine (60).[38]

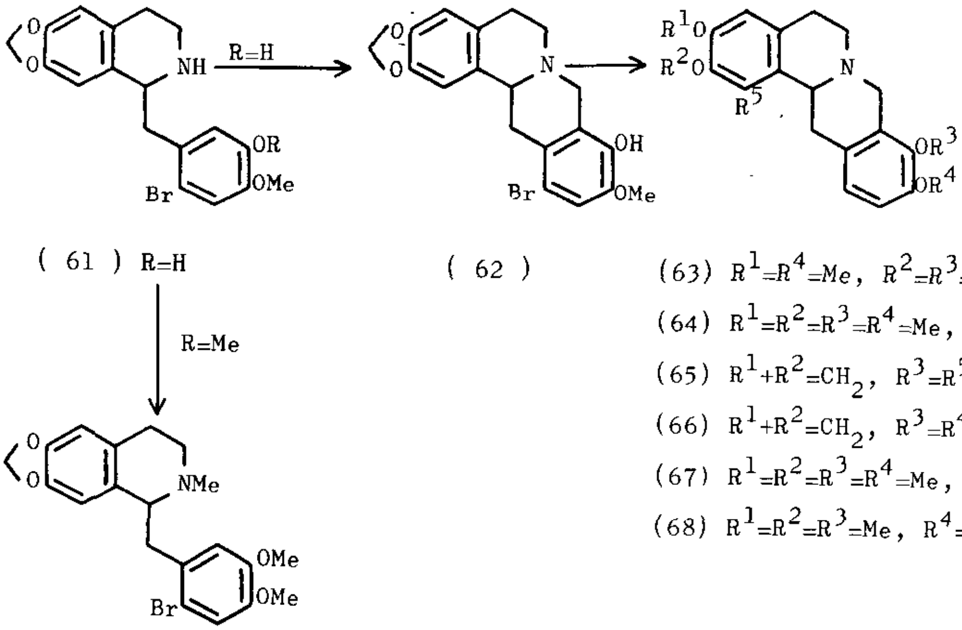
Chart 22



	R^1	R^2	Yield(%)	Ref
(54)	Me	OMe	13.5	13,38
(55)	CH_2Ph	OMe	18.0	35
(56)	Me	$OCH_2C_6H_5$	27.5	35
(57)	Me	H	21.5	36

The same idea has been applied to total synthesis of the 9,10-dioxygenated tetrahydroprotoberberine alkaloids, scoulerine (63),[39] tetrahydropalmatine (64),[39,40] nandinine (65),[41] canadine (66),[41] capaurine (67),[42], capaurimine (68)[43] and related compounds.[44] For example, condensation of 1-(2-bromo-5-hydroxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (61) hydrochloride with formalin on a water bath gave 12-bromonandinine (62) in 81 % yield, whose debromination with lithium aluminium hydride afforded nandinine (65). Although acid catalyses the berberine bridge formation, this type cyclisation could not proceed in the absence of the phenolic hydroxy-group at the appropriate position as shown in the formation on N-methylisoquinoline (69).[45] Thus, this reaction is a kind of phenolic cyclisation.

Chart 23



(61) R=H

(62)

(63) $R^1=R^4=Me$, $R^2=R^3=R^5=H$

(64) $R^1=R^2=R^3=R^4=Me$, $R^5=H$

(65) $R^1+R^2=CH_2$, $R^3=R^5=H$, $R^4=Me$

(66) $R^1+R^2=CH_2$, $R^3=R^4=Me$, $R^5=H$

(67) $R^1=R^2=R^3=R^4=Me$, $R^5=OH$

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

(69)

Tetrahydroprotoberberine synthesis occurs in a neutral medium; thus, 1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxyisoquinoline (70) and norreticuline (71) reacted with formalin in ethanol without acid to give the O-methylcoreximine (72) and coreximine (73), respectively, in good yield,[11] but ortho-cyclisation product could not be obtained although this reaction conditions resemble physiological conditions,[46 - 48] whose example is shown in a total synthesis of nandinine (65),[46] kikemanine (74),[48] and scoulerine (63).[47]

In summary, we have found that heating 3-hydroxyphenethylamines with carbonyl compounds in alcohol without acid gave the 1,2,3,4-tetrahydro-6-hydroxyisoquinolines having mono- or disubstituent at C - 1 position, and this phenolic cyclisation could be applied to the synthesis of 7,8-dioxygenated isoquinolines as a key intermediate for the total synthesis of the alkaloids whose preparation would be difficult by other methods. Specifically, this reaction is an effective method for the synthesis of compounds sensitive for acid such as the 1,2,3,4-tetrahydro-4-hydroxyisoquinolines.

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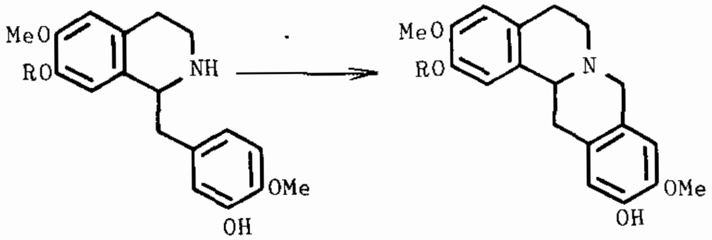
Chart 24

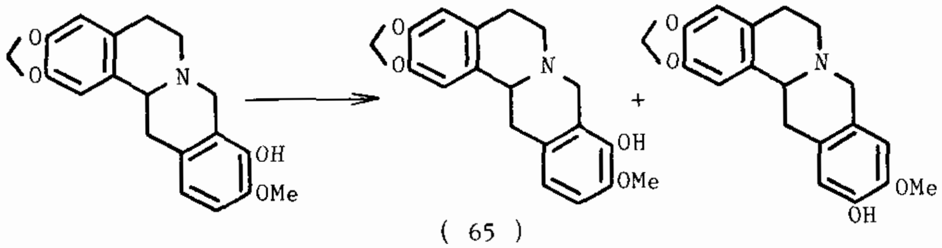


(70) R=Me

(71) R=H

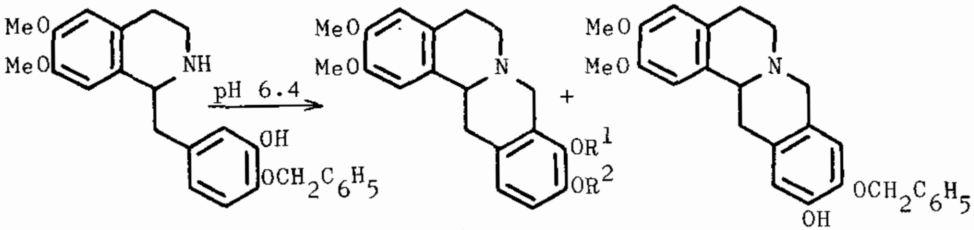
(72) R=Me, 69 %

(73) R=H 75 %



(65)

pH 1.0	71.0 %	18.0 %
6.0	5.1	18.3
7.2	3.3	17.5
7.8	——	11.4



R^1=H, R^2=CH$_2$Ph 52 %   13 %

(74) R^1=Me, R^2=H

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