HETEROCYCLES, Vol. 6, Nos. 9, 10, 1977

SOME RECENT WORK ON PROTOBERBERINES AND TETRAHYDROPROTOBERBERINES - A REVIEW†

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This review is dedicated to Professor Tetsuji Kametani on his completion of 60 years, the greater part of which he dedicated to enriching our knowledge of the chemistry of alkaloids in general and isoquinoline alkaloids in particular. During the last one decade and more, there has been a continuous stream of publications from his laboratory dealing with various aspects of isoquinoline alkaloid chemistry. We owe a debt of gratitude to him and his colleagues for their rich contributions. There has been a vigorous school of research in Japan working on isoquinoline alkaloids and therefore, we thought it appropriate to choose the above subject as a token of tribute to Professor Kametani, his coworkers and all our other Japenese colleagues who have been working in the field of alkaloids. This article has for its background the excellent reviews of Jeffs (P.W. Jeffs, "The Alkaloids", ed. by R.H.F. Manske, Academic Press, New York, 1967, Vol.9, pp.41-115) and Shamma (M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, pp.268-314). It is by no means exhaustive and only certain aspects of protoberberine chemistry are being highlighted here. The authors may be pardoned if much interesting material has been left out.

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† Dedicated to Professor Tetsuji Kametani on the occasion of his 60th birthday.

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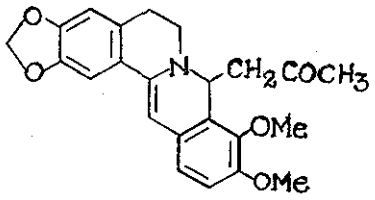
1. Acetone Berberine

1.1. Structure of Acetone Berberine

When berberinium salts are treated with acetone in the presence of strong alkali, a yellow crystalline compound, m.p. 168-169°, is obtained for which Gadamer[1] assigned structure (1) (8-acetonyldihydroberberine). This compound exhibits

Scheme 1

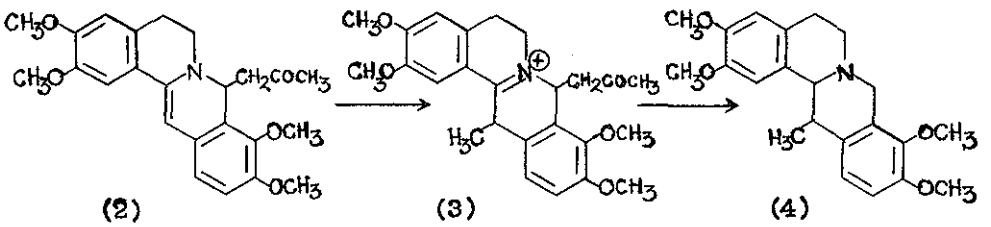


(1)

fascinating aspects of enamine chemistry. Acetonylberberine has been used for the syntheses of 13-methyltetrahydroprotoberberines. The alkaloids synthesised by this method are thalictricavine,[2] corydaline,[3] corysamine[4] and corydalidzine.[5]

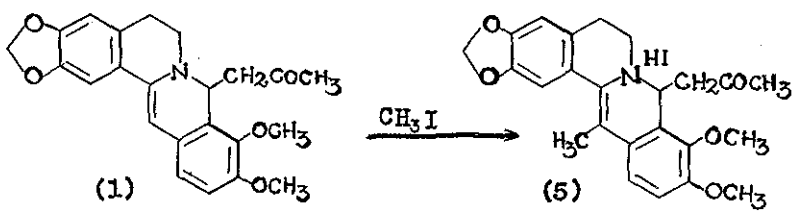
Freund and Fleischer[6] were perhaps the first to study the action of methyl iodide on berberineacetone. Reduction of the adduct yielded 13-methyltetrahydroberberine. von Bruchhausen[3] reacted palmatineacetone (2) with methyl iodide and on reduction, the product yielded dl-corydaline (4). This reaction was represented as follows.

Scheme 2



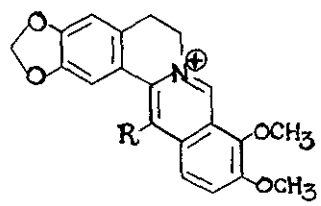
Bersch[7] formulated the reaction of berberineacetone and methyl iodide as follows.

Scheme 3



But Takemoto and Kondo[2] assigned structure (6a, R=CH_3) to the substance obtained on application of methyl iodide to acetone-berberine, on the basis of its analytical values, ir and uv spectral data. Similar products (6b) and (6c) were obtained by reacting with ethyl iodide and propyl iodide respectively.

Scheme 4



(6a) R = CH_3
(6b) R = CH_2CH_3
(6c) R = $CH_2CH_2CH_3$

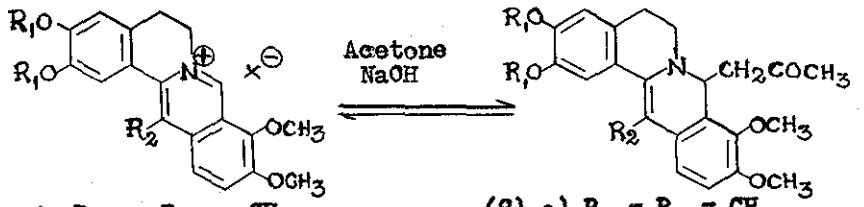
These products could be reduced with tin and hydrochloric acid, sodium borohydride or lithium aluminium hydride and depending on experimental conditions used during reduction, 13-alkyl substituted tetrahydroprotoberberines were obtained besides tetrahydroberberines as also 13-alkyldihydroberberines.

Charubala and Pai[8] confirmed structure (6a) by a study of

its pmr spectrum, molecular weight determination, ir and uv spectral data.

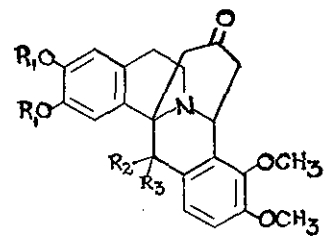
In a masterly piece of investigation well planned and executed with the aid of modern analytical and spectral techniques, Naruto and coworkers[9] have established that the socalled acetone-berberine is not a homogeneous product, but is a mixture of at least three products, the major one being the 8-acetonyldihydro-berberine (1), contaminated with a few percent of 8,13a-propano-berberine (9c) formed as a result of intramolecular Michael condensation of the acetone adduct, and the berberinium hydroxide.

Scheme 5



(7) a) $R_1 = R_2 = CH_3$
b) $R_1R_1 = CH_2$; $R_2 = CH_3$
c) $R_1R_1 = CH_2$; $R_2 = H$

(8) a) $R_1 = R_2 = CH_3$
b) $R_1R_1 = CH_2$; $R_2 = CH_3$
c) $R_1R_1 = CH_2$; $R_2 = H$

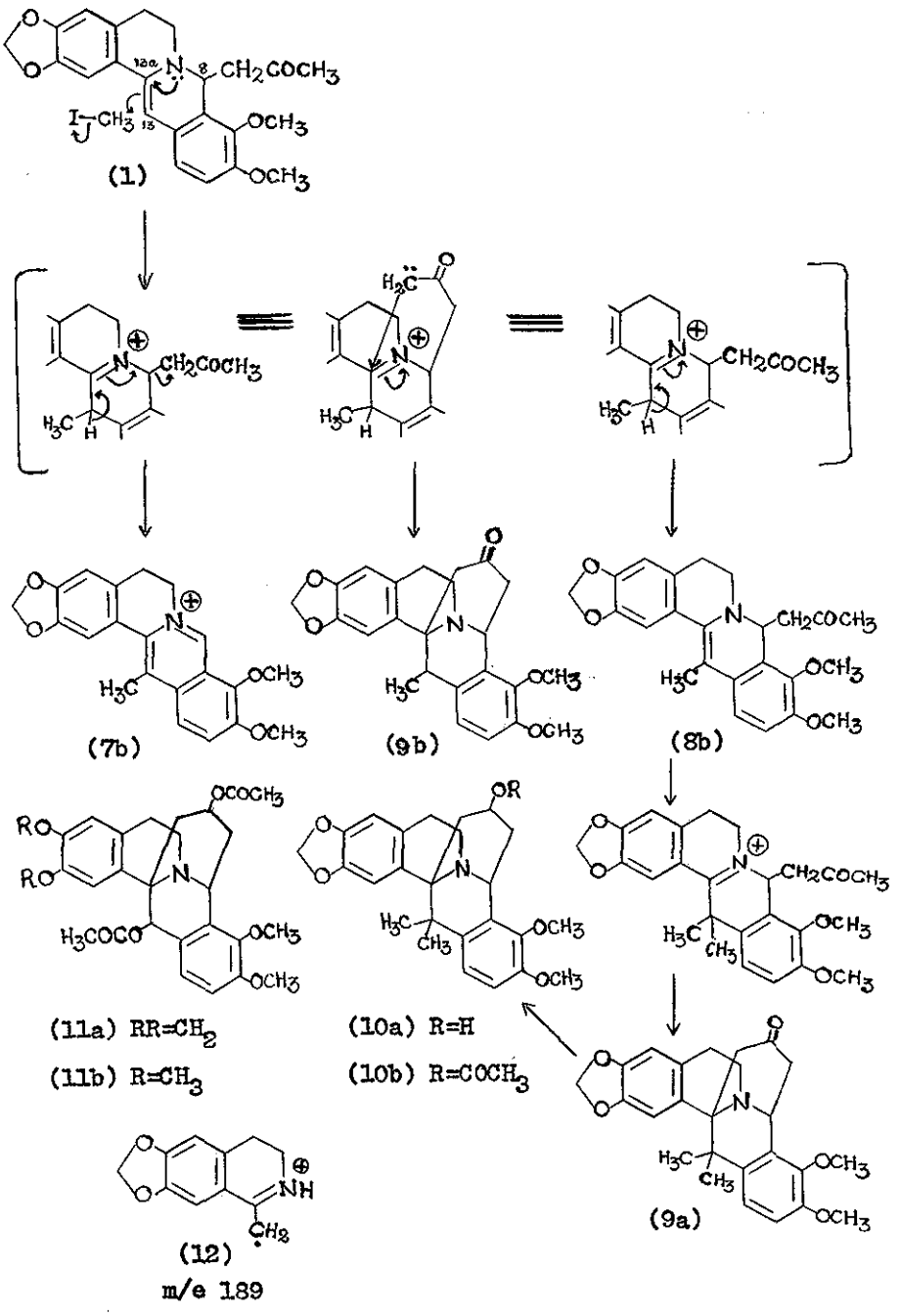


(9) a) $R_1R_1 = CH_2$; $R_2 = R_3 = CH_3$
b) $R_1R_1 = CH_2$; $R_2 = CH_3$; $R_3 = H$
c) $R_1R_1 = CH_2$; $R_2 = R_3 = H$

This has been established at least in three cases of crude acetone adducts of quaternary protoberberinium salts, viz., 1) dehydrocorydalinium chloride (7a), 2) 13-methylberberinium chloride (7b) and 3) berberinium chloride (7c) respectively. The purification and separation of these individual compounds presented the authors with difficulty. They showed the presence of these compounds in the mixture by tlc comparison with authentic samples and also from product analysis of reactions carried out on the crude acetone adduct. These authors also found that the reaction of acetoneberberine with methyl iodide gave besides 13-methylberberinium iodide (7b,X=I) and berberinium iodide (7c,X=I), two hitherto unisolated products, 8,13a-(2'-oxopropano)-13,13-dimethylberbine derivative (9a) and 8,13a-(2'-oxopropano)-13-methylberbine derivative (9b). The structures of the new products were deduced from chemical and spectral data.

From the fact that 13-methylacetoneberberine (8b) prepared from (7b) gave compound (9a or 9b) on methylation with methyl iodide, a tentative mechanism was proposed for the reaction as shown in Scheme 6. According to this mechanism, the excess of alkyl halide and the alkaline medium are favourable for the formation of 8,13a-propanoberbine derivatives. In practice, the yields of (9a) and (9b) increased in general with addition of sodium hydroxide or triethylamine in the presence of excess of methyl or allyl halide in the reaction medium.[9] The structure proof of (9a) depended upon reduction to alcohol (10a), which was characterised as the acetate (10b). Acetates (11a)(derived from neoxyberberineacetone (18)(vide infra)) and (11b) serves as examples for the interpretation of the pmr of (10b).

Scheme 6

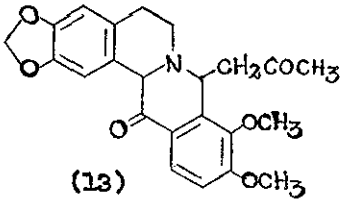


Analogous reaction with allyl bromide gave rise to 8,13a-(2'-oxopropano)-13-allyl-(corresponding to (9b)) and 13,13-diallyl-berbine derivatives (corresponding to (9a)) and with n-propyl chloride, similar 13-n-propyl and 13,13-di-n-propyl derivatives. (9a) and (9b) exhibited an intense peak at m/e 189 corresponding to the characteristic fragment (12) of 8,13a-propanoberbine in their mass spectra.[9]

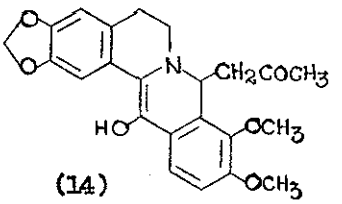
1.2. Permanganate Oxidation Products of Acetone Berberine

In 1911 Pyman[10] oxidised acetoneberberine dissolved in acetone, with aqueous potassium permanganate in the cold and on work up of the product, obtained a crystalline compound, m.p. 228-229°, which he named neoxyberberine acetone. Pyman considered structures (13) and (14) for this compound and preferred (13), since the compound was insoluble in sodium hydroxide. Treatment

Scheme 7



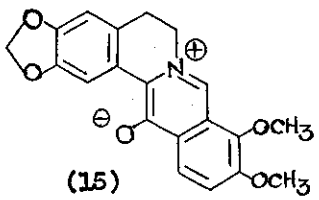
(13)



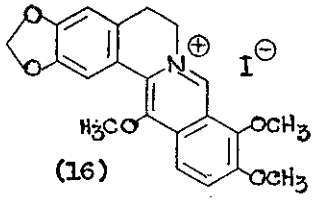
(14)

of neoxyberberineacetone with acid, followed by basification, gave compound (15), a phenol betaine, recognised as such by its behaviour towards methyl iodide in affording 13-methoxyberberinium iodide (16). Takemoto and Kondo[11] reinvestigated the structure

Scheme 8



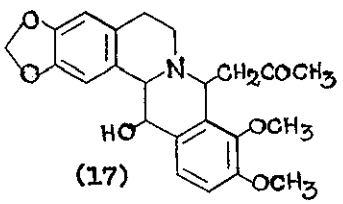
(15)



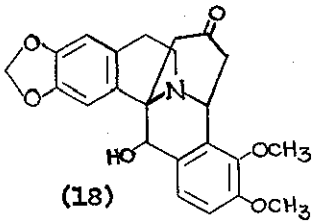
(16)

of neoxyberberineacetone and assigned structure (17) on the basis of uv and ir spectra of the parent compound and its acetyl derivative. Jeffs[12] critically examined the data on neoxyberberineacetone and preferred structure (14). In 1966, Iwasa and Naruto[13] reinvestigated the structure of neoxyberberineacetone. On the basis of pmr data and several chemical reactions, the structure was revised to (18) (8,13a-(2'-oxopropano)-13-hydroxy-2,3-methylenedioxy-9,10-dimethoxydibenzo [a,g] -quinolizidine).

Scheme 9



(17)

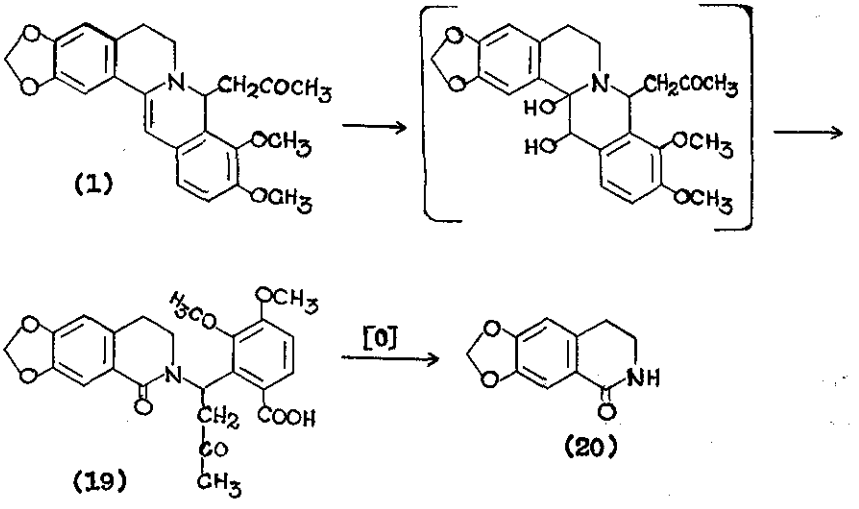


(18)

In 1972, Kondo and Takemoto[14] isolated a new acidic substance m.p. 235°(d) from the oxidation product of acetoneberberine. This compound was assigned structure (19) (2-(2,3-dimethoxy-6-carboxy-α-acetonylbenzyl)-1-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline), based on uv, ir, pmr and mass spectral data, specially from the uv absorption spectrum which showed maxima at 262 nm (log ε 4.03) and 301 nm (log ε 3.70). These authors anticipated the acidic compound to be a derivative of the noroxyhydrastinine type. Under more drastic oxidation conditions using excess

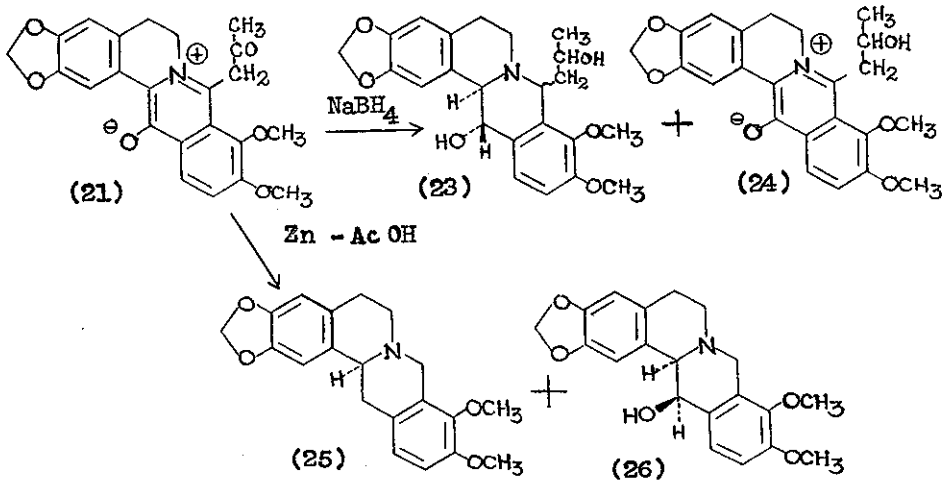
potassium permanganate in an acid solution,(19) gave noroxyhydrastinine (20). They suggested the following reasonable mechanism for the formation of (19) from acetoneberberine (1).

Scheme 10



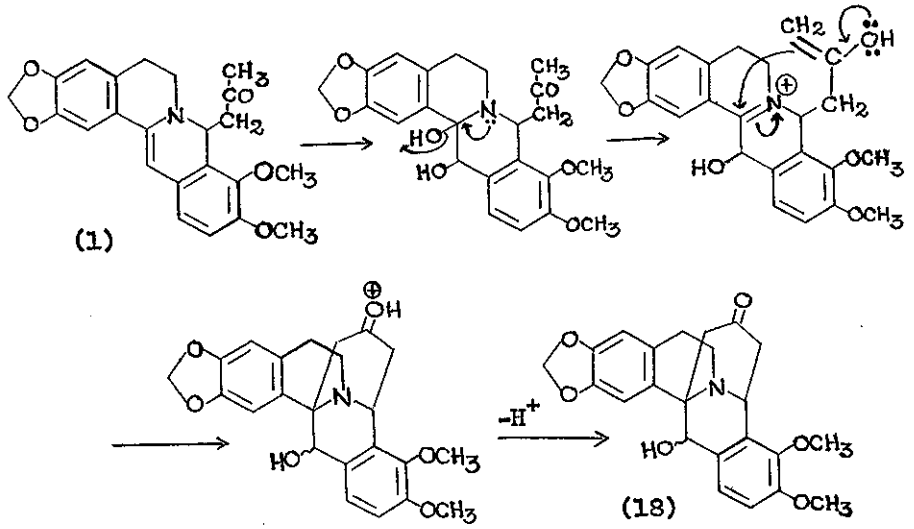
Two additional compounds were later isolated by these authors[15] and identified as (21) and (22). Reduction of (21) with sodium borohydride afforded 8-(2-hydroxypropyl)-13-hydroxytetrahydroberberine (23) and 8-(2-hydroxypropyl)-13-oxidoberberinium (24), while reduction with zinc dust in aqueous acetic acid led to the concurrent elimination of the acetonyl group to form tetrahydroberberine (25) and 13-β-hydroxytetrahydroberberine (dl-ophiocarpine) (26).

Scheme 11

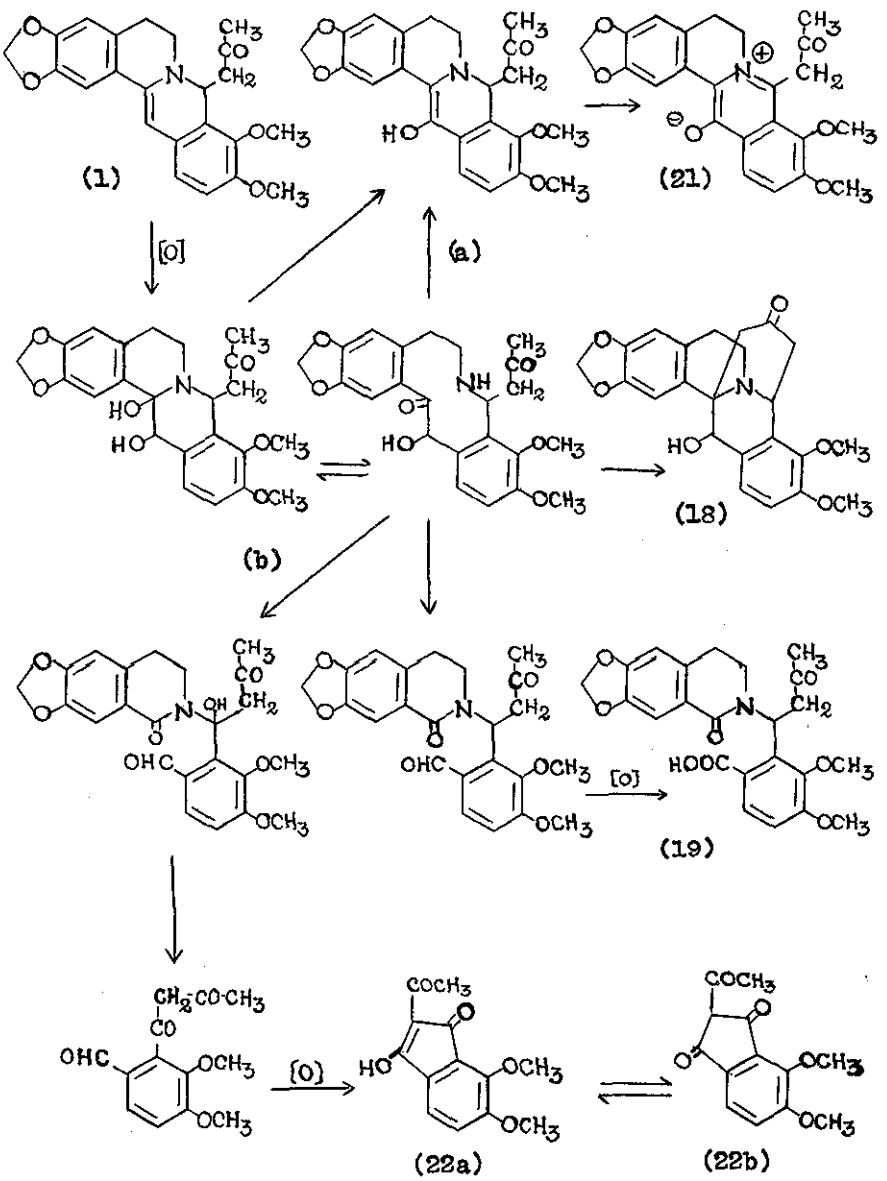


The formation of neoxyberberineacetone and other oxidation products from the acetone adduct was envisaged as follows.

Scheme 12

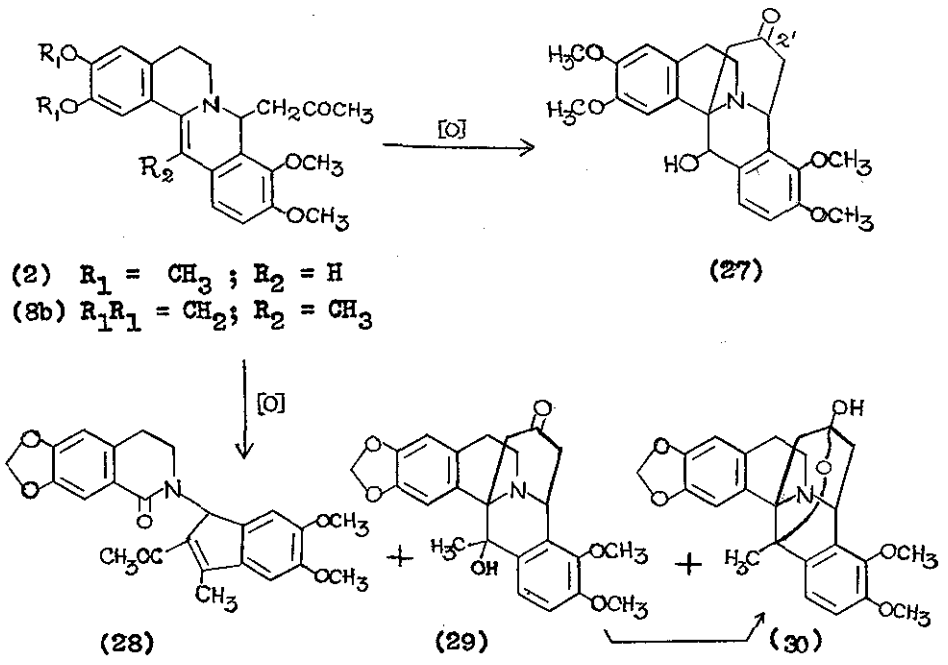


Scheme 13



Naruto and coworkers[16] extended their earlier studies[13] on oxidation of acetoneberberine to acetone adducts of other berberinium salts. They found that oxidation of acetone-palmatine (2) with potassium permanganate proceeded as in the case of acetoneberberine to give 8,13a-propanoberbine derivative (27). On the other hand, 13-methylacetoneberberine (8b) reacted with potassium permanganate to form mainly a lactam (28), as a result of the oxidative fission of C_{13}-C_{13a} double bond, together with minor 8,13a-propanoberbine products (29) and (30).

Scheme 14



(2) R_1 = CH_3 ; R_2 = H
(8b) R_1R_1 = CH_2; R_2 = CH_3

(27)

(28) major product

(29)

(30)

Lactam (28) is analogous to compound (19), as proposed by Kondo and Takemoto,[14] for the minor product of potassium permanganate

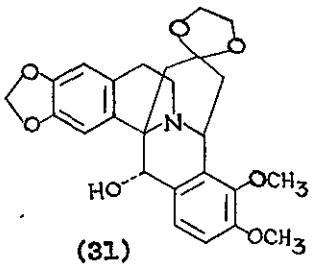
oxidation of acetoneberberine (1). However, it is interesting to note that oxidation of 13-methylacetoneberberine proceeds *via* oxidative fission of C_{13}-C_{13a} double bond, whereas 13-unsubstituted acetoneberberine type enamines are oxidised to give 8,13a-propanoberbine derivatives as major products. A rational explanation for the effect of the methyl group at the 13-position on the course of oxidation can not be given with the data available.[16]

1.3. Stereochemical Consideration of Neoxyberberineacetone

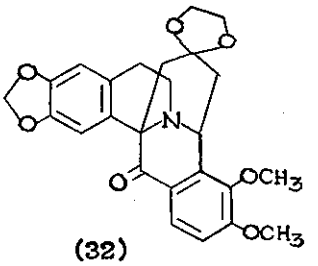
In 1969, Charubala, Nagarajan and Pai[17] had undertaken a study of the oxidation product of acetoneberberine and on the basis of pmr, ir and uv spectral data, they confirmed the structure proposed by Naruto *et al.*[13] for neoxyberberine acetone. They also attempted to solve the stereochemical aspects of the structure; these problems being (i) the nature of B/C ring fusion and (ii) the relative disposition of the 2'-oxopropano bridge and the OH group. Their work is summarised below.

Neoxyberberineacetone (18) was converted to the ethyleneketal (31), m.p. 196-198°, the ir spectrum of which lacked the saturated carbonyl band at 1705 cm^{-1}. This was oxidised with pyridine-chromium trioxide to the ketone (32), m.p. 277-278°. This showed an aromatic ketone band at 1670 cm^{-1} in the ir. The uv spectrum was also consistent with the presence of an aromatic ketone chromophore, in addition to the alkoxybenzene chromophore present in the starting alcohol (31). The ketoketal (32) was reduced with sodium borohydride to yield an alcohol (33), which appeared to be homogeneous on tlc and was different from the starting ketal alcohol (31).

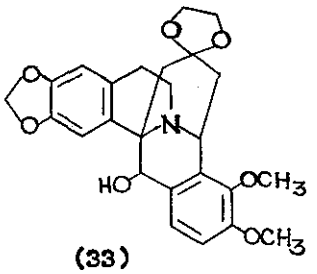
Scheme 15



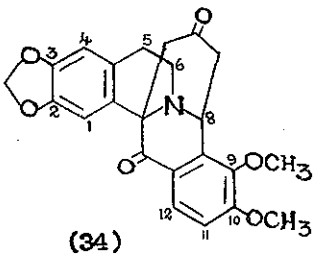
(31)



(32)



(33)



(34)

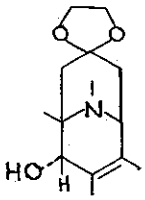
Neoxyberberineacetone (18) itself could be oxidised by pyridine-chromium trioxide to the diketone (34), m.p. 228-230°. It showed two bands in the ir spectrum in the carbonyl region, at 1680 and 1710 cm^{-1}, characteristic, respectively, of aromatic and saturated ketones. The uv spectrum of (34) was consistent with the presence of an aromatic ketone.

The oxidation experiment showed that a secondary benzyl alcohol group was present in neoxyberberineacetone, confirming the findings of the Japanese authors.

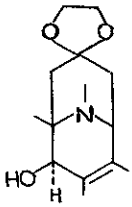
The reduction of ketalketone (32) by sodium borohydride to the alcohol (33) can be tentatively used to derive the relative stereochemistry. The " 2'-oxopropanoketal " bridge is a sterically bulky entity. The attack of sodium borohydride on the adjacent benzylic carbonyl must take place from the side opposite to this

bridge to give the cis alcohol (33). Since this is different from the starting ketal (31), the latter will have trans stereochemistry. (Naruto[18] also considered that hydroxyl group at C_{13} and propanobridge at C_{13a} were trans without adducing any reason.)

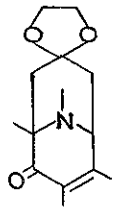
Scheme 16



(31)



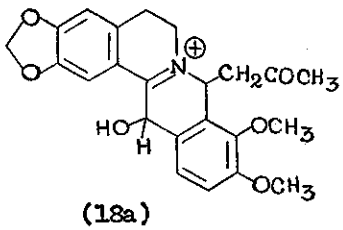
(33)



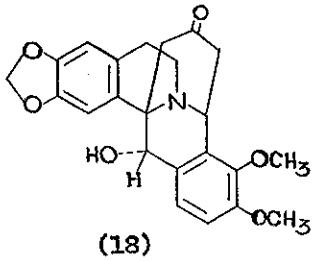
(32)

The same stereochemistry holds for neoxyberberineacetone (18) if the configuration of the hydroxyl group is assumed to be unchanged in the ketalisation process. A further factor in support of this stereochemistry is available from the mode of formation of (18). It is reasonable to assume that (31) arises from (18a) by the addition of active methyl to the iminium bond. Since this is more likely to occur from the side opposite to the OH group in (18a), the product (18) would have the OH and the 2'-oxopropano group in a trans configuration.

Scheme 17



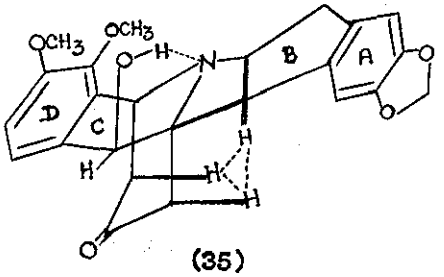
(18a)



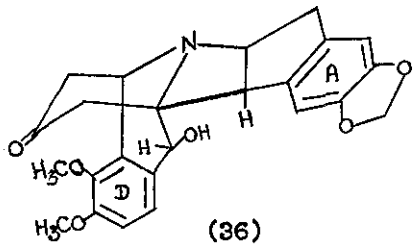
(18)

The B/C ring fusion in neoxyberberineacetone (18) was next considered. The mechanism of formation of (18) from berberine is such that the final product will have the thermodynamically more stable configuration. For tetrahydroberberine itself a trans B/C junction is considered more stable provided there is no bulky C_{13} substituent (vide infra). The 2'-oxopropano bridge in (18) makes the situation more complex. Dreiding model of neoxyberberineacetone (18) with a B/C trans-quinolizidine junction (35), has the 2'-oxopropano bridge in a cyclohexane ring, which is cis fused to the B ring and has two severe '1,4-diaxial' interactions (shaded bonds). But it has a relatively unhindered OH with possibilities to hydrogen bond with nitrogen.

Scheme 18



(35)



(36)

Of the two possible cis-quinolizidine ring junctions, in one the ketone bridge can not be built. The other one (36) has the 2'-oxopropano bridge in a cyclohexane, trans fused to the B ring. The Dreiding model shows one severe OH-H interaction. An assessment of the relative severity of these two interactions is not easy, but it may be reasonable to presume that structure (36) may be the less strained one from an overall point of view.

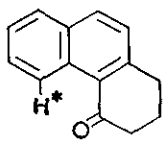
A study of the pmr spectrum of the diketone (34), which had the following features, seems to support a B/C cis-quinolizidine junction.

C_{12}	proton	:	doublet at 7.78 ppm (J=8.5 Hz) for 1H
C_{11}	proton	:	doublet at 6.92 ppm (J=1.5 Hz) for 1H
C_1	proton	:	singlet at 7.02 ppm for 1H
C_4	proton	:	singlet at 6.57 ppm for 1H
OCH_2O	protons	:	singlet at 5.93 ppm for 2H
C_8	proton	:	quartet at 4.85 ppm for 1H
OCH_3	protons	:	singlet at 3.93 ppm for 6H
other	protons	:	between 2.30 and 3.50 ppm.

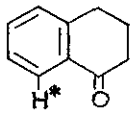
Examination of the Dreiding models of the diketone (34) having B/C trans or cis fusion shows that in the former, both the C_1 and C_{12} protons should be considerably deshielded by the C_{13} carbonyl group, the former more than the latter. The chemical shifts of the protons at C_{12} and C_1 can be expected to be comparable to those of the starred protons in structures (38) and (39) respectively. The chemical shift of the starred proton in structure (38) is 8.07 ppm; that of (39) with either trans or cis stereochemistry is unfortunately not available from the literature; but the chemical shift of the starred proton in the related compound (37)

is known to be 9.42 ppm.[19]

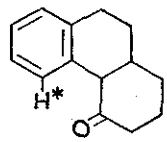
Scheme 19



(37)



(38)



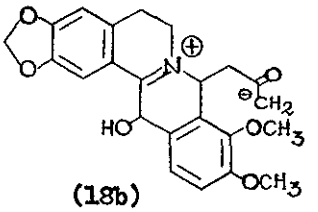
(39)

With a cis B/C ring fusion in (34) the carbonyl group at position-13 should selectively deshield the C_{12} proton and should have no effect on the C_1 proton. From the pmr spectral data cited earlier the C_{12} proton is seen to be selectively deshielded. Hence the B/C cis fusion in (34) is derived. As there is no reason to believe that in the oxidation of neoxyberberineacetone (18) to the diketone (34), the B/C ring fusion would have been affected, it can be speculated that structure (36) depicts the full stereochemistry of neoxyberberineacetone.

The presence or absence of Bohlmann bands in the ir spectrum has been used in protoberberine chemistry extensively for characterising the stereochemistry of B/C ring junction (vide infra). However this technique may not be applicable to neoxyberberineacetone (18), since two of the three carbon atoms adjacent to nitrogen are substituted. The 100 MHz pmr spectrum of (18) in $CDCl_3$ solution showed two or perhaps even three species to be present, and was thus of little use in the elucidation of geometry. Since the pmr spectra of ketal (32) and the diketone (34) showed but one species to be present, it can be inferred that an equilibrium is set up in solution among two or more diastereoisomers

corresponding to the gross structure of (18) through intermediacy of species (18b). Neoxyberberineacetone (18) itself is a homogeneous crystalline solid as judged by m.p. and tlc behaviour.

Scheme 20



(18b)

It thus appears that the intriguing problem of its three dimensional structure can be solved only by X-ray crystallographic method.

2. Stereochemistry of Tetrahydroprotoberberines

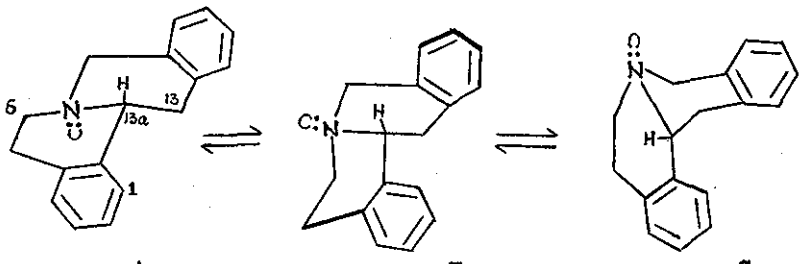
The dibenzo[a,g]quinolizidine structure forms the skeleton of the tetrahydroprotoberberine alkaloids. Bohlmann[20] has demonstrated that trans fused quinolizidines in which the nitrogen lone pair electrons are trans to at least two axial hydrogen atoms on carbons adjacent to it, show in their ir spectrum a group of prominent bands in the 2700-2800 cm^{-1} region. This criterion has often been used to assign trans fused conformation to such systems.[21] Kessar,[22] however, states that ir and pmr criteria as such are able to detect only the presence of trans fused conformations and are inadequate to exclude even substantial quantities of cis conformations. Most of the tetrahydroprotoberberines have 2,3,9,10- or 2,3,10,11- oxygenation pattern; and in all such cases the Bohlmann bands have invariably been observed and hence these have been considered to have the energetically favourable

trans-quinolizidine ring junction. Distortions and deviations however occur when positions-1,8 or 13 are substituted and these will be considered now. Tetrahydroprotoberberines carrying substituents at position-1 or 13 are treated in sections 2.1, 2.2, 2.3, 2.4 and 2.5 while those substituted at position-8, which have been discovered in nature very recently are dealt with in section 2.6.

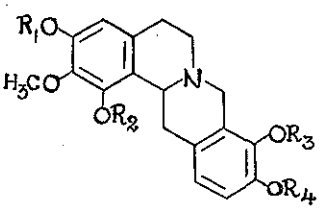
2.1. 1-Substituted Tetrahydroprotoberberines

X-ray analysis of the hydrobromides of (-)-capaurine (40) and (±)-isocapaurimine (41) and (-)-capaurimine-p-bromobenzoate (42) revealed that they exist in the cis-quinolizidine form B in the crystalline state.[23] All these alkaloids, as also compound (43) (the O-methyl ether of (40)), showed no Bohlmann bands in their ir spectra in chloroform solution consistent with deductions from their X-ray crystallographic study that they have ring B/C junction cis fused. Now if rings B and C of the dibenzo[a,g]quinolizidine assume half-chair conformations, it can be envisaged to exist as an equilibrium mixture of one trans A and two cis conformations B and C. The unsubstituted dibenzo[a,g]quinolizidine exists mainly in the thermodynamically stable trans-quinolizidine conformation.[24] In the capaurine series, it can be considered that an energetically unfavourable non-bonded interaction of the C_1 substituent with the C_{13} hydrogens destabilised the trans form A. Such an unfavourable interaction still remains in the other cis form C, which may be the least preferred one. Thus cis form B becomes more important for the 1-substituted tetrahydroprotoberberines. It was hence first inferred that 1-substituted tetrahydroprotoberberines exist in ring B/C cis configuration with B conformation.

Scheme 21



A B C

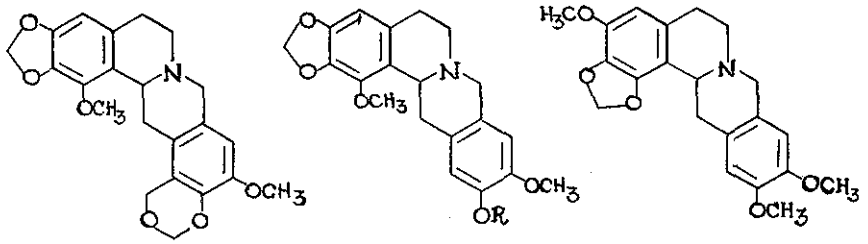


(40) $R_1 = R_3 = R_4 = CH_3$; $R_2 = H$ (-)-capaurine

(41) $R_1 = R_3 = H$; $R_2 = R_4 = CH_3$ (±)-isocapaurimine

(42) $R_1 = R_3 = CH_3$; $R_2 = H$; $R_4 = CO$-C$_6$H$_4$-Br (-)capaurimine-p-bromobenzoate

(43) $R_1 = R_2 = R_3 = R_4 = CH_3$ (-)-O-methylcapaurine



(44) (45) R = CH_2Ph (47)

(46) R = H

But the situation was not straightforward as the data in table I show. Thus Kametani et al.[25] concluded in conformity with Kessar's[22] earlier statement that Bohlmann bands in the crystalline

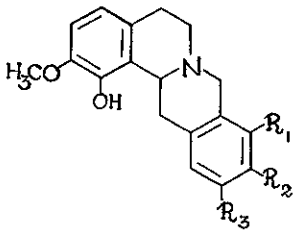
Table I

Compound No	Bohlmann bands	
	KBr	$CHCl_3$ Solution
(-)-(40)	Present	
(±)-(40)	absent	
(-)-(42)	absent	
(-)-(42) (R_4=H)	absent	
(-)-(43)	present	absent
(±)-(43)	absent	
(±)-(44)		absent
(±)-(45)	present	absent
(±)-(46)		absent
(±)-(47)	present	present

state provide ambiguous criteria and that there is a possibility that conformation of the quinolizidine system in the solid state may depend upon the crystalline nature.

Caseadine, caseamine and caseanadine are naturally occurring tetrahydroprotoberberines which have been assigned structures (48), (49) and (50) respectively.[26] Their ir spectra in chloroform solution show Bohlmann bands. Synthetic (±)-(48) also shows Bohlmann bands in chloroform solution. It may be worthwhile to examine by X-ray crystallography whether these alkaloids contain B/C cis or trans conformation (For a further discussion of the pmr spectrum of (48), see section 2.4).

Scheme 22



(48) R_1=H; R_2=R_3=OCH_3
(49) R_1=H; R_2=OH; R_3=OCH_3
(50) R_1= R_2=OCH_3; R_3=H

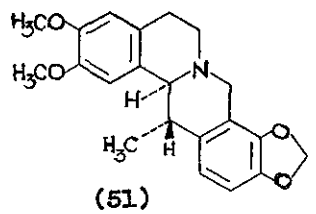
Thus while 1-unsubstituted protoberberines occur in the thermodynamically more stable trans conformation, the situation is not so clear in molecules with a substituent at position-1. Those with 1-OH, or 1-OCH_3 substitution may occur in cis-quinolizidine form. But 1,2-methylenedioxytetrahydroprotoberberines seem to occur only in trans conformation judging by the ir spectrum of (47). In the latter case, one wonders whether the C-O bond at position-1, being part of the 5-membered methylenedioxy ring is just a shade distorted in such a way as to reduce the steric interference between the oxygen atom and the hydrogen at C_{13}.

Very recently Takao and Iwasa[27] have carried out quantitative ir spectroscopic studies in the 2700-2800 cm^{-1} region to assess the usefulness of Bohlmann bands in deducing quinolizidine conformation. This is reviewed in section 2.3.

2.2. 13-Methyltetrahydroprotoberberines

The problem of the geometry of the quinolizidine ring assumes great importance in the case of 13-methyltetrahydroprotoberberines. Here invariably all naturally occurring 13-methyltetrahydroprotoberberines that are isolated have been shown to have the trans B/C ring except thalictrifoline (51), which is the only naturally occurring alkaloid of this series with cis B/C ring junction.[28]

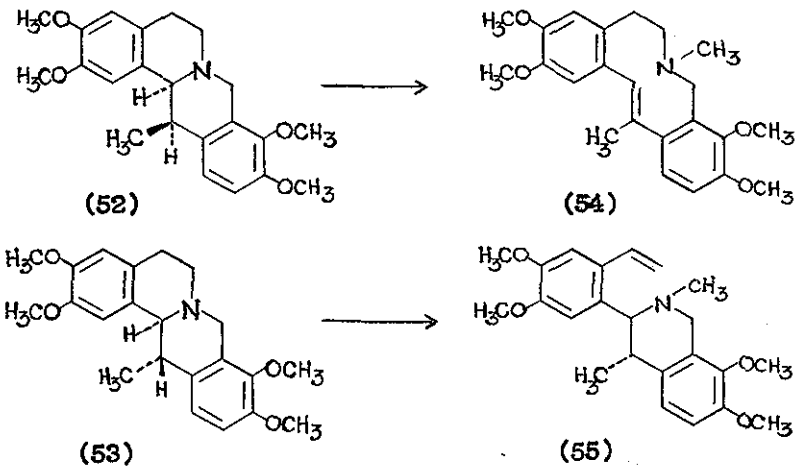
Scheme 23



(51)

13-Methyltetrahydroprotoberberine alkaloids could be oxidised to the corresponding berberinium salts and then reduced with lithium aluminium hydride, sodium borohydride or zinc and sulphuric acid, when a mixture of cis and trans isomers (with respect to substituents at C_{13} and C_{13a}) could be obtained. The first of two such stereoisomers studied are corydaline (52) and mesocorydaline (53). These were assigned the stereochemistry by Bersch[29] by subjecting them to Hofmann degradation and isolating two entirely different compounds. Corydaline (52) gave compound (54) and mesocorydaline (53) gave (55). Corydaline (52) showed Bohlmann bands in its ir

Scheme 24



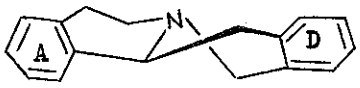
(52) (54)

(53) (55)

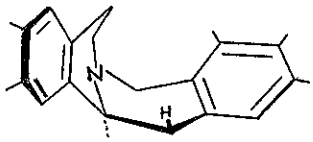
spectrum in solution, while mesocorydaline (53) did not. So corydaline was assigned the B/C trans and mesocorydaline B/C cis conformations. Jeffs[12,30] has given a critical account of the factors involved in the formation of two different Hofmann degradation products. Kondo[31] used the ease of oxidation of these two stereoisomers with mercuric acetate to the corresponding berberinium salts. Jeffs, contrary to Kondo's arguments, established that the B/C trans compounds are oxidised faster than B/C cis compounds. pK_a values have also been used to assign cis, trans conformations. The B/C cis compound is a stronger base than B/C trans compound and hence moves relatively slower on tlc than the trans compound.[32] One of the simplest and most elegant methods of assigning conformation has been that used by Shamma[32] i.e. the rate of methiodide formation.

The rate of quaternisation would depend upon the ease of approach of methyl iodide to the nucleophilic nitrogen. Examination of Dreiding models of the single trans and two cis-quinolizidines reveals that the nitrogen atom in the trans model is more hindered than the cis, and correspondingly will alkylate slower than the latter. It is also obvious that substituents at positions-13 and 8, and their conformation will have a profound influence on the rate. By use of this method, Shamma established in conformity with Kametani's work[23], that capaurine (40) and capaurimine (42, R_4=H) exist in a conformation with a cis B/C juncture with two half-chair rings (F in Scheme 25). The other tetrahydroprotoberberines to which conformations were assigned [32] by this method are canadine (25), tetrahydro-ψ-epiberberine (56), thalictricavine (57), mesothalictricavine (58) and compounds (59) and (60).

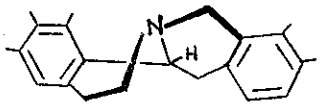
Scheme 25



D

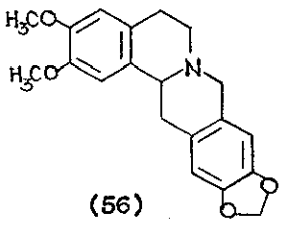


E

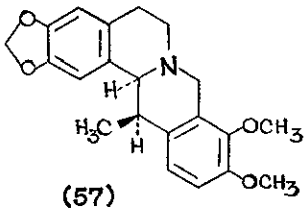


F

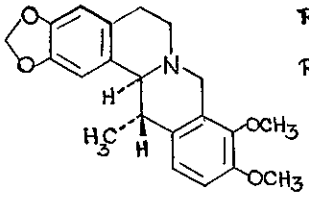
Scheme 26



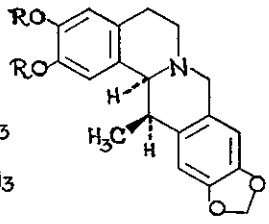
(56)



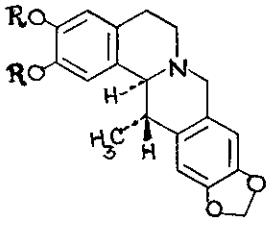
(57)



(58)



(59 R=CH_3)
(61 R+R=CH_2)



(60 R=CH_3)
(62 R+R=CH_2)

Recently, Kolb and Stefanovic[33] have commented that, of the different methods available for the determination of stereochemistry of the indolizidine and quinolizidine systems, the most reliable method is the measurement of the rate constants of quaternisation of the bridgehead nitrogen with methyl iodide.

Table II[34] gives the rate constants k for the methiodide formation of four 13-methyltetrahydroprotoberberines (59-62), from which it is clear that cis-quinolizidine compounds react at a much faster rate than their corresponding trans compounds, in agreement with the findings of Shamma et al.[32]

Table II

	trans-quinolizidine (59)	(61)	cis-quinolizidine (60)	(62)
Rate x 10^4 sec^{-1} (31.5°)	1.3 1.3[a]	6.4	99.62 341[a]	98.70
C-CH_3 doublet[b] δ, ppm	0.93	0.94	1.48	1.44
R_f (tlc, silica gel, $CHCl_3$:MeOH:EtOAc=40:1:2)	0.8	0.8	0.3	0.3

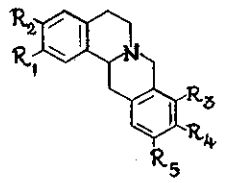
[a] at 25° ref.32 [b] vide infra

The value of k for the trans compound studied does not change significantly with temperature and the most likely conformation is A. The cis compound can exist in conformations B or C and is perhaps an equilibrium mixture in solution. At lower temperatures B is expected to be in preponderance, where the lone pair on nitrogen is not sterically hindered, while at higher temperatures, it perhaps has to move to conformation C, where the axial methyl

group comes in proximity to the nitrogen lone pair and this naturally makes the rate of quaternisation slower.

Kinetic data on quaternisation of alkaloids (25), (56) and (63-66) are presented in Table III.[34]

Table III

(±)-compound		substituents R_1	R_2	R_3	R_4	R_5	k x 10^4 sec^{-1} 31.5°
	(56)	OCH_3	OCH_3	H		OCH_2O	17.99
	(63)	OCH_3	OCH_3	OCH_2O		H	7.20
	(64)	OCH_2O		H		OCH_2O	10.67
	(65)	OCH_2O		OCH_2O		H	7.34
	(66)	OCH_2O		H	OCH_3	OCH_3	21.11
	(25)	OCH_2O		OCH_3	OCH_3	H	18.69

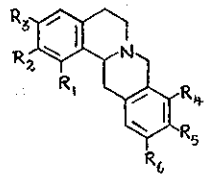
All these compounds have relatively lower reaction rates comparable to the trans-quinolizidine compounds of the C_{13} methyl series. Hence in accordance with the general view all these compounds exist in solution with B/C trans ring fusion.

The rate of quaternisation of the tertiary nitrogen in these compounds would depend upon the basicity also. So, the effect of substitution pattern on the basicity of nitrogen becomes another important factor besides stereochemical considerations of the different conformations. Here it must be borne in mind however that the stereochemistry by itself can influence the basicity. Table III indicates a trend towards faster rates for the 10,11-substituted compounds compared to those of the corresponding 9,10-substituted ones, considering the pairs (56) and (63), (64) and (65) and (66) and (25), which is in accordance with their

observed mobility on tlc. It is to be noted that all these are likely to have a trans quinolizidine junction and the difference in basicity is only due to the varying substitution pattern.

In Table IV[34] are given the rates of quaternisation of a few tetrahydroprotoberberines, which contain a phenolic group.

Table IV

(±)-compound		substituents R_1	R_2	R_3	R_4	R_5	R_6	k x 10^4 sec^{-1} 31.5°
	(67)	H	OCH_2O		OH	OCH_3	H	29.52
	(68)	H	OCH_3	OCH_3	OH	OCH_3	H	32.00
	(69)	H	OCH_3	OH	H	OCH_2O		40.30
	(48)	OH	OCH_3	H	H	OCH_3	OCH_3	44.00

All these four compounds have intermediate rates between the cis and trans-quinolizidine series. Their rate constants, particularly of (±)-(69) and (±)-caseadine (48) approach more towards the values that would be expected for the cis-quinolizidines, even after allowing for the increased basicity of these compounds because of 10,11-oxygenation. Shamma et al.,[32] while dealing with the stereochemistry of capaurine (40) and capaurimine (42 R_4=H). had pointed out that their rate constants 78 and 89 (both at 25°) were indicative of the predominance of cis-quinolizidine conformation. Similarly, it is possible to propose that (±)-caseadine (48) exists in solution preponderantly in the cis-quinolizidine conformation. However in view of our findings that phenolic tetrahydroprotoberberines have a faster rate of quaternisation compared to the corresponding alkoxy derivatives, it is obvious

that such deductions must be made with caution and may conceivably lead to wrong conclusions.

2.3 IR Spectroscopy - Bohlmann Bands

Takao and Iwasa[27] have recently made significant contributions to evaluate the use of Bohlmann bands in deciding the nature of the B/C ring junction in tetrahydroprotoberberines. For this purpose they studied 22 tetrahydroprotoberberines which were classified into three categories; class I containing 10 alkaloids, all of which had earlier been accepted to contain ring B/C trans, on the basis of the presence of Bohlmann bands; class II, capaurine (40), capaurimine (42 R_4=H)(and their derivatives), which had once been considered by Kametani et al.[35] as having trans B/C juncture on the basis of the presence of Bohlmann bands but later shown to have cis B/C ring juncture on the basis of X-ray crystallographic studies [23] and class III, meso-13-methyl (C_{13}-H, C_{13a}-H trans) tetrahydroprotoberberines, all which had been shown to belong to the B/C cis form, on the basis of pmr spectral data and the absence of Bohlmann bands.

The necessities for the study arose because there was some confusion and difference of opinion whether ir absorptions in the 2600-2830 cm^{-1} region can be considered to be Bohlmann bands without exception. The ir spectra of tetrahydroprotoberberines show two bands at ca 2750 and ca 2800 cm^{-1} (these bands being termed as X and Y bands respectively). The apparent molecular absorptivity (ε) and apparent integrated intensity (β) of these bands were measured. The magnitude of these values and the substitution pattern of rings A and D helped these authors to classify the alkaloids as mentioned above. A study of the

deuterated (at positions C_6,C_8 and C_{13a}) derivatives of alkaloids in class I enabled them to conclude that their X and Y bands were indeed Bohlmann bands. Extending their study and arguments to class III alkaloids, these authors concluded that although these were predominantly cis-quinolizidines, the B/C trans form was present as a minor, but definite component of the equilibrium mixture. These conclusions were substantiated by studies on the corresponding deuterated derivatives.

The results of studies on alkaloids of class II may be summarised as follows. Kametani et al.[23c] had attributed the X and Y bands of capaurine (40) to the OH group at C_1. However, it was found out that the X and Y bands do not change on deuteration of the OH group, showing that there was contribution from trans-quinolizidine and that the proportion of this form in the equilibrium mixture was lower than those in class III. This conclusion was also supported by pmr spectra. It was seen that among the alkaloids of group II the values of ε_x and ε_y decreased in the order of bulkiness of the substituent at C_1 i.e., $OH<OCH_3<OCOCH_3$ $<OCOC_6H_4Br$, with a corresponding increase of the cis component in the equilibrium mixture.

It may therefore be concluded that in tetrahydroprotoberberines, the B/C trans form should predominate overwhelmingly in the equilibrium mixture of class I and the B/C cis form in that of class III, while the position of the equilibrium would be shifted to the B/C trans side in the class II compared to class III. Since the substituents at C_1 and C_{13} are closer to each other in the B/C trans form than in the cis, substitution at these

positions should decrease the stability of the B/C trans form more than that of the B/C cis form, thus favouring the latter.

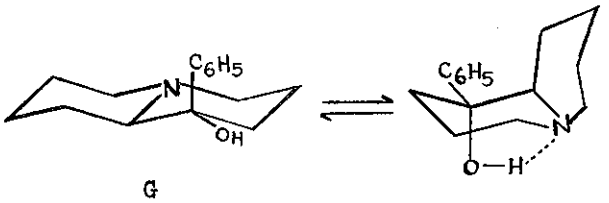
On the basis of the study of Bohlmann bands in the ir spectra in the crystalline state, Takao and Iwasa[27] concluded that in class I and III, the preferred conformation present in solution is retained in the crystal state, i.e., class I compounds adopt the B/C trans form and class III compounds the B/C cis form. In the alkaloids of class II, in which the position of the equilibrium is shifted in solution to the B/C trans side compared to class III, the crystal contains only one of the configurations, and it is interesting to note that in certain cases the nature of the B/C ring junction is different between the optically active compound and the racemate.

Thus Takao and Iwasa's quantitative studies validate Kessar's earlier qualitative proposals.[22] It clearly indicates the limitation of exclusive qualitative dependence on the Bohlmann bands for assignment of stereochemistry for B/C ring junction in tetrahydroprotoberberines and also establishes the fact that an equilibrium mixture of cis and trans (which may be preponderantly cis or preponderantly trans) forms exists, in practice, in all cases.

In this connection, it is interesting to point out that recently the ir spectra of trans-1,10-H-1-hydroxyquinolizidines have been studied [36] using long-path-length cells and 2% of the cis fused conformation detected in the equilibrium mixture. 1-Hydroxy-1-(phenyl-trans-10-H)-quinolizidine was shown to exist

as a conformational mixture of 60% trans fused (G) and 40% cis fused (H) ring conformations.[37]

Scheme 27



G H

2.4. PMR Spectroscopy in Assignment of Stereochemistry

2.4.1. 1-Substituted Tetrahydroprotoberberines

The angular proton at C_{13a} of a trans conformation in benzo[a]- and indolo[a]-quinolizidines resonates at a field higher than δ 3.8, whereas both cis conformations are characterised by a downfield signal below δ 3.80 for this proton.[38] However, it is normally difficult to observe this signal in the pmr spectra of tetrahydroprotoberberines in $CDCl_3$ solution, because the signals due to methoxyl groups appear at δ 3.80. When the spectra are taken in deuteriotoluene, the signals due to the angular protons are shifted downfield and separated from the signals due to the methoxyl groups. Kametani and coworkers[25] studied the pmr spectra of compounds in deuteriotoluene. (-)-O-Methylcapaurine (43), (±)-orientalidine (44) and (±)-(45) showed the angular proton at δ 4.26, 4.24 and 4.37 ppm respectively, as a quartet (J=12 and 4 Hz). On the other hand, the angular proton of the bases (47 and 64) appears at δ 3.96 and 3.50 respectively, as a quartet (J=15 and 4 Hz). From the above chemical shifts, it was deduced

that in the former three compounds the quinolizidine system adopted predominantly the cis conformation. The splitting pattern of the angular proton in (43), (44) and (45) suggests that the cis form is not C but B. The difference between the chemical shifts of the angular protons of 3-methoxy-1,2-methylenedioxytetrahydroprotoberberine (47) and (64) was considered to be due to the anisotropy of the oxygen substituent at the C_1 position in the former.

In this connection, it is interesting to report on caseadine with structural and stereochemical implications. Table V[39] gives the pmr spectral data of (-)-caseadine (48) and the synthetic compound (±)-(48) in $CDCl_3$ and C_6D_6.

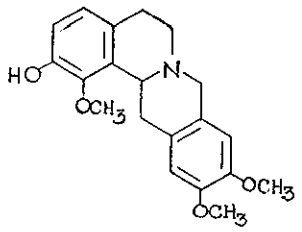
Table V

	220 MHz- PMR Chemical Shifts (δ, ppm)-			
	(-)-caseadine (48)		(±)-(48)	
	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
OCH_3	3.84(s)	3.21 (s)	3.85 (s)	3.22 (s)
	3.85 (s)	3.39 (s)	3.86 (s)	3.39 (s)
	3.87 (s)	3.49 (s)	3.89 (s)	3.49 (s)
C_{13a}-H	4.10 (q) (J= 12 and 4 Hz)	4.29 (q)	4.15 (q) (J= 12 and 4 Hz)	4.36 (q)
C_9 and C_{12}-H	6.58 (s)	6.42 (s)	6.59 (s)	6.39 (s)
	6.61 (s)	6.53 (s)	6.61 (s)	6.48 (s)
C_3-H	6.66 (d) (J= 8 Hz)	6.44 (d)	6.67 (d) (J= 8 Hz)	6.43 (d)
C_4-H	6.76 (d) (J= 8 Hz)	6.62 (d)	6.77 (d) (J= 8 Hz)	6.60 (d)

The 220 MHz pmr spectrum of both showed the angular proton at δ 4.15 and 4.10 ppm in $CDCl_3$ and at δ 4.36 and 4.29 in C_6D_6,

as a quartet (J=12and 4 Hz). This indicates that natural caseadine and the synthetic compound may exist in the cis conformation B. This proton was not identified in the natural alkaloid, but the presence of trans-quinolizidine nucleus was inferred only on the basis of the presence of Bohlmann bands in its ir spectrum.[26] Kametani et al.[40] and Iida et al.[41] have reported the pmr spectral data for the synthetic compound, but no mention has been made regarding conformation. The signal at δ 4.05 ($CDCl_3$) was however assigned to the angular proton.[40] The ir spectra of (-)-caseadine and of the synthetic compound in chloroform solution were found to be nonidentical both by Kametani et al.[40] and by us.[39] Kametani, therefore, suggested the alternative structure (70) for caseadine. Since ir spectra have been compared in solution, the

Scheme 28



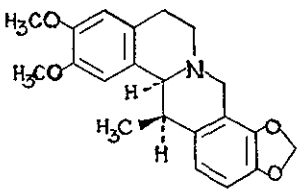
(70)

observed differences can not be attributed to differences in stereochemistry. On the other hand, as is seen from Table V, chemical shifts of various protons of caseadine and the synthetic (±)-compound are very close, especially those of the methoxyl groups which are practically identical. It appears somewhat doubtful whether (70) with a methoxyl at C_1 can account for this observation. The problem calls for further studies.

2.4.2 13-Substituted Tetrahydroprotoberberines

The stereochemistry of 13-methyltetrahydroprotoberberines have also been established by a study of their pmr spectra.[42,43] The group represented by thalictricavine (57) and cavidine (Base II) (71) was deduced to have a trans-quinolizidine and that by mesothalictricavine (58) and thalictrifoline (51) was considered to have a cis-quinolizidine system.

Scheme 29



(71)

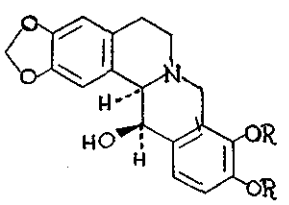
There are three noticeable differences between the two groups of diastereomers[42]-the chemical shift of the C-CH_3 group (see Table II), the coupling constant between the protons at C_{13} and C_{13a} and the chemical shift of the two protons at C_8. The chemical shift of the C-CH_3 in those compounds with cis hydrogens is about δ 1.0 while it is about δ 1.5 in the systems with trans hydrogens at these centres, an observation also made earlier by Shamma et al.[32] for two synthetic 13-methyltetrahydroprotoberberines. In the systems in which the hydrogens are trans, the C-CH_3 group lies nearly in the plane of ring D and is therefore deshielded. The coupling constants between H-13 and H-13a are about 3.0 Hz in the systems with cis hydrogens and about 7.5 Hz in the systems with trans hydrogens. In the trans fused system of corydaline (52), the C_8 protons have a large difference in chemical shifts,

δ 3.49 and 4.19; but in the cis fused system incorporated in meso-corydaline (53), this difference is quite small, namely δ 3.97 and 4.14.

In their independent and concurrent study, Govindachari et al.[43] have deduced the conformations for dl-thalictricavine (57) and dl-mesothalictricavine (58). In the former, the C-CH_3 was found as a doublet at δ 0.93 and in the latter at δ 1.43. Based upon this observation the α and β forms of tetrahydro-13-methyl-ψ-coptisine (61 and 62) were identified. The α-isomer had the methyl doublet at δ 0.94 while the β-isomer had this doublet at δ 1.44.[44]

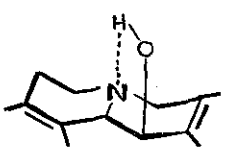
Ophiocarpine (72)[45, 12] and 13-β-hydroxystylopine (73)[46] are two 13-hydroxytetrahydroprotoberberine alkaloids. Based on ir and pmr spectral data, these alkaloids are shown to exist in B/C trans conformation with a hydrogen bonded hydroxyl, as indicated in the partial structure K.

Scheme 30



(72) R= CH_3

(73) R + R= CH_2



K

2.5. CMR Spectroscopy

2.5.1. 1-Substituted Tetrahydroprotoberberines

It was expected that some of the carbons of the cis-quinolizidines would resonate at a higher field than in the trans-

quinolizidine owing to γ-effects.[47] Kametani and coworkers[25] have pointed out that the preferential conformation in the dibenzo [a,g] quinolizidines can be determined by the comparison of the chemical shift of C_6. Tetrahydroprotoberberines with a hydrogen at C_1 show the signal due to C_6 at 54 $\pm$1 ppm, even if the pattern of the substituents on ring A and D are changed. Compound (47) showed the signal at 51.1 ppm, indicating a preference for trans-quinolizidine. For (-)-capaurine (42 R_4=H), (-)-O-methylcapaurine (43) and compounds (45) and (46), the signal due to C_6 appear at 49.3, 48.3, 47.1 and 46.9 ppm respectively. Owing to the steric interaction between the C_1-OR and C_{13}-hydrogens in these four compounds the quinolizidine conformation must be shifted over toward the cis form B.

2.5.2. 13-Methyltetrahydroprotoberberines

The stereochemistry of 13-methyltetrahydroprotoberberines was recently studied by the application of cmr spectroscopy.[48] It has been deduced from pmr studies that corydaline (52) is a trans-quinolizidine and meso-corydaline (53) is a cis-quinolizidine, in which the methyl groups are axial and equatorial respectively in ring C. The change from a trans to a cis conformation is evident in the upfield shift of carbons C_5,C_6,C_8 and C_{13} and is attributed to γ-gauche interactions [49] in the cis compound. On the other hand C_{13a} moves slightly downfield, a trend also observed in the quinolizidine systems. The methyl group also moves downfield as it changes from an axial to an equatorial position, and a similar shift is observed at C_1 (see Table VI).

Table VI
CMR Chemical Shifts (δ, ppm)

Compound	C_1	C_5	C_6	C_8	C_{13}	C_{13a}	C-CH_3
corydaline (52)	109	29.4	51.5	54.5	38.4	63.1	18.4
mesocorydaline (53)	112.1	28.1	47.0	51.1	34.6	64.2	22.4
cavidine (71)	108.8	29.3	51.3	53.4	38.7	63.2	18.5
thalictrifoline(51)	112.0	27.6	46.9	49.8	34.2	63.8	22.4
O-methylcapaurine (43)		30.0	48.3	53.3	33.0	55.5	

It is of interest that a similar downfield shift is observed in the proton spectrum at these two positions.[42] Both steric and anisotropic effects may play a role in causing the observed changes.

The analogous diastereomeric pair cavidine (71) and thalictrifoline were also examined and gave similar results.[48] It is apparent then that cmr spectroscopy may be used to assign the relative configuration to the 13-methyltetrahydroprotoberberines. However the changes occurring in carbon chemical shifts due to stereochemical changes are quite complex and differ according to whether substitution at position-1 or 13 is causing the distortion. Kametani et al.[25] found that the quinolizidine system is preferentially in the cis form, when a methoxy group is present at C_1, based on the upfield shift of the signal at C_6. Comparison of the published spectra of (43)[25] with those of (52), (53) and (71) revealed some interesting differences.[48] Whereas in the cis-quinolizidines like (53), C_5, C_6, C_8 and C_{13} all undergo upfield shifts relative to the trans-quinolizidines like (52), only C_6 and C_{13} are appreciably affected in (43). C_5 and C_8 of (43) are

negligibly affected as compared to the 13-methyl compounds. Thus the conformations of the cis-quinolizidines resulting from the methoxyl substitution at C_1 must differ appreciably from those of the cis-quinolizidines resulting from methyl substitution at C_{13}. The origin of this difference is not apparent from the data available and further work is necessary to resolve the problem.[48]

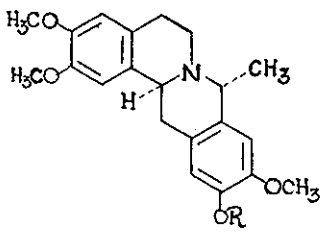
In this connection, Kametani et al.[25] have pointed out that chemical shifts of C_8 can be made use of to differentiate between 9,10 and 10,11-substituted tetrahydroprotoberberines. The C_8 of the 9,10-substituted compounds appeared at a higher field than 54.0 ppm, while the C_8 of the 10,11-substituted ones resonates at a lower field than 57.0 ppm. The steric perturbation by the C_9 substituent caused this difference, a fact which is useful for the structure determination of natural products. It is noteworthy that the signal of C_8 remains unaffected whether there is OH or OCH_3 at C_9.[48] The oxygen atom at C_9 thus appears to be implicated.

Yoshikawa et al.[50] studied the cmr spectra of quaternary protoberberines in deuteriotrifluoroacetic acid and determined their preferential conformations by comparison of the chemical shifts of C_6 and $N\text{-}CH_3$ groups.

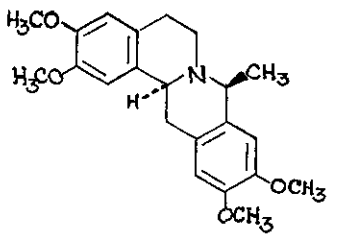
2.6. Stereochemistry of 8-Methyltetrahydroprotoberberines

Corytenchirine (74) is the first reported example of a naturally occurring 8-substituted tetrahydroprotoberberine,[51] although a synthetic compound coralydine (76) was known earlier.[52]

Scheme 31



(74) R=H
(75) R=CH_3

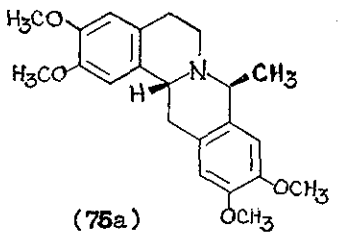


(76)

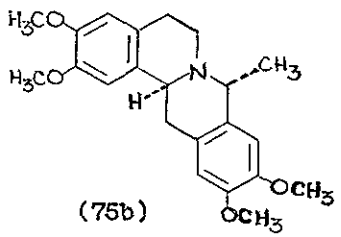
Coralydine (76) and O-methylcorytenchirine (75) are stereoisomers. Comparison of the pmr and ir spectra of these two compounds enabled these authors to determine their stereochemistry. The signal due to the methyl group of coralydine (76) at C_8 appeared at lower field (δ 1.53) than that of O-methylcorytenchirine (75) (δ 1.40) and the C_8-H signal of the former was at higher field (δ 3.6 - 3.8) than that of the latter (δ 4.06). The chemical shifts of C_8-H of both these bases were determined by a decoupling technique. In the ir spectrum, coralydine showed characteristic absorptions in the region 2700-2800 cm^{-1}, but O-methylcorytenchirine showed no absorption in this region. It was therefore deduced that the C_8-H of coralydine (76) is axially disposed and cis to C_{13a}-H (and hence B/C trans), whereas C_8-H and C_{13a}-H of O-methylcorytenchirine (75) are trans (and hence B/C cis). cis-Conformation of corytenchirine (74) is also supported by the chemical shift of C_6 (48.6 ppm).[53]

Brossi et al.[54] synthesised the optical isomers of coralydine (76a, 76b) and O-methylcorytenchirine(75a, 75b). trans-Juncture of ring B/C in (76a) was inferred from the presence of Bohlmann

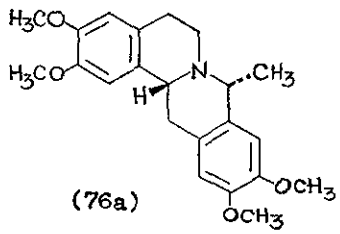
Scheme 32



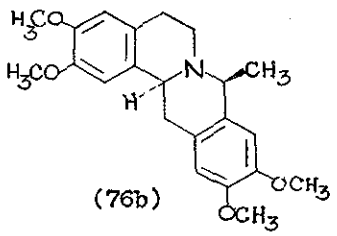
(75a)



(75b)



(76a)



(76b)

bands in its ir spectrum in chloroform; the absence of these bands in the case of (75a) showed a cis B/C fusion. Since the authors felt that the ring junction in tetrahydroprotoberberines, as well as the conformation of the hydrogen at position-8 can not be unequivocally derived with the help of pmr and cmr spectra, X-ray analyses of the bases (+)-coralydine (76a) and O-methylcorytenchirine (75a) were carried out. In the case of coralydine, the C_8 methyl group and C_{13a}-H have the same R-configuration; B/C ring carbons trans fused. In O-methylcorytenchirine (75a) B/C rings are cis fused; the configuration of methyl group at C_8 is S, the hydrogen atom at C_{13a} is R. X-ray analysis of 2,6-dibromo-4-nitrophenolate of (75a) however yielded surprising result; this salt exists as a diastereomeric mixture of equal proportions of cis and trans fused quinolizidines. The existence of a mixture was also noted from the pmr spectrum of the protonated

form of (76a) which was seen to exist as a 1:1 mixture of cis and trans-quinolizidines. However, the bases recovered from the acidic solution appeared once again in the original pure cis or trans-quinolizidine forms.

It may be commented here in passing that this is perhaps a unique instance wherein a conformational change of protoberberine brought about by acid has been demonstrated by pmr spectroscopy. Variable temperature pmr studies of protoberberines substituted at C_1, C_8 or C_{13} must throw valuable light on conformations and their equilibria and may be worthwhile to undertake.

2.7. Absolute Configuration

The assignment of absolute configuration of alkaloids of the tetrahydroprotoberberine series has been well reviewed by Jeffs[12] and recently by Kametani.[55] The absolute configuration of tetrahydroprotoberberines has been established chemically and spectroscopically. Among the 13-methyltetrahydroprotoberberines, those belonging to the corydaline (52) series, having a trans-quinolizidine system have been assigned absolute configuration based upon the similarity of their ord spectra to that of canadine (25). It was assumed that the substituent at position-13 in the corydaline series will not affect the ord spectrum significantly. However this can not be extended to thalictrifoline (51), since this has a different (cis) geometry for the quinolizidine system. The problem awaits solution either by X-ray crystallographic study or chemical means. The exciton chirality method[56] may also find a fruitful application in this problem.

Interesting results were obtained in the attempted synthesis of (±)-thalictrifoline. If successful they were to be extended to

the problem of resolving the absolute configuration. These results are presented in section 6.

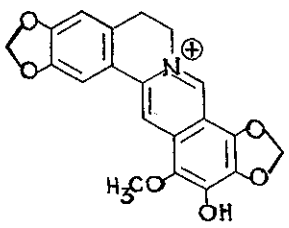
3. PMR Spectroscopy in Assigning Positions of Substituents

An earlier section (2.4.) dealt with the use of pmr spectroscopy in elucidating stereochemistry. This section describes its considerable application in locating peripheral substituents.

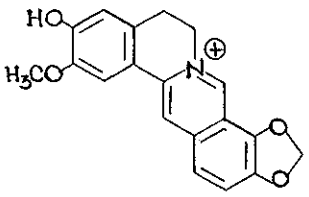
Oxygenation pattern in ring D of tetrahydroprotoberberines may be deduced from an examination of the protons at C_8. In the case of 9,10-substitution, an AB quartet is invariably observed ($\delta_A \sim 4.35$, $\delta_B \sim 3.65$, $J_{AB} \sim 16$ Hz), but the high field segment is likely to be obscured by methoxyl signals. In alkaloids with 10,11-substitution the C_8 protons appear to be a broad singlet (δ 4.05) partially underlying the O-methyl signals.[57]

Jewers and coworkers[58] studied the pmr spectra of nineteen different protoberberinium salts. In the light of this study, they found that the published pmr data of alkaloid B (77) isolated from Coptis groenlandica[59] was inconsistent with the structure assigned. They revised the structure as (78) and gave it the trivial name groenlandicine. This structure has recently been confirmed by the synthesis of its tetrahydro derivative,[60] which

Scheme 33



(77)



(78)

was found to be identical with the tetrahydro derivative of alkaloid B..

Suguna and Pai[61] examined the chemical shifts of the methylenedioxy group attached to $C_{2,3}$, $C_{9,10}$ and $C_{10,11}$ positions both in protoberberinium salts and the corresponding tetrahydroprotoberberines. In the case of tetrahydroprotoberberines the chemical shifts of methylenedioxy protons are very nearly the same (δ 5.93 ± 0.07) whether the group is in position $C_{2,3}$, $C_{9,10}$ or $C_{10,11}$. But in the case of berberinium salts the protons of methylenedioxy group at $C_{2,3}$ are observed at δ 6.10, while the protons of the methylenedioxy group at $C_{9,10}$ or $C_{10,11}$ are shifted downfield to about δ 6.40, presumably due to the greater aromaticity of ring C compared to that of ring B.

Naruto et al.[62] inferred the location of the methoxy and hydroxy groups in ring D of 2,3,9,10-substituted tetrahydroprotoberberine type alkaloids from the signal pattern of the aromatic proton region of the pmr spectra measured in dimethyl sulphoxide-d_6 solution. They pointed out that those compounds with C_9-OH and C_{10}-OCH_3 show the signals due to C_{11} and C_{12} protons as an AB quartet (J=8.5 Hz), while those having $C_{9,10}$-dimethoxy (or C_9-OCH_3 and C_{10}-OH) groups show the signal of C_{11} and C_{12} protons as a singlet of coincident chemical shift. The structure of capaurimine (42 R_4=H) was thus established, since the C_{11} and C_{12} protons appear as a singlet at δ 6.65.

In connection with the studies on the tautomerism of quaternary salts, Santavy et al.,[63] observed that the chemical shifts of the protons at C_8 and C_{13} in protoberberinium salts is

affected by the position of the substituents of the aromatic nucleus D. Substitution by a methoxyl group at C_9 and C_{10} causes a slight diamagnetic shift (0.02-0.04 ppm) of the signal of the proton at C_8 corresponding to its position in the unsubstituted compound. Substitution by methylenedioxy group causes a diamagnetic shift of the signal of this proton by about 0.27 ppm. Oxygen substituents at C_{10} and C_{11} cause an upfield shift of this proton by 0.37 ppm (dimethoxy groups) and by 0.60 ppm (methylenedioxy group). The change in the chemical shift shows that the electron accepting effect of quaternary nitrogen is smaller when substitution in the positions 10,11 takes place compared to that in the positions 9,10. In either case, the signal of the resonance of the proton at C_{13} is shifted upfield due to substitution with methoxyl compared to that on substitution by a methylenedioxy group The position of this signal is not affected by the change in the position of the substituents from C_9 to C_{11}. The chemical shift of the proton at C_{13} is only affected by a different inductive effect of the oxygen substituent at C_{10} (OCH_3 or OCH_2O).

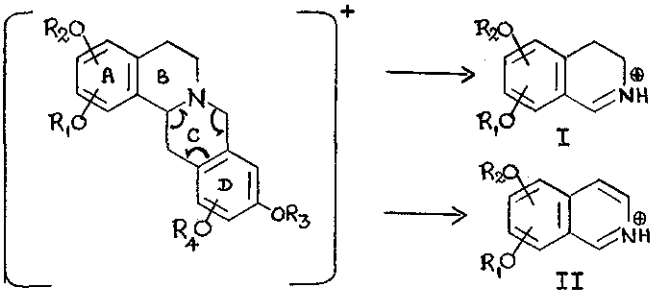
On conversion of the quaternary salt into a pseudo base, the chemical shifts were pushed upfield, the most marked shift was that of the hydrogen at C_{13} (2.6 to 2.9 ppm).[64]

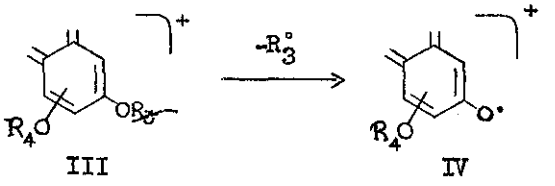
4. Mass Spectrometry

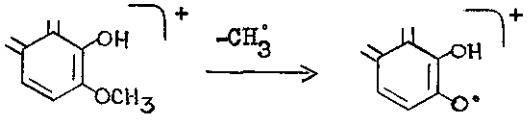
Tetrahydroprotoberberines undergo facile fission at the two benzylic bonds as shown in Scheme 34 in what amounts to a retro-Diels-Alder reaction. The mode of formation of ions II, III and IV has been discussed by Ohashi et al.[65] Those alkaloids with a hydroxyl group in ring D are characterised by the presence of a base peak corresponding to ion I. Moreover, 9-hydroxy-10-methoxy

compounds may be differentiated from their 9-methoxy-10-hydroxy analogues. Those with the former substitution pattern preferentially expel a methyl radical from the equivalent of ion III, yielding an ion m/e 135, whereas the latter lose a hydrogen radical giving rise to a new ion at m/e 149. But it is not

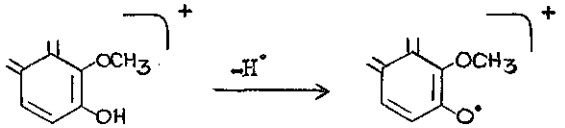
Scheme 34







m/e 150 m/e 135



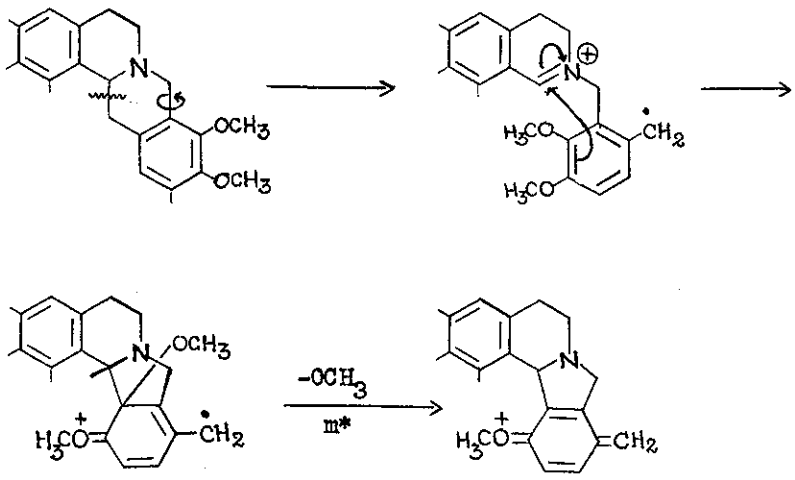
m/e 150 m/e 149

possible to differentiate between a 10-hydroxy-11-methoxy compound and another with a reverse arrangement, because ion III from the two systems are equivalent.

In tetrahydroprotoberberines with 9,10-dimethoxy substitution, the molecular ion and ion IV are more intense relative to the base peak of the spectrum, than they are in those with 10,11-dimethoxy substitution.[57]

Richter and Hanssen [66] studied the mass spectral fragmentation pattern of 23 different tetrahydroprotoberberines. 9-Methoxy tetrahydroprotoberberines were found to exhibit pronounced $(M-OCH_3)^+$ ions in their mass spectra as compared to isomers or homologues lacking such substitution, yet carrying methoxyl substituents at other sites. The proposed mechanism for this preferential loss of 9-substituent is as follows.

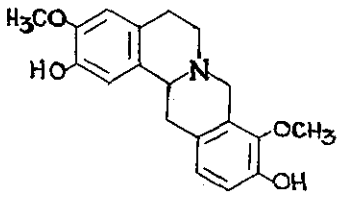
Scheme 35



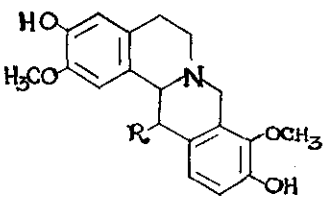
Cleavage of 13,13a- bond severing ring C is for obvious energetic reasons, the most favourable introductory step probably responsible for most of the fragmentation processes observed within this class. One of the conceivable pathways enabling re-cyclisation of the resulting 'open' molecular ion by ionic (in contrast to radical type) attack at C_9 can be visualised as shown.

(-)-Stepholidine (79), which was earlier isolated and whose structure was assigned by two different group of workers,[67,68] was shown to exhibit a significant ($M-OCH_3$) peak at m/e 296, thus confirming the 9-methoxy substitution.[66] This structure has recently been confirmed by its synthesis through different routes.[69] Similarly, discretamine[70] was assigned structure (80); this was synthesised by Tani et al.[5] in connection with the synthesis of corydalidzine (81) though the synthetic compound has not been compared with the natural sample.

Scheme 36



(79)



(80) R=H
(81) R=CH_3

Berberine and other pseudobases do not exhibit the expected molecular ion peak. Instead it was found that berberine disproportionates into dihydroberberine and oxyberberine.[71]

Mass spectral fragmentation of tetrahydroprotoberberine

methiodide is initiated by pyrolytic decomposition with elimination of hydrogen iodide or methyl iodide. The resulting spectrum is considerably similar to that of the corresponding tetrahydroprotoberberine; it contains predominantly fragments of the tertiary alkaloid formed by pyrolysis. The constitution of escholidine iodide was thus studied by Slavik et al.[72] Several other quaternary metho salts were also found to behave similarly.[73]

5. Ultraviolet Spectroscopy

Tetrahydroprotoberberines absorb in 282-289 nm region with occassionally a shoulder near 230-240 nm. Substantial absorption also occurs around 210 nm, but generally this band has not been reliably recorded or has gone unmentioned. Tetrahydroprotoberberines substituted at $C_{2,3,10,11}$ can not be readily differentiated from their $C_{2,3,9,10}$ analogues.[74] Introduction of a methylenedioxy instead of two methoxyl groups gives rise to a bathochromic shift of the uv absorption bands at 282-289 nm and at 230-240 nm.[75]

A drastic alteration of the uv spectrum occurs, however in the case of protoberberinium salts when changing from 9,10- to 10,11-substitution pattern. The 9,10-substituted salts show a minimum at 301-310 nm, while their 10,11-counterparts show strong absorption in this region, in the form of a peak or a shoulder.[74]

There does not seem to be a record of shifts in uv spectra of phenolic tetrahydroprotoberberines in the presence of sodium hydroxide, when the hydroxyl group is in different positions of

the aromatic nucleus. The uv spectra of tetrahydroprotoberberines with hydroxyl group in different positions were run in alcohol and alcohol + 0.1 M sodium hydroxide solutions. The alkali induced shift was about 5 to 6 nm in compounds containing one hydroxyl group.[76] This shift does not seem to be of help in fixing up the position of the hydroxyl group in the tetrahydroprotoberberine skeleton, unlike as in the case of aporphines.[77]

The effect of anions and also the effect of the polarity of the solvent on the position of the uv bands of protoberberinium salts were studied by Preininger et al.[78] The differences between the uv spectra of 9,10-substituted protoberberinium and the corresponding 10,11-substituted protoberberinium bases are caused by the location of the substituents in the aromatic ring D. The electron donor oxygen substituent at C_{11} has a considerable effect on the polarity of the isoquinoline system, which is responsible for the differences observed in the position of uv bands in these pseudobases. The tautomerism of the quaternary bases of 9,10- and 10,11-substituted protoberberinium compounds has been studied by uv spectroscopy.[63] Pseudobase formation by addition of a methoxide ion has also been studied by uv spectroscopy in eighteen different protoberberinium cations.[64]

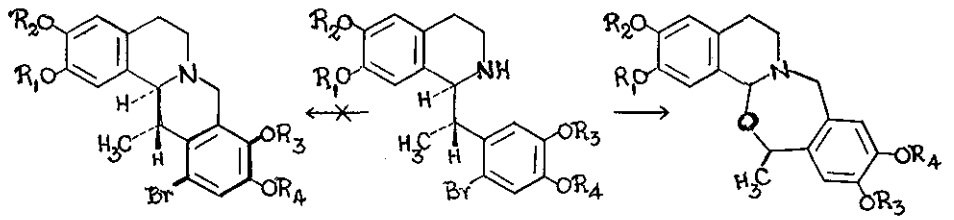
6. Synthetic Experiments

The methods in use for the synthesis of tetrahydroprotoberberines and berberinium salts have been exhaustively reviewed by Pelz,[79] Shamma[24] and Kametani.[55] Some of the recent publications which have dealt with synthetic aspects are by Shamma and Georgiev,[80] Nagata et al.,[81] Ninomiya et al.[82] and by Lenz.[83]

Cavidine (71) and Base II have recently been compared[84] and were found to be identical. Base II was synthesised by Ninomiya et al.[82] Dehydrobase II was found to be identical with dehydrothalictrifoline [85] and it was further reduced to (±)-thalictrifoline (51) and (±)-cavidine(71). Much before the appearance of this publication, Natarajan et al.[86] had initiated the synthesis of (±)-thalictrifoline (51) by an extension of the method employed by Shamma for 13-methyltetrahydroprotoberberines.[32] The goal was not realised but interesting results were obtained, which are reported here. Compound (82a) was prepared (which is the only diastereoisomer obtained on reduction of its dihydroisoquinoline precursor, probably due to the steric influence of the bromine substituent) and subjected to Mannich reaction under a variety of conditions. Interestingly, the product of the reaction was not the expected (±)-12-bromothalictrifoline (83a), but a rearranged product, whose structure was established as a hexahydrooxazepinoisoquinoline represented by (84a). The novel reaction has been extended[87] to two other analogues (82b and 82c). The structure of (84b) was confirmed by X-ray studies and a reasonable mechanism for this transformation has also been proposed.[86] Experiments have been carried out to check the stereospecificity/selectivity of the transformation.[87]

The Mannich reaction thus having failed to give the required product, the N-formyl derivative (85a) of (82a) was prepared and then subjected to phosphorous oxychloride cyclisation, followed by reduction with sodium borohydride. The products obtained were the two diastereoisomeric 10,11-substituted tetrahydroprotoberberines (59) and (60). These two products were also obtained

Scheme 37



(83) (82) (84)

a) $R_1 = R_2 = CH_3$; $R_3 + R_4 = CH_2$
b) $R_1 + R_2 = CH_2$; $R_3 + R_4 = CH_2$
c) $R_1 + R_2 = CH_2$; $R_3 = R_4 = CH_3$

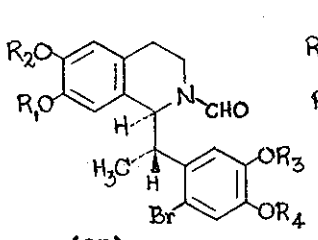
when freshly distilled phosphorous oxybromide was used. However, when crude(undistilled) phosphorous oxybromide was the cyclising reagent, it was noticed, after sodium borohydride reduction, that apart from (59) and (60) another compound (86a), which had the bromine intact,was isolated in very small amounts.[88] It was found that a mixture of phosphorous pentoxide and phosphorous pentabromide (2:1) in benzene effected the cyclisation very well giving rise to four products, two of which contained bromine (86a) and (87a) and the other two were (59) and (60). The two bromo compounds on debromination gave (59) and (60), respectively, thus indicating that the original bromine was eliminated before cyclisation and subsequent rebromination had taken place. That the bromine in (86a) and (87a) was in ring A, and not in ring D was shown by mass spectrum and the most probable position was fixed as C_4 based on steric considerations. A point in favour of using phosphorous pentoxide-phosphorous pentabromide mixture is that the total yields are good (75-80%)and reproducible and that both the cis and trans-

quinolizidine isomers are obtainable in equal amounts. This method was extended to (85b) and similar results were obtained.[89]

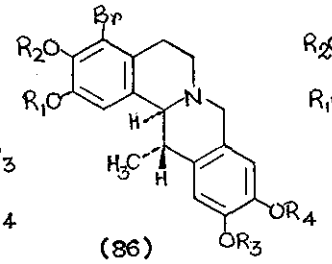
Scheme 38

(85a) ——— (59) + (60) + (86a) + (87a)

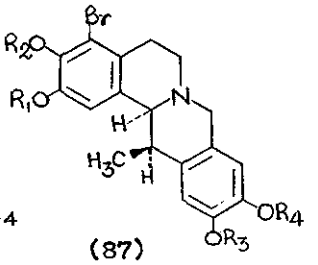
(85b) ——— (61) + (62) + (86b) + (87b)



(85)



(86)



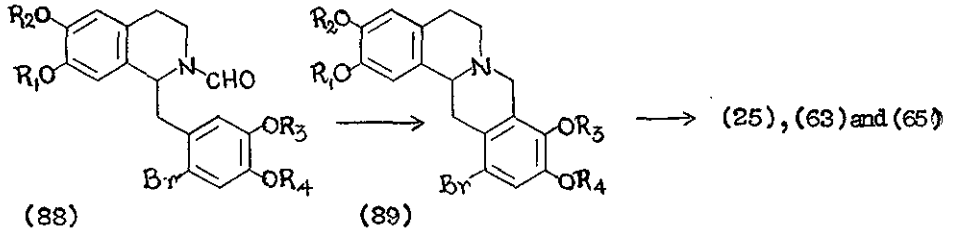
(87)

a) $R_1 = R_2 = CH_3$; $R_3 + R_4 = CH_2$

b) $R_1 + R_2 = R_3 + R_4 = CH_2$

When there is no methyl group in the α-position of the N-formyl-1-benzyl-1,2,3,4-tetrahydroisoquinoline, as in (88), cyclisation by crude phosphorous oxybromide followed by sodium borohydride reduction gave rise to 12-bromo compounds, in rather low yields, which could then be debrominated to the 9,10-oxygenated tetrahydroprotoberberines. Accordingly Pai and coworkers[90] synthesised dl-canadine (25), dl-sinactine (63) and dl-stylopine (65).

Scheme 39



(88) (89) → (25), (63) and (65)

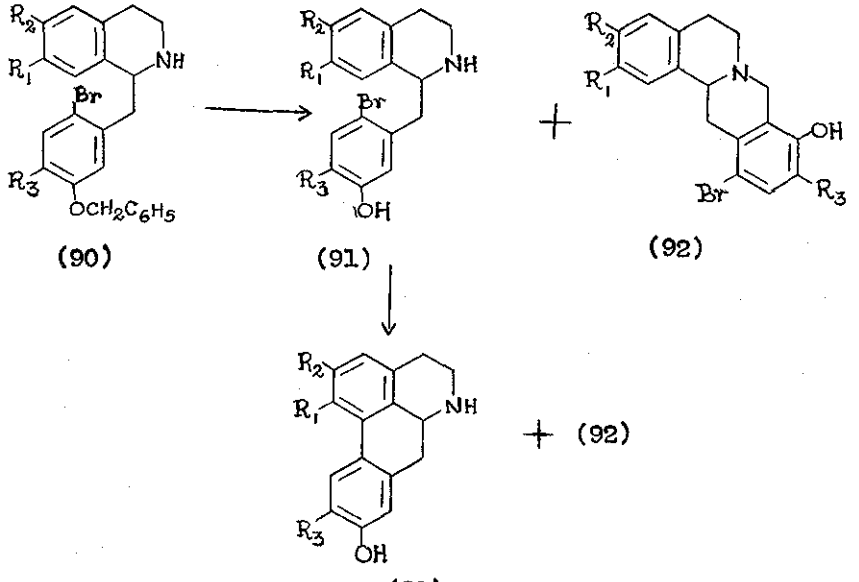
a) $R_1 + R_2 = CH_2$; $R_3 = R_4 = CH_3$

b) $R_1 = R_2 = CH_3$; $R_3 + R_4 = CH_2$

c) $R_1 + R_2 = R_3 + R_4 = CH_2$

Interesting formation of tetrahydroprotoberberines has also been observed during the course of the photochemical synthesis of phenolic noraporphines. For this synthesis it became necessary to prepare a number of 1-(5-benzyloxy-2-bromobenzyl)-1,2,3,4-tetrahydroisoquinolines with one or more methoxyl groups in either ring A or C of the benzylisoquinoline. During the debenzylation of these tetrahydroisoquinolines (90) to give the corresponding phenolic bases (91), it was observed that in addition to the expected bases, 12-bromotetrahydroprotoberberines (92) were invariably formed. When the phenolic isoquinolines (91) were

Scheme 40



(90) (91) (92)

(93) + (92)

(90),(91),(92) and (93) a) $R_1 + R_2 = OCH_2O$; $R_3 = OCH_3$

(90),(91),(92) and (93) b) $R_1 + R_2 = OCH_2O$; $R_3 = H$

(90) c) $R_1 = OBz$; $R_2 = R_3 = OCH_3$

(91),(92) and (93) c) $R_1 = OH$; $R_2 = R_3 = OCH_3$

subjected to photolysis, besides the expected noraporphines (93), 12-bromotetrahydroprotoberberines (92) were again found among the other products of reaction.[91] This was further investigated in compounds having different substituents and in all cases, similar observations were made.[92] The 12-bromotetrahydroprotoberberines have been debrominated catalytically. This study has recently been extended to an ethoxy substituted compound and preliminary investigation shows that an 8-methyltetrahydroprotoberberine is formed both during debenzylation and photolysis.[93]

When we finalised this manuscript, our attention was drawn to an interesting article by Pavelka and Kovar,[94] which deals with the synthesis and absorption spectra of some 13-alkyl, 13-alkoxy, 9-alkoxy and 8-oxo derivatives of berberine and the related compounds.

Acknowledgement

The authors thank the Council of Scientific and Industrial Research, New Delhi, India for a Post-doctoral Fellowship to H. Suguna and a Scientific Pool Officership to S. Natarajan.

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Received, 6th June, 1977