

Chapter IV

Discussion

There was no previous report on the chemical constituents of the stem bark of *Fissistigma polyanthoides*. In this present work, the isolation of two flavonoids and an alkaloid were carried out. The structures of these compounds were elucidated by analysis of spectroscopic data.

Structure elucidation of compound HEX-A

Compound HEX-A was obtained as yellow-gold prism crystal.

The ei mass spectrum (Figure 8, page 83) exhibited molecular ion peak at m/z 332 (50%) thus the molecular formula should be $C_{18}H_{20}O_6$ with an index of hydrogen deficiency of 9.

An absorption band at 3434 cm^{-1} in its ir spectrum (Figure 9, page 84) indicated the presence of one or more hydroxyl group in the structure. An absorption band at 1605 cm^{-1} suggested the presence of carbonyl function in the structure.

An integration curve of ^1H NMR spectrum (Figure 12, page 87) gived, 9 signals with ratio 1:1:4:1:3:3:3:2:2 for a total of 20 hydrogen atoms. The ^1H NMR spectrum

exhibited three methoxy singlets at δ 3.8, δ 3.87 and δ 3.99 ppm and two hydroxy singlet at δ 12.41 and δ 7.55 ppm. The multiplicity low field signals ranging from δ 7.15 to δ 7.27 ppm established five aromatic protons while a doublets of doublets signals at δ 2.99 and δ 3.41 ppm established the two methylene protons at C- β and C- α of the dihydrochalcone nucleus.

The ^1H , ^1H COSY spectrum (Figure 14, page 89) exhibited the coupling of the protons at C- α and C- β .

The ^{13}C NMR spectrum (Figure 15, page 90) exhibited 16 signals thus should established 16 carbon atoms in the structure but from the calculated molecular structure there must be 18 carbon atoms. This suggested that there must be 2 pairs of equivalent chemical shifts of carbon atoms.

This is supported by ^1H , ^{13}C COSY spectrum (Figure 16, page 91) showing correlation between protons and carbons, to which it attached. The carbon signals at δ 45.85 and δ 30.98 ppm showed correlation with proton at δ 3.41 and δ 2.99 ppm respectively. The three signals of carbon atoms at δ 60.87, δ 61.07 and δ 61.41 ppm showed correlation with the signal of three methoxy protons at δ 3.80, δ 3.87 and δ 3.98 ppm respectively.

The assignments of the carbon signals and the position of the substituents were evidenced by COLOC spectrum (Figure 18, page 93). The long range coupling of the carbons at δ 137.52, δ 144.95 and δ 148.79 ppm to the methoxy protons at δ 3.80, δ 3.87 and δ 3.98 ppm suggested the positions of carbons to which the methoxyl group attached.

There were no long range coupling of these three carbons to other protons except the hydroxy proton suggested that the three methoxyl groups and one hydroxyl group should be on the ring A. The long range correlation from H on C are summarized in Table 4.

Table 4 ^{13}C and ^1H NMR assignments of compound HEX-A with long-range correlation data between carbons and protons

Position	C (δ ppm)	H (δ ppm)	long-range correlation from C on H observed in COLOC spectrum
1	142.50	-	-
2	129.24 ^a	7.27	-
3	129.18 ^a	7.27	-
4	126.69	7.15	-
5	129.18 ^b	7.27	-
6	129.24 ^b	7.27	-

Table 4 ^{13}C and ^1H NMR assignments of compound HEX-A with long-range correlation data between carbons and protons (cont.)

Position	C (δ ppm)	H (δ ppm)	long-range correlation from C on H observed in COLOC spectrum
1'	111.39	-	2'-OH
2'	150.91	-	-
3'	137.52	-	3' - OCH ₃ , 2' -OH
4'	148.79	-	4' - OCH ₃ , 5' -OH
5'	136.07	-	5' - OH
6'	144.95	-	5'-OH, 6'-OCH ₃
α	45.85	3.41 (2H, dd, $J=7.63, 8.64$)	
β	30.98	2.99 (2H, dd, $J=7.63$)	H-2, H-6
CO	208	-	β
3'-OCH ₃	60.87	3.80 (3H, s)	-
4'-OCH ₃	61.07 ^c	3.87 (3H, s)	-
6'-OCH ₃	61.41 ^c	3.98 (3H, s)	-
2'-OH		12.41 (1H, s)	-
5'-OH		7.55 (1H, s)	-

aa, bb, cc may be interchanged

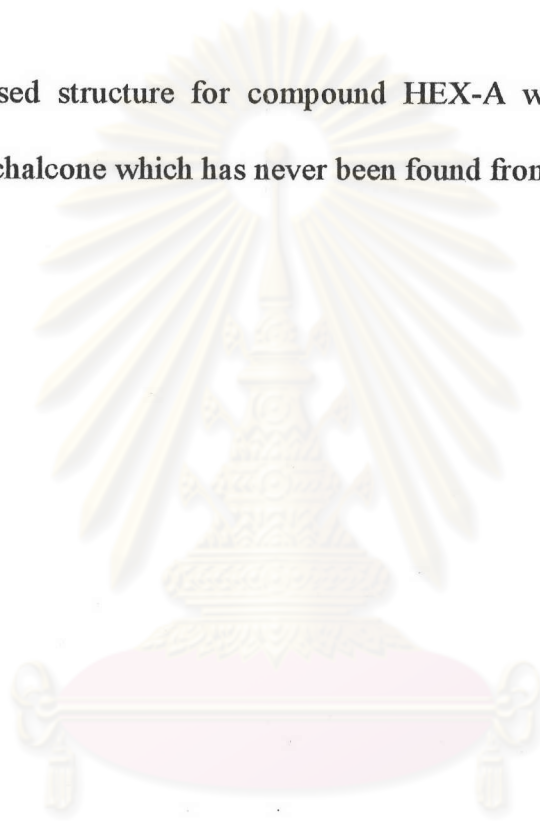
The signal of carbon resonance at δ 126.69 ppm showed correlation with the signal of one proton at δ 7.15 ppm so assigned as C - 4. The two signals of carbons at δ 129.24, and δ 129.18 ppm showed correlation with four aromatic proton at δ 7.27 ppm. was assigned as four carbon atoms in aromatic ring. (C-2, C-3, C-5, and C-6) and these signals may be interchanged.

The signal of carbonyl carbon appear at δ 208 ppm. The signal of carbon at δ 142.50 ppm was assigned as C - 1 because of the long range correlation with the aromatic proton at δ 7.27 ppm. In the same way, the signals of carbons at δ 30.98 and δ 45.85 ppm that showed correlation with proton at C - α and C - β in ^1H , ^{13}C COSY spectrum the first signal at δ 30.98 ppm was assigned as C - β because of the long range correlation with the aromatic proton at δ 7.27 ppm. So the later signal at δ 45.85 ppm was assigned as C - α .

Now we will consider the signal of carbons at δ 150.91, δ 148.79, δ 144.95, δ 137.52, δ 136.07 and δ 111.39 ppm. The signal of carbons at δ 111.39, δ 150.91 and δ 137.52 ppm. showed long range correlation with the signal of the hydroxy proton at δ 12.41 ppm. The signal at δ 111.39 had been assigned as C-1' as well as the signal at δ 150.91 was assigned as C-3' because it showed long range correlation with the methoxy proton at δ 3.80 ppm., so the signal at δ 137.52 was assigned as C-2'. The signal of carbons at δ 148.79, δ 144.95 and δ 136.07 ppm. showed long range correlation with the signal of the hydroxy proton at δ 7.55 ppm. The signals at δ

148.79 and δ 144.95 ppm also showed long range correlation with the methoxy proton at δ 3.98 and δ 3.87 ppm respectively, so assigned as C-4' and C-6' while the signals at δ 136.07 ppm. was assigned as C-5'. The signals at C-4' and C-6' may be interchanged.

So the proposed structure for compound HEX-A was 2', 5'-dihydroxy-3',4',6' trimethoxydihydrochalcone which has never been found from natural source.



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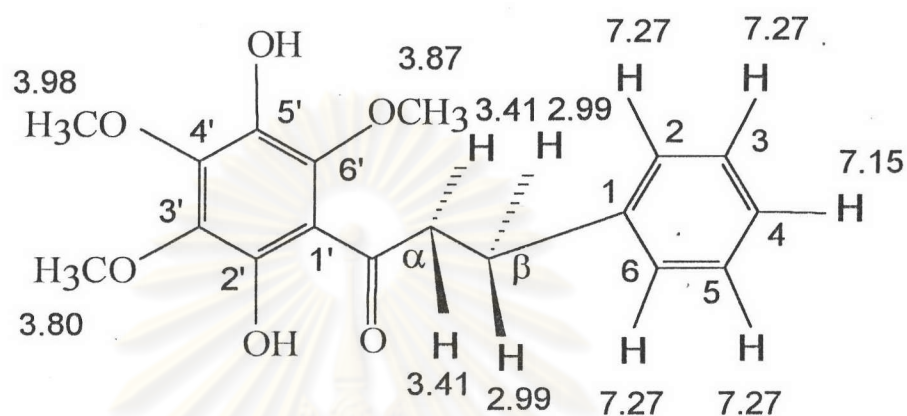


Figure 1 ^1H NMR chemical shifts assignments of compound HEX-A

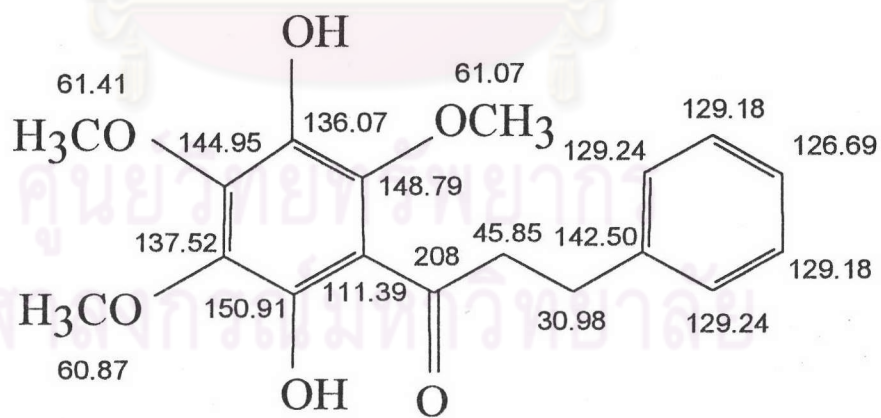
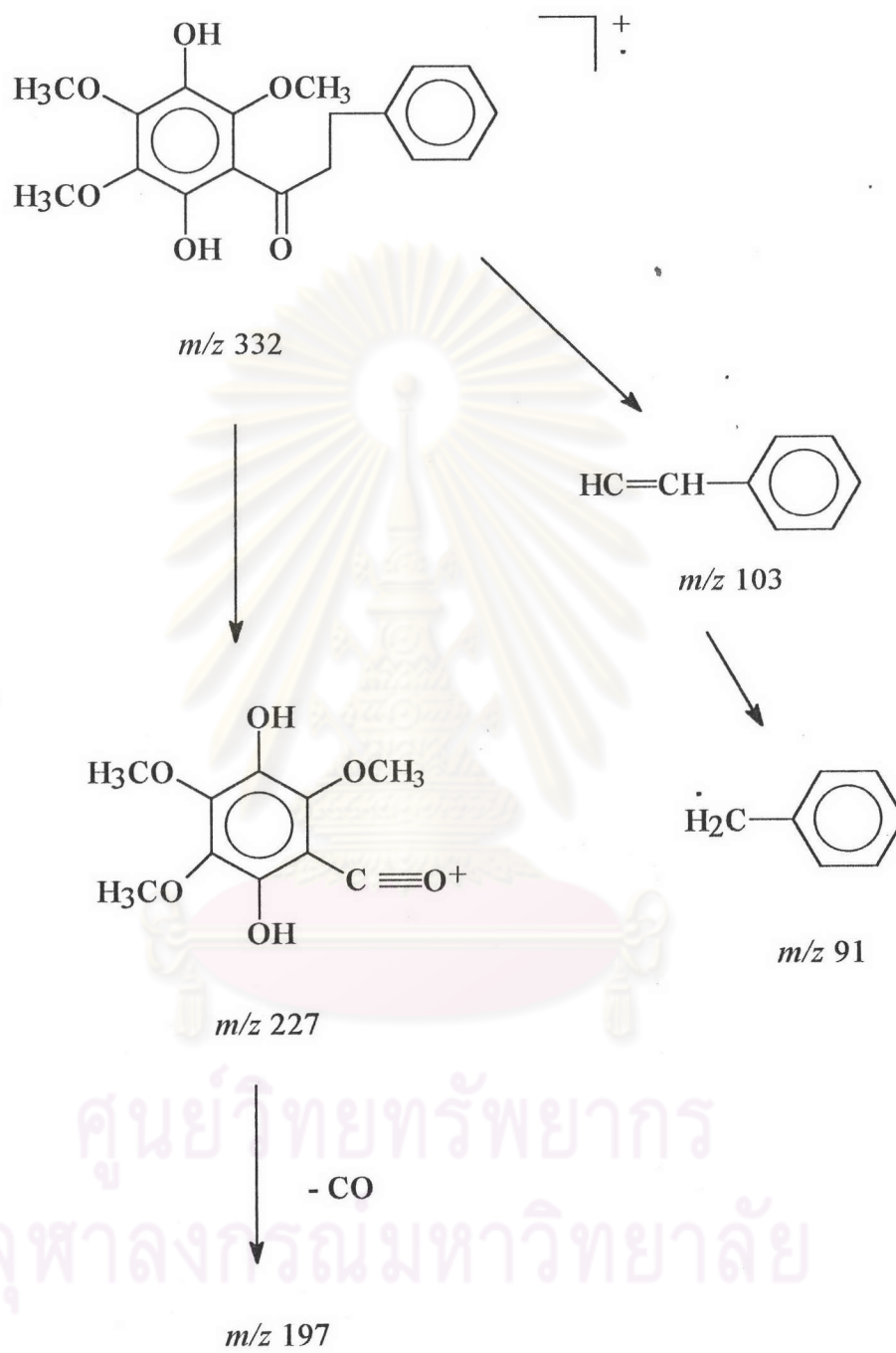


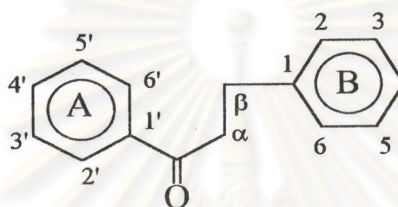
Figure 2 ^{13}C NMR chemical shifts assignments of compound HEX-A



Scheme 2 Mass fragmentation Pattern of HEX-A

Dihydrochalcones

Dihydrochalcones are classified as a small group of flavonoids. They are open chain flavonoids in which the two aromatic rings are joined by a three carbon, α , β -saturated carbonyl system (Harborne *et al.*, 1975).



The numbering system is different from the system used for flavonoid types that possess heterocyclic rings. In dihydrochalcones, the A ring is given the primed numbers and the B ring given the unprimed numbers (Bohm, 1988).

The Occurrence of dihydrochalcone in Annonaceae were summarized in Table 5

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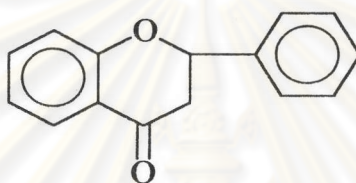
Table 5 The Occurrence of dihydrochalcones in Annonaceae

		Substituents		Trivial name	Source	References
OH	OMe		Other			
2',4'	6'	3'-C-(2-Hydroxy - benzyl)		Uvaretin	<i>Uvaria acuminata</i> <i>U. kiskii</i>	Bohm, 1982 Tammami <i>et al.</i> , 1977.
2',4'	6'			Uvangoletin	<i>U. angolensis</i>	Muhammad and Waterman, 1985.
2',4'	6'	3',5'-Di-C -methyl		Angoletin	<i>U. angolensis</i>	Bohm, 1982
6'	2', 4'	3',5'-Di-C -(2- hydroxybenzyl)		Dihydroflavokawin-B	<i>U. angolensis</i>	Bohm, 1982
2',4'	6'			Anguветin	<i>U. angolensis</i>	Muhammad and Waterman, 1985.
2',4'	6'	3'-C -(2-Hydroxy - benzyl); 5'-C -methyl			<i>U. angolensis</i>	Hufford and Oguntimein, 1982.
2',6'		Di-(2-hydroxybenzyl)			<i>U. angolensis</i>	Muhammad and Waterman, 1985.
		but one is cyclized				
2',4'	6'	5'-C -(2-Hydroxy- benzyl)		Isouvaretin or chaumuvarin	<i>U. angolensis</i> <i>U. chamae</i>	Bohm, 1982 Okorie, 1977.

Structure elucidation of compound HEX-B

Compound HEX-B was obtained as a pale yellow-green needle crystals.

The feature of UV spectrum (Figure 23, page 98) exhibited the characteristic of a flavanone chromophore (the UV absorption maxima at 280 and 358 nm). (Harborne *et al*, 1975)



The ei mass spectrum (Figure 21, page 96) exhibited molecular ion peak at m/z 330 (22.5%) thus molecular formula should be $C_{18}H_{18}O_6$ with an index of hydrogen deficiency of 10.

An absorption band at 3402 cm^{-1} in its ir spectrum (Figure 22, page 97) indicated the presence of one or more hydroxyl group in the structure. An absorption band at 1680 cm^{-1} suggested the presence of carbonyl group in the structure.

An integration curve of ^1H NMR spectrum (Figure 26, page 101) gave, from low - to - high field, 2:2:1:1:1:3:3:3:1:1 for a total of 18 hydrogen atoms. The ^1H NMR spectrum exhibited three methoxy protons singlets at δ 3.86, δ 3.92 and δ 4.10 ppm and one hydroxyl proton singlet at δ 5.59 ppm. The signals at δ 7.38, δ 7.43 and δ 7.48 ppm established five aromatic protons while the doublets of doublets signals at

δ 2.87, δ 3.02 and δ 5.43 ppm established the two protons at C-3 and one proton at C-2 respectively.

The ^1H , ^1H COSY spectrum (Figure 29, page 104) exhibited the coupling of the protons at C-3 and C-2.

The ^{13}C NMR spectrum exhibited 16 peaks thus should established 16 carbon atoms in the molecule but from the analysis of various data, the structure should possessed 18 carbon atoms. This suggests that there must be 2 pairs of equivalent chemical shift of carbon atom.

This is supported by ^{13}C , ^1H COSY spectrum (Figure 30, page 105) showing correlation between protons and carbons, to which it attached. A carbon signal at δ 45.79 ppm showed correlation with protons at δ 2.87 and δ 3.02 ppm, so it was assigned as C-3. The three signals of carbon atoms at δ 61.75, δ 61.25 and δ 61.43 ppm showed correlation with the signal of three methoxy protons at δ 3.92, δ 4.10 and δ 3.86 ppm respectively, but the positions of these methoxyl groups will certainly be considered from the analysis of COLOC spectrum.

The assignments of the carbon signals and the position of the substituents were evidenced by COLOC spectrum (Figure 33, page 108). The long range coupling of the carbons at δ 147.26, δ 142.29 and δ 137.63 ppm to the methoxy protons at δ 4.10,

δ 3.92 and δ 3.86 ppm settled the positions of carbons to which the methoxy protons attached.

There are no long range coupling of these three carbons to other protons except the hydroxy proton, so it is suggested that the three methoxyl groups and one hydroxyl group should be on the ring A. The long range correlation from H on C are summarized in table 6.

Table 6 ^{13}C and ^1H NMR assignments of compound HEX-B with long-range correlation data between carbons and protons

Position	C (δ ppm)	H (δ ppm)	long-range correlation from C on H observed in COLOC spectrum
1	-	-	-
2	79.28	5.43 (1H, dd, $J=13$, 3.05 Hz)	H-3
3	45.79	2.87 (1H, dd, $J=17$, 3.05 Hz) 3.02 (1H, dd, $J=13$, 17 Hz)	
4	189.87	-	H-2, H-3
5	147.26 ^a	-	6-OH, 5-OCH ₃
6	136.96	-	6-OH
7	142.29 ^a	-	6-OH, 7-OCH ₃
8	137.63	-	8-OCH ₃
9	149.64	-	-

Table 6 ^{13}C and ^1H NMR assignments of compound HEX-B with long-range correlation data between carbons and protons (Cont.)

Position	C(δ ppm)	H(δ ppm)	long-range correlation from C on H observed in COLOC spectrum
10	110.87	-	H-3
1'	138.74	-	H-2, H-3', H-5'
2'	125.89	7.48	H-4', H-2, H-6'
3'	128.73	7.43	H-5'
4'	128.55	7.38	H-2', H-6'
5'	128.73	7.43	H-4'
6'	125.89	7.48	H-4', H-2, H-2', ,H-5'
5-OCH ₃	61.25	4.10 (3H, s)	-
7-OCH ₃	61.75	3.92 (3H, s)	-
8-OCH ₃	61.43	3.86 (3H, s)	-
6-OH		5.59 (1H, s)	-

^a assignment may be interchanged

The signal of carbon at δ 79.28 ppm showed correlation with the signal of one proton at δ 5.43 ppm so assigned as C-2. The three signals of carbons at δ 125.89, δ 128.73 and δ 128.55 ppm have correlation with five aromatic protons at δ 7.48,

δ 7.43 and δ 7.38 ppm respectively so these were assigned as five carbon atoms in aromatic ring.

The signal of carbonyl carbon at δ 189.87 ppm was assigned as the C-4, while the signal of carbons at δ 110.87, δ 138.74 and δ 149.64 ppm showed no correlation with any proton, so were assigned as quaternary carbon. The signal at δ 110.87 ppm showed long range correlation with the signal of one proton at δ 2.87 ppm, so it was assigned as C-10. The signal of carbon at δ 138.74 ppm showed long range correlation with the signal of protons at δ 3.02, δ 5.43 ppm. and two aromatic protons at δ 7.43 ppm, so it was assigned as C-1 resonance. The last signal at δ 149.64 ppm. showed no long range correlation with any signal was assigned as C-9 and as a result the substituent on C-8 should be methoxyl group.

Now we will consider the signal of carbons at δ 147.26, δ 142.29, δ 137.63 and δ 136.96 ppm. The signals at δ 142.29, δ 147.26 and δ 136.96 ppm showed long range correlation with the signal of the hydroxy proton at δ 5.53 ppm. The signals at δ 147.26 and δ 142.29 ppm also showed long range correlation with methoxy protons at δ 4.10 and δ 3.92 ppm. respectively, so hydroxy proton should be attached the carbon at δ 136.96 ppm. and the position should be assigned as C-6 or C-7. Because of there were no change of signal in the UV spectrum when added $\text{AlCl}_3 + \text{HCl}$ or $\text{NaOAc} + \text{H}_3\text{BO}_3$ to MeOH (Figure 24 and 25. page 99 and 100). This indicated that hydroxyl group could not attach at C-5 or C-7 respectively, (Harborne *et al*, 1975) so the

hydroxyl group should be assigned as C-6. The signal at δ 142.29 and δ 147.26 may be interchanged at C-5 and C-7. The last signal at δ 137.63 ppm showed long range correlation with methoxy proton at δ 3.86 should be assigned as C-8.

So the proposed structure for compound HEX-B was 6-hydroxy-5,7,8-trimethoxyflavanone which was reported as isopedicin isolated from *Didymocarpus pedicelleta* family Gesneriaceae. (Bose and Adityachaudhury, 1978).



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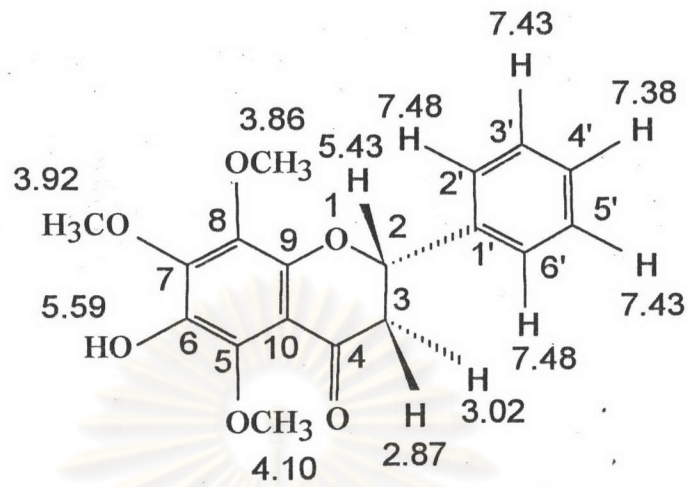


Figure 3 ^1H NMR chemical shifts assignment of compound HEX-B

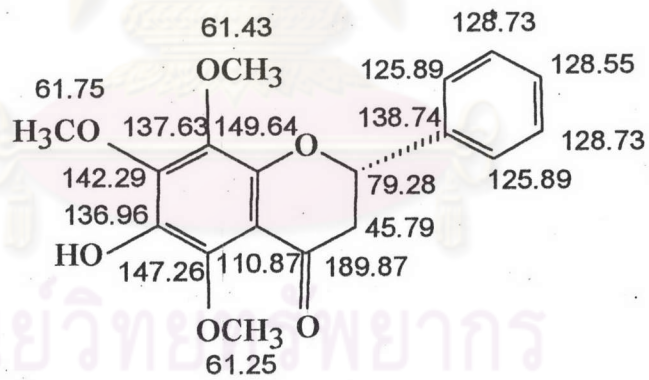
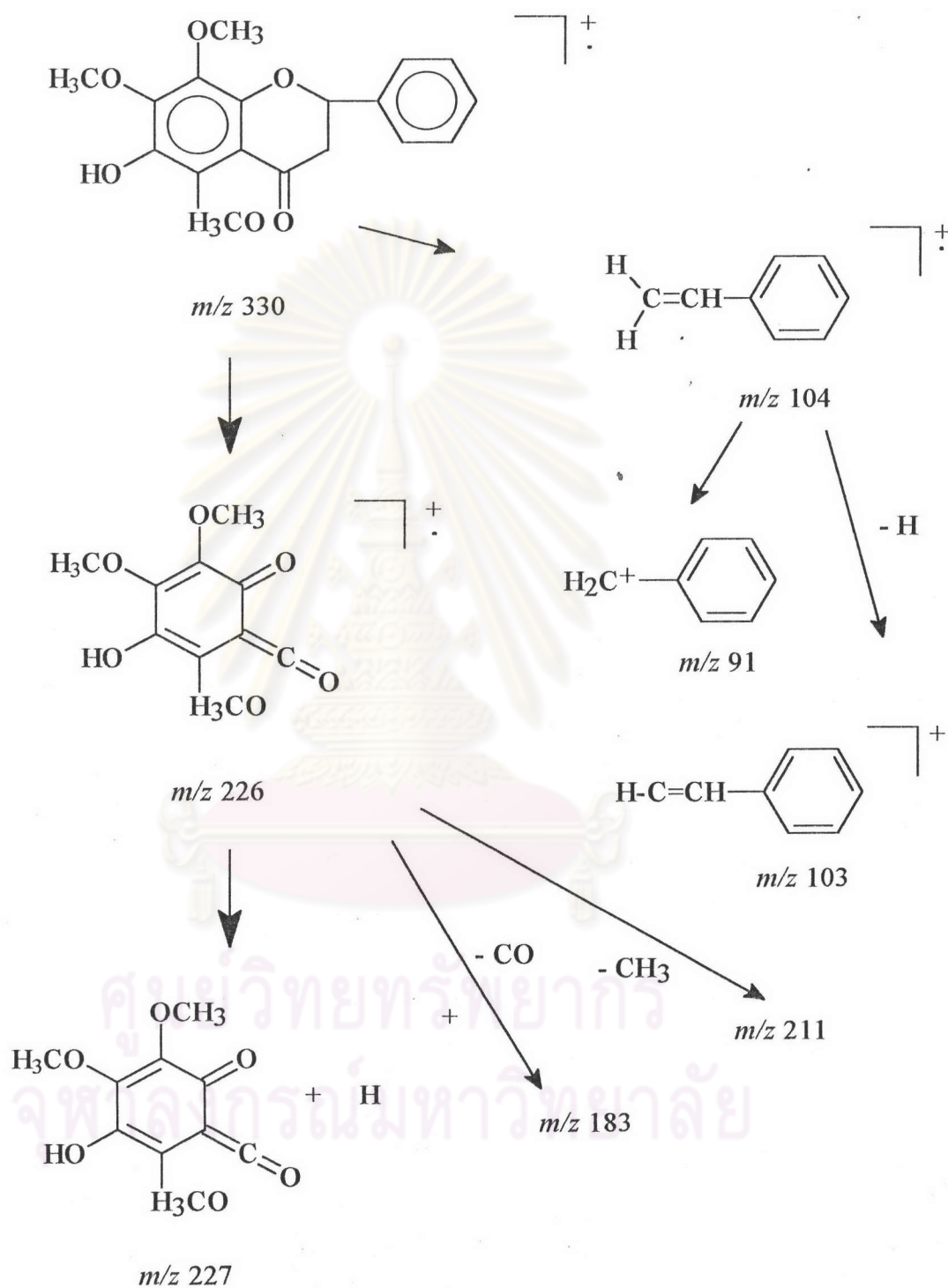


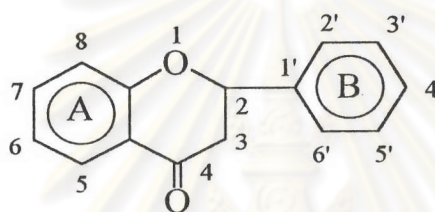
Figure 4 ^{13}C NMR chemical shifts assignment of compound HEX-B



Scheme 3 Mass fragmentation Pattern of HEX-B

Flavanones

Flavanones are based upon structure, 2-phenyl-benzopyran-4-one; classified in flavonoid group. The parent compound has not yet been reported to occur naturally. The simplest plant flavanone has a hydroxyl group at position 7 (Harborne *et al.*, 1975).



The numbering system for flavanones uses primed numbers for ring B and unprimed numbers for ring A.

Since carbon-2 of the flavanone molecule is a centre of asymmetry, the phenyl substituent at that position can be either in the (2*S*) configuration with that group indicated as being below the plane of the page or (2*R*) with the group indicated as being above the plane of the page. The former configuration is considered to be natural one (Bohm, 1988).

The occurrence of flavanones in Annonaceae were summarized in Table 7.

Table 7 The Occurrence of flavanones in Annonaceae

OH	Substituents		Trivial name	Source	References
	OMe	Other			
8	5,6,7			<i>Fissistigma kwangsiense</i>	Shang <i>et al.</i> , 1994.
5, 7	5,6,7	6, 8-Di-C -methyl	Desmethoxy - matteucinol	<i>Oxymitra velutina</i> <i>Uvaria afzelii</i>	Achenbach and Hemrich, 1991. Bohm, 1988.
7	5	6, 8-Di-C -methyl		<i>U. angolensis</i>	Hufford and Oguntimein, 1982.
7	5	8-C -(2-Hydroxybenzyl)	5-Methylchama - netin	<i>U. angolensis</i>	Hufford and Oguntimein, 1982.
5, 7		8-C -(2-Hydroxybenzyl)	Chamanetin	<i>U. ferruginea</i>	Kolpinid <i>et al.</i> , 1985.

Biological activity of flavanones

Although flavanones are known as the minor flavanoids, they possess several important biological activities being useful in pharmacy and other industries (Harborne *et al.*, 1975).

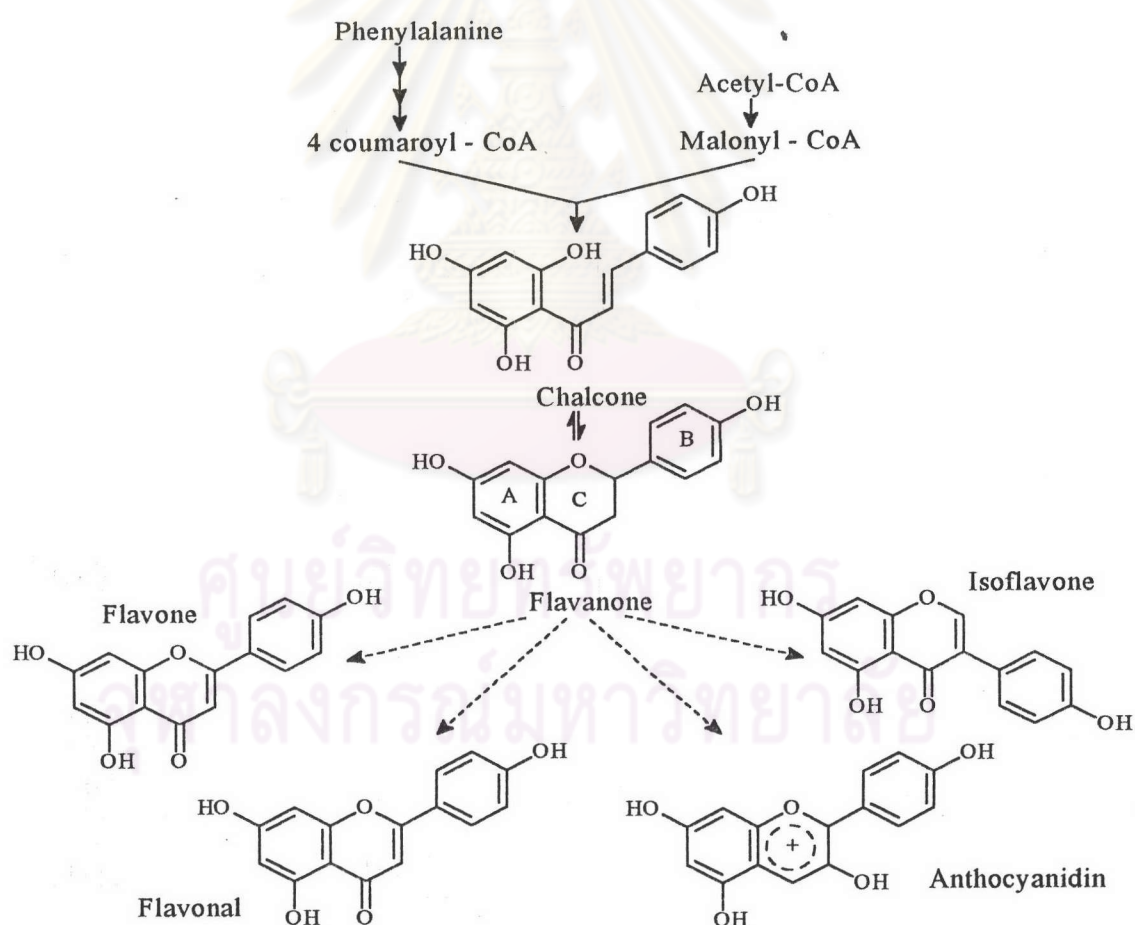
Kamat and co-workers (1981) reported the antimicrobial activity of the flavanone 'abyssinones', isolated from *Erythrina abyssinica*. These compounds were active against *Staphylococcus aureus*, *Bacillus subtilis*, and to a lesser extent, *Micrococcus lysodeikticus*. Significant activity was also recorded against the yeasts *Saccharomyces cerevisiae* and *Candida utilis* and the fungi *Sclerotinia libertiana*, *Mucor mucedo* and *Rhizopus chinensis*.

The flavanone sigmoidin A and B exhibited a significant antibacterial activity against gram positive bacteria ; *Staphylococcus aureus* and *Bacillus subtilis* at 50 ppm. (Forman *et al.*, 1983)

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Biosynthesis of Dihydrochalcone and Flavanone

Dihydrochalcone and Flavanone are classified as the flavonoids which are biosynthetically closely related with a chalcone of which being the common intermediate. The carbon skeleton is derived from acetate and phenylalanine. Ring A is formed by a head to tail condensation of three acetate units and ring B as well as carbon atoms 2, 3 and 4 of the heterocyclic ring C arise from phenylalanine. The biosynthetic relationships of the flavonoids as concluded mainly from labelling experiments *in vivo* are illustrated in scheme 1 (Bohm, 1982).



Scheme 4 The biosynthesis of flavonoid.

Structure elucidation of compound ALK 1

Compound ALK 1 was obtained as white needle crystals.

The mass spectrum of ALK 1 (Figure 36, page 111) exhibited the molecular ion peak at m/z 357 (97%), and molecular formula should be $C_{20}H_{23}NO_5$ with an index of hydrogen deficiency of 9. The fragmentation pattern indicative of tetrahydroprotoberberines moiety could be rationalized (Scheme 5) from the following data.

The IR spectrum (Figure 37, page 112) contained an absorption band at 2936 cm^{-1} (OH stretch) and two signals at 2839 cm^{-1} and 2751 cm^{-1} (both weak) which corresponded to Bohlmann band.

Compound ALK 1 was assigned as a tetrahydroprotoberberine derivative by the subsequent analysis of ^1H NMR (Figure 38, page 113), ^{13}C NMR (Figure 44, page 119) ^1H , ^1H COSY (Figure 41, page 116) and HMBC (Figure 47, page 122) spectra.

The ^1H NMR spectrum exhibited three methoxy singlets at δ 3.82, δ 3.88 and δ 3.90 ppm and three aromatic protons at δ 6.80, δ 6.83 and δ 6.36 ppm. Other five signals at δ 4.22, δ 3.58, δ 3.24, δ 2.83 and δ 2.59 ppm exhibited nine aliphatic protons. From the mass fragmentation pattern indicated that there should be one aromatic proton on ring A. The signal of aromatic proton at δ 6.36 ppm was assigned

as H - 4 of which showing correlation with C at δ 100.61 ppm in the ^{13}C , ^1H COSY spectrum.

From the ^{13}C , ^1H COSY spectrum, the methoxy protons at δ 3.82, δ 3.88 and δ 3.90 ppm showed the correlation with C at δ 60.68, δ 55.91 and δ 60.98 ppm.

The doublet protons signals at δ 6.80 ($J = 8.54$) and δ 6.83 ($J = 8.24$) ppm established two aromatic protons arranged in ortho positions showing the attachment with C at δ 114.65 and δ 124.86 ppm respectively. The four methylene protons at C-5 and C-6 gave rise to complex multiplets at δ 2.83, δ 3.24 and δ 2.59 ppm could be located on C at δ 23.02 and δ 50.97 ppm and were assigned as C-5 and C-6 respectively. The chemical shift of C-6 should be more downfield than C-5 by the withdrawal electrons effect of neighbouring nitrogen at C-6. The two protons signals at δ 3.58 and δ 4.22 ppm (d, $J = 15.56$) were assigned as protons on C-8 at δ 53.93 ppm.

Now we will consider the assignment of carbon from HMBC spectrum. The signal of proton at 6.80 showed correlation with C at 143.16 and 127.03 ppm, so assigned as C-9 and C-12a respectively. C-9 should be more lowfield than C-12a.

The signal of proton at δ 6.83 ppm showed correlation with C at δ 127.87 ppm and δ 146.50 ppm of which were assigned as C-8a and C-10 respectively.

In the same way, C-2, C-4a and C-14a were assigned by analysing the relationships from proton at δ 6.36 ppm, where as C-14 from H-8. The long range correlation from H on C are summarized in Table 8.

Table 8 ^{13}C and ^1H NMR assignments of compound ALK1 with long-range correlation data between carbons and protons

Position	C (δ ppm)	H (δ ppm)	long-range correlation from H on C observed in HMBC spectrum
1	146.36	-	-
2	150.50	-	-
3	133.68	-	-
4	100.62	6.36 (1 H, s)	C - 2, C - 4a
4 a	133.55	-	-
5	23.02	-	-
5 ax		2.83 (1 H, m)	-
5 eq		2.83 (1 H, m)	-
6	50.97	-	-
6 ax		3.24 ^a (1 H, m)	-
6 aq		2.59 ^a (1H,ddd, $J=11,10,5.5$)	-
8	53.93	-	-
8 ax		3.58 ^b (1 H, d, $J=15.56$ Hz)	-
8 eq		4.22 ^b (1 H, d, $J=15.56$ Hz)	C - 14
8 a	127.86	-	-

Table 8 ^{13}C and ^1H NMR assignments of compound ALK1 with long-range correlation data between carbons and protons (Cont.)

Position	C (δ ppm)	H (δ ppm)	long-range correlation from H on C observed in HMBC spectrum
9	143.16	-	-
10	146.50	-	-
11	114.05	6.80 (1 H, d, $J=8.39$ Hz)	C - 12a, C - 9
12	124.87	6.83 (1 H, d, $J=8.39$ Hz)	-
12 a	127.03	-	-
13	36.10	-	C - 8, C - 10
13 ax		2.83 ^c (1 H, m)	-
13 eq		3.24 ^c (1 H, dd, 9.76, 3.36)	-
14	59.55	3.58 (1 H, dd, $J = 11, 3.6$)	-
14 a	114.66	-	-
2 -OCH ₃	55.92	3.88 (3H, s)	-
3 -OCH ₃	60.99	3.90 (3 H, s)	-
9-OCH ₃	60.69	3.82 (3 H, s)	-

^{a, b, c} assignment may be interchanged

The proposed structure for compound ALK 1 was 1,10 dihydroxy-2,3,9-trimethoxytetrahydroprotoberberine which has been reported as capaurimine isolated from *Corydalis pallida* and *C. montana* family Fumariaceae (Kametani *et al*, 1968).

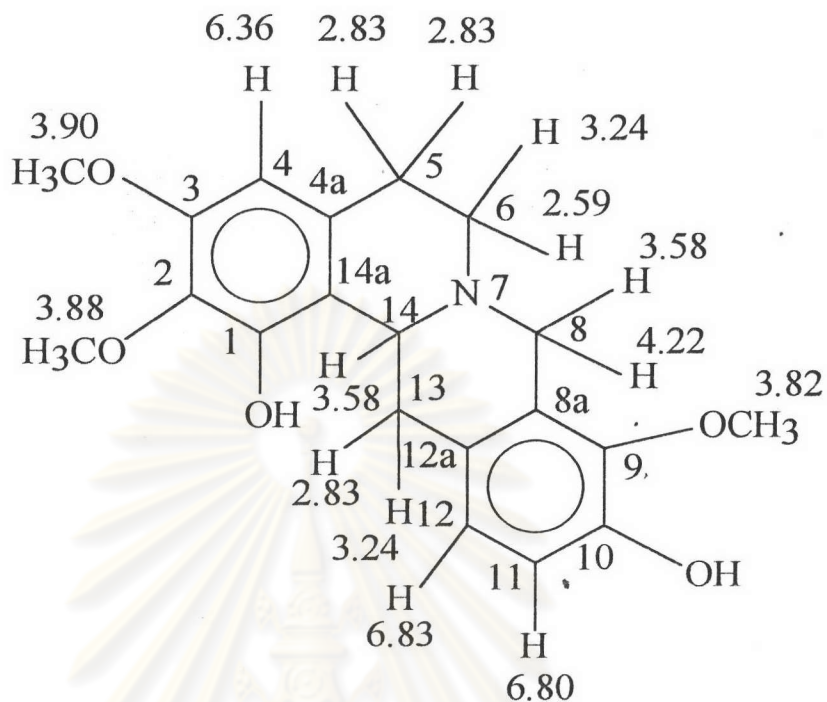


Figure 5 ^1H NMR chemical shifts assignments of compound ALK 1

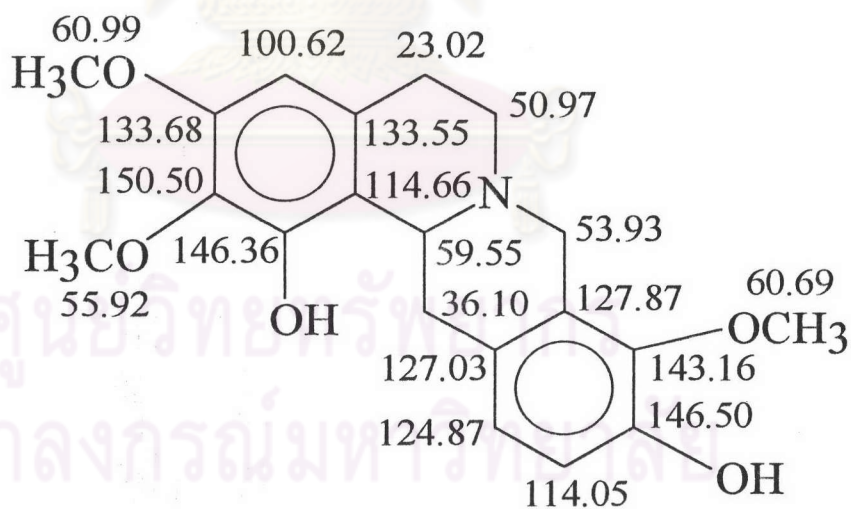
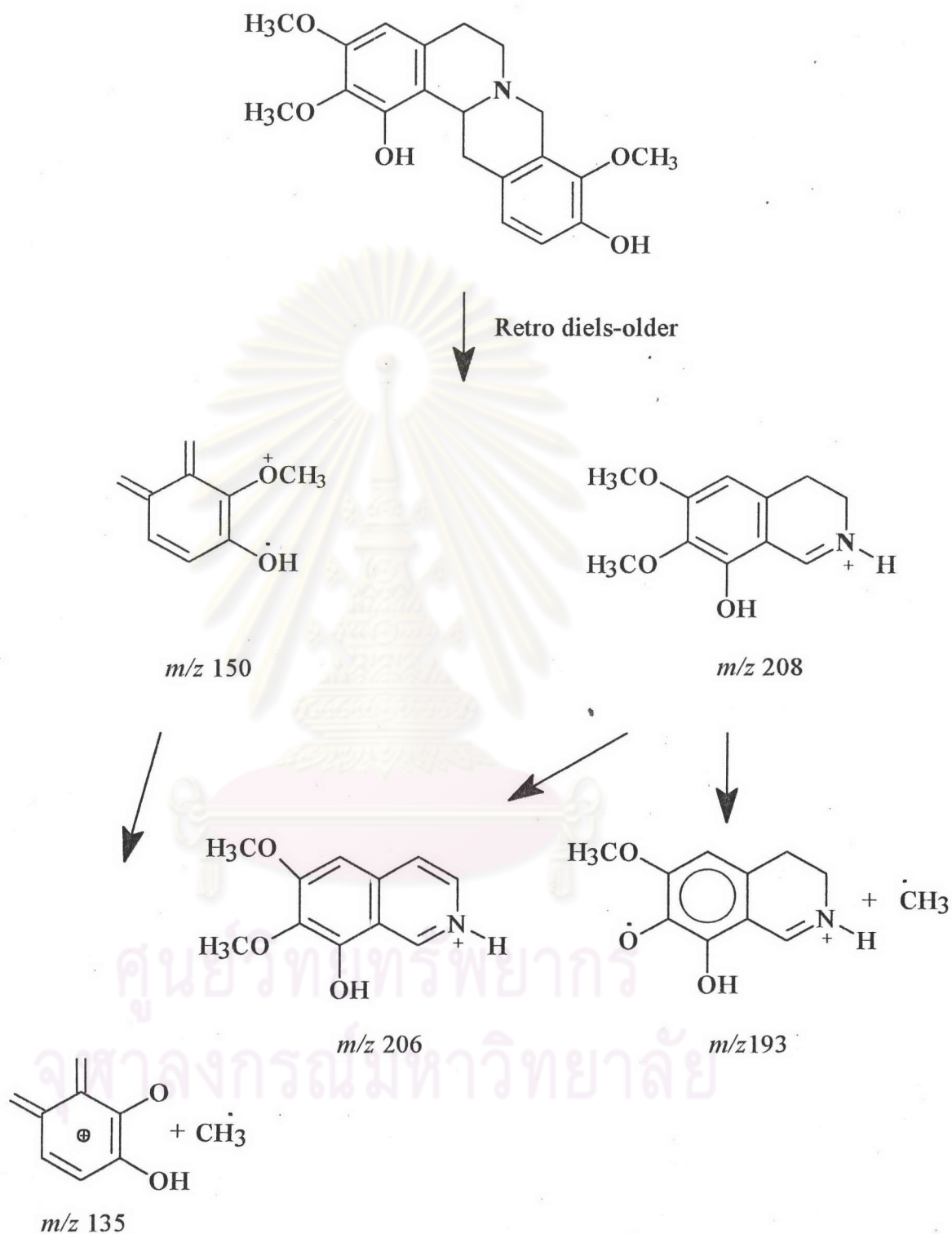


Figure 6 ^{13}C NMR chemical shifts assignments of compound ALK 1

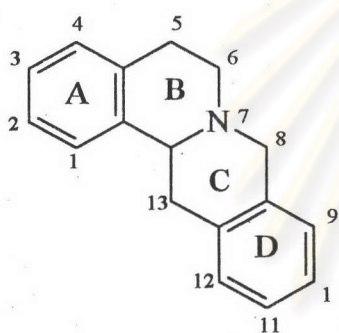


Scheme 5 Mass fragmentation Pattern of ALK 1

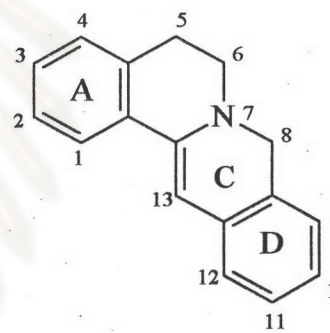
Tetrahydroprotoberberines

Tetrahydroprotoberberine is one of the naturally occurring protoberberine alkaloid. Apart from tetrahydroprotoberberine, its quarternary, *N*-methyl quarternary and salts, as well as the dihydroderivatives has been reported.

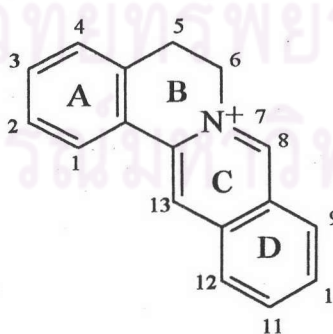
The basic structures of these groups are shown as follow



Tetrahydroprotoberberine



Dihydroprotoberberine



Quarternary protoberberine salt

Substituents are usually present at C-2 and C-3 and at C-9 and C-10 or at C-10 and C-11. It is called "pseudo" variety in the case of C-10 and C-11 are substituted. There may be a hydroxyl or methoxyl group present at C-1. Sometimes, a methyl group is found at C-8 or C-13 and in a few cases an alcoholic hydroxyl is located at C-13 or C-5 (Shamma, 1972).

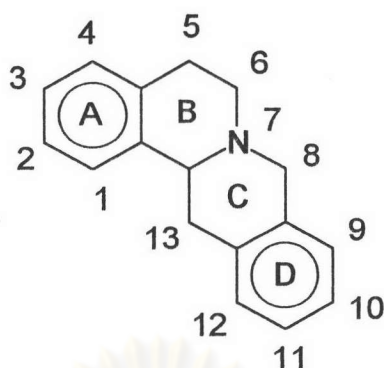
The occurrence of tetrahydroprotoberberines in Annonaceae were summarized in Table 9.

Table 9 Occurrence of tetrahydroprotoberberines in Annonaceae

Alkaloid	Formula	Plant	Reference
Aequaline (discretamine)	10	<i>Duguetia calycina</i>	Bhakuni and Jain, 1986
		<i>D. discolor</i>	Bhakuni and Jain, 1986
		<i>Fissistigma glaucescens</i>	Lu <i>et al.</i> , 1985
		<i>F. oldhamii</i>	Lu <i>et al.</i> , 1985
		<i>Mitrella kenii</i>	Bhakuni and Jain, 1986
		<i>Schefferomitra subaequalis</i>	Bhakuni and Jain, 1986
		<i>Xylopiya buxifolia</i>	Bhakuni and Jain, 1986
		<i>X. discreta</i>	Leboeuf <i>et al.</i> , 1981
Coreximine	28	<i>Annona montana</i>	Leboeuf <i>et al.</i> , 1981
		<i>Annona muricata</i>	Leboeuf <i>et al.</i> , 1981
		<i>Asimina triloba</i>	Leboeuf <i>et al.</i> , 1982

Table 9 Occurrence of tetrahydroprotoberberines in Annonaceae (cont.)

Alkaloid	Formula	Plant	Reference
Corypalmine (discretamine)	29	<i>Pachpodanthium confine</i>	Leboeuf <i>et al.</i> , 1982
		<i>P. staudtii</i>	Bhakuni and Jain, 1986
		<i>Xylophia discreta</i>	Bhakuni and Jain, 1986
10-Demethylxylopinine	30	<i>Duguetia calycina</i>	Leboeuf <i>et al.</i> , 1982
Discretine	31	<i>Pachypodanthium staudtii</i>	Bhakuni and Jain, 1986
		<i>Xylophia discreta</i>	Leboeuf <i>et al.</i> , 1982
Isocorypalmine	32	<i>Pachypodanthium confine</i>	Leboeuf <i>et al.</i> , 1982
		<i>Pachypodanthium staudtii</i>	Leboeuf <i>et al.</i> , 1982
Kikemanine (schefferine)	33	<i>Polyalthia oligosperma</i>	Bhakuni and Jain, 1986
		<i>Schefferomitra subaequalis</i>	Leboeuf <i>et al.</i> , 1982
Stepholidine	34	<i>Monanthotaxis cauliflora</i>	Leboeuf <i>et al.</i> , 1982
Tetrahydropalmatine	18	<i>Fissistigma glaucesens</i>	Lu <i>et al.</i> , 1985
		<i>F. oldhamii</i>	Lu <i>et al.</i> , 1985
		<i>Pachypodanthium confine</i>	Leboeuf <i>et al.</i> , 1982
Xylopinine	35	<i>Polyalthia oligosperma</i>	Bhakuni and Jain, 1986
		<i>Xylophia buxifolia</i>	Bhakuni and Jain, 1986
		<i>X. discreta</i>	Leboeuf <i>et al.</i> , 1982



Tetrahydroprotoberberine skeleton structure

Table 10 Substituents pattern of some tetrahydroprotoberberines

Alkaloid	Formula	2	3	9	10	11
Aequaline (Discretamine)	10	OMe	OH	OMe	OH	-
Coreximine	28	OH	OMe	-	OMe	OH
Corypalmine	29	OMe	OH	OMe	OMe	-
(-)-Demethylxylopinine	30	OMe	OMe	-	OH	OMe
Discretine	31	OMe	OH	-	OMe	OMe
Isocorypalmine	32	OH	OMe	OMe	OMe	-
Kikemanine (Schefferine)	33	OMe	OMe	OMe	OH	-
Stepholidine	34	OH	OMe	OMe	OH	-
Tetrahydropalmatine	18	OMe	OMe	OMe	OMe	-
Xylopinine	35	OMe	OMe	-	OMe	OMe

Biological activity of tetrahydroprotoberberines

The protoberberine alkaloids and their derivatives show at least three types of biological activity. These are antimicrobial, antileukemic and antineoplastic (Manske, 1975).

(-) Tetrahydrocoptisine used in neuropsychopharmacological study with mice and rats indicated methylene dioxy-substituted tertiary base play a major role of possessing antipsychotic and neuroleptic activities (Bhakuni and Jain, 1986).

N-methyltetrahydroberberine was found to produce a transient decrease (30-40 mm Hg) in systolic blood pressure of pentobarbital-anesthetized cats (Manske, 1975).

Tetrahydroberberine was observed to increase colchicine mediated antimitosis *in vivo* fibroblast growth. Intraperitoneal administration of the alkaloid in a dosage of 40-65 mg/Kg to mice resulted in potentiation of hexobarbital narcosis, reduction in spontaneous activity, antagonism of amphetamine induced scratching response (Manske, 1975).