HOFMANN ELIMINATION WITH DIAZOMETHANE ON QUATERNARY BENZYLTETRAHYDROISOQUINOLINE RELATED ALKALOIDS§

Sheng-Teh Lu* and Ian-Lih Tsai
School of Pharmacy, Kaohsiung Medical College, 100 Shih-Chuan 1st Road, San-Min District, Kaohsiung, Taiwan, R.O.C.

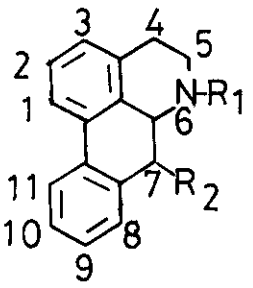
Abstract — The investigation have been made to the reaction of a large excess of diazomethane on the quaternary benzyltetrahydroisoquinoline related alkaloids, aporphines, benzyltetrahydroisoquinolines, pavines and protopine. From the structural elucidation of the reaction products, it has been found that the first and second Hofmann elimination proceeded.

The reaction of diazomethane with acid, acid halides, acid anhydrides, phenols, enols, olefines, active methylenes, or carbonyl compounds has been investigated, extensively.[1] In these cases, the reaction products are the inserting of methyl group or addition products of diazomethane. In 1975, Soine and coworkers[2] firstly reported that when (+)-tubocurarine, (+)-isotubocurarine and (+)-condocurarine belonging to bisbenzyltetrahydroisoquinoline alkaloids were treated at room temperature with an excess of diazomethane, the Hofmann elimination type methine bases of their O-methylation products afforded. Then they[3] applied the same reaction to tetrahydroisoquinoline alkaloids, (±)-laudanosine methiodide and (+)-carnegine methiodide and presumed the reaction mechanism as the β-H on C-4 of benzyltetrahydroisoquinoline base lead to a styrene product and those on C-α leading to a stilbene product that were proceeded by an E2 mechanism.

In order to prove the reaction mechanism, the additional experiments were carried out for the benzyltetrahydroisoquinoline related alkaloids, aporphines, benzyltetrahydroisoquinolines, pavines and protopine (Table 1). For this purpose, firstly, as the representative aporphine alkaloid, (+)-glaucine was brought into experimental material. (+)-Glaucine (1) methiodide which was prepared from (+)-glaucine and methyl iodide was treated with a large excess of ethereal solution of diazomethane

Table 1. The alkaloids used for reaction with diazomethane.

Aporphines:



	R_1	R_2	1	2	9	10	11
(+)-Glaucine (1)	Me	H	OMe	H	OMe	OMe	H
(+)-N-Methyllaurotetanine (2)	Me	H	OMe	H	OH	OMe	H
(+)-Boldine (3)	Me	H	OMe	OH	OH	OMe	H
(+)-Xanthoplanine (4)	$(Me)_2$	H	OMe	OMe	OH	OMe	H
(+)-Dicentrine (5)	Me	H	OCH_2O		OMe	OMe	H
(+)-N-Methylactinodaphnine (6)	Me	H	OCH_2O		OH	OMe	H
(+)-O-Methylisocorydine (7)	Me	H	OMe	OMe	H	OMe	OMe
(+)-Isocorydine (8)	Me	H	OMe	OMe	H	OMe	OH
(+)-Magnoflorine (9)	$(Me)_2$	H	OH	OMe	H	OMe	OH
(+)-O-Methylbulbocapnine (10)	Me	H	OCH_2O		H	OMe	OMe
(+)-N-Methylnandigerine (11)	Me	H	OCH_2O		H	OH	OMe
(-)-N-Methylxylopine (12)	Me	H	OCH_2O		OMe	H	H
(-)-Roemerine (13)	Me	H	OCH_2O		H	H	H
(-)-Ushinsunine (14)	Me	OH	OCH_2O		H	H	H

Anhydroushinsunine (15)

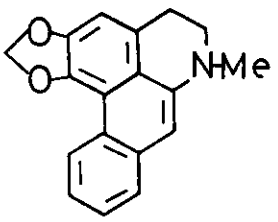
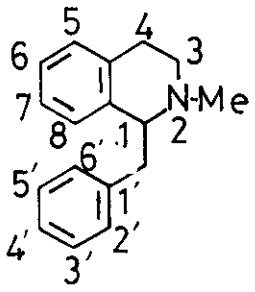


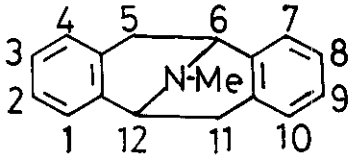
Table 1 (continued)

Benzyltetrahydroisoquinolines:



	6	7	3'	4'
(+)-Laudanosine (16)	OMe	OMe	OMe	OMe
(+)-Reticuline (17)	OMe	OH	OH	OMe
(+)-O-Methylarmepavine (18)	OMe	OMe	H	OMe
(+)-Armepavine (19)	OMe	OMe	H	OH

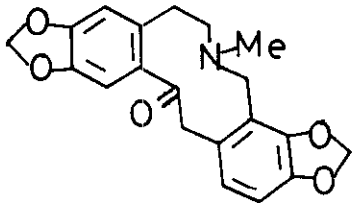
Pavines:



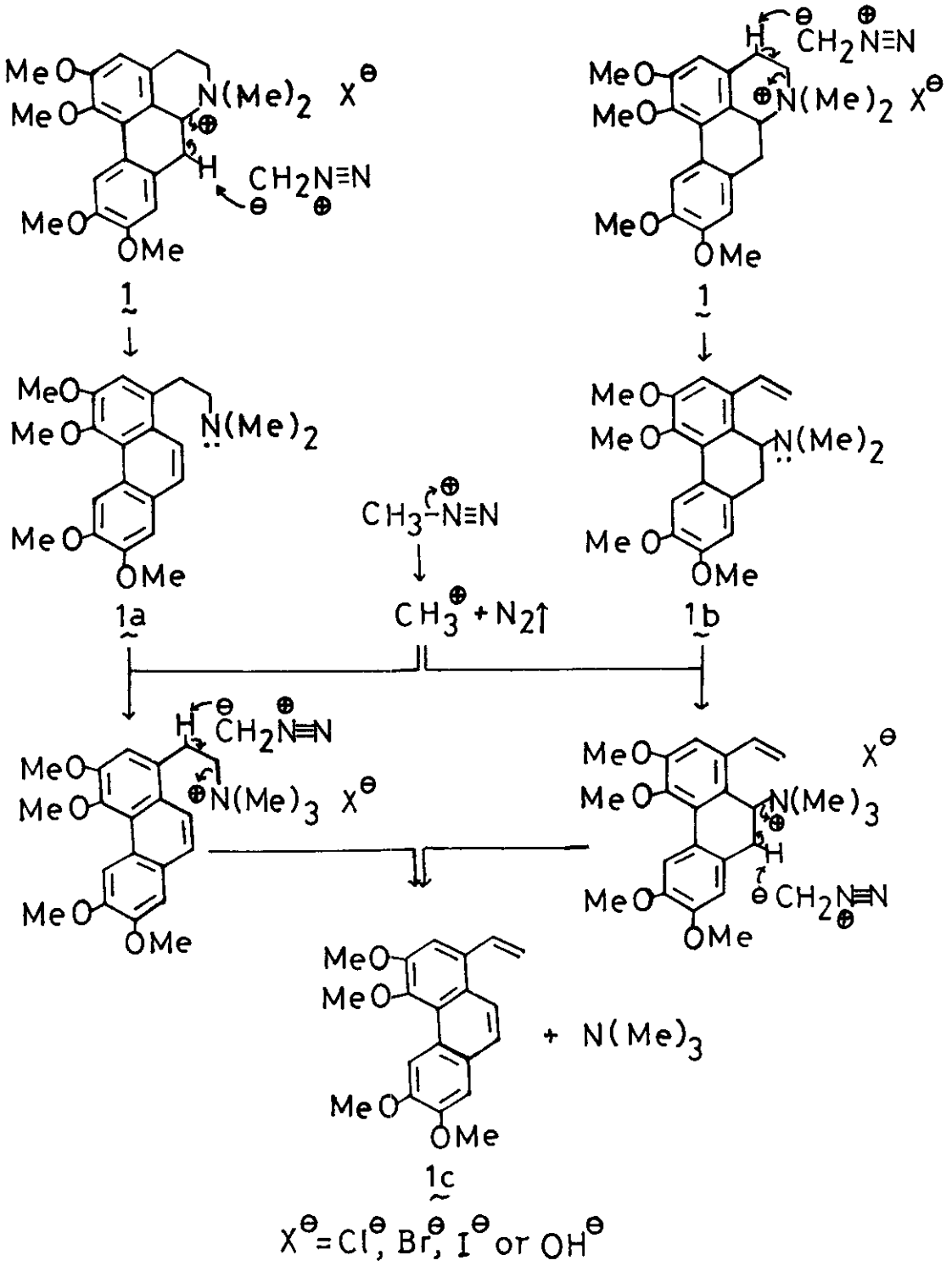
	2	3	8	9
(-)-Eschscholtzine [(-)-Crychine] (20)		OCH_2O		OCH_2O
(+)-Eschscholtzidine [(+)-O-Methylcaryachine] (21)		OCH_2O	OMe	OMe

Protopines:

Protopine (22)

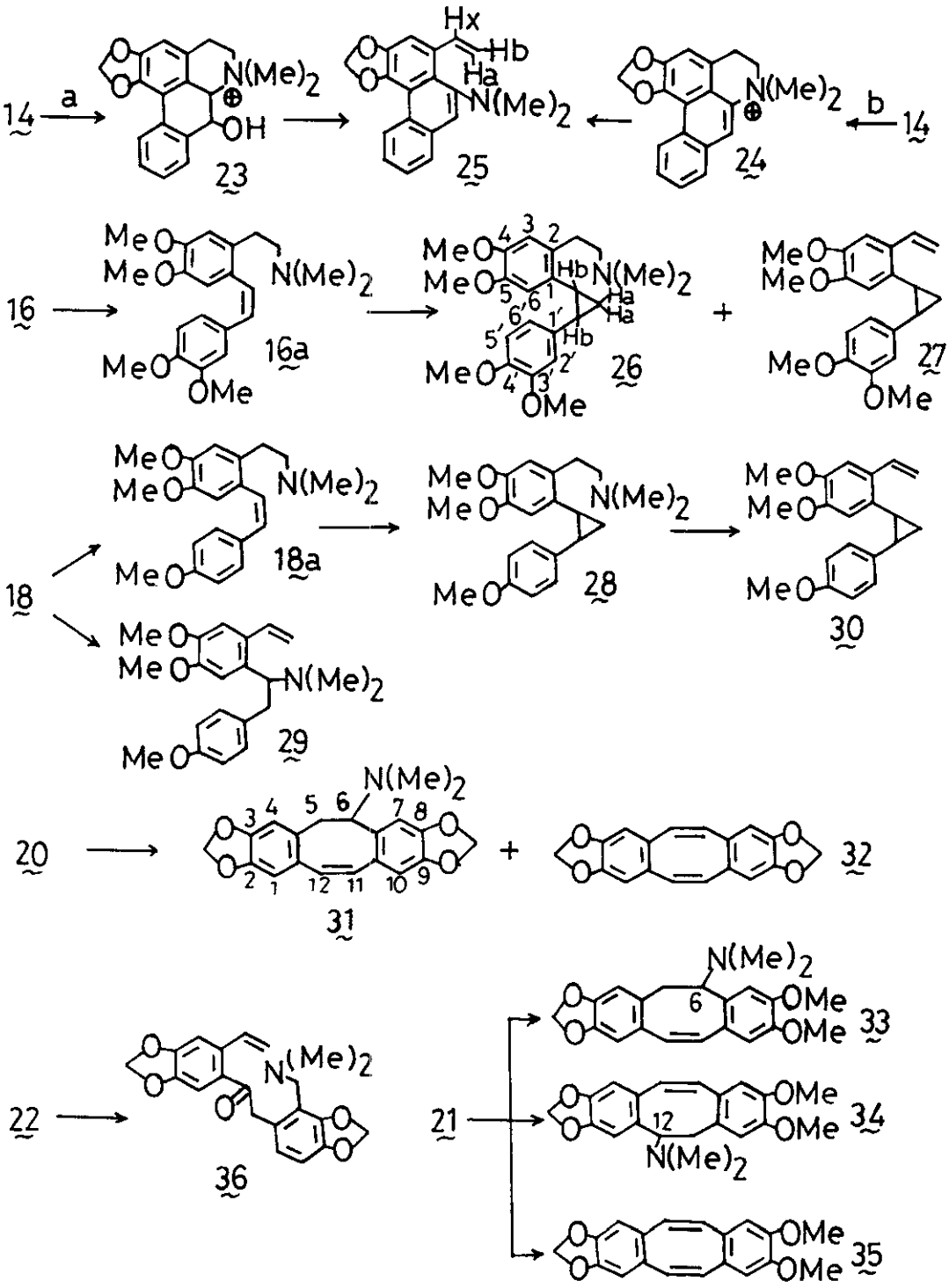


containing a small amount of methanol for five days at room temperature. The ether solution was evaporated to dryness under reduced pressure at room temperature. The residue which has a pungent fishy, ammoniacal odor of trimethylamine was extracted with ether, divided into ether soluble part and insoluble part. From the ether soluble part, glaucine methine, 1-(N,N-dimethylamino)ethyl-3,4,6,7-tetramethoxyphenanthrene (Rf 0.18) (1a), glaucine isomethine, 1-vinyl-3,4,6,7-tetramethoxy-10-N,N-dimethylamino-9,10-dihydrophenanthrene (Rf 0.31) (1b), and glaucine bismethine (the des-N-compound), 1-vinyl-3,4,6,7-tetramethoxyphenanthrene (Rf 0.70-0.76) (1c), were obtained by separating with the preparative tlc method. The uv spectrum of 1a exhibits the characteristic absorption curve of phenanthrene. In the aromatic proton region of the ^{1}Hnmr spectrum of 1a, there are two doublets at δ 7.46 and 7.76 (each 1H, d, J=8.52 Hz) which are assigned 9-H and 10-H in phenanthrene nucleus in addition to one N,N-dimethylamino group at δ 2.39 (6H, s) and four methoxyl groups at 3.90 (3H, s), 4.03 (6H, s), and 4.06 (3H, s). In the uv spectrum of 1b, with $[\alpha]_D^{20}$ -62° (MeOH), there is a maximum absorption at 258 sh(3.63) and 307(3.44) nm(log ε). The ^{1}Hnmr spectrum of 1b exhibits a vinyl group at δ 5.60 and 5.30 (each 1H, dd), and δ 7.13 (1H, dd), besides one N,N-dimethylamino group at δ 2.09 (6H, s) and four methoxyl groups at δ 3.63 (3H, s), 3.90 (6H, s) and 3.93 (3H, s). Both 1a and 1b were identified with the authentic samples which were prepared by the Hofmann elimination with the ethanolic KOH on glaucine (1) methiodide, respectively. The uv spectrum of 1c exhibits a phenanthrene absorption curve. In the ^{1}Hnmr spectrum of 1c, four methoxyl groups, one vinyl group, and five aromatic protons were observed. The identification of 1c was established by the comparison with the authentic sample of 1-vinyl-3,4,6,7-tetramethoxyphenanthrene which prepared by the Hofmann elimination with the ethanolic KOH on glaucine methine (1a) methiodide. On the other hand, from the ether insoluble part, the unreacted 1 methiodide was recovered. That is to say that the reaction of a large excess of diazomethane on (+)-glaucine (1) methiodide takes place firstly the first and then the second Hofmann elimination. The reaction also arises at the dark place. When diazomethane was reacted with (+)-glaucinium hydroxide, the same products, 1a, 1b and 1c were obtained. Both 1a and 1b produced by the first Hofmann elimination risen from (+)-glaucine cation and diazomethane immediately react with methyl cation generated at same time, and from quaternary cations of 1a and 1b, which proceed to the second Hofmann elimination with the excess diazomethane. On the results, a des-N compound 1c affords. The assumed reaction mechanism was shown in the Scheme 1.


MeO
MeO
N(Me)2 X⊖
H
CH2N≡N
⊖ ⊕
MeO
OMe
1
1a
1b
CH3–N≡N
CH3⊕ + N2↑
N(Me)3 X⊖
1c
+ N(Me)3
X⊖ = Cl⊖, Br⊖, I⊖ or OH⊖

Scheme 1

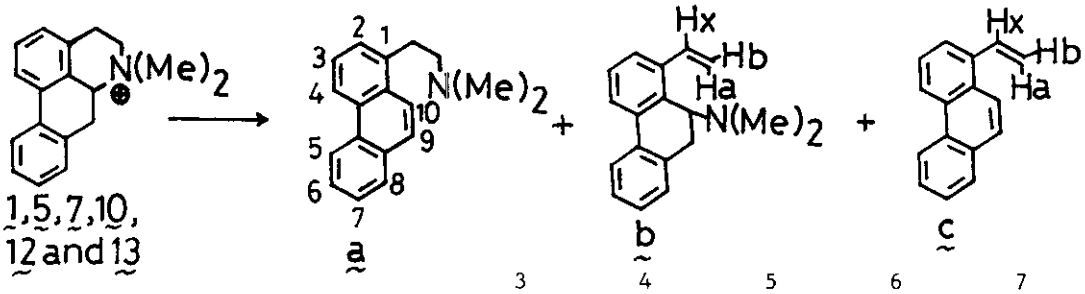
In generally, if the phenolic aporphinium salts are used as starting materials, the first and the second Hofmann eliminations proceed after O-methylation of the phenolic hydroxyl groups. For example, in the case of xanthoplanine (4) chloride, N-methyllaurotetanine (2) methiodide and boldine (3) methiodide, each reaction products are same with those of glaucine (1) methiodide. Magnoflorine (9) iodide and isocorydine (8) methiodide give the same reaction products with O-methylisocorydine (7) methiodide. N-Methylnandigerine (11) methiodide get the same reaction products with O-methylbulbocapnine (10) methiodide, and N-methylactinodaphnine (6) methiodide produces the same reaction products with dicentrine (5) methiodide. In the case of (+)-reticuline (17) methiodide, it affords the same products with (+)-laudanosine (16) methiodide, armepavine (19) methiodide give the same products with O-methylarmepavine (18) methiodide. Therefore, we showed only the non-phenolic alkaloids.
The further experiments were carried out for the other several aporphine alkaloids. In the case of (-)-ushinsunine (14) which has a hydroxyl group at C_7 position in the aporphine nucleus only one product whose data are agreeable with 1-vinyl-3,4-methylenedioxy-10-N,N-dimethylaminophenanthrene (25) appeared in the literature[4] from the ether soluble part afforded. From this result, we presumed two possible pathways:
(a) The C_7-OH group hindered CH_2N_2 from abstracting C_7-H atom. Therefore the Hofmann elimination only proceeds by abstracting C_4-H atom, and then the phenanthrene nucleus is formed by the dehydration between the OH group and the neighbouring proton.
(b) After anhydroushinsunine (15) methiodide was formed by the dehydration of C_7-OH group and C_{6a}-H atom of (-)-ushinsunine (14) methiodide, the Hofmann elimination only proceeds by abstracting C_4-H atom. When the same reaction was made for anhydroushinsunine (15) methiodide, the same product, 1-vinyl-3,4-methylenedioxy-10-N,N-dimethylaminophenanthrene, with the case of ushinsunine (14) methiodide was yielded.
The same experiments were carried out for (-)-roemerine (13) methiodide and (-)-N-methylxylopine (isolaureline) (12) methiodide. On the results, the methines and the des-N-compounds only were obtained, but it could not to get any isomethine. The reaction products were characterized as shown in Experimental part.
The other related isoquinoline alkaloids, (+)-laudanosine (16) and (+)-O-methylarmepavine (18) belonging to benzyltetrahydroisoquinolines, (-)-eschscholtzine [(-)-crychine] (20) and (+)-O-methyleschscholtzidine [(+)-O-methylcaryachine] (21) belonging to pavines and protopine (22) have been also investigated by the same method as aporphines. The methiodides of these alkaloids prepared by ordinary method were treated



Scheme 2

with CH_2N_2, respectively. The ether soluble part of reaction products consisting of several compounds was separated by preparative tlc method, respectively. The results were shown in the Scheme 2. Soine and coworkers have already reported that the Hofmann elimination with CH_2N_2 on (±)-laudanosine (16) methiodide afforded laudanosine methine (16a)[3]. This time, we obtained the main product which has a cyclopropane ring in the molecule formed by the addition of methylene group on the double bond of cis-laudanosine methine (16a), α,β-methylene laudanosine methine (26) and a small amount of the des-N-compound of 26, α,β-methylene-2-vinyl-4,5,3',4'-tetramethoxystilbene (27). In the case of the methine base (18a) of O-methylarmepavine methiodide (18), it is also presumed that the same path takes place as 18a ⟶ 28 ~ 30, but the route from 29 to 30 is still not clear. These compounds, 26, 27, 28, and 30, which have a cyclopropane ring in the molecule were all agreeable with their chemical structures, because of the following facts [(a) ~ (d)], respectively. (a) In the uv spectra, each absorption curve does not coincide with that of the methine and isomethine bases, [$\lambda_{max.}^{MeOH}$ nm(log ε): 26: 330(4.19), 296(4.13) and 212(4.42); 27: 320 (3.78), 288(3.85), 230sh(4.14) and 212(4.30); 28: 330(3.97), 300(3.97) and 224(4.00); 30: 328sh(3.53), 310(3.86), 270(3.91) and 220(4.01)]. (b) In the ^{1}Hnmr spectra, there are not any signals corresponding to ethylenic protons of the methine base, but there are signals corresponding to the methylene and methine groups. [26: 2.27 (2H, d, J=7 Hz, Ha), 3.57 (2H, d, J=7 Hz, Hb); 27: 2.78 (2H, d, J=7 Hz, Ha), 3.60 (2H, d, J=7 Hz, Hb); 28: 2.28 (2H, d, J=7 Hz, Ha), 3.65 (2H, d, J=7 Hz, Hb); 30: 2.80 (2H, d, J=7 Hz, Ha), 3.55 (2H, d, J=7 Hz, Hb)]. (c) They are all optical active. $[\alpha]_D^{23}$: 26: -12° (c=0.1, MeOH); 27: -30° (c=0.1, MeOH); 28: -15° (c=0.1, MeOH); 30: -33° (c=0.1, MeOH). (d) In the mass spectra of 26, 27, 28, and 30, though their molecular ion peaks are all very small, but their base peaks all appear at m/z M^+-14 positions because of the elimination of methylene group from the cyclopropane rings, respectively. [m/z(%): 26: $C_{23}H_{31}O_4N$, 385(1.3)(M^+), 371(100); 27: $C_{21}H_{24}O_4$, 340(4.1)(M^+), 326(100); 28: $C_{22}H_{29}O_3N$, 355(0.6)(M^+), 341(100); 30: $C_{20}H_{22}O_3$, 310(1.5)(M^+), 296(100)]. From (-)-eschscholtzine [(-)-crychine] (20) methiodide, eschscholtzine methine (31) and the des-N-compound, eschscholtzine bismethine (32) afforded. Both eschscholtzine methine (31) and eschscholtzine bismethine (32) were identified with authentic samples which were prepared by the first and the second Hofmann elimination with KOH on (-)-eschscholtzine (20) methiodide, respectively. On the other hand, from (+)-eschscholtzidine [(+)-O-methylcaryachine] (21) methiodide, two kinds of the

Table 2: The reaction products of some of the aporphine with diazomethane.



	3	4	5	6	7
1-a, -b, and -c	OMe	OMe	H	OMe	OMe
5-a, -b, and -c	OCH_2O		H	OMe	OMe
7-a, -b, and -c	OMe	OMe	OMe	OMe	H
10-a, -b, and -c	OCH_2O		OMe	OMe	H
12-a, -b, and -c	OCH_2O		H	H	OMe
13-a, -b, and -c	OCH_2O		H	H	H

Table 3: The yields of the reaction products of the quaternary nonphenolic alkaloids MeI (200 mg) with diazomethane.

	Yields					
	methines		isomethines		bismethines	
	mg	%	mg	%	mg	%
Glaucine (1) MeI	20	13.55	5	3.39	10	7.72
Dicentrine (5) MeI	20	13.49	5	3.37	14	10.82
O-Methylisocorydine (7) MeI	6	4.07	20	13.55	6	4.63
O-Methylbulbocapnine (10) MeI	5	3.38	20	13.49	6	4.64
N-Methylxylopine (12) MeI	29	20.42	—	—	8	6.54
Roemerine (13) MeI	15	10.67	—	—	6	5.04
Ushinsunine (14) MeI	—	—	108	80.13	—	—
Anhydroushinsunine (15) MeI	—	—	58	41.24	—	—
Laudanosine (16) MeI	30	19.84	—	—	6	4.41
O-Methylarmepavine (18) MeI	16	10.48	3	2.05	5	3.73
Eschscholtzine (20) MeI	26	17.94	—	—	7	5.58
Eschscholtzidine (21) MeI	35	22.79	(C_6-N-Me_2 isomer)		19	14.75
	22	14.32	(C_{12}-N-Me_2 isomer)			
Protopine (22) MeI	28	19.21	—	—	—	—

methine bases (Rf 0.2 and 0.33) which are positional isomers where the N,N-dimethylamino group locates at C_6- or C_{12}- position yielded. In the ^{1}Hnmr of both methines (Rf 0.2 and 0.33), the chemical shifts of C_7- and C_{10}-aromatic protons neighbouring to methoxyl groups may appear at lower field than that of C_1- and C_4-aromatic protons neighbouring to the methylenedioxy groups in 33 and 34, respectively. Moreover, the chemical shifts of both C_7-H in 33 and C_1-H in 34 which close by N,N-dimethylamino group may appear at lower field than that of C_{10}-H in 33 and C_4-H in 34 which do not have deshielding effect of N,N-dimethylamino group, respectively. Therefore, the chemical structures of the two methine bases with Rf 0.2 and 0.33 obtained from (+)-eschscholtzidine (21) methiodide will be able to exhibit as 33 and 34, respectively. And the des-N-compound, eschscholtzidine bismethine (35) which was identified with the second Hofmann elimination product of eschscholtzidine (21) methiodide with KOH was obtained. The reaction with a large excess of CH_2N_2 on protopine (22) methiodide yielded only one methine base with mp 125-127°C and $[\alpha]_D^{23}$ ±0°. The chemical shifts of its ^{1}Hnmr are agreeable with protopine methine (36). Besides of there are still several products which are assumed the addition products of CH_2N_2 on the carbonyl group and/or vinyl group of 22 and 36.

As the above results, the four oxygenated (1,2,9,10- or 1,2,10,11-) aporphines take place the first and the second Hofmann elimination and forms the methines, isomethines and bismethines. In the yields of the reaction products are shown in Table 3. In 1,2,9,10-oxygenated aporphinium alkaloids, the ratio of the yields of the methine and the isomethine is about 4 : 1. On the other hand, in the 1,2,10,11-oxygenated aporphinium alkaloids, the yields of the isomethine are about fourfold to that of the methine.

EXPERIMENTAL

All mps are uncorrected and taken on a Yanaco micro-melting point apparatus. Optical rotations were measured on a Jasco model Dip-181 Digital Polarimeter. Uv absorption spectra were scanned on a Beckmann model 34 Spectrophotometer. Ir spectra were taken on a Hitachi model 260-30 Infrared Spectrophotometer. The ^{1}Hnmr spectra were taken on a Varian EM 360 L 60 MHZ Spectrometer with TMS as internal standard and chemical shifts were recorded in δ (ppm) units. Mass spectra were measured with a Jeol JMS-D-100 Mass Spectrometer at 75 ev. Silica gel (60-120 mesh) and neutral alumina (Merck)

were used for column chromatography and silica gel GF-254 for tlc.

General Procedure for the Hofmann Elimination with Diazomethane — The tertiary alkaloids shown in Table 1 were all treated with CH_3I in order to derive to the quaternary salts, respectively, The ether solution of diazomethane which was prepared from nitrosomethylurea (10-20 g), ether (200-400 ml), and 50% KOH (50-100 ml) was added to the MeOH solution of the quaternary salt (200 mg). The mixture evolving N_2 gas was left along for five days at room temperature. The ether solution was evaporated to leave a fishy yellowish viscous residue under reduced pressure at room temperature. The residue was extracted with ether to divide into ether soluble part and insoluble part. The ether soluble part which shown three spots (Rf 0.18, 0.35 and 0.75) in tlc (silica gel, MeOH) was separated by preparative tlc (silica gel, MeOH) method. From each of Rf 0.18, 0.35 and 0.75, methines, isomethines and bismethines (des-N compounds) were obtained, respectively. From the ether insoluble part, the original quaternary salt was recovered. If the phenolic alkaloid was used, the original and its O-methylated quaternary salts are recovered from this part.

Hofmann Elimination with Diazomethane on (+)-Glaucine (1) Methiodide — When 200 mg of (+)-glaucine (1) methiodide was treated by the general procedure described above, glaucine methine (1a), glaucine isomethine (1b) and glaucine bismethine (1c) were obtained from the ether soluble part. Each of these products was identified by the comparison of uv, ir, ^{1}Hnmr spectra and $[\alpha]_D$ with authentic samples which were prepared by the first and second Hofmann degradation with KOH on (+)-glaucine (1) methiodide and glaucine methine (1a) methiodide, respectively. From the ether insoluble part, glaucine (1) methiodide was recovered.

Hofmann Elimination with Diazomethane on Glaucinium (1) Hydroxide — The ethereal solution of diazomethane prepared by the above method was added on the methanol solution of glaucinium (1) hydroxide which was prepared by shaking glaucine (1) methiodide (300 mg) with the excess of silver oxide (about 500 mg) that was freshly precipitated from methanol solutions of silver nitrate and potassium hydroxide. The mixture was left alone for five days at room temperature, and then, it was treated by the general procedure described above. Glaucine methine (1a), glaucine isomethine (1b), and glaucine bismethine (1c) afforded. These products were identified with authentic samples, respectively.

Hofmann Elimination with Diazomethane on N-Methyllaurotetanine (2) Methiodide — The ethereal solution of diazomethane prepared by the ordinary method was added in

the methanol solution of N-methyllaurotetanine (2) methiodide and left alone for five days at room temperature. The mixture was treated as described in the general procedure. Glaucine methine (1a), glaucine isomethine (1b) and glaucine bismethine (1c) were obtained from the ether soluble part and N-methyllaurotetanine (2) methiodide and glaucine (1) methiodide were recovered from the ether insoluble part.

Glaucine Methine (1a) — Colorless needles with mp 91-95°C (Me_2CO), (lit.[5] 70-71°C). $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.18 (MeOH, silica gel). Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 368(2.55), 348(2.55), 323(3.68), 286sh(3.91) and 268(4.40). ^{1}Hnmr ($CDCl_3$) δ: 2.39 [6H, s, $N(CH_3)_2$], 3.90 (3H, s, OCH_3), 4.03 (6H, s, OCH_3 x 2), 4.06 (3H, s, OCH_3), 7.15 (1H, s, C_2-Ar. H), 7.16 (1H, s, C_8-Ar. H), 7.46 (1H, d, J=8.52 Hz, C_9-Ar. H), 7.76 (1H, d, J=8.52 Hz, C_{10}-Ar. H), 9.23 (1H, s, C_5-Ar. H). Methiodide: Colorless prisms with mp 274-276°C (MeOH), (lit.[5] 275-276°C). $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Ir (KBr), tlc and mixed mp coincide with glaucine methine (1a) methiodide.

Glaucine Isomethine (1b) — Colorless needles with mp 117-120°C (Me_2CO). $[\alpha]_D^{23}$ -62° (c=0.1, MeOH). Rf 0.31. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 307(3.44), 258sh(3.63), 228(4.26). ^{1}Hnmr ($CDCl_3$) δ: 2.09 [6H, s, $N(CH_3)_2$], 3.63 (3H, s, OCH_3), 3.90 (6H, s, OCH_3 x 2), 3.93 (3H, s, OCH_3), 5.30 and 5.60 (each 1H, dd, Jax=16 Hz, Jbx=10 Hz, Jab=1.5 HZ, Hb and Ha of styrene), 6.70 (1H, s, C_2-Ar. H), 6.96 (1H, s, C_8-Ar. H), 7.13 (1H, dd, Hx of styrene), 8.10 (1H, s, C_5-Ar. H).

Glaucine Bismethine (1c) — Colorless needles with mp 125-129°C (Me_2CO), (lit.[6] 141-143°C). $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.73. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 368(2.81), 322 (3.59), 288sh(3.83), 267(4.21) and 227(3.98). ^{1}Hnmr ($CDCl_3$) δ: 3.90 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 4.07 (6H, s, OCH_3 x 2), 5.47 and 5.73 (each 1H, dd, Jax=18 Hz, Jbx=11 Hz, Jab=2 Hz, Hb and Ha of styrene), 7.17 (1H, s, C_2-Ar. H), 7.30 (1H, dd, Hx of styrene), 7.37 (1H, s, C_8-Ar. H), 7.50 (1H, d, J=8.4 Hz, C_9-Ar. H), 7.83 (1H, d, J=8.4 Hz, C_{10}-Ar. H), 9.23 (1H, s, C_5-Ar. H).

The same reaction was made for the other benzyltetrahydroisoquinoline related alkaloids shown in the Table 1. The data (mp, $[\alpha]_D$, uv and ^{1}Hnmr) of the reaction products yield from these alkaloids were shown as in the following, respectively (Table 2 and Scheme 2).

Dicentrine Methine (5a) — Colorless needles with mp 155-159°C (Me_2CO), (lit.[7] 158-159°C). $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.14. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 372(2.85), 354(2.85), 325(3.32), 288sh(3.50) and 268(4.10). ^{1}Hnmr ($CDCl_3$) δ: 2.40 [6H, s, $N(CH_3)_2$], 4.00 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 6.17 (2H, s, OCH_2O), 7.07 (1H, s, C_2-Ar. H),

7.17 (1H, s, C_8-Ar. H), 7.45 (1H, d, J=8.3 Hz, C_9-Ar. H), 7.75 (1H, d, J=8.3 Hz, C_{10}-Ar. H), 8.53 (1H, s, C_5-Ar. H).

Dicentrine Isomethine (5b) — Colorless needles with mp 135-140°C. $[\alpha]_D^{23}$ -84° (c=0.1, MeOH). Rf 0.30. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 307(3.44), 258sh(3.63) and 228(4.26). ^{1}Hnmr ($CDCl_3$) δ: 2.10 [6H, s, $N(CH_3)_2$], 3.94 (3H, s, OCH_3), 4.07 (3H, s, OCH_3), 5.27 and 5.36 (each 1H, dd, Jax=17 Hz, Jbx=10 Hz, Jab=1.5 Hz, Hb and Ha of styrene), 6.20 (2H, s, OCH_2O), 6.50 (1H, s, C_2-Ar. H), 6.77 (1H, s, C_8-Ar. H), 7.13 (1H, dd, Hx of styrene), 7.63 (1H, s, C_5-Ar. H).

Dicentrine Bismethine (5c) — Colorless needles with mp 183-185°C, $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.70. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 372(2.49), 336(3.19) and 272(3.57). ^{1}Hnmr ($CDCl_3$) δ: 3.98 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 5.37 and 5.67 (each 1H, dd, Jax=17 Hz, Jbx=11 Hz, Jab=1.5 Hz, Hb and Ha of styrene), 6.17 (2H, s, OCH_2O), 7.10 (1H, s, C_2-Ar. H), 7.28 (1H, s, C_8-Ar. H), 7.40 (1H, d, J=8.3 Hz, C_9-Ar. H), 7.77 (1H, d, J=8.3 Hz, C_{10}-Ar. H), 8.45 (1H, s, C_5-Ar. H).

O-Methylisocorydine Methine (7a) — $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.18. Uv: $\lambda_{max.}^{MeOH}$ nm (log ε): 368(2.57), 344(2.87), 320(3.57), 286sh(3.74) and 264(4.22). ^{1}Hnmr ($CDCl_3$) δ: 2.38 [6H, s, $N(CH_3)_2$], 3.63 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 4.00 (6H, s, OCH_3 x 2), 7.13 (1H, s, C_2-Ar. H), 7.20 (1H, d, J=8.3 Hz, C_7-Ar. H), 7.33 (1H, d, J=8.3 Hz, C_8-Ar. H), 7.43 (1H, d, J=8.3 Hz, C_9-Ar. H), 7.53 (1H, d, J=8.3 Hz, C_{10}-Ar. H). $C_{22}H_{27}O_4N$, m/z (%): 369 (M^+, 100), 353 (5.6), 324 (25), 311 (33.3)

O-Methylisocorydine Isomethine (7b) — $[\alpha]_D^{23}$ -184° (c=0.1, MeOH). Rf 0.36. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 310(3.52), 257(4.26) and 232(4.32). ^{1}Hnmr ($CDCl_3$) δ: 2.07 [6H, s, $N(CH_3)_2$], 3.63 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.25 and 5.60 (each 1H, dd, Jax=17 Hz, Jbx=11 Hz, Jab=1.5 Hz, Hb and Ha of styrene), 6.83 (1H, s, C_2-Ar. H), 6.86 (1H, d, J=8.4 Hz, C_7-Ar. H), 7.03 (1H, d, J=8.4 Hz, C_8-Ar. H), 7.16 (1H, dd, Hx of styrene). m/z (%): 369 (M^+, 100), 354 (56.3), 325 (90), 324 (30), 310 (25). Anal. calcd. for $C_{22}H_{27}O_4N$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.54; H, 7.42; N, 3.84.

O-Methylisocorydine Bismethine (7c) — $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.73. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 370(2.79), 338(3.33), 266(3.79) and 228(3.83). ^{1}Hnmr ($CDCl_3$) δ: 3.64 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 5.35 and 5.60 (each 1H, dd, Jax=17 Hz, Jbx=11 Hz, Jab=1.5 Hz, Hb and Ha of styrene), 7.12 (1H, s, C_2-Ar. H), 7.23-7.57 (5H, m, C_7-~C_{10}-Ar. H and Hx of styrene).

O-Methylbulbocapnine Methine (10a) — $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.21. Uv: $\lambda_{max.}^{MeOH}$

nm(log ε): 390(2.55), 370(2.55), 325(3.33), 304(3.25), 262(4.20), 248sh(3.95) and 220(3.75). ^{1}Hnmr ($CDCl_3$) δ: 2.37 [6H, s, $N(CH_3)_2$], 3.73 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 6.10 (2H, s, OCH_2O), 7.10 (1H, s, C_2-Ar. H), 7.20 (1H, d, J=10 Hz, C_7-Ar. H), 7.30 (1H, d, J=10 Hz, C_8-Ar. H), 7.50 (1H, d, J=10 Hz, C_9-Ar. H), 7.63 (1H, d, J=10 Hz, C_{10}-Ar. H). $C_{21}H_{23}O_4N$, m/z (%): 353 (M^+, 100), 309 (21.1), 308 (84.2), 295 (10.5).

O-Methylbulbocapnine Isomethine (10b) — $[\alpha]_D^{23}$ -364° (c=0.1, MeOH). Rf 0.41. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 318(3.36), 266(4.23) and 234(4.28). ^{1}Hnmr ($CDCl_3$) δ: 2.10 [6H, s, $N(CH_3)_2$], 3.70 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.23 and 5.57 (each 1H, dd, Jax=17 Hz, Jbx=11 Hz, Jab=1.5 Hz, Hb and Ha of styrene), 5.87 and 6.07 (each 1H, d, J=1.5 Hz, OCH_2O), 6.82 (1H, s, C_2-Ar. H), 6.85 (1H, s, J=8.4 Hz, C_7-Ar. H), 7.00 (1H, d, J=8.4 Hz, C_8-Ar. H), 7.16 (1H, dd, Hx of styrene). $C_{21}H_{23}O_4N$, m/z (%): 353 (M^+, 100), 308 (82.3), 294 (12.4).

O-Methylbulbocapnine Bismethine (10c) — $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.73. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 370(2.79), 338(3.33), 266(3.79) and 228(3.83). ^{1}Hnmr ($CDCl_3$) δ: 3.70 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 5.37 and 5.63 (each 1H, dd, Jax=16 Hz, Jbx=10 Hz, Jab=1.5 Hz, Hb and Ha of styrene), 6.07 (2H, s, OCH_2O), 7.13 (1H, s, C_2-Ar. H), 7.20 (1H, dd, Hx of styrene), 7.23 (1H, d, J=10 Hz, C_7-Ar. H), 7.33 (1H, d, J=10 Hz, C_8-Ar. H), 7.47 (1H, d, J=10 Hz, C_9-Ar. H), 7.67 (1H, d, J=10 Hz, C_{10}-Ar. H).

N-Methylxylopine Methine (12a) — Colorless needles with mp 90-92°C (Me_2CO), (lit.[8] 99°C). $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.3. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 370(3.27), 350(3.58), 325(4.03), 292(4.33), 272(4.73), 256(4.73), 238(4.57) and 216(4.50). ^{1}Hnmr ($CDCl_3$) δ: 2.37 [6H, s, $N(CH_3)_2$], 3.93 (3H, s, OCH_3), 6.17 (2H, s, OCH_2O), 7.07 (1H, s, C_2-Ar. H), 7.17 (1H, d, J=2 Hz, C_8-Ar. H), 7.20 (1H, dd, J=8 Hz and J=2 Hz, C_6-Ar. H), 7.47 (1H, d, J=9 Hz, C_9-Ar. H), 7.83 (1H, d, J=9 Hz, C_{10}-Ar. H), 8.97 (1H, d, J=8 Hz, C_5-Ar. H). m/z (%): 323 (M^+, 100), 279 (11.5), 278 (10.4), 265 (52.1). Anal. calcd. for $C_{20}H_{21}O_3N$: C, 74.28; H, 6.55; N, 4.33. Found: C, 73.66; H, 6.41; N, 4.44.

N-Methylxylopine Bismethine (12c) — Colorless sand crystals with mp 130-134°C (Me_2CO). $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.75. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 336(3.59), 272 (4.23) and 226(4.16). ^{1}Hnmr ($CDCl_3$) δ: 3.97 (3H, s, OCH_3), 5.40 and 5.80 (each 1H, dd, Jax=17 Hz, Jbx=10 Hz, Jab=1.5 Hz, Hb and Ha of styrene), 6.20 (2H, s, OCH_2O), 7.13 (1H, s, C_2-Ar. H), 7.14 (1H, dd, Hx of styrene), 7.17 (1H, d, J=2 Hz, C_8-Ar. H), 7.20 (1H, dd, J=8 Hz and J=2 Hz, C_6-Ar. H), 7.50 (1H, d, J=9 Hz, C_9-Ar. H), 7.93 (1H, d, J=9 Hz, C_{10}-Ar. H), 9.00 (1H, d, J=8 Hz, C_5-Ar. H).

Roemerine Methine (13a) — Colorless prisms with mp 83-85°C (Me_2CO), (lit.[9] 81°C). $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.3. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 370(3.32), 352(3.38), 324 (3.89), 286(4.09), 252(4.52) and 242(4.46). ^{1}Hnmr ($CDCl_3$) δ: 2.37 [6H, s, $N(CH_3)_2$], 6.23 (2H, s, OCH_2O), 7.13 (1H, s, C_2-Ar. H), 7.33-7.90 (5H, m, C_6- ~ C_{10}-Ar. H), 9.10 (1H, m, C_5-Ar. H). $C_{19}H_{19}O_2N$, m/z (%): 293 (M^+, 100), 248 (80.9), 235 (54.4).

Roemerine Bismethine (13c) — $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.8. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 370(2.79), 320(3.39), 285sh(3.67), 260(3.97), 250(3.97), 238(3.96) and 220(4.04). ^{1}Hnmr ($CDCl_3$) δ: 5.40 and 5.67 (each 1H, dd, Jax=17 Hz, Jbx=10 Hz, Jab=1.5 Hz, Hb and Ha of styrene), 6.27 (2H, s, OCH_2O), 7.23 (1H, s, C_2-Ar. H), 7.40-7.97 (6H, m, C_6- ~ C_{10}-Ar. H and Hx of styrene), 9.06 (1H, m, C_5-Ar. H). $C_{17}H_{12}O_2$, m/z (%): 248 (M^+, 100), 235 (85.7).

Ushinsunine Isomethine (25) — Colorless needles with mp 93-95°C (Me_2CO), (lit.[4] 108-109°C). $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.62. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 336(3.95), 264 (4.57), 238(4.45) and 218(4.29). ^{1}Hnmr ($CDCl_3$) δ: 2.57 [6H, s, $N(CH_3)_2$], 5.00 and 5.43 (each 1H, dd, Jax=17 Hz, Jbx=11 Hz, Jab=1.5 Hz, Hb and Ha of styrene), 6.03 (2H, s, OCH_2O), 7.00 (1H, s, C_2-Ar. H), 7.13 (1H, s, C_9-Ar. H), 7.30-7.57 (4H, m, C_6- ~ C_8-Ar. H and Hx of styrene), 8.93 (1H, m, C_5-Ar. H).

α,β-Methylene Laudanosine Methine (26) — Colorless needles with mp 79-81°C (Me_2CO). $[\alpha]_D^{23}$ -12° (c=0.1, MeOH). Rf 0.27. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 330(4.19), 296 (4.13) and 212(4.42). ^{1}Hnmr ($CDCl_3$) δ: 2.27 (2H, d, J=7 Hz, Ha), 2.37 [6H, s, $N(CH_3)_2$], 3.57 (2H, d, J=7 Hz, Hb), 3.90 (6H, s, OCH_3 x 2), 3.96 (6H, s, OCH_3 x 2), 6.53 (1H, s, C_6-Ar. H), 6.73 (2H, s, C_3-, C_2'-Ar. H), 6.97 (1H, d, J=10 Hz, C_6'-Ar. H), 7.23 (1H, d, J=10 Hz, C_5'-Ar. H). m/z (%): 385 (M^+, 1.3), 371 (100), 220 (22), 151 (12.7). Anal. calcd. for $C_{23}H_{31}O_4N$: C, 71.66; H, 8.10; N, 3.63. Found: C, 70.96; H, 7.89; N, 3.76.

α,β-Methylene Laudanosine Bismethine (27) — $[\alpha]_D^{23}$ -30° (c=0.1, MeOH). Rf 0.8. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 320(3.78), 288(3.85), 230sh(4.14) and 212(4.30). ^{1}Hnmr ($CDCl_3$) δ: 2.78 (2H, d, J=7 Hz, Ha), 3.60 (2H, d, J=7 Hz, Hb), 3.80 (3H, s, OCH_3), 3.90 (6H, s, OCH_3), 5.13 and 5.53 (each 1H, dd, Jax=17 Hz, Jbx=10 Hz, Jab=1.5 Hz, Hb and Ha of styrene), 6.53 (1H, s, C_6-Ar. H), 6.68 (2H, s, C_3-, C_2'-Ar. H), 6.93 (1H, d, J= 8 Hz, C_6'-Ar. H), 7.00 (1H, dd, Hx of styrene), 7.13 (1H, d, J=8 Hz, C_5'-Ar. H). $C_{21}H_{24}O_4$, m/z (%): 340 (M^+, 4.1), 326 (100), 151 (89.6).

α,β-Methylene O-Methylarmepavine Methine (28) — $[\alpha]_D^{23}$ -15° (c=0.1, MeOH). Rf 0.25. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 330(3.97), 300(3.97) and 224(4.00). ^{1}Hnmr ($CDCl_3$) δ: 2.28 (2H,

d, J=7 Hz, Ha), 2.33 [6H, s, $N(CH_3)_2$], 3.65 (2H, d, J=7 Hz, Hb), 3.80 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.53 (1H, s, C_6-Ar. H), 6.70 (1H, s, C_3-Ar. H), 6.97-7.57 (4H, m, $C_{6'}$-, $C_{5'}$-, $C_{3'}$-, $C_{2'}$-Ar. H). $C_{22}H_{29}O_3N$, m/z (%): 355 (M^+, 0.6), 341 (100), 220 (16.1), 121 (13.6).

O-Methylarmepavine Isomethine (29) — $[\alpha]_D^{23}$ +49° (c=0.1, MeOH). Rf 0.4. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 300(3.23), 260(3.79) and 220(4.18). ^{1}Hnmr ($CDCl_3$) δ: 2.27 [6H, s, $N(CH_3)_2$] 3.67 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.97 and 5.20 (each 1H, dd, Hb and Ha of styrene), 6.60-6.77 (6H, m, Ar. H), 7.00 (1H, dd, Hx of styrene). $C_{21}H_{27}O_3N$, m/z (%): 341 (M^+, 2.8), 220 (100), 177 (63.9), 121 (13.9).

α,β-Methylene O-Methylarmepavine Bismethine (30) — $[\alpha]_D^{23}$ -33° (c=0.1, MeOH). Rf 0.7. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 328sh(3.53), 310(3.86), 270(3.91) and 220(4.01). ^{1}Hnmr ($CDCl_3$) δ: 2.80 (2H, d, J=7 Hz, Ha), 3.55 (2H, d, J=7 Hz, Hb), 3.70 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.10 and 5.53 (each 1H, dd, Jax=16 Hz, Jbx=10 Hz, Jab=1.5 Hz, Hb and Ha of styrene), 6.50 (1H, s, C_6-Ar. H), 6.63 (1H, s, C_3-Ar. H), 6.73-7.50 (5H, m, $C_{6'}$-, $C_{5'}$-, $C_{3'}$-, $C_{2'}$-Ar. H and Hx of styrene). $C_{20}H_{22}O_3$, m/z (%): 310 (M^+, 1.5), 296 (100), 192 (23.5), 121 (96).

Eschscholtzine Methine (31) — $[\alpha]_D^{23}$ +41° (c=0.1, MeOH). Rf 0.37. Uv: $\lambda_{max.}^{MeOH}$ nm (log ε): 295(3.53), 225sh(3.93) and 208(4.11). ^{1}Hnmr ($CDCl_3$) δ: 2.23 [6H, s, $N(CH_3)_2$], 5.78 and 5.82 (each 2H, d, J=1.5 Hz, OCH_2O), 6.50 (2H, s, C_1-, C_4-Ar. H). 6.60 (2H, s, C_{11}-, C_{12}-stilbene H), 6.64 (1H, s, C_7-Ar. H).

Eschscholtzine Bismethine (32) — $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.76. Uv: $\lambda_{max.}^{MeOH}$ nm (log ε): 298(3.58) and 214(3.97). ^{1}Hnmr ($CDCl_3$) δ: 5.90 and 5.97 (each 2H, d, J=1.5 Hz, OCH_2O), 6.50 (2H, s, C_1-, C_4-Ar. H), 6.57 (4H, s, C_5-, C_6-, C_{11}-, C_{12}-stilbene H), 6.67 (2H, s, C_7-, C_{10}-Ar. H).

6-N-Methyleschscholtzidine Methine (33) — $[\alpha]_D^{23}$ -14° (c=0.1, MeOH). Rf 0.2. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 296(4.25) and 230(4.72). ^{1}Hnmr ($CDCl_3$) δ: 2.23 [6H, s, $N(CH_3)_2$], 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.80 and 5.87 (each 2H, s, J=1.5 Hz, OCH_2O), 6.50 (2H, s, C_1-, C_4-Ar. H), 6.62 (1H, s, C_{10}-Ar. H), 6.68 (1H, s, C_7-Ar. H), 6.75 (2H, s, C_{11}-, C_{12}-stilbene H). $C_{21}H_{23}O_4N$, m/z (%): 353 (M^+, 100), 338 (37.5), 322 (44), 309 (56.3), 308 (37.5), 293 (37.5), 278 (25).

12-N-Methyleschscholtzidine Methine (34) — $[\alpha]_D^{23}$ -35° (c=0.1, MeOH). Rf 0.33. Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 296(4.01) and 230(4.42). ^{1}Hnmr ($CDCl_3$) δ: 2.20 [6H, s, $N(CH_3)_2$], 3.77 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 5.73 and 5.77 (each 1H, d, J=1.5 Hz, OCH_2O), 6.43 (1H, s, C_4-Ar. H), 6.46 (1H, s, C_1-Ar. H), 6.60 (2H, s, C_7-, C_{10}-Ar. H), 6.74

(2H, s, C_5-, C_6-stilbene H). $C_{21}H_{23}O_4N$, m/z (%): 353 (M^+, 100), 338 (33.3), 322 (25), 309 (54.2), 308 (37.5), 283 (25), 278 (25).

Eschscholtzidine Bismethine (35) — $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Rf 0.76. Uv: $\lambda_{max.}^{MeOH}$ nm (log ε): 298(3.56) and 214(3.98). ^{1}Hnmr ($CDCl_3$) δ: 3.75 (6H, s, OCH_3 x 2), 5.80 and 5.83 (each 1H, d, J=1.5 Hz, OCH_2O), 6.48-6.90 (8H, m, C_1-, C_4-, C_7-, C_{10}-Ar. H and C_5-, C_6-, C_{11}-, C_{12}-stilbene H). $C_{19}H_{16}O_4$, m/z (%): 308 (M^+, 100), 293 (62.5), 278 (62.1).

Protopine Methine (36) — Colorless needles with mp 125-127°C (Me_2CO). $[\alpha]_D^{23}$ ±0° (c=0.1, MeOH). Uv: $\lambda_{max.}^{MeOH}$ nm(log ε): 320sh(3.44), 292(3.56) and 240(3.93). ^{1}Hnmr ($CDCl_3$) δ: 2.14 [6H, s, $N(CH_3)_2$], 3.30 (2H, s, C_{15}-methylene H), 4.23 (2H, s, C_8-methylene H), 5.20 and 5.50 (each 1H, dd, Jax=16 Hz, Jbx=10 Hz, Jab=1.5 Hz, Hb and Ha of styrene), 5.90 and 6.00 (each 2H, d, J=2 Hz, OCH_2O), 6.60 (1H, s, C_2-Ar. H), 6.62 (1H, s, C_5-Ar. H), 6.99 (1H, s, C_{11}-Ar. H), 7.10 (1H, dd, Hx of styrene), 7.20 (1H, s, C_{10}-Ar. H).

ACKNOWLEDGEMENT

We gratefully thank Prof. Chiu-Ming Chen, National Tsing Hua University, for the mass measurements, Prof. Mou-Yung Yeh, National Cheng Kung University, for the elemental analysis, and Mr. Chorng-Shii Liou, Kaohsiung Medical College, for the measurements of ^{1}Hnmr spectra.

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§. This paper forms part XXX of " Studies on the Alkaloids of Formosan Lauraceous Plants " by Sheng-Teh Lu.

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Received, 9th November, 1987