PREPARATION OF *N*-ALKYLNORPAVINES *VIA* COMPETITIVE *N*-DEALKYLATION OF QUATERNARY PAVINES

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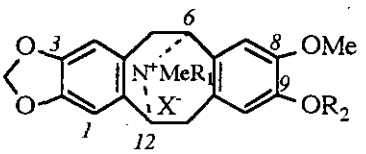
Abstract — *N*-Alkyl quaternary pavine salts were converted into *N*-alkyl tertiary pavines by refluxing ethanolamine, *via* a competitive *N*-dealkylation mechanism. The following *N*-dealkylation order was observed: benzyl> allyl > Me > Et > ^{n}Pr ≥ ^{n}Bu. Further study indicated that *N*-alkyl- and *N*-acylpavines could be obtained from *N*-methyl tertiary pavines in a one-pot reaction (acid anhydride/ allyl bromide or alkyl halide, reflux). This finding provides an alternative method for preparing *N*-alkyl tertiary pavines.

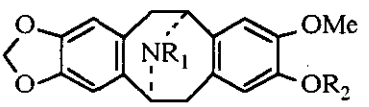
Recently *N*-methyl tertiary pavine (-)-caryachine (**1**), isolated from *Cryptocarya chinensis* H.[1] or obtained from *N*-demethylation of the quaternary (-)-caryachine *N*-metho salt (**I**),[2] was found to possess potent ion channel blocking action especially on I_{Na} (IC_{50}= 1.5 μM, rat single ventricular cells).[3] Being interested in exploring the potential use of this type compounds on cardiovascular system, we turned our attention to the preparation of *N*-alkyl tertiary pavines for further studying their biological activity.



	R_1	R_2		R_1	R_2
I	Me	H	**IIIa**	Pr	Me
Ia	Me	Me	**IIIb**	Pr	Bn
Ib	Me	Bn	**IVa**	Bu	Me
IIa	Et	Me	**IVb**	Bu	Bn
IIb	Et	Bn	**Va**	allyl	Me
			VIa	Bn	Me

I-Ib ClO_4^- salt

IIa-IIb I^- salt **III-VI** Br^- salt



	R_1	R_2
1	Me	H
2	Et	H
3	Pr	H
4	Bu	H
5	allyl	H
6	Bn	H
7	Ac	H
8	propionyl	H

	R_2
a series	Me
b series	Bn
c series	Ac
d series	propionyl

N-Alkyl tertiary pavines could be prepared by direct *N*-alkylation of norpavines, obtained from two methods: i. von Braun reaction of *N*-methylpavines ($BrCN/CHCl_3$, reflux), followed by acid hydrolysis of

*N*CN group (90% HOAc, reflux); ii. *N*-demethylation with 2,2,2-trichloroethyl chloroformate, followed by reductive cleavage (Zn/ 90% HOAc) of the resultant carbamate.[2] Motivated by the facile *N*-demethylation of *N*-methyl quaternary pavines with ethanolamine under reflux,[2] we thought that *N*-alkyl tertiary pavines could be prepared in the similar manner using *N*-alkyl quaternary pavines as starting materials. Here we report the outcome of this alternative method.

(-)-*O*-Methyl- and *O*-benzylcaryachine *N*-methoperchlorate (**Ia** and **Ib**) were prepared from *O*-methylation (MeI/K_2CO_3, MeOH, reflux, 99.7%) and *O*-benzylation (BnBr/K_2CO_3, MeOH, reflux, 96.9%), respectively, of caryachine *N*-methoperchlorate (**I**).[2] They were converted to the corresponding *N*-methyl tertiary pavines (**1a**)[1] (80.3%) [m/z 339 (M^+), δ_{OMe} 3.86 and 3.76] and **1b**[2] (98.5%) by reacting with ethanolamine under reflux. *N*-Alkyl quaternary pavines (**II-V**) were prepared by treating **1** with alkyl halide either neat (**III-IV**) or in MeCN (**II, V**) in a sealed tube under reflux overnight. Under such conditions, the formation of major product, **IVb** (68.0%), was accompanied with the production of two minor tertiary products (**4b**) (8.3%) [m/z 457 (M^+) and δ ($NC_3H_6C\underline{H}_3$) 0.89 (t, 3H, J=5.8 Hz)] and (**1b**) (4.5%). This result is rationalized by further thermolysis of **IVb** and the competitive *N*-dealkylation at higher reaction temperature (*n*-BuBr, bp 100-104°C).

Table 1. Conditions and results of competitive *N*-dealkylation on quaternary pavines by ethanolamine*

Entry	Reactant mg (μmol)	Reagent (ml)	Product mg (μmol)	Yield (%)
1	**IIa** 233.0 (470)	1	**1a** 30.0 (88) **2a** 65.7 (190)	17.1 39.5
2	**IIb** 300.8 (530)	1	**1b** 28.5 (69) **2b** 99.4 (230)	13.0 44.0
3	**IIIa** 98.4 (210)	1	**1a** 7.6 (22) **3a** 47.4 (130)	10.5 60.6
4	**IIIb** 381.3 (710)	5	**1b** 31.9 (77) **3b** 204.3 (460)	10.9 65.1
5	**IVa** 231.4 (490)	1	**1a** 30.0 (88) **4a** 113.4 (300)	18.2 61.2
6	**IVb** 430.1 (780)	1.5	**1b** 15.8 (38) **4b** 203.2 (440)	4.9 57.1
7	**Va** 116.7 (250)	1	**1a** 36.3 (110) **5a** 10.4 (28)	42.2 11.2
8	**VIa** 146.7 (288)	1	**1a** 82.0 (242) **6a** 0	84.0 0

*Reagent: ethanolamine; reaction temperature 160°C; reaction time 3 h.

Respective reaction of **II-V** with ethanolamine (160°, 3 h) yielded two tertiary pavine products, **1** (**a** or **b**) and the *N*-alkylnorpavines **2-5** (**a** or **b**) from each reactant in an isolated total yield of 53.4 to 79.4% (Table 1). However, using **VIa** as starting material gave a sole product (**1a**) (84%) *via* *N*-debenzylation. No Hofmann degradation products were found in this reaction as that using *N*,*N*-dimethyl quaternary pavine salts as starting materials. Apparently, these products were produced *via* a competitive *N*-dealkylation mechanism. As exemplified in the Table, the following *N*-dealkylation order was observed: benzyl> allyl > Me > Et > ^{n}Pr ≥ ^{n}Bu.

N-Dealkylation of flexible alkyl quaternary ammonium salts by ethanolamine has been reported.[4] This study found that dealkylation order from the rigid pavines is similar to the flexible skeletons and is useful for the preparation of *N*-alkyl tertiary pavines but not for those with *N*-allyl or *N*-benzyl substituents, both of which are readily attacked by the nucleophile, rendering *N*-benzylnorpavine not traceable and the low yield of **5a**.

Table 2. Conditions and results of competitive *N*-dealkylation and *N*-acylation on caryachine (**1**) and *O*-acetylcaryachine (**1c**) in a one-pot reaction

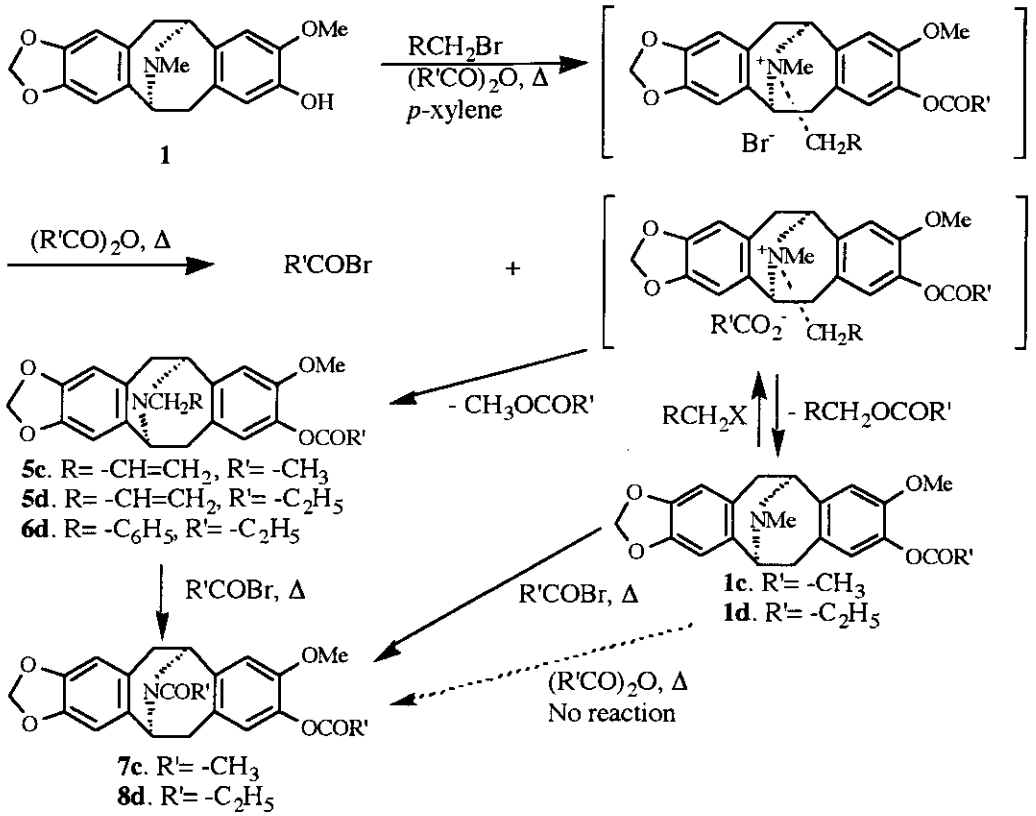
Entry	Reactant	Reagent		Time	Product	Yield
	mg (μmol)	Halide	Solvent	(d)	mg (μmol)	(%)
1	**1c** 55.6 (150)	**A** 66 μl (763 μmol)	**A** 3 ml	1	**1c** 5.0 (14) **5c** 15.2 (39) **7c** 26.2 (66)	9.0 25.5 43.8
2	**1c** 49.8 (140)	**A** 60 μl (693 μmol)	**A** 3 ml	5	**1c** 6.0 (16) **5c** 9.1 (23) **7c** 18.6 (47)	12.2 17.4 35.3
3	**1** 102.0 (314)	**A** 54 μl (624 μmol)	**B** 4 ml	1	**1d** 36.3 (95) **5d** 81.8 (200) **8d** 0	30.4 64.0 0
4	**1** 100.5 (309)	**A** 54 μl (624 μmol)	**B** 4 ml	2	**1d** 26.1 (69) **5d**,30.5 (75) **8d** 50.3 (120)	22.2 24.2 38.5
5	**1** 100.2 (308)	**A** 54 μl (624 μmol)	**B** 4 ml	3	**1d** 10.3 (29) **5d** 16.3 (40) **8d** 91.2 (220)	9.3 13.0 69.9
6	**1** 153.9 (474)	**B** 110 μl (925 μmol)	**B** 4 ml	1	**1d** 20.6 (54) **6d** 74.1 (160) **8d** 35.2 (83)	11.4 34.2 17.6
7	**1** 100.2 (308)	**B** 74 μl (622 μmol)	**B** 4 ml	2	**1d** 12.5 (33) **6d** 7.5 (16) **8d** 92.5 (220)	10.0 5.3 70.9

*Reagents: Halide A. allyl bromide, B. benzyl bromide; Solvent A. Ac_2O-*p*-xylene (1: 1), B. propionic anhydride-*p*-xylene (1: 1); reaction under reflux.

N-Dealkylation could take place intramolecularly if the salt form is halide or acetate, serving as nucleophile as ethanolamine does. This reaction must carry out under aprotic conditions (e.g. MeCN/*p*-xylene) [5] which make the molecule as ion pair to facilitate the reaction. Since the formation of desired *N*-alkylnorpavines is competitive, we thought the presence of much excess alkyl halide (allyl or benzyl halide) will increase the yield of these products. Considering these, the conditions composed of *N*-alkylation and competitive *N*-dealkylation in one pot were chosen. This approach led to the successful preparation of **5c** (43%) [m/z 393 (M^+); *N*-allyl protons at δ 5.90 (1H, m), 5.25 (1H, d, J=16.2 Hz), 5.15 (1H, d, J=11.6 Hz) and 3.23 (2H, d, J=6.2 Hz)], from **1c** with allyl bromide/*p*-xylene under reflux.

The poor solubility of quaternary alkaloids in this aprotic condition or even MeCN/*p*-xylene (1: 1), however, limited the reaction to a smaller scale. To solve this problem, polar aprotic solvents with higher boiling points (to facilitate thermolysis) such as Ac_2O and propionic anhydride were used to replace acetonitrile. Based on this modification, *O*-acetylcaryachine (**1c**) was obtained as a sole product (74%) upon treatment of the acetate salt of **1** with Ac_2O/ xylene under reflux. This condition solved the solubility problem. In addition, it gives only one product, instead of two yielded under ethanolamine condition.[2]

Reacting with acid anhydride under reflux, tertiary aporphines yielded the *N*-acylsecoaporphines.[6] In the same condition, we observed that no reaction occurred for *N*-alkyl tertiary pavines (**1c**, **4c** and **5c**). In the presence of much excess of alkyl halide or allyl bromide, the tertiary pavine (**1**), however, yielded the unexpected *N*-acyl norpavine (**8d**) besides the corresponding *N*-alkyl- or *N*-allylnorpavine (**5d**), [m/z 407 (M^+); δ 5.92 (m, -C<u>H</u>=CH_2), 5.25 (d, J=15.4 Hz) and 5.16 (d, J=11.3, Hz) for -CH=C<u>H_2</u>, 1.21 (t, J=7.3 Hz, -$OCOCH_2C$<u>H_3</u>)], under refluxing propionic anhydride- *p*-xylene (1: 1) in a sealed tube for 1 to 5 days (Table 2). It is worth noting that the *N*-acyl product (**7c** or **8d**) is composed of two inseparable geometric isomers in 1: 1 ratio revealed in the ^1H nmr spectra, for instance in **8d**, δ 6.56 and 6.58 for H-1 in each isomer. These geometric isomers are arisen from the delocalization of the lone pair electrons of the amide nitrogen. Reduction of **8d** with $LiAlH_4$ yielded a single product (**3**), $[\alpha]^{24}_D$ -216° (c= 0.85, MeOH); m/z 353 (M^+); δ 6.55 (s, H-1 and H-7), 6.48 (s, H-4), 6.38 (s, H-10), 4.04 (d, J=5.4 Hz, H-6 and H-12), 0.89 (t, J=7.2 Hz, *N*-C_2H_5C<u>H_3</u>). That compound (**3**) is identical to the product obtained from catalytic hydrogenation (H_2, Pd-C) of **3b** confirmed **8d** being the *N*-propionyl derivative. Further studies indicated that the *N*-acyl compounds are the major products in the presence of allyl, benzyl and alkyl halides for a longer reaction time (> 2 days). The optimal reaction time for better yield of *N*-alkyl tertiary pavines is about 1 day.



Scheme 1. Competitive *N*-dealkylation and *N*-acylation on (-)-caryachine (**1**) in a one-pot reaction

By reacting with the ammonium halide, acid anhydrides were converted *in situ* to the more reactive acyl halides which were then nucleophilically attacked by the amine nitrogen. The leaving halide, subsequently, attacked the *N*-alkyl group intramolecularly to give the *N*-acyl products (Scheme 1). It was noted that amide product was not traceable upon reacting **1** with pivaloyl chloride. This could be due to the presence of decomposed HCl product in the reagent, which reacted with **1** readily to give **1**.HCl that would stop further reaction.

This study discloses some chemical properties of pavine alkaloids. The results suggest that various *N*-alkyl tertiary pavines can be prepared more directly *via* competitive *N*-dealkylation of readily prepared quaternary pavines. The conditions (allyl or benzyl halide, acyl anhydride- xylene, reflux) found for *N*-allylation, benzylation are even more useful to prepare pavines containing those relatively good leaving groups in the *N*-dealkylation reaction. The latter conditions giving the unexpected *N*-acylation of pavines after longer reaction time provide an alternative facile way to prepare various *N*-alkyl tertiary pavines.

EXPERIMENTAL

The physical data of prepared compounds were obtained from the following instruments: $[\alpha]_D$: JASCO DIP-370 digital polarimeter; ir (KBr disc): JASCO ir Report-100 spectrophotometer; uv (MeOH): Hitachi U-2000 spectrophotometer; nmr ($CDCl_3$ unless other specified): Bruker AC-80 or AMX 400; EIms: Finnigan Mat TSQ-700 Mass spectrometer (70 eV unless other specified); HRms: Jeol JMX-HX110 Mass spectrometer; tlc (SiO_2, Merck Art. 5735, 0.2 mm) [MeOH-$CHCl_3$ (1: 9)] visualized under uv 254 nm and by Dragendorff spray reagent.

(-)-*O*-Methylcaryachine (**1a**). The mixture of caryachine *N*-methoperchlorate (**I**, 32.64 g, 74.18 mmol), K_2CO_3 (15.40 g, 111.60 mmol), MeOH/Me_2CO (1:1, 150 ml) and MeI (23.4 ml, 375.88 mmol) in a 250 ml RB flask was heated under reflux overnight. After cooling, the precipitate was filtered out and washed with MeOH. Evaporation of filtrate and washings gave an nmr and tlc essentially pure product (**Ia**) (33.60 g, 99.7%): mp 260-261° C (I^- salt, Me_2CO). Part of the product (16.75 g, 36.89 mmol) and ethanolamine (50 ml) was heated under reflux for 3 h. To the cooled reaction mixture was added H_2O to a volume of 200 ml which was adjusted to pH 9 with solid NH_4Cl, extracted with $CHCl_3$ (200 ml x 5). The combined $CHCl_3$ layer was dried (brine, $MgSO_4$), and evaporated under reduced pressure to give a liquid residue which was purified on a silica gel column eluted with 0-5% MeOH in $CHCl_3$ to give **1a**[1] (oil, 10.04 g, 80.3%): Rf 0.36; $[\alpha]_D^{24}$ -255.8° (c=1.06, MeOH); ^{1}H-nmr δ 6.57 (2H, s, H-1 and 7), 6.41 (2H, s, H-4 and 10), 3.86 (3H, s, 8-OMe), 3.76 (3H, s, 9-OMe), 5.80 (1H) and 5.84 (1H) (each d, J=1.4 Hz) (OC$\underline{H_2}$O), 2.49 (3H, s, NMe); EIms (%) m/z $[M]^+$ 339 (51), 205 (64), 204 (65),189 (23), 188 (100).

O-Benzylcaryachine (**1b**). Similar to the preparation of **Ia**, crude solid (**Ib**) was obtained from the refluxing mixture of **I** (ClO_4^-, 4.86 g, 11.04 mmol), K_2CO_3 (2.29 g, 16.57 mmol), MeOH (50 ml) and BnBr (2.60 ml, 21.86 mmol). This crude product was washed with toluene to remove unreacted BnBr and related compounds to give an nmr and tlc essentially pure product (**Ib**)[2] (5.67 g, 96.9%): mp 244-245°C (Me_2CO); ^{1}H-nmr δ (Me_2CO-d_6) 7.04 (1H, s), 6.88 (2H, s), 6.63 (1H, s), 5.99 (2H, s, OC$\underline{H_2}$O), 3.83 (3H, s, 8-OMe), 3.44 (6H, s, N^+Me_2), 5.00 (2H, s, benzyl CH_2) and 7.19-7.53 (5H, m, benzyl C_6H_5); EIms (%) m/z $[M\text{-}ClO_4]^+$ 430 (1), $[M\text{-}MeClO_4]^+$ 415 (2), 324 (10), 280 (17), 188 (50), 91 (100). Compound (**Ib**) (5.67 g, 10.7 mmol) and ethanolamine (12 ml, 199 mmol) was heated under reflux (165-170°) for 3 h. Similar work-up to that of the preparation of **1a** yielded a sole pure product (**1b**)[2] (oil, 4.51 g, 98.5%): Rf 0.44; ^{1}H-nmr δ 6.53 (1H, s, H-1), 6.41 (1H, s, H-4), 6.48 (1H, s, H-7), 6.60 (1H, s, H-10), 3.82 (3H, s, 8-OMe), 5.80 (1H) and 5.83 (1H) (each d, J=1.4 Hz, OC$\underline{H_2}$O), 5.05 (2H, s, benzyl

CH_2) and 7.31 (5H, m, benzyl C_6H_5), 2.49 (3H, s, NMe); EIms (%) m/z $[M]^+$ 415 (12), 324 (8), 280 (15),189 (12), 188 (17), 91 (100).

N-Alkyl quaternary pavines **IIa**, **IIb**, **Va**, and **VIa**. The mixture of **1a** (236.3 mg, 0.70 mmol), EtI (0.12 ml, 1.50 mmol) and MeCN (3 ml) was placed in a screw-tight sealed tube (25 ml). The mixture after degassing by vacuum was heated under reflux overnight and was evaporated to give a give a residue which was washed with ether to remove the unreacted **1a** and other impurity to give a sole amorphous pure product **IIa** (278.6 mg, 80.7%): HRms m/z $[M\text{-MeI}]^+$ 353.1628 (calcd for $C_{21}H_{23}NO_4$, 353.1627); EIms (%) m/z $[M\text{-MeI}]^+$ 353 (43), $[M\text{-EtI}]^+$ 339 (29), 218 (70), 204 (49), 202 (100), 188 (78), 174 (16).

In a similar manner to the preparation of **IIa**, reacting with allyl bromide, **1a** yielded **Va** (amorphous, 72.6%): HRms m/z $[M\text{-MeBr}]^+$ 365.1607 (calcd for $C_{22}H_{23}NO_4$, 365.1627); EIms (%) m/z $[M\text{-MeBr}]^+$ 365 (20), [M-allyl bromide]$^+$ 339 (54), 230 (12), 214 (18), 204 (67), 190 (22), 188 (100).

Reacting with ethyl iodide (0.15 ml, 1.88 mmol) in MeCN (5 ml), **1b** (367.4 mg, 0.89 mmol) yielded **IIb** (amorphous, 396.8 mg, 78.5%) and a tertiary product (**2b**) (51.1 mg, 13.5%), both of which were separated on a silica gel column (18 g, 70-230 mesh) eluted with 0-10% MeOH in $CHCl_3$. **IIb**: HRms m/z $[M\text{-MeI}]^+$ 429.1935 (calcd for $C_{27}H_{27}NO_4$, 429.1940); EIms (%) m/z $[M\text{-MeI}]^+$ 429 (91), $[M\text{-EtI}]^+$ 415 (31), 294 (99), 280 (36), 202 (100), 188 (35), 142 $[MeI]^+$ (20), 91 (68). **2b**: oil, Rf 0.52; ir (ν, cm^{-1}) 2960, 1613, 1517, 1500, 1480, 1377, 1109, 1040, 940, 923, 740, 700; ^{1}H-nmr δ 6.55 (1H, s, H-1), 6.39 (1H, s, H-4), 4.07 (2H, d, J=5.4 Hz, H-6 and 12), 6.47 (1H, s, H-7), 6.61 (1H, s, H-10), 3.82 (3H, s, 8-OMe), 4.99 (2H, s, benzyl CH_2) and 7.30 (5H, m, benzyl C_6H_5), 5.78 (1H) and 5.82 (1H) (each d, J=1.4 Hz, $OC\underline{H_2}O$), 1.17 (3H, t, J=6.9 Hz, $NCH_2C\underline{H_3}$); Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 73.71; H, 6.40; N, 2.69. HRms m/z $[M]^+$ 429.1940 (calcd for $C_{27}H_{27}NO_4$, 429.1940); EIms (20 eV) (%) m/z 430 (29), $[M]^+$ 429 (100), 338 (31), 294 (58), 202 (60).

Reaction of **1a** (101.6 mg, 0.30 mmol) with benzyl bromide (72 μl, 0.60 mmol) in MeOH (5 ml) under reflux overnight yielded semi-solid product residue which was washed with ether to remove the excess reagent (BnBr) and the unreacted **1a** and other impurity to give amorphous **VIa** (146.7 mg, 96.0%): HRms m/z $[M\text{-MeBr}]^+$ 415.1790 (calcd for $C_{26}H_{25}NO_4$, 415.1790); EIms (%) m/z $[M\text{-MeBr}]^+$ 415 (17), $[M\text{-BnBr}]^+$ 339 (49), 280 (17), 264 (19), 204 (58), 188 (77), 91 (100).

N-Alkyl quaternary pavines **III** and **IV**. The mixture of **1a** (137.1 mg, 0.40 mmol) and *n*-propyl bromide (5 ml, 55 mmol) in a screw-tight sealed tube (25 ml) was degassed and heated under reflux overnight. Evaporation of the reaction mixture gave a semi-solid residue which was washed with ether to

remove the unreacted **1a** and other impurity to give a sole and tlc pure product **IIIa** (amorphous, 120.7 mg, 64.7%): HRms m/z [M-MeBr]$^+$ 367.1771 (calcd for $C_{22}H_{25}NO_4$, 367.1784); Elms (%) m/z [M-MeBr]$^+$ 367 (72), [M-PrBr]$^+$ (83), 232 (78), 216 (89), 204 (86), 188 (100), 174 (14).

In a similar manner to the preparation of **IIIa**, reaction of **1b** (377.6 mg, 0.91 mmol) with *n*-propyl bromide (5 ml, 55 mmol) gave **IIIb** (amorphous, 472.8 mg, 96.6%): HRms m/z [M-MeBr]$^+$ 443.2113 (calcd for $C_{28}H_{29}NO_4$, 443.2096); Elms (%) m/z [M-MeBr]$^+$ 443 (92), [M-*n*-PrBr]$^+$ 415 (31), 280 (36), 216 (100), 188 (33), 91 (66). Reaction of **1a** (260.2 mg, 0.77 mmol) with *n*-BuBr (5 ml, 45.6 mmol) afforded **IVa** (amorphous, 266.3 mg, 80.4%): HRms m/z [M-MeBr]$^+$ 381.1926 (calcd for $C_{23}H_{27}NO_4$, 381.1940); Elms (%) m/z [M-MeBr]$^+$ 381 (69), [M-*n*-BuBr]$^+$ 339 (24), 246 (82), 230 (100), 188 (34).

Reaction of **1b** (475.9 mg, 1.15 mmol) with *n*-BuBr (5 ml, 45.6 mmol) under reflux (110°C) overnight afforded **IVb** (amorphous, 430.1 mg, 68.0%) and a tertiary product (**4b**) (35.9 mg, 8.3%) with recovery of **1b** (21.5 mg) after separation on a silica gel column (22 g, 70-230 mesh) eluted with 0-5% MeOH in $CHCl_3$.

IVb: Elms (%) m/z 457 [M-MeBr]$^+$ (12), 415 [M-*n*-BuBr]$^+$ (93), 280 (100), 230 (10), 188 (96), 91 (85).

4b: oil, Rf 0.70; ir (ν, cm^{-1}) 2930, 1517, 1480, 1377, 1040, 927, 740, 700; ^{1}H-nmr δ 6.55 (1H, s, H-1), 6.40 (1H, s, H-4), 4.04 (2H, d, J=5.6 Hz, H-6 and 12), 6.47 (1H, s, H-7), 6.60 (1H, s, H-10), 3.82 (3H, s, 8-OMe), 5.00 (2H, s, benzyl CH_2) and 7.30 (5H, m, benzyl C_6H_5), 5.79 (1H) and 5.83 (1H) (each d, J=1.4 Hz, OCH_2O), 0.89 (3H, t, J=5.8 Hz, $NC_3H_6CH_3$); HRms m/z [M]$^+$ 457.2253 (calcd for $C_{29}H_{31}NO_4$, 457.2253); Elms (20 eV) (%) m/z 458 (36), [M]$^+$ 457 (100), 366 (9), 322 (19), 230 (15).

General procedure of competitive *N*-dealkylation on quaternary pavines **II-VI**. **IIa** (233.0 mg, 0.47 mmol) and ethanolamine (1 ml, 16.6 mmol) was heated at 160° for 3 h. After similar work-up procedure as for preparation of **1a**, the product residue was purified on a silica gel column (5 g, 70-230 mesh) eluted with 0-1% MeOH in $CHCl_3$ to give **1a** (30 mg, 17.1%) and **2a** (oil, 65.7 mg, 39.5%).

In a similar manner using conditions listed in Table 1, **1b** and **2b** were obtained from **IIb**; **1a** and **3a** were obtained from **IIIa**; **1b** and **3b** were obtained from **IIIb**; **1a** and **4a** were obtained from **IVa**; **1b** and **4b** were obtained from **IVb**; **1a** and **5a** were obtained from **Va**; **1a** was obtained from **VIa**.

2a: oil, Rf 0.52; $[\alpha]_D^{24}$ -218.4° (c=0.92, MeOH); ir (ν, cm^{-1}) 2907, 1610, 1507, 1503, 1480, 1377, 1230, 1040, 940, 927; uv λ max (log ε) 230 (sh, 4.13), 291 (4.09) nm; ^{1}H-nmr δ 6.57 (2H, s, H-1 and 7), 6.40 (2H, s, H-4 and 10), 4.08 (2H, d, J=5.6 Hz, H-6 and 12), 3.82 (3H, s, 8-OMe), 3.75 (3H, s, 9-OMe), 5.78 (1H) and 5.83 (1H) (each d, J=1.4 Hz, OCH_2O), 1.17 (3H, t, J=6.9 Hz, NCH_2CH_3); Anal.

Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 70.21; H, 6.51; N, 3.75%. HRms m/z $[M]^+$ 353.1610 (calcd for $C_{21}H_{23}NO_4$, 353.1627); EIms (%) m/z $[M]^+$ 353 (44), 218 (81), 202 (100).

3a: oil, Rf 0.56; $[\alpha]_D^{24}$ -232.3° (c=0.93, MeOH); ir (ν, cm^{-1}) 2927, 1610, 1517, 1370, 1257, 1230, 1107, 1040, 927, 860, 740; ^{1}H-nmr δ 6.57 (2H, s, H-1 and 7), 6.40 (1H, s, H-4), 6.42 (1H, s, H-10), 4.05 (2H, d, J=5.6 Hz, H-6 and 12), 3.82 (3H, s, 8-OMe), 3.75 (3H, s, 9-OMe), 5.78 (1H) and 5.82 (1H) (each d, J=1.4 Hz, $OC\underline{H_2}O$), 0.90 (3H, t, J=6.9 Hz, $NC_2H_4C\underline{H_3}$); Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.17; H, 6.93; N, 3.57%. HRms m/z $[M]^+$ 367.1790 (calcd for $C_{22}H_{25}NO_4$, 367.1783); EIms (%) m/z $[M]^+$ 367 (40), 232 (87), 216 (100), 174 (15).

4a: oil, Rf 0.60; $[\alpha]_D^{24}$ -198.9° (c=0.90, MeOH); ir (ν, cm^{-1}) 2925, 1610, 1517, 1480, 1370, 1100, 1040, 927, 840; ^{1}H-nmr δ 6.56 (2H, s, H-1 and 7), 6.38 (1H, s, H-4), 6.41 (1H, s, H-10), 4.04 (2H, d, J=5.6 Hz, H-6 and 12), 3.81 (3H, s, 8-OMe), 3.73 (3H, s, 9-OMe), 5.75 (1H) and 5.79 (1H) (each d, J=1.1 Hz, $OC\underline{H_2}O$), 0.88 (3H, t, J=6.4 Hz, $NC_2H_4C\underline{H_3}$); Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 70.64; H, 7.15; N, 3.19%. HRms m/z $[M]^+$ 381.1944 (calcd for $C_{23}H_{27}NO_4$, 381.1940); EIms (%) m/z $[M]^+$ 381 (43), 246 (86), 230 (100), 174 (16).

5a: oil, Rf 0.62; $[\alpha]_D^{24}$ -203.8° (c=0.90, MeOH); ir (ν, cm^{-1}) 2913, 1640, 1608, 1500, 1379, 1040, 1003, 923; ^{1}H-nmr δ 6.57 (1H, s, H-1), 6.40 (1H, s, H-4), 6.56 (1H, s, H-7), 6.43 (1H, s, H-10), 4.07 (2H, br d, J=5.6 Hz, H-6 and 12), 3.34 (1H, dd, J=5.6, 16.0 Hz, H-5α), 2.57 (1H, dd, J=2.0, 16.0 Hz, H-5β), 3.30 (1H, dd, J=5.6, 16.0 Hz, H-11α), 2.53 (1H, dd, J=2.0, 16.0 Hz, H-11β), 3.82 (3H, s, 8-OMe), 3.75 (3H, s, 9-OMe), 5.78 (1H) and 5.83 (1H) (each d, J=1.1 Hz, $OC\underline{H_2}O$), 5.93 (1H, ddt, J=17.2, 9.5 and 6.4 Hz, $-C\underline{H}=CH_2$), 5.20 (1H, dd, J=17.2, 1.3 Hz) and 5.16 (1H, dd, J=9.5 and 1.3 Hz) ($-CH=C\underline{H_2}$), 3.28 (1H, dd, J=6.6, 13.5 Hz) and 3.20 (1H, dd, J=6.6, 13.5 Hz) ($N-C\underline{H_2}$); HRms m/z $[M]^+$ 365.1602 (calcd for $C_{22}H_{23}NO_4$, 365.1627); EIms (%) m/z $[M]^+$ 365 (63), 230 (73), 214 (100), 190 (22), 174 (17).

3b: oil, Rf 0.66; ir (ν, cm^{-1}) 2928, 1517, 1373, 1259, 1040, 937, 740, 700; ^{1}H-nmr δ 6.56 (1H, s, H-1), 6.40 (1H, s, H-4), 4.04 (2H, d, J=5.5 Hz, H-6 and 12), 6.48 (1H, s, H-7), 6.61 (1H, s, H-10), 3.83 (3H, s, 8-OMe), 5.00 (2H, s, benzyl CH_2) and 7.30 (5H, m, benzyl C_6H_5), 5.78 (1H) and 5.82 (1H) (each d, J=1.4 Hz, $OC\underline{H_2}O$), 0.90 (3H, t, J=7.0 Hz, $NC_2H_4C\underline{H_3}$); HRms m/z $[M]^+$ 443.2101 (calcd for $C_{28}H_{29}NO_4$, 443.2096); EIms (20 eV) (%) m/z 444 (28), $[M]^+$ 443 (100), 352 (20), 308 (39), 216 (34).

N-Dealkylation and *N*-acylation on caryachine (**1**) and *O*-acetylcaryachine (**1c**) in a one-pot reaction.

A. Preparation of caryachine (**1**) and *O*-acetylcaryachine (**1c**). Caryachine (**1**) was prepared by catalytic hydrogenation of the *O*-benzyl derivative (**1b**).[2] **1c** was prepared from **I** by the following method. The mixture of Ac_2O/ *p*-xylene (1:1, 50 ml) and **I** (OAc^-, 5.00 g), obtained by anionic exchange (Amberlite IRA 410, OAc^- form), in a 250-ml screw-tight sealed tube was degassed *in vacuo* and heated at 140°C for 4 days. The reaction mixture was evaporated *in vacuo* and the residue was partitioned between H_2O (pH 9.0, 100 ml) and $CHCl_3$ (100 ml x3). The combined $CHCl_3$ layer was washed with brine solution, dried over $MgSO_4$) and evaporated to give a residue which was purified *via* a silica gel column (100 g, 70-230 mesh) eluted with 0-5% MeOH in $CHCl_3$ to give a sole pure product (**1c**) (oil, 3.40 g, 74.8%): Rf 0.50; ir (ν, cm^{-1}) 1737 (ester), 1507, 1483, 1241, 1040, 940; ^{1}H-nmr δ 6.54 (1H, s, H-1), 6.40 (1H, s, H-4), 3.96 (2H, d, J=5.5 Hz, H-6 and 12), 6.66 (1H, s, H-7), 6.62 (1H, s, H-10), 3.77 (3H, s, 8-OMe), 5.78 (1H) and 5.84 (1H) (each d, J=1.4 Hz, OCH_2O), 2.49 (3H, t, J=7.0 Hz, NCH_3), 2.22 (3H, s, OAc); HRms m/z $[M]^+$ 367.1407 (calcd for $C_{21}H_{21}NO_5$, 367.1419); EIms (20 eV) (%) m/z $[M]^+$ 367 (25), 325 (100), 232 (6), 190 (48), 188 (73).

B. Competitive *N*-dealkylation and *N*-acylation on *O*-acetylcaryachine (**1c**) A 25-ml screw-tight tube containing mixture of **1c** (49.8 mg, 136 μmol), allyl bromide (60 μl, 690 μmol) and Ac_2O/ *p*-xylene (1:1, 3 ml) was degassed *in vacuo* and was heated at 140°C for 5 days. The reaction mixture was evaporated *in vacuo* and the residue was purified on a silica gel column (5 g, 70-230 mesh) eluted with 0-5% MeOH in $CHCl_3$ to give **5c** (9.1 mg, 17.4%), **7c** (18.6, 35.3%) and **1c** (6.0 mg, 12.2%).

5c: oil, Rf 0.73; ir (ν, cm^{-1}) 2900, 1760 (ester), 1640, 1620, 1504, 1480, 1280, 1040, 980, 920, 907; ^{1}H-nmr δ 6.53 (1H, s, H-1), 6.40 (1H, s, H-4), 4.10 (2H, d, J=5.5 Hz, H-6 and 12), 6.66 (1H, s, H-7), 6.62 (1H, s, H-10), 3.77 (3H, s, 8-OMe), 5.80 (1H) and 5.85 (1H) (each d, J=1.4 Hz, OCH_2O), 2.23 (3H, s, OAc), *N*-allyl at δ 5.90 (1H, m), 5.25 (1H, d, J=16.2 Hz), 5.15 (1H, d, J=11.6 Hz) and 3.23 (2H, d, J=6.2 Hz); HRms m/z $[M]^+$ 393.1568 (calcd for $C_{23}H_{23}NO_5$, 393.1576); EIms (20 eV) (%) m/z 394 (12), $[M]^+$ 393 (100), 258 (6), 214 (26).

7c: amorphous; ir (ν, cm^{-1}) 2907, 1760 (ester), 1640, 1620, 1503, 1480, 1260, 1223, 1200, 1040, 923; ^{1}H-nmr δ 6.57 (6.59) (1H, s, H-1), 6.41 (6.39) (1H, s, H-4), 5.94 (5.89) (1H) and 5.06 (5.11) (1H) each doublet (J=5.2 Hz) (H-6 and H-12), 6.73 (6.71) (1H, s, H-7), 6.64 (6.66) (1H, s, H-10), 3.78 (3.76) (3H, s, 8-OMe), 5.83 (1H) and 5.85 (1H) (each d, J=1.0 Hz, OCH_2O), 2.22 (3H, s, OAc), 2.14 (3H, s, NAc); HRms m/z $[M]^+$ 395.1505 (calcd for $C_{22}H_{21}NO_6$, 395.1369); EIms (%) 396 (19), $[M]^+$ 395 (100), 353 (62), 310 (48), 174 (44).

In a similar manner using conditions listed in Table 2, **1d**, **5d**, **6d** and **8d** were obtained from **1**.

1d: oil, Rf 0.28 (5% MeOH/$CHCl_3$); ir (ν, cm^{-1}) 2910, 1760 (ester), 1504, 1257, 1224, 1140, 1127, 1040, 921; ^{1}H-nmr δ 6.54 (1H, s, H-1), 6.40 (1H, s, H-4), 4.04 (2H, d, J=5.8 Hz, H-6 and 12), 6.66 (1H, s, H-7), 6.62 (1H, s, H-10), 3.76 (3H, s, 8-OMe), 5.80 (1H) and 5.84 (1H) (each d, J=1.2 Hz, $OC\underline{H_2}O$), 1.20 (3H, t, J=7.6 Hz, $OCOCH_2C\underline{H_3}$), 2.52 (3H, s, NMe); HRms m/z $[M]^+$ 381.1575 (calcd for $C_{22}H_{23}NO_5$, 381.1576); EIms (%) $[M]^+$ 381 (81), 324 (15), 190 (23), 188 (100), 57 (6).

5d: oil, Rf 0.58 (5% MeOH/$CHCl_3$); ir (ν, cm^{-1}) 2920, 1760 (ester), 1507, 1482, 1260, 1040, 923; ^{1}H-nmr δ 6.53 (1H, s, H-1), 6.40 (1H, s, H-4), 4.09 (2H, d, J=5.5 Hz, H-6 and 12), 6.65 (1H, s, H-7), 6.63 (1H, s, H-10), 3.76 (3H, s, 8-OMe), 5.79 (1H) and 5.84 (1H) (each d, J=1.4 Hz, $OC\underline{H_2}O$), 1.21 (3H, t, J=7.3 Hz, $OCOCH_2C\underline{H_3}$), *N*-allyl at δ 5.92 (1H, m), 5.25 (1H, d, J=15.4 Hz), 5.16 (1H, d, J=11.3 Hz) and 3.25 (2H, d, J=6.1 Hz); HRms m/z $[M+H]^+$ 408.1788 (calcd for $C_{24}H_{26}NO_5$, 408.1811); EIms (%) $[M]^+$ 407 (45), 350 (15), 310 (14), 214 (100), 57 (16).

6d: oil, Rf 0.80 (5% MeOH/$CHCl_3$); ir (ν, cm^{-1}) 2910, 1760 (ester), 1507, 1480, 1257, 1039, 940, 740, 700; ^{1}H-nmr δ 6.51 (1H, s, H-1), 6.42 (1H, s, H-4), 4.00 (2H, d, J=5.3 Hz, H-6 and 12), 6.63 (2H, s, H-7 and 10), 3.74 (3H, s, 8-OMe), 5.80 (1H) and 5.84 (1H) (each d, J=1.0 Hz, $OC\underline{H_2}O$), 1.22 (3H, t, J=7.2 Hz, $OCOCH_2C\underline{H_3}$), δ 3.70 (2H, br s) and 7.36 (5H, m) (*N*-Bn); HRms m/z $[M]^+$ 457.1891 (calcd for $C_{28}H_{27}NO_5$, 457.1890); EIms (%) $[M]^+$ 457 (45), 366 (8), 322 (19), 264 (100), 91 (50), 57 (40).

8d: amorphous, Rf 0.60 (5% MeOH/$CHCl_3$); ir (ν, cm^{-1}) 2900, 1760 (ester), 1620, 1507, 1480, 1280, 1260, 1140, 1103, 1040, 920; ^{1}H-nmr δ 6.56 (6.58) (1H, s, H-1), 6.39 (6.36) (1H, s, H-4), 5.97 (1H, d, J=6.0 Hz, H-6 or H-12), 5.06 (5.11) (1H, each d, J=6.0 Hz, H-6 or H-12), 6.75 (6.71) (1H, each s, H-7), 6.63 (6.65) (1H, each s, H-10), 3.76 (3.75) (3H, s, 8-OMe), 5.81/ 5.79 (1H) and 5.83/5.81 (1H) (each d, J=1.0 Hz, $OC\underline{H_2}O$), 1.22 (1.19) (3H, t, J=7.6 Hz, $OCOCH_2C\underline{H_3}$), 1.11 (3H, t, J=7.5 Hz, $NCOCH_2C\underline{H_3}$); HRms m/z $[M]^+$ 423.1679 (calcd for $C_{24}H_{25}NO_6$, 4423.1682); EIms (%) 424 (13), $[M]^+$ 423 (76), 367 (67), 310 (64), 230 (35), 176 (44), 174 (100), 57 (51).

Preparation of **5c** from **1c** by reacting with allyl bromide *via* thermolysis. The mixture of **1c** (100 mg, 278 μmol), *p*-xylene (5 ml) and allyl bromide (0.12 ml, 1.39 mmol) in a sealed tube was heated at 50°C overnight, and then 150°C for 1 day. The mixture was evaporated and the residue was purified on a silica gel column (6 g, 70-230 mesh) eluted with 0-15% Me_2CO in toluene to give **5c** (46.4 mg, 42 %) and **1c** (27.5 mg, 27 % recovery).

Preparation of **7c** from **1** with MeI/Ac_2O in a one-pot reaction. The mixture of **1** (50 mg, 154 μmol), *p*-xylene (1.0 ml), Ac_2O (1.0 ml, 10.6 mmol) and MeI (0.5 ml, 8.0 mmol) in a sealed tube was heated at 150°C for 2 day. The mixture was evaporated and the residue was purified on a silica gel column (6 g, 70-230 mesh) eluted with 10-25% Me_2CO in toluene to give **7c** (60 mg, quantitative yield).

Reaction of 1 with pivaloyl chloride. The mixture of **1** (50 mg, 154 μmol), *p*-xylene (0.5 ml) and pivaloyl chloride (0.5 ml, 4.06 mmol) in a sealed tube was heated at 140°C for 2 day. The mixture was evaporated and the residue was analyzed by tlc plate which showed no amide products since those uv quenched products showed positive reaction toward Dragendorff's reagent.

N-Propylnorcaryachine (**3**). Compound (**3b**) (189 mg, 0.43 mmol) in EtOH (3 ml) was hydrogenated with 5% Pd/C (50 mg) and H_2 (1 atm) at room temperature overnight. The suspension was filtered with the aid of Celite. The residue after evaporation of the filtrate and the MeOH washing was purified on a silica gel column eluted with 5% MeOH in $CHCl_3$ to give **3** (oil, 105 mg, 70%): $[\alpha]_D^{24}$ -216.5° (c= 0.85, MeOH); Rf 0.42; ir (ν, cm^{-1}) 3433, 2925, 1500, 1482, 1297, 1251, 1228, 1036, 925; ^{1}H-nmr δ 6.55 (2H, s, H-1 and H-7), 6.48 (1H, s, H-4), 4.04 (2H, d, J=5.4 Hz, H-6 and 12), 6.38 (1H, s, H-10), 3.82 (3H, s, 8-OMe), 5.78 (1H) and 5.82 (1H) (each d, J=1.1 Hz, OCH_2O), 0.89 (3H, t, J=7.2 Hz, $NC_2H_4CH_3$); HRms m/z $[M]^+$ 353.1610 (calcd for $C_{21}H_{23}NO_4$, 353.1627); EIms (%) $[M]^+$ 353 (60), 352 (26), 218 (100), 216 (98), 174 (15).

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