

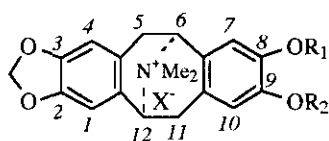
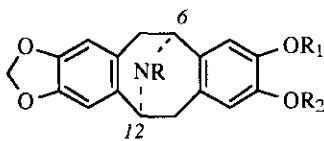
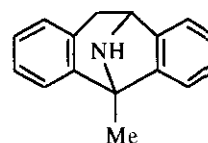
N-DEMETHYLATION STUDIES OF PAVINE ALKALOIDS

Shoei-Sheng Lee*, Yi-Chu Liu, Shu-Hwei Chang, and Chung-Hsiung Chen

School of Pharmacy, National Taiwan University, Taipei, Taiwan, R. O. C.

Abstract — The *N*-norpavines, ring homologues of MK-801—a potent NMDA receptor antagonist, were prepared from *N*-methyl quaternary pavines by two nucleophilic reaction steps: *N*-methyl quaternary ammonium salts into tertiary amine by reacting with NaHTE (ethanolamine/ Δ or OAc⁻ salt/ DMF, Δ); tertiary amine into *N*-norpavines by the von Braun reaction and subsequent hydrolysis.

With the increasing population of aged people, the accompanying diseases such as Alzheimer disease have become a worldwide issue. The activation of NMDA (*N*-methyl-D-aspartic acid) receptor has been recognized as a mechanism for damaging brain cells.¹ Hence the development of NMDA receptor antagonist such as MK-801² to revive or protect the brain cells has become a hot topic. The skeleton of MK-801 is ring homologue of pavinane. Based on this, some pavine analogs have been prepared and tested for their bioactivity.³ Here we report an alternative method in preparing these biologically active bases from the chemical modification of the *N*-methyl quaternary pavine (-)-caryachine *N*-metho salt (1), a major alkaloid (about 0.2% w/w in the stems) isolated as perchlorate salt from *Cryptocarya chinensis* H. (Lauraceae).⁴

1. R₁ = Me, R₂ = H, X = ClO₄4. R₁ + R₂ = CH₂, X = I5. R₁ = R₂ = Me, X = I, (6-*R*, 12-*R*)10. R₁ = Me, R₂ = Bn, X = ClO₄2. R = R₁ = Me, R₂ = H6. R = Me, R₁ + R₂ = CH₂7. R = R₁ = R₂ = Me, (6-*R*, 12-*R*)8. R = CN, R₁ = R₂ = Me, (6-*R*, 12-*R*)9. R = H, R₁ = R₂ = Me, (6-*R*, 12-*R*)11. R = R₁ = Me, R₂ = Bn

MK-801

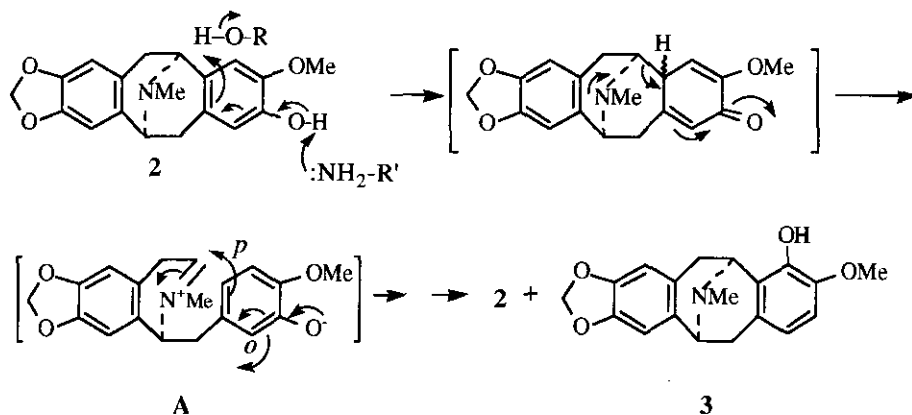
Conversion of a quaternary ammonium salts into a secondary amine involves two *N*-demethylation reactions. The first task *N*-demethylation of *N*-methyl quaternary alkaloids generally took place via nucleophilic attack. Although

this reaction had been achieved by treating an *N*-methyl quaternary pavine with triethylenediamine in DMF,⁵ we found that following reagents and conditions are facile and useful for this purpose.

Treatment of **1** (Cl^- salt, 400 mg in 4.0 ml abs. EtOH) with a wine red solution of sodium hydrogentelluride (NaHTe), prepared *in situ* from NaBH_4 (300 mg) and Te powder (255 mg) in EtOH (7.5 ml),⁶ yielded a sole product (**2**) (250 mg, 73% yield). Compound (**2**) shows the following ^1H -nmr signals: δ (CDCl_3) 6.55 (H-1 and H-7), 6.48 (H-4), 6.39 (H-10), 5.81 (OCH_2O , AB quartet, $J = 1.4$ Hz), 3.83 ($\text{O}-\text{CH}_3$) and 2.49 ($\text{N}-\text{CH}_3$), identical to those of (-)-caryachine, previously isolated from the same plant.⁷

Treatment of **1** (493 mg, OAc^- form from ClO_4^- salt *via* Amberlite IRA 400 OAc^-) with DMF (5 ml) under reflux for 48 h⁸ produced **2** in 79% isolated yield. Unlike the unpleasant odor of MeHTe - the accompanying product of the NaHTe reaction, the workup of this reaction (condensation and recrystallization of the residue from Me_2CO) is relatively simple and is preferable to the preparation of caryachine in a smaller scale.

While treating **1** with ethanolamine (165°C , N_2 , 0.5-1 h), two products were isolated in a total yield of about 86%. The product of higher polarity was characterized as (-)-**2** from its identical physical properties to the authentic sample. The less polar product shows the following ^1H -nmr signals: δ (CDCl_3 , 300 MHz) 6.64 and 6.45 (AB quartet, H-9 and H-10, $J = 8.4$ Hz), 6.55 (H-1), 6.39 (H-4), 5.82 and 5.77 (OCH_2O , $J_{\text{AB}} = 1.6$ Hz), 4.33 (d, $J = 5.6$ Hz, H-6), 3.95 (d, $J = 5.1$ Hz, H-12), 3.78 ($\text{O}-\text{CH}_3$) and 2.50 ($\text{N}-\text{CH}_3$), identical to those of neocaryachine (**3**), a minor phenolic pavine recently isolated from the bark of *C. chinensis*.⁹ When another two quaternary pavines- (-)-eschscholtzine *N*-methiodide (**4**) and (+)-eschscholtzidine *N*-methiodide (**5**),⁴ both of which were prepared from reacting the free bases with methyl iodide- were treated with ethanolamine, only the *N*-demethylated product, (-)-eschscholtzine (**6**) and (+)-eschscholtzidine (**7**), respectively, was detected and isolated in a yield of 75 to 85%.



The unexpected product (3) in this reaction might be obtained from the rearrangement of 2 via a common immonium intermediate (A) which yielded products (2) and (3), respectively, from the cyclization either from *para* or *ortho* position of the phenolic group, as depicted in the Scheme. This postulation indicates that *N*-demethylation reaction occurs first, followed by the rearrangement with the retention of stereochemistry. This is the case since 2 under the same reaction conditions yielded 3 together with the regeneration of 2 in about 1:1 ratio. The reversal reaction by using 3 as starting material yielded 2 as well. Since 4 and 5 are nonphenolic whereas 1 is a phenolic compound, the potential formation of phenolate/quinone type intermediate would play a major role for this rearrangement. Thus, when ethanolamine (pH 12.05, 0.1 N aq. soln.)^{10a} was replaced by a weaker base pyridine (pH 8.5, 0.2 M aq. soln.),^{10b} no reaction took place under the same reaction conditions.

The latter two reagents and conditions usually cause Hofmann degradation such as in the case of the aporphine magnoflorine.¹¹ Thus, the exclusive *N*-demethylation for *N*-methyl quaternary pavines would be rationalized by the rigid conformation in the pavine skeleton. This special conformation also facilitates the conversion of pavines into *N*-norpavines, which has been reported by treating 2 with ethyl chloroformate, followed by base.¹² We found that the *N*-demethylation of pavinane was also achieved by the von Braun reaction. Thus (+)-*N*-cyanonorescholtzidine (8) [ir 2200 cm⁻¹ for N-CN, $\delta_{\text{H-6}}$ and $\delta_{\text{H-12}}$ 4.67 (d, *J*=5.4 Hz) (CDCl₃)] was obtained in 80% yield from 7, $\delta_{\text{H-6}}$ and $\delta_{\text{H-12}}$ 4.00 (d, *J*=5.8 Hz) (CDCl₃),¹³ by adding BrCN (in CH₂Cl₂)¹⁴ dropwise under refluxing. Other *N*-cyanonorpavines were prepared from 2 and 6 in the similar manner in the yield of 40 to 85% with the recovery of starting material. The anhydrous conditions and the addition of the reagent with refluxing are very critical for this reaction. Alkaline hydrolysis of 8 (KOH/ethyleneglycol-H₂O=4:1, Δ , 12 h) yielded (+)-norescholtzidine (9) (82%)— $[\alpha]_{\text{D}}^{28} +154.8^\circ$ (c 1.0, MeOH), ir 3430 cm⁻¹ for NH, $\delta_{\text{H-6}}$ and $\delta_{\text{H-12}}$ 4.38 (d, *J*=5.6 Hz) (CDCl₃). We observed that this hydrolysis (90% HOAc_{aq} under reflux for 3-5 h) can take place in very good yield (77-100%).

The ethanolamine reaction was applied for preparing neocaryachine (3) which was used as a synthon for the preparation of dimeric pavines. A larger-scale preparation of caryachine (2) (>5 g) was carried out starting from 1 (ClO₄⁻ form) by three reaction steps. First, 1 was converted into its *O*-Benzyl derivative (10)—mp 244-245°C; δ 7.40 (m) and 5.03 (s) for 9-OBn and δ 5.11 (d, *J*= 5.8 Hz) for H-6 and H-12 (Me₂CO-*d*₆)—by reacting 1 with BnCl/ K₂CO₃/ Me₂CO, Δ ; then *N*-demethylation of 10 with ethanolamine to give *O*-benzylcaryachine (11)—¹H-nmr (CDCl₃) δ 7.31 (m) and 5.05 (s) for 9-OBn and δ 3.94 (d, *J*= 5.8 Hz) for H-6 and H-12. The catalytic hydrogenation of 11 gave 2 in an overall 60% yield from 1 (ClO₄⁻ form).

Preliminary *in vitro* biological tests of these pavines have been performed. It is worth noting that *N*-norpavines and *N*-methyl quaternary pavines show opposite effects in isometric muscle twitch experiments of mouse diaphragm. The former such as 9 (HCl salt) increased direct twitches while the latter such as 1 (Cl⁻ form) showed curare- like activity as that reported.¹⁵ The pavine such as 2 did not have apparent effects.

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