N-DEMETHYLATION STUDIES OF PAVINE ALKALOIDS

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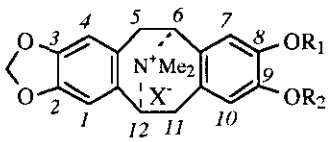
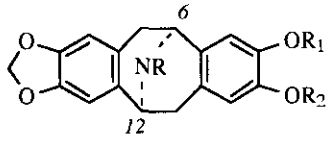
Abstract — The *N*-norpavines, ring homologues of MK-801– a potent NMDA receptor antagonist, were prepared from *N*-methyl quaternary pavines by two nucleophilic reaction steps: *N*-methyl quaternary ammonium salts into tertiary amine by reacting with NaHTe (ethanolamine/Δ or OAc^- salt/ DMF, Δ); tertiary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

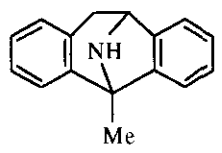
With the increasing population of aged people, the accompanying diseases such as Alzheimer disease have become a worldwide issue. The activation of NMDA (*N*-methyl-D-aspartic acid) receptor has been recognized as a mechanism for damaging brain cells.[1] Hence the development of NMDA receptor antagonist such as MK-801[2] 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. R_1= Me, R_2= H, X= ClO_4
4. R_1+R_2= CH_2, X= I
5. R_1=R_2= Me, X= I, (6-*R*,12-*R*)
10. R_1= Me, R_2= Bn, X= ClO_4



2. R=R_1= Me, R_2= H
6. R= Me, R_1+R_2= CH_2
7. R=R_1=R_2= Me, (6-*R*,12-*R*)
8. R= CN, R_1=R_2= Me, (6-*R*,12-*R*)
9. R= H, R_1=R_2= Me, (6-*R*,12-*R*)
11. R=R_1= Me, R_2= Bn



MK-801

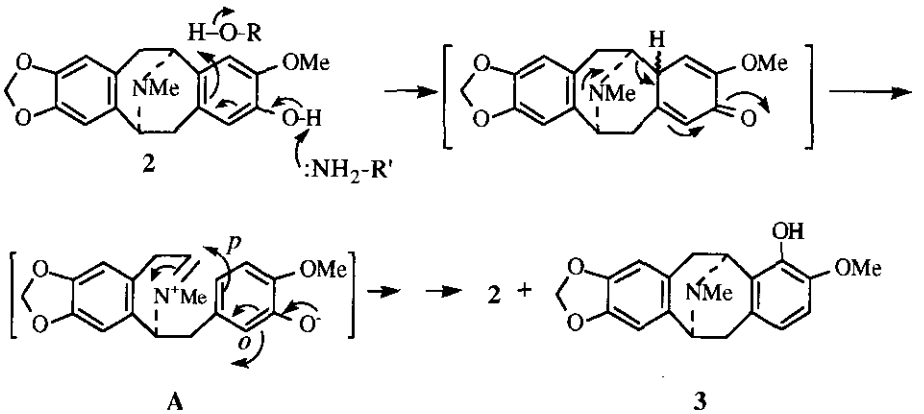
Conversion of a quaternary ammonium salts into a secondary amine involves two *N*-demethylation reactions. The first task *N*-demethylation of *N*-methyl quaternary alkaloids generally took place *via* nucleophilic attack. Although

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 ^{1}H-nmr signals: δ ($CDCl_3$) 6.55 (H-1 and H-7), 6.48 (H-4), 6.39 (H-10), 5.81 ($OC\underline{H}_2O$, AB quartet, J= 1.4 Hz), 3.83 (*O*-$C\underline{H}_3$) and 2.49 (*N*-$C\underline{H}_3$), 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 h[8] 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 sacle.

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 ^{1}H-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 ($OC\underline{H}_2O$, J_{AB}=1.6 Hz), 4.33 (d, J=5.6 Hz, H-6), 3.95 (d, J=5.1 Hz, H-12), 3.78 (*O*-$C\underline{H}_3$) and 2.50 (*N*-$C\underline{H}_3$), 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*-methoiodide (**4**) and (+)-eschscholtzidine *N*-methoiodide (**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%.



2 **A** **3**

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*-cyanonoreschscholtzidine (**8**) [ir 2200 cm^{-1} for N-CN, $\delta_{H\text{-}6}$ and $\delta_{H\text{-}12}$ 4.67 (d, J=5.4 Hz) ($CDCl_3$)] was obtained in 80% yield from **7**, $\delta_{H\text{-}6}$ and $\delta_{H\text{-}12}$ 4.00 (d, J=5.8 Hz) ($CDCl_3$),[13] by adding BrCN (in CH_2Cl_2)[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-H_2O=4:1, Δ, 12 h) yielded (+)-noreschscholtzidine (**9**) (82%)– $[\alpha]_D^{28}$ +154.8° (c 1.0, MeOH), ir 3430 cm^{-1} for NH, $\delta_{H\text{-}6}$ and $\delta_{H\text{-}12}$ 4.38 (d, J=5.6 Hz) ($CDCl_3$). 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** (ClO_4^- 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 (Me_2CO-d_6)– by reacting **1** with BnCl/ K_2CO_3/ Me_2CO, Δ; then *N*-demethylation of **10** with ethanolamine to give *O*-benzylcaryachine (**11**)– ^{1}H-nmr ($CDCl_3$) 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** (ClO_4^- 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.

ACKNOWLEDGEMENT

We are grateful to National Science Council, R.O.C., for support of this research under Grant NSC 79-0412-B002-15 and NSC 82-0412-B002-113.

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Received, 21st April, 1993