TOTAL SYNTHESIS OF (±)-MECAMBRIDINE

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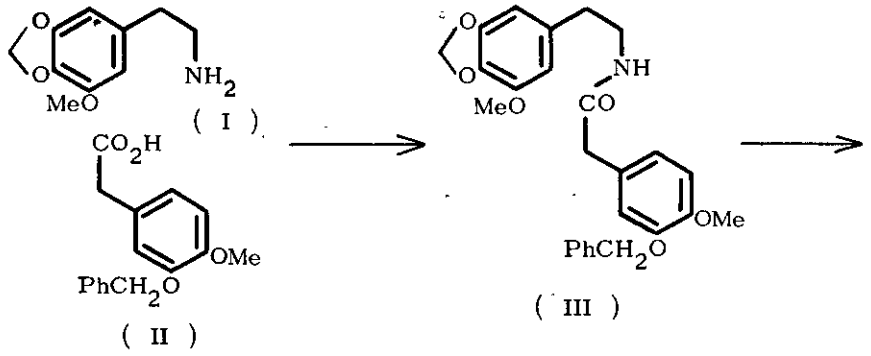
Hydroxymethylation of the phenolic tetrahydroprotoberberine (VII) yielded O-demethylmecambridine (VIII), which on methylation with diazomethane afforded (±)-mecambridine (XII). This work proved the structure of this base to be 7,8,13,14-tetrahydro-12-hydroxymethyl-1,10,11-trimethoxy-2,3-methylenedioxyprotoberberine.

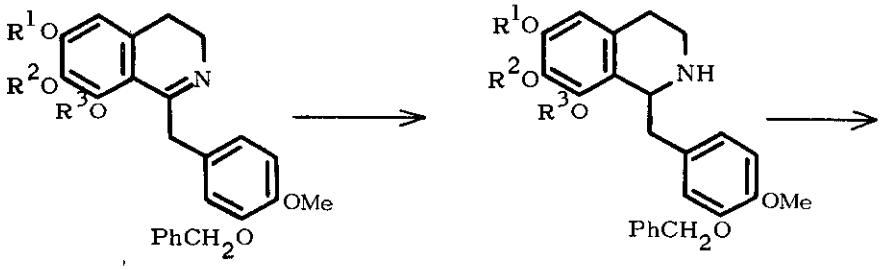
Mecambridine, an alkaloid from Papaver species,[1] was initially assigned structure (XIII) on the basis of spectral analysis combined with some chemical degradations.[2] Later, biogenetic consideration of this base, and uv spectral analysis of the bismethine derivatives showed that the structural assignments should be modified to XII.

We have also investigated the structure of mecambridine from a synthetic point of view and now wish to report the total synthesis of (±)-mecambridine, which proves the structure of this base to be the 10,11,12-trisubstituted tetrahydroprotoberberine (XII).

Fusion of 3-methoxy-4,5-methylenedioxyphenethylamine (I)[4] with 3-benzyloxy-4-methoxyphenylacetic acid (II) at 180° for 1 h gave amide (III), mp 126 - 127° [ν max (KBr) 3210 and 1640 cm^{-1}], which was subjected to a Bischler-Napieralski reaction with phosphoryl chloride in dry boiling benzene for 2 h to afford a mix-

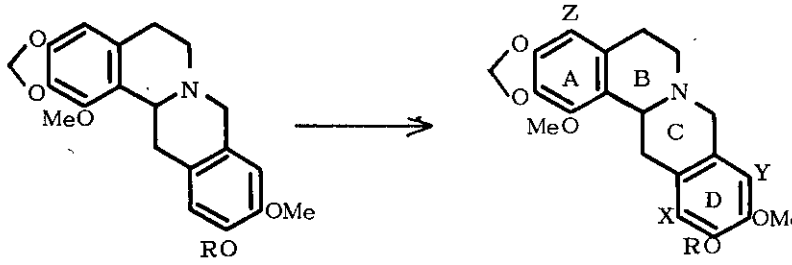


(I) (II) (III)



(IVa) $R^1+R^2=CH_2$, R^3=Me
(IVb) R^1=Me, $R^2+R^3=CH_2$

(Va) $R^1+R^2=CH_2$, R^3=Me
(Vb) R^1=Me, $R^2+R^3=CH_2$



(VI) R=CH_2Ph
(VII) R=H

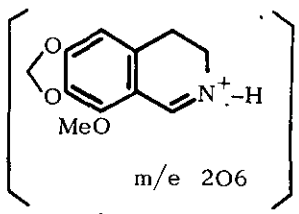
(VIII) X=CH_2OH, Y=Z=R=H
(IX) X=Z=R=H, Y=CH_2OH
(X) X=Y=R=H, Z=CH_2OH
(XI) X=CH_2OAc, Y=Z=H, R=Ac
(XII) X=CH_2OH, Y=Z=H, R=Me
(XIII) X=Z=H, Y=CH_2OH, R=Me

ture of 8-methoxy-6,7-methylenedioxy (IVa) [ν max ($CHCl_3$) 1641 cm^{-1}] and 6-methoxy-7,8-methylenedioxy (IVb) [ν max ($CHCl_3$) 1628 cm^{-1}] 3,4-dihydroisoquinolines. Therefore, cyclization occurred ortho and para to the methoxy group. The mixture was separated by crystallization of the hydrochlorides to give IVa hydrochloride as a viscous syrup (picrate, mp 179 - 181°) and IVb hydrochloride, mp 165 - 167°. The reduction of both hydrochlorides with sodium borohydride afforded the tetrahydroisoquinolines, characterized as their hydrochlorides; Va, mp 199 - 202° (decomp.) and Vb, mp 180 - 182° (decomp.). The structure of both products was assigned by nmr spectral analysis (δ $CDCl_3$) of the free bases; thus, the former base [3.85 (3H, s, OMe), 3.98 (3H, s, OMe), 5.10 (2H, s, $OC\underline{H}_2Ph$), 5.83 (2H, s, OCH_2O), 6.27 (1H, s, 5 - H), 6.55 (3H, broad s, 3',5'- and 6' - H), and 7.35 (5H, broad, $OCH_2C_6\underline{H}_5$)] showed methoxy-methyl and methylenedioxy-methylene protons at 3.98 and 5.83 as singlets, respectively, and the latter base [3.82 (6H, s, 2 x OMe), 5.07 (2H, s, $OC\underline{H}_2Ph$), 5.92 (2H, distorted q, OCH_2O), 6.22 (1H, s, 5 - H), 6.76 (3H, broad s, ArH) and 7.31 (5H, broad, $OCH_2C_6\underline{H}_5$)] showed the corresponding resonances at 3.82 as a singlet and 5.92 as a distorted quartet. It has been well known that the 8-methoxy group in 1,2,3,4-tetrahydroisoquinolines is deshielded and resonates at ~3.95,[5] and the methylenedioxy function gives rise to two doublets corresponding to a small difference in chemical shifts between the two non-equivalent protons when a bulky group is located in the neighborhood of this function.[6] Therefore, the former base could be assigned the 8-methoxy-6,7-methylenedioxyisoquinoline structure (Va), and the latter the isomeric 6-methoxy-7,8-methylenedioxy structure (Vb).

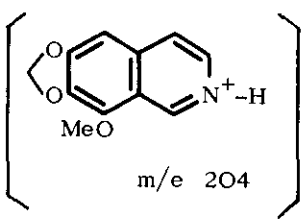
A Mannich reaction of Va with 37 % formalin and acetic acid at 100° for 2 h gave the tetrahydroprotoberberine (VI), mp 145 - 146° [nmr ($CDCl_3$) δ 3.80 (3H, s, OMe), 3.92 (3H, s, OMe), 5.02 (2H, s, $OC\underline{H}_2Ph$), 5.79 (2H, s, OCH_2O), 6.27 (1H, s, 4 - H), 6.53 (2H, broad s, 9- and 12 - H), and 7.3 (5H, broad,

$OCH_2C_6H_5$)], which on debenzylation with ethanolic hydrochloric acid afforded the phenolic protoberberine (VII), mp 192 - 194° [ν max ($CHCl_3$) 3550 cm^{-1} (OH); nmr ($CDCl_3$) δ 3.80 (3H, s, OMe), 3.96 (3H, s, OMe), 5.82 (2H, s, OCH_2O), 6.29 (1H, s, 4 - H), 6.49 (1H, s, 12 - H), and 6.56 (1H, s, 9 - H)].

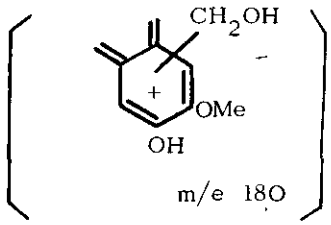
Hydroxymethylation[7,8] of VII with 37 % formalin and 1N sodium hydroxide at room temperature with stirring for 5 h gave 12-hydroxymethylprotoberberine (VIII) as a yellow viscous syrup [m/e 385 (M^+)]. The position of hydroxymethyl group was determined by the spectral methods. The mass spectrum showed three intense ions at m/e 206 (XIV), 204 (XV), and 180 (XVI), which suggested hydroxymethyl group present at ring C or D and ruled out structure X. The nmr spectrum [($CDCl_3$) δ 3.80 (3H, s, OMe), 3.95 (3H, s, OMe), and 5.85 (2H, s, OCH_2O)] revealed two aromatic protons at 6.31 and 6.46, indicating the presence of hydrogen on ring A. Moreover, this spectrum showed the presence of a hydroxymethyl group (4.64, s) on aromatic ring D, shifted downfield to 5.04 in the spectrum of the acetyl derivative (XI) [ν max ($CHCl_3$) 1725 and 1755 cm^{-1}; nmr ($CDCl_3$) δ 1.99 (3H, s, OCOMe), 2.30 (3H, s, OCOMe), 3.78 (3H, s, OMe), 3.97 (3H, s, OMe), 5.84 (2H, s, OCH_2O) and 6.31 (1H, s, 4 - H)]. An aromatic proton signal at 6.46 of VIII was shifted to 6.66 in the spectrum of the acetyl compound (XI).[9] Thus, the aromatic proton is <u>meta</u> to a phenolic hydroxy group and ruled out a product with structure IX.



(XIV)



(XV)



(XVI)

Methylation of VIII with diazomethane gave (±)-mecambridine (XII), whose ir ($CHCl_3$) and nmr ($CDCl_3$) spectra [δ 3.81 (6H, s, 2 x OMe), 3.97 (3H, s, OMe), 4.63 (2H, s, $ArCH_2OH$), 5.83 (2H, s, OCH_2O), 6.30 (1H, 4 - H) and 6.56 (1H, s, 9 - H)] were superimposable with those of the natural compounds.

Thus we have accomplished the total synthesis of (±)-mecambridine, which corroborated the structure suggested by Šantavý.

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