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TERPENOID ALKALOIDS FROM MURRAYA KOENIGII SPRENG. - II.[1] THE CONSTITUTION OF CYCLOMAHANIMBINE, BICYCLOMAHANIMBINE, AND MAHANIMBIDINE.[2]

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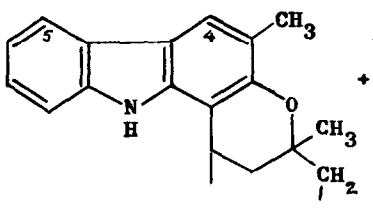
In the course of continuing search for new types of compounds of pharmacological interest from the leaves of Murraya koenigii Spreng, (fam. Rutaceae) three new bases possessing novel structures have been isolated in addition to the known mahanimbine.[3]

The first new alkaloid named cyclomahanimbine, $C_{23}H_{25}NO$ (M^+, 331), m.p. 146°, $[\alpha]_D^{23}$ 0° ($CHCl_3$), ν max. (KBr) 3425 (-NH), 1615, and 1602 cm^{-1} (ar. system), had a u.v. spectrum, λ max. (EtOH) 246, 251, 257, 307, and 341 mμ (logϵ 4.51, 4.28, 4.06, 3.96, and 3.35 respectively) indicating the presence of a carbazole nucleus as in tetrahydromahanimbine.[3] The n.m.r. spectrum (CCl_4) showed the following signals*: 8.64, s, 6, two methyls - one -O-C-$\underline{CH_3}$ and the other =C-$\underline{CH_3}$- both overlapping; 7.67, s, 3, ar. $\underline{CH_3}$; 6.89, bd, 1, benzylic methine proton; 5.28, bd, 2, -C=$\underline{CH_2}$; 2.45, bs, 1, -$\underline{NH}$; 2.37, s, 1, ar. proton ($C_4\underline{H}$); the other aromatic protons ($C_5\underline{H}$) appear at 2.12 (1, m) and in the region 2.57 to 3.00τ (3 protons) respectively. On reduction with Pt catalyst cyclomahanimbine yielded the dihydro- derivative, m.p. 136-7°. The

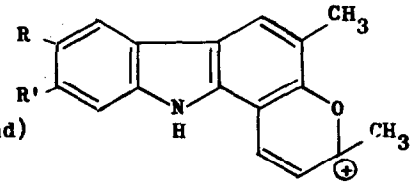
*τ, multiplicity (s, singlet; d, doublet; bd, broad doublet, and m, multiplet), number of protons under the peak and assignment given:

n.m.r. spectrum (CCl_4) of this compound was similar to that of the parent compound except that the two methylene protons at 5.28τ had disappeared; instead a doublet for three protons (J = 5.5 c.p.s.) appeared at 9.43τ and the methyl signal at 8.64τ in the parent compound had also become a doublet at 8.80τ. All this evidence considered along with the known presence of mahanimbine in the leaves of this plant pointed clearly towards a partial structure (I):



(I)

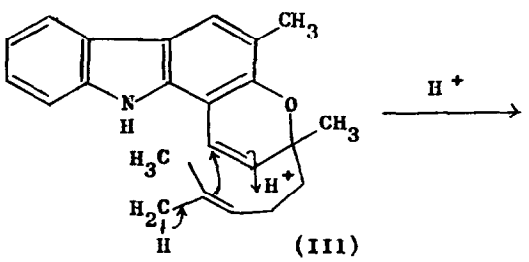
1 C_5 unit + (1 double bond)



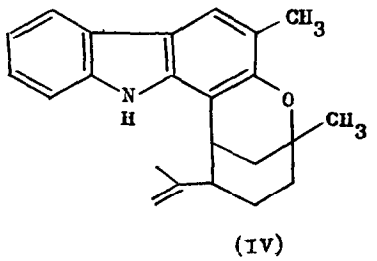
(IIa; R = R' = H)
(IIb; R = R' = OMe)
(IIc; R = OMe; R' = H)

This partial structure received support from the mass spectrum of cyclomahanimbine which showed, apart from the M^+ peak at m/e 331 the base peak at m/e 248. The latter corresponded to the ion (IIa) also obtained in the mass spectrum of mahanimbine[3] (III). Analogous peaks at m/e 308 and m/e 278 corresponding to (IIb and IIc) were obtained in the mass spectra of koenigicine and koenimbin.[4]

The known functions of cyclomahanimbine and its molecular formula, $C_{23}H_{25}NO$, now require it to be pentacyclic. Further, the fact that mahanimbine had the same molecular formula led directly to the mechanistically feasible structure (IV) for the new base as shown:



(III)



(IV)

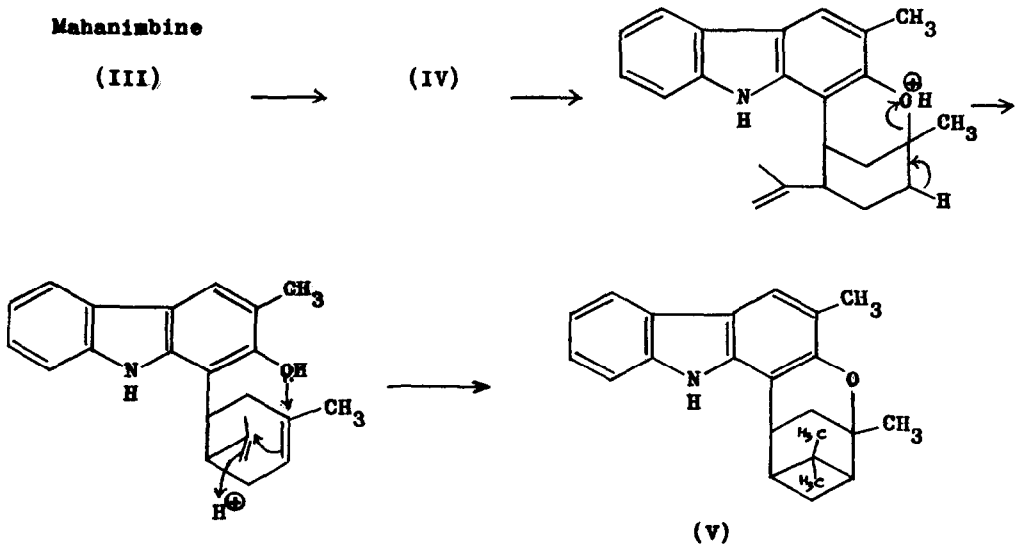
Methylation of cyclomahanimbine with methyl iodide and sodium hydride in dry benzene gave N-methylcyclomahanimbine, $C_{24}H_{27}NO$, m.p. 169-70°. In the n.m.r. spectrum (CCl_4) of this compound the N-$\underline{CH_3}$ signal appeared as a singlet (3H) at 6.14τ and the benzylic methine proton moved downfield to 6.04τ whereas the =C-$\underline{CH_3}$ protons had moved upfield to 8.80τ. The rest of the protons appeared at the same place as in the parent compound.

All the physico-chemical data on cyclomahanimbine and its derivatives thus fit in nicely with the structure proposed.

The second alkaloid again had the molecular formula, $C_{23}H_{25}NO$ (M^+, 331), m.p. 145°, $[\alpha]_D^{23°}$ - 1.23° ($CHCl_3$), ν max. (KBr) 3455 (-NH), 2950, 2920, 2850 (C-methyls), 1625, 1605 (ar. system), 1375 and 1365 cm^{-1} (gem dimethyl group). Its u.v. spectrum, λ max. (EtOH) 242, 255, 260, 305, and 331 mμ (logϵ 4.61, 4.43, 4.40, 4.21, and 3.62 respectively) indicated that it had the same type of chromophore as in (IV). The n.m.r. spectrum ($CDCl_3$) showed the following signals*: 9.29, s, 3, -C-$\underline{CH_3}$ in a cyclobutane ring; 8.57, s, 3, -C-C-$\underline{CH_3}$; 8.47, s, 3, -C-$\underline{CH_3}$ in a cyclobutane ring; 7.64, s, 3, ar.$\underline{CH_3}$; 6.74, bd, 1, benzylic methine proton; 2.26, s, 1, ar. proton ($C_4\underline{H}$). There were 5 more protons in the region 1.92 to 2.95τ - 1 for -$\underline{NH}$ and 4 for ar. protons. The absence of signals for any olefinic protons was supported by lack of hydrogen uptake during catalytic reduction experiments. The mass spectrum showed the M^+ peak at m/e 331 (base peak) and ions at m/e 248 (82%). The combined evidence thus pointed strongly to the partial structure (I) plus a C_5 unit. As there was no other double bond in the molecule, it was apparent that it had a hexacyclic structure. Further, mahanimbine dissolved in benzene and shaken with silica gel(48 hrs.) or Dowex 50W-X8 ion exchange resin (H^+) yielded this new base. All this data could be summarized in the formula (V) for this base which is now named as bicyclomahanimbine.

The conversion of mahanimbine into bicyclomahanimbine could be explained as follows and in view of the ease with which the side-chain of the former undergoes cyclisation even under mild acidic conditions, it is

possible that bicyclomahanimbine is, in fact an artifact.

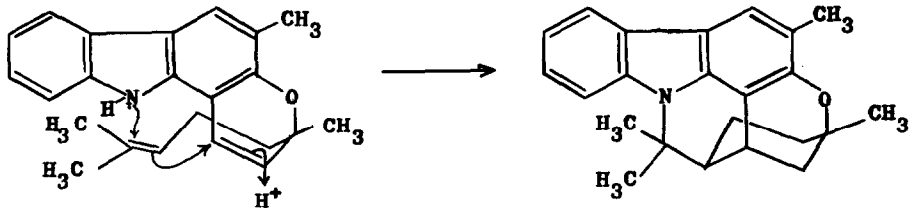


Bicyclomahanimbine, methylated as in the case of cyclomahanimbine, yielded the N-methyl derivative, m.p. 156°. Its mass spectrum showed M^+ peak at m/e 345 and the base peak at m/e 262. In the n.m.r. spectrum ($CDCl_3$), the N-$\underline{CH_3}$ peak showed up at 5.97τ and the benzylic methine proton, as in the case of cyclomahanimbine, moved downfield by 0.80τ to 5.94τ. This data is in complete accord with the structure of bicyclomahanimbine now suggested.

The third alkaloid, mahanimbidine, $C_{23}H_{25}NO$ (M^+, 331), m.p. 266° was optically inactive. Its u.v. spectrum, λ max. (EtOH) 241, 257, 307, and 335 mμ (logϵ 4.62, 4.37, 4.20, and 3.51 respectively) suggested that the basic chromophore was the same as in the previous two compounds. The i.r. spectrum (KBr) showed peaks at 2970, 2935, 2900 (C-methyls), 1640, 1600 (ar. system), 1380 and 1370 cm^{-1} (gem dimethyl group). Significantly, there was no absorption band for either the -OH or -NH group. The n.m.r. spectrum ($CDCl_3$) showed the following signals*: 8.74, s, 3, -C-$\underline{CH_3}$ of gem dimethyl; 8.57, s, 3, -O-C-$\underline{CH_3}$; 8.10, s, 3, the other -C-$\underline{CH_3}$ of the gem dimethyl;

7.67, s, 3, ar. CH_3; 6.67, bm, 1, benzylic methine proton; 2.00 to 2.87, m, 5, ar. protons. There was no signal for -NH nor for any olefinic protons. The mass spectrum of the base[m/e 331 (M^+), 316 (base peak), 248]implicated once again the ion (IIa) as part of the structure.

Applying the reasoning as in the previous two cases, it was apparent that mahanimbidine had a hexacyclic structure and that the carbazole N was common to two rings. The combined data led directly to the structure (VI) for mahanimbidine. Mechanistically, such a structure could be easily visualized to be derived from mahanimbine as shown:



(III) (VI)

In view of the striking structural resemblance of these alkaloids from Murraya koenigii Spreng. to the cannabis constituents[5] on the one hand and acronycine[6,7] from Acronychia baueri Schott (fam. Rutaceae) on the other, these compounds merit a detailed evaluation of their biological activity. This is now in progress.

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