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Reactions of the carbazole alkaloid Mahanimbine with mineral acid, Lewis acid and *m*-chloroperbenzoic acid

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Mahanimbine, a C_{23} carbazole alkaloid, has been isolated from the leaves of *Murraya koenigii* Spreng. This carbazole alkaloid, with a C_5H_9 ring residue, on reaction with different acids shows some interesting results. Structures of the naturally occurring compound as well as the synthetic products have been ascertained on the basis of 1D and 2D NMR spectroscopic data. In this paper is discuss isolation, structure elucidation and some chemical transformations of mahanimbine on reaction with mineral acid, Lewis acid and *m*-chloroperbenzioc acid.

Keywords: *Murraya koenigii*, carbazole alkaloids, mahanimbine, Lewis acid, mineral acid

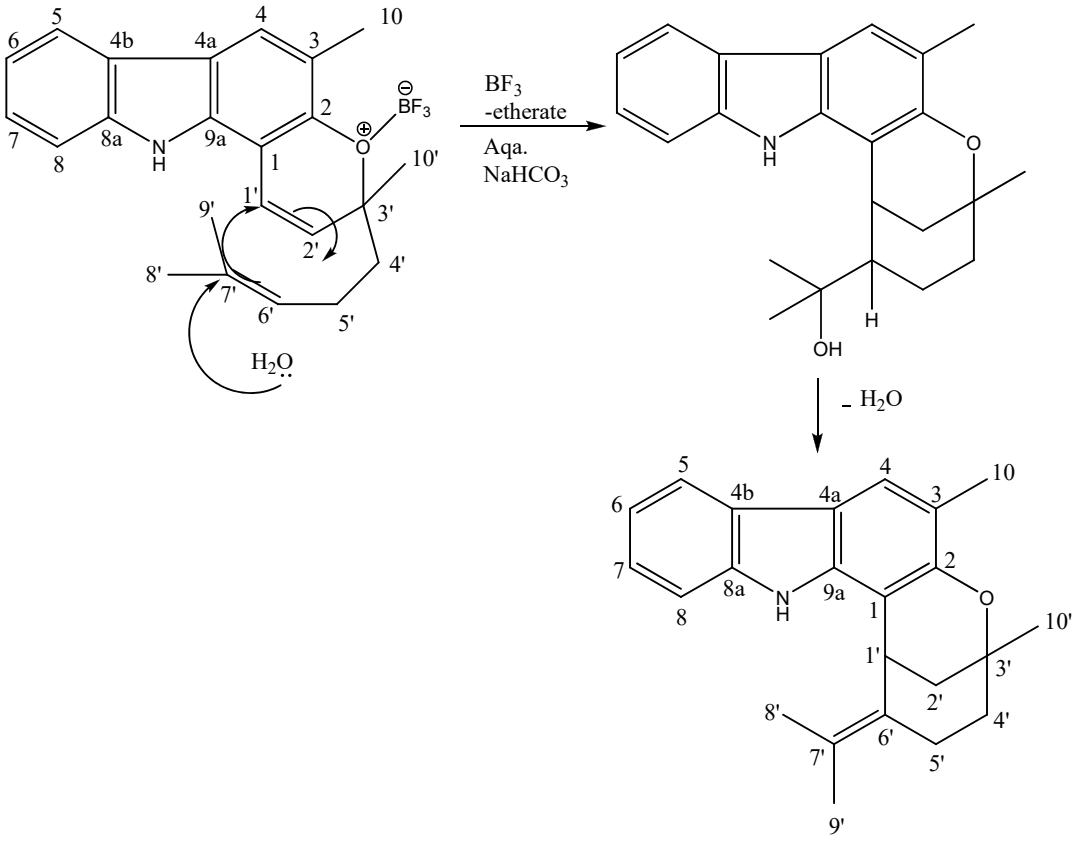
The plant *Murraya koenigii* (L.) Spreng. belonging to the family Rutaceae is native to India and now distributed in most of southern Asia. The leaves of this plant are well-known as curry leaves and have been used as one of the important herbs of south Indian cooking. Various parts of the plant have been used in traditional medicine for the treatment of headache, toothache and stomachaches, influenza, rheumatism, traumatic injury, and insect and snake bites, and as an antidysentric as well as an astringent. Intake of the leaves can increase digestive secretions and relieve nausea, indigestion and vomiting[1]. The leaves and bark are used in analgesia and local anesthesia and for the treatment of eczema and dropsy[2]. Chloroform extract of the root bark of *M. koenigii* displayed significant cytotoxic activity against cultured KB cell.

Murrayanine is the first carbazole alkaloid isolated from the stem bark of *M. koenigii*. After that a number of carbazole alkaloids have been isolated from this plant, possessing C_{13}, C_{18} and C_{23} skeletons[3-6]. A number of derivatives of these carbazole alkaloids were also prepared, many of which showed potent biological activities[7-9].

Mahanimbine[10] was isolated from the leaves of *Murraya koenigii* Spreng, popularly known as curry leaves tree. Spectroscopic studies revealed that the compound is a pyranocarbazole alkaloid with a C_{23} skeleton. The compound also has a C_5H_9 side chain. Application of the Lewis acid BF_3-etherate on mahanimbine **1** resulted in the cyclisation of its side chain furnishing a penta-cyclic compound **2** (Scheme I), whereas in presence of mineral acid mahanimbine was converted into cyclomahanimbine **3** (Scheme II). Compound **2** was later proved to be an isomer of cyclomahanimbine **3**. On the other hand, reaction of mahanimbine **1** with *m*-chloroperbenzioc acid resulted in the formation of an interesting product **4** containing both an epoxy ring as well as two hydroxyl functionalities (Scheme III).

Results and Discussion

Reaction of mahanimbine **1** with BF_3-etherate resulted in the cyclisation of its C_5H_9 side chain and a penta-cyclic product **2** was formed. The ^{1}H NMR spectrum of the product showed signals for five aromatic protons at δ 7.44 (H-4), 7.63(H-5), 7.34(H-6), 7.89(H-7) and 7.14(H-8). It also showed signals for one benzylic methine at δ 4.26 (H-1'), one aromatic methyl at δ 2.13 (H-10) and one gem-dimethyl group at δ 1.43(H-8' and H-9'). The product displayed 23 signals in the ^{13}C NMR spectrum (five aromatic doublets, one aromatic methyl, one gem-dimethyl, one oxygen-bearing quaternary carbon, seven aromatic singlets, three characteristic aliphatic triplets, one C-C double bond, one benzylic methine and one aliphatic methyl). The product has close structural resemblance with cyclomahanimbine **3**. The major distinguishing factor between **2** and cyclomahanimbine **3** is the number of



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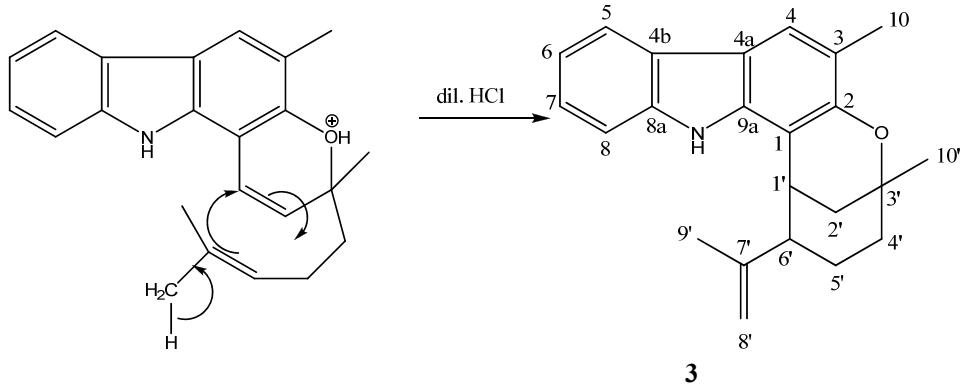
Scheme I — Mechanism for the formation of compound **2**

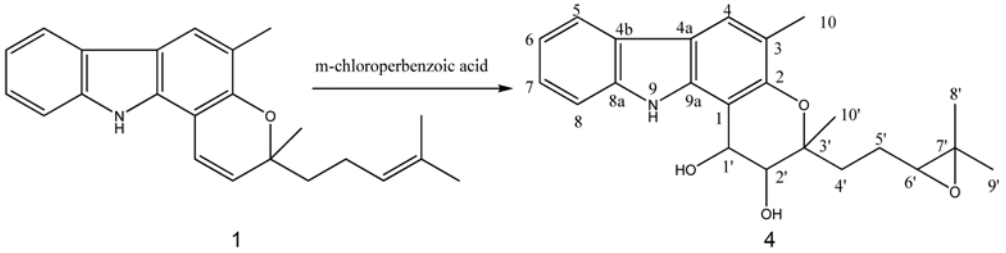


3

Scheme II — Mechanism for the formation of compound **3**

quartets and triplets in ^{13}C NMR spectrum. In cyclomahanimbine **3**, there are three quartets and four triplets, whereas in **2** there are four quartets and three triplets. Finally, compound **2** was confirmed to be an isomer of cyclomahanimbine **3** by the comparison of its spectral data (Table I and Table II) to that of cyclomahanimbine **3** [11].

Reaction of mahanimbine with dil.HCl again resulted in the cyclisation of its C_5H_9 side chain and another penta-cyclic product was formed. The ^{1}H NMR spectrum of the product showed signals for five aromatic protons at δ 7.69 (H-4), 7.88(H-5), 7.13(H-6), 7.25(H-7) and 7.63(H-8). It also showed signals for one benzylic methine at δ 3.38, one aromatic methyl at δ 2.32 and one olephinic double bond. The product displayed 23 signals in the ^{13}C NMR spectrum (five aromatic doublets, one aromatic methyl, one oxygen- bearing quaternary



Scheme III — Epoxidation of mahanimbine **1**

Table I — ^{13}C NMR Chemical shifts (δ, $CDCl_3$, 150 MHz) of compounds **1, 2, 3** and **4**

Carbon	**1**	**2**	**3**	**4**
C-1	104.2	107.1	105.2	105.0
C-2	149.9	153.2	153.6	148.9
C-3	116.6	132.3	119.8	118.5
C-4	121.2	119.2	119.0	121.3
C-4a	118.4	117.9	117.6	115.9
C-4b	123.9	124.4	124.3	118.5
C-5	119.3	119.1	119.5	119.2
C-6	110.3	110.3	110.2	110.6
C-7	124.2	123.6	123.5	119.3
C-8	119.5	119.3	119.1	123.9
C-8a	139.4	139.3	139.4	139.6
C-9a	134.8	136.8	138.3	138.4
C-10	16.1	16.6	16.7	16.3
C-1’	117.5	32.1	36.2	70.4
C-2’	128.5	23.1	37.4	82.1
C-3’	78.1	74.1	73.9	77.8
C-4’	40.7	36.2	39.9	27.6
C-5’	22.7	40.8	23.1	27.0
C-6’	124.2	120.8	48.7	50.9
C-7’	131.7	114.8	150.0	42.7
C-8’	17.6	20.5	112.0	28.1
C-9’	25.7	20.4	21.6	30.4
C-10’	25.8	28.9	28.9	23.0

carbon, seven aromatic singlets, four characteristic aliphatic triplets, one C-C double bond, one benzylic methine and one aliphatic methyl). Finally the product was confirmed to be cyclomahanimbine **3** by comparing its spectral data with the reported spectral data (Table I and Table II) of cyclomahanimbine **3** [11].

Reaction of mahanimbine **1** with *m*-chloroperbenzoic acid resulted in epoxidation at both the double bonds in mahanimbine. The characteristic doublets at 117.5(C-1’) and 128.5(C-2’) disappeared in the ^{13}C NMR spectra of the product. Instead two new doublets appeared at 70.4 and 82.1 ppm assignable to C-1’ and C-2’ respectively. In the final product this epoxide opened and this was confirmed by the peak at *m/z* 386[M-18+23] in the mass spectra of the product **4**. The chemical shifts at 50.9 and 42.7 ppm were assigned to the carbons containing the epoxide in the side chain. Other proton and carbon assignments were made on the basis of 2D NMR (HSQC, HMBC, NOESY, COSY) spectroscopy (Figure 1).

Therefore, mahanimbine **1,** on reaction with mineral acid (dil.HCl) and Lewis acid (BF_3-etherate) afforded cyclomahanimbine **3** and one isomer of cyclomahanimbine **4**, respectively. Again, action of *m*-chloroperbenzoic acid on mahanimbine **1** resulted epoxidation on both the double bonds of mahanimbine **1,** one in the pyran ring and another in the side chain.

Experimental Section

TLC was carried out on silica gel 60 F_{254} (Merck) plates and spots were visualized by spraying with Liebermann-Burchard reagent followed by heating at 120°C. Column chromatography was performed on silica gel mesh 60-120 (Merck). The mass spectra were recorded on a Q-TOF-Micromass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a BRUKER AVANCE 600 MHz NMR with TLC-cryoprobe using TMS as internal standard. Data are presented as follows: Chemical shift (in ppm on the δ scale relative to δ_{TMS} = 0), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad), coupling constant (*J*/Hz).^{1}H NMR and ^{13}C NMR spectra were recorded at 600 MHz and 150 MHz respectively.

Plant material

The dried leaves and stem bark of *Murraya koenigii* were collected from Shantiniketan (India). A voucher specimen has been deposited at IICB, Kolkata, India.

Extraction and isolation

The powdered and dried leaves of *Murraya koenigii* (2 Kg.) were extracted with MeOH at RT and concentrated under vacuum at 40ºC to afford 15 g of

Table II — ^{1}H NMR chemical shifts (δ, $CDCl_3$, 600 MHz) of compounds **1, 2, 3** and **4**

Proton	**1**	**2**	**3**	**4**
H-4	7.66 s	7.44 s	7.69 s	7.74 s
H-5	7.90 d (*J*=7.8Hz)	7.63 m	7.88 d (*J*=7.2Hz)	7.92 d (*J*=7.8Hz)
H-6	7.37 d (*J*=7.8Hz)	7.34 d (*J*=7.8Hz)	7.13 m	7.38 d (*J*=7.8Hz)
H-7	7.31 m	7.89 (*J*=7.8Hz)	7.25 m	7.17 t (*J*=7.2) (*J*=7.2) (*J*=7.2)
H-8	7.16 m	7.14 m	7.63 m	7.29 t (*J*=7.2)
H-9	7.86 s	–	–	8.27 s
H-10	2.33 s	2.13 s	2.32 s	2.32 s
H-1’	6.65 d (*J*=9.6Hz)	4.26 m	3.38 d (*J*=2.4Hz)	5.29 d (*J*=4.2Hz)
H-2’	5.66 d (*J*=9.6Hz)	2.08,1.86 m	2.32,2.02 m	3.89 d (*J*=4.2Hz)
H-3’	–	–	–	–
H-4’	1.76 m	1.66,1.55 m	1.88,1.63 m	1.50 m
H-5’	2.16 m	2.01,1.91 m	1.43,1.25 m	1.69 m
H-6’	5.11 m	–	2.53 d (*J*=2.4Hz)	1.98
H-7’	–	–	–	–
H-8’	1.57 s	1.43 s	4.79,4.72 s	1.38 s
H-9’	1.65 s	1.43 s	1.63 s	1.74 s
H-10’	1.45 s	1.49 s	1.48 s	1.32 s

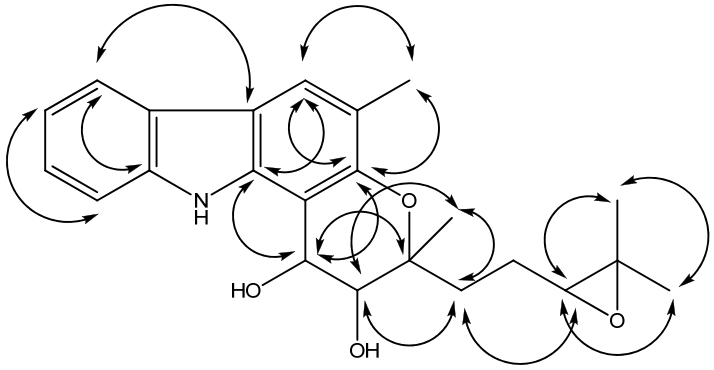


Figure 1 — Important HMBC correlations of compound **4**

extract. The MeOH extract was chromatographed on a column of silica gel (mesh size 60-120). Gradient elution was carried out with petroleum ether (bp 60-80ºC) followed by various mixtures of petroleum ether and benzene (3:1, 1:1, 1:3 and 100% benzene) and again various mixtures of benzene and chloroform (200 mL. each). Fractions giving similar spots were combined. Repeated chromatography of the fractions resulted in the isolation of mahanimbine **1** along with few other carbazole alkaloids. ^{13}C and ^{1}H NMR data of compounds **1** are given in Table I and Table II respectively.

Reaction of mahanimbine 1 with BF_3-Et_2O

25 mg of mahanimbine **1** was dissolved in 10 mL of dry and distilled benzene. 2-3 drops of freshly distilled BF_3-etherate was added to it, when colour of the reaction mixture became dark blue. The reaction mixture was stirred at RT for 10 minutes using a magnetic stirrer. Progress of the reaction was monitored by TLC. Benzene was evaporated under reduced pressure. The reaction mixture was neutralized by adding 10% aqueous $NaHCO_3$ solution, when the dark blue colour disappeared. Then it was extracted with $CHCl_3$ using a separating funnel and washed with water (3 times). Then again it was concentrated under reduced pressure. TLC (Solvent system: Petroleum ether: Benzene = 1:1) showed the presence of a prominent spot with very little amount of impurity. The major product **2** was purified by preparative TLC using Petroleum ether: Benzene = 1:1 as solvent system. MS: *m/z* 332[M+1], ($C_{23}H_{25}NO$); ^{1}H NMR (Table II) and ^{13}C NMR (Table I).

Conversion of mahanimbine 1 into cyclomahanimbine 3

50 mg of mahanimbine **1** was dissolved in 15 mL of dry and distilled benzene. 1 mL conc. HCl was added to it. The reaction mixture was stirred at RT for 1 hour using a magnetic stirrer. Progress of the reaction was monitored by TLC. Benzene was evaporated under reduced pressure. Finally the product mixture was extracted with $CHCl_3$ using a separating funnel and washed with water (3 times). Then again it was concentrated under reduced pressure. TLC (Solvent system: Petroleum ether: Benzene = 1:1) showed the presence of a prominent spot with very little amount of impurity. The major product was purified by column chromatography (using silica gel). Cyclomahanimbine **3** was eluted with Petroleum ether: Benzene = 1:3. MS: *m/z* 354[M+23], ($C_{23}H_{25}NO$); ^{1}H NMR (Table II) and ^{13}C NMR (Table I).

Epoxidation of mahanimbine 1

50 mg of mahanimbine **1** was dissolved in 15 mL of dry and distilled dichloromethane. 1 pinch of *m*-chloroperbenzoic acid was added to it. The reaction mixture was stirred under ice-cold condition for two and half hours using a magnetic stirrer. Progress of the reaction was monitored by TLC. Dichloromethane was evaporated under reduced pressure. The product mixture was extracted with $CHCl_3$ using a separating funnel and washed with water (3 times). Then again it was concentrated under reduced pressure. TLC (Solvent system: 100% Benzene) showed the presence of a prominent spot with very little amount of impurity. The major product was purified by column chromatography (using silica gel). Compound **4** was eluted with Petroleum ether: Benzene = 1:3. MS: *m/z* 386[M-18+23],($C_{23}H_{27}NO_4$); ^{1}H NMR (Table II) and ^{13}C NMR (Table I).

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