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ON THE CONSTITUTION OF MURRAYANINE, A CARBAZOLE DERIVATIVE ISOLATED FROM *MURRAYA KOENIGII* SPRENG

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Abstract—From the stem-bark of *Murraya koenigii* Spreng, a new carbazole derivative, named murrayanine, has been isolated. It has been formulated as 1-methoxy-3-formylcarbazole (I).

Murraya koenigii Spreng. (Fam. Rutaceae) is an Indian medicinal plant commonly known as "curry-leaf tree" and used externally to cure eruptions.[1] The leaves[2] have been found to yield an essential oil, the chief constituents of which are caryophyllene, cadinene, cadinol, *d*-sabinene. Scopoletin occurs in the flower.[3]

The use of the stem-bark in medicine prompted this investigation and in the present communication the structure of murrayanine, a constituent of the stem-bark and previously isolated and characterized,[4] has been determined.

A petroleum ether extract of the dry mature stem-bark yields a solid residue from which three major crystalline fractions may be isolated by chromatography over alumina. One of these yields an optically inactive, neutral, colourless crystalline substance, m.p. 168°, named murrayanine and found to be homogeneous by paper chromatography.[5]

The compound is soluble in benzene, chloroform, ethanol, methanol etc. but insoluble in petroleum ether. It sublimes unchanged at 110–25°/0·05 mm and produces a yellow colour in conc. sulphuric acid, a wine-red colour in a mixture of conc. sulphuric and nitric acids; and with isatin and conc. sulphuric acid an orange-red colour is developed. The compound reduces ammoniacal silver nitrate solution. It contains one methoxy group, forms a picrate, N-methyl derivative, an oxime (II) and a 2,4-dinitrophenyl hydrazone (III).

Analysis of the compound and its mol. wt determination by the Rast method agree with the formula $C_{14}H_{11}O_2N$. The mol. wt was confirmed by mass spectral measurements, revealing a molecular ion peak at m/e 225.[6]

The UV absorption spectrum of the compound is strikingly similar to those of 3-formylcarbazole[7] and 1,4-dimethyl-3-formylcarbazole[8] as shown in Table 1.

[1] K. R. Kirtikar and B. D. Basu, *Indian Medicinal Plants* (2nd edition) p. 472. L. M. Basu, 49 Leader Road, Allahabad, India (1933).
[2] S. Dutta, *Indian Soap J.* **23**, 201 (1958).
[3] K. Aghoramurthy and T. R. Seshadri, *J. Sci. Ind. Res.* **11B**, 411 (1957).
[4] B. K. Barman, Thesis, Calcutta University, 1963 and unpublished data.
[5] D. P. Chakraborty and P. K. Bose, *J. Indian Chem. Soc.* **33**, 905 (1956).
[6] We are indebted to Prof. K. Biemann and Dr. B. Das of M.I.T., Cambridge, Mass., U.S.A. for the mass spectral data.
[7] Private communication from Prof. G. Buchi, M.I.T., Cambridge, Mass., U.S.A., is thankfully acknowledged.
[8] P. A. Cranwell and J. E. Saxton, *J. Chem. Soc.* 3482 (1962).

TABLE 1. ULTRAVIOLET ABSORPTION SPECTRA OF MURRAYANINE AND RELATED COMPOUNDS*

Murrayanine	λ_{max} 238 (4·47), 247 (4·30), 274 (4·56), 289 (4·56), 335 (4·16)
1,4-Dimethyl-3-formyl-carbazole	λ_{max} 237 (4·39), 242 (shoulder 4·34), 274·5 (4·51), 287 (4·42), 330 (4·00)
3-Formylcarbazole	λ_{max} 238 (4·40), 244 (shoulder 4·30), 273 (4·52), 288 (4·49), 327 (4·09)
1-Methoxycarbazole (IX)	λ_{max} 240 (4·59), 252 (shoulder 4·39), 286 (3·84), 320 (3·46)
1-Methoxy-3-hydroxy-methylcarbazole (IV)	λ_{max} 225 (4·42), 242 (4·58), 252 (4·49), 258 (shoulder 4·26), 290 (3·94), 330 (3·55).

* Log ε values are given in parentheses.

The IR spectrum of murrayanine ($CHCl_3$) shows peaks at 3450 (—NH— function) 2800, 1681 (aromatic aldehyde), 1631, 1613, 1585 cm^{-1} (aromatic ring). The peaks (KBr) at 850 and 725 cm^{-1} indicate the presence of tetra- and di-substituted benzene rings respectively.

The NMR spectrum indicates the presence of an aldehydic proton at 589 c/s ($\delta = 9{\cdot}98$), one NH proton at 528 c/s ($\delta = 8{\cdot}80$), six aromatic protons, two protons at 485 c/s ($\delta = 8{\cdot}09$), four at 443 c/s ($\delta = 7{\cdot}39$) and three protons of a methoxyl group attached to a benzene nucleus at 238 c/s ($\delta = 3{\cdot}96$). The presence of eleven protons indicated by NMR further support the molecular formula and the spectrum confirms the presence of an aldehyde and a NH function.

Reduction with potassium borohydride, yields an alcohol, $C_{14}H_{13}NO_2$, m.p. 127° (IV), the IR spectrum of which shows bands at 3500 (hydroxyl), 3275 (NH function) and 1645 cm^{-1} (an aromatic system). The UV spectrum of the compound is very similar to that of 1-methoxycarbazole. Wolff-Kishner reduction of murrayanine affords the hydrocarbon $C_{14}H_{13}ON$ (V). Further proof for the aldehyde function is provided by condensation of the compound and its N-methyl derivative (VI) with malonic acid in presence of pyridine to the corresponding cinnamic acids (VII and VIII). Oxidation of murrayanine with silver oxide affords an acid $C_{14}H_{11}O_3N$, as expected.

The structure of murrayanine may thus be expanded to $C_{12}H_6$ (—NH) ($—OCH_3$) (—CHO).

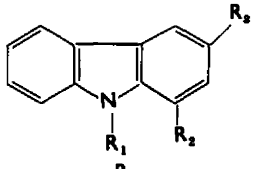
Zinc dust distillation of murrayanine furnishes carbazole which is also obtained from compounds containing reduced carbazole systems as in strychnine,[9] aspidospermine,[10] quebrachamine[11] and bis-nor-c-curarine.[12] Similarly, 2-amino-2′-hydroxy-5-methyldiphenylamine and 2-chloro-2-bromo-3,5,4′-trimethyldiphenylamine, also yield carbazoles.[13] Ajamaline yields carbazole on zinc dust distillation.[14] The UV spectrum of murrayanine is, however, very different from that of diphenylamine (λ_{max} 285, log ε 4·39). The signal of the NH proton of diphenylamine is at 322·8 c/s ($\delta = 5{\cdot}38$) in its NMR spectrum. This shows that the NH protons of murrayanine and diphenylamine are different and, therefore, the presence of a diphenylamine skeleton in murrayanine is not likely, the evidence being in favour of a carbazole

[9] G. R. Clemo, W. H. Perkin and R. Robinson, *J. Chem. Soc.* 1989 (1927).
[10] B. Witkop, *J. Amer. Chem. Soc.* **70**, 3712 (1948).
[11] B. Witkop, *J. Amer. Chem. Soc.* **79**, 3197 (1957).
[12] H. Schmid, A. Ebnother and P. Karrer, *Helv. Chim. Acta* **33**, 1486 (1950).
[13] K. Fries, R. Boker and F. Wallbaum, *Liebigs Ann.* **509**, 73 (1934).
[14] F. A. L. Anet, Mrs. D. Chakravarti, R. Robinson and E. Schlittler, *J. Chem. Soc.* 1242 (1954).

skeleton. The position of the methoxyl group in murrayanine was determined by decarbonylation[15] with Pd-C to 1-methoxycarbazole (IX).

3-Methylcarbazole is obtained when the Wolff-Kishner reduction product of murrayanine is subjected to zinc dust distillation indicating the presence of a formyl group at either position 3 or 6. A comparison of UV spectra reveals the spectrum of murrayanine as being very similar to that of 3-formylcarbazole and distinctly different from those of 1-formyl-, 2-formyl- or 4-formyl-carbazole.[7]

Therefore, murrayanine may be formulated either as 1-methoxy-3-formylcarbazole (I) or 1-methoxy-6-formylcarbazole, but formula I is supported by the presence of four aromatic protons at 443 c/s ($\delta = 7{\cdot}39$) in the NMR spectrum.



	R_1	R_2	R_3
(I)	H	OCH_3	CHO
(IV)	H	OCH_3	CH_2OH
(V)	H	OCH_3	CH_3
(VI)	CH_3	OCH_3	CHO
(VII)	H	OCH_3	CH=CH.COOH
(VIII)	CH_3	OCH_3	CH=CH.COOH
(IX)	H	OCH_3	H
(X)	H	H	H
(XI)	H	H	CH_3
(XII)	H	OCH_3	COOH

EXPERIMENTAL

All m.p.s are uncorrected. Alumina used for chromatography was of Brockmann grade. Pet. ether refers to fraction, b.p. 40–60°. Samples for analysis were dried *in vacuo* over P_2O_5 at 80° for 24 hr.

Isolation of murrayanine (I). The air-dried finely powdered mature bark (1 kg) of *M. koenigii* was extracted in a Soxhlet for 36 hr with pet. ether. After removal of the solvent, the dried residue in dry benzene (50 ml) was absorbed over alumina (435 g). The column was first eluted with pet. ether (9 fractions) and then with benzene, 200 ml being collected each time. Murrayanine was obtained from the 25 to 64th fractions as a colourless granular solid, m.p. 162–164° after washing with pet. ether. After repeated crystallization and sublimation at 110–115° (0·05 mm) colourless needles of murrayanine, m.p. 168°, were obtained (yield 0·07%); *Rf* 0·69 (alcohol–acetic acid water, 34:4:31). (Found: C, 74·82; H, 5·09; N, 6·29; OCH_3, 14·05; mol. wt. (Rast) 226·8. $C_{14}H_{11}O_2N$ requires: C, 74·67; H, 4·89; N, 6·22; OCH_3, 13·78%; mol. wt. 225).

Picrate of murrayanine. The picrate was prepared as fine orange needles and crystallized from a mixture of benzene and pet. ether, m.p. 198–200°, dec. (Found: N, 12·45. $C_{20}H_{14}O_9N_4$ requires: N, 12·33%).

Oxime of murrayanine (II). Murrayanine (110 mg) and hydroxylamine hydrochloride (300 mg) were dissolved in aldehyde-free EtOH (4 ml) and pyridine (2 ml). The mixture was refluxed for 5 hr, cooled, poured into ice-water and kept over-night. The resultant granular solid was repeatedly washed with hot water and finally crystallized from benzene–pet. ether as needles, m.p. 150–153°. After purification by chromatography over acid-washed alumina with ethyl acetate as the eluent, it separated as colourless needles, m.p. 155–156°. (Found: C, 69·50; H, 5·35; N, 11·78. $C_{14}H_{12}O_2N_2$ requires: C, 70·00; H, 5·00; N, 11·67%).

2,4-Dinitrophenylhydrazone of murrayanine (III). Murrayanine (20 mg) was dissolved in acetone-free MeOH (10 ml) and to this was added a methanolic solution of 2,4-dinitrophenylhydrazine

[15] G. Buchi and E. W. Warnhoff, *J. Amer. Chem. Soc.* **81**, 4433 (1959).

sulphate (0·25%, 10 ml). An immediate red ppt was formed which was almost insoluble in all common organic solvents. The compound did not melt even at 300°. (Found: N, 17·52, $C_{20}H_{18}O_5N_6$ requires: N, 17·28%).

N-Methyl derivative of murrayanine (VI). Murrayanine (29 mg) in dry acetone (15 ml) was refluxed with MeI (1·5 g) and anhydrous K_2CO_3 (2 g) for 3 hr. The product was crystallized from benzene–pet. ether as cream-coloured needles, m.p. 148–149°. (Found: C, 75·12; H, 5·53; N, 6·20. $C_{16}H_{13}O_3N$ requires: C, 75·31; H, 5·48; N, 5·86%). The IR spectrum of the compound showed absence of the —NH— band.

Reaction with malonic acid (VII). A mixture of murrayanine (125 mg; 1 mole), malonic acid (115 mg; 2 moles), pyridine (2 ml) and piperidine (0·2 ml) was heated at 80° for 1 hr, then at 100° for 2 hr and finally refluxed for ½ hr. On pouring the mixture, after cooling, into 12% HCl aq (50 ml), a yellowish granular solid was obtained which was crystallized from benzene as yellow needles, yield 120 mg; m.p. 252°, dec. (Found: C, 71·69; H, 4·78; N, 5·32. $C_{16}H_{13}O_3N$ requires: C, 71·91; H, 4·87; N, 5·24%). The compound evolves CO_2 with $NaHCO_3$ aq. UV λ_{max} 218 (log ε 4·36), 245 (log ε 4·51), 256 (log ε 4·42), 281 (log ε 4·58), 320 (log ε 4·17).

Reaction of malonic acid with N-methylmurrayanine. The N-methyl (VIII) derivative was similarly prepared, m.p. 208–209°, dec. (Found: C, 72·75; H, 5·54; N, 5·20. $C_{17}H_{15}O_3N$ requires: C, 72·60; H, 5·34; N, 4·98%). The compound is soluble in $NaHCO_3$ aq.

Borohydride reduction product of murrayanine (IV). Potassium borohydride (197 mg), dissolved in dry MeOH (75 ml), was added to a methanolic solution (25 ml) of murrayanine (200 mg). The solution was kept at room temp for 18 hr, and then concentrated at red. press. Excess borohydride was decomposed with HCl aq and the mixture extracted with ether. The product obtained by the removal of ether was dissolved in acetone and chromatographed over alumina (9 g). Repeated crystallization of the product of ether eluent from benzene–pet. ether yielded needle-shaped crystals; m.p. 127°. (Found: C, 73·81; H, 5·68; N, 5·92. $C_{14}H_{13}O_2N$ requires: C, 74·00; H, 5·77; N, 6·16%).

Wolff-Kishner reduction product of murrayanine (V). Murrayanine (350 mg) was mixed with hydrazine hydrate (99–100%; 350 mg), KOH (350 mg) and diethylene glycol (3·5 ml). The mixture was heated at 200° for 1 hr, cooled, poured into iced water and extracted with benzene (6 × 50 ml). The combined benzene extract was washed with 5% HCl aq (40 ml) and water (40 ml), dried (Na_2SO_4) and the solvent removed. The resulting oily product was further purified by distillation at 125°/0·05 mm yielding a colourless oil. (Found: C, 79·63; H, 6·33; N, 6·38. $C_{14}H_{13}ON$ requires: C, 79·62; H, 6·16; N, 6·63%). It formed a deep red crystalline picrate m.p. 184°.

Zinc dust distillation of murrayanine—formation of carbazole (X). Murrayanine (224 mg) was intimately mixed with Zn dust (10 g) and distilled at 400–450° in a hard glass tube closed at one end. The crystalline mass which was deposited at the cooler part of the tube was taken up in ether and chromatographed over alumina (3 g) with benzene as eluent (1 ml). The solid left on removal of benzene was crystallized from benzene–pet. ether as white flakes; m.p. 218–224°. The substance was further purified by sublimation at 110–115° (0·03 mm) and crystallization from the same solvent; m.p. 228–230°, yield 3 mg. When mixed with pure carbazole (240–242°) it melted at 237–238°*. (Found: C, 86·27; H, 6·04; N, 8·23. $C_{12}H_9N$ requires: C, 86·19; H, 5·43; N, 8·38%). Like carbazole it gave an olive green colouration with conc. H_2SO_4 and a bluish green colouration with conc. H_2SO_4 and conc. HNO_3. UV (degraded product), λ_{max} 235 (log ε 4·46), 258 (log ε 4·20), 294 (log ε 4·01). UV (pure carbazole), λ_{max} 234 (log ε 4·51), 257 (log ε 4·14), 293 (log ε 4·05).

Picrate of X. The compound (6 mg) was dissolved in dry benzene (2 ml) and a solution of picric acid (6 mg) in benzene (2 ml) was added. The precipitate, obtained on concentration of the solution, crystallized from benzene-pet. ether as silky red needles; m.p. 180–182°. (Found: N, 13·92. $C_{18}H_{12}O_7N_4$ requires: N, 14·14%). The picrate melted at 182–183° when mixed with a specimen of carbazole picrate (m.p. 184°).

Decarbonylation product of murrayanine (IX). Murrayanine (300 mg) was thoroughly mixed with Pd-C (20%; 150 mg) and heated at 270° for 15 min in a N_2 atm. After cooling, the mass was extracted with dry EtOH and the oily liquid left after removal of the solvent was distilled at 100° (0·03 mm). The distillate on keeping for several days crystallized to a cluster of needles which on recrystallization from benzene–pet. ether yielded colourless needles, m.p. 69–70°. (Found: C, 78·93; H, 5·61; N, 7·01. $C_{13}H_{11}ON$ requires: C, 79·19; H, 5·62; N, 7·11%). This was identified as 1-methoxycarbazole,

* The m.p. of carbazole has been variously recorded[9,12] from 220–225° to 244°.

by mixed m.p. determination and comparison of the UV spectrum with that of a synthetic specimen of 1-methoxycarbazole m.p. 69° prepared according to the method of Barnes *et al.*[16]

Picrate of (IX). The above substance (25 mg) in alcohol (5 ml) was mixed with a saturated alcoholic solution of picric acid (25 mg) in alcohol. The precipitate was crystallized from benzene–pet. ether, yield 20 mg; m.p. 144–145°. (Found: N, 13·25. $C_{19}H_{14}O_8N_4$ requires: N, 13·14%).

Zinc dust distillation product of (V)*—formation of* (XI). The compound V (75 mg) was intimately mixed with Zn dust (10 g) and distilled at 400–450° in a hard glass tube closed at one end. The crystalline products which concluded at the cooler part of the tube were taken up in ether and chromatographed over alumina (3 g). On eluting the column with benzene–pet. ether (1:1; 10 ml), removal of the solvent and crystallization of the residue from pet. ether, colourless flakes were obtained, yield 3 mg, m.p. 198–201°. (Found: C, 86·04; H, 6·16; N, 7·52. $C_{13}H_{11}N$ requires: C, 86·15; H, 6·12; N, 7·73%). This compound was identified as 3-methylcarbazole by mixed m.p. and paper chromatographic behaviour. For comparison, a pure specimen of 3-methylcarbazole, m.p. 200–203°, was prepared according to the method of Barclay and Campbell.[17] UV of degradation product (XI), λ_{max} 230 (log ε 4·57), 237 (log ε 4·58), 242 (log ε 4·37), 259 (log ε 4·22) 296 (log ε 4·2) 329 (log ε 3·6). UV of synthetic specimen, λ_{max} 230 (log ε 4·61), 236 (log ε 4·63), 243 (log ε 4·37) 260 (log ε 4·27), 296 (log ε 4·28), 330 (log ε 3·60).

Oxidation of murrayanine with silver oxide—formation of (XII). Murrayanine (250 mg) was refluxed with Ag_2O (from 0·5 g $AgNO_3$) in 20 ml 50% EtOH containing 0·8 g NaOH for 36 hr. The solution was acidified with dil. HCl aq and extracted with ether. The residue obtained after removal of ether was dissolved in benzene and chromatographed over a column of silica gel. From the chloroform eluent an amorphous, almost colourless substance, m.p. 200–205°, was obtained. This product on sublimation and subsequent crystallization from MeOH yielded a product, m.p. 240–241°. (Found: C, 69·89; H, 4·64; N, 5·97. $C_{14}H_{11}NO_3$ requires: C, 69·70; H, 4·60; N, 5·81%). The compound was soluble in $NaHCO_3$ aq.

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[16] C. S. Barnes, K. H. Pausacker and C. I. Schubert, *J. Chem. Soc.* 1381 (1949).
[17] B. M. Barclay and N. Campbell, *J. Chem. Soc.* 530 (1945).