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STRUCTURES OF MURRAYASTINE, MURRAYALINE, AND PYRAYAFOLINE; THREE NEW CARBAZOLE ALKALOIDS FROM MURRAYA EUCHRESTIFOLIA[1)]

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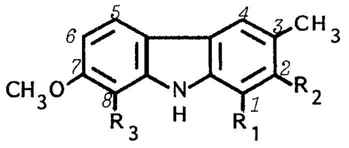
The structures of murrayastine (1), murrayaline (2), and pyrayafoline (3), new carbazole alkaloids from Murraya euchrestifolia Hayata (Rutaceae) collected in Taiwan, have been determined by spectral and synthesis experiments.

KEYWORDS —— murrayastine; murrayaline; pyrayafoline; Murraya euchrestifolia; Rutaceae; carbazole alkaloid; palladium acetate

During a current project dealing with the constituents of Murraya plants (Rutaceae), we have demonstrated the presence of many kinds of monomeric carbazoles, carbazolequinones, and dimeric carbazole alkaloids in the root bark of Murraya euchrestifolia Hayata collected in Taiwan.[2)] This paper describes the isolation and structure elucidation of three new carbazole alkaloids named murrayastine (1), murrayaline (2), and pyrayafoline (3) from the stem bark of the same plant material.[3)]

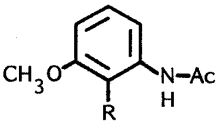
Murrayastine (1), $C_{16}H_{17}NO_3$, [m/z 271.1191 (M^+, found); 271.1207, calcd; m/z: 271 (M^+, 100%), 256, 228, 213, 197, 183, and 170] was obtained as colorless syrup (yield : 0.0005% from dried bark). The UV [λ_{max} (MeOH): 224, 247, 255, 298, 322, and 336 nm] and IR spectra [ν_{max} ($CHCl_3$): 1630 and 1585 cm^{-1}] showed absorptions typical of a carbazole nucleus.[4)] The ^1H-NMR spectrum[5)] contained signals attributable to an aryl methyl [δ 2.47 (3H, s)] and three methoxy groups [δ 3.95, 3.96, and 4.00 (each 3H, s)]. In the aromatic proton region, two one-proton singlets (δ 6.65 and 7.32), and AB-type signals [δ 6.80 and 7.56 (each 1H, d, J = 8 Hz)] were observed. Among these aromatic proton signals, lower signals at δ 7.32 (1H, s) and 7.56 (1H, d) were assignable to H-4 and H-5, respectively.[4)] In NOE experiments, irradiation of the aryl methyl proton at δ 2.47 revealed 12.4% and 21.6% enhancements of the signals at δ 6.65 (H-2) and 7.32 (H-4), respectively. These spectral results suggest the structure 1 for murrayastine. Further evidence comes from the synthesis of 1. Condensation (Cu, K_2CO_3, pyridine) between 1-bromo-2-methoxy-4-methylbenzene (5)[6)] and 7[7)] followed by hydrolysis with 20% KOH-EtOH afforded diphenylamine (9),[8,9)] mp 73-75°C, as colorless prisms from hexane. Treatment of 9 with palladium acetate [$Pd(OAc)_2$][10)] in dimethylformamide (DMF) led to 1, which was found to be identical with natural murrayastine by comparison of the IR, MS, and ^1H-NMR spectra.

Murrayaline (2), $C_{16}H_{15}NO_3$, [m/z 269.1002 (M^+, found); 269.1050, calcd] was isolated as pale yellow prisms from acetone, mp 248-250°C, yield: 0.0003%, and showed the following spectral data: UV λ_{max} (MeOH): 226, 260 (sh.), 304, and 383 nm; IR ν_{max} (KBr): 3370, 1650, 1630, 1600, 1590, and 1580 cm^{-1}; MS m/z: 269 (M^+, 100%), 254, 226, 211, 198, 183, and 167. The observation of a one-proton singlet at δ 10.58 together with the IR band at 1650 cm^{-1} revealed the presence of a formyl moiety in the molecule. Further, the ^{1}H-NMR spectrum of murrayaline showed signals assignable to an aryl methyl [δ 2.35 (3H, s)] and two methoxy groups [δ 3.90 and 3.98 (each 3H, s)] as well as four aromatic protons [δ 6.91 (1H, s), 7.95 (1H, s), 6.77 (1H, d, J = 9 Hz), and 8.02 (1H, d, J = 9 Hz)] similar to those of murrayastine (1). However, in NOE experiments, irradiation of the aryl methyl proton (δ 2.35) gave a 17.6% enhancement only of the signal at δ 7.95 assignable to H-4. Further, a 26.9% enhancement of the signal at δ 6.91 (H-1), and an 18.8% at δ 6.77 (H-6) were observed on irradiation of the methoxy signal at δ 3.90 and at δ 3.98, respectively. These data suggest that the location of substituents in the murrayaline molecule was 2, 3, 7, and 8, unlike murrayastine (1), and that the methyl and formyl moieties were attached at C-3, and C-8, respectively. Synthesis of 2 was also carried out as follows: Condensation of 1-bromo-3-methoxy-4-methylbenzene (6)[11] and 8[12] which was prepared from 2-allyl-3-hydroxyacetanilide,[13] followed by alkaline hydrolysis led to diphenylamine (10).[14] Treatment of 10 with $Pd(OAc)_2$, and then acid gave 2,[9,15] mp 246-248°C, as pale yellow prisms from acetone, which was found to be identical with natural murrayaline (IR, ^{1}H-NMR, and MS). This is the first isolation of a carbazole alkaloid having a one-carbon unit at the ring considered biogenetically to be derived from an anthranilate.[16]



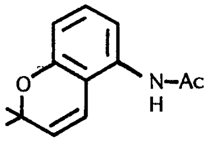
1 : $R_1=OCH_3$, $R_2=H$, $R_3=OCH_3$

2 : $R_1=H$, $R_2=OCH_3$, $R_3=CHO$



7 : $R=OCH_3$

8 : $R=CH(OCH_3)_2$



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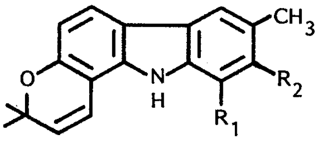
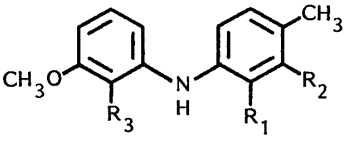


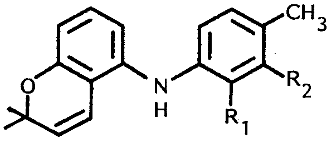
3 : $R_1=H$, $R_2=OCH_3$

4 : $R_1=OCH_3$, $R_2=H$



9 : $R_1=OCH_3$, $R_2=H$, $R_3=OCH_3$

10 : $R_1=H$, $R_2=OCH_3$, $R_3=CH(OCH_3)_2$



12 : $R_1=H$, $R_2=OCH_3$

13 : $R_1=OCH_3$, $R_2=H$

Pyrayafoline (3), $C_{19}H_{19}NO_2$, [m/z 293.1399 (M^+, found); 293.1414, calcd] was obtained as colorless plates from ether, mp 228-231°C; yield: 0.0002%; UV λ_{max} (MeOH): 222, 239, 286 (sh.), 295, and 334 nm; IR ν_{max} (KBr): 1625, 1605, and 1590 cm^{-1}; MS m/z: 293 (M^+), 278 (100%), 263, and 234. In the ^{1}H-NMR spectrum of pyrayafoline, an appearance of AB-type signals at δ 5.67 and 6.58 (each 1H, d, J = 10 Hz) together with a six-proton singlet at δ 1.47 suggested the presence of a dimethylpyran ring system in the molecule. Other ^{1}H-NMR signals [δ 2.33 (3H, s), 3.89 (3H, s), 6.67 (1H, d, J = 8 Hz), 6.83 (1H, s), 7.62 (1H, s), 7.63 (1H, d, J = 8 Hz), and 7,77 (1H, br s)] were similar to those of murrayaline (2) except for a formyl and a methoxy proton signal. To confirm the structure of this alkaloid, synthesis of 3 and 4 was attempted as follow: the diphenylamine (12)[9,17], prepared by condensation between 11[18] and 6[11] was treated with Pd(OAc)$_2$ in DMF to give 3[9,15] as colorless plates, mp 230-232°C, which was found to be identical with natural pyrayafoline (IR, ^{1}H-NMR, and MS). The isomer 4,[9,19] colorless oil, was also synthesized from 13[9,20] [mp 87-88°C, yellow plates, prepared from 11[18] and 5[6]] by cyclization with Pd(OAc)$_2$ in DMF, and it showed a ^{1}H-NMR spectrum different from that of natural pyrayafoline. These results led us to assign the structure 3 to pyrayafoline.

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3) The plant material was collected at Kuantaochi, Nantou Hsien, Taiwan, on August, 1983.

4) D. P. Chakraborty, "Fortschritte der Chemie organischer Naturstoffe," Vol. **34**, ed. by W. Herz, H. Grisebach, and G. W. Kirby, Springer-Verlag, New York, 1977, p. 299.

5) All ^{1}H-NMR spectra were recorded in $CDCl_3$. Chemical shifts were shown in δ-values with TMS as internal reference.

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7) Prepared from the corresponding phenol [M. G. Sundaram, J. Labelled Comp. Radiopharm., **18**, 489 (1981)].

8) **9**: ^{1}H-NMR δ: 7.24 (1H, d, J = 9 Hz), 7.00-6.28 (6H, overlapped), 3.84 (3H, s), 3.83 (3H, s), and 2.31 (3H, s).

9) Satisfactory elemental composition was obtained by high resolution mass spectrometry.

10) B. Akermark, L. Eberson, E. Jonsson, and E. Pettersson, *J. Org. Chem.*, **40**, 1365 (1975).

11) M. Ando and S. Emoto, *Bull. Chem. Soc. Jpn.*, **51**, 2435 (1978).

12) **8**:9) ^{1}H-NMR δ: 9.11 (1H, br s), 8.00 (1H, d, J = 8 Hz), 7.24 (1H, t, J = 8 Hz), 6.61 (1H, d, J = 8 Hz), 5.82 (1H, s), 3.81 (3H, s), 3.43 (6H, s), and 2.14 (3H, s).

13) G. Brancaccio, G. Lettieri, and R. Viterbo, *J. Org. Chem.*, **38**, 831 (1973).

14) **10**: ^{1}H-NMR δ: 7.57-5.37 (6H, overlapped), 6.22 (1H, d, J = 8 Hz), 5.76 (1H, s), 3.76 (3H, s), 3.70 (3H, s), 3.38 (6H, s), and 2.10 (3H, s).

15) The reaction product cyclized to another orientation could not be detected.

16) D. P. Chakraborty, *J. Indian Chem. Soc.*, **46**, 177 (1969).

17) **12**: ^{1}H-NMR δ: 7.17-6.17 (7H, overlapped), 5.63 (1H, d, J = 10 Hz), 5.47 (1H, br s), 3.73 (3H, s), 2.09 (3H, s), and 1.44 (6H, s).

18) Synthesized by a similar method according to the following literature: J. M. Evans, C. S. Fake, T. C. Hamilton, R. H. Poyser, and E. A. Watts, *J. Med. Chem.*, **26**, 1582 (1983).

19) **4**: ^{1}H-NMR δ: 7.95 (1H, br. s), 7.66 (1H, d, J = 8.5 Hz), 7.28 (1H, s), 6.67 (1H, dd, J = 8.5 & 1 Hz), 6.62 (1H, s), 6.61 (1H, dd, J = 10 & 1 Hz), 5.65 (1H, d, J = 10 Hz), 3.96 (3H, s), 2.29 (3H, s), and 1.48 (6H, s).

20) **13**: ^{1}H-NMR δ: 7.12-6.28 (7H, overlapped), 5.81 (1H, br s), 5.58 (1H, d, J = 10 Hz), 3.85 (3H, s), 2.28 (3H, s), and 1.41 (6H, s).

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