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BISMURRAYAFOLINE-A AND -B, TWO NOVEL "DIMERIC" CARBAZOLE ALKALOIDS FROM *MURRAYA EUCHRESTIFOLIA*

Hiroshi Furukawa,* Tian-Shung Wu, and Tomoko Ohta

Faculty of Pharmacy, Meijo University
Yagoto, Tempaku, Nagoya 468, Japan

The structures of bismurrayafoline-A (1) and -B (5), the first and the second naturally occurring "dimeric" carbazole alkaloids isolated from *Murraya euchrestifolia* Hayata (Rutaceae) have been determined by spectral and chemical experiments.

KEYWORDS —— bismurrayafoline-A; bismurrayafoline-B; *Murraya euchrestifolia*; Rutaceae; carbazole alkaloid; murrayafoline-A; murrayafoline-B

In continuation of our study[1)] of alkaloids from *Murraya euchrestifolia* Hayata (Rutaceae) collected in Taiwan, we have isolated and characterized two new dimeric carbazole alkaloids, bismurrayafoline-A (1) and -B (5).

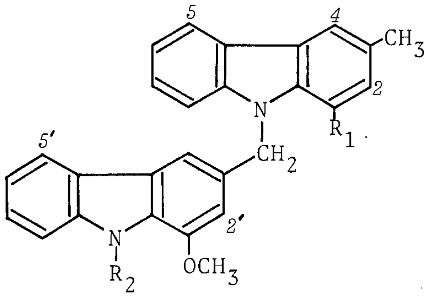
Bismurrayafoline-A (1), mp 176-177°C (colorless needles from ether), was obtained in 0.0025% yield from ethanol extracts of the plant collected in December, and was found to have the molecular formula $C_{28}H_{24}N_2O_2$. The presence of carbazole skeleton in the molecule was easily deduced by the UV spectrum[3)] [λ_{max}(MeOH) nm (log ε): 228(4.81), 244(4.95), 253(sh., 4.84), 284(sh., 4.15), 293 (4.30), and 340(3.92)]. The mass spectrum contained a molecular ion peak at m/z 420 and the most important peak at m/z 210, which was also the base peak, was due to a half of the molecule. These findings strongly suggest a dimeric carbazole structure of bismurrayafoline-A (1). The ^{1}H-NMR($CDCl_3$) spectrum indicated the presence of an aryl methyl (δ 2.46), and two methoxy (δ 3.71 and 3.82) groups. In the aromatic proton region, a 2H-singlet (δ 6.62) assignable to H-2 and H-2' and two lower-field 1H-doublets (δ 7.72 and 7.85, each J=7Hz), characteristic of H-5 and H-5' in the carbazole nucleus,[2)] were observed. And 8H-signals in a complex pattern from δ 7.0 to 7.6 including two 1H-singlets (δ 7.32 and 7.36) due to H-4 and H-4', also appeared. Further, an appearance of a 2H-singlet at δ 5.83 coupled with observation of a strong fragment peak at m/z 210 suggested the presence of a benzylic methylene group directly bonded to a nitrogen atom.

These spectral results suggested the structure of bismurrayafoline-A for 1 corresponding to the dimer of murrayafoline-A (4) which we previously isolated as one of monomeric carbazole alkaloids from the same plant source.

In order to confirm the structure of bismurrayafoline-A (1), treatment of this alkaloid with sodium in liquid ammonia at -75°C afforded 2 as colorless needles, mp 156-158°C. The mass spectrum of the product showed a molecular ion peak at m/z 390 together with fragment ions at m/z 210 (100%) and 181. The ^{1}H-NMR($CDCl_3$) spectrum showed only one methoxy signal at δ 3.78 among other signals [δ 2.52 (3H, s, aryl-CH_3), 5.60 (2H, s, benzylic-CH_2), and 6.68 (1H, s, H-2')]. Methylation of 2 with CH_3I-K_2CO_3 in acetone gave the N-methylated compound 3 as colorless granules, mp 167-169°C. In the ^{1}H-NMR spectrum, an N-methyl signal newly appeared at δ 4.04 in addition to other signals [δ 2.48 (3H, s, aryl-CH_3), 3.65 (3H, s, OCH_3), 5.52 (2H, s, benzylic-CH_2), and 6.61 (1H, s, H-2')]. In the mass spectrum of 3, the fragments occurring from the benzylic C-N bond fission appeared at m/z 224 (100 %) and 181 as compared to m/z 210 and 181 in the case of 2. These results indicated that the methoxy group attached at the upper carbazole nucleus in formula 1 had been substituted for a hydrogen atom by liq. NH_3/Na reaction of bismurrayafoline-A (1), instead of the cleavage of the benzylic C-N bond.

Next, we attempted the hydrogenolysis of bismurrayafoline-A (1) with 5% Pd-C in methanol containing a small amount of HCOOH to furnish murrayafoline-A (4) as the sole product, which was identified with the authentic specimen by comparisons of the ^{1}H-NMR and IR spectra.

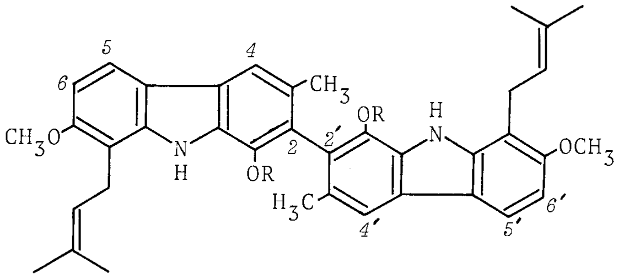
On the basis of the chemical and spectral results stated above, we assigned the structure 1 to bismurrayafoline-A.



(1) $R_1=OCH_3$, $R_2=H$

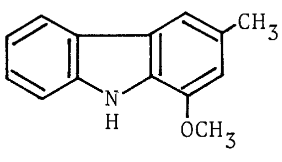
(2) $R_1=R_2=H$

(3) $R_1=H$, $R_2=CH_3$

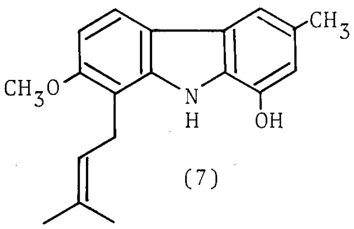


(5) R=H

(6) R=Ac



(4)



(7)

Bismurrayafoline-B (5), colorless needles from acetone, mp 260°C (dec.) was isolated from the acetone extracts of the plant collected in February. The molecular formula $C_{38}H_{40}N_2O_2$ was deduced by high resolution mass spectrometry (M^+ 588.29829, Calcd for $C_{38}H_{40}N_2O_2$ 588.29869). Bismurrayafoline-B showed the following spectral properties: UV λ_{max}(MeOH) nm: 225(sh.), 240, 265(sh.), 285(sh.), 312, and 333(sh.); IR ν_{max}($CHCl_3$) cm^{-1}: 3550, 3450, and 1615; ^{1}H-NMR ($CDCl_3$-acetone-d_6) δ: 2.46 (6H, s, aryl-CH_3), 3.86 (6H, s, OCH_3), 6.79 (2H, d, J=8Hz), 6.78 (2H, s, OH), 7.69 (2H, d, J=8Hz), 7.73 (2H, s, H-4, -4'), 7.92 (2H, s, NH), and [1.24 (6H, s), 1.28 (6H, s), 3.36 (4H, d, J=8Hz), 5.01 (2H, m): prenyl]; ^{13}C-NMR($CDCl_3$-DMSO-d_6) δ: 16.85 (q), 17.08 (q), 23.93 (t), 24.86 (q), 56.75 (q), 102.26 (s), 104.78 (d), 111.04 (s), 117.18 (s and d), 118.18 (s), 118,41 (s), 121,45 (d), 121.86 (d), 123.68 (s), 137.89 (s), 140.29 (s), 150.35 (s), and 154.74 (s); MS m/z (%): 588 (M^+, 100), 517(24), and 294(M^{++}, 10). The UV spectrum showed an almost typical carbazole chromophore[2] which on addition of alkali exhibited a bathochromic shift of phenols. The observation of the molecular ion peak at m/z 588 as a base peak in the mass spectrum, and the appearance of only 19 carbon signals in the ^{13}C-NMR spectrum suggested a dimeric structure of bismurrayafoline-B, in which two equivalent monomer units were disposed in symmetrical manner. Further, the ^{1}H-NMR signal pattern of the ^{1}H-NMR spectrum of bismurrayafoline-B (5) was similar to that of murrayafoline-B (7),[3] taking into account some differences of chemical shifts and a lack of the singlet due to H-2. These facts suggested that two monomer units composed the dimer was murrayafoline-B (7) which co-occurred with bismurrayafoline-B (5). Treatment of bismurrayafoline-B with Ac_2O in pyridine at room temperature gave diacetate (6). ^{1}H-NMR($CDCl_3$) δ: 1.90 (6H, s, OAc), 2.36 (6H, s, aryl-CH_3), 3.86 (6H, s, OCH_3), 6.82 (2H, d, J=8Hz, H-6, -6'), 7.64 (2H, s, NH), 7.80 (2H, d, J=8Hz, H-5, -5'), and 7.86 (2H, s, H-4, -4'), and [1.15 (6H, s), 1.22 (6H, s), 3.38 (4H, d, J=8Hz), and 5.04 (2H, t, J=8Hz): prenyl]. IR ν_{max} ($CHCl_3$): 1740 cm^{-1}. MS m/z (%): 672 (M^+, 46), 630 (100), 588 (69), and 336 (M^{++}, 4). In studies of NMR nuclear Overhauser effects of the diacetate (7), irradiation of the aryl methyl protons (δ 2.36) gave a 9.1% enhancement of the singlet at δ 7.86 (H-4 and H-4'). Irradiation of the methoxy protons (δ 3.86) caused a 16.3% area increase of the doublet at δ 6.82 (H-6 and H-6'). The presence of a lower-field singlet due to H-4 and H-4', and a lack of the signal assignable to H-2 and H-2' in ^{1}H-NMR spectra both of bismurrayafoline-B (5) and its diacetate (6) revealed the location of the linkage of two monomer units at C-2 and C-2'.

These spectral results led us to propose the structure 5 to bismurrayafoline-B.

Many monomeric carbazole alkaloids have been isolated from Rutaceous plants.[2, 4, 5] However, the occurrence of "dimeric" carbazoles have never been known in nature, and our paper describes the first and the second isolation of dimeric carbazole alkaloids from a natural source.[6]

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3) Murrayafoline-B (**7**) has been isolated from the same plant, and characterized by a chemical correlation with murrayaquinone-B.1) The structural elucidation of murrayafoline-B (**7**) was presented at the 103rd Annual Meeting of the Pharmaceutical Society of Japan (Tokyo, April, 1983), and will be reported elsewhere. Murrayafoline-B (**7**): ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s, aryl CH_3), 3.90 (3H, s, OCH_3), 6.56 (1H, s, H-2), 6.82 (1H, d, J=9Hz, H-6), 7.32 (1H, s, H-4), 7.72 (1H, d, J=9Hz, H-5), and [1.72 (3H, s), 1.88 (3H, s), 3.60 (2H, d, J=8Hz), and 4.30 (1H, t, J=8Hz): prenyl].

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5) J. A. Joule, "*The Alkaloids*," Specialist Periodical Reports of The Chemical Society, Vol. **1**, 150 (1971); Vol. **2**, 209 (1972); Vol. **3**, 187 (1973); Vol. **4**, 284 (1974); Vol. **5**, 191 (1975); J. E. Saxton, *ibid*., Vol. **6**, 190 (1976); Vol. **7**, 184 (1977); Vol. **8**, 149 (1978); Vol. **9**, 151 (1979); Vol. **10**, 141 (1981); Vol. **11**, 145 (1982).

6) A "binary" carbazole alkaloid, murrafoline, has been isolated from the same plant, and characterized.7)

7) A. T. McPhail, T.-S. Wu, T. Ohta, and H. Furukawa, *Tetrahedron Letters*, 1983, (in press)

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