

A NEW MONOQUATERNARY BISBENZYLISOQUINOLINE ALKALOID FROM *STEPHANIA TETRANDRA*

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ABSTRACT.—A new monoquaternary bisbenzylisoquinoline alkaloid, (+)-2-*N*-methylfangchinoline [4], was obtained from the root of *Stephania tetrandra*, the traditional Chinese medicine "fen-fang-ji," along with three known bisbenzylisoquinoline alkaloids 1–3.

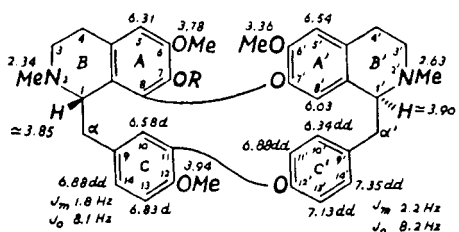
The traditional Chinese medicine "fen-fang-ji," the root of *Stephania tetrandra* S. Moore (Menispermaceae), has been used as an analgesic, diuretic, and detumescent for thousands of years in China. The main alkaloid, tetrandrine [1], has been demonstrated to have broad pharmacological activities including analgesic, antitumor, hypotensive, antimicrobial, and antiarrhythmic effects (1). It also inhibits platelet aggregation and acts as a Ca^{+2} antagonist (1).

Our continuing study of the root of *S. tetrandra* has yielded (+)-2-*N*-methylfangchinoline [4] and the known alkaloids (+)-tetrandrine [1] and (+)-fangchinoline [2], both of which are major components, and (+)-2-*N*-methyltetrandrine [3] (2,3).

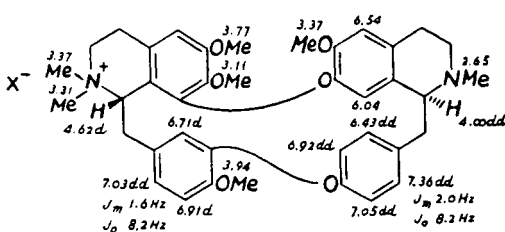
The new monoquaternary bisbenzylisoquinoline (+)-2-*N*-methylfangchinoline

[4], $\text{C}_{38}\text{H}_{43}\text{O}_6\text{N}_2\text{Cl}\cdot\text{H}_2\text{O}$, showed a mass spectral molecular ion at m/z 623, accompanied by the base peak m/z 609 $[\text{M} - 15 + 1]^+$. The other fragment ion peaks were nearly identical with those of fangchinoline [2]. The mass spectrum, in fact, suggested that 4 was similar to 2 except for a mass spectral mol wt which was 15 mu more than for 2.

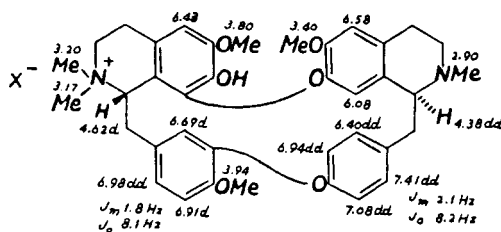
The ^1H nmr spectrum of 4 was very close to those of fangchinoline [2] and 2-*N*-methyltetrandrine [3], with the important difference that there are two quaternary *N*-methyl singlets (δ 3.17 and δ 3.20) in 4, indicating that 4 is a monoquaternary bisbenzylisoquinoline. The absorption for H-1' always appears as a doublet of doublets, whereas that for H-1 assumes the shape of a singlet or a doublet in the 8-7' , 11-12' pattern dimer (4). Therefore, for 4, the H-1 ab-



- 1 R=Me
 2 R=H (^1H nmr)



3



4

sorption that was stronger downfield at δ 4.62 in the shape of a doublet than H-1' at δ 4.38 as a doublet of doublets indicated that the quaternary *N*-methyl groups were adjacent to H-1; i.e., they were located on the left-hand side in the molecule. An nOe analysis further confirmed the site of the quaternary *N*-methyl groups. In particular, reciprocating nOe's were observed between H-1' (dd, δ 4.38) and H-8' (s, δ 6.08). Additionally, the H-1' signal (δ 4.38) was enhanced through irradiation of the 2'-*N*-methyl (s, δ 2.90), and H-10 (d, δ 6.69) was affected by irradiation of H-1 (d, δ 4.62). All assignments of the substituents were confirmed by spin decoupling experiments and nOe analyses.

The cd spectrum of **4** was similar to that of **2**, and the *N,N,O*-methiodide of **4** was characterized by identical ir and cd spectra corresponding to those of the authentic sample, which pointed to the 1*S*, 1'*S* chirality, as in (+)-fangchinoline [**2**].

EXPERIMENTAL

ISOLATION.—The dried roots (10 kg) of *S. tetrandra* were purchased in the southeast of China under the Chinese name "fen-fang-ji"; this material was examined and identified by Professor Cuisheng Fan, Jiangxi College of Traditional Chinese Medicine, where a voucher specimen is deposited. Its powder was extracted with EtOH at room temperature. The solvent was evaporated under reduced pressure, and the residue was treated with 2.5% HCl. The mixture was filtered, and the filtrate was basified with NH₄OH and extracted with CHCl₃ to give an alkaloidal fraction (148 g). The fraction was repeatedly chromatographed on columns of Si gel. Elution of the columns with CH₂Cl₂ gradually enriched with MeOH provided tetrandrine [**1**] (40 g); fangchinoline [**2**] (6 g); 2-*N*-methyltetrandrine [**3**] (30 mg); and 2-*N*-methylfangchinoline [**4**] (150 mg). Compounds **3** and **4** were purified by preparative tlc on Si gel plates by using the system CHCl₃-MeOH-NH₄OH (10:1:trace). All compounds are colorless needle crystals. ¹H-nmr spectra were obtained at 400 MHz in CDCl₃. The cims spectrum was determined on a Nicolet FTMS-2000 spectrometer.

(+)-2-*N*-METHYLTETRANDRINE [**3**].—Col-

orless needles (Me₂CO): mp 192–196° (chloride); [α]_D +245° (c = 0.074, CHCl₃); λ max (EtOH) 280 nm (log ϵ 3.84), λ min 257 (log ϵ 3.60); fabms *m/z* [M]⁺ 637; eims *m/z* 622 (60), 621 (41), 620 (6), 607 (10), 591 (4), 485 (2), 431 (9), 430 (12), 396 (24), 395 (87), 381 (44), 335 (7), 206 (3), 205 (2), 198.5 (21), 198 (86), 192 (41), 191 (7), 190 (11), 175 (41), 174 (66), 58 (40); $\Delta\epsilon$ (nm) +89 (219), +4 (272), +3 sh (289), positive tail.

(+)-2-*N*-METHYLFANGCHINOLINE [**4**].—Colorless needles (Me₂CO/MeOH): mp 205–208° (chloride); [α]_D +256° (c = 0.9, MeOH). *Anal.* calcd for C₃₈H₄₃O₆N₂Cl·H₂O: C 67.39, H 6.70, N 4.14; found C 67.26, H 6.75, N 3.91; λ max (MeOH) 281 nm (log ϵ 3.83), λ min 257 (log ϵ 3.47); cims *m/z* [M]⁺ 623 (10), 609 (100), 607 (35), 593 (17), 471 (6), 417 (9), 416 (20), 382 (17), 381 (61), 206 (8), 205 (18), 192 (71), 191 (16), 190 (48), 174 (38), 58 (72); $\Delta\epsilon$ (nm) +101 (218), +6 (270), +4 sh (288), positive tail.

N,N,O-METHYLATION OF **4**.—Compound **4** (10 mg) was refluxed with MeI (0.5 ml) in 10% methanolic KOH solution at pH 11 for 0.5 h. The solvent was evaporated, and the residue crystallized with EtOH and yielded the all-methiodide (+)-2,2'-*N,N*-dimethyltetrandrine (7 mg), which was identified by comparison with an authentic sample (ir, cd, and tlc).

(+)-2-*N*-METHYLFANGCHINOLINE [**4**].—NOed's OMe-6 \rightleftharpoons H-5, \rightleftharpoons OMe-6' \rightleftharpoons H-5', H-8' \rightleftharpoons H-1', H-1' \rightleftharpoons 2'-NMe, H-1 \rightleftharpoons 2-NMe, H-1 \rightleftharpoons H-10, OMe-12 \rightleftharpoons H-13.

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