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FOUR NEW BISBENZYLISOQUIONOLINE ALKALOIDS FROM THE ROOT OF STEPHANIA TETRANDRA (FEN-FANG-JI)

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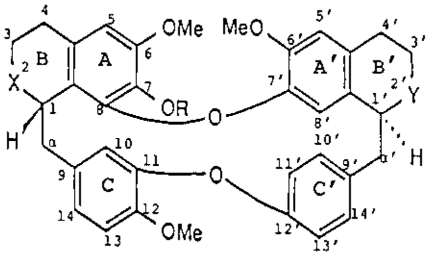
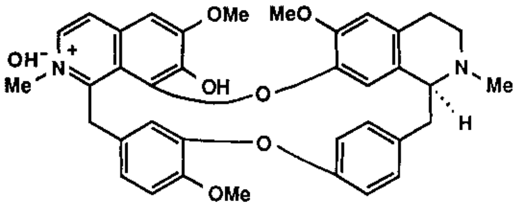
Abstract——Four new bisbenzylisoquinoline (BBI) alkaloids named fenfangjines A, B, C and D were isolated from the root of Stephania tetrandra S. Moore, the Chinese traditional medicine "Fen-Fang-Ji", along with thirteen known alkaloids (1-13). The chemical structures of fenfangjines A, B, C and D were respectively determined to be (14),(15),(16) and (17) by spectral analyses and chemical methods.

The Chinese traditional medicine "Fen-Fang-Ji", the root of Stephania tetrandra S. Moore (Menispermaceae), demonstrated to have antiinflammatory, antiallergic and hypotensive effects in experimental animals.[1] The main alkaloid tetrandrine(1) was shown to be effective to hypertension in a clinical test.

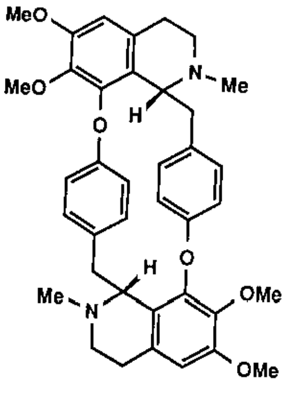
The methanolic extract of the root and its following alkaloidal fraction showed the inhibitory activities[2] against angiotensin converting enzyme I (ACE). Repeated chromatographic separation of alkaloidal fraction gave thirteen known alkaloids, tetrandrine(1),[3,4] fangchinoline(2),[4,5] tetrandrine 2′-N-α-oxide(3),[6] tetrandrine 2′-N-β-oxide(4),[6] 2-N-methyltetrandrinium chloride(5),[7] 2′-N-methyltetrandrinium chloride(6),[7] 2,2′-N,N-dimethyltetrandrinium dichloride(7),[8] cycleanine(8),[4,9] cyclanoline chloride(9),[9,10] stephenanthrine(10),[11] magnoflorine chloride(11),[9,12] alkaloid AA-1(12),[13] oblongine chloride(13),[14] and four new bisbenzylisoquinoline (BBI) derivatives named fenfangjines A(14), B(15), C(16) and D(17). Their yields are 0.0014%, 0.006%, 0.008% and 0.005%, respectively. The active concentrations of BBI alkaloids as inhibitors of ACE are all in the 10^{-3}-10^{-4}M range. This communication discribes the structural elucidations of fenfangjines A(14), B(15), C(16) and D(17).



	R	X	Y
(1)	Me	N-Me	N-Me
(2)	H	N-Me	N-Me
(3)	Me	N-Me	$\mathrm{N}^{\mathrm{Me}}_{\dashrightarrow \mathrm{O}}$
(4)	Me	N-Me	$\mathrm{N}^{\mathrm{Me}}_{\rightarrow \mathrm{O}}$
(5)	Me	$\overset{+}{\mathrm{N}}{}^{\mathrm{Me}}_{\mathrm{Me}}$	N-Me
(6)	Me	N-Me	$\overset{+}{\mathrm{N}}{}^{\mathrm{Me}}_{\mathrm{Me}}$
(7)	Me	$\overset{+}{\mathrm{N}}{}^{\mathrm{Me}}_{\mathrm{Me}}$	$\overset{+}{\mathrm{N}}{}^{\mathrm{Me}}_{\mathrm{Me}}$
(14)	Me	$\mathrm{N}^{\mathrm{Me}}_{\rightarrow \mathrm{O}}$	N-Me
(15)	H	N-Me	$\mathrm{N}^{\mathrm{Me}}_{\dashrightarrow \mathrm{O}}$
(16)	H	N-Me	$\mathrm{N}^{\mathrm{Me}}_{\rightarrow \mathrm{O}}$



(17)



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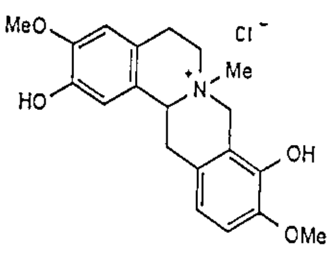

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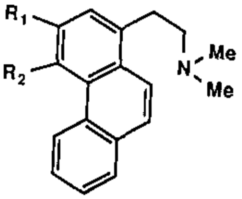
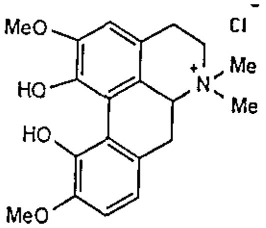


(10) $R_1 = R_2 = -OCH_2O-$

(11) $R_1 = OH$, $R_2 = OMe$



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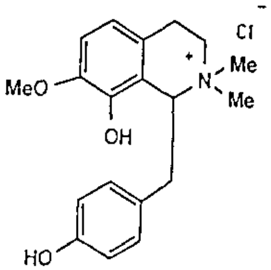

(13)

Fenfangjine A(14), colorless needles (from acetone), mp 174-176°C, $C_{38}H_{42}O_7N_2$ (by high resolution mass spectrometry, Found 638.3033; Calcd 638.2992), $[\alpha]_D^{24}$ +328.2° (c=1.043,$CHCl_3$). The EI-ms spectrum of (14) showed following fragments : m/z 638 $[M]^+$, 622$[M-16]^+$, 395, 381, 198. The fragmentation pattern under m/z 622 was very similar to that of tetrandrine(1), $C_{38}H_{42}O_6N_2$.[3,4] The ^{1}H-nmr spectrum ($CDCl_3$) of fenfangjine A(14),δ2.62(3H,s,2′-NCH_3), 3.08(3H,s,2-NCH_3), 3.14(3H,s,7-OCH_3), 3.43 (3H,s,6′-OCH_3), 3.76(3H,s,6-OCH_3), 3.95(3H,s,12-OCH_3), 4.91(1H,d,J=9.8Hz,1-H), 5.92 (1H,s,8′-H), 6.39(1H,s,5-H), 6.43(1H,dd,J=8.3,2.0Hz,10′-H), 6.50(1H,s,5′-H), 6.68 (1H,dd,J=8.1,2.0Hz,14-H), 6.78(1H,d,J=2.0Hz,10-H), 6.84(1H,d,J=8.1Hz,13-H), 6.92 (1H,dd,J=8.3,2.4Hz,11′-H), 6.99(1H,dd,J=8.3,2.4Hz,13′-H), 7.34(1H,dd,J=8.3,2.0Hz, 14′-H), was very similar to that of (1) except for N-methyl signal of 2-position. The N-methyl signal of 2-position of (1) showed at δ2.33,[3,4] while that of fenfangjine A shifted to lower field by 0.75 ppm to show at δ3.08. This indicated fenfangjine A was a 2-N-oxide of tetrandrine(1). It was reported that N-methyl signals at 2-position of tetrandrine 2-N-β,2′-N-β-dioxide and tetrandrine 2-N-β,2′-N-α-dioxide exhibited at δ3.06.[6] From the above data, fenfangjine A was elucidated as tetrandrine 2-N-β-oxide.

Fenfangjine B(15), $C_{37}H_{40}O_7N_2$ (by high resolution ms, Found 624.2843; Calcd 624.2835), colorless prisms (from EtOH), mp 211-213°C, $[\alpha]_D^{25}$ +242.5°(c=0.640,$CHCl_3$-

MeOH). The EI-ms spectrum of (15) showed following fragments: m/z 624[M]$^+$, 608 [M-16]$^+$, 381, 191. The ir spectrum (KBr) of (15) shows absorption of hydroxyl group at 3420 cm^{-1}. The ^{1}H-nmr spectrum ($CDCl_3$-CD_3OD) of (15), δ2.32(3H,s,2-NCH_3), 3.34 (3H,s,2′-NCH_3), 3.34(3H,s,6′-OCH_3), 3.71(3H,s,6-OCH_3), 3.92(3H,s,12-OCH_3), 4.44 (1H,dd,J=11,5Hz,1′-H), 6.08(1H,s,8′-H), 6.24(1H,dd,J=8.3,2.0Hz,10′-H), 6.26(1H,s, 5-H), 6.56(1H,s,5′-H), 6.56(1H,d,10-H), 6.81(1H,dd,J=8.3,2.4Hz,11′-H), 6.87(2H,m, 13,14-H), 7.15(1H,dd,J=8.3,2.4Hz,13′-H), 7.30(1H,dd,J=8.3,2.0Hz,14′-H), was similar to that of fangchinoline(2)^4 except for N-methyl signal of 2′-position. The N-methyl signal of 2′-position of fangchinoline(2) showed at δ2.62, while that of fenfangkine B shifted to lower field by 0.75 ppm to show at δ3.34. This indicated fenfangjine B was a 2′-N-oxide of fangchinoline(2). Methylation of fenfangjine B afforded tetrandrine 2′-N-α-oxide(3).^{6} From the above data, fenfangjine B was elucidated as fangchinoline 2′-N-α-oxide.

Fenfangjine C(16) was obtained as colorless needles (from EtOH), mp 165-166°C, $C_{37}H_{40}O_7N_2$(by high resolution ms, Found 624.2834; Calcd 624.2835), $[\alpha]_D^{25}$ +239.4° (c=0.630,MeOH); EI-ms m/z: 624[M]$^+$, 608[M-16]$^+$, 381, 191; ^{1}H-nmr ($CDCl_3$): δ2.39 (3H,s,2-NCH_3), 2.94(3H,s,2′-NCH_3), 3.37(3H,s,6′-OCH_3), 3.78(3H,s,6-OCH_3), 3.88(3H, s,12-OCH_3), 4.72(1H,dd,J=11,5Hz,1′-H), 6.18(1H,s,8′-H), 6.22(1H,dd,J=8.3,2.0Hz, 10′-H), 6.32(1H,s,5-H), 6.56(1H,s,5′-H), 6.77(1H,d,J=2.0Hz,10-H), 6.77(1H,dd,J=8.3, 2.4Hz,11′-H), 6.85(1H,d,J=8.3Hz,13-H), 6.92(1H,dd,J=8.3,2.0Hz,14-H), 6.96(1H,dd, J=8.3,2.4Hz,13′-H), 7.43(1H,dd,J=8.3,2.0Hz,14′-H). The EI-ms, ir and ^{1}H-nmr spectral data of fenfangjine C(16) indicated fenfangjine C was a 2′-N-oxide of fangchinoline (2), same as fenfangjine B(15). The N-methyl signal of 2′-position of fenfangjine C shifted to lower field by 0.32 ppm to show at δ2.94. Methylation of fenfangjine C afforded tetrandrine 2′-N-β-oxide(4).^{6} From the above data, fenfangjine C was elucidated as fangchinoline 2′-N-β-oxide.

Fenfangjine D(17), $(C_{37}H_{37}O_6N_2)^+(OH)^-\cdot 1/2H_2O$ (Anal. calcd: C,70.35, H, 6.22,N, 4.43. Found: C, 70.16, H, 5.99, N,4.67), was obtained as an orange amorphous powder. The HCl salt of (17), mp$>$300°C, $[\alpha]_D^{25}$ +67.8°(c=0.116,MeOH), was obtained as an orange granules from MeOH and acetone. The $C_{37}H_{37}O_6N_2$ moiety of fenfangjine D was confirmed by the observation of the peak at m/z 605 in FD-ms. The ^{1}H-nmr spectrum ($CDCl_3$) of (17), δ2.52(3H,s,2′-NCH_3), 3.24(3H,s,6′-OCH_3), 3.84(3H,s,6-OCH_3), 3.88(3H,s,12-OCH_3), 4.31(3H,s,2-NCH_3), 4.32, 5.53(each 1H,d,J=16Hz,α-H), 6.05(1H,s,8′-H), 6.51(1H,d-like, 10′-H), 6.53(1H,s,5-H), 6.61(1H,d,J=2.0Hz,10-H), 6.70(1H,d-like,14-H), 6.85(1H, d-like,11-H), 6.86(1H,d,J=8.3Hz,13-H), 7.03(1H,d-like,13′-H), 7.05(1H,s,5′-H), 7.49

(1H,d-like,14′-H), 7.75(1H,d,J=6.6Hz,4-H), 7.86(1H,d,J=6.6Hz,3-H), showed two sets of characteristic signals at δ4.32, 5.53 and δ7.75, 7.86. The former are assignable to methylene protons of α-position and the latter are ascribable to the two olefinic protons of 3,4-position. Three aliphatic carbon signals at δ61.5(C-1,d), 44.4(C-3, t) and 22.0(C-4,t) on B ring observed in the ^{13}C-nmr spectrum ($CDCl_3$) of fangchinoline(2) disappeared, while three aromatic carbon signals exhibited at δ150.1(C-1,s), 127.0(C-3,d) and 121.0(C-4,d) in fenfangjine D(17) (in $CDCl_3$). From the above spectral data, fenfangjine D was readily formulated as 1,3,4-tridehydrofangchinolinium hydroxide. Finally we succeeded in conversion of fangchinoline(2) into 1,3,4-tridehydrofangchinolinium hydroxide(17) on oxidation by manganese dioxide in ethanol in 65% yield.

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