Communications to the Editor

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YADANZIOSIDE P, A NEW ANTILEUKEMIC QUASSINOID GLYCOSIDE FROM BRUCEA JAVANICA (L.) MERR WITH THE 3-O-(β-D-GLUCOPYRANOSYL)BRUCEANTIN STRUCTURE

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A new antileukemic quassinoid glycoside, yadanzioside P, was isolated from "Ya-dan-zi", the seeds of Brucea javanica (L.) Merr. The structure was determined to be 3-O-(β-D-glucopyranosyl)-bruceantin by ^{1}H- and ^{13}C-NMR spectral measurement and enzymatic hydrolysis. The NMR spectral inspection indicates that a quassinoid glycoside formulated as 3-O-(β-D-glucopyranosyl)bruceantin is not bruceantinoside B, but yadanzioside P.

KEYWORDS —— quassinoid glycoside; yadanzioside P; 3-O-(β-D-glucopyranosyl)bruceantin; Brucea javanica; Simaroubaceae; bruceantinoside B; antileukemic activity; NMR

Seeds of Brucea javanica (L.) MERR, known as "Ya-dan-zi" in Chinese folklore, have been used as a Chinese medicine for cancer. The main components with an antileukemic activity have been investigated by Polonsky,[1] Geissman,[2] and Lee.[3] In our studies on the bitter principles in simaroubaceous plants, we examined constituents in the polar fraction of the methanol extract of "Ya-dan-zi" and reported about twenty new bitter principles.[4] We also investigated some minor components and isolated a new bitter quassinoid glycoside, named yadanzioside P (1). This paper describes the spectral evidence that the quassinoid glycoside formulated as 3-O-(β-D-glucopyranosyl)bruceantin is yadanzioside P (1).

The methanol extract of the defatted seeds of B. javanica was partitioned between dichloromethane and water. The organic layer was subjected to separation by chromatography on silica gel and silicic acid, a reversed phase chromatography on a Lobar column Lichroprep RP-8, and gel chromatography on Toyopearl HW-40S. This afforded yadanzioside P (1) in ca. 0.0002% yield, mp 193-198 °C, $[\alpha]_D^{23}$ +7.0° (c=1.7, EtOH), and $[\alpha]_D^{22}$ -45° (c=1.7, C_5H_5N).[5] The compound (1) was found to be a hexoside with a molecular formula, $C_{34}H_{46}O_{16}$, from the ^{13}C-NMR spectrum (Table I) and a fragment ion peak at m/z 548.2272 ($C_{28}H_{36}O_{11}$) ascribable to the aglycone in the EI-MS. The ^{1}H-NMR spectrum of 1 showed a singlet signal at δ 2.04 due to $C_{(4)}$-CH_3 and also revealed the presence of a β-glucopyranosyl moiety (δ 5.48, d, J=7.1 Hz due to an anomeric proton, δ 4.35, dd, J=11.7 and 5.1 Hz due to 6''-H, and δ 4.48, dd, J=11.7 and 2.7 Hz due to 6''-H'). Hydrolysis of 1 with β-glucosidase afforded bruceantin (2)[6] as the sole aglycone. Comparing the ^{13}C-NMR spectrum of yadanzioside P with those of bruceoside B (3),[3,7] yadanziosides B (4),[4b] I (5),[4a], and L (6)[4a] led to the formulation of 3-O-(β-D-glucopyranosyl)bruceantin (1) for yadanzioside P.

However, a quassinoid glycoside, bruceantinoside B (7), mp ca. 200 °C (dec.), $[\alpha]_D^{25}$ -3.6° (c 0.5, C_5H_5N), was isolated from Brucea antidysenterica, and the same structure as 1 was assigned on the basis of the ^{13}C-NMR spectrum (Table I) and

acid hydrolysis by Okano et al.[8] The physical and spectral comparisons demonstrated that yadanzioside P (1) and bruceantinoside B (7) are obviously different compounds. In the ^{1}H-NMR spectra of quassinoid glycosides with a 3-O-(β-glucosyl)-2-keto-3-ene structure in the A-ring, such as bruceoside B (3) and yadanziosides B, I, and L (4, 5, and 6), signals due to $C_{(4)}$-CH_3 and $C_{(10)}$-CH_3 appear around δ 2.04 and δ 1.7, respectively, in C_5D_5N (Table II). The ^{13}C-NMR spectra of these glycosides exhibit signals due to C-1, C-2, C-3, and C-4 around

Table I. ^{13}C-NMR Spectra of Yadanziosides P (1), B (4), I (5), and L (6), Bruceoside B (3), Bruceantinoside B (7), Bruceantin (2), and Brucein A (8) Measured at 22.5 MHz in C_5D_5N

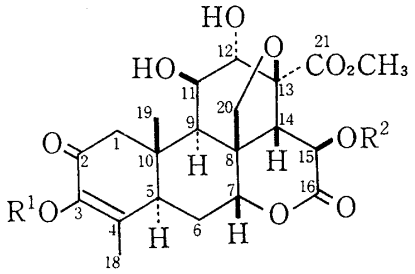
No. of carbon	1	4	5	6	3	7[8]	2	8[4b]
1	51.5t	51.1t	51.0t	51.1t	51.1t	44.1	50.1t	50.1t
2	193.6s	193.6s	193.6s	193.6s	193.6s	199.7	193.0s	192.2s
3	147.9s[a]	147.9s[c]	148.0s[f]	147.9s[h]	148.1s[j]	146.4	146.0s	146.0s
4	146.7s[a]	146.2s[c]	146.8s[f]	146.6s[h]	146.5s[j]	125.8	128.2s	128.1s
5	43.4d	43.3d	43.4d	43.4d	43.4d	40.8	42.5d	42.4d
6	29.4t	29.3t	29.3t	29.4t	29.4t	29.6	29.7t	29.6t
7	83.4d	83.5d	83.5d	83.4d	83.3d	83.0	83.6d	83.7d
8	46.0s	46.1s	46.0s	46.0s	45.9s	46.6	46.2s	46.2s
9	42.1d	42.2d	42.1d	42.1d	42.0d	42.1	42.5d	42.4d
10	40.9s	40.8s	40.8s	40.8s	40.8s	48.8	41.4s	41.4s
11	73.1d	73.1d	72.9d	73.0d	72.9d	71.3	73.1d	73.1d
12	75.9d	76.0d	76.0d	76.0d	75.9d	76.2	75.8d	75.8d
13	82.7s	82.7s	82.7s	82.7s	82.6s	82.6	82.7s	82.8s
14	50.5d	50.6d	50.3d	50.5d	50.4d	52.3	50.5d	50.7d
15	68.3d	68.4d	68.7d	68.3d	68.1d	68.7	68.3d	68.4d
16	168.2s	168.1s	168.0s	168.2s	168.2s	168.4	168.2s	168.1s
18	15.3q	15.3q	15.3q	15.3q	15.3q	14.5	13.4q	13.4q
19	15.9q	15.8q	15.8q	15.9q	15.8q	18.9	15.8q	15.7q
20	73.6t	73.6t	73.5t	73.6t	73.6t	73.6	73.7t	73.8t
21	171.3s	171.6s[d]	171.3s	171.2s	171.2s	171.1	171.3s	171.6s
OMe	52.4q	52.4q	52.4q	52.4q	52.4q	50.7	52.3q	52.3q
1'	165.8s	171.2s[d]	169.8s	166.4s	165.3s	165.9	165.9s	171.3s
2'	113.5d	43.3t	20.6q	112.8d	115.8d	113.4	113.5d	43.3t
3'	167.2s	25.9d		168.2s	158.5s	167.3	167.1s	25.9d
4'	38.1d	22.4q		73.2s	27.0q	38.1	38.2d	22.4q
5'	16.7q	22.5q		15.5q	20.2q	16.7	16.7q	22.5q
6'	20.7q			28.9q		20.7	20.7q	
7'	20.7q			28.9q		20.7	20.7q	
1"	104.9d	104.9d	104.8d	104.9d	104.7d	100.7		
2"	76.1d	75.7d	75.9d	75.9d	75.9d	74.5		
3"	78.6d[b]	78.6d[e]	78.5d[g]	78.6d[i]	78.5d[k]	78.7		
4"	71.6d	71.6d	71.5d	71.6d	71.5d	71.3		
5"	78.4d[b]	78.4d[e]	78.3d[g]	78.4d[i]	78.3d[k]	78.3		
6"	62.9t	62.8t	62.8t	62.9t	62.7t	62.4		

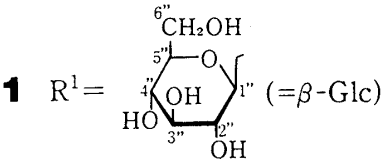
a) The assignment of these signals may be reversed. b)-k) are the same as a).

Table II. ^{1}H-NMR[a] Spectra of Yadanziosides P (1), B (4), I (5), and L (6), Bruceoside B (3), and Bruceantinoside B (7)

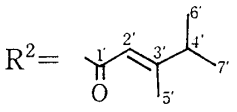
	1[b]	4[c]	5[b]	6[b]	3[b]	3[d,3]	7[e,8]
$C_{(4)}$-Me	2.04 s	2.04 d (1.2)	2.04 s	2.03 s	2.04 s	2.01 s	1.86 s
$C_{(10)}$-Me	1.67 s	1.71 s	1.69 s	1.69 s	1.71 s	1.42 s	1.40 s
15-H	6.85 d (13)	6.9 br	6.80 d (13)	6.85 d (13)	6.83 d (13)	6.09 d (13)	
CO_2Me	3.79 s	3.84 s	3.81 s	3.71 s	3.78 s	3.74 s	3.78 s

a) Coupling constants are expressed in Hz in parentheses. b) Measured at 90 MHz in C_5D_5N. c) Measured at 400 MHz in C_5D_5N. d) Measured at 100 MHz in CD_3OD. e) Measured at 100 MHz in C_5D_5N.





1 R^1= (=β-Glc)



R^2=

Numbering of carbon atoms on the $C_{(15)}$-O side chain is conventional.

2 R^1= H R^2=

3 R^1= β-Glc R^2=

4 R^1= β-Glc R^2=

5 R^1= β-Glc R^2=

6 R^1= β-Glc R^2=

8 R^1= H R^2=

δ 51, 193, 148, and 146, respectively (Table I). The shift values of these protons and carbon atoms of yadanzioside P (1) were in good agreement with those mentioned above. But those of bruceantinoside B (7) are considerably different from these values (Tables I and II). These discrepancies strongly indicate that bruceantinoside B (7) could not be the 3-O-glucoside of bruceantin (2). So yadanzioside P (1) is proposed as 3-O-(β-D-glucopyranosyl)bruceantin.

It is noteworthy that yadanzioside P (1) showed a significant antileukemic activity[9] against murine P388 lymphocytic leukemia; the ILS values were 15.5 and 28.9% at 5 and 10 mg/kg/day dose levels, respectively. Although about twenty

quassinoid glycosides have been isolated from "Ya-dan-zi" so far, none has shown significant activity; the ILS values were less than 25%.[10] The fact that yadanzioside P (1) showed a significant activity suggests that the (2E)-3,4-dimethyl-2-pentenoyl moiety at $C_{(15)}$-O plays an important role in the antileukemic activity of both bruceantin (2) and yadanzioside P (1).

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5) IR (KBr) 3460, 1740, 1670, 1640, 1060, 1040, and 1030 cm^{-1}; UV (EtOH) 222 nm (ε 16500) and 252 nm (ε 8800); ^{1}H-NMR (270 MHz, C_5D_5N) δ: 0.85 (6H, d, J=6.8 Hz, 4'-CH_3), 1.73 (3H, s, 10-CH_3), 2.05 (3H, s, 4-CH_3), 2.16 (3H, br s, 3'-CH_3), 3.09 (1H, br d, J=13 Hz, 14-H), 3.79 (3H, s, CO_2CH_3), 4.35 (1H, dd, J=11.7 Hz and 5.1 Hz, 6"-H), 4.48 (1H, dd, J=11.7 Hz and 2.7 Hz, 6"-H'), 4.78 (1H, br d, J=3.2 Hz, 11-H), 5.1 (3H, br, 7-H, 12-H, and 20-H), 5.48 (1H, d, J=7.1 Hz, 1"-H), 5.87 (1H, s, 2'-H), and 6.61 (1H, br, 15-H); ^{13}C-NMR (Table I); MS (EI) m/z (%) 548 ([M - $C_6H_{10}O_5$]$^+$; 0.6), 530 (0.3), 512 (0.5), 486 (0.6), 468 (0.1), 454 (0.2), 438 (1), 420 (1.3), 402 (1.7), 392 (1.1), 386 (1.1), 356 (0.8), 111(100), 73 (67), and 60 (94); HR-MS (EI) m/z 548.2272. Calcd for $C_{28}H_{36}O_{11}$: m/z 548.2257.
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9) In vivo activity was assayed according to the standard National Cancer Institute procedure.

$$\text{ILS}(\%) = \left(\frac{\text{Mean survival time (day) of the test group}}{\text{Mean survival time (day) of the control group}} - 1 \right) \times 100$$

The ILS value of bruceantin (2) was 64.9% at 2 mg/kg/day under the same conditions as those for 1.
10) The ILS values of yadanziosides A, B, C, D, E, F, G, I, J, and K and bruceoside A were 7.1, 4.1, 2.0, 9.2, 7.1, 7.1, 4.1, 9.2, 4.1, 9.2, and 2.0% at 10 mg/kg/day dose levels, respectively. Yadanzioside L showed cytotoxicity at the same dose level.

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