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TWO NEW QUASSINOID GLYCOSIDES, YADANZIOSIDES N AND O ISOLATED FROM SEEDS OF Brucea javanica (L.) MERR

Toshiro Sakaki, Shin Yoshimura, Takahiko Tsuyuki,* Takeyoshi Takahashi,*
Tadashi Honda,† and Toshihiro Nakanishi†
Department of Chemistry, Faculty of Science, The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113, Japan
†Suntory Institute for Biomedical Research, Wakayamadai, Shimamoto-cho,
Mishima-gun, Osaka 618, Japan

Summary: Two new quassinoid glycosides, yadanziosides N and O (1 and 2), were isolated from "Ya-dan-zi", seeds of Brucea javanica (L.) MERR and the aglycone (4) of 2 was found to exhibit an antitumor activity against the murine P388 lymphocytic leukemia.

Bitter principles of Simaroubaceous plants have been extensively investigated from the interest in the structure elucidation and useful biological activities.[1] Previously we reported several quassinoids and quassinoid glycosides from "Ya-dan-zi", seeds of Brucea javanica (L.) MERR.[2] This paper describes the structure determination of two new quassinoid glycosides, yadanziosides N and O (1 and 2) isolated from "Ya-dan-zi" and an antitumor activity of the aglycone (4).

The methanolic extract of defatted seeds of B. javanica was partitioned between dichloromethane and water. The organic layer was subjected to separation by silica-gel chromatography, gel chromatography using Toyopearl HW-40S and a Lobar column Lichroprep RP-8 to afford yadanziosides N (1; ca. 0.0001% yield) and O (2; ca. 0.0002% yield) together with other known quassinoids.[2]

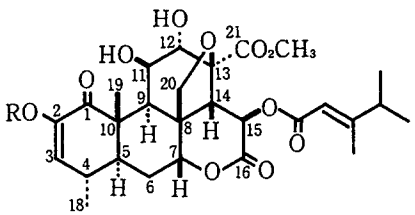
Yadanzioside N (1),[3] mp 175-180 °C, $[\alpha]_D^{24}$ + 7.6° (c 1.8, EtOH) was shown to be a hexoside from a doublet signal at δ 5.47 (J=7.0 Hz) due to an anomeric proton in the ^{1}H NMR spectrum, a peak at m/z 733 ($[M+Na]^+$) in SI-MS, and a peak at m/z 548 ($[M-C_6H_{10}O_5]^+$) in EI-MS.

On heating with 1.5 M sulfuric acid in methanol, 1 afforded an aglycone (3) and D-glucose (identified by GLC after trimethylsilylation). The aglycone (3),[4] mp 180-183 °C, $[\alpha]_D^{24}$ +30° (c 0.7, EtOH), gave the molecular peak at m/z 548.2282 (calcd for $C_{28}H_{36}O_{11}$: m/z 548.2257) and a base peak at m/z 111 due to the acyl group ($C_6H_{11}CO$) of the side chain in EI-MS. The UV absorption maxima appeared at 220 nm (ε 16000) and 267 (ε 6000) in ethanol solution, the latter of which was shifted to 314 nm (ε 4000) on addition of alkali, indicating the the presence of a diosphenol moiety.

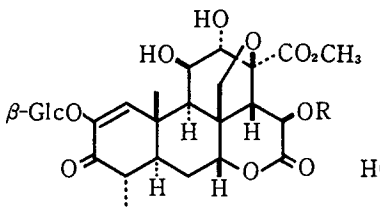
In the ^{1}H NMR spectrum of 1, a doublet signal due to $C_{(11)}$-H appeared at δ 6.20, which is lower than that of bruceantin (5)[5]. Irradiation of the signal

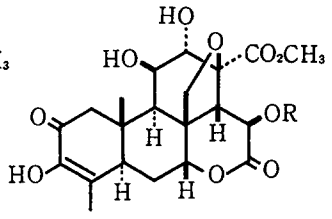
due to $C_{(4)}$-H at δ 2.24 resulted in sharpening of the signals at δ 0.87 due to $C_{(4)}$-Me and at δ 6.10 due to $C_{(3)}$-H. In the ^1H NMR spectrum of 3, a doublet signal due to $C_{(4)}$-Me was observed at δ 1.11 and an olefin proton at C-3 appeared at δ 5.74 with a coupling constant, J=2.4 Hz. Therefore, A-ring of the aglycone (3) was suggested to be the same as that of norquassin. From these observations and ^1H and ^{13}C NMR-spectral comparison with bruceantin (5), the aglycone (3) was shown to be an isomer with 1-keto-2-ene structure of bruceantin (5).

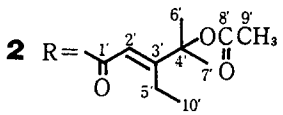
Yadanzioside N (1) exhibited UV absorption maxima at 222 nm (ε 13000) and 255 nm (ε 5000) and no shift was observed on addition of alkali, indicating that the glycoside linkage occurred through the $C_{(2)}$-oxygen atom of 3. Therefore, the structure of yadanzioside N (1) was determined to be methyl 2-(β-D-gluco-pyranosyloxy)-13β,20-epoxy-15β-[(2E)-3,4-dimethyl-2-pentenoyloxy]-11β,12α-dihydroxy-1,16-dioxo-2-picrasen-21-oate.



1 R = β-Glc
3 R = H







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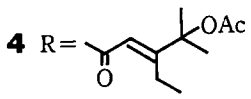

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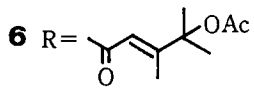
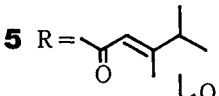
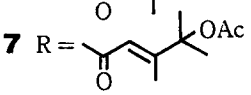


6 R =



5 R =



7 R =

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

Yadanzioside O (2),[6] mp 183-188 °C, $[\alpha]_D^{21}$ +20° (c 2.0, EtOH), was inferred to be a hexoside with the same skeleton as yadanzioside G (6) except for $C_{(15)}$-O side chain from the comparison of the ^1H and ^{13}C NMR spectra; an additional triplet signal was observed at δ 22.0 in the ^{13}C NMR spectrum of 2. Since the ^1H NMR spectrum of 2 revealed the presence of an acetoxyl, two methyl, an ethyl groups assignable to the side chain together with an olefin proton, the side chain could be formulated as 15-O-(4-acetoxy-3-ethyl-4-methyl-2-pentenoyl). The geometry of the double bond was determined to be (2E) by difference NOE measurement of 2 at 400 MHz; on saturation of the signal due to C-2' at δ 6.10, an increase in area of the signal at δ 1.49 and 1.51 due to the C-4' geminal methyl group was observed.

The position of β-D-glucopyranosyl group, whose anomeric proton was observed at δ 5.28 as a doublet signal (J=8.1 Hz), was determined to be the same as those of yadanzioside G (6) and yadanziosides A, C, F, and J[2] by ^1H and ^{13}C NMR spectral comparison.

Enzymatic hydrolysis of yadanzioside O (2) with β-glucosidase afforded an aglycone (4),[7] mp 138-143 °C, $[\alpha]_D^{27}$ +23° (c 0.6, EtOH), which gave no molecular ion but a fragment ion peak at m/z 560 due to a loss of acetic acid.

Table 1 ^{13}C NMR spectra

No. of carbon	1[a]	2[a]	3[b]	4[b]	5[c]	6[a]	7[c]
1	199.6s	129.6d	201.0s	48.6	48.7t	129.7d	48.8
2	146.4s	148.8s	143.7s	192.1	192.2s	148.8s	192.0
3	125.5d	194.6s	121.3d	144.1	144.2s	194.7s	144.2
4	31.6d	43.9d	30.7d	127.8	127.9s	43.9d	127.6
5	36.9d	40.4d	36.5d	41.9	41.2d	40.4d	41.2
6	28.8t	30.0t	28.5t	29.1	29.2t	30.1t	29.2
7	83.0d	83.4d	82.4d	82.6	82.4d	83.5d	82.4
8	46.7s	46.6s	46.1s	45.4	45.5s	46.6s	45.5
9	44.2d	41.4d	43.9d	41.9	41.9d	41.4d	42.0
10	48.9s	39.6s	47.3s	41.1	41.2s	39.6s	41.2
11	75.1d	73.5d	72.9d	71.0	71.1d	73.4d	71.1
12	76.3d	76.0d	76.1d	75.7	75.9d	76.0d	76.4
13	83.0s	82.6s	81.2s	81.3	81.4s	82.6s	81.4
14	50.9d	50.3d	51.6d	51.5	51.7d	50.2d	51.6
15	68.8d	68.6d	66.7d	66.2	66.0d	68.7d	66.3
16	168.2s	168.0s	168.2s	166.9	167.0s	168.0s	166.8
18	14.5q	12.5q	14.8q	13.3	13.3q	12.5q	13.3
19	18.9q	18.0q	19.0q	15.5	15.5q	18.0q	15.5
20	73.7t	73.6t	73.6t	74.1	74.1t	73.7t	74.1
21	171.1s	171.1s	171.6s	171.8	171.8s	171.7s	171.7
OMe	52.3q	52.6q	52.8q	53.4	52.9q	52.6q	53.3
1'	166.0s	165.2s	165.2s	164.2	165.0s	165.7s	164.8
2'	113.6d	113.8d	111.8d	112.0	111.8d	113.7d	112.0
3'	167.2s	169.5s	169.6s	169.6	169.6s	169.5s	169.5
4'	38.1d	82.7s	38.3d	82.4	38.4d	82.3s	82.3
5'	16.7q	22.0t	17.1q	22.1	17.0q	14.5q	14.6
6'	20.7q	26.2q	20.8q	26.5	20.8q	26.4q	26.3
7'	20.7q	26.5q	20.8q	26.5	20.8q	25.8q	26.2
8'		168.6s		170.9		163.3s	165.8
9'		21.7q		21.9		21.4q	21.6
10'		14.6q		14.2			
1''	100.9d	102.0d				102.0d	
2''	74.7d	74.6d				74.6d	
3''	78.9d	78.8d				78.8d	
4''	71.5d	71.3d				71.4d	
5''	78.6d	78.4d				78.4d	
6''	62.5t	62.4t				62.4t	

a) Measured at 22.5 MHz in C_5D_5N. b) Measured at 67.5 MHz in $CDCl_3$.
c) Measured at 22.5 MHz in $CDCl_3$.

The ^1H and ^{13}C NMR spectra showed that A ring posseses 3-hydroxy-3-en-2-one structure, which is identical with that of bruceantinol (7),[8] and therefore, the structure of the aglycone of 2 was shown to be formulated as 4.

From these observations the structure of yadanzioside O (2) was firmly established to be methyl 2-(β-D-glucopyranosyloxy)-13β,20-epoxy-15β-[(2E)-4-acetoxy-3-ethyl-4-methyl-2-pentenoyloxy]-11β,12α-dihydroxy-3,16-dioxo-1-

picrasen-21-oate.

The aglycone (4) of yadanzioside O (2) showed a significant antitumor activity[9] against the murine P388 lymphocytic leukemia and the ILS values were 37.1 and 47.2% at 2 and 4 mg/kg/day dose levels, respectively.

Yadanzioside N (1) constitutes a new type bruceoside with a quassin-type A-ring. Yadanzioside O (2) is a bruceoside with the largest carbon number in the 15-O side chain so far, and its aglycone (4) is expected to be a highly potential antitumor compound.

References

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3) IR (KBr) 3420, 1740, 1680, 1640, 1080, 1045, and 1020 cm^{-1}; EI-MS m/z 548, 530, 438, 420, 402, 372, 345, 315, and 111; ^1H NMR (400 MHz, C_5D_5N) δ 0.85 (6H, d (7.0); 4'-Me), 0.87 (3H, d (8.8); 4-Me), 1.87 (3H, s; 10-Me), 2.18 (3H, s; 3'-Me), 3.77 (3H, s; OMe), 4.57 (1H, d (11); 6''-H), 4.90 (1H, br s; 12-H), 5.12 (1H, d (7.7); 20-H), 5.13 (1H, br s; 7-H), 5.47 (1H, d (7.0); 1''-H), 5.89 (1H, s; 2'-H), 6.10 (1H, d (2.2); 3-H), and 6.20 (1H, d (4.4); 11-H).

4) IR (KBr) 3460, 1750, 1685, 1645, 1050, and 1010 cm^{-1}; EI-MS m/z 548, 530, 512, 420, 402, 372, 345, 315, and 111; ^1H NMR (270 MHz, $CDCl_3$) δ 1.06 (6H, d (6.8); 4'-Me), 1.11 (3H, d (7.0); 4-Me), 1.62 (3H, s; 10-Me), 2.14 (3H, d (1.1); 3'-Me), 3.78 (3H, s; OMe), 4.29 (1H, br s; 12-H), 4.66 (1H, br s; 7-H), 4.70 (1H, d (7.9); 20-H), 5.44 (1H, br; 11-H), 5.66 (1H, br s; 2'-H), 5.74 (1H, d (2.4); 3-H).

5) S. M. Kupchan, R. W. Britton, J. A. Lacadie, M. F. Ziegler, and C. W. Siegel, J. Org. Chem., 40, 648 (1975).

6) IR (KBr) 3430, 1740, 1680, 1640, 1065, 1050, and 1020 cm^{-1}; UV (EtOH) 224 nm (ε 15000) and 254 nm (ε 8000); SI-MS m/z 805 $(M+Na)^+$; ^1H NMR (270 MHz, C_5D_5N) δ 1.16 (3H, d (8.1); 4-Me), 1.24 (3H, t (8.1); 5'-Me), 1.49 (3H, s; 4'-Me), 1.51 (3H, s; 4'-Me), 1.63 (3H, s; 10-Me), 1.94 (3H, s; OAc), 2.67 (1H, m; 5'-H), 2.78 (1H, m; 5'-H), 3.86 (3H, s; OMe), 5.05 (1H, d (8.1); 20-H), 5.28 (1H, d (8.1); 1''-H), 6.10 (1H, s; 2'-H), and 7.27 (1H, s; 1-H).

7) IR (KBr) 3450, 1740, 1640, and 1060 cm^{-1}; UV (EtOH) 222 nm (ε 15000) and 278 nm (ε 7000); EI-MS m/z 560, 438, 420, 402, 392, 354, 278, 140, 123, 111, and 60; ^1H NMR (270 MHz, $CDCl_3$) δ 1.13 (3H, t (7.3); 5'-Me), 1.40 (3H, s; 10-Me), 1.57 (6H, s; 4'-Me), 1.85 (3H, d (2.2); 4-Me), 2.03 (3H, s; OAc), 2.59 (2H, q (7.3); 5'-H), 3.81 (3H, s; OMe), 4.73 (1H, d (7.3); 20-H), and 5.78 (1H, s; 2'-H).

8) J. Polonsky, J. Varenne, T. Prange, and C. Pascard, Tetrahedron Lett., 21, 1853 (1980).

9) In vivo activity was assayed according to the standard National Cancer Institute procedure.

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

The ILS value of bruceantin (5) was 68.0% at 2 mg/kg/day dose level, however, a severe toxicity was observed at 4 mg/kg/day dose level.

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