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NEW QUASSINOID GLYCOSIDES, YADANZIOSIDES A - H, FROM *BRUCEA JAVANICA*

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Eight new antileukemic quassinoid glycosides, yadanziosides A - H (1 - 8) were isolated from seeds of *Brucea javanica* and their structures were determined by chemical transformation and spectral analysis.

KEYWORDS——bitter principle; antileukemic; quassinoid; glycoside; Simaroubaceae; *Brucea javanica*; ^{1}H-NMR; ^{13}C-NMR

As a continuation of studies on bitter principles of Simaroubaceous plants, glycosides in *Brucea javanica* (L.) MERR were investigated.[1)] This paper describes the structures of eight new quassinoid glycosides, some of which showed antileukemic activities against the murine P-388 lymphocytic leukemia.

The methanolic extract of defatted seeds of *B. javanica* was partitioned between dichloromethane and water. The organic layar, on evaporation, gave a residue, which was dissolved in hot methanol. After cooling, brusatol,[2)] which precipitated as crystals, was filtered. The filtrate was evaporated *in vacuo* and subjected to separation by silica-gel column chromatography. After elution with benzene-ethyl acetate, elution with ethyl acetate-methanol afforded fractions containing crude glycosides. The combined fractions were separated by silica-gel chromatography (elution: lower layer of chloroform-methanol-water), and then either by partition chromatography on silicic acid (elution: chloroform-ethanol), a Lobar column Lichroprep RP-8 (elution: methanol-water), or Toyopearl HW-40S (elution: methanol) to give eight new glycosides, yadanziosides A (1; 0.01%), B (2; 0.002%), C (3; 0.001%), D (4; 0.001%), E (5; 0.002%), F (6; 0.001%), G (7; 0.01%), and H (8; 0.001%) together with known brusatol,[2)] dehydrobrucein A,[3)] brucein D,[4)] brucein E,[4)] bruceoside A,[5)] bruceoside B,[5)] and yadanziolide A.[1)]

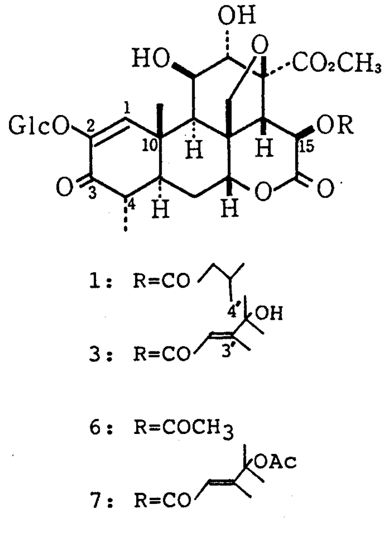
Yadanzioside B (2), mp 189-195°C; IR (KBr) 3425, 1735, and 1635 cm^{-1}; UV (EtOH) 255 nm, gave a peak at *m/z* 707 due to [M+Na]$^+$ in SI-MS, from which the molecular formula, $C_{32}H_{44}O_{16}$, was deduced, and was shown to be a hexoside from an appearance of a peak at *m/z* 522.2082 corresponding to [M-$C_6H_{10}O_5$]$^+$ in the EI-high resolution mass spectrum. ^{1}H- and ^{13}C-NMR spectra suggest that yadanzioside B (2) must be a β-D-glucoside of brucein A (9).[3),6)] Glycosylation shifts (Δδ +18.1 ppm and Δδ +1.9 ppm) of the signals due to C-3 and C-4 respectively were observed in the ^{13}C-NMR, indicating that D-glucose is attached at C-3 of the aglycone. An anomeric proton was observed at δ 5.46 as a doublet (*J*=7.3 Hz) in the ^{1}H-NMR spectrum. On acid hydrolysis with 1M H_2SO_4-methanol, 2 gave brucein A (9), and hydrolysis with HCl-methanol afforded methyl D-glucoside, which was identified by GLC after trimethylsilylation. Thus the structure of yadanzioside B (2) was determined to be 3-*O*-β-D-glucosyl brucein A.

Yadanzioside A (1), mp 200-204°C; IR (KBr) 3400, 1740, 1675, and 1625 cm^{-1}; UV (EtOH) 256 nm, was shown by SI-MS to be a glucoside with the same molecular formula as that of 2. Yadanzioside A (1) was hydrolyzed with β-glucosidase at 37°C to give brucein A (9). Since a doublet signal due to $C_{(4)}$-CH_3 of the aglycone part of 1 was observed at δ 1.13 (*J*=6 Hz), the brucein A moiety isomerizes into a 3-keto-1-ene structure and forms the glycoside linkage through an oxygen atom on C-2. The structure of yadanzioside A (1) was formulated as 2-*O*-β-D-glucosyl brucein A.

Yadanzioside C (3), mp 204-209°C; IR (KBr) 3445, 1740, 1680, and 1640 cm^{-1}; UV (EtOH) 221 and 254 nm, gave a peak at *m/z* 749 due to $[M+Na]^+$ in SI-MS, which corresponds to the molecular formula, $C_{34}H_{46}O_{17}$. On acid hydrolysis with 1M H_2SO_4-methanol and with HCl-methanol, 3 afforded brucein C (10)[3,6,7] and methyl D-glucoside, respectively. Since a doublet signal due to $C_{(4)}$-CH_3 was observed at δ 1.19 (*J*=6.7 Hz) in the ^1H-NMR of 3, the structure of yadanzioside C (3) was determined to be 2-*O*-β-D-glucosyl brucein C.

Yadanzioside F (6), mp 202-207°C; IR (KBr) 3450, 1740, 1680, and 1630 cm^{-1}; UV (EtOH) 256 nm, exhibited a peak at *m/z* 643 due to $[M+H]^+$ in SI-MS, indicating the molecular formula $C_{29}H_{38}O_{16}$, and was hydrolyzed with β-glucosidase to give brucein B (11).[3,6] Since the $C_{(4)}$-CH_3 of 6 was observed as a doublet signal at δ 1.15 (*J*=5 Hz), yadanzioside F (6) was formulated as 2-*O*-β-D-glucosyl brucein B.

Yadanzioside G (7), mp 180-185°C; IR (KBr) 3450, 1740, 1685, and 1645 cm^{-1}; UV (EtOH) 222 and 253 nm, afforded a peak at *m/z* 791 due to $[M+Na]^+$ in SI-MS, corresponding to the molecular formula, $C_{36}H_{48}O_{18}$, and was hydrolyzed with β-

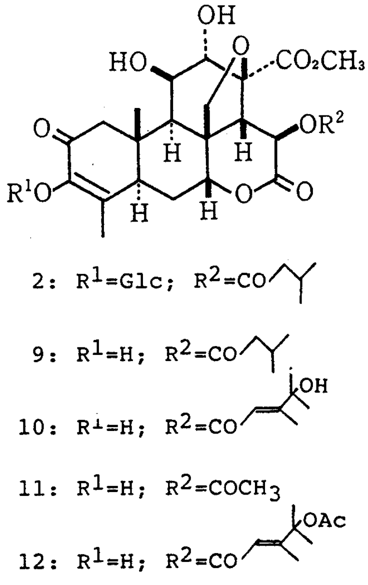


1: R=CO

3: R=CO

6: R=COCH3

7: R=CO



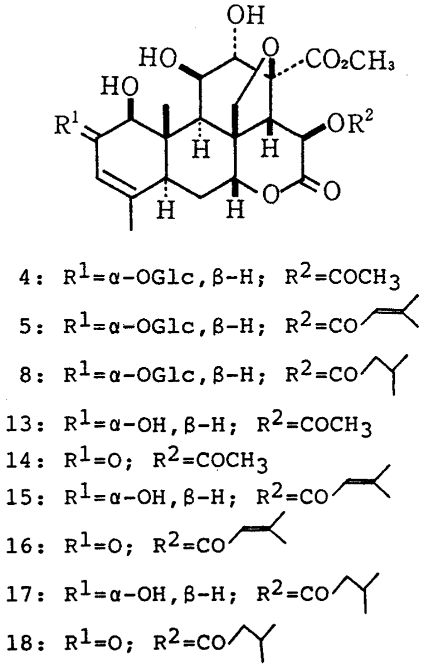
2: R¹=Glc; R²=CO

9: R¹=H; R²=CO

10: R¹=H; R²=CO

11: R¹=H; R²=COCH3

12: R¹=H; R²=CO



4: R¹=α-OGlc,β-H; R²=COCH3

5: R¹=α-OGlc,β-H; R²=CO

8: R¹=α-OGlc,β-H; R²=CO

13: R¹=α-OH,β-H; R²=COCH3

14: R¹=O; R²=COCH3

15: R¹=α-OH,β-H; R²=CO

16: R¹=O; R²=CO

17: R¹=α-OH,β-H; R²=CO

18: R¹=O; R²=CO

glucosidase to give bruceantinol (12).[3,7] In the ^{1}H-NMR spectrum of 7, a doublet signal due to $C_{(4)}$-CH_3 was observed at δ 1.17 (*J*=6 Hz). The structure of yadanzioside G (7) was formulated as 2-*O*-β-D-glucosyl bruceantinol.

Yadanzioside D (4), mp 207-212°C, exhibited the IR-absorption bands due to hydroxyl (3430 cm^{-1}) and δ-lactone (1745 cm^{-1}), but no UV absorption maximum characteristic of a conjugated carbonyl group. In the EI-MS of 4, a peak at *m/z* 480 due to an aglycone appeared and the ^{1}H-NMR spectrum suggests the presence of an acetoxyl group. On hydrolysis with β-glucosidase, 4 yielded the aglycone (13), $C_{23}H_{30}O_{11}$, ^{1}H-NMR δ: 1.52, 1.55, 2.09, 3.78, 4.01, and 6.76; MS *m/z*: 482, 464, 446, 440, 422, and 404. The aglycone (13) was oxidized with MnO_2 to give isobrucein B (14).[8,9] Since a doublet signal due to $C_{(1)}$-H appeared at δ 4.01 ($J_{1,2}$=8 Hz) in the ^{1}H-NMR of 13 and a glycosylation shift (Δδ +11.0 ppm) due to C-2 was observed in the ^{13}C-NMR spectrum, the configuration of $C_{(2)}$-OH of 13 was established to be α-equatorial and the glycoside linkage occurred through the C-2 oxygen atom. The structure of yadanzioside D (4) was determined to be the β-D-glucoside of the allylic alcohol (13) derived from isobrucein B (14).

Yadanzioside E (5), mp 190-195°C; IR (KBr) 3450, 1740, and 1645 cm^{-1}, possesses the molecular formula, $C_{32}H_{44}O_{16}$, deduced from a peak at *m/z* 707 due to $[M+Na]^+$ in SI-MS and was hydrolyzed with β-glucosidase to afford an aglycone (15), ^{1}H-NMR δ: 1.54, 1.66, 2.14, 3.74, 4.02, 5.08, and 6.75. This was treated with MnO_2 to yield a keto alcohol (16), ^{1}H-NMR δ: 1.19, 1.94, 1.96, 2.19, 3.78, and 6.23; MS *m/z*: 520, 502, 484, 437, 420, 402, 388, 374, 345, and 315, the structure of which could be established by ^{1}H-NMR and MS spectra. The structure of yadanzioside E (5) was thus determined to be the β-D-glucoside of 15.

Yadanzioside H (8), mp 180-185°C; IR (KBr) 3450, 1750, and 1640 cm^{-1}, has the molecular formula, $C_{32}H_{46}O_{16}$, deduced from a peak at *m/z* 709 due to $[M+Na]^+$ in SI-MS and was hydrolyzed with β-glucosidase to give an aglycone (17), ^{1}H-NMR δ: 0.94, 0.97, 1.52, 1.53, 3.80, 3.98, and 6.82, which on oxidation with MnO_2 afforded isobrucein A (18).[10] The position of the glycoside linkage was determined to be C-2 from the glycosylation shift (Δδ +11.0 ppm). Yadanzioside H (8), on hydrogenation (10% Pd-C/EtOH), gave a dihydro derivative, which was identical with a

Table I. ^{1}H-NMR Spectra (90MHz, C_5D_5N)[a] of Yadanziosides A-H (1-8)

	1	2[b]	3[b]	4	5	6	7	8
1-H	7.22s	3.25d(16)	7.29s	c)	c)	7.22s	7.25s	c)
2-H	-	-	-	4.45m	4.42m	-	-	4.42m
3-H	-	-	-	5.72brs	5.69brs	-	-	5.69brs
15-H	6.84d(13)	6.9br	6.8br	6.78d(12)	6.76d(13)	6.76d(13)	6.81d(13)	6.82d(13)
$C_{(4)}$-Me	1.13d(6)	2.04d(1.2)	1.19d(6.7)	1.43brs	1.43brs	1.15d(5)	1.17d(6)	1.42brs
$C_{(10)}$-Me	1.61s	1.71s	1.63s	1.43brs	1.43brs	1.63s	1.64s	1.42brs
CO_2Me	3.84s	3.84s	3.73s	3.77s	3.72s	3.81s	3.89s	3.79s
2'-H	c)	c)	6.77d(1.2)	-	5.82brs	-	6.06s	c)
3'-Me	0.96d(6) 0.99d(6)	0.95d(6.7) 0.98d(6.7)	2.40brs	-	1.67s 2.14s	-	2.26s	0.94d(6) 0.97d(6)
4'-Me	-	-	1.41s 1.42s	-	-	-	1.42s 1.46s	-
-OAc	-	-	-	2.09s	-	2.10s	1.95s	-
Anomeric -H	c)	5.46d(7.3)	5.37d(7.0)	4.93d(8)	4.94d(6)	c)	c)	c)

a) Coupling constants in Hz in parentheses. b) Measured at 400 MHz. c) Not measured.

Table II. ^{13}C-NMR Spectra (22.5 MHz, C_5D_5N) of Yadanziosides A-H (1-8)

	δ
1	12.5q, 17.9q, 22.4q, 22.5q, 25.8d, 30.0t, 39.5s, 40.6d, 41.3d, 43.3t, 43.8d, 46.6s, 50.4q, 52.3d, 62.3t, 68.4d, 71.3d, 73.4d, 73.7t, 74.5d, 75.9d, 78.3d, 78.7d, 82.6s, 83.5d, 102.0d, 129.6d, 148.8s, 168.1s, 171.1s, 171.6s, 194.6s
2	15.3q, 15.8q, 22.4q, 22.5q, 25.9d, 29.3t, 40.8s, 42.2d, 43.3d, 43.3t, 46.1s, 50.6d, 51,1t, 52.4q, 62.8t, 68.4d, 71.6d, 73.1d, 73.6t, 75.7d, 76.0d, 78.4d, 78.6d, 82.7s, 83.5d, 104.9d, 146.2s, 147.9s, 168.1s, 171.2s, 171.6s, 193.6s
3	12.6q, 15.6q, 18.0q, 28.9q, 28.9q, 30.0t, 39.7s, 40.5d, 41.4d, 43.8d, 46.7s, 50.3d, 52.4q, 62.4t, 68.4d, 71.3d, 73.2s, 73.6d, 73.8t, 74.7d, 76.1d, 78.6d, 79.0d, 82.6s, 83.5d, 102.0d, 112.9d, 129.3d, 149.2s, 166.5s, 168.2s, 168.3s, 171.2s, 194.5s
4	12.1q, 20.6q, 20.7q, 28.3t, 43.0d, 43.1d, 44.4s, 46.7s, 50.6d, 52.2q, 62.8t, 68.8d, 71.7d, 74.1t, 75.5d, 75.6d, 76.1d, 78.6d, 78.7d, 81.2d, 82.5s, 84.3d, 84.9d, 107.0d, 124.3d, 135.8s, 168.0s, 169.7s, 171.5s
5	12.1q, 20.2q, 20.8q, 27.0q, 28.3t, 42.9d, 43.1d, 44.4s, 46.7s, 50.6d, 52.2q, 62.7t, 68.2d, 71.6d, 74.1t, 75.6d, 75.7d, 76.0d, 78.5d, 78.6d, 81.2d, 82.5s, 84.2d, 84.8d, 106.9d, 116.0d, 124.3d, 135.9s, 158.2s, 165.3s, 168.2s, 171.4s
6	12.6q, 18.0q, 20.6q, 30.0t, 39.6s, 40.6d, 41.4d, 43.9d, 46.6s, 50.5q, 52.3d, 62.4t, 68.8d, 71.3d, 73.4d, 73.7t, 74.7d, 76.1d, 78.5d, 78.8d, 82.7s, 83.6d, 102.0d, 129.5d, 148.8s, 168.0s, 169.7s, 171.3s, 194.5s
7	12.5q, 14.5q, 18.0q, 21.4q, 25.8q, 26.4q, 30.1t, 39.6s, 40.4d, 41.4d, 43.9d, 46.6s, 50.2d, 52.6q, 62.4t, 68.7d, 71.4d, 73.4d, 73.7t, 74.6d, 76.0d, 78.4d, 78.8d, 82.3s, 82.6s, 83.5d 102.0d, 113.7d, 129.7d, 148.8s, 163.3s, 165.7s, 168.0s, 169.5s, 171.7s, 194.7s
8	12.1q, 20.7q, 22.4q, 25.5q, 25.8d, 28.3t, 43.1d, 43.1d, 43.3t, 44.4s, 46.7s, 50.8d, 52.2q, 62.8t, 68.4d, 71.6d, 74.1t, 75.5d, 75.7d, 76.1d, 78.6d, 78.7d, 81.2d, 82.5s, 84.3d, 84.9d, 107.0d, 124.3d, 135.8s, 168.2s, 171.4s, 171.6s

tetrahydro derivative of yadanzioside E (5). Thus the structure of yadanzioside H (8) was formulated as the β-D-glucoside of the allylic alcohol (17) derived from isobrucein A (18).

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