New Glycosidic Constituents of *Abutilon pakistanicum*

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Pakisides A and B (**1** and **2**, resp.), new catalpol-type iridoid glycosides, and a new glycoside, **3**, of scutellarein have been isolated from the AcOEt-soluble fraction of the whole plant of *Abutilon pakistanicum*, along with buddlejoside and lapachol. The structures of new compounds were elucidated by spectroscopic techniques including ^{1}H-and ^{13}C-NMR (DEPT), and 2D-NMR experiments.

Introduction. – The genus *Abutilon* (Malvaceae) is represented by 150 species which are distributed mainly in subtropical regions of Asia and other parts of the world. Generally, the leaves, roots, and stems of *Abutilon* species contain considerable amounts of mucilage due to which these are used for the treatment of rheumatism, and as demulcents and diuretics [1–3]. One of the species of this genus is *Abutilon pakistanicum* which commonly grows in southern parts of Pakistan. Our previous investigations on this species have resulted in the isolation and structure elucidation of steroids [4], flavonoid glycosides [5][6], and a triterpene [7]. The ethnopharmacological and chemotaxonomic importance of the genus *Abutilon* prompted us to re-investigate the chemical constituents of *Abutilon pakistanicum*. Here, we report the isolation and structure elucidation of two new catalpol-type iridoid glycosides named as pakisides A and B (**1** and **2**, resp.) along with a new glycoside, **3**, of scutellarein from the AcOEt-soluble fraction. Buddlejoside [8] and lapachol [9] have also been isolated for the first time from this species (*Fig. 1*).

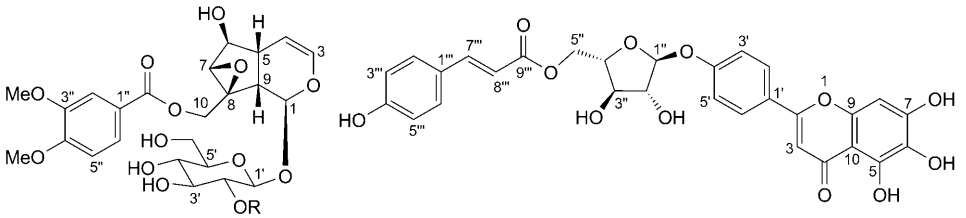

Fig. 1. *Structures of pakisides A and B* (**1** and **2**, resp.), *and compound* **3**

Results and Discussion. – The MeOH extract of the whole plant was divided into fractions soluble in hexane, $CHCl_3$, AcOEt, BuOH, and H_2O. Column chromatography of the AcOEt-soluble fraction provided compounds **1**–**5** as described in *Exper. Part*.

Pakiside A (**1**) was obtained as colorless gummy solid. The molecular formula was determined as $C_{24}H_{30}O_{13}$ by HR-FAB-MS (positive-ion mode; $[M+H]^+$ peak at *m/z* 527.1764 (calc. 527.1753)). The IR spectrum showed absorption bands of OH (3400 cm^{-1}), ester C=O (1695 cm^{-1}), C=C−O (1635 cm^{-1}), and an aromatic ring (1508 cm^{-1}). The UV spectrum was characteristic of catalpol-type iridoids with a maximum at 278 nm [10]. In the EI-MS, the peaks at *m/z* 364 and 345 resulted from the loss of a hexose moiety and dimethoxybenzoate group, respectively. The presence of dimethoxybenzoyl moiety was also confirmed by a base peak at *m/z* 165. The molecular formula of **1** was confirmed by broad-band and DEPT ^{13}C-NMR spectra which showed 24 signals of two Me, two CH_2, fifteen CH groups, and five quaternary C-atoms (*Table 1*). The spectrum showed diagnostic signals for an iridoid moiety, a hexose unit, and a dimethoxybenzoate group. The signals of the iridoid moiety were observed at δ(C) 141.0 and 101.9 due to one olefinic bond. It further displayed signals of four CH−O C-atoms at δ(C) 94.2, 80.0, 65.0, and 62.1, in addition to the resonance of an CH_2O C-atom at δ(C) 62.5. The signals of the remaining CH C-atoms were at δ(C) 41.9 and 38.0. The signals of a hexose unit were at δ(C) 98.6, 76.5, 76.0, 73.0, 69.6, and 61.2. The C-atoms of the dimethoxybenzoate residue resonated at δ(C) 166.4, 153.3, 148.5, 124.0, 112.0, 110.2, 55.9, and 55.0, respectively.

Table 1. *^{1}H- and ^{13}C-NMR Data of* **1** *and* **2**. At 500 and 125 MHz, respectively, in C_5D_5N; δ in ppm, *J* in Hz.

	1		**2**	
	δ(H)	δ(C)	δ(H)	δ(C)
H−C(1)	4.87 (*d*, *J* = 9.0)	94.2	5.09 (*d*, *J* = 9.5)	93.0
H−C(3)	6.16 (*dd*, *J* = 1.5, 6.0)	141.0	6.41 (*dd*, *J* = 1.5, 6.0)	141.0
H−C(4)	4.83 (*d*, *J* = 4.0, 6.0)	101.9	4.95 (*dd*, *J* = 4.5, 6.0)	101.7
H−C(5)	2.51–2.53 (*m*)	38.0	2.58–2.59 (*m*)	38.0
H−C(6)	4.96 (*d*, *J* = 7.0)	80.0	5.06 (*d*, *J* = 7.5)	80.0
H−C(7)	3.65 (br. *s*)	62.1	3.68 (br. *s*)	62.0
C(8)	–	65.0	–	65.0
H−C(9)	2.52–2.55 (*m*)	41.9	2.56–2.57 (*m*)	41.8
CH_2(10)	3.88 (*d*, *J* = 13.0), 5.02 (*d*, *J* = 13.0)	62.5	3.73 (*d*, *J* = 13.0), 5.01 (*d*, *J* = 13.0)	62.6
H−C(1′)	4.64 (*d*, *J* = 8.0)	98.6	4.59 (*d*, *J* = 8.0)	97.8
H−C(2′)	3.17–3.19 (*m*)	73.0	3.21–3.02 (*m*)	76.4
H−C(3′)	3.21–3.23 (*m*)	76.0	3.03–3.05 (*m*)	70.2
H−C(4′)	3.28–3.30 (*m*)	69.6	3.13–3.15 (*m*)	73.4
H−C(5′)	3.13–3.15 (*m*)	76.5	3.16–3.18 (*m*)	77.4
CH_2(6′)	3.55 (*dd*, *J* = 5.0, 12.0)	61.2	3.88 (*dd*, *J* = 5.1, 13.0)	61.3
C(1″)	–	121.7	–	121.3
H−C(2″)	7.38 (*d*, *J* = 2.0)	112.0	7.45 (*d*, *J* = 2.0)	111.7
H−C(3″)	–	148.5	–	148.4
C(4″)	–	153.3	–	153.2
H−C(5″)	6.75 (*d*, *J* = 8.5)	110.2	7.08 (*d*, *J* = 8.5)	111.1
H−C(6″)	7.61 (*dd*, *J* = 2.0, 8.5)	124.0	7.62 (*dd*, *J* = 2.0, 8.5)	123.4
C=O	–	166.4	–	166.4
*Me*O−C(2″)	3.77 (*s*)	55.9	3.81 (*s*)	55.5
*Me*O−C(3″)	3.76 (*s*)	55.0	3.83 (*s*)	55.7
*Me*O−C(2′)	–	–	3.30 (*s*)	58.1

The ^{1}H-NMR spectrum (*Table 1*) exhibited the signals of vicinal olefinic H-atoms of the iridoid moiety at δ(H) 6.16 (*dd*, $J = 1.5, 6.0$, 1 H) and 4.83 (*dd*, $J = 4.0, 6.0$, 1 H). The CH–O H-atoms resonated at δ(H) 4.96 (*d*, $J = 7.0$, 1 H), 4.87 (br. *d*, $J = 9.0$, 1 H), 3.65 (br. *s*, 1 H), and the CH_2O H-atoms at δ(H) 5.02 (*d*, $J = 13.0$ Hz, 1 H) and 3.88 (*d*, $J = 13.0$, 1 H). The vicinal CH H-atom resonances appeared as *multiplet*s at δ(H) 2.59 and 2.51–2.53. The anomeric H-atom of the hexose unit resonated at δ(H) 4.64 (*d*, $J =$ 8.0 Hz, 1 H). The larger coupling constant confirmed β-glycosidic linkage. The aromatic signals were due to a 3,4-dimethoxybenzoate moiety.

Hydrolysis in basic medium yielded 3,4-dimethoxybenzoic acid and an iridoid glucoside, which could be identified as catalposide by comparison of physical and spectral data with those reported in [11][12]. The downfield shift of the resonances of C(10) and its attached H-atoms allowed us to assign the ester moiety to C(10) which was subsequently confirmed by HMBC experiments showing ^3J correlation of both the CH_2O H-atoms at C(10) with C=O C-atom signal of the ester at δ(C) 166.4. The hydrolysis in acidic medium provided the free sugar, which could be identified as D-glucose through sign of its optical rotation and comparison of retention times (t_R) of its Me_3Si (TMS) ethers with t_R value of a standard sample in gas chromatography. The attachment of glucose was confirmed by ^3J correlation of the anomeric H-atom signal at δ(H) 4.64 with that of C(1) at δ(C) 94.2. The HMQC, HMBC (*Fig. 2*), and NOESY (*Fig. 2*) correlations were in agreement with the assigned structure of pakiside A (**1**) as 10-*O*-(3″,4″-dimethoxybenzoyl)catalposide (*Fig. 1*).

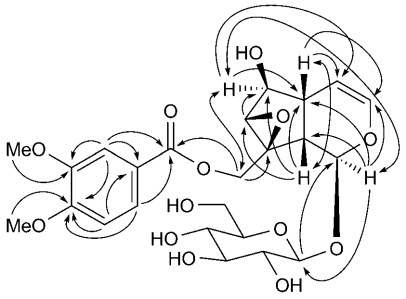

Fig. 2. *Key HMBC* (H → C) *and NOESY* (H ↔ H) *correlations of* **1**

Pakiside B (**2**) was obtained as colorless gummy solid with the molecular formula $C_{25}H_{32}O_{13}$ deduced from HR-FAB-MS (positive-ion mode; *m/z* 541.1916 ($[M+H]^+$)). The UV and IR spectra were similar to those of **1**. The ^{1}H- and ^{13}C-NMR spectra were also similar to those of **1** except the presence of additional signals due to a MeO group (δ(H) 3.30 and δ(C) 58.1). The presence of an additional MeO group in the sugar moiety was evident by a common $[M - \text{sugar}]^+$ peak in EI-MS at *m/z* 364. It could be assigned to C(2′) due to a downfield shift of C(2′) signal compared to **1** and also on the basis of HMBC showing ^3J correlation of MeO H-atom resonance at δ(H) 3.01 with that of C(2′) (δ(C) 76.4). Irradiation of MeO H-atoms caused NOE on neighboring H-atoms at C(1′) and C(3′), providing conclusive evidence of the presence of 2′-*O*-methylglucose moiety. The rest of the HMBC and NOESY correlations were similar to those of **1**, allowing us to retain the same configuration. The structure of pakiside B (**2**) could thus be assigned as 10-*O*-(3″,4″-dimethoxybenzoyl)-2′-*O*-methylcatalposide.

Compound **3** was obtained as a yellow gummy solid. It gave a violet coloration with $FeCl_3$, and a positive reaction with *Molish* and *Shinoda* reagents [13]. The molecular formula was determined to be $C_{29}H_{24}O_{12}$ by HR-FAB-MS (positive-ion mode) showing the $[M+H]^+$ peak at m/z 565.1354. The UV spectrum showed maxima at 282 and 334 nm. On addition of $AlCl_3$ and $AlCl_3$/HCl, bathochromic shifts of 39 and 28 nm of band 1 were observed, being characteristic of scutellarein [14]. The IR spectrum showed bands of OH (3400 cm^{-1}), ester C=O (1700 cm^{-1}), conjugated C=O (1660 cm^{-1}), and olefinic (1620 cm^{-1}) functionalities. The ^{1}H- and ^{13}C-NMR signals (*Table 2*) displayed characteristics of a scutellarein moiety with an esterified sugar residue. The anomeric H-atom signal was observed as a *doublet* at δ(H) 6.29 ($J=$ 7.2 Hz, 1 H) along with other CH and CH_2 signals (*Table 2*). The presence of an (*E*)-*p*-coumaroyl moiety was also evident (olefinic H-atom signals at δ(H) 7.75 (*d*, $J=$ 16.0, 1 H) and 6.41 (*d*, $J=16.0$, 1 H); and 7.44 (*d*, $J=8.7$, 2 H) and 7.12 (*d*, $J=8.7$, 2 H). The ^{1}H- and ^{13}C-NMR signals of the sugar moiety characterized it as α-L-arabinofuranoside [15]. This was confirmed by acid hydrolysis, which provided besides scutellarein and (*E*)-*p*-coumaric acid, a glycone which was identified as L-arabinofuranose by gas chromatography. The ester moiety was deduced to be at C(5″) from the downfield shift of the CH_2(5″) resonance and confirmed by ^3J correlations of CH_2(5″) (δ(H) 4.77) with C=O C-atom of the ester moiety (δ(C) 167.2). Thus compound **3** was determined as scutellarein 4′-*O*-α-L-[5″-*O*-(*E*)-*p*-coumaroyl]arabinofuranoside.

Table 2. *^{1}H- and ^{13}C-NMR Data of* **3**. At 500 and 125 MHz, respectively, in C_5D_5N; δ in ppm, J in Hz.

	δ(H)	δ(C)		δ(H)	δ(C)
C(2)	–	162.6	H–C(1″)	6.19 (*d*, $J=7.2$)	103.9
H–C(3)	6.68 (*s*)	99.8	H–C(2″)	3.82–3.91 (*m*)	75.9
C(4)	–	178.6	H–C(3″)	3.81–3.83 (*m*)	71.2
C(5)	–	153.2	H–C(4″)	4.33–4.35 (*m*)	78.3
C(6)	–	130.0	CH_2(5″)	4.77 (*dd*, $J=5.4$, 11.7)	64.1
C(7)	–	157.0	C(1‴)	–	126.1
H–C(8)	6.67 (*s*)	94.5	H–C(2‴)	7.44 (*d*, $J=8.7$)	130.6
C(9)	–	157.7	H–C(3‴)	7.12 (*d*, $J=8.7$)	116.7
C(10)	–	103.0	C(4‴)	–	161.3
C(1′)	–	121.8	H–C(5‴)	7.12 (*d*, $J=8.7$)	116.7
H–C(2′)	8.37 (*d*, $J=9.0$)	131.8	H–C(6‴)	7.44 (*d*, $J=8.7$)	130.6
H–C(3′)	7.22 (*d*, $J=9.0$)	116.0	H–C(7‴)	7.75 (*d*, $J=16.0$)	145.1
C(4′)	–	157.2	H–C(8‴)	6.41 (*d*, $J=16.0$)	114.8
H–C(5′)	7.22 (*d*, $J=9.0$)	116.0	C(9‴)	–	167.2
H–C(6′)	8.37 (*d*, $J=9.0$)	131.8	*H*O–C(5)	13.16 (*s*)	–

Experimental Part

General. Column chromatography (CC): silica gel (SiO_2; 250–400 mesh; *E. Merck*, D-Darmstadt). TLC: SiO_2 *60* F_{254} plates (*E. Merck*, D-Darmstadt). Optical rotations: *Jasco DIP-360* digital polarimeter. UV Spectra: *Hitachi UV-3200* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Jasco 302-A* spectrophotometer; in KBr; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker* 500 MHz instrument; δ in ppm rel. to Me_4Si as internal standard, J in Hz. EI-, and HR-FAB-MS: *Jeol JMS-HX-110* and *JMS-DA-500* mass spectrometers with glycerol as matrix; in m/z (rel. %).

Plant Material. The whole plant of *Abutilon pakistanicum* JAFRI and ALI (8 kg) was collected from Karachi in June 2004 and identified by Prof. *Surraiya Khatoon*, Department of Botany, University of Karachi. A voucher specimen was deposited with the Herbarium (KUH # 697) of the University of Karachi.

Extraction and Isolation. The whole plant of *A. pakistanicum* was shade-dried, ground, and extracted with MeOH (3×20 l) at r.t. The combined MeOH extract (350 g) was divided into hexane-, $CHCl_3$-, AcOEt-, BuOH-, and H_2O-soluble fractions. The AcOEt-soluble fraction (35 g) was subjected to CC eluting with mixtures of hexane/AcOEt in increasing polarity. Elution with hexane/AcOEt 7:3 provided a major fraction (3 g), which was again chromatographed and eluted with mixtures of hexane/AcOEt to obtain subfractions: *A* (hexane/AcOEt 6:4), *B* (hexane/AcOEt 4:6), *C* (hexane/AcOEt 2.5:7.5), and *D* (hexane/AcOEt 1:9). *Fr. A* provided a semi-pure compound, which, on subsequent prep. TLC ($CHCl_3$/MeOH 6:4), yielded lapachol (10 mg). *Fr. B* was subjected to prep. TLC ($CHCl_3$/MeOH 7:3) to yield compound **3** (8 mg) as yellow gummy solid. *Fr. C* was further chromatographed and eluted with hexane/AcOEt 2:8 to obtain buddlejoside (8 mg) and pakiside A (**1**) (20 mg) from the top and tail fractions, resp. Increasing the polarity with hexane/AcOEt 1:9 provided another semi-pure compound, which, on subsequent prep. TLC ($CHCl_3$/MeOH 8:2), yielded pakiside B (**2**) (15 mg).

Pakiside A (=*10*-O-*(3″,4″-Dimethoxybenzoyl)catalposide*=*[(1a*S*,1b*S*,2*S*,5a*R*,6*S*,6a*S*)-2-(β*-D-*Glucopyranosyloxy)-1b,5a,6,6a-tetrahydro-6-hydroxyoxireno[4,5]cyclopenta[1,2-*c*]pyran-1a(2*H*)-yl]methyl 3,4-Dimethoxybenzoate*; **1**). Colorless gummy solid. $[\alpha]_D^{25} = -115.0$ ($c = 0.02$, MeOH). UV (MeOH): 278 (4.3). IR (KBr): 3400, 1675, 1635, 1040. ^{1}H- and ^{13}C-NMR: see *Table 1.* EI-MS: 364 (10), 345 (25), 181 (65), 165 (100). HR-FAB-MS (pos.): 527.1764 ($[M+H]^+$, $C_{24}H_{31}O_{13}^+$; calc. 527.1765).

Pakiside B (=*10*-O-*(3″,4″-Dimethoxybenzoyl)-2′*-O-*methylcatalposide*=*[(1a*S*,1b*S*,2*S*,5a*R*,6*S*,6a*S*)-1b,5a,6,6a-Tetrahydro-6-hydroxy-2-[(2*-O-*methyl-β*-D-*glucopyranosyl)oxy]oxireno[4,5]cyclopenta[1,2-*c*]pyran-1a(2*H*)-yl]methyl 3,4-Dimethoxybenzoate*; **2**). Colorless gummy solid. $[\alpha]_D^{25} = -100.0$ ($c = 0.03$, MeOH). UV (MeOH): 278 (4.5). IR (KBr): 3400, 1675, 1635, 1040. ^{1}H- and ^{13}C-NMR: see *Table 1.* EI-MS: 364 (10.3), 194 (11), 184 (25), 181 (65), 165 (100). HR-FAB-MS (pos.): 541.1916 ($[M+H]^+$, $C_{25}H_{33}O_{13}^+$; calc. 541.1921).

Scutellarein-4′-O-*α*-L-*[5″*-O-*(*E*)*-p*-*Coumaroyl]arabinofuranoside* (=*5,6,7-Trihydroxy-2-[4-({5*-O-*[(2*E*)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]-α*-L-*arabinofuranosyl}oxy)phenyl]-4*H*-1-benzopyran-4-one*; **3**). Yellow gummy solid. $[\alpha]_D^{25} = -87.7$ ($c = 0.04$, MeOH). UV (MeOH): 282 (4.0), 334 (3.8). IR (KBr): 3400, 1700, 1660, 1620. ^{1}H- and ^{13}C-NMR: see *Table 2.* EI-MS: 372 (12), 286 (21), 194 (15), 164 (100), 148 (20). HR-FAB-MS (pos.): 565.1354 ($[M+H]^+$, $C_{29}H_{25}O_{12}^+$; calc. 565.1345).

Alkaline Hydrolysis of **1**. A mixture of **1** (5 mg) and 0.5% NaOH (2 ml) was heated at 60° for 45 min. The mixture was neutralized with 0.2% HCl and chromatographed on polyamide with $CHCl_3$/MeOH. Elution with $CHCl_3$/MeOH 97:3 provided a pure compound which crystallized from EtOH (m.p. 178–180°) and could be identified as 3,4-dimethoxybenzoic acid by comparison of physical and spectral data with those reported in [16]. Elution with $CHCl_3$/MeOH 85:15 furnished the iridoid glucoside which melted at 160°, resolidified, and melted again at 209–211° (dec.), $[\alpha]_D^{20} = -173$ ($c = 0.02$, EtOH). It was identified as catalposide by comparison of physical and spectral data with those reported in [17].

Acid Hydrolysis of **1**. A soln. of **1** (4 mg) in MeOH (5 ml) containing 1N HCl (2 ml) was refluxed for 4 h, concentrated under reduced pressure, diluted with H_2O, and extracted with AcOEt. The aq. phase was concentrated to obtain the sugar moiety which was identified as D-glucose by the sign of its optical rotation ($[\alpha]_D^{23} = +51.8$ ($c = 0.02$, MeOH)). It was further confirmed by comparing retention times of its Me_3Si (TMS) ethers (α-anomer, 3.7 min; β-anomer, 5.1 min) with t_R of a standard sample in gas chromatography (GC). Preparation of TMS ether and its subsequent GC was carried out according to the protocol described in [18]. The aglycone was a mixture of products which could not be worked up due to paucity of material.

Acid Hydrolysis of **3**. A soln. of **3** (1 mg) was refluxed in 10% HCl for 40 min. The resulting aq. mixture was extracted with AcOEt. The residue from the org. phase was subjected to prep. TLC (hexane/AcOEt 3:1) to obtain (*E*)-*p*-coumaric acid (crystalline solid; m.p. 210–213°) and scutellarein (yellow leaflets; m.p. 347–349°).

The aq. phase was neutralized with Ag_2CO_3, filtered, and the solvent was removed under N_2. The residue was dissolved in pyridine (0.2 ml), and 0.1M L-cystein methyl ester hydrochloride in pyridine

(0.1 ml) was added. After heating for 2 h, 1-(trimethylsilyl)-1*H*-imidazole (0.1 ml) was added, and the mixture was heated at 60° for 1 h. After drying the mixture, the residue was partitioned with hexane and H_2O (1 ml each). The org. phase was analyzed by GC according to the protocol described in [19] and L-arabinofuranose was identified by comparison of t_R (7.56 min; standard 7.57 min).

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