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Iridoids from *Scutellaria albida* ssp. *albida*

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Abstract

Three iridoid glycosides, 6′-*O*-*E*-*p*-coumaroylgardoside (**1**), 6′-*O*-*p*-*E*-coumaroyl-8-*epi*-loganic acid (**2**) and scutelloside (**3**) were isolated from the aerial parts of *Scutellaria albida* subsp. *albida*, in addition to an anomeric mixture in equilibrium of one iridoid aglycone (**4**, **4a**), nine iridoid glycosides (**5**–**13**), four known phenylethanoid glycosides (**14**–**17**), and six known phenolic derivatives (**18**–**23**).

Keywords: *Scutellaria albida* subsp. *albida*; Lamiaceae; Iridoids; Phenylethanoid glycosides; Phenolic derivatives

1. Introduction

Scutellaria albida L. ssp. *albida* (Lamiaceae) is an herbaceous perennial plant, often somewhat woody at the base. The plant has a general distribution from N. Italy to the Balkan peninsula and Crimea (Bothmer, 1985). Several species of the genus *Scutellaria* present antispasmodic, diaphoretic and febrifuge properties and are used in folk medicine (Duke, 1986).

In previous research into *S. albida* L. ssp. *albida*, apigenin, hispidulin and luteolin glycosides have been isolated (Skaltsa et al., 1996). In further study, the essential oil of the plant has been investigated (Skaltsa et al., 2000). In this paper, we report on the isolation and structural elucidation of three new iridoid glycosides, 6′-*O*-*E*-*p*-coumaroylgardoside (**1**), 6′-*O*-*p*-*E*-coumaroyl-8-*epi*-loganic acid (**2**) and scutelloside (**3**) in addition to 10 known iridoid aglycones and glycosides (**4**–**13**), four known phenylethanoid glycosides (**14**–**17**), and six simple phenolic derivatives (**18**–**23**).

2. Results and discussion

The methanolic extract of the aerial parts of *S. albida* ssp. *albida* after being successively chromatographed on silica gel columns and RP-HPLC, yielded along with the three new iridoid glycosides, an anomeric mixture in equilibrium of one iridoid aglycone (**4**, **4a**), namely dihydrocatalpogenine (C-1) α-epimer (**4**)/β-epimer (**4a**) (Gao et al., 1997), nine known iridoid glycosides, catalpol (**5**) (Çalis et al., 1993a; Chaudhuri and Sticher, 1981), albidoside (**6**) (Çalis et al., 1993a), picroside III (**7**) (Weinges and Künstler, 1977), dihydrocatalpol (**8**) (Huang et al., 2006), 10-descinnamoylglobularinin (**9**) (Chaudhuri et al., 1979), globularin (**10**) (Foderaro and Stermitz, 1992), (Çalis et al., 2002), gardoside (**11**) (Albach et al., 2004), 8-*epi*-loganic acid (**12**) (Damtoft et al., 1984), macfadyenoside (**13**) (Bianco et al., 1974), four known phenylethanoid glycosides, martynoside (**14**) (Warashina et al., 1992), isomartynoside (**15**) (Çalis et al., 1984), deacyl-martynoside (**16**) (Çalis et al., 1984, 1993b), acteoside (**17**) (Andary et al., 1982) and six known phenolic derivatives, *E*-*p*-coumaric acid (**18**) (Harborne, 1984), *E*-caffeic acid (**19**) (Harborne, 1984), *E*-ferulic acid (**20**) (Harborne, 1984), *E*-*p*-coumaroylglucoside (**21**) (Harborne, 1984), vanilloloside (**22**)

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(Ida et al., 1994) and benzyl-β-glucopyranoside (**23**) (Schwab and Schreier, 1988) were also isolated. The known compounds **4**–**23** were identified by spectral analysis and direct comparison of their physical properties with those reported previously for these compounds.

Compound **1** was obtained as yellowish oil. 1D and 2D NMR spectra showed that **1** consisted of a gardoside moiety esterified to a *p*-coumaroyl group. In the ^{1}H NMR spectrum, downfield shifts of sugar protons H-6a′ and H-6b′ (at δ 4.47 and 4.38 respectively) were observed, which indicated esterification at C-6′ of the β-glucopyranosyl moiety. The HSQC spectrum offered further support for the proposed structure of **1**. The C-6′ resonance of the β-glucopyranose was typically deshielded by 2.3 ppm (α-effect) while the C-5′ resonance was shifted upfield by 2.5 ppm (β-effect) due to the acylation of the primary hydroxyl function. HMBC confirmed the position of the *p*-coumaroyl residue by showing a clear long-range correlation peak between the carbonyl carbon (δ 168.7) and both H-6a′ and H-6b′ (δ 4.47 and 4.38) of the glucopyranosyl unit. Therefore **1** was assigned as 6′-*O*-*E*-*p*-coumaroyl-gardoside.

Compound **2** was obtained as yellowish oil. 1D and 2D NMR spectra showed that **2** consisted of a 8-*epi*-loganic acid moiety esterified to a *p*-coumaroyl group at C-6′. Structure elucidation strategy was very similar compared to **1** and confirmed that **2** was the hitherto unknown 6′-*O*-*p*-*E*-coumaroyl-8-*epi*-loganic acid.

Compound **3** was obtained as amorphous substance. In the ESI-MS spectrum no molecular ion peak was observable and the dominating fragment showed a *m*/*z* at 200 [M−glucose; (calcd for $C_{15}H_{24}O_{11}$: 380.13182)].

The ^{1}H NMR, ^{13}C NMR, HSQC and COSY spectral data suggested that **3** had a nine carbon catalpol-like iridoid structure, attached to a β-glucopyranosyl moiety at C-1. An HMBC correlation peak between H-1′ [δ 4.68 (d, $J = 7.8$ Hz)] and C-1, confirmed the attachment of the sugar unit. The ^{1}H NMR spectrum displayed two acetal protons [δ 5.63 (d, $J = 1.6$ Hz, H-1), 5.27 (d, $J = 2.7$ Hz, H-3)], two oxygenated methine protons [δ 4.04 (dd, $J = 7.4$, 0.9 Hz, H-7), 4.03 (dd, $J = 7.4$, 2.6 Hz, H-6)], two oxygenated methylene protons [δ 3.98 (d, $J = 12.4$ Hz, H-10a), 3.60 (d, $J = 12.4$ Hz, H-10b)], two methine protons [δ 2.53 (dd, $J = 9.5$, 1.6 Hz, H-9), 2.30 (ddd, $J = 9.5$, 7.8, 2.6 Hz, H-5)] and two methylene protons [δ 2.44 (dd, $J = 13.4$, 7.8 Hz, H-4a (β)), 1.67 (dd, $J = 13.4$, 2.7 Hz, H-4b (α))].

The absence of signals of olefinic protons in the ^{1}H NMR spectrum, showed that the double bond usually occurring between the positions 3 and 4 did not exist. There were also signals characteristic of the β-glucopyranosyl group (Table 1).

Table 1
Spectral data of compounds **1**–**3** in CD_3OD (^{1}H 400 MHz, ^{13}C 100 MHz)

Position	**1**		**2**		**3**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	5.25 d ($J = 4.2$)	96.5	5.28 d ($J = 5.0$)	95.6	5.63 d ($J = 1.6$)	93.6
3a	7.13 s	147.2	7.29 s	150.4	5.27 d ($J = 2.7$)	96.0
3b	–		–			
4a	–	113.5	–	115.6	2.44 dd ($J = 13.4$, 7.8)	35.3
4b	–		–		1.67 dd ($J = 13.4$, 2.7)	
5	3.19 d ($J = 8.0$)	31.0	3.03 m	32.2	2.30 ddd ($J = 9.5$, 7.8, 2.6)	35.7
6a	1.90–2.10 m	40.9	1.9 m	41.5	4.03 dd ($J = 7.4$, 2.6)	86.0
6b			1.78 m		–	
7	4.39 m	72.8	3.78 m	79.2	4.04 dd ($J = 7.4$, 0.9)	74.7
8	–	150.9	2.05 m	45.4	–	79.9
9	2.9 m	45.9	2.46 m	43.2	2.53 dd ($J = 9.5$, 1.6)	48.0
10a	5.19 *brd* ($J = 7.5$)	112.0	1.02 d ($J = 7.4$)	14.4	3.98 d ($J = 12.4$)	62.0
10b			–		3.60 d ($J = 12.4$)	
11	–	171.2	–	172.7	–	–
1′	4.65 d ($J = 8.0$)	99.5	4.68 d ($J = 8.2$)	99.9	4.68 d ($J = 7.8$)	99.1
2′	3.25 dd ($J = 9.5$, 8.0)	73.5	3.24 dd ($J = 8.0$, 7.9)	74.8	3.18 dd ($J = 8.6$, 7.8)	75.1
3′	3.40 t ($J = 9.5$)	77.0	3.40–3.34 m	77.9	3.19–3.40 m	78.3
4′	3.33 t ($J = 9.5$)	70.9		71.7		72.0
5′	3.50 m	74.8	3.55 m	75.7		78.1
6′a	4.47 dd ($J = 12.0$, 2.2)	63.8	4.50 dd ($J = 12.1$, 2.7)	64.4	3.87 d ($J = 12.4$)	62.9
6′b	4.38 dd ($J = 12.0$, 6.2)		4.39 dd ($J = 12.0$, 6.2)		3.66 d ($J = 12.4$)	
1″	–	160.1	–	161.8	–	–
2″ and 6″	7.57 d ($J = 8.5$)	130.2	7.46 d ($J = 8.6$)	131.2	–	–
3″ and 5″	6.80 d ($J = 8.5$)	115.7	6.80 d ($J = 8.5$)	116.7	–	–
4″	–	127.9	–	127.1	–	–
7″	7.63 d ($J = 16.0$)	147.0	7.64 d ($J = 16.4$)	146.9	–	–
8″	6.36 d ($J = 15.7$)	114.9	6.36 d ($J = 16.4$)	114.9	–	–
9″	–	168.7	–	169.8	–	–

Assignments were made using HSQC and HMBC data.

The small coupling of H-1 ($J = 1.6$ Hz) with H-9 (δ 2.53), confirmed the β-orientation of H-9, since H-1 is known to be α-orientated in naturally occurring iridoid glucosides (Tietze et al., 1980), and suggested a dihedral angle close to 60°. The large coupling of H-9 ($J = 10$ Hz) with the adjacent proton H-5 (δ 2.30) confirmed the β-orientation of H-5, indicating a dihedral angle near 0° and thus demonstrating that the stereochemistry of the catalpol ring fusion was *cis*. No other vicinal couplings to H-9 were observed, so it was concluded that C-8 (δ 79.9) was quaternary.

The COSY spectrum offered no coupling signals between H-5 and H-4α (δ 1.67) as also between H-4β (δ 2.44) and H-3, indicating that their dihedral angles were nearly 90°. Furthermore, H-3 showed a small coupling with H-4α ($J = 2.7$) thus suggesting an equatorial position for H-3.

The existence of a dihedral angle of 90° between H-4β and H-3 combined with the clear long-range correlation signals between H-10a and C-3 in the HMBC spectrum, gave evidence of an ether linkage between C-3 and C-10 (and not between C-3 and C-8) (Iwagawa et al., 1991), thus confirming that **3** had a rigid three ring skeleton. The NOESY spectrum exhibited correlation signals between H-7 and H-9, H-7 and H-5, confirming thus the β-orientation of H-7 and consequently the α-orientation of the hydroxyl group at C-7. Also, NOE signals occurred between H-6 and H-4α, leading to the conclusion that H-6 had α-orientation. Finally, the signals between H-10b and H-1 revealed that the ether linkage between C-3 and C-10 had α-configuration. Based upon the data mentioned above, the proposed structure for scutelloside is that shown in Fig. 1.

The main products of the plant are catalpol (**5**) and albidoside (**6**), with catalpol being a useful taxonomic marker for the genus *Scutellaria* (Cole et al., 1991). The isolation of compounds **1**, **2**, **11** and **12** is important for biosynthetic reasons. It is known that 8-*epi*-loganic acid and consequently gardoside biosynthetically occur from 8-*epi*-deoxyloganic acid (Damtoft, 1994), while loganic acid is formed via different pathway and therefore the exact determination of the configuration at C-8 is of considerable taxonomic significance (Jensen et al., 1989; Naas and Rimpler, 1996).

The C-1 epimers **4** and **4a** were isolated as an inseparable mixture. This is the first time that these free iridoid aglycones have been isolated from the Lamiaceae family. Only once before they were isolated and identified from *Pedicularis striata* – Scrophulariaceae (Gao et al., 1997).

Though similar iridoids possessing a rigid three ring skeleton have been previously reported (Iwagawa et al., 1991; Jia et al., 1999; Yoshikawa et al., 1986; Kim et al., 2006), scutelloside (**3**) is the first iridoid glucoside bearing such a skeleton to be isolated from the genus *Scutellaria* (see Fig. 2).

3. Experimental

3.1. General

^{1}H, ^{13}C and 2D NMR spectra were recorded in CD_3OD on Bruker DRX-400 and Bruker AC-200 (50.3 MHz for ^{13}C NMR) instruments at 295 K. Chemical shifts are given in parts per million (ppm) and were referenced to the solvent signals at 3.31 ppm and 49.5 ppm for ^{1}H and ^{13}C

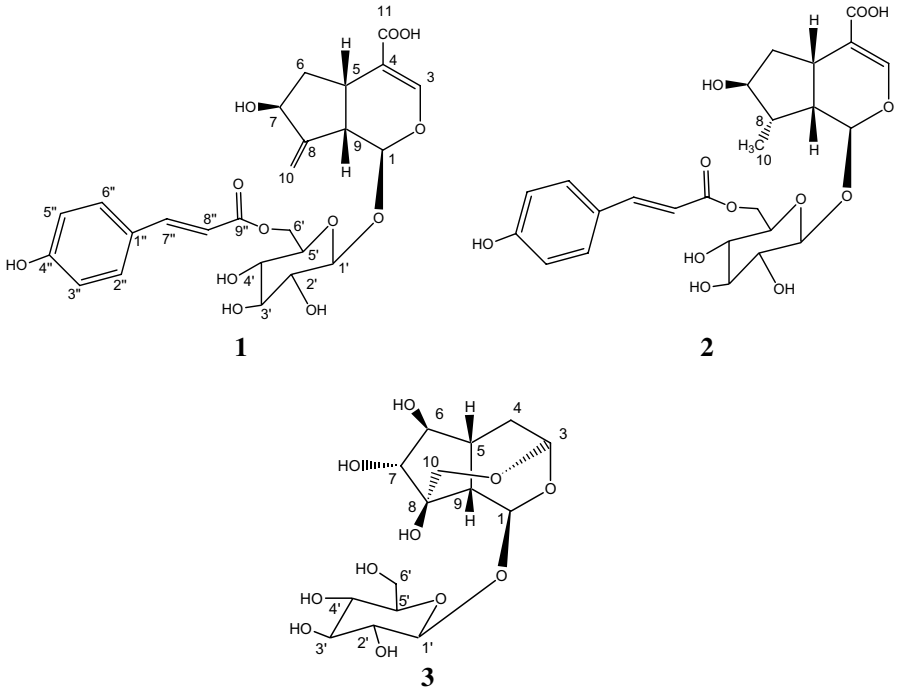

Fig. 1. Structures of compounds **1**–**3**.

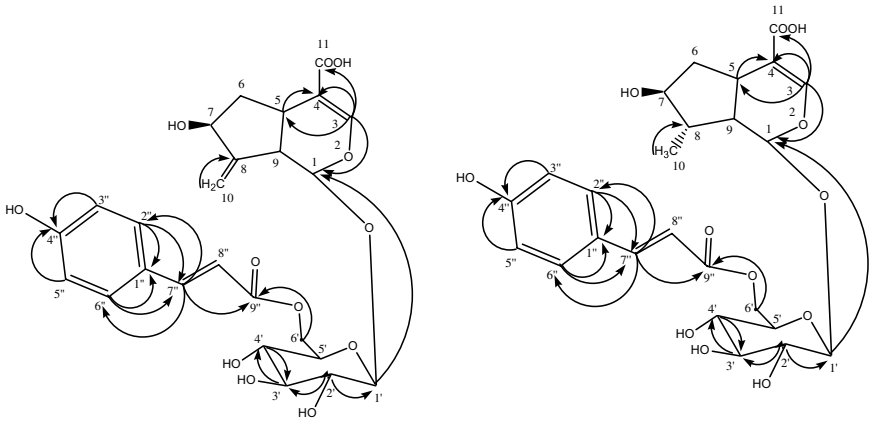

Fig. 2. Selected HMBC correlations for **1** and **2**.

NMR, respectively. COSY, HSQC, HMBC and NOESY were performed using standard Bruker microprograms. IR spectra were obtained on a Perkin–Elmer PARAGON 500 FT-IR spectrophotometer. UV spectra were recorded on a Shimadzu UV-160A spectrophotometer. ESI mass spectra were measured on a TSQ 7000 spectrometer using a spray voltage of 4 kV and a heated capillary of 200 °C (MeOH + 10 mmol/l NH_4Ac). Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Vacuum-liquid chromatography (VLC) was carried out on Silica Gel 60H (Merck, Art. 7736). Column chromatography (CC) was carried out on Silica Gel 60 (Merck, Art. 9385). Preparative HPLC was performed on Jasco system equipped with a PU 980 pump, RI-930 refractive index detector (Jasco Corporation, Tokyo, Japan) and a reversed phase column, Kromasil C_{18} 250 × 10 mm column (see Fig. 3).

3.2. Plant material

The aerial parts of *S. albida* ssp. *albida* were collected at Mount Pelion (Central Greece) in June 2001. The plant was authenticated by Dr. T. Constantinidis (Institute of Systematic Botany, Agricultural University of Athens) and a voucher specimen was deposited in the Herbarium (ACA-Lazari & Gousiadou 001).

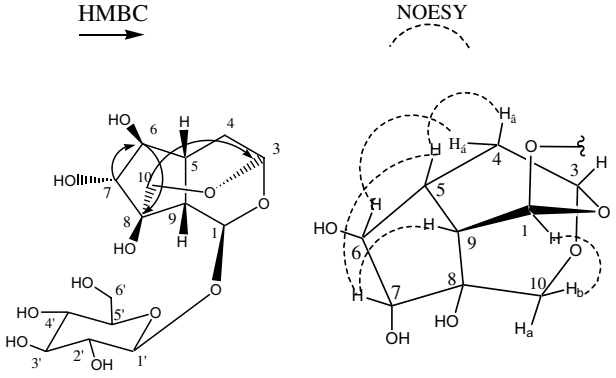

Fig. 3. Selected HMBC and NOESY correlations for **3**.

3.3. Extraction and isolation

Fresh aerial parts of *S. albida* ssp. *albida* (480 g) were successively extracted at room temperature with acetone, MeOH and MeOH–H_2O 5:1 (2 L of each solvent, twice, 48 h). The dried MeOH extract (27.6 g) was subjected to VLC over silica gel (10 × 8 cm) using as eluent CH_2Cl_2–MeOH mixtures of increasing polarity to yield finally seven fractions (MA′–MR′). Fraction MK′ (110.0 mg; eluted with CH_2Cl_2–MeOH 50:50) was pure compound **5**. Fraction MM′ (8.7 g; eluted with CH_2Cl_2–MeOH 65:35–60:40) was further applied to VLC over silica gel using EtOAc–MeOH and yielded 16 fractions (MM′A–MM′P). Fraction MM′E (370 mg; eluted with EtOAc–MeOH 90:10) was submitted to CC on silica gel (CH_2Cl_2–MeOH 95:5–50:50) and yielded three fractions, which were further subjected to RP-HPLC: fraction MM′EC (25.5 mg; MeOH–H_2O 35:65) yielded compound **2** (1.4 mg); t_R 11.0. Fraction MM′K (1.1 g; eluted with EtOAc–MeOH 76:24–75:25) was subjected to VLC over silica gel (10 × 8 cm) using H_2O–MeOH as eluent and yielded five fractions (MM′KA–MM′KE). Further purification by TLC on silica gel of fraction MM′KA (eluted with H_2O) yielded compound **5** (18.8 mg). Fraction MM′D was submitted to CC over Sephadex LH-20 (MeOH) and yielded six fractions (MM′DA–MM′DF). Fraction MM′DC after HPLC with MeOH–H_2O 15:85 yielded compound **3** (2.2 mg); t_R 9.5 min. Further purification by TLC on silica gel of fractions MM′DD and MM′DF yielded compounds **6** (19.1 mg) and **17** (5.9 mg), respectively. Fraction MM′E (370 mg; EtOAc–MeOH 90:10) was submitted to CC on silica gel (CH_2Cl_2–MeOH 95:5–50:50) and yielded three fractions, which were further subjected to RP-HPLC: fraction MM′EC (25.5 mg; MeOH–H_2O 35:65) yielded compounds **1** (1.4 mg); t_R 11.0 min, **18** (2.7 mg); t_R 8.0 min, **19** (2.5 mg); t_R 6.52 min and **22** (2.2 mg); t_R 6.30 min. Fraction MM′ED (26.0 mg; MeOH–H_2O 25:75) yielded compounds **16** (2.5 mg); t_R 30.0 min and **20** (3.0 mg); t_R 10.0 min. Fraction MM′EF (33.6 mg; MeOH–H_2O 35:65) yielded **21** (1.5 mg); t_R 16.8 min. Fraction MM′J

(904.5 mg; EtOAc–MeOH 80:20–77:23) was submitted to CC on silica gel (EtOAc–MeOH–H_2O 90:10:1–70:30:3) and finally yielded three fractions: fraction MM′JE′ (73.1 mg) was further purified by HPLC using as eluent MeOH–H_2O 5:95 and yielded compounds **11** (3.2 mg); t_R 20.0 min and **12** (2.7 mg); t_R 31.0 min. Fractions MM′JK′ (86.9 mg) and MM′JT′ (160.2 mg) were further purified by HPLC with MeOH–H_2O 10:90 and yielded compounds **9** (3 mg); t_R 12.0 min,**13** (2.5 mg); t_R 10.83 min and **8** (3.3 mg); t_R 9.76 min respectively. Finally, fraction MK′ (3.6 g; CH_2Cl_2–MeOH 70:30) subjected to CC on silica gel with EtOAc–MeOH (97:3–70:30) yielded fraction MK′F (30 mg) which after HPLC with MeOH–H_2O 9:11 yielded compounds **4** and **4a** (5.5 mg); t_R 7.2 min, **7** (1.5 mg); t_R 10.2 min, **10** (1.6 mg); t_R 22.0 min, **14** (4.7 mg); t_R 26.4 min, **15** (1.3 mg); t_R 38.0 min and **23** (1.6 mg); t_R 10.7 min.

3.4. 6′-*O*-*E*-*p*-coumaroylgardoside (*1*)

Yellowish oil; $[\alpha]_D^{20}$ − 4.29 (*c* 0.12, MeOH); UV/vis (MeOH) λ_{max} nm (log ε): 300.5^{sh} (4.42), 312 (4.89); IR (film): ν_{max} cm^{-1}: 3352 (O–H), 2914 (C—H), 1644 (C=O), 1607 (C=C); for ^1H and ^{13}C NMR spectra, see Table 1; HR-ESI-MS *m/z* 519.1499 $[M-H]^-$ (calcd for $C_{25}H_{27}O_{12}$: 519.1503).

3.5. 6′-*O*-*E*-*p*-coumaroyl-8-epi-loganic acid (*2*)

Yellowish oil; $[\alpha]_D^{20}$ − 50.67 (*c* 0.15, MeOH); UV/vis (MeOH) λ_{max} nm (log ε): 298^{sh} (3.53), 309 (4.03); IR (film) ν_{max} cm^{-1}: 3352 (O–H), 2914 (C—H), 1644 (C=O), 1607 (C=C); for ^1H and ^{13}C NMR spectra, see Table 1; HR-ESI-MS *m/z* 521.1670 $[M-H]^-$ (calcd for $C_{25}H_{29}O_{12}$: 521.1659).

3.6. Scutelloside (*3*)

Amorphous powder; $[\alpha]_D^{20}$ − 3.43 (*c* 0.22, MeOH); UV/vis (MeOH) λ_{max} nm (log ε): 264^{sh} (0.73) ; IR (film) ν_{max} cm^{-1}: 3352 (O–H), 2914 (C–H); for ^1H and ^{13}C NMR spectra, see Table 1; ESI-MS and HR-ESI-MS no molecular or pseudomolecular ion observable.

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